INFECTIOUS COMPLICATIONS OF BLOOD TRANSFUSION: VIRUSES

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Viruses transmissible by blood transfusion

Plasma borne viruses

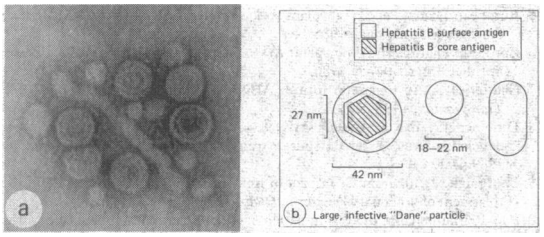
- Hepatitis B and delta agent
- Hepatitis A (rarely)
- Non-A, non-B hepatitis (one agent of which is hepatitis C)
- ? Other hepatitis viruses
- Serum parvovirus B19
- HIV-I and HIV-II (also cellular)

Cell associated viruses

- Cytomegalovirus
- Epstein-Barr virus (more than 95% of adults are immune)
- HTLV-I (causes human T cell leukaemia and tropical spastic paraparesis)
- HTLV-II (clinical relevance not clear; may be more common than HTLV-I in the West)

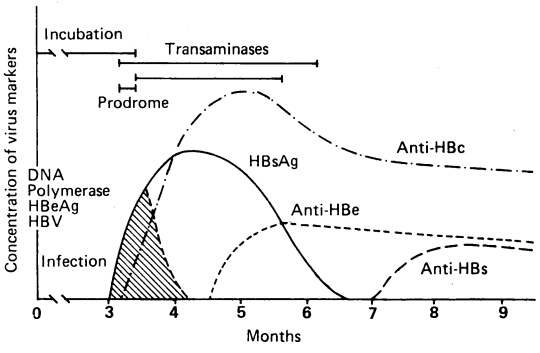
Most of the transfusion transmitted complications are caused by viral infections, several of which are currently arousing considerable public and medical interest. Effective antiviral agents are still not yet available to treat most viral infections, so the safety of blood and blood components has to rely solely on "self exclusion" by potential donors who are at risk of contracting viruses that are transmissible by transfusion (often transmitted sexually or by drug misuse) and on laboratory screening for evidence of microbial infection. So far inactivation methods are only available for certain products made from pooled plasma. This is a brief review of the range of viruses that are transmitted by transfusion and their properties.

Hepatitis B virus



Hepatitis B virus particles (*a*) electron micrograph and (*b*) diagram.

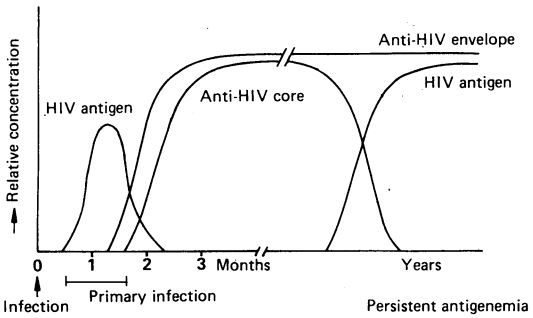
The hepatitis B virus is 42 nm in diameter and contains DNA. Reports of the isolation of a cross reacting variant, hepatitis B virus type 2, have not yet been verified. It is plasma borne and easily transmitted by all blood components and most blood products (for example, factor VIII). It is not transmitted by pasteurised albumin. The chance of transmission is enhanced when plasma is pooled for the manufacture of blood products. The incubation period ranges from two to six months but is usually about four. Although it is extremely infectious when injected and is resistant to both chemical and heat inactivation, the number of transfusion transmitted cases has been drastically reduced by screening and the few that do occur are usually caused by pooled plasma products. Inactivation of pooled plasma products may reduce this even further.



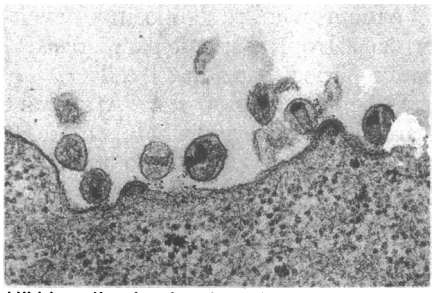
Typical course of an acute infection with hepatitis B virus (HBV). HBeAg—hepatitis Be antigen; HBsAg—hepatitis B surface antigen; HBc—hepatitis B core.

Screening for hepatitis B surface antigen (HBsAg) is mandatory. Assays for antibody to hepatitis core (total antibody or IgM) are available for diagnosing acute hepatitis B infection. Assay for hepatitis B core antibody should not replace that for HBsAg screening of donors. Screening for the delta agent is unnecessary as the delta agent depends on hepatitis B virus to provide its surface antigen. Screening for antibody to HBsAg can be used to identify donors whose plasma is suitable for the preparation of hepatitis B immunoglobulin. Hepatitis B virus is detected in 1/1000 donors, or less, because donors at high risk of having HIV are now excluding themselves. Vaccine is available for protecting recipients of the products of pooled plasma who are negative for hepatitis B (for example, previously untreated haemophiliac patients) and for patients who need regular transfusions (for example, those with thalassaemia).

HIV



Pattern of serological markers in HIV infection. The period of antigenaemia during primary infection may be much shorter and even undetectable.



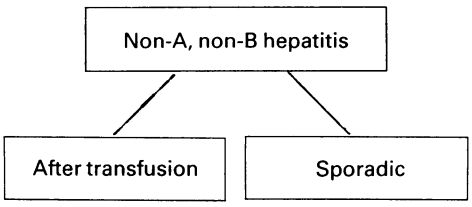
HIV-I replicating in a lymphocytic leukaemia cell line cutlure.

HIV-I was transmitted by transfusion before screening was introduced and before donors at high risk started excluding themselves from giving blood. HIV-II occurs mainly in west Africa. Both are retroviruses 100 nm in diameter that carry their own RNA dependent DNA polymerase (reverse transcriptase). Before screening was introduced, HIV had been transmitted by whole blood, red cell components, platelet concentrates, and fresh frozen plasma. It can contaminate factor VIII and factor IX concentrates, but it is inactivated by heat and chemicals. It has not been transmitted by albumin, immunoglobulins, or antithrombin III. The length of time before seroconversion is rarely longer than three months, and a primary illness similar to glandular fever may occur. The incubation period for AIDS is variable, with a likely median time of seven years in adults (though the period is shorter for infants).

Screening for HIV antibody is by an "antiglobulin" or "competitive" enzyme linked immunosorbent assay (ELISA), and recently latex and gelatin particle "sandwich" assays have been introduced. In most countries screening is only for antibody to HIV-I, as the incidence of HIV-II is low outside west Africa. Screening for HIV antigen is not indicated in a country with such a low prevalence as the United Kingdom, as it is unlikely that any extra infectious donors would be identified in addition to those positive for HIV antibody.

Transmission of HIV by transfusion has been extremely rare since the introduction of screening, but if it occurs in infants it leads more rapidly to serious disease than in adults. HIV antibody is found in about 1/70 000 donations in the United Kingdom, and the number is steadily decreasing. "Seroconverting" donations (those negative for HIV antibody but infectious because of recent infection) are therefore extremely rare. Only one donation from a seronegative donor is known to have transmitted HIV infection in the United Kingdom since screening started in 1985. The virus can be inactivated in blood products by treatment with heat or chemicals, but blood and blood components (for example, platelets) cannot be treated in either of these ways.

Non-A, non-B hepatitis



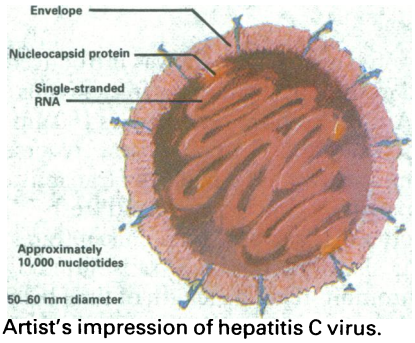
- **Diagnosis by exclusion of:**
  Hepatitis B virus
  Hepatitis A virus
  Cytomegalovirus
  Epstein-Barr virus

- **Hepatitis C virus:**
  Suggested name for the agent causing most (?all) non-A, non-B hepatitis. Antibody to this agent can be detected by a new assay. This uses antigen cloned from plasma from a chimpanzee infected with material known to transmit non-A, non-B hepatitis.

There may be at least two different viruses that transmit non-A, non-B hepatitis. Recently an assay has been developed in which cloned peptides can react with antibody to the "non-B" agent that is the cause of most of the non-A, non-B hepatitis that might develop as a result of transfusion. The virus is probably plasma borne (it may also be intracellular, but we do not yet know), and it is likely to be transmitted in the same ways as hepatitis B virus. The incubation period is from two to 26 weeks, depending on the agent. The agent detected by the new test (and popularly referred to as "hepatitis C virus") seems to be of the longer incubation type.

Some countries (including the United States) require screening for antibody to hepatitis B core and measurement of alanine aminotransferase activity. Most donations with abnormal markers, however, do not transmit non-A, non-B hepatitis, so "surrogate" screening leads to unnecessary waste of blood donations. The principal causes of increased alanine aminotransferase activity in the United Kingdom are obesity and alcohol consumption. In addition, some donations may transmit the disease despite having normal markers. Specific screening may be possible in future; an assay for hepatitis C antibody is available, but it has not yet been introduced into the routine screening regimen in the United Kingdom.

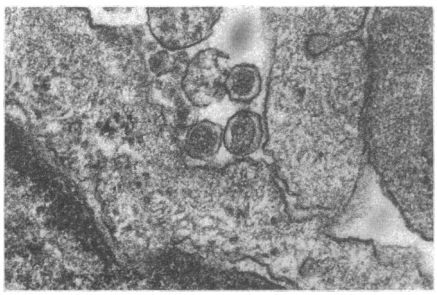
In the United States, before screening for HIV antibody was introduced, about 10% of transfusions caused significant increases in transaminase activity in recipients, and there were occasional cases of hepatitis; this figure has now been reduced to less than 7%. There are, however, large geographical variations and rates have come down since exclusion of donors at risk of HIV infection and surrogate screening were introduced. Acute infection is usually mild, but some patients do develop chronic liver disease (though the extent and importance of this in the United Kingdom is debatable). Large prospective studies on the chronicity of non-A, non-B hepatitis that has been transmitted by transfusion are needed, particularly



Artist's impression of hepatitis C virus.

in the United Kingdom, where roughly 1-2% of recipients of blood transfusions cause significantly increased transaminase activities. The carrier rate in the United Kingdom is unknown, but in the United States it was estimated at 3-7% before screening for HIV antibody was introduced. The prevalence of antibody to hepatitis C virus in the United States has recently been reported to be about 1%, similar to that in the United Kingdom. Some methods of heat inactivation of factors VIII and IX will prevent or minimise transmission. Haemophiliacs who have received effectively inactivated factor VIII have proved negative for antibody to hepatitis C virus in contrast to those who received uninactivated concentrate with a worldwide prevalence of about 70%, an anti-hepatitis C virus prevalence similar to that in intravenous drug users.

Adult T cell leukaemia; human T cell leukaemia virus

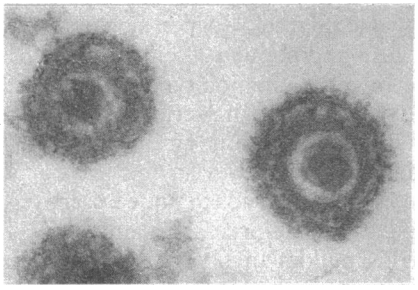

HTLV-I particles between cell membranes in lymphocyte culture.

Human T cell leukaemia virus (HTLV-I) is a retrovirus. The importance of HTLV-II is not clear. In the West it is associated with intravenous drug use and world wide has been found in a few cases of hairy cell leukaemia; much of what has been reported as antibody to HTLV-I is likely to be antibody to HTLV-II. It is associated with white cells and not transmitted in plasma. The incubation period for adult T cell leukaemia is about 20 years, but even then only about 1% of patients who are seropositive develop the disease. HTLV-I can also (rarely) cause tropical spastic paraparesis, which seems to have a shorter incubation period than adult T cell leukaemia. The infection is endemic in the Caribbean, parts of Africa, and Japan where 3-6% of the population are seropositive and where, before mandatory screening, transmission by transfusion was quite common.

ELISAs and gelatin particle assays are being evaluated for screening in the United Kingdom, but confirmation of positive results is difficult because other retroviruses may cross react. It is also difficult to differentiate between the antibodies to HTLV-I and HTLV-II unless advanced (and expensive) technology, such as the polymerase chain reaction, is available.

Cytomegalovirus

Screening of donors for cytomegalovirus is only necessary for immunosuppressed recipients


Cytomegalovirus particles showing characteristic herpesvirus morphology ×100 000.

Cytomegalovirus is a member of the herpes group of viruses, and latent infection of white cells in seropositive subjects may allow recrudescence of the virus either from the donor or from the host. Viraemia in healthy donors is rare. The incubation period is up to 12 weeks, and blood transfusion can cause primary infection, reactivation of an endogenous latent infection, or reinfection with a different strain of the virus.

Complement fixation tests, ELISAs, or latex tests are used for screening. Because severe (and sometimes fatal) cytomegalovirus disease may occur only after transmission to immunosuppressed patients, selective screening of donors is sufficient to fulfil the demands of, in particular, recipients of bone marrow transplants and low birthweight premature infants. Granulocyte transfusions that are seropositive for cytomegalovirus are especially likely to transmit the virus. Between 3% and 12% of donor units have the potential for transmitting the virus (especially, but not exclusively, if cytomegalovirus antibody IgM is detectable), but there is no screening test to identify specifically those seropositive donors who are likely to be infectious. About half of all donors in the United Kingdom are seropositive, and the rate increases with age. It also depends on the socioeconomic background of the subject and the geographical location. Components from which the white cells have been partially or totally removed (for example, by special filters) have a reduced risk, and frozen red cells (from which the glycerol has been removed) and washed red cells tend not to transmit cytomegalovirus because of their low white cell content. Cytomegalovirus antibody IgG given intravenously together with antiviral agents may help to ameliorate the effects of infection in immunosuppressed patients.

Parvovirus B19

- Risk of transmission by components minute

Although serum parvovirus is not usually pathogenic when transmitted by transfusion, B19 can lead to an aplastic crisis in a patient with chronic haemolytic anaemia (such as sickle cell anaemia) because of its inhibitory effect on red cell precursors. The risk of transmission by transfusion of non-pooled components is minute because there is no carrier state and the period

- Inactivated by heat

of viraemia is short. The titre of virus during the period of viraemia, however, is high and infectious units of plasma can contaminate batches of factor VIII; over 90% of recipients of untreated factor VIII are likely to be seropositive. Heat treatment of freeze dried factor VIII at 80°C for 72 hours seems to inactivate the virus.

Conclusion

Likely future classification of viruses causing viral hepatitis

- Hepatitis A virus—"infectious hepatitis"
- Hepatitis B virus—"serum hepatitis"
- Hepatitis C virus—principal } agents of non-A, non-B hepatitis
- Hepatitis ? virus—less common } agents of non-A, non-B hepatitis
- Hepatitis D virus—delta agent
- Hepatitis E virus—enteric or epidemic

The number of infections that are potentially transmissible by blood transfusion seems daunting. In the United Kingdom, however, the incidence of most of these infections in the general population is low. Most potential donors who are at high risk have voluntarily stopped giving blood, and blood that is given is carefully screened, so the absolute numbers of infectious complications of blood transfusion are minute.

Patients are at much greater risk if they do not have transfusions when they genuinely need them than they are from the possible complications of transfusion, particularly as physicians are now more aware of the risks and more discerning in their prescriptions of blood or its components.

The following illustrations are reproduced by kind permission: Typical course of hepatitis B virus infection—*British Journal of Hospital Medicine*; pattern of serological markers—Abbott Diagnostics Ltd; the Dane particle—Butterworth Scientific Ltd; electron micrographs of HIV-I and HTLV-I—Dr D Robertson and Professor R A Weiss, Chester Beatty Laboratories, Institute of Cancer Research; the artist's impression of hepatitis C virus—Ortho Diagnostic Systems; and the cytomegalovirus particles—J E Richmond, Public Health Laboratory Service Virus Reference Laboratory.

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How To Do It

Pay your way through medical school

A P Armstrong

Kenneth Baker, the former education secretary, stated in the House of Commons on 9 November 1988, that the government's proposals to introduce student loans from September 1990 represent "an important step away from the dependency culture" and added that "giving students a financial stake in their own future . . . will encourage greater economic awareness and self-reliance" (press release from the Department of Education and Science, number 347, 1988). It is not known at present what effect loans will have on the applications to medical schools, though some believe they may act as a disincentive to study medicine as it would entail relying on loans for five years or more.[1] Recently, the *BMJ* reported that the government also proposes to increase undergraduate fees for medicine from £607 currently to £3200 a year by 1991.[2] The implications of the proposed increase in educational fees will mean that self financed students would have to find £16 000 for the five year undergraduate course in medicine.

I have written this article to provide guidance to prospective graduate medical students about alternative sources of funding based on my own experiences in applying to educational trusts and charities.

Discretionary grants

Currently, most undergraduate students receive a mandatory grant as a right: students studying for a second degree, however, are not entitled to one. Graduate students may sometimes receive a discretionary grant from their local education authority, though the reasons why some graduates may be funded in this way and others not do not have to be revealed by individual authorities. In a survey of dental graduates studying medicine undertaken by Langton over half did not receive a grant during their medical studies, though almost 35% did receive support during the clinical years of the course.[3] An estimated 15-20 000 students are self financed presently, having to pay their course fees as well as their maintenance.[2]

The possibility of obtaining a discretionary grant from a local education authority varies in different parts of the country. There does not seem to be any common theme as to which students or courses may be considered eligible. In my year at medical school two students receive a discretionary grant whereas a third does not, though all are graduates and all live within the boundaries of Birmingham Education Authority. Medical students who decide to appeal against the decision of their local education authority not to give them a grant should consult the National Union of Students, who may be able to offer some advice about the best way to pursue an appeal.

Moonlighting and borrowing

During the preclinical years of the course part time work to supplement income is a real possibility, but with progression into the clinical years the available time to "moonlight" is drastically reduced. Even so, graduate medical students such as dental surgeons and opticians are usually able to survive financially by working during their spare time. It is not as easy for graduates in non-vocational subjects whose qualification does not provide easy access to part time employment.

Inevitably, many graduates soon find that the funds

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Br Med J 1990;300:453-4