Red blood cell transfusions in acute paediatrics

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S L Morley

ABSTRACT
Red blood cell (RBC) transfusions should usually be given only to restore or maintain oxygen delivery to vital organs and tissues. Medical history has clearly documented the importance of blood transfusion in saving lives threatened by acute haemorrhage or severe anaemia. The availability of blood products has facilitated many surgical and medical advances, allowing the support of patients who could not have previously survived invasive therapies. Consequently, the use of blood products has increased steadily over the past half century. However, recent years have seen much greater emphasis on the consequences and costs of transfusion, leading to widespread attempts to restrict blood product use. Balancing the risks and benefits of transfusion has become increasingly complex; while restricting transfusion reduces unwanted effects and cost, the thresholds at which the risks of poor oxygen carriage outweigh these are not always clear. Children have different physiology and pathology than adults and many aspects of transfusion practice are poorly researched in the young. This article discusses the most recent evidence available from adult and paediatric research to guide clinical RBC transfusion practice in acute paediatrics. It also discusses the current provision of RBC components for children.

Red blood cells (RBCs) are transfused more frequently than any other blood component, but overall RBC usage in the UK has been declining. In 2006/7 the UK blood services issued 2 235 638 RBC components (this represents a decrease of 18% since 1999/2000). Only 2.8% of RBCs issued in England are specialist paediatric products and therefore many children receive the standard adult red cell component (red cells in additive solution). However, the precise proportion of issues that are transfused to children is not known but can be estimated based on recent epidemiological studies. A regional UK report showed that 4.2% of RBCs are transfused to children under 18 years of age including 1.7% to infants under 1 year. A recent UK study sampled transfusion recipients from 29 representative hospitals supplied by the English National Blood Service and demonstrated that 4% of RBC recipients are aged less than 16 years (with the great majority of paediatric patients being under 4 years of age).

A non-concurrent study of paediatric patients (18 years of age or below) admitted to 35 US children’s hospitals in 2001–2005 found that of 51 720 children studied, 4.8% received blood components (the majority of which were RBCs). Those with malignancies and haematological disorders were most commonly transfused. Only 0.95% of transfused children in the study were reported to have developed a transfusion related complication.

PHYSIOLOGY
What is a normal haemoglobin level?
Normal haemoglobin varies with age and sex. Haemoglobin frequently rises in the first day of life due to changes in blood volume and can be maximised by delayed clamping of the cord. Subsequently it falls to a nadir at around 2–3 months of age due to decreased RBC production (this nadir is generally lower in premature infants where it may commonly drop to 8 g/dl). Levels then rise and are approximately equal in males and female until puberty (at 12 years of age mean haemoglobin is 14 g/dl for boys and 13.5 g/dl for girls). Anaemia in acute or critical illness may be exacerbated by numerous factors including blood loss (due to haemorrhage or sampling), reduced RBC production (due to nutritional deficits, inflammatory processes or low erythropoietin levels) and increased RBC turnover due to haemolysis.

RBCs and oxygen delivery
RBCs should usually be given only to increase the oxygen carrying capacity of blood in situations where oxygen delivery may otherwise be inadequate. They may occasionally be used by specialists for other applications (exchange transfusion in neonates or sickle cell anaemia and chronic transfusion to reduce haematopoesis in haemoglobinopathies). Much has been written about the use of RBC transfusion in the chronically transfused and in perinatology and a discussion of these indications is outside the scope of this article. It might be expected that the threshold for transfusion of RBCs should be lower for children than adults as children generally have lower normal haemoglobin levels than adults and rarely have the underlying cardiorespiratory disease or vascular compromise common in many adult patients. Children (certainly those outside the neonatal period) should be better able to compensate for anaemia by improving cardiac output and oxygen uptake.

RBCs are important determinants of global oxygen delivery to vital organ systems but also have specific influence over how circulating oxygen is transferred to the tissues at the microcirculatory level. Global oxygen delivery is dictated by cardiac
output and arterial oxygen content according to the following formula:

\[
\text{Oxygen delivery} = \text{cardiac output (stroke volume \times heart rate)} \times \text{arterial oxygen content (haemoglobin concentration \times 1.36 \times oxygen saturation)}.
\]

In chronic anaemia the physiological response is to increase cardiac output and thus anaemia effectively uses up some of the cardiac reserve. This may have greater significance in individuals with impaired cardiac reserve through cardiovascular disease or critical illness or neonates in the transitional period. In addition, anaemia leads to a redistribution of blood flow to critical organ systems and to an increase in RBC 2,3-DPG (causing a right shift of the oxygen dissociation curve). A similar right shift occurs in critical illness, specifically due to acidosis, hypercapnia and fever. This protective shift leads to increased unloading of oxygen in tissues that are poorly perfused or metabolically overactive.

Tissue oxygen delivery is influenced by RBC oxygen content and also by the regulation of RBC flow through the microcirculation. Dysfunction of the microcirculation during critical illness (especially sepsis) prevents effective delivery of oxygen and can lead to tissue hypoxia despite adequate cardiac output and arterial oxygen content. Haemoglobin in the RBC may act as an oxygen sensor allowing the RBC to regulate blood flow within the microcirculation by release of vasodilators such as nitric oxide and adenosine triphosphate (ATP). Research studies commonly assess tissue hypoxaemia using oxygen consumption (VO₂), blood lactate levels, mixed venous oxygen saturation or markers of regional perfusion such as gastric tonometry. There is little evidence that RBC transfusion improves these indices in adult studies as long as the patient has a baseline haemoglobin level of at least 8 g/dl.

How much haemoglobin do we need?

Animal experiments suggest that the critical haemoglobin level for oxygen delivery (ie, the level, in normovolaemia, below which oxygen consumption is supply dependent) lies between 3 and 4 g/dl haemoglobin. Acute normovolaemic haemodilution to 5 g/dl in healthy resting human adult volunteers is broadly well tolerated and does not produce inadequate oxygen delivery as measured by decreased oxygen consumption, increased lactate production or ECG changes. However, these individuals do exhibit increased heart rate and a decline in memory and higher cerebral functioning, suggesting that tissue oxygen delivery may be borderline at this haemoglobin level.

In otherwise well adults and older children, it seems likely that 5 g/dl is, therefore, the threshold at which anaemia (especially acute anaemia) becomes clearly detrimental. Determining this threshold for individuals with pathology or undergoing surgical procedures is complex. In patients who do not wish to be transfused, a pre-operative haemoglobin level between 5 and 6 g/dl leads to increased mortality. Anaemia is also less well tolerated in adults with cardiovascular disease. Recent studies focussing on restriction of blood transfusion suggest that allowing haemoglobin levels to decline to 7 g/dl before transfusion is not detrimental in stable adults and children in the intensive care setting. It is unclear, however, whether utilising this restrictive strategy demonstrates that 7 g/dl produces adequate oxygen delivery and equal clinical outcomes to maintaining higher haemoglobin levels or whether the similar outcomes are attributable to the negative effects of increased transfusion in the less restrictive groups.

Circulatory effects of RBC transfusion

Transfusion in the normovolaemic subject causes a short-lived increase in central venous pressure and an associated decrease in vital capacity. There is a rapid readjustment in plasma volume in the healthy subject leading to restoration of circulating volume in less than an hour. This readjustment may be delayed in patients with reduced renal function. The rise in haemoglobin secondary to transfusion leads to a reduction in RBC production.

NEGATIVE EFFECTS OF TRANSFUSION

The major adverse effects of transfusion include acute and delayed transfusion reactions and transfusion transmitted infections, and are described in detail elsewhere. Much public and clinical concern has been focused on transfusion transmitted infection. Currently, the risks of transmission of known viral infections are extremely low (hepatitis B: 1 in 600 000 donations; hepatitis C: 1 in 40 000 000 donations; HIV: 1 in 4 000 000 donations). The risks of transmission of variant-CJD (vCJD) in UK patients is difficult to quantify and will be discussed in more detail below.

The effects of storage on RBCs

It has been proposed that the effect of storage on RBCs may impair their function within the microcirculation. The human RBC lifespan is approximately 120 days, at the point of donation
the age of individual cells is variable and the viability of cells is reduced with increased length of storage. In the first 24 h after transfusion, non-viable cells are rapidly lost from the recipient’s circulation. 2,3-DPG is also lost from stored red cells causing a left shift in the oxygen dissociation curve (reducing release of oxygen from RBCs to the tissues). RBCs have lost almost all their 2,3-DPG after 14 days of storage in SAG-M, but 95% of 2,3-DPG activity is restored within 72 h after transfusion into a recipient’s circulation.24 Stored RBCs undergo a shape change with prolonged storage, losing their discoid shape and becoming less deformable. Storage also leads to red cell lysis and small amounts of free haemoglobin accumulate (less than 1% of total haemoglobin at 35 days). The RBC Na⁺K⁺ ATPase is sensitive to cold leading to an increase in RBC sodium and plasma potassium over time. It is unlikely that the level of potassium accumulation in appropriately stored units is harmful, although concerns have been raised about the potential for harm to neonates undergoing exchange transfusion.

Changes in RBC structure and function due to storage might all be expected to alter effective interaction with the microcirculation. Free haemoglobin is a potent scavenger of NO that causes vasoconstriction.25 Storage of RBCs also increases their adherence to vascular endothelium and may reduce microvascular flow,26 although this effect may be reduced by pre-storage leucodepletion.27 There is evidence that the reduction in 2,3-DPG levels through storage does not affect oxygen delivery or extraction.28

A large prospective study in the adult ICU setting showed that transfused patients had a longer requirement for intensive care, more organ dysfunction and higher mortality than those who were not transfused29 and that outcomes worsened in those who received more transfusions. Similar findings were reported in a smaller study of 295 paediatric intensive care patients.30 Prolonged storage time has been linked in retrospective studies to increased mortality, pneumonia, infection, multiorgan failure and length of stay.31 Although there is some evidence that patients receiving blood stored for longer periods have poorer outcomes, no benefits were noted in a pilot study comparing use of fresh blood against stored blood.32

**Immunomodulation by transfusion**

Many of the negative effects of transfusion have been attributed to immunomodulation in the recipient. This was initially demonstrated in a study showing reduced rejection of renal allografts in polytransfused patients.33 An association between the recurrence of malignancies and the administration of blood transfusions has also been reported.34 35 Transfusion was found to cause a dose dependent increase in the risk of peri-operative infection36 and has been linked with increased risk of multi-organ failure in surgical patients.37 Immunomodulation may be largely due to the presence of donor lymphocytes in transfused components. Leucodepletion may reduce these negative effects,30 39 and similar benefits have been described using autologous blood.40

**COMPONENT PRODUCTION**

In recent decades separation of whole blood into multiple components prior to storage and transfusion has become standard practice in the UK and many other countries. This permits optimal usage of donated products but also allows transfusions to be targeted more effectively to the needs of the patient. Briefly, whole blood donations are drawn into plastic packs containing an anticoagulant/preservative solution, usually citrate phosphate dextrose (CPD). Citrate chelates calcium and acts as an anticoagulant, and dextrose supports red cell metabolism and prolongs storage time. The whole blood unit is filtered to remove leucocytes, platelets may be produced by centrifugation and most of the plasma is drawn off. A standard unit of red cells in additive solution in the UK contains the red cell portion of a single donation with around 20 ml of residual donor plasma. The remainder of the plasma volume is replaced with a saline based additive solution containing adenine, glucose and mannitol (usually called SAG-M) which improves RBC viability and shelf-life. The precise specification is shown in table 1.

**RBC COMPONENTS AVAILABLE FOR CHILDREN AND NEONATES**

RBCs for transfusion in utero or to children under 1 year of age are prepared from blood donated by donors who have given at least one previous donation within the past 2 years. A number of specialist components are produced for neonatal use (for these purposes a neonate is defined as an infant with a corrected age of less than 4 weeks post-term) and these are also detailed in table 1. Neonatal RBCs may be provided in full units or split packs. It is considered good practice to issue a split pack for any neonate who is predicted to need more than one top-up transfusion within the 35-day unit shelf-life to reduce donor exposure.

Currently, the blood provided for neonates and children in the UK is stored in SAG-M. SAG-M blood has lower residual plasma than whole blood or blood stored with CPD alone and may, therefore, be less likely to transmit vCJD (the majority of vCJD infectivity resides in the white cells and plasma of whole blood). Concerns have been raised about potential toxicity associated with the mannitol in SAG-M where very high volumes are transfused to neonates. For this reason, blood for higher volume exchange transfusions for neonates is provided without SAG-M (the anticoagulant is therefore CPD). The units are plasma reduced but retain more plasma than standard red cell bags to allow the haematocrit to be provided within a tight haematocrit range of 0.5–0.55. This allows neonatal staff to accurately predict the likely influence on the haematocrit of the patient and to prevent a
Best practice

Table 1 Specification of red blood cell components available for use in neonates and children in the UK*

<table>
<thead>
<tr>
<th>Red cells in additive solution</th>
<th>Neonatal red cells (either full unit or neonatal split packs)</th>
<th>Red cells for large volume neonatal transfusion (not exchange)</th>
<th>Red cells for exchange transfusion</th>
<th>Red cells for intrauterine transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>282 ml</td>
<td>43 or 282 ml</td>
<td>282 ml</td>
<td>324 ml</td>
</tr>
<tr>
<td>Additive solution/anticoagulant</td>
<td>SAG-M/CPD</td>
<td>SAG-M/CPD</td>
<td>SAG-M/CPD</td>
<td>–/CPD</td>
</tr>
<tr>
<td>Residual plasma volume</td>
<td>20 ml</td>
<td>20 ml in a full unit</td>
<td>20 ml</td>
<td>100–120 ml</td>
</tr>
<tr>
<td>Haematocrit (target specification)</td>
<td>0.5–0.6</td>
<td>0.5–0.6</td>
<td>0.5–0.6</td>
<td>&gt;0.7</td>
</tr>
<tr>
<td>Leucodepletion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Maximum time since donation</td>
<td>35 days</td>
<td>35 days</td>
<td>5 days</td>
<td>5 days</td>
</tr>
<tr>
<td>CMV status</td>
<td>Negative or positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HbS status</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Negative</td>
</tr>
<tr>
<td>Shelf-life</td>
<td>35 days</td>
<td>35 days</td>
<td>5 days</td>
<td>5 days or 24 h from irradiation</td>
</tr>
<tr>
<td>Irradiation</td>
<td>Not routine</td>
<td>Not routine</td>
<td>Not routine</td>
<td>Yes</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; CPD, citrate phosphate dextrose; SAG-M, saline based additive solution containing adenine, glucose and mannitol.

Infection associated with blood transfusion in the UK and three of the four recipients developed symptoms of vCJD. All four cases had received transfusions of non-leucodepleted RBCs between 1996 and 1999. The majority of the infectivity in blood components is believed to reside in WBCs and plasma. Measures to reduce the risk of transmission of infection through blood components include:

- measures in donor selection including exclusion of blood donors who have received a blood component or bone donation in the UK since 1 January 1980,
- withdrawal of any blood components from any individual who develops vCJD,
- universal leucodepletion of blood components,
- reduction of plasma in cellular components,
- importation of fresh frozen plasma for children under 16 years of age (with recent importation of cryoprecipitate).

Efforts are progressing to develop and validate prion reduction filtration for blood components.

**Irradiation**

Cellular blood components can be irradiated with gamma irradiation to inactivate lymphocytes that could cause transfusion associated graft-versus-host disease (TA-GvHD). Increasingly, X-irradiation has been shown to be effective and will also be used. Gamma irradiation can cause increased RBC fragility and shorten the expected shelf-life of red cell components. It is recommended that RBCs irradiated for exchange transfusion or intrauterine blood transfusion (IUT) are used within 24 h of irradiation; for other purposes the recommended shelf-life of irradiated RBCs is 14 days. Recommended indications for provision of irradiated cellular blood components are outlined in box 1. Irradiation is not routinely recommended for premature or term neonates unless they fulfil one of the listed indications. If cell mediated immunodeficiency is clinically suspected, then...
irradiated products should be provided while confirmation of the suspected diagnosis is sought.

**APPROPRIATE USE OF TRANSFUSED RBCS**

The decline in RBC transfusion in the UK in recent years has been driven by the efforts of clinicians to ensure appropriate use. The greatest improvements have been made in reducing transfusion associated with surgical procedures. There is good evidence in many settings that adoption of a co-ordinated local policy which incorporates techniques to minimise blood loss and well defined transfusion guidelines, can significantly reduce the use of blood components. Table 2 outlines the approaches that can be successfully employed in both medical and surgical settings.
and prognosis must be considered. A lower haemoglobin level may be appropriate in patients who are clinically stable and who have no further risk factors for ongoing anaemia (eg, stable post-operative surgical cases).

**Erythropoietin**
A large randomised study of adult patients in critical care demonstrated a 19% reduction in RBC transfusion in the group that received a once weekly dose of rHu erythropoeitin (with enteral iron). Recombinant erythropoietin has also been extensively studied in neonatal practice and can effectively stimulate erythropoiesis. It has been used in the treatment of anaemia pre-operatively both alone and in the setting of autologous blood donation.

Although erythropoietin can raise haemoglobin and reduce transfusion in a number of settings, its cost effectiveness and safety have not been demonstrated. It may be beneficial in selected groups of patients but cannot be generally recommended.

**RBC TRANSFUSION IN SPECIAL CIRCUMSTANCES**

**Massive blood loss**
Massive blood loss has been variously defined as the loss of one blood volume within 24 h or alternatively, in the acute setting, a 50% loss of blood volume within 3 h. In children, estimation of blood volume is dependent on age as well as weight. Younger children have a higher proportion of their weight as blood than older children and levels are lower in obese individuals. In children over 3 months of age blood volume may be estimated using 70 ml/kg bodyweight, whereas for premature infants 90–100 ml/kg and for term infants 80–90 ml/kg may be more suitable. In adults the commonest causes of massive blood loss include vascular and cardiac surgery, upper gastrointestinal bleeding, obstetric emergencies and trauma. Although all these aetologies may occur in children under 16 years of age, they are comparatively rare. Other causes of massive blood loss and transfusion requirement in children include extracorporeal membrane oxygenation and exchange transfusion for neonatal hyperbilirubinaemia or sickle cell emergencies. Other procedures such as scoliosis surgery or craniosynostosis repair may also be significant.

**Severe sepsis**
In the adult ICU setting, employing a higher transfusion trigger for patients with early severe
plasma lactate is high. mixed venous saturations are persistently low or raising haemoglobin levels in severe sepsis where children, but consideration could be given to support this higher transfusion trigger in adults or control arm. No additional evidence is available to bin levels and improved outcome compared to the received more transfusions, had higher haemoglobin-

10 g/dl and the algorithm was employed for the first 6 h of ICU care. The patients in the study arm had higher haemoglobin levels and improved outcome compared to the control arm. No additional evidence is available to support this higher transfusion trigger in adults or children, but consideration could be given to raising haemoglobin levels in severe sepsis where mixed venous saturations are persistently low or plasma lactate is high.

Cyanotic heart disease
Infants with cyanotic congenital heart disease may have significant impairment in arterial blood saturation and the potential for inadequate cardiac output leading to poor oxygen delivery. Infants with low cardiac output states due to non-cyanotic heart disease or those on extracorporeal cardiovascular support may be similarly affected. This has led to many centres adopting higher transfusion thresholds for these children, especially when they require surgery or intensive care. At present there is no clear evidence to support or refute this practice.

HOW MANY RBCS TO TRANSFUSE
Deciding the volume of blood that is required to achieve the desired haemoglobin level is clearly important. Each transfusion episode should provide sufficient haemoglobin to optimise oxygen carriage without compromising cardiovascular status. In critically ill patients it has been common to limit transfusions to between 10 and 20 ml/kg and in stable patients formulae have been produced based on bodyweight. Underestimating the volume that can be transfused in young children can lead to large portions of a blood pack being discarded unnecessarily and this in turn may lead to the patient receiving a subsequent transfusion to make up the shortfall, thus increasing donor exposure. Transfusion practice has been affected by the reduction in the haematocrit of standard RBC packs due to the use of additive solutions and leucodepletion. Two retrospective surveys have investigated transfusion formulae in the setting of paediatric intensive care. These formulae use either the haematocrit of the RBCs to be transfused or, alternatively, a predefined “transfusion factor” to calculate the expected outcome of transfusion. Both studies determined that the currently recommended formulae were underestimating the volume of packed RBCs needed to raise haemoglobin and they proposed new formulae. Davies et al recommended that the transfusion factor be calculated using the haematocrit of the packed RBCs. In the UK at present the average haematocrit of paediatric and adult packed RBCs is 0.56 and so according to this formula the transfusion factor would be 3/0.56 or 5.36. Morris et al recommended a transfusion factor of 4.8 (at a time when the haematocrit was 0.69), so with current packed RBCs the equivalent transfusion factor would now be 5.9 using this method. It seems most likely, therefore, that a transfusion factor of 5 (or slightly greater) is most likely to be effective. Thus the current best formula for top-up transfusion would be either:

\[
\text{Transfused volume (packed RBCs)} = \text{bodyweight (kg)} \times \text{desired Hb increment (g/dl)} \times (3/\text{Hct of packed RBCs})
\]

Or where the haematocrit of the packed RBCs is unknown:

\[
\text{Transfused volume (packed RBCs)} = \text{bodyweight (kg)} \times \text{desired Hb increment (g/dl)} \times 5
\]

For most small children (below 15 kg) requiring top-up transfusion from a haemoglobin of 7 g/dl, it

Table 3  Current recommendations for the haemoglobin level (threshold) below which transfusion is considered*

<table>
<thead>
<tr>
<th>Neutonal patients</th>
<th>Threshold haemoglobin level (g/dl)</th>
<th>Source references</th>
<th>Controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia in first 24 h of life</td>
<td>12 (Hct 0.36)</td>
<td>Gibson et al 41</td>
<td>Kirpalani et al 32, Bell et al 44</td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>12</td>
<td>Gibson et al 51</td>
<td>Kirpalani et al 32, Bell et al 44</td>
</tr>
<tr>
<td>CPAP/chronic oxygen dependence</td>
<td>11</td>
<td>Gibson et al 51</td>
<td>Kirpalani et al 32, Bell et al 44</td>
</tr>
<tr>
<td>No requirement for oxygen/late anaemia†</td>
<td>7–8</td>
<td>Gibson et al 51</td>
<td>Kirpalani et al 32, Bell et al 44</td>
</tr>
</tbody>
</table>

Paediatric patients
- Acutely ill children 7
- Massive blood loss 8

Circumstances where higher thresholds are commonly used
- ECMO 12–15
- Cyanotic congenital heart disease requiring surgery/intensive care 10–12
- Early severe sepsis 10

*Based upon evidence from randomised clinical trials (where available) or clinical opinion and practice; †if symptomatic.

CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation.

For most small children (below 15 kg) requiring top-up transfusion from a haemoglobin of 7 g/dl, it
is desirable to achieve a post-transfusion haemoglobin level within the normal range (approaching 11 g/dl) where this can be provided from a single donor. A rise of 4 g/dl assuming a transfusion factor of 5 would lead to a transfusion of about 20 ml/kg of packed RBCs. Ideally, transfusion should be informed by close monitoring of the actual increment in haemoglobin and the clinical status of the patient. For children of 15 kg and above, where this cannot be provided from a single unit of packed RBCs, donor exposure can best be reduced by following the recommended adult practice for top-up transfusion, which advises single unit transfusion with subsequent monitoring of haemoglobin concentration and clinical status before further RBCs are prescribed.

**SUMMARY**

RBC transfusion is safer than ever before, but recent emphasis on the appropriate use of blood has been largely driven by concerns relating to transfusion transmitted infection. Evidence has also emerged in recent years suggesting that transfusion may worsen clinical outcomes in acutely ill patients in all age groups. These concerns have led to improved techniques for the preparation of blood components, and formulations of specialist components for infants and children have evolved. A number of recent paediatric and neonatal studies have emphasised the role of transfusion thresholds and understanding the evidence base will enable paediatricians to ensure that acutely ill children are transfused only when it is likely to be beneficial. The development of local guidelines to prevent blood loss and guide transfusion is important in implementing appropriate use of blood components.

**Competing interests:** None.

**REFERENCES**

23. HPA. Estimated frequency (or risk) of infectious donations entering the UK blood supply. London: Health Protection Agency, 2008.
Archivist

Genes and language impairment

Most children are speaking well by the age of 6 or 7 years. An important minority (around 5%), however, have unexplained difficulty with aspects of speech and language and are said to have specific language impairment. Genetic factors are known to be important: children with specific language impairment are four times as likely as other children to have a family history of the condition and the concordance rate among monozygotic twins is twice that among dizygotic twins. Nevertheless, there is confusion about which genes are involved. Different studies have produced different results.

Abnormalities of one gene, FOXP2, are known to cause a rare autosomal dominant form of developmental verbal dyspraxia with expressive and receptive language impairment. This gene encodes a transcription factor with many targets in the brain. Now researchers in Oxford and Los Angeles (Sonja C Vernes and colleagues. *New England Journal of Medicine* 2008;359:2357–45; see also Editorial, ibid: 2381–3) have looked for genes regulated by FOXP2 and honed in on one of them, CNTNAP2 at chromosome 7q35–q36. This gene encodes CASPR2, a neuroxin (a protein that acts as a neuronal cell surface receptor) and is richly expressed in human language-related brain circuits. They then analysed CNTNAP2 single nucleotide polymorphisms (SNPs) in children with specific language impairment and found a significant association between one SNP in particular and difficulty with repetition of nonsense words, said to be a well defined feature (endophenotype) of specific language impairment. Abnormalities in this region of the genome have also been implicated in children with language delays and autism.

The FOXP2-CNTNAP2 pathway may be involved in specific language impairment. The writer of the editorial raises many questions. Why concentrate on CNTNAP2 when many other candidate genes have been identified? Why has the 7q35–q36 locus never been implicated before? Why rely on nonsense word repetition rather than other tests? One gene, one clinical manifestation of a polygenic, multifaceted syndrome: a step along the way.