

## CHAPTER 1

# Introduction: recent evolution of transfusion medicine

*Ian M. Franklin*

Scottish National Blood Transfusion Service, University of Glasgow, Glasgow, Scotland

In the previous introductions to the two earlier editions of *Practical Transfusion Medicine*, an attempt was made to cover a broad sweep of issues of importance in the field. Much of what was included remains relevant, but in this new third edition, a few contemporary issues will be covered to highlight areas of potential development that will have an impact before a fourth edition is published.

As before, blood safety takes centre stage, although there has been some shift in emphasis. In 2004, concerns were over SARS and West Nile virus, the second of which remains important although the impact, at least in North America, appears to be waning as the population develops greater immunity. The wide acceptance by all governments of global warming driven by human activity has been accompanied by the recognition that many infectious diseases previously considered to be tropical are encroaching on temperate countries. The outbreaks of Chikungunya infection in Italy and dengue in the southern US are good examples and are leading to greater concerns over maintaining blood safety. These effects are often made worse by a reduced emphasis on public health systems, by increased international travel and reduced mosquito eradication programmes. These issues are explored in detail in Chapter 16.

Concerns over emerging infections have brought pathogen reduction systems back into the spotlight after a period of decline following the formation of red cell-directed antibodies in recipients of two products in phase 1 trials. An alternative approach to the prevention of transfusion-transmitted infections would be wider testing, ideally perhaps using a generic flavivirus nucleic acid testing (NAT) to detect dengue and Chikungunya viruses. Other expensive interventions, including the introduction of prion reduction filters, are under active consideration and/or development, particularly in the UK and Republic of Ireland, where bovine spongiform encephalopathy (BSE) and then variant Creutzfeldt–Jakob disease (vCJD) have been most prevalent. Happily, the number of new cases of vCJD has fallen to five in each of the past 3 years, and none in the first half of 2008. But concerns remain about a possible later wave of cases in donors who have the less susceptible genotype. What is certain is that vCJD is a transfusion-transmissible agent, albeit very rarely, which has a high degree of probability of disease transmission when transfused shortly before the donor develops evidence of symptoms. So far, all four transmissions of vCJD have occurred prior to the introduction of universal leucocyte reduction in the UK, and the small number of new clinical cases means that the number of persons known to be at risk has not increased recently. This is good news, but not sufficient for complacency. Therefore, trials of prion

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reduction filters are progressing and some tough decisions will need to be taken soon regarding implementation, assuming that the trials of prion-filtered blood go according to plan. Disadvantages are the cost and also that red cells are lost in the process. The former seems the most difficult issue. At least there will be no perceived problem for donors, which would not be the case for a prion disease test. Though still appearing to be a little way off, the obstacles to successful implementation of a vCJD test will be significant, as described in Chapter 15.

In terms of cost, testing for hepatitis C by NAT continues despite a very high cost indeed per case avoided. Given that the legacy of perceived problems with past blood safety remains with us 15–25 years on – a public inquiry is about to commence in Scotland on this very issue – it appears unlikely that ceasing to perform such a test would be desirable or even politically possible. It will be particularly important to evaluate and assess new safety interventions or tests thoroughly prior to full implementation since ceasing to do any measure that contributes to blood safety appears all but impossible once established.

The high cost of new blood safety initiatives introduced over the past 10 years has been the subject of much discussion within the extended blood transfusion community, particularly as measures against prion transmission are approaching the point at which decisions must be made. Typically, new blood safety interventions cost in excess of US\$1,000,000 per quality-adjusted life year (QALY) versus an accepted cost per therapeutic QALY of US\$50–100,000 and UK£30,000. More recently, it has been acknowledged that, while high, these costs are not disproportionate to other blood safety procedures introduced in the past. A rational framework for making decisions about which new blood safety measures should be introduced would be most welcome.

Early in 2008, an influential paper was published suggesting, in a retrospective observational study of a large number of patients, that receiving blood older than 14 days post-collection led to an adverse outcome compared with patients receiving younger, fresher red cell transfusions. This

followed on from data from the same group at the Cleveland Clinic and a study from Bristol, UK, amongst other studies, which suggested that receiving a blood transfusion was an independent adverse effect for survival following cardiac surgery.

No one doubts that blood transfusion has a major role in saving life in traumatic and obstetric emergencies, and it is essential to have blood and other blood components available to support major surgery and bone marrow failure. Over the past decades, anxieties about blood safety have tended to be attached to the risks of transfusion-transmitted infections, although these are now extremely rare, or to the more common hazards of a transfusion administration error or transfusion-related acute lung injury. What is emerging now as a more important issue is that transfusion may be an independent risk factor for reduced survival after certain serious events. These include admission to a critical care unit and coronary artery bypass surgery, but may not be confined to these areas of practice.

The first and still the most influential report to question the advisability of a liberal transfusion policy was the transfusion requirements in critical care (TRICC) study. This was well designed and organised, adequately powered and delivered a clear conclusion. A hard end-point – improved survival – was associated with a more restrictive transfusion regime. In neonates, more red cell transfusions conferred no benefit and a recent study in acute lung injury/adult respiratory distress syndrome showed an adverse impact of red cell transfusion. Quite why less transfusion should be as good or better than more is not clear, but these data do fit with a considerable literature from the past decades of often weakly powered studies that have suggested, but never proven, that transfusion is associated with more postoperative infections or recurrent cancer. These transfusion studies are difficult to perform and to analyse, especially as there would appear to be an obvious correlation between the amount of blood required to support a patient and the complexity and risk of the procedure, and how ill the patient is. However, by concentrating on one standard surgical intervention, which has traditionally been associated with a high rate of

transfusion, many of these confounding variables have been controlled in recent studies. Coronary artery bypass graft surgery is a common, relatively serious procedure that requires considerable transfusion support to be available – even if many patients do not need blood. Three large retrospective studies have shown that receiving a perioperative blood transfusion is an independent risk factor for short- and long-term survival following cardiac surgery. The differences are not trivial, and avoiding a transfusion could offer at least a 5% improved survival. Although two of the major studies were in the US, where leucocyte reduction of red cell transfusions is not universal, it does not appear to be due simply to an adverse impact of passenger white cells in the transfusions. In the absence of appropriate randomised controlled trials, a potent potential negative impact of transfusion now places the burden of proof on those who use a permissive transfusion regime.

Avoiding a transfusion should not be taken to extremes, however, since pre- and intraoperative anaemia correlates with postoperative renal failure and cerebral dysfunction. Preoperative anaemia, at least for elective surgery, can usually be treated adequately, so transfusion should be avoidable in most cases. Intraoperative anaemia should be amenable to surgical and anaesthetic technique. As with most areas of medicine and life, common sense and a sense of perspective are essential.

Certainly in the UK, the consistent application of known methods to reduce or avoid transfusion has not happened – despite successive initiatives by the chief medical officers in the UK to deliver *better blood transfusion*. Gardner (see Further Reading) also implies that in the US, the peak of enthusiasm for transfusion alternatives may have passed. This state of affairs cannot be allowed to continue. The evidence appears compelling that for elective cardiac surgery – at least – a comprehensive transfusion management programme should be developed for each patient. Preoperative correction of anaemia, peri- and intraoperative blood avoidance interventions and a scrupulous attention to bloodless surgical technique must become the standard of care.

It is likely that such a programme should be developed for all patients about to undergo surgery which has a high probability of needing a transfusion, and particularly for those with cancer. One problem, which the recent study of older blood versus younger blood highlights, is the lack of similar studies in conditions other than heart disease. It is therefore premature to divert supplies of younger red cells to cardiac cases at the expense of other patient groups who may benefit equally. It would seem better to redouble efforts to safely avoid transfusion altogether which would improve supplies of younger transfusions for everybody who really needs blood.

How is this to be delivered? Probably not through further ‘top-down’ initiatives on blood transfusion practice, although educational and awareness programmes delivered through hospital transfusion teams remain important. One important stakeholder in all this is the patient, and it is currently unlikely that their opinion will be sought, since there is no requirement for formal consent for transfusion in the UK. This can no longer be left up on the ‘too difficult’ shelf, looked at occasionally by anxious transfusion medicine specialists. Outcome differences with or without transfusion of upwards of 5% surely must be shared with the patient, who should be informed of the mechanisms by which blood transfusion will be avoided and provided, if necessary. None of the methods by which transfusion may be safely avoided are obscure, or difficult. Some may cost money, but if outcomes improve, the total cost should be modest indeed.

Previous debates – mainly within the transfusion community – about consent for transfusion have foundered on concerns about what represents ‘consent’, when is consent ‘informed’, is a signature necessary, what about incapable/unconscious patients, or whether there is time in the day to do it – the ‘can’t be bothered’ argument. However, other countries have found no such difficulties, although the recall of patients about what they have been told is often poor. While these niceties are being debated, people – your family member and mine – are being denied their opportunity to share in their care, unless they happen to be a Jehovah’s Witness or have an aversion to blood not based on scripture.

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Current Scottish guidelines (see further reading) state that 'The decision to transfuse is made following consideration of the potential risks and benefits of, and the alternatives to, transfusion. Where possible, this is discussed between the clinician and patient (or their legal guardian) in advance of transfusion'. It seems unlikely that this will be delivered without a formal requirement to obtain consent prior to transfusion.

At present, the search for perfection is obstructing a sensible, pragmatic attempt to engage patients by seeking their consent to transfusion. In many hospitals, written consent is obtained for bone marrow biopsies and removal of indwelling venous catheters, for example, but not for blood transfusion. Even the most basic system for consent to transfuse would empower those who wish to engage in that aspect of their care. Such a process would also require physicians and surgeons who obtain the consent to be aware of transfusion hazards and alternatives and to ensure that their own practice is current with respect to this area. Certainly, the body of evidence is increasingly supportive of the proposition that the safest transfusion is the one safely avoided.

#### Further reading

Brunkard JM, Cifuentes E & Rothenberg SJ. Assessing the roles of temperature, precipitation, and enso in dengue re-emergence on the Texas–Mexico border region. *Salud Publica Mex* 2008;50:227–234.

Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ & Durham SJ. Effect of blood transfusion on

long-term survival after cardiac operation. *Ann Thorac Surg* 2002;74:1180–1186.

Gardner TJ. To transfuse or not to transfuse. *Circulation* 2007;116:458–460.

Hebert PC, Wells G, Blajchman MA *et al.*, for Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999;340:409–417.

Jackson B, Busch M, Stramer S & AuBuchon J. The cost-effectiveness of NAT for HIV, HCV, and HBV in whole-blood donations. *Transfusion* 2003;43:721–729.

Kirpalani H, Whyte RK, Andersen C *et al.* The premature infants in need of transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *J Pediatr* 2006;149:301–307.

Koch CG, Li L, Duncan AI *et al.* Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. *Ann Thorac Surg* 2006;81:1650–1657.

Koch CG, Li L, Sessler DI *et al.* Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med* 2008;358:1229–1239.

Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L & Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation* 2007;116:2544–2552.

Netzer G, Shah CV, Iwashyna TJ *et al.* Association of RBC transfusion with mortality in patients with acute lung injury. *Chest* 2007;132:1116–1123.

QIS\_Scotland. *Clinical Standards – September 2006. Blood Transfusion*. Edinburgh: NHS Quality Improvement Scotland, 2006, p. 40.

Rezza G, Nicoletti L, Angelini R *et al.* Infection with Chikungunya virus in Italy: an outbreak in a temperate region. *Lancet* 2007;370:1840–1846.