Transfusion-related hepatitis

Blood and blood products are of great medical benefit, but like all medications carry their own risk profile. Prominent among these is hepatitis. The work of Krugman in the 1960s clearly identified an enterically transmitted short incubation period virus and a parenterally transmitted long incubation period virus. These were later categorized and named, respectively, hepatitis A (HAV) and hepatitis B (HBV). With the development of markers for HAV and HBV, it became clear that other viruses were involved in some patients with post-transfusion hepatitis. The nomenclature was then established describing this group as Non-A Non-B (NANB). In 1989 Houghton and colleagues described a third virus, hepatitis C (HCV). It is clear that over ninety per cent of NANB hepatitis is due to HCV. Hepatitis D (HDV) is a virus which occurs only in persons affected with HBV. Hepatitis E (HEV) is an enterically transmitted virus with high mortality in pregnant women. Other viruses which can transmit hepatitis include Epstein/Barr virus and cytomegalovirus. Other viral infective agents transmitted in blood include human immunodeficiency virus (HIV), human lymphotropic virus (HTLV) and parvovirus. Non-viral agents include malaria, syphilis, yersinia enterocolitica, babesia microti and trypanosoma cruzi.

In 1986, donor screening for surrogate markers (elevated alanine aminotransferase and antibody to hepatitis B core antigen—anti HBc) of NANB began. In 1990 an enzyme-linked immunosorbent assay (ELISA) to detect antibodies to HCV was introduced. These screening techniques have led to a significant reduction in seroconversion to HCV in recipients. Multiply transfused patients and those requiring clotting factor concentrates are most at risk. The overall post-transfusion hepatitis risk is now estimated at approximately 3 per 10,000 units transfused. Patients with thalassaemia, haemophilia, those who require multiple transfusion during surgery and those requiring repeated haemodialysis are at greatest risk. A huge outbreak of HBV occurred among US troops in the Pacific War Zone in 1942. This followed the use of contaminated yellow fever vaccine. Norman and colleagues have recently assessed the risk of primary liver cancer (HCC) in survivors. A slight excess mortality was found in those who had suffered subclinical hepatitis. These authors also concluded that immunocompetent males rarely become carriers after hepatitis B infection. In recent times, outbreaks have been traced to other contaminated blood products such as commercial clotting factor concentrates and immunoglobulins. Two recent outbreaks have been traced to Anti-D immunoglobulins used in Rhesus incompatibility.

Hepatitis C is the cause of most non-A non-B hepatitis. It is a positively stranded RNA virus of approximately 9400 nucleotides distantly related to the flavi and pesti viruses. Several major serotypes exist. Hepatitis C exists in blood as free virus and virus complexed with antibodies. It may be directly cytotoxic, but this is only a minor mechanism of liver injury. It infects monocytes and macrophages and infection is associated with cytotoxic T cells. Its viral envelope glycoprotein has a hypervariable region (the E2/NS1 region). Only 25% of acute HCV patients are icteric, and most have minimal symptoms. Fifty to seventy-five per cent of post-transfusion HCV patients will have abnormal transaminase and hepatic histology after twelve months. It has been estimated that 20% may progress to cirrhosis in the first decade of infection. It seems likely that virus genotype and level of viraemia are significant factors influencing whether progression to cirrhosis occurs. Infection with other viruses, older age of onset, and alcohol abuse are factors which increase the risk of progressive liver disease. High mutation might explain the intermittent nature of chronic HCV infection. A recent study in a patient with agammaglobulinaemia showed that the absence of neutralizing antibody allowed persistence of the dominant viral strain. It is now well established that HCV is more than just a liver disease. It may present to the dermatologist in the form of porphyria cutanea tarda or to the haematologist as essential mixed cryoglobulinaemia. Other associated diseases include idiopathic thrombocytopenia, glomerulonephritis and an unusual corneal ulcer (Mooren's ulcer). A recent report suggests that hepatitis E may be transmitted by blood. The significance
of these findings is still uncertain. Transmission of hepatitis A (HAV) to haemophiliacs has shown that solvent detergent treatment does not destroy non lipid-enveloped viruses. Treatment of transfusion-related virus hepatitis is still unsatisfactory. Most experience has been gained with the use of interferons. Interferons are proteins which interfere with several steps in the viral life cycle. They also modify cellular and humoral immune response. Treatment of HBV is targeted at patients with active disease and viral replication. Only patients with raised transaminases (over twice normal) who are HBV-DNA-positive should be treated. Interferon inhibits HBV replication, but is effective in less than 50% of cases of chronic HBV. Thirty to forty per cent of patients with chronic hepatitis B will respond, and clear hepatitis Be antigen and HBV DNA from the serum. Five to ten million units three times weekly, or 4.5 to 5 million units daily, subcutaneously or intramuscularly, should be given for 4 months. Second-generation nucleoside analogues are another form of anti-viral treatment. The disastrous results following the use of fialuridine, with five deaths in the first 15 patients treated, has jolted the hepatology world. It is speculated that Lamivudine or Famciclovir may be effective and safer.

Most experience and treatment of HCV has been with alpha-interferon. Its use in acute HCV infection is still contentious. The best results have been obtained in chronic infection where cirrhosis has not developed, but response also appears to be affected by the genotype present, with Simmonds Type 1 (Okamoto type 11) apparently the poorest response group. It remains to be shown that virus genotype per se is an independent predictive factor. The overall cure rate is probably less than 25% of those treated. Treatment regimes vary, but currently it appears that patients should be given interferon for twelve months. For the initial three months, the dose should be 3 million units/m² three times weekly, and for the following nine months patients should be given 2 million units/m² three times weekly. Success is achieved if the serum ALT levels remain normal and the serum tests negative for HCV-RNA a year after stopping treatment with normal liver histology. Interferon treatment is contraindicated in patients with autoimmune disease.

How then can blood and blood products be made safe? Dodd defined the key measures as encouraging autologous transfusion and intra-operative blood salvage, the use of voluntary as opposed to paid donors (though this has been disputed for plasma derivatives), laboratory testing of donors, and viral inactivation procedures for pooled plasma products. In the US, whole blood is subjected to seven tests for markers of infection. In the UK, the viruses routinely screened for in blood donors are HIV, HBV and HCV. The risk of transmitting HBV is of the order of 1:200,000 per unit. About 50% of those infected will have symptoms, but hospital treatment will be required in less than 5%. While infection with HCV becomes chronic in 90%, symptomatic liver disease is uncommon. Indeed, viraemia may persist in the absence of liver disease. Donahue and colleagues estimate that HCV transmission is of the order of 3 per 10,000 units transfused, although newer tests may well have reduced this risk quite substantially. These authors also point out that transfusion-associated hepatitis due to HCV is likely to remain a complication, because the window period for the virus is 3–4 months, and a person may be a seronegative carrier. On the other hand, Seif and colleagues found no excess mortality 18 years after diagnosis of post-transfusion NANB hepatitis. A zero-risk blood supply is probably unattainable. It is estimated that about 3:1000 will contract serious or fatal illness post-transfusion, although not all of these will have hepatitis. By contrast, a large study in the USA found that no fewer than 6/1000 hospitalized patients died of accidental or preventable causes.

Blood products are thus already very safe. Prevalence rates for transfusion-associated hepatitis have dropped from in excess of 30% in the 1960s to less than 1% in the 1990s. The use of volunteer donors whose blood is carefully screened has made the risk of transfusion-related hepatitis following use of cellular components of blood very small. Viral inactivation steps, such as pasteurization, dry heat and solvent detergent treatment destroy most viruses which escape detection at donor screening. Vaccination of haemophiliacs against HAV would overcome the possible danger of transmission in clotting factor concentrates. In the short term, pursuing further improvements in virucidal steps is likely to prove of most benefit in reducing the risk of transfusion-related hepatitis even further.

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References


