INFECTIOUS COMPLICATIONS OF BLOOD TRANSFUSION: BACTERIA AND PARASITES

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Bacteria and parasites transmissible by blood transfusion

Bacteria

- *Treponema pallidum* (syphilis)
- Brucellosis (donors giving a history are not accepted in the United Kingdom)

Parasites

- *Plasmodium* species (malaria)
- *Trypanosoma cruzi* (Chagas' disease)

  Endemic in Latin America. Parasite present in 75% of seropositive subjects, and between 1% and 22% of donors in Latin America are seropositive
- *Toxoplasma gondii*

  Only a risk in granulocytes transfused to immunosuppressed seronegative recipients
- *Babesia microti* (Nantucket fever)

  Potential risk in North America

Long before the transmission of HIV became a prominent potential hazard of blood transfusion, considerable skill in preventing the transmission of infection by transfusion had already been developed in the Blood Transfusion Service. The first and most important step in maintaining a safe blood supply will always be a rigorous process of selection of prospective blood donors (see The blood donor and tests on donor blood). The second is the use of specific microbiological screening tests.

Agents transmissible by transfusion can be either cell associated—for example, cytomegalovirus and human T cell leukaemia virus type I (HTLV-I)—or plasma associated—for example, hepatitis B virus—or both (HIV). If they are plasma associated, pooling large numbers of units of plasma (for example, 15 000 to 20 000 as in the production of factor VIII) greatly increases the chances of disseminating such contaminants. Even without pooling, treatment with blood components may result in up to four or five patients being infected by a single contaminated donation.

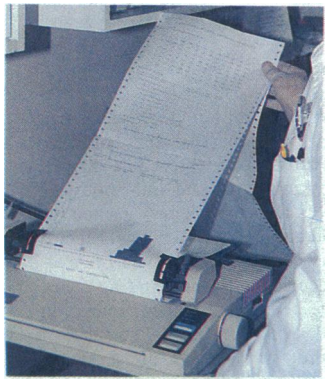
Properties of infections transmissible by transfusion

The hallmark of transfusion transmitted infections is **persistence**

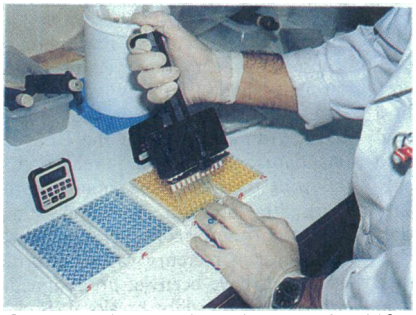
Agents transmitted by blood transfusion often possess a combination of some or all of the following properties:

- They are present in the blood for long periods, sometimes in high titres
- They have the ability to cause subclinical infections or only mild symptoms
- They have long incubation periods (sometimes years) before clinical signs appear
- They may exist in a latent or carrier state, or both
- They are stable in blood stored at 4°C.

Screening tests for blood donations



Screening of blood donations is analysed by computer. Results of each microplate are plotted as histograms.



Stopping the reaction—last step in ELISA.

Screening tests are paradoxically usually directed at antibody to the agent rather than antigens for the agent, except in the case of hepatitis B virus. Antibody screening tests are markers for certain persistent or chronic infections and therefore indicate a potential for infectivity, especially when the inoculum is as large as a unit of blood or a blood component.

Screening tests for blood donations

Mandatory in the United Kingdom:

- Hepatitis B surface antigen
- Antibody to HIV-I
- Antibody to *Treponema pallidum* (syphilis)

Optional (selected recipients):

- Antibody to cytomegalovirus

Mandatory in the United States and some European countries:

- "Surrogate" tests for non-A, non-B hepatitis (antibody to hepatitis B core and alanine aminotransferase activity)

Tests under review:

- Antibody to HTLV-I (now mandatory in United States)
- Antibody to HIV-II (? combined test with anti-HIV-I)
- HIV antigen
- Antibody to hepatitis C virus
- Antibody to *Plasmodium falciparum* (malaria)

Table of predictive value

Prevalence 1:10 000
Specificity 99%
False positive rate 1:100
100 False positives for every true positive

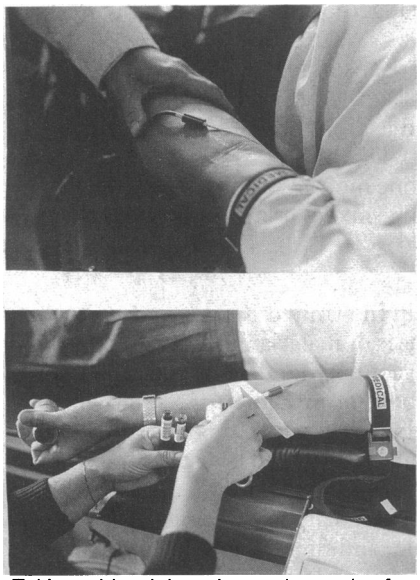
Various agents may be transmitted by transfusion, but in the United Kingdom there are only three screening tests for blood donations that are currently mandatory. They are hepatitis B surface antigen for hepatitis B virus, antibody to HIV-I, and antibody to *Treponema pallidum* (syphilis). Tests for several other agents are available, but it has not yet been considered necessary to extend the present range.

The range of techniques for screening includes haemagglutination, enzyme linked immunosorbent assay (ELISA), radioimmunoassay, and latex or gelatin particle agglutination. For a test to be suitable for screening blood for transfusion several conflicting demands have to be met.

In addition, the quality control of microbiological screening for transfusion in the United Kingdom is difficult because the occurrence of donations positive for hepatitis B virus, HIV, or syphilis is rare. In contrast to blood grouping, in which every sample produces a "positive" result of some sort, in microbiological screening tests most donor serum samples are negative. Great vigilance is therefore required in carrying out the routine screening tests. In low prevalence populations even an apparently low rate of false positive results from a screening test implies that a positive reaction has little predictive value. If—for example—an agent has an incidence of 1/10 000 donations, then a test with a specificity of 99% will produce a false positive reaction once in every 100 donations, or 100 false positive reactions for every true positive. It is therefore imperative that any donor samples that give a positive reaction to any of the mandatory screening tests should be sent to a reference laboratory for confirmation before the donor is informed of the results. Most transfusion centres in the United Kingdom use assays for HIV antibody that have low false positive rates, and they all have access to reference laboratories that carry out a battery of confirmatory tests, which virtually eliminates the possibility of mislabelling uninfected donors.

Specificity is vital if the confidence of donors is to be maintained, and it must not be forgotten in the search for increased sensitivity. Fortunately modern molecular biological methods have produced remarkable improvements in the sensitivity and specificity of assays for HIV antibody.

Bacterial complications of transfusion

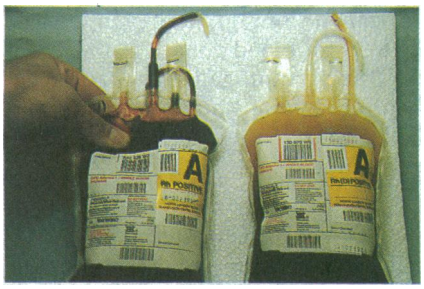


Taking a blood donation and samples for laboratory screening after thorough cleansing of the arm.

Bacteria such as staphylococci can contaminate some blood transfusions at the time of collection; citrate, the blood's own bactericidal powers, and cold storage will, however, destroy most such contaminants.

Bacterial complications of transfusion are rare in the United Kingdom because of the use of sterile, disposable, collection sets and clean phlebotomy techniques. When they do occur, however, they can rapidly be fatal, principally as a result of endotoxic shock. Exogenous contaminants can be introduced into the blood during collection or (rarely) during processing or the preparation and storage of platelets. At present most blood components are prepared in closed systems; blood is collected in multiple packs and the possibility of microbes entering the packs is negligible. On the other hand, those components prepared in an open system (such as washed cells or filtered blood) should be processed in sterile rooms and given a limited (24 hours) shelf life.

Common environmental contaminants that have been reported as causing serious (and often fatal) bacterial infections include pseudomonads, achromobacters, and coliforms—that is, Gram negative bacteria that grow preferentially at 4-8°C or at room temperature, but not at 37°C. Such bacteria use citrate as a source of energy, and this leads to the clotting of stored blood.

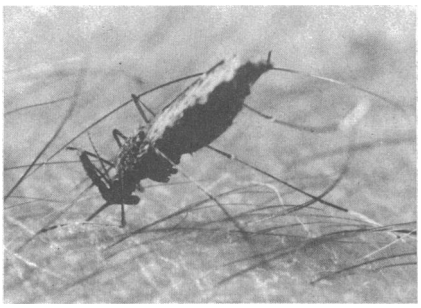


If units of blood are left to settle, bacterial haemolysis can be detected. Uninfected unit shows clear demarcation between plasma and red cells (right), in contrast to haemolysed unit (left).

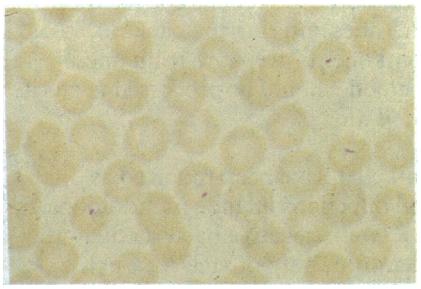
Treponema pallidum.

Demands of a successful screening test:

- Sensitivity
- Specificity
- Ease of handling (bulk testing, training, and automation)
- Speed
- Low cost



Central American malaria vector *Anopheles albimanus* feeding on a person.



Ring forms of *Plasmodium falciparum* within red blood cells.

Reactions to the transfusion of contaminated blood usually develop within minutes, with alarming signs and symptoms: chills, rigors, fever, nausea, vomiting, bloody diarrhoea, abdominal and muscle pains, hypotension (often leading to shock with flushing and dry skin), renal failure, haemoglobinuria, and disseminated intravascular coagulation.

Bacteria that may cause low grade or asymptomatic infections in the donor (such as *Salmonella* or *Yersinia* species) are sometimes an endogenous source of contamination. Bacteria that do not grow well in blood stored at 4°C will grow rapidly in platelet concentrates that are routinely stored at 20-22°C. Fatal salmonella septicaemia has been caused by contaminated platelet concentrates.

As soon as it is suspected that a contaminated unit is being, or has been, transfused the transfusion should be stopped and blood samples as well as the packs of any units transfused should be sent to the blood bank and microbiology laboratory for investigation. The patient should be treated as if he or she has septic shock before the results of laboratory investigations are available. Broad spectrum antibiotics and hydrocortisone should be given intravenously, together with adequate fluid replacement and vasopressive drugs.

Treponema pallidum (syphilis)

T pallidum can be transmitted by fresh blood and platelets because it is only inactivated by refrigeration for 72 hours. It is not transmitted by products fractionated from pooled plasma such as factor VIII. The incubation period varies from four weeks to four and a half months, the average being nine to 10 weeks. It is only rarely transmitted by transfusion, but when it is it presents as a secondary eruption. It responds to treatment with antibiotics, usually a course of benzylpenicillin (two megaunits).

Screening for the antibody is mandatory, and is usually by the cardiolipin assay or the (more specific) *T pallidum* haemagglutination assay. In early primary syphilis, at the height of infectivity, screening tests may be negative. The detection rate is low because most positive donors have had the infection and been treated. Donors with acute or latent infection are rare. The value of screening is mainly to identify donors who may have contracted other sexually transmitted diseases.

Malaria

Plasmodium falciparum is the most dangerous of the human malarial parasites; the others are *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*. The organisms are absolutely restricted to red blood cells and may contaminate components such as platelets. Freezing plasma will lyse any contaminated red cells and is therefore safe, but malaria parasites can survive storage of blood at 4°C for at least a week. The incubation period is from one week to one month, but for *P malariae* it may be several months. Special note should be taken of unexplained fevers after transfusion.

Occasional transmissions still occur in the United Kingdom despite the careful taking of histories. Of 18 374 cases of malaria in Britain reported to the Malaria Reference Laboratory between 1977 and 1986, only four were caused by blood transfusion. Subjects born or brought up in areas where malaria is endemic can be accepted as donors of whole blood if, three years after their arrival in the United Kingdom, their blood is tested for antibody to *P falciparum* and is negative. The time limit is six months after arrival for subjects who have travelled to areas where malaria is endemic. ELISAs or immunofluorescence assays are available, and there is considerable cross reaction among organisms. If a diagnosis of malaria after transfusion is made conventional treatment should be started. Primaquine should not be used, however, as the parasite will be restricted to the red cells.

Conclusion

The following procedure should be carried out before all transfusions to minimise the chance of bacterial contamination:

- Check that the pack is intact (no tears or pin holes)
- Ensure that blood is stored at the correct temperature with minimal time spent at room temperature (except platelets)
- Do not warm units of blood before transfusion
- Look at packs that have been standing undisturbed to see if there is evidence of haemolysis (for example, a purple mass of red cells or brown or red plasma), or clotting, which may be indicative of bacterial contamination. The interface between cells and plasma should be clearly defined.

The illustration of *T pallidum* is reproduced by courtesy of Professor H P Lambert and Gower Medical Publishing, that of the ring forms of *P falciparum* by courtesy of Dr P Hewitt and Gower Medical Publishing, and that of *Anopheles albimanus* by kind permission of the Liverpool School of Tropical Medicine.

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Letter from . . . Chicago

Boredom

George Dunea

"All men are bores," wrote Kierkegaard, somewhat condescendingly, from the perspective of a gloomy climate and temperament. He further suggested, during his early aesthetic period, that nobody would be so great a bore as to bother to refute his statement; and he divided humanity into those who bore themselves and those who bore others. Those who bore themselves, among whom he apparently included himself, he considered the aristocrats. Of the others, "the mob, the crowd, the infinite multitude of men in general," he had little good to say. They, like the poor, will always be with us. They are the grown ups whom the children find so exceedingly boring; the professors who bore their pupils; the pupils who in their turn drive their teachers to distraction. They are the attending physicians who bore their students and residents on ward rounds. One of ours, when I was a medical student, was an excellent doctor of the old school but a dull teacher. His rounds lasted for ever as he spent hours examining patients and talking to them instead of talking to us. Sometimes he would even send us out of the room so that he could discuss delicate matters in private. He prescribed placebos such as kaolin and gentian, claiming that most illnesses were self limiting. He gave us no little lectures on specific topics but went on and on from patient to patient while we daydreamed, wishing that we were on the rounds of the brilliant young teacher who had everything so nicely worked out and systematised.

We now learn that the dull eyed monster of boredom also spreads his mean tentacles into the world of business. He does, however, exert discrimination in selecting his victims. Entrepreneurs are affected most, we read in Mr Harvey Mackay's *Swim with the Sharks*, a manual on getting wet without being eaten. Plodding professional managers, on the other hand, seem able to contentedly repeat the same task, presumably like our attending physician. In order to "outsell, outmanage, and outmotivate your competition" you need both types working harmoniously as a team, each member respecting his own and the other's limitations. But the distinction remains; and we read that the entrepreneurs "scratch before they itch," soon becoming restless and needing to move into action, always seeking new challenges and new worlds to conquer, setting the pace and determining the agenda. But they lack an eye for detail, administer poorly, and dislike bureaucracy, organisation charts, and operating manuals.

In medicine, a discipline requiring a compulsive attention to detail, managerial types are likely to be in the majority. But we also find the entrepreneurial types. We see them as the easily bored students who never came to the dissecting room but learnt their anatomy from Boileau Grant's coloured plates. Bored by lectures, they studied from a set of notes often illicitly purchased. Bored by rounds, they stayed away while future managerial types wrote down every word and picked up every dropped pearl. Later they became flamboyant surgeons, innovators, sometimes television personalities. Eventually, however, they were joined in boredom by many a managerial type who also became tired of lectures, seminars, committees, working parties, airy theories, abstract speculations, algorithms, reorganisations, criteria for promotion, and budgetary considerations.

Nothing but dress, undress, dream, and gaze

But now we must imagine ourselves not as plodding managers or flamboyant entrepreneurs but of the appropriate gender and time in history to be transported through Ms Croutier's "harem" to the seraglio at Topkapi in Constantinople. Again boredom is the order of the day. For there is nothing to do for the young women but to dress and primp and undress, to dream and bathe and play games, to gaze at the Bosphorus with its ships coming and going, to write, to jockey for better positions like some university professors. But oh—never to walk alone on a deserted country road, not even to go out in the sun. "My skin is like marble," says one of the Circassian odalisques, "it has never been touched by the sun." What medical problems they had we shall never know, nor have the psychologists studied the effects of the boredom and loneliness of being forever locked up in the palace. But there seems to have been quite a bit of mixing of genes, the supply of wives and concubines being constantly replenished from the slave markets of all parts of the empire, especially by fair, doe eyed beauties from the Caucasus, Circassia, Georgia, and Abkhasia. And if the sultans after Süleyman the Magnificent turned out to be imbeciles it must have been from environmental causes, from being confined for years in the notorious kafes or cages to avoid the possibility of wars of succession.

But no harem would be complete without its eunuchs, black and white, a testimony of man's inhumanity to man. We read that the practice of

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