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# Effectiveness and safety of blood transfusion: have we lost the plot?

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**ABSTRACT** Blood safety is a high priority. As a result of many additional safety measures the risks of transmitting known infective agents is remarkably low. However, some blood safety measures are quite remarkably expensive by any conventional health economic standards. It is therefore surprising that much of our current blood prescribing is not founded on any reliable evidence. We question the logic of spending even more on safety measures that offer marginal benefits unless we also invest more to understand rather better when, and for who, transfusion is really beneficial. On 1 March 2005, the Royal College of Physicians of Edinburgh is holding a one-day meeting to investigate this balance of priorities. See www.rcpe.ac.uk/events/transfusion.html

**KEYWORDS** Blood, cost, economics, safety, transfusion, trials.

**LIST OF ABBREVIATIONS** Acquired immunodeficiency syndrome (AIDS), bovine spongiform encephalopathy (BSE), fresh, frozen plasma (FFP), intensive care unit (ICU), nucleic acid testing (NAT), quality adjusted life year (QALY), variant Creutzfeldt-Jacob disease (vCJD)

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This one-day meeting, chaired by Lord Mackay of Drumadoon, has a distinguished faculty of speakers and panellists. The aim is to open up a wider public discussion of some basic questions about future policy and spending on blood transfusion. Since the seventies, transfusion, at least in the richer countries, has become very much less likely to transmit infection. This has been achieved by an imposing list of safety measures (Table 1). This is excellent news for patients, but raises an issue that we believe needs to be debated. The proposition is that we are now concentrating too much on safety, and not enough on answering basic questions about the benefits that transfusion can offer in different clinical situations. Here we offer a few points to fuel the discussion – with no claim to be either comprehensive or unbiased.

**TABLE 1** Developments in microbiological safety of blood transfusion: 1970–2006

| | |
|---|---|
| Hepatitis B tests | 1970 |
| HIV donor exclusions | 1984 |
| HIV antibody test | 1985 |
| Hepatitis C antibody test | 1992 |
| Hepatitis C NAT test | 1997 |
| Import plasma for fractionation | 1999 |
| HTLV1 antibody | 2001 |
| Leucocyte-free blood components | 2001 |
| Pathogen-reduced clinical plasma | 2002–4 |
| SARS exclusions | 2003 |
| WNV exclusions | 2003 |
| HIV NAT | 2004 |
| Import clinical plasma | 2004 |
| Bacterial diversion system | 2004 |
| Ban previously-transfused blood donors | 2004 |
| WNV NAT | 2004 |
| HBcAb | 2004 |
| Bacterial culture for platelet release | 2004 |
| Prion removal filtration | ? 2005 |
| Pathogen-reduced Platelets | ? 2005 |
| Pathogen-reduced red cells | ? 2006 |
| Test for vCJD agent in blood donors | ? 2006 |

## BELIEF AND KNOWLEDGE: WHO BENEFITS FROM BLOOD TRANSFUSION?

Transfusion has a long history. In Edinburgh, for example, the donor service was started in the 1920s by an individual who was moved by the disaster of a friend's wife dying of obstetric haemorrhage. In its early days, transfusion was seen to be a life saving intervention when a patient was *in extremis* due to severe blood loss. This was before we had all the modern armouries of resuscitation, anaesthesia, surgery, and intensive care. Over the middle years of the twentieth century transfusion grew from these beginnings into a major business and an established essential element of a modern

health system. Only quite recently have we begun seriously to apply the disciplines of evidence-based medicine to ask 'When and for who does transfusion really contribute to a better outcome?' The follow-on question is whether we prescribe transfusion according to the best evidence for effectiveness.

In the UK, about 2·5 million units of blood components are distributed annually of which 40–50% are used in surgery or intensive care. The use of blood in these contexts has only recently begun to be re-evaluated using methods that would now be considered capable of yielding meaningful conclusions. There has still only been one single, large, randomised trial of transfusion in critically ill adult patients.[1] This compared major outcomes (mortality in ICU and 30 days after discharge) in ICU patients who were randomised to receive red cell transfusion so as to maintain Hb levels at either 100–120 g/l or 90–100 g/l. The main finding was that, overall, patients did as well (or possibly better) with the more restrictive transfusion regime. There was, however, a suggestion that patients with ischaemic heart disease may have fared better with the more liberal transfusion regime. The same group of investigators have just published a similar trial in neonates judged to need red cell transfusion, and in these patients also it seems that a liberal transfusion regime is no more effective than a conservative one.[2]

While these observations challenge conventional clinical wisdom about the indications for red cell transfusion, they are entirely consistent with studies showing that resting healthy volunteers tolerate blood loss (with isovolaemic fluid replacement) down to Hb levels around 50 g/l with no evidence of inadequate oxygenation. Extending this type of observation to critically ill patients, a recent explanatory trial found that transfusion of two units of red cells had no detectable effect on any measurable parameter of regional or global oxygenation in ICU patients whose Hb was below 80 g/l.[3] In a totally different context, there is evidence that a highly restrictive approach to red cell transfusion may be appropriate for children with severe acute or chronic anaemia. Lackritz *et al.* were able to study children admitted to a district hospital in Kenya. They found that transfusion only improved survival if the admission haemoglobin level was below 35 g/l (or below 45 g/l with specified clinical signs of hypoxaemia) and where transfusion could be given within 24 hrs of admission.

There are equally challenging questions about the real benefits that patients obtain from the 300,000 units or so of FFP that are supplied annually for patients in the UK. Stanworth *et al.* from the UK Blood Services Systematic Reviews Group assessed 57 trials on the clinical use of FFP.[4] Only three of these were designed and powered so that they could provide reliable conclusions. One showed that FFP was ineffective in preventing neonatal intracranial haemorrhage. The second showed that FFP offered no benefit in the treatment of acute pancreatitis. The third indicated plasma exchange with simple infusion of FFP for the treatment of thrombotic thrombocytopaenic purpura. The other 54 trials, covering all the 'textbook and guideline' indications for plasma infusion, were all judged to lack the quality, power, or both, to provide a useful conclusion.

A large double-blind, randomised controlled trial of human albumin showed it was equivalent to – no better or no worse than – saline solution.[5]

### *How big are the risks of receiving a transfusion in the UK?*

From 1996–2003, during which 23 million units of blood components were supplied, the incidence of serious adverse reactions (expressed per 100,000 units of blood supplied) was, death 0·2 and major morbidity 1·1, of which 0·6 was transfusion related acute lung injury and 0·2 was infection – mostly bacterial. The chance that a unit of blood might transmit one of the viruses for which blood is tested is estimated at HIV 0·014, HCV 0·024 and HBV 0·176 per 100,000 units. The risk of being transfused the wrong unit of blood puts more patients at risk (6 per 100,000) including ABO incompatible blood (1 per 100,000). In the context of other healthcare related risks, these risks are small.[6]

### *The cost of safer blood*

In 1995, blood components for the UK cost the taxpayer about £250 million (at 2004 sterling values). Today, similar quantities cost us about £500 million. The increase is mainly due to newer anti-microbial tests and processes. Some of these are good value for money by any standards, but some offer only marginal increments in safety at a surprisingly high price. For example the use of NAT to supplement serological tests for Hepatitis C and HIV is estimated to cost between $5·8 million and $8·4 million per QALY.[7]

Some processes that chemically inactivate viruses in plasma concurrently reduce the levels of natural anticoagulants (proteins S and C), increasing the risk of thrombosis in some patients. New 'sterilisation' processes developed for red cells and platelets use DNA cross-linking chemicals. It may be difficult to prove that even tiny residual quantities could not, in the long term, have a mutagenic effect in the recipient.[8]

### *More safety but less efficacy and less blood available?*

Apart from being expensive, some of the new microbiological safety measures may reduce the efficacy of blood or the available supply. The red cell content of a blood pack is now reduced by at least 10% due to tests and safety measures. Some patients will therefore need

to be given more units for the same effect. As we discuss below, this may increase risk and could negate the safety gains that were sought. The other concern is that – as every regular donor knows – blood safety measures make it ever more difficult to be accepted as a donor. The recent decision not to accept donations from people who have previously had a transfusion has excluded about 10% of donors.

### *Variant Creutzfeldt-Jacob disease*

The management of the BSE epidemic and the rather late recognition that there is a human form, vCJD, was heavily criticised in the Phillips report.[9] This, and worldwide experience with AIDS and hepatitis, has encouraged policy makers to take a highly precautionary approach to blood safety that conflicts with conventional assessments of value for money in health spending. In the UK there are known to be 17 blood donors who later developed vCJD. Fifty recipients of blood from these donors were identified, of whom 18 were still alive. Two of the 50 recipients are known to have been infected. One has since died with clinical vCJD; the other had histological signs of infection but died of unrelated causes.[10] Precautionary measures to mitigate the risk of transmission of vCJD include removing leucocytes from all blood components at an annual cost of £70 million, enough to fund the blood supplies of several African countries. Leucodepletion may remove about half of the infectious agent, but on current estimates of infectivity levels in blood, leucocyte-removal alone is unlikely to remove the risk of transmission.[11] New processes soon to be available may reduce vCJD infectivity by perhaps 10,000 fold, but could add £100 million per year to the blood services bill. The cost of avoiding an infection cannot be estimated but is certain to be enormous.

We propose, for debate, that these large and recurring expenditures on blood safety should be balanced against the costs of the clinical trials still needed to provide the basis for rational use of blood components and of the various technologies that may avoid or reduce the need for transfusion. The decisions should involve, be understood and be accepted by, a well-informed public.

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# Medical history section


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