

## Recent developments

### Blood transfusion medicine

Fiona Regan, Clare Taylor

In the past few years there has been increasing concern about blood transfusion safety. Avoidable transfusion errors, mostly in patient identification, remain a serious cause of injury and death. There is also heightened awareness of the risk of transmission of viral and bacterial infections. Of particular concern in Britain is the (theoretical) possibility of transmission of variant Creutzfeldt-Jakob disease.

This review puts these risks in perspective (table) and describes the new measures that have been introduced to improve blood safety. It also describes changes in attitude and practice that will affect users of blood in all disciplines, including general practitioners advising patients of the pros and cons of transfusion. Finally it emphasises the need for careful education and training of all those involved in blood prescribing and blood component administration.

#### Methods

Our review is based on information from the annual reports of Serious Hazards of Transfusion ([www.shot.demon.co.uk/](http://www.shot.demon.co.uk/)), the guidelines of the British Committee for Standards in Haematology ([www.bcshguidelines.com/](http://www.bcshguidelines.com/)), and the chief medical officer's second "Better Blood Transfusion" meeting ([www.doh.gov.uk/bbt2](http://www.doh.gov.uk/bbt2)). We also cite relevant recent publications by leading clinicians and scientists.

#### New measures to reduce transfusion errors

Avoidable transfusion errors remain an important if uncommon cause of death and injury. In the United States fatal misidentification errors are estimated to occur in 1 in 600 000 to 1 in 800 000 transfusions and non-fatal errors occur in 1 in 12 000 to 1 in 19 000 cases.<sup>2,3</sup> UK data from the Serious Hazards of Transfusion (SHOT) reports suggest an error incidence of 335 per 5.5 million units of red cells transfused. The most commonly reported adverse event, "incorrect blood component transfused," accounted for nearly 70% of reports in 1999-2000.<sup>4</sup> Incompatibility in ABO blood groups was reported 97 times and led directly to four deaths and 29 cases of immediate major morbidity.

After the second SHOT report, updated UK national guidelines to minimise the risk of giving the wrong blood were published.<sup>5</sup> In the past two years many hospitals have introduced hospital-wide "adverse

#### Summary points

Human error is a cause of transfusion related morbidity and mortality: these errors are entirely avoidable

The adoption of a lower "transfusion trigger" is gaining acceptance

Whether or not variant Creutzfeldt-Jakob disease is transmissible by transfusion, it may have a considerable impact on availability of blood for transfusion

Concerted efforts must now be made to reduce inappropriate blood use and to use alternatives and blood sparing agents

Pilot studies of barcode patient identification systems are assessing their feasibility in various clinical settings

Phase III clinical trials of blood substitutes (haemoglobin solutions and perfluorocarbons) are in progress

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incident reporting" schemes to identify and analyse such incidents and "near misses." Transfusion errors feature prominently among these incidents (personal communication, F Regan). Existing adverse clinical incident reporting schemes will probably soon feed into a central UK reporting scheme managed by the National Patient Safety Agency to generate national information and recommendations. Recognition that educating staff and

Risks of red blood cell transfusion (adapted from British Committee for Standards in Haematology (2001)<sup>1</sup>)

Risk factor	Estimated frequency per unit transfused	Deaths per million units
Acute haemolytic reactions	1 in 250 000 to 1 in 1 000 000	0.67
Hepatitis B	1 in 100 000 to 1 in 400 000*	<0.5
Hepatitis C	1 in 3 000 000†	<0.5
HIV	1 in 4 000 000	<0.5
Bacterial contamination of red cell concentrates	1 in 500 000	<0.25

\*Data from Kate Soldan, National Blood Service and Central Public Health Laboratory.

†Data from Dr Pat Hewitt and Dr John Barbara, National Blood Service, North London.



**Fig 1** Checking patient identification details on blood unit against wristband before transfusion

implementing robust hospital transfusion protocols being needed to prevent errors has resulted in these factors being incorporated in the Clinical Negligence Scheme for Trusts. However, training all staff involved in blood administration or taking samples for cross matching, including locum and agency staff, will be difficult without adequate resources.

Internationally, new information technology systems are being developed to design error out of the transfusion process.<sup>6</sup> These are based on a unique barcode on each patient's wristband, which is transferred on to the patient's cross match blood samples and transferred to each unit of blood prepared for that patient. This barcode is matched electronically with the patient's wristband before administering blood (fig 1). Pilot studies are currently assessing the feasibility of these systems in various settings including day wards, presurgical admission clinics, and inpatient wards.

### Measures to reduce the risk of transfusing variant Creutzfeldt-Jakob disease

Safety measures to minimise the risk of transmitting known infections through transfusion include donor selection and exclusion, testing of donor blood, and post-collection processing such as leucodepletion and viral inactivation (see below). National haemovigilance schemes to monitor adverse transfusion events have been introduced in many countries,<sup>4 7 8</sup> and EU-wide data are being collated by the European Haemovigilance Network. Similar systems exist in the United States and Canada.

Despite these measures, the possibility of transmission of new infectious agents, including variant Creutzfeldt-Jakob disease (vCJD), remains. Although there is no evidence of vCJD transmission in humans,

concern has been provoked by a study in which one of 19 asymptomatic sheep, 318 days after being given 5 g of cow brain infected with bovine spongiform encephalopathy (BSE) in their feed, seemed to transmit BSE to a second sheep via a 400 ml blood transfusion.<sup>10 11</sup> Although no other studies have been published to validate this finding, steps have already been taken in Britain to reduce the possible risk of vCJD transmission by transfusion (box 1).<sup>12</sup> In addition, the Department of Health's Advisory Committee on the Microbiological Safety of Blood and Tissues for Transplantation is considering excluding blood donors who themselves received transfusions between 1980 and 1996. The problem with this is it would result in a loss of about 10% of donors, and, without a corresponding reduction in blood use, blood stocks would be severely jeopardised. Furthermore, the blood supply would probably be further reduced if a blood test for vCJD becomes available.<sup>13</sup>

Several companies are working to produce a screening test for vCJD, and one is likely to be available within two years. Once it is, the National Blood Authority will be under pressure to introduce it. (In recent litigation in relation to the transfusion of hepatitis C the National Blood Authority was found at fault for supplying a defective product, and the avoidable delay in implementing an available hepatitis C test was highlighted.<sup>14</sup>) Anonymous testing will not be an option: under EU law, donors must give consent for all tests performed on their blood and must be informed of any test results on which the national blood authority acts (for example, discards their blood). It is likely that many donors will not agree to be tested, as the burden of knowledge will affect not only their health and happiness, but could affect availability of life insurance policies. Importing blood from BSE-free countries may seem attractive, but, as most countries face periodic blood shortages, it is unlikely that sufficient blood would be available to replace the UK blood supply of around 2.7 million units of red cells a year.

### Reducing unnecessary transfusion and use of alternatives to blood

Considerable variation in transfusion practice for elective surgery is well documented (fig 2).<sup>15</sup> Reducing unnecessary exposure to blood components by blood saving measures is particularly important in healthy patients undergoing elective surgery (box 2). A recent publication for anaesthetists summarises good transfusion practices in surgical patients.<sup>16</sup> Implementation has been problematic, however, as until recently blood has been perceived as a safe and unlimited resource, and it has been difficult to secure funding for blood saving measures.

About half of all blood transfused in the United Kingdom is to surgical patients (National Blood Service internal audit). To reduce the amount of blood used in elective surgery, detailed planning at each stage of patient care is required (box 3, fig 3). Although the cost of the blood component may be saved, other costs may be incurred and there may be no overall saving in the short term. Long term savings relating to the potential cost of transfusion transmitted infection, immunomodulation (long term mild immune suppression which occurs in recipients of blood components

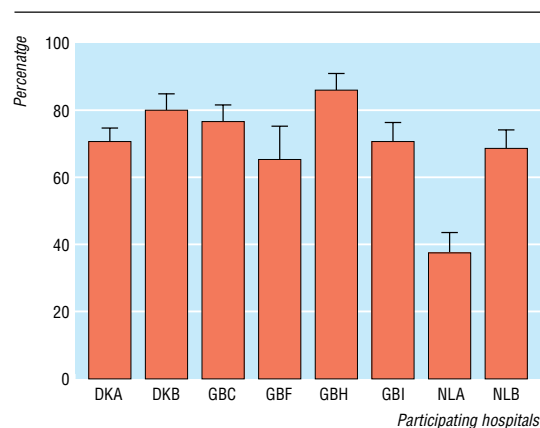
#### Box 1: Steps taken to reduce risk of vCJD transmission via blood

##### In United Kingdom from 1999

- Ban on using UK plasma for manufacture of fractionated products (such as albumin, clotting factors, immunoglobulins)
- Leucodepletion of all blood, platelets, fresh frozen plasma, and cryoprecipitate (as leucocytes believed to have key role in vCJD pathogenesis)

##### In other countries (such as United States, Canada, New Zealand)

- People who have lived in the United Kingdom for >6 months between 1980 and 1996 excluded as blood donors



**Fig 2** Mean (SE) proportion of patients undergoing total hip replacement perioperatively transfused with red blood cell units in each of the participating hospitals in Europe, after adjustment for age, sex, preoperative packed cell volume, and blood loss (adapted from McClelland et al (1998)<sup>7</sup>)

### Box 2: Reasons to reduce blood exposure

- Immunological complications
- Red cell alloantibodies: haemolytic transfusion reaction
- HLA antibodies: refractoriness
- Transfusion related acute lung injury, post-transfusion purpura, transfusion associated graft versus host disease, etc
- Errors and “wrong blood” episodes
- Infections (bacterial, viral, and possibly prion)
- Immunomodulation (risk of infection or malignancy)
- Litigation
- Limited resource

and can result in poorer outcome<sup>17</sup>), and litigation may be substantial but are difficult to quantify.

Implementing strategies to reduce the requirements for blood transfusion requires effective teamwork, adequate resources, and a clear understanding of the rationale for it. Blood substitutes, such as haemoglobin solutions and perfluorocarbons, are in phase III clinical trials, but their short half lives may limit usefulness.<sup>18, 19</sup> Another approach to reducing unnecessary transfusion would be to enforce, either locally or nationally, a policy of blood components being prescribed only by senior doctors.

### Appointment of specialist transfusion practitioners

Over the past three years, specialist practitioners of transfusion have been appointed in over 40 UK hospitals, echoing similar developments in Europe and the United States.<sup>8, 9</sup> Most are senior nurses, but some are doctors or biomedical scientists. These posts have been created to implement recommended policies to reduce inappropriate prescribing of blood components.<sup>20</sup> Although the cost of employing specialist transfusion practitioners has deterred some trusts, it has been found repeatedly that the savings from reducing inappropriate prescribing of blood products exceed the cost of employment.

The main role of the specialist transfusion practitioners is to educate staff and patients about the pros and cons of blood transfusion and to support the development and evaluation of transfusion protocols and guidelines. They also facilitate audit and implementation strategies to improve blood ordering and administration.<sup>21</sup> Where appropriate, practitioners may be directly involved in near patient testing and cell salvage techniques.

### New developments in safety of plasma products

Blood components are becoming safer as more sensitive screening tests for viruses are introduced. In the United Kingdom all cellular blood components have been leucodepleted at source since November 1999 to reduce the potential transmission of vCJD, thought to be facilitated by B lymphocytes.<sup>22</sup> Leucodepletion also reduces transmission rates of other cell associated viruses such as cytomegalovirus.<sup>23</sup> The recent introduction of a nucleic acid test for hepatitis C in fresh frozen plasma, blood, and platelets<sup>24</sup> has reduced the “window period” from 70 days (for antibody testing) to 13 days, and the chance of transmission by a unit of blood from 1 in 250 000 to 1 in 3 million.<sup>22</sup>

To reduce risks further, viral inactivation steps, routinely applied to pooled fractionated products such

### Box 3: Methods of minimising transfusion

#### Preoperative planning

- History and examination including surgical or bleeding history
- Full blood count, “group and save,” blood chemistry, coagulation, haematinics
- Consider autologous blood deposit
- Consider erythropoietin to boost haemoglobin concentration
- Treat iron or folate deficiency
- Stop aspirin prophylaxis if possible

#### Day of admission

- Check if taking aspirin, non-steroidal anti-inflammatory drugs, anticoagulants
- Repeat full blood count and “group and save”
- Weigh patient, calculate blood volume, and estimate blood loss that would reduce packed cell volume to 0.22
- Consider acute normovolaemic haemodilution and intraoperative or postoperative cell salvage
- Consider drugs to reduce bleeding (such as aprotinin)

#### During surgery

- Be prepared for longer duration to secure haemostasis
- Consider hypotensive surgery if appropriate
- Avoid hypothermia—give all fluids through a warmer
- Use of near patient testing
- Consider fibrin glues and sealants

#### Postoperative care

- Accept lower postoperative haemoglobin concentration
- Accept transfusions of just one unit of blood, to exceed transfusion trigger
- Use continuous face mask oxygen if patient has low haemoglobin concentration
- Prescribe iron and folic acid routinely
- Consider tranexamic acid



Fig 3 Intraoperative red blood cell salvage

as albumin or immunoglobulin solutions, could now be applied to fresh frozen plasma and possibly cellular components.<sup>22</sup>

Pooling of plasma from over 1000 donors is required for solvent detergent treatment of fresh frozen plasma and fractionated products, for efficiency of processing and product standardisation. Pooling theoretically allows contamination of the entire pool by an infectious agent from one donor. Although the treatment kills enveloped viruses such as hepatitis B and C and HIV, not all non-enveloped viruses are affected (such as hepatitis A and parvovirus). Serological and polymerase chain reaction testing of the plasma pools is also carried out, but not all known agents are tested for, and some transmissions of parvovirus have occurred.<sup>25</sup> Use of solvent detergent treated plasma is widespread, and in some European countries the use of untreated plasma is banned. An alternative is methylene blue treatment, which can be applied to single units of plasma. This inactivates a broader spectrum of viruses

but is more costly and time consuming. Methylene blue is also potentially more toxic.<sup>26</sup>

The UK Advisory Committee on Microbiological Safety of Blood and Tissues is currently considering for which groups of patients fresh frozen plasma from UK donors should be virally inactivated. It is also looking at possible alternative sources of fresh frozen plasma. Methylene blue treatment of fresh frozen plasma, from UK donors is being introduced from May 2002 for children and infants born after 1 January 1996, the date when vCJD was officially excluded from the human food chain in Britain.

Solvent detergent and methylene blue treatments have no effect on bacteria or prions—there is no known suitable way of inactivating prions, which are resistant even to extremes of temperature. However, bacterial contamination of blood components, especially of platelets, is a more important cause of mortality and morbidity from blood transfusion than is viral transmission.<sup>4</sup> A third method of pathogen inactivation is therefore being considered that not only inactivates all viruses but also kills bacteria, parasites, and lymphocytes. Psoralen S-59 and ultraviolet light are used together to treat individual platelet concentrates in the Helix system, which cross links DNA and RNA.<sup>27</sup> Another psoralen, S-303, is in development for use in red cell concentrates. Although expensive and labour intensive, this system could inactivate all potential pathogens except prions. In addition, this treatment would make it unnecessary to irradiate blood components to prevent transfusion associated graft versus host disease as the donor lymphocytes responsible would be killed. In the future it may become the pathogen inactivation system of choice, unless it is overtaken by new developments.

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Competing interests: CT has a transfusion data manager funded by Ortho-Biotech, which manufactures erythropoietin, and has received fees and travel costs from the company for speaking at a symposium.

#### Additional educational resources

- Serious Hazards of Transfusion (SHOT) ([www.shot.demon.co.uk/](http://www.shot.demon.co.uk/))
- British Committee for Standards in Haematology. BCSH guidelines ([www.bcsanguinelines.com/](http://www.bcsanguinelines.com/))
- Department of Health. UK CMOs' better blood transfusion conference ([www.doh.gov.uk/bbt2](http://www.doh.gov.uk/bbt2))
- NHS. Building a Safer NHS for patients ([www.doh.gov.uk/buildsafenh/index.htm](http://www.doh.gov.uk/buildsafenh/index.htm)). Gives details of the National Patient Safety Agency
- NHS Litigation Authority ([www.nhs.uk/welcome\\_to\\_nhsli.htm](http://www.nhs.uk/welcome_to_nhsli.htm)). Gives details of the Clinical Negligence Scheme for Trusts
- European Haemovigilance Network ([www.ehn-org.net](http://www.ehn-org.net))

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## Lesson of the week

# Interpretation of rubella serology in pregnancy—pitfalls and problems

Jennifer M Best, Siobhan O'Shea, Graham Tipples, Nicholas Davies, Saleh M Al-Khusaiby, Amanda Krause, Louise M Hesketh, Li Jin, Gisela Enders

Rubella acquired in the first 12 weeks of pregnancy is associated with a 90% risk of congenital malformations. Although rare in many industrialised countries, because of the success of vaccination programmes, rubella continues to occur where uptake of the vaccine is low and in many developing countries with no vaccination programme. The World Health Organization has therefore encouraged all countries to assess their rubella status and introduce immunisation and surveillance, if appropriate.<sup>1</sup> As the clinical diagnosis of rubella is unreliable, serological tests are needed for a diagnosis, especially when a patient is pregnant or has been in contact with a pregnant woman.<sup>2</sup> Diagnosis is usually made by detection of rubella specific IgM. Although commercial assays are available, they vary in format, sensitivity, and specificity.<sup>3</sup> Furthermore, rubella specific IgM may be present a year or more after natural infection or vaccination and after asymptomatic reinfection.<sup>4-8</sup> False positive results may also be due to cross reacting IgM antibodies or rheumatoid factor.<sup>9</sup> Consequently, in countries with limited laboratory facilities and expertise, diagnosis of rubella in pregnancy is problematic. It is essential that laboratory results be interpreted in the context of full clinical details, to avoid misinterpretation of results and to minimise anxiety for the patient, especially if termination of pregnancy is considered. Here we discuss six cases referred initially to the Department of Virology at Guy's and St Thomas's Hospital Trust from February to September 2000.

## Case reports

Clinical information on the patients and laboratory test results are shown in the table. Five patients were referred from outside the United Kingdom, four because rubella specific IgM had been detected in the absence of a rash.

Patients 1 to 4 had no history of rash or contact with a rash, and in patients 2, 3, and 4 rubella IgM tests had been conducted without any clear clinical indication. In all of these patients except patient 3

positive rubella IgM results were confirmed, but rubella IgG avidity was high, indicating past rather than recent infection. In addition, detection of IgG antibodies to the E2 glycoprotein of rubella virus by immunoblot in patients 1 and 2 indicated that primary infection occurred more than five months previously, indicating persistence of rubella IgM.<sup>10</sup> Rubella specific IgM was not detected in serum samples from patient 3 when tested in the United Kingdom. Prenatal diagnosis offered to patients 1, 2, and 3 at 18-22 weeks' gestation provided further reassurance that their babies were unlikely to have congenital rubella infection (table).<sup>11 12</sup>

Rubella IgM antibodies in case 4 were detected locally using indirect enzyme immunoassays, which are more likely to give non-specific results than antibody capture assays.<sup>3</sup> Retesting in two reference laboratories gave negative results in M antibody capture assays but a weak positive result in an indirect assay. This patient was therefore reassured that she had not had primary rubella, as she had a history of rubella vaccination and high avidity rubella specific IgG was detected.

Patient 5 was of particular concern. Rubella specific IgM was not detected locally, but the patient's obstetrician misinterpreted the laboratory results and advised termination of pregnancy.

Patient 6 presented with rash and fever at 33 weeks' gestation. A vesicular scrape was taken and a diagnosis of chickenpox made by immunofluorescence. However, low positive results were obtained in rubella IgM and parvovirus B19 IgM assays. Such false positive IgM results may be explained by cross reacting antibodies known to be induced by some viral infections and autoimmune disease.<sup>6 9 13</sup> It is therefore of interest that this patient gave a weak positive result in the Rose Waaler assay and during childhood had suffered from rheumatic fever and required mitral valve replacement.

## Discussion

These cases show that results of rubella IgM assays conducted on serum samples from pregnant women should always be interpreted with caution. Any history of rash

## Clinical and laboratory expertise is essential for evaluating rubella specific IgM test results in pregnancy

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