Long-term survival after blood transfusion: a population based study in the North of England

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BACKGROUND: Blood transfusion may transmit infectious diseases with long incubation periods. Estimation of the risks of transmission of such disease requires knowledge of long-term survival of transfused patients. No such information is available in the UK, where there is particular concern about possible transmission by transfusion of variant CJD.

STUDY DESIGN AND METHODS: Information on survival after transfusion and demographics was collected for all patients transfused during June 1994 in a population of 2.9 million served by a single blood center.

RESULTS: A total of 2899 patients were transfused with 10,760 units of RBCs (99% of RBCs issued during the study period). Follow-up to death or 5 years was completed for 98.2 percent, and 46.9 percent of all transfusion recipients were alive at 5 years; 41 percent of transfused RBC units and 36 percent of transfused FFP were given to patients who were alive at 5 years. Median age at transfusion was 67 years (mean, 60.9 years). Shorter patient survival was associated with increasing patient age, increasing numbers of RBC units transfused, transfusion of plasma or PLTs, and nonsurgical indications for transfusion.

CONCLUSIONS: Posttransfusion survival is lower than estimated in previous decades in other countries. This is probably due to a relative increase in use of transfusion for older patients and for medical indications. Our figures may be used to predict and stratify the risk of infections, such as variant CJD, amongst different groups of transfusion recipients.

Blood transfusion can transmit infectious agents, such as bacteria and viruses. The introduction of new tests on donor blood such as NAT for HCV has had a major impact on the cost of blood with small benefits to the recipients. The cost-effectiveness of such testing has been questioned.[1] Information on the long-term survival of transfused patients may be used for analysis of the costs and benefits of such interventions and to predict the number of cases of clinically evident transmitted disease due to agents with a long incubation period.[2]

In the UK there is, at present, particular concern regarding variant CJD (vCJD). Animal models have shown that transmission of prion disease by transfusion is possible.[3] More recently, a case of vCJD has been reported in a patient who had been transfused with blood from a donor who subsequently developed the disease and who was probably incubating the condition at the time of donation.[4] If, as seems likely, vCJD is transmissible by blood

ABBREVIATIONS: NHS = National Health Service; NSTS = National Health Service; vCJD = variant CJD.

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transfusion in humans, it is probable that the incubation period before clinical disease is apparent will be measured in years.

Although studies of survival after transfusion have been performed in other countries, there is no information on long-term survival after blood transfusion for British patients. With the risk of vCJD in mind, we therefore conducted a retrospective and population-based study of survival after blood transfusion in the North of England. This study was not intended to assess the effects of blood transfusion itself on the long-term survival of recipients.

MATERIALS AND METHODS

Setting

The Newcastle center of the National Blood Service was the sole supplier of labile blood components to 18 National Health Service (NHS) hospital blood banks in the North of England during the study period. These hospitals deliver a full range of medical and surgical services, including all major tertiary care services, to a stable and geographically defined population of 2.9 million. Private and military hospitals in the region use less than 1 percent of the regional blood supply.

Data collection

We visited all NHS hospital blood banks in the region and used computer or paper records to identify patients transfused during the calendar month of June 1994. Patients receiving allogeneic or autologous RBCs, FFP, PLT concentrates, and cryoprecipitate either individually or in combination were included. Patient demographics and the details of all products transfused during the month were collected from blood bank records.

Where patients were transfused on more than one occasion during the study period, survival was calculated from the date of the first transfusion. Where patients were transfused in more than one hospital, the records were combined. Information was not collected on blood that was cross-matched but not transfused.

The patient information system of each hospital was searched for a date of death or the date last seen within that hospital. For patients where no date of death was recorded, we used the patient's NHS number to obtain follow-up information from the NHS Strategic Tracing Service (NSTS). The NSTS is a central register of all patients in England and Wales registered with a general practitioner (http://www.nhsia.nhs.uk/nsts). The information held includes NHS number, name, date of birth, sex, and, where appropriate, date of death. The database is updated regularly with information from general practitioners (via local Health Authorities) and the Registrar of Births and Deaths (via the Office of National Statistics).

The specialty of the treating consultant associated with the first transfusion during the study was collected from the hospital information systems.

Ethics

The Northern and Yorkshire Multi-center Research Ethics Committee reviewed the study protocol and classified it as an audit not requiring formal ethical approval. We obtained the permission of the Caldicott Guardian (who is responsible for ensuring patient confidentiality) of each NHS hospital trust in the region before identifying transfused patients and removing patient identifiable information from that trust.

Analysis and statistical methods

Records were entered into a database (Access 2000, Microsoft Corporation, Redmond, WA) and were analyzed using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego CA) and Microsoft Excel 2000 (Microsoft Corporation). The data have been analyzed by the number of transfusion recipients surviving (patient survival) and by the number of units of blood components transfused to surviving patients (unit survival). Survival curves were drawn using the Kaplan Meier method and survival curves were compared using a log-rank test with a log-rank test for trend where appropriate. The effects of patient and transfusion variables on survival were assessed by fitting a proportional hazards model assuming a Weibul survival distribution. The fit of the model was checked using quantile plots.

To calculate expected survival rates for the study population, we used Interim Life Tables, produced by the Government Actuary's Department, adjusted for the sex and for the age at time of transfusion of the patients (http://www.gad.gov.uk). Actual and expected survival were compared using a Standardized Mortality Ratio (SMR), with expected survival expressed as 100 percent. Estimates of the region's population for 1994 (based on the 1991 census) were obtained from the Population Estimates Unit of the Office of National Statistics (http://www.statistics.gov.uk).

RESULTS

Data were collected from all 18 NHS hospital blood banks served by the Newcastle blood center.

Transfusion recipients

We identified 2899 patients who received a transfusion during the study period, of whom 32 were transfused at

more than one of the region's hospitals. These patients received 10,760 units of RBCs, 2395 PLTs concentrates, 1162 units of FFP, 241 units of cryoprecipitate, 39 autologous RBC units, and 3 units of autologous FFP.

A total of 1608 patients were female (55.5%; 95% CI, 53.7-57.2). The mean age at transfusion was 60.9 years (median, 67 years; range, 0-103 years). The sex and age of one recipient and the ages of a further nine were not available. The age and sex distribution of recipients is shown in Fig. 1.

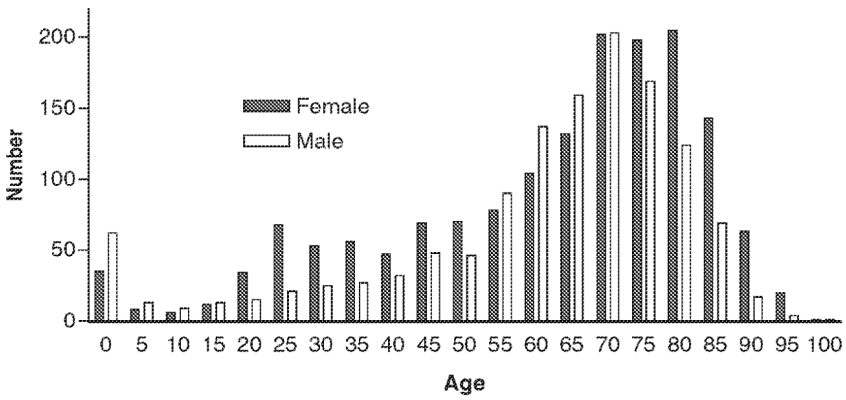

Fig. 1. Age and sex distribution of all transfusion recipients.

Over the study period of 30 days, 99 patients per 100,000 population were transfused, equating to an annual transfusion rate of 4472 units of RBCs per 100,000 population.

Blood component use

The Newcastle blood center issued 11,252 RBC units, with a maximum possible shelf life of 35 days, during June 1994. Mean monthly RBC issues during 1994 were 10,971 units. During the study period, 390 unused RBC units were returned. Based on these figures, we have information on the clinical use of 99 percent of allogeneic RBC units presumed to be transfused during the study period. A small number of units may be discarded untransfused within the hospital, which would improve this figure further.

We found records detailing the transfusion of 87 percent of the 2762 whole PLT-derived concentrates (shelf life of 5 days) issued from the transfusion center during June 1994. We do not have records for untransfused units discarded by hospital blood banks during that period, but current estimates for hospital wastage are 6 to 10 percent of issued units. Single-donor PLT concentrates were not issued during the study period.

FFP and cryoprecipitate can be stored for up to 12 months before being thawed for clinical use. During 1994, the Newcastle center issued an average of 1442 units of FFP per month (range, 1156-1770). Mean return to the blood center of damaged FFP was 55 units per month (range, 17-105). Undamaged FFP thawed but not transfused was not returned to the center. Records of FFP transfused in June 1994 therefore account for 84 percent of average net monthly issues to hospitals during 1994 (average monthly issues less the average number of FFP units returned).

Records for transfusion of cryoprecipitate during June 1994 account for 65 percent of the average monthly issues (368 units) during the whole year, but there was wide variation in issues between individual months (range, 254-648 units).

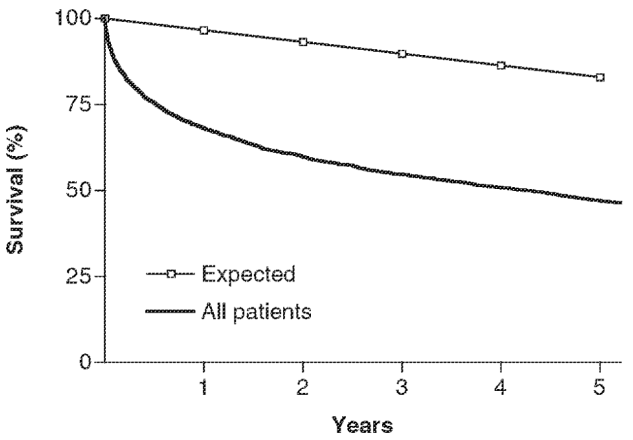

Fig. 2. Overall survival of all transfused patients and expected survival for an age/sex matched cohort.

Follow-up

Information on death or survival of the study population was available for 98.2 percent at 5 years after transfusion and for 96.3 percent at 7 years after transfusion.

Analysis by patients

Survival for all patients and expected survival based on government actuarial figures is shown in Fig. 2. Median survival for all transfused patients was 51 months. Overall survival of patients at 2 years was 59.4 percent (95% CI, 57.6-61.2). Overall survival at 5 years was 46.9 percent (95% CI, 45.1-48.7). Overall survival of patients at 7 years was 41.3 percent (95% CI, 39.5-43.1).

The survival of patients stratified by age at time of transfusion is presented in Table 1.

The survival of patients stratified by number of units of RBCs received during the study period is shown in Fig. 3. Increasing numbers of units transfused was associated with poorer survival in an unadjusted analysis (log-rank test, $p < 0.0001$; log-rank test for trend, $p < 0.0001$).

Patients transfused with PLT concentrates (n = 172), with or without other components, had a median survival of 9 months compared to 54 months for those who did not receive PLTs (n = 2727). Five-year survival was 32 and 47 percent, respectively (Fig. 4).

Patients transfused with FFP (n = 253), with or without other components, had a median survival of 31 months compared to 53 months for those who did not receive plasma (n = 2646). Five-year survival was 42 and 47 percent, respectively (Fig. 5).

Information on the treating consultant's specialty was available for 1544 patients (53%). Medical patients (n = 683) had a median survival of 19 months compared with 79 months for surgical patients (n = 743). Patients transfused in obstetrics and gynecology (n = 118) had a 5-year survival of 88 percent and median survival was not reached (Fig. 6). Mean RBC use (±1 SD) per patient during June 1994, by specialty, was 4.0 (±4.5) for medical patients, 3.8 (±3.9) for surgical patients, and 3.1 (±1.3) for obstetrics and gynecology patients.

TABLE 1. Overall survival according to patient age at time of transfusion

Age (years)	Number	Median survival (months)	2-year overall survival (%)	5-year overall survival (%)
0	83	NR*	78	78
1-9	42	NR	90	85
10-19	55	NR	80	78
20-29	143	NR	96	94
30-39	154	NR	83	79
40-49	221	NR	71	61
50-59	315	60	61	50
60-69	604	51	59	48
70-79	761	31	52	36
80-89	448	18	40	21
>89	63	10	29	11

* NR = not reached.

Analysis by units

Of transfused RBC units, 53 percent were given to recipients who were alive at 2 years, and 41 percent were given to recipients who were alive at 5 years. The median survival of an individual RBC unit (per component survival) was 31 months.

Of transfused units of FFP, 46 percent were given to recipients who were alive at 2 years, and 36 percent were given to recipients who were alive at 5 years. The median per component survival of FFP was 19 months.

Of PLT units, 32 percent were given to recipients who were alive at 2 years, and 24 percent of PLT units were given to recipients who were alive at 5 years.

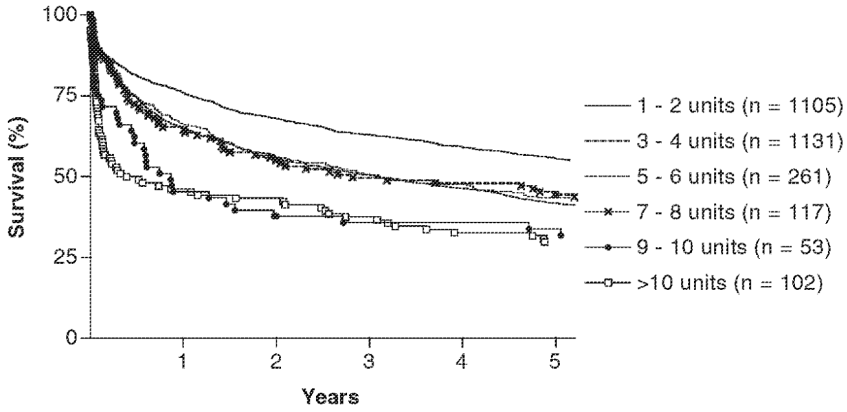

Fig. 3. Overall patient survival by number of RBC units received during the study period.

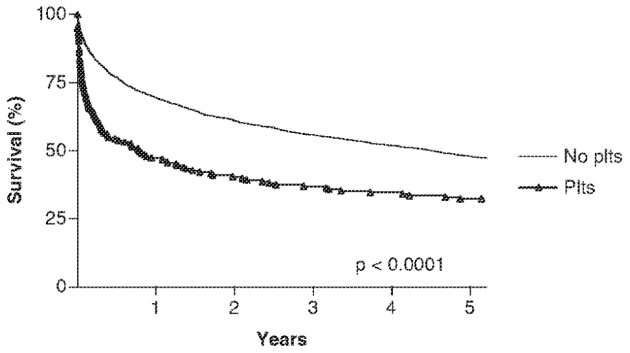

Fig. 4. Overall survival of PLT recipients compared with transfusion recipients not receiving PLTs.

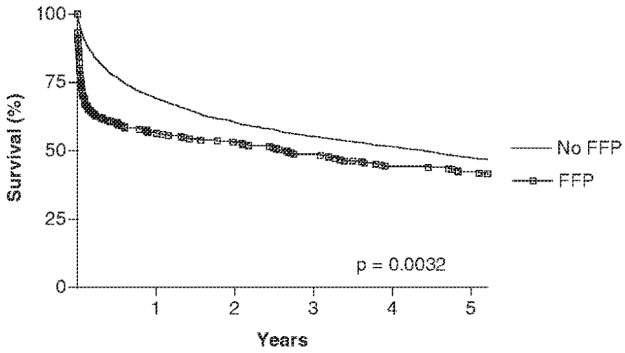

Fig. 5. Overall survival of FFP recipients compared with transfusion recipients not receiving FFP.

The median per component survival of PLTs was 6 months.

Figure 7 shows per component survival for RBCs, FFP, and PLTs.

Multivariate analysis

The relation between survival and patient and transfusion variables was investigated using the proportional hazards method described. For this analysis, patients receiving non-RBC components only were excluded. The following categorical variables were included: Age of recipient (divided into three groups: <50 years, 50-74 years, >74 years), sex of recipient, number of units of RBCs transfused during the study period (divided into 4 groups: 1-2, 3-4, 5-6, and >6 units), and transfusion or not of non-RBC components. All variables were independently associated with survival (Table 2). Patients who were older, of male sex, who had more RBC transfusions, or who received PLTs or plasma transfusion either alone or in addition to RBCs, had shorter survival.

Multivariate analysis was also undertaken for the subset of patients for whom a specialty code of medicine or surgery was recorded. Obstetric and gynecology patients, who not unexpectedly showed marked differences by sex, age, and survival from other patients, were excluded from this analysis. This showed that specialty is independently associated with posttransfusion survival (medical survival < surgical survival) and that age, sex, number of RBC units transfused, and use of non-RBC products remain independently associated with survival (Table 3).

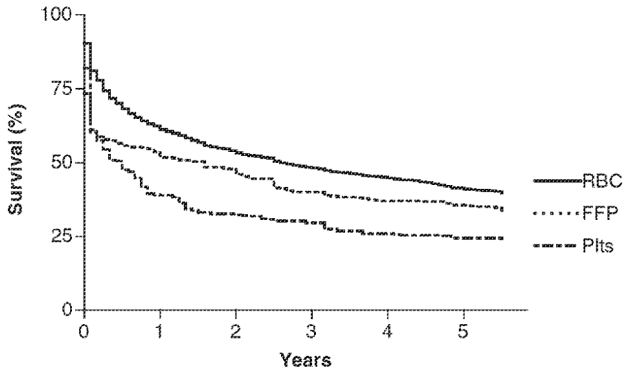

Fig. 7. Analysis by units: percent units transfused to surviving patients.

DISCUSSION

We retrospectively identified 2899 patients transfused during June 1994 in a population-based study and

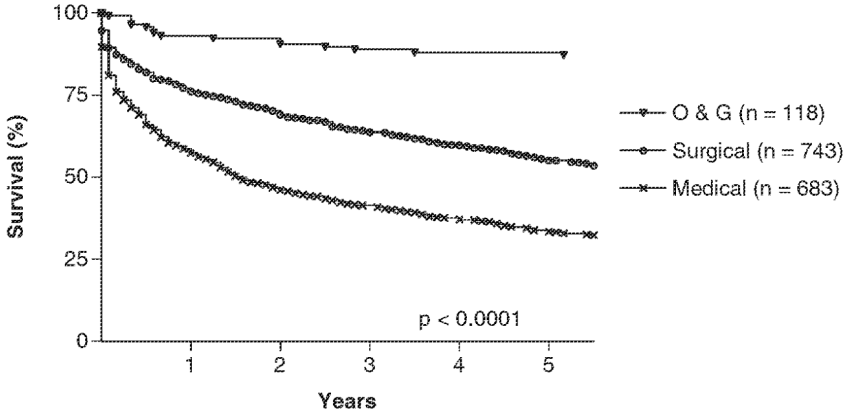

Fig. 6. Survival of patients transfused for medical, surgical, or obstetric, and gynecologic indications.

TABLE 2. Results of multivariate analysis: all patients

Variable	Mortality hazard ratio	95% CI	p value
Sex			
M:F	1.24	1.12-1.37	<0.001
Age			
<50	1.00		
50-75	3.04	2.57-3.60	<0.0005
≥75	5.57	4.69-6.61	
RBC units			
1-2	1.00		
3-4	1.30	1.16-1.45	
5-6	1.20	1.01-1.44	<0.0005
>6	1.44	1.20-1.73	
Non-RBC products	1.67	1.41-1.99	<0.0005
Use/No use			

TABLE 3. Results of multivariate analysis: medical and surgical patients

Variable	Mortality hazard ratio	95% CI	p value
Sex			
M:F	1.26	1.09-1.45	0.001
Age			
<50	1.00		
50-75	2.52	2.01-3.18	<0.0005
≥75	4.59	3.62-5.81	
RBC units			
1-2	1.00		
3-4	1.24	1.05-1.45	0.045
5-6	1.14	0.89-1.45	
>6	1.29	1.01-1.64	
Non-RBC products			
Use/No use	1.64	1.31-2.06	<0.0005
Specialty			
Surgical/medical	0.51	0.45-0.59	<0.0005

TABLE 4. Comparison with previous studies of survival after transfusion

	Year	Patients	Age (mean)	Female (%)	RBC	Overall survival (%) 1 year	2 year	40 month	5 year
Vamvakas[7,8] (US)	1981	802	57	56	3,755	76	70	64	60
Whyte[9] (NZ)	1984	367	NA	55	1,385	79	78	NA	69
Tynell[10] (Sweden)	1993	1,904	66	56	6,435	66	NA	51	NA
Newcastle (UK)	1994	2,899	61	55	10,760	68	59	53	47

achieved greater than 98-percent follow-up to 5 years. Of all patients transfused with any blood component, 46.9 percent were alive at 5 years. Poorer patient survival was independently associated with male sex, increasing age, increasing numbers of RBC units transfused, and transfusion of non-RBC components. Medical indication for transfusion was an independent predictor of poor survival in the subgroup of patients in whom this data was collected.

We have details of RBC transfusions that account for 99 percent of net issues from the blood center during June 1994 or net monthly issues during the whole of 1994. PLT concentrates have a shelf life of only 5 days and typically have a higher wastage rate within hospital blood banks than RBCs. We recorded transfusion of 87 percent of PLT issues, which, allowing for likely wastage of this component, probably represents greater than 90 percent of transfused PLTs. We have compared FFP and cryoprecipitate use with their average monthly issues from the blood center because of their long shelf life and unpredictable use in hospitals.

The survey included all patients transfused during a single calendar month. Seasonal variation in hospital practice, and hence transfusion, may occur during a year. However recent studies of RBC use in our region showed good agreement on transfusion rates for major indications between three 14-day periods in June 1999, October 2000, and November 2001.[5,6] We therefore consider that our data are likely to be an accurate representation of transfusion practice for this population during 1994.

Information on the specialty of the treating physician at the time of the transfusion was incomplete. The available information was mostly from teaching and other large hospitals. Despite this limitation, the differences in survival by specialty were pronounced and we believe informative.

The results of our study are compared with relevant previous studies in Table 4. Vamvakas and Taswell[7,8] followed up all patients transfused during 1981 from a population of 92,006 in Olmsted County, MN. In 1994, in a similar study to ours, Whyte[9] identified patients transfused in Canterbury, New Zealand (population 341,500) during a 40-day period in 1984. These two studies found similar results to each other, documenting survival of approximately 76 to 79 percent at 12 months and 60 to 69 percent at 5 years. More recently, Tynell et al.[10] examined survival in a mixed cohort of transfused patients in Sweden, some population based and others randomly selected. Their findings for posttransfusion survival of patients and "per-component survival" of 47 percent at 40 months are remarkably similar to ours ("per-component" survival for RBCs in our study was also 47% at 40 months) despite the difference in mean age of transfused patients.

Vamvakas and Goldstein[11] have recently reported results of a lookback study at the New York University medical center for patients transfused with blood from HCV-positive donors between 1988 and 1996. Results from lookback studies at single centers may not always agree with population-based surveys. Despite these limitations, they found post-transfusion survival that was not dissimilar from those of Tynell et al.[10] or from our findings, suggesting that a reduction in posttransfusion survival compared to earlier studies is a common feature across industrialized western countries.

Other than minor qualifications, such as the low incidence of transfusion for inherited disorders of Hb, we have no reason to suppose that medical and surgical practice in our region is different than that elsewhere in the UK. Therefore, the results may be extrapolated to a wider population.

Transfusion practice has shown considerable change in recent years. Any study that reports on long-term survival after transfusion must necessarily be retrospective and the findings for a cohort of patients transfused 5 years ago may not accurately predict survival of patients transfused today. Based on the differences we have observed by recipients' sex, age, number of units transfused, use of non-RBC components, and by specialty of the treating physician, it is possible to extrapolate the likely survival of patients using knowledge of current patterns of transfusion. For example, if the age of transfusion recipients rises or there is increasing use of transfusion for medical indications, lower long-term survival after transfusion would be expected. We have recently documented that for the population studied, medical indications now account for over half of all RBC use and that the proportion of RBCs given for medical indications increases with age of the recipients.[5,6] Demographic trends predict an aging population, and, therefore, despite possible improvement in medical care and longevity, posttransfusion survival is

likely to be shorter in the future. However, caution should be exercised, because despite their independent significance in multivariate analysis, there are likely to be confounding factors linking these variables. The grouping of survival according to units received per patient (Fig. 3) in particular was unexpected, and we believe it is likely due to the number of units received for certain indications rather than any effect of blood transfusion on survival.

Our survey was carried out primarily to assess the number of transfusion recipients who survived long enough to be at risk of possible transfusion-acquired vCJD. Experimental work has shown that prion disease may be transmitted in sheep by transfusion of whole blood, taken in the preclinical stage of infection, from an animal infected orally with the bovine form of disease.[3] The incubation period of transfusion-acquired disease was similar to that for dietary acquisition in these animals. As of January 2004, there have been 146 cases of vCJD in humans in the UK. The median age at diagnosis was 26 years (cases diagnosed up to January 2001). Eight of the patients diagnosed with vCJD have been confirmed as blood donors. A lookback exercise has identified the recipients of their donations.[12] One of these recipients developed vCJD 7 years after receiving the transfusion, the donor having died 3 years after donating the blood.[4] The length of incubation of vCJD in humans may be variable and dependent on factors such as genetic susceptibility and the route of infection, but it has been estimated at 16.7 years for the presumed dietary route for patients homozygous for methionine at codon 129 of the prion protein.[13] From this information it is likely that the incubation period of possible transfusion-acquired vCJD in humans is at least 5 years and possibly similar to that of the dietary route of infection. Our figures show that 46.9 percent of patients (who received 41% of transfused RBCs and 36% of transfused FFP) were alive at 5 years, and 41.3 percent of patients (who received 36% of transfused RBCs and 29% of transfused FFP) were alive at 7 years.

Current donor selection guidelines in the UK allow for many of these recipients to donate blood 5 years after blood transfusion, which may be capable of further transmitting prion disease. It has been suggested that recipients who have become donors could act as a reservoir of self-perpetuating infection after the initial dietary risk of infection has passed. In our study, 23 percent of all transfusion recipients (who received 20% of transfused RBCs) were both alive at 5 years and eligible by age alone to donate blood. Therefore, unless many recipients become donors, the infectivity per unit is high, and each donates many units, vCJD and similar agents are unlikely to be perpetuated by transfusion.

The information we have gathered is not intended to and cannot address any specific effect of transfusion itself on survival.

CONCLUSION

We have found posttransfusion survival in our region to be shorter than documented elsewhere in previous decades. This is probably due to a combination of changing population demographics, increasing medical indications for transfusion, and lower transfusion triggers in surgical patients. Our findings may be used to predict how many recipients of blood will survive long enough to be at risk of transfusion-transmitted diseases with long incubation periods. This information may be used in assessing the cost benefit of new tests or policies applied to blood donation.

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