The effect of universal leukoreduction on postoperative infections and length of hospital stay in elective orthopedic and cardiac surgery

Charlotte A. Llewelyn, Rod S. Taylor, Audrey A.M. Todd, Warren Stevens, Mike F. Murphy, and Lorna M. Williamson for the Leucodepletion Study Group

BACKGROUND: A before and after study was undertaken to investigate the effect of universal leukoreduction (ULR) in the UK on postoperative length of hospital stay (LOS) and infections.

STUDY DESIGN AND METHODS: Consecutive patients undergoing elective coronary artery bypass grafting or total hip and/or knee replacement in 11 hospitals received non-WBC-reduced RBCs before implementation of ULR (T1, n = 997) or WBC-reduced RBCs after implementation of ULR (T2, n = 1098).

RESULTS: Patients in T1 and T2 were comparable except patients in T2 received on average more units of RBCs but had lower discharge Hct levels. Postoperative LOS (T1, 10 ± 8.9 days; T2, 9.6 ± 6.9 days) and the proportion of patients with suspected and proven postoperative infections (T1, 21.0%; T2, 20.0%) were unchanged before and after ULR (LOS, hazard ratio 1.01, 95% CI 0.92-1.10; infections, OR 0.83, 95% CI 0.77-1.02). Subgroup analysis showed no significant interaction between storage age or dose of blood on responsiveness of primary outcomes to ULR. Secondary outcomes were unchanged overall. Analysis by surgical procedure gave conflicting results with both increased mortality (p = 0.031) and an increased proportion of cardiac patients with proven infections (p = 0.004), whereas the proportion of orthopedic patients with proven infections was reduced (p = 0.002) after ULR.

CONCLUSION: Implementation of ULR had no major impact on postoperative infection or LOS in patients undergoing elective surgical procedures who received transfusion(s). Smaller effects, either detrimental or beneficial of ULR, cannot be excluded.

There is evidence that perioperative transfusion is an independent risk factor for postoperative infection in orthopedic[1-4] and cardiac[5,6] patients. This so-called immunomodulatory effect of transfusion has been attributed to donor WBCs[7] and consistent with this hypothesis is the observation that blood from which the buffy coat had been removed failed to induce beneficial immunosuppression in potential renal transplant recipients.[8] A great deal of effort has been expended in trying to establish whether removal of WBCs from blood components results in measurable reductions in postoperative infection and

ABBREVIATIONS: BC-RBC(s) = RBCs with buffy coat removal; CABG = coronary artery bypass grafting; C1 = control patients who did not receive a transfusion (1999); C2 = control patients who did not receive a transfusion (2000); LOS = postoperative length of stay; LRTI(s) = lower respiratory tract infection(s); RCT(s) = randomized controlled trial(s); T1 = patient group that received RBCs before implementation of ULR (1999); T2 = patient group that received WBC-reduced RBCs after the implementation of ULR (2000); THR(s) = total hip replacements; TKR(s) = total knee replacement(s); ULR = universal leukoreduction of blood supply by filtration before storage; UTI(s) = urinary tract infection(s).

From the National Blood Service, Cambridge and Oxford Centres, England; the University of Birmingham, Birmingham; the Scottish National Blood Transfusion Service, Edinburgh; the London School of Hygiene and Tropical Medicine, London; the University of Oxford, Oxford; and the University of Cambridge, Cambridge, UK.

Address reprint requests to: Charlotte Llewelyn, National Blood Service–Cambridge Center, Long Road, Cambridge, CB2 2PT, England, UK; e-mail: charlotte.llewelyn@nbs.nhs.uk.

This work was supported by a grant from the Department of Health and the National Blood Service.

Received for publication October 2, 2003; revision received November 27, 2003, and accepted November 28, 2003.

TRANSFUSION 2004;44:489-500.

cancer recurrence in surgical patients who received transfusion(s).[7,9-11] Other benefits associated with provision of WBC-reduced blood have been reported recently such as decreased fever[12-14] and resultant antibiotic use,[13,14] reduced RBC alloimmunization,[15] reductions in mortality and multiple organ dysfunction syndrome,[14,16] and improved clinical outcomes in premature infants.[17]

When the study described here began, randomized trials examining the effect of leukoreduction on postoperative outcomes had given conflicting results. Reduced postoperative infection rates were reported in trials of patients undergoing surgery for colorectal cancer[18-20] and cardiac bypass grafting,[21] whereas other trials in colorectal cancer patients[22-24] and in patients undergoing gastrointestinal surgery[25] failed to show any benefits.

Because hospital-acquired infection is a major predictor of postoperative stay,[26,27] some investigators have also reported cost savings in surgical patients receiving WBC-reduced RBCs attributable to shortened postoperative length of stay (LOS),[25] whereas others have not.[13] In mid-1998, a decision was taken by the Department of Health that all blood components in the UK should be leukoreduced to minimize the risk of variant CJD transmission. The planned implementation of universal leukoreduction of blood supply by filtration before storage (ULR) provided an opportunity to examine clinical outcomes in surgical patients who would not previously have received leukoreduced components. Because a randomized trial was no longer possible, we performed a prospective cohort study in patients undergoing elective cardiac or orthopedic surgery before and after ULR, to examine the effect of ULR on a large group of surgical patients who received transfusion(s). We also sought to determine whether patient treatment costs would increase after implementation of ULR owing to a combination of increased manufacturing costs and either unchanged or detrimental outcomes or, alternatively, whether ULR had the potential to be a cost-neutral intervention if costs were fully balanced by savings arising from improved outcomes. To provide large numbers of patients in each cohort who did not receive a transfusion, we chose to study patients having total hip replacement (THR) and total knee replacement (TKR) surgery, for which prestudy transfusion rates were 40 to 60 percent. To provide a more heavily transfused group, we also studied patients having coronary artery bypass grafting (CABG) surgery, where transfusion rates were greater than 80 percent. Data from patients who did not receive a transfusion in both cohorts were collected to monitor possible temporal changes in the outcomes being studied. In contrast to some previous studies,[20,21,23] patients in the "before" WBC-reduction arm were transfused with RBCs from which the buffy coat had not been removed, thus maximizing their exposure to donor WBCs.

MATERIALS AND METHODS

Study population and design

A two-cohort prospective, observational multicenter study recruiting consecutive adult patients undergoing elective cardiac (four hospitals) or orthopedic surgery (seven hospitals) was performed with ethics committee approval. Cardiac patients underwent nonemergency CABG, whether primary or redo procedures, with or without aortic or mitral valve replacement or endarterectomy. Orthopedic patients underwent elective THR or TKR, whether primary or redo operations. Bilateral procedures were included if performed during the same operation.

Data collection of Cohort 1 (before implementation of ULR) began at each site between January and May 1999 and continued until an agreed number of patients had been recruited at each hospital (approx., 5 months). Cohort 2 was studied in the same months in 2000 when all patients received leukoreduced blood. Each hospital followed its own transfusion protocols to determine when patients received transfusion(s). Data were also collected on all patients who did not receive a transfusion undergoing the same procedures during the study period for comparison.

Data collection and analysis

Data were collected by research nurses or audit staff by review of hospital notes and computer information systems after the patient's discharge. The same data collectors were used in both years, except at two sites. Data were compiled onto a database (Access 97, Microsoft) and converted to computer software (STATA V.6, StataCorp LP, College Station, TX) for analysis. Specified primary outcomes were postoperative LOS, defined as days between the operation and discharge from the acute ward (days on intensive care unit and/or high dependency unit plus orthopedic or cardiac ward) and new suspected and proven postoperative infections for which antibiotics were prescribed (excluding topical antibiotics and antibiotics given for routine operative cover or continuation of a preoperative prescription) plus local symptoms and/or signs as follows: urinary tract infections (UTIs) with two of 1) fever with no other recognized cause, 2) urgency, 3) frequency, or 4) dysuria; lower respiratory tract infections (LRTIs) with new or increased production of sputum and/or fever (>38°C) with appropriate chest signs including consolidation and/or chest X-rays showing new or progressive infiltrate; or wound infections with purulent discharge in or exuding from the wound. Bacteremia and/or septicemia were also recorded, as were infections at other sites. All infections occurring up to final discharge home (including any stay in rehabilitation) were included in the analysis, regardless of when the first transfusion was given. Infections

where a clinical decision was made not to treat with antibiotics were excluded from the analysis.

Secondary outcomes were hospital-proven postoperative infection, requiring clinical symptoms as described above leading to antibiotic prescription *plus* positive microbiology culture (except that a physician's diagnosis of pneumonia sufficed as confirmation of LRTIs) and major noninfectious postoperative complications (defined as one or more of the following: cardiac arrest, infarction, renal impairment requiring dialysis, confirmed deep vein thrombosis and/or pulmonary embolism, respiratory failure, and return to operating room for bleeding from surgical wound site). Other secondary outcomes were postoperative mortality (in hospital plus up to 90 days after discharge home), hospital readmissions, and evidence of new infections after discharge. Data on postdischarge events were collated from hospital computer systems and the patient case record and censored at 90 days.

Blood component preparation and characteristics

During 1999 (Cohort 1), UK Transfusion Services were producing both unmodified RBCs and RBCs with buffy coat removal (BC-RBCs), the latter required for PLT production. Increasing numbers of WBC-reduced RBCs were also appearing in hospital stock as the change over to ULR commenced. During Cohort 1, blood banks in participating hospitals directed RBCs to patients having the procedures under study. Patients inadvertently receiving transfusions with BC-RBCs or WBC-reduced RBCs were excluded from analysis, unless they had also received at least 2 units of unmodified RBCs. Patients undergoing previously deposited autologous blood donation were excluded. During 2000 (Cohort 2), all blood was WBC-reduced in UK Transfusion Service processing laboratories within 48 hours of collection by filtration either of whole blood (LST1, MacoPharma, Mouvaux, France; T2926, NPBI, Bad Homburg, Germany; RS2000, RZ200, Baxter, Deerfield, IL) or of BC-RBCs (R2000, Baxter; T2916, NPB1). WBC counting was performed with PI staining and flow cytometry according to manufacturers' instructions. The required specification was fewer than 5×10^6 WBCs per unit in 99 percent of units with 95 percent statistical confidence.[28] Quality monitoring was performed according to BEST guidelines[29] and showed that the specification was being met in all processing centers during the period of the study.

Statistical analysis

At 80 percent power and 5 percent significance, a sample size of 400 to 500 patients who received transfusion(s) was adequate to allow the study to detect an effect size of 0.125, where effect size = mean difference ÷ SD difference. This calculation was based on mean baseline LOS (± SD) of 6.8 ± 7.9 days for cardiac and 13.7 ± 7.6 days for orthopedic patients. Comparisons of patient characteristics for patients who received non-WBC reduced RBCs before implementation of ULR (T1) versus patients who received WBC-reduced RBCs after implementation of ULR (T2) and control patients who did not receive a transfusion in 1999 (C1) versus control patients who did not receive a transfusion in 2000 (C2) were performed by t test or chi square test. No corrections were made for multiple comparisons. Binary outcomes were analyzed by logistic regression, and time-dependent variables by Cox proportional hazards method; these were expressed as ORs or hazard ratios with 95 percent CIs, respectively. Patients who died postoperatively had their results censored in the LOS analysis. The model was adjusted for baseline characteristics (age, sex, preoperative infection rate, comorbidity, preoperative Hb level, primary procedure [or not], and center). Comorbidity was predefined as presence of one or more of the following on admission: congestive cardiac failure, coronary heart disease (for orthopedic patients only), respiratory failure, renal failure, hepatic failure, diabetes mellitus, rheumatoid arthritis, patient on steroids or other immunosuppressive drugs, hemiplegia or paraplegia, chronic mental illness, or hospitalization within the past 3 months for a medical condition. Missing values for preoperative Hb level (19/3942) were replaced by imputation. It was decided not to adjust for operation time, blood loss, cumulative drain loss, lowest postoperative Hb level, or predischarge Hb levels, given the level of missing values for these variables. The (subgroup) effect of RBC dose and storage age of blood were examined with interaction terms within the regression model to investigate the effect on the primary outcomes of RBC dose (receipt of ≥ 3 units vs. < 3 units) and storage age of blood (receipt of ≥ 3 units > 17 days old vs. < 3 units > 17 days old). Mean ward bed occupancy figures for the months of March to July between Cohort 1 and 2 were compared by the paired t test (two-tailed). Hospital costs per inpatient stay were calculated from The National Health Service Reference Costs Initiative, which is an annual comprehensive cost assessment of services across all hospitals in the UK.[30] The costs of ULR were obtained from the National Blood Service management accounts and expressed as the additional cost of WBC-reduced RBCs charged to hospitals.

RESULTS

Patient enrollment and follow-up

Eighty-eight percent (3942/4482) of patients assessed for inclusion were evaluable, of which approximately half were transfused with RBCs (Fig. 1). The exclusion rate was higher in Cohort 1 owing to patients who inadvertently received a transfusion with WBC-reduced RBCs

(184 patients, 82 at one cardiac center that received an unexpectedly high proportion of WBC-reduced RBCs in the run-up to ULR). Follow-up data to 90 days after discharge were obtained for 75 percent (2989/3942) of patients (Fig. 1). Missing follow-up data were accounted for mainly by patients attending outpatient clinics at referring hospitals, where there was no ethical approval for data collection.

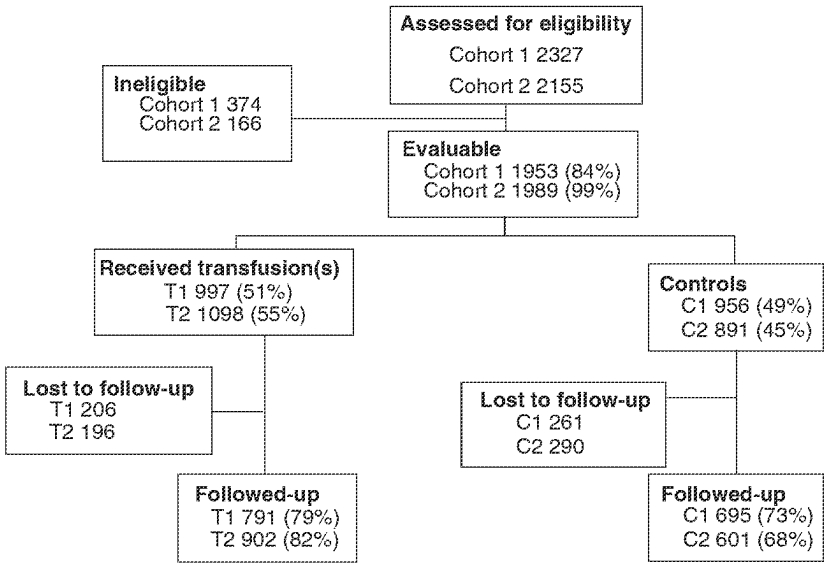

Fig. 1. Number of patients enrolled in study, number of patients evaluable, and number of patients followed up in Cohort 1 (1999) and Cohort 2 (2000), respectively.

Patient characteristics and blood and drain losses

Table 1 shows the baseline characteristics of patients enrolled in the study before and after ULR. Overall, patients in each cohort who received transfusion(s) were similar with respect to weight, age, comorbidity, and preoperative Hb levels, with the majority undergoing primary surgical procedures. More men received operations in T2 and the incidence of preoperative infections (mainly UTIs diagnosed in the preadmission clinic and treated before surgery) decreased in T2. These differences, which were adjusted for in the analysis, were attributable to orthopedic patients. Cardiac patients underwent longer operation times in T2, but this was not accompanied by changes in the

TABLE 1. Patient characteristics in the two cohorts studied before and after ULR*

	Received transfusion(s)			Did not receive transfusion		
	Before ULR (T1), n = 997	After ULR (T2), n = 1098	p value	Before ULR (C1), n = 956	After ULR (C2), n = 891	p value
Baseline characteristics						
Weight (kg)	75.1 ± 15.7	75.7 ± 14.8	0.367	79.6 ± 15.6	80.6 ± 16.0	0.195
Age (years)	68.6 ± 11.1	69.2 ± 10.2	0.172	68.0 ± 10.4	68.1 ± 10.3	0.760
Sex (male (%)	471 (47.2)	600 (54.6)	0.001	422 (44.1)	423 (47.5)	0.151
Infection (%)	65 (6.5)	45 (4.1)	0.013	29 (3.0)	32 (3.6)	0.503
Comorbidity† (%)	318 (31.8)	341 (31.1)	0.680	309 (32.3)	249 (28.0)	0.041
Hb level (g/dL)	13.2 ± 1.4	13.3 ± 1.4	0.066	13.7 ± 1.2	13.8 ± 1.2	0.306
Before and after operation						
Primary procedure (%)	842 (84.5)	959 (87.3)	0.058	896 (93.7)	857 (96.2)	0.017
Drain losses (mL)	886 ± 666	967 ± 753	0.014	663 ± 422	618 ± 409	0.026
Lowest Hb level (g/dL)	9.6 ± 1.6	9.3 ± 1.5	<0.0001	10.5 ± 1.3	10.4 ± 1.3	0.013
Discharge Hb level (g/dL)	11.0 ± 1.3	10.7 ± 1.3	<0.0001	10.8 ± 1.3	10.6 ± 1.2	0.012
Cardiac procedures						
Total number (%)	391 (39.2)	461 (42.0)		85 (8.9)	92 (10.3)	
Redos	10 (2.6)	10 (2.2)	0.709	2 (2.4)	8 (8.7)	0.068
Valve replacement (%)	40 (10.2)	46 (10.0)	0.903	2 (2.4)	5 (5.4)	0.293
Operation length (min)	215 ± 63	234 ± 69	0.001	184 ± 57	199 ± 64	0.125
Orthopedic procedures						
Total number (%)	606 (60.8)	637 (58.0)		871 (91.1)	799 (89.7)	
Redos‡	145 (23.9)	129 (20.2)	0.118	58 (6.7)	26 (3.3)	0.001
TKR (%)	194 (32.0)	242 (38.0)	0.027	443 (50.9)	408 (51.1)	0.934
Operation length (min)	135 ± 51	135 ± 56	0.786	116 ± 37	119 ± 35	0.101

* Data presented as mean ± SD or number (%) of patients.
† Patients with one or more of following conditions: coronary heart disease, congestive cardiac failure, chronic mental illness, dementia, diabetes mellitus, hemiplagia and/or paraplagia, hospitalization within past 3 months, hepatic failure, renal failure, respiratory failure, rheumatoid arthritis, on steroids and/or immunosuppressants.
‡ Includes bilateral procedures and THR plus TKR.

percentage of cardiac patients undergoing aortic and/or mitral valve replacement in addition to coronary artery grafts (Table 1) or in the proportion undergoing single versus multiple bypass grafts (data not shown). Overall, baseline characteristics did not differ in patients who did not receive a transfusion over the same time period, except for a slight rise in the proportion of patients having primary procedures and a fall in comorbidity (Table 1).

TABLE 2. Transfusion data before and after ULR*

	Before ULR (T1), n = 997	After ULR (T2), n = 1098	p value
Number of RBC units/patient	2.8 ± 1.56	3.3 ± 2.98	<0.0001
Cardiac	3.1 ± 1.8	4.0 ± 4.0	<0.0001
Orthopedic	2.7 ± 1.5	2.9 ± 2.0	0.115
Number of patients (%) receiving			
1 unit of RBCs	114 (11.4)	78 (7.1)	
2-3 units of RBCs	476 (47.7)	540 (49.2)	
>3 units of RBCs	407 (40.8)	480 (43.7)	0.003†
FFP/cryoprecipitate	84 (8.4)	108 (12.1)	0.008
PLTs	75 (7.5)	110 (12.3)	0.0004

* Mean number ± SD of RBCs or WBC-reduced RBCs (T2).
† Chi-square test for trend.

Estimated operative blood losses were not available for cardiac patients and were recorded in only 50 percent of orthopedic case notes. No difference in mean (± SD) blood loss was observed between cohorts for orthopedic patients who received transfusion(s) (T1, 938 ± 686 mL, n = 384; T2, 916 ± 753 mL, n = 380) or those who did not receive a transfusion (C1, 487 ± 413 mL, n = 377; C2, 499 ± 305 mL, n = 326). Data on cumulative postoperative drain losses were available for 90 percent of patients in each cohort. Drain losses increased in patients who received transfusion(s) and decreased in patients who did not receive a transfusion after ULR (Table 1). These findings were attributable to cardiac patients, with losses unchanged in orthopedic patients. Postoperative cell salvage from drains was undertaken at four orthopedic centers, mostly in patients not receiving RBCs and in those undergoing TKRs. The proportion of orthopedic patients receiving postoperative cell salvage from drains was 5.0 percent (30/606) in T1 and 4.4 percent (28/637) in T2, with corresponding values in controls of 14.5 percent (126/871) and 16.4 percent (146/799), respectively.

Transfusion data

Overall, 41 percent of patients in T1 received a total of 2838 units of RBCs, and 44 percent in T2 received a total of 3649 units of WBC-reduced RBCs. Transfusion rates before ULR varied between centers from 16 to 69 percent among orthopedic centers (n = 7) and from 67 to 95 percent among cardiac centers (n = 4) and remained consistent 1 year later after introduction of ULR (orthopedic center range, 26%-82%; cardiac center range, 66%-89%). The mean number of units of RBCs transfused per patient increased after ULR, owing largely to increased RBC transfusion in cardiac patients (Table 2), notably at two cardiac centers where mortality increased after ULR. Patients tended to receive more RBC units in T2, with fewer patients receiving a single RBC unit (Table 2). The timing of RBC transfusions was similar in each cohort, with 83 percent (n = 2355) of units in T1 and 82 percent (n = 2987) in T2 being given up to 24 hours from the time of surgery. The proportion of patients receiving FFP and/or cryoprecipitate rose from 8 to 12 percent after ULR, as did the proportion given PLTs (Table 2). Both patients who received transfusion(s) and patients who did not receive a transfusion exhibited a significant fall in the lowest and discharge Hb levels between cohorts (Table 1), the magnitude of which is not clinically relevant.

Primary outcomes

Postoperative LOS. Postoperative LOS values given in Table 3 (interval between operation and discharge from acute ward) do not include the interval between admission and operation which was comparable between cohorts both for patients who received transfusion(s) (T1 1.6 ± 2.2 days vs. T2 1.5 ± 2.6 days) and patients who did not receive a transfusion (C1 1.3 ± 2.7 days vs. C2 1.2 ± 2.1 days), as was LOS in intensive care unit and/or high dependency unit (data not shown). Postoperative LOS also excludes any extra period of rehabilitation care received (usually at local referring or other hospitals) before final discharge home. The proportion of patients who received additional rehabilitation did not change between cohorts (T1 23% vs. T2 23%), with LOS in rehabilitation of 9.1 ± 9.8 (n = 191) days in T1 and 8.0 ± 8.7 days (n = 221) in T2. Fewer patients who did not receive transfusion(s) received rehabilitation care in Cohort 2 (C1 16% vs. C2 11%) and LOS in rehabilitation was reduced (C1, 8.9 ± 7.7 days, n = 127; C2, 6.5 ± 7.5 days, n = 86).

Overall, there was no difference in postoperative LOS for patients who received transfusion(s) before or after ULR, with postoperative LOS for cardiac and orthopedic patients going in opposite directions (Table 3A). In cardiac patients, the increase in postoperative LOS was approximately 1 day, which just reached significance before adjustment for covariates but was not significant after adjustment. Postoperative LOS was comparable between cohorts for cardiac patients who did not receive a transfusion. In orthopedic patients, there was a significant decrease in LOS of 1.2 days after ULR, both before and after adjustment for covariates. Nevertheless, LOS also fell

TABLE 3. Comparison of primary outcomes before and after ULR in (A) patients who received transfusion(s) and (B) patients who did not receive a transfusion*

	Before ULR	After ULR	Unadjusted ratio	p value	Adjusted ratio†	p value
A. Received transfusion(s)	n = 997	n = 1098				
Postoperative LOS	10.0 ± 8.9	9.6 ± 6.9	1.05 (0.96-1.14)	0.321	1.01 (0.92-1.10)	0.905
Cardiac	7.4 ± 3.6	8.3 ± 6.4	0.87 (0.76-1.00)	0.048	0.89 (0.77-1.02)	0.089
Orthopedic	11.7 ± 10.6	10.5 ± 7.1	1.15 (1.03-1.28)	0.017	1.16 (1.04-1.30)	0.010
Postoperative infections‡	209 (21.0)	220 (20.0)	0.94 (0.76-1.17)	0.600	0.83 (0.67-1.04)	0.099
Cardiac	118 (30.2)	144 (31.2)	1.05 (0.78-1.41)	0.739	0.91 (0.67-1.23)	0.501
Orthopedic	91 (15.0)	76 (11.9)	0.77 (0.55-1.06)	0.112	0.72 (0.52-1.00)	0.056
B. Did not receive a transfusion	n = 956	n = 891				
Postoperative LOS	8.2 ± 4.1	7.8 ± 3.7	1.11 (1.02-1.22)	0.020	1.10 (1.00-1.20)	0.050
Cardiac	7.3 ± 8.3	6.6 ± 3.2	0.95 (0.70-1.28)	0.729	0.99 (0.72-1.34)	0.923
Orthopedic	8.3 ± 3.4	7.9 ± 3.8	1.12 (1.02-1.23)	0.024	1.11 (1.00-1.22)	0.042
Postoperative infections§	93 (9.7)	93 (10.4)	1.08 (0.80-1.46)	0.631	1.08 (0.80-1.46)	0.627
Cardiac	14 (16.5)	18 (19.6)	1.23 (0.57-2.66)	0.593	1.42 (0.60-3.40)	0.426
Orthopedic	79 (9.1)	75 (9.4)	1.04 (0.75-1.45)	0.823	1.03 (0.74-1.44)	0.851

* Values given are mean ± SD or number (%) of patients; with ratios expressed as hazard ratios or ORs for postoperative LOS and postoperative infections, respectively, with 95% CI in parentheses.
† Adjusted for following covariates: age, center, comorbid conditions, preoperative Hb level, preoperative infection, type of operation (primary vs. redos + bilateral procedures) and sex.
‡ Excludes 12 patients in T1 and 15 patients in T2 with clinical symptoms of infection not treated with antibiotics.
§ Excludes 5 patients in C1 and 7 patients in C2 with clinical symptoms of infection not treated with antibiotics.

significantly in orthopedic patients who did not receive a transfusion by 0.4 days (Table 3B). This raised the possibility that part or all of the shortening in LOS seen in transfused orthopedic patients may be due to factors other than ULR, such as increased pressure on beds. Nevertheless, mean monthly bed occupancy for the 27 wards contributing orthopedic patients did not differ between cohorts (data not shown).

It was assumed at the beginning of the study that patients who developed suspected and proven postoperative infections requiring antibiotic treatment would stay in hospital longer than patients who did not and that the subset of patients with microbiologically proven infections would have the longest postoperative LOS. This assumption held true both before and after ULR, in patients who received transfusion(s) and patients who did not receive a transfusion. Combining data for all evaluable patients (n = 3942) gave mean (± SD) postoperative LOS values of 8.3 ± 4.8, 12.4 ± 11.2, and 17.8 ± 15.3 days for patients with no infections, suspected and proven infections treated with antibiotics, and proven postoperative infections, respectively.

New suspected and proven postoperative infections. A total of 235 suspected and proven infections were recorded in 209 patients in T1 compared to 254 infections in 220 patients in T2. Thirteen percent (28/209) of these patients in T1 and 12 percent (27/220) in T2 had infection(s) before receipt of the first transfusion. These were not excluded from the analysis. Suspected and proven infections occurring within 24 hours of surgery (T1, n = 50; T2, n = 55) may not have been influenced by perioperative transfusion. Excluding these would not have altered the conclusions. Overall, the proportion of patients who received transfusion(s) with new suspected and proven postoperative infections treated with antibiotics did not differ before or after ULR (Table 3A). Patients who did not receive a transfusion showed no change in postoperative infection rate between cohorts, either overall or when data were analyzed by surgical procedure (Table 3B).

When analyzed by procedure, suspected and proven infection rates in cardiac patients were unchanged (approx., 30%) but in orthopedic patients declined from 15 to 11 percent (adjusted OR, 0.72; 95% CI, 0.52-1.00; p = 0.056). Table 4 lists all new suspected and proven postoperative infections by site. A total of 11.5 percent (24/209) of patients in T1 and 12.2 percent (27/220) of patients in T2 had infections at more than one site. In cardiac patients, there was a doubling in the proportion with bacteremia and/or septicemia, surgical wound infections, and infections at other sites (not LRTI or UTI) after ULR. Orthopedic patients showed a small decrease in surgical wound infections, with no marked change in infections at other sites. Patients in both cohorts who did not receive a transfusion had similar rates of infections at all sites (Table 4).

Effect of dose of blood or storage age on primary outcomes before and after ULR. Subgroup analysis showed no interaction between either dose of blood or storage age on responsiveness of primary outcomes to ULR (Table 5).

Secondary outcomes

Mortality. There was no significant difference between cohorts in overall mortality to 90 days after discharge in patients who received transfusion(s). Death rate

TABLE 4. Site of new suspected and proven postoperative infections for which antibiotics were prescribed before and after ULR in patients who received transfusion(s) and patients who did not receive a transfusion*

	Received transfusion(s)		Did not receive a transfusion	
	Before ULR (T1), n = 997	After ULR (T2), n = 1098	Before ULR (C1), n = 956	After ULR (C2), n = 891
Surgical wound	59 (5.9)	63 (5.7)	34 (3.6)	26 (2.9)
Cardiac	16 (4.1)	31 (6.7)	3 (3.5)	4 (4.3)
Orthopedic	43 (7.1)	32 (5.0)	31 (3.6)	22 (2.8)
Lower respiratory tract	117 (11.7)	123 (11.2)	32 (3.3)	34 (3.8)
Cardiac	96 (24.6)	97 (21.0)	12 (14.1)	12 (13.0)
Orthopedic	21 (3.5)	26 (4.1)	20 (2.3)	22 (2.8)
Urinary tract	28 (2.8)	23 (2.1)	19 (2.0)	28 (3.1)
Cardiac	6 (1.5)	8 (1.7)		2 (2.2)
Orthopedic	22 (3.6)	16 (2.5)	19 (2.0)	26 (3.3)
Bacteremia/septicemia	5 (0.5)	10 (0.9)	5 (0.5)	
Cardiac	2 (0.5)	9 (2.0)	1 (1.2)	
Orthopedic	3 (0.5)	1 (0.2)	4 (0.5)	
Other site†	26 (2.6)	34 (3.1)	13 (1.4)	14 (1.6)
Cardiac	9 (2.3)	21 (4.6)		1 (1.1)
Orthopedic	17 (2.8)	13 (2.0)	13 (1.5)	13 (1.6)

* Data presented as total number of infections, with percentage infected patients shown in parentheses.
† Includes IV access sites, gastrointestinal tract, cellulitis, subacute bacterial endocarditis, pericarditis, ear, mouth, nonsurgical wounds, and pyrexia of unknown origin where treated with antibiotics.

TABLE 5. Subgroup analysis of storage age and dose of blood on primary outcomes before and after ULR

	Before ULR (T1), n = 997	After ULR (T2), n = 1098	OR/HR* (95% CI)	p value
Postoperative infections†				
Dose of blood				
≥3 units	123/407 (30.2%)	122/480 (25.4%)	0.79 (0.59-1.06)	0.111
<3 units	86/590 (14.6%)	98/618 (15.9%)	1.10 (0.81-1.51)	0.536
Age of blood				
≥3 units ≥ 17 days old	44/188 (23.4%)	52/192 (27.1%)	1.21 (0.76-1.93)	0.410
<3 units ≥ 17 days old	165/809 (20.4%)	168/906 (18.5%)	0.89 (0.70-1.14)	0.359
Postoperative LOS‡				
Dose of blood				
≥3 units	11.03 ± 10.33	10.06 ± 6.77	1.06 (0.93-1.21)	0.411
<3 units	9.28 ± 7.61	9.18 ± 7.01	1.05 (0.94-1.18)	0.396
Age of blood				
≥3 units ≥ 17 days old	12.16 ± 12.87	10.59 ± 7.17	1.08 (0.86-1.33)	0.427
<3 units ≥ 17 days old	9.49 ± 7.55	9.34 ± 6.86	1.02 (0.93-1.12)	0.588

* OR = OR for postoperative infections; HR = hazard ratio for LOS. Values given are unadjusted for covariates.
† Values given are numbers of patients with suspected and proven postoperative infections/total number transfused (%): p = 0.073 and p = 0.371, respectively, for interaction of dose and storage age of RBCs on postoperative infections.
‡ Values given are means ± SD: p = 0.912 and p = 0.598, respectively, for interaction of dose and storage age on LOS.

was unchanged in orthopedic patients, but increased in cardiac patients after ULR (Table 6A) with the majority of cardiac deaths (16/18) in Cohort 2 occurring at two cardiac centers that recorded concomitant rises in proven postoperative infections (T1, 5%; T2, 20%) and the number of patients returned to the operating room for bleeding (T1, 4.4%; T2, 12.6%), respectively. All cardiac deaths owing to infection were recorded in Cohort 2 at the two centers where mortality rose.

The results of this analysis do not take into account losses to follow-up, but because 84 percent (31/37) of deaths occurred in the hospital, it has been assumed that all patients lost to follow-up were still alive at 90 days. A sensitivity analysis was carried out in which all patients without follow-up data were presumed dead at 90 days. This had the effect of changing the mortality data from a nonsignificant increase in Cohort 2 to a nonsignificant reduction. Mortality rates did not differ between cohorts in patients who did not receive a transfusion (Table 6B).

Proven postoperative infections. There was no overall difference in proven postoperative infections in patients who received transfusion(s) before or after ULR, with changes in cardiac and orthopedic patients of roughly equal magnitude but in opposite directions (Table

TABLE 6. Secondary outcomes before and after ULR in (A) patients who received transfusion(s) and (B) patients who did not receive transfusion*

	Before ULR	After ULR	Unadjusted OR† (95% CI)	p value	Adjusted OR† (95% CI)	p value
A. Received transfusion(s)	n = 997	n = 1098				
Proven infections‡	69 (6.9)	75 (6.8)	0.99 (0.70-1.38)	0.935	0.92 (0.65-1.29)	0.617
Cardiac	19 (4.9)	49 (10.6)	2.32 (1.34-4.03)	0.002	2.27 (1.30-3.94)	0.004
Orthopedic	50 (8.3)	26 (4.1)	0.47 (0.29-0.77)	0.003	0.45 (0.28-0.74)	0.002
Major complications§	83 (8.3)	106 (9.7)	1.17 (0.87-1.59)	0.289	1.07 (0.40-1.52)	0.478
Cardiac	43 (10.9)	67 (14.5)	1.38 (0.91-2.07)	0.126	1.33 (0.87-2.03)	0.179
Orthopedic	40 (6.6)	39 (6.1)	0.92 (0.58-1.46)	0.730	0.86 (0.54-1.38)	0.542
Mortality¶	12 (1.2)	25 (2.2)	1.82 (0.91-3.65)	0.088	1.74 (0.86-3.52)	0.124
Cardiac	5 (1.3)	18 (3.9)	3.08 (1.14-8.29)	0.026	3.05 (1.11-8.37)	0.031
Orthopedic	7 (1.2)	7 (1.1)	0.82 (0.28-2.43)	0.716	0.85 (0.28-2.61)	0.775
Readmissions¶	86 (8.6)	81 (7.4)	0.84 (0.61-1.16)	0.292	0.84 (0.61-1.16)	0.286
Cardiac	40 (11.6)	32 (8.2)	0.65 (0.40-1.06)	0.087	0.64 (0.39-1.06)	0.085
Orthopedic	46 (10.3)	49 (9.6)	1.10 (0.67-1.54)	0.946	1.03 (0.67-1.58)	0.891
Post-discharge infections¶	28 (2.8)	29 (2.6)	0.93 (0.56-1.59)	0.814	0.96 (0.56-1.63)	0.869
Cardiac	14 (4.0)	10 (2.6)	0.60 (0.27-1.35)	0.216	0.78 (0.33-1.83)	0.569
Orthopedic	14 (3.1)	19 (3.7)	1.30 (0.65-2.61)	0.735	1.31 (0.64-2.69)	0.755
B. Did not receive transfusion	n = 956	n = 891				
Proven infections‡	25 (2.6)	32 (3.6)	1.39 (0.82-2.36)	0.227	1.42 (0.83-2.40)	0.199
Cardiac	4 (4.7)	3 (3.3)	0.68 (0.15-3.14)	0.624	0.52 (0.10-2.77)	0.444
Orthopedic	21 (2.4)	29 (3.6)	1.52 (0.86-2.70)	0.147	1.55 (0.87-2.80)	0.136
Major complications§	38 (4.0)	17 (1.9)	0.47 (0.26 -0.84)	0.011	0.45 (0.25-0.80)	0.007
Cardiac	4 (4.7)	2 (2.2)	0.45 (0.08-2.52)	0.364	0.36 (0.05-2.30)	0.284
Orthopedic	34 (3.9)	15 (1.9)	0.47 (0.25-0.87)	0.016	0.44 (0.24-0.82)	0.010
Mortality¶	5 (0.5)	4 (0.4)	0.86 (0.23-3.19)	0.819	0.85 (0.23-3.19)	0.810
Cardiac	0 (0)	1 (1.1)	—	—	—	—
Orthopedic	5 (0.6)	3 (0.4)	0.65 (0.16-2.73)	0.560	0.66 (0.16-2.79)	0.574
Readmissions¶	46 (4.8)	44 (4.9)	1.03 (0.67-1.57)	0.126	1.06 (0.69-1.62)	0.799
Cardiac	8 (10.1)	8 (9.1)	0.93 (0.35-2.48)	0.884	1.11 (0.67-3.37)	0.849
Orthopedic	38 (6.2)	36 (6.9)	1.05 (0.67-1.67)	0.823	1.09 (0.68-1.74)	0.730
Post-discharge infections¶	26 (2.7)	17 (1.9)	0.70 (0.37-1.29)	0.250	0.69 (0.37-1.28)	0.240
Cardiac	6 (7.5)	2 (2.5)	0.30 (0.06-1.49)	0.141	0.34 (0.06-1.92)	0.222
Orthopedic	20 (3.2)	15 (2.9)	0.81 (0.42-1.59)	0.545	0.85 (0.43-1.68)	0.632

* Data presented as number (%) of patients.
† Values are ORs except for mortality data, which is given as hazard ratios, adjusted for following covariates: age, center, comorbid conditions, preoperative Hb level, preoperative infection, type of operation (primary vs. redos plus bilateral procedures), and sex.
‡ Defined as antibiotic prescription plus clinical symptoms and microbiologic or other confirmatory evidence.
§ Defined as cardiac arrest, infarction, renal impairment requiring dialysis, return to operating room for bleeding, confirmed deep vein thrombosis, or pulmonary embolism.
¶ Censored at 90 days after discharge; figure not adjusted for losses to follow-up (see Fig. 1).

6A). Proven infections increased significantly from 5 to 11 percent in cardiac patients and in orthopedic patients decreased significantly from 8 to 4 percent, levels comparable with orthopedic patients who did receive a transfusion. These findings were significant before and after adjustment for confounding variables (Table 6A). In contrast, no changes in proven infections were observed in either cardiac or orthopedic patients who did not receive a transfusion over the same time period (Table 6B).

Major postoperative complications. No changes in major postoperative complications were observed in patients who received transfusions after ULR, either overall or when the results for orthopedic and cardiac patients were analyzed separately (Table 6A). Nevertheless, in patients who did not receive a transfusion, major postoperative complications decreased significantly after ULR, both before and after adjustment for confounding variables (Table 6B). This effect was confined to orthopedic patients, and may explain the concomitant shortening of LOS (Table 3B).

Readmissions and infections after discharge. There was no change between cohorts in readmissions or evidence of infections within the 90 days after final discharge home in either patients who received transfusion(s) or patients who did not receive a transfusion (Table 6A and 6B).

Cost implications of ULR

With 2001 UK prices (and a pounds to dollars conversion of 1.5) a unit of WBC-reduced RBCs cost $128, of which $40 per unit was added to cover the additional costs of leukoreduction (NBS data). Patients who received transfusion(s) after ULR also received on average an extra 0.5 unit per patient, leading to a total additional cost of $176 per patient. No reduction in postoperative LOS or suspected

and proven postoperative infections was observed after ULR, so there were no hospital cost savings to offset against the increased costs. Overall, ULR has therefore resulted in slightly increased costs in this group of surgical patients who received transfusion(s). Given the conflicting findings between cardiac and orthopedic patients, the additional cost of providing WBC-reduced RBCs to cardiac patients may be higher than estimated above, whereas for orthopedic patients implementation of ULR may have resulted in savings, given mean estimated inpatient costs per day for acute orthopedic wards across the UK in 1999/2000 of $518.[30]

DISCUSSION

This study showed that implementation of ULR in the UK did not appear to be associated with demonstrable benefits on either LOS or new postoperative infections in patients undergoing two elective surgical procedures (CABG and THR and/or TKR), which together account for a high proportion of surgical blood usage in the UK.[31] Our results for these primary outcomes are consistent with three cardiac randomized controlled trials (RCTs),[12,16,21] a randomized trial of ULR for all hospital patients,[13] and two other observational studies carried out before and after implementation of ULR programs in Canada[14] and France.[32] We used non-buffy-coat-reduced RBCs in the "before" arm to maximize the difference in WBC exposure between patients who received transfusion(s) before and after ULR, as did three other studies,[12-14] but took no account of timing of postoperative infection in relation to transfusion. A meta-analysis of RCT found no overall benefit of leukoreduction on postoperative infection rates, except when studies with BC-RBCs as a control were excluded.[11] The results of our study and others[12-14] suggest no clear benefit from implementation of ULR for decreasing postoperative infections and LOS.

After implementation of ULR, patients received slightly more units overall but had lower discharge Hct levels. Part of this may relate to the study design, in which patients in the before arm were allocated buffy-coat-replete RBCs, containing approximately 30 mL more RBCs than BC-RBCs. Nevertheless, the loss of RBCs during the leukoreduction manufacturing process may also have contributed to these results. Neither the difference in RBC exposure (increase of 0.5 units) nor the difference in postoperative Hb level (decrease of 0.3 g/dL for lowest and discharge Hb values) after ULR is likely to be clinically relevant.

Both the presence of WBCs and the secretion of adverse factors into solution during storage are postulated to play a role in mediating the so-called "TRIM" effect.[33,34] We hypothesized that the impact of ULR would be greatest for patients receiving a higher number of units and/or those exposed to RBCs with prolonged storage times, but found no interaction between either of these variables on primary outcomes in response to ULR. In a recent study of 897 cardiac patients, prolonged storage of RBCs did not increase morbidity outcomes, including LOS in intensive care unit and severe postoperative infection rates.[35] In our study, infection rates in patients receiving at least 3 units were reduced from 30 to 25 percent by ULR, but remained unchanged at approximately 15 percent before and after ULR in patients receiving fewer than 3 units. Van de Watering et al.[21] also observed no overall effect of ULR on postoperative infections or LOS in CABG patients, but found that infections were reduced from 31 to 24 percent in patients receiving more than 3 units. In a subsequent RCT of CABG patients also undergoing valve replacement, who have higher transfusion requirements, infection rates were 31 percent in the arm given BC-reduced RBCs and 22 percent in the WBC-reduced arm.[16] These results suggest that any effect of ULR in reducing postoperative infections may be restricted to patients given at least 3 units blood.

In agreement with some[12,13] but not all studies[14,16,21] and a meta-analysis[36] we saw no reduction in mortality after implementation of ULR in the UK, with overall mortality of 1.2 and 2.2 percent before and after ULR. This nonhomogenous rise in mortality was not significant after adjustment for confounding variables. Our conclusion that overall mortality, readmission rates, and infections after discharge were unchanged following ULR ignores the 20 percent loss of patients to follow-up. A sensitivity analysis in which these patients were all treated as dead at 90 days did not alter the conclusions. Mortality was unchanged in orthopedic patients but rose in cardiac patients from 1.3 to 3.9 percent after ULR. Although significant, these values lie within the 99 percent CIs for crude mortality rates in patients undergoing isolated CABG procedures at the four cardiac centers during the entire study period (1999-2001).[37] Our study was not powered around mortality unlike the Canadian study in which it was concluded that ULR was potentially associated with decreased mortality.[14] This was based on an analysis of the results in which patients who died within 48 hours of surgery were excluded, resulting in a fall in mortality from 7.0 to 6.2 percent before and after ULR.[14] When these patients were included no difference in adjusted mortality was found, as in our study.

An unexpected finding of our study was the conflicting results between cardiac and orthopedic patients, with beneficial effects on hospital stay, antibiotic prescription and proven infection in THR and/or TKR, and adverse effects in CABG patients. These contradictory findings were not explained by major changes in patient characteristics or transfusion rates, which were broadly comparable between cohorts and may have arisen by chance. Because of the before versus after study design data collectors could not be blinded to the use of WBC-reduced RBCs, so

our study is subject to observer bias. We tried to minimize observer bias by choosing relatively hard endpoints, such as postoperative LOS on acute ward, which is not open to differences in interpretation. Nevertheless, LOS can be affected by variables such as early mortality and changing hospital policies. Predefined criteria were used in advance to define suspected and proven infections, which had to be accompanied by therapeutic administration of antibiotics. We did not restrict our definition of postoperative infections to serious nosocomial infections or exclude UTIs as in some other studies.[12,14] It has been suggested that inclusion of UTIs could bias the results unless adjustment is made for number of days with indwelling urinary catheters.[38] Nevertheless, we observed no differences between cohorts in the proportion of patients with urinary catheters or with UTIs. Temporal trends may be an important source of bias in any observational study, as observed in a previous study in which a fall in LOS after WBC-reduced RBCs were provided for CABG patients continued after the policy was abandoned.[39] We therefore included patients who did not receive a transfusion undergoing the same surgical procedures for comparison. Cardiac patients who did receive a transfusion showed no changes in primary outcomes before and after implementation of ULR. In orthopedic patients who did not receive a transfusion, however, postoperative LOS decreased by 0.4 days in Cohort 2, without any change in infection rates. Thus the apparent beneficial effect of ULR seen in orthopedic patients who did receive transfusion(s) may also be due to unexplained factors and should be treated with caution. There have been no previous clinical trials of leukoreduction in orthopedic patients with the same endpoints. Although in the study by Dzik et al.[13] subanalyses were performed on certain patient groups, orthopedic patients were not studied separately; likewise, the Canadian study[14] included hip fractures, but not patients having elective THR and/or TKRs. Future RCTs in orthopedic patients would be necessary to investigate the effect of ULR on LOS and postoperative infection rates in these patients. The increase in proven infections and mortality observed in cardiac patients who received transfusion(s) in Cohort 2 might be due to a detrimental effect of ULR, although an alternative explanation is that patients had more difficult operations in Cohort 2, as indicated by the increased operation times and postoperative drain losses. Two cardiac centers were responsible for the rise in mortality after ULR: at one, patients were accommodated in temporary wards during refurbishment of the cardiac wards, and at the other, more patients required repeat thoracotomy for bleeding in Cohort 2. No other factors were identified by investigators at these two centers, which could account for the rise in mortality.

In summary, our study showed that, as in Canada[14] and France,[32] the introduction of ULR in the UK did not result in any significant improvement in postoperative LOS or infections among a large group of patients undergoing elective orthopedic or cardiac surgery who received transfusion(s). Secondary outcomes showed significant differences in the proportion of patients with proven infection, with conflicting results for cardiac versus orthopedic patients. The possibility cannot be ruled out that ULR may have small detrimental effects in cardiac patients and beneficial effects in orthopedic patients. Subgroup analysis failed to demonstrate a significant effect of storage age or dose of blood transfused on primary outcomes. Economic savings were not demonstrated, because increased manufacturing costs of providing WBC-reduced RBCs were not offset by savings in hospital costs, and patients required on average more WBC-reduced RBCs after implementation of ULR.

ACKNOWLEDGMENTS

The Leucocyte Depletion Study Group consisted of Mike Murphy, MD, and Lorna Williamson, MD (principal Investigators); Charlotte Llewelyn, MD (study/data manager); Rod Taylor, PhD (statistician); Warren Stevens, PhD (economic health analyst); John Burman, MD, Chris Constant, Simon Donell, Sarah Green, Ian Lowden, John Newman, Dr John Parker Williams, Dr Jennie Wimperis, Mike Shanaghan, Dr Nuala Simpson, and Audrey Todd, MD (investigators); and B. Allan, Avril Cairns, Karen Campbell, Joan Cannon, Rachel Evans, M. Jheeta, Caroline Lewis, Sarah Loftus, Jane Lushey, Shauna Masters, Kate O'Grady, Joyce Palmer, Dr Diego Perez, Liz Pirie, Sue Rhodes, Des Robson, and Dr Marcelo Shibata (data collectors). In addition, we are grateful to all the surgeons, hematologists, and blood bank staff at the participating hospitals for their support, to Mary Bailie for assistance with data entry, and to Professor Jean-Pierre Allain, University of Cambridge, for constructive comments on the manuscript.

REFERENCES

1. Triulzi DJ, Vanek K, Ryan DH, et al. A clinical and immunologic study of blood transfusion and postoperative bacterial infection in spinal surgery. Transfusion 1992;32: 517-24.
2. Murphy P, Heal JM, Blumberg N, et al. Infection or suspected infection after hip replacement surgery with autologous or homologous blood transfusions. Transfusion 1991;31:212-7.
3. Innerhofer P, Walleczek GL, Luz G, et al. Transfusion of buffy-coat depleted blood components and risk of postoperative infection in orthopedic patients. Transfusion 1999;39:625-32.
4. Carson JL, Altman DG, Duff A, et al. Risk of bacterial infection associated with allogeneic blood transfusion among patients undergoing hip fracture repair. Transfusion 1999;39:694-700.
5. Ottino G, De Paulis R, Pansini S, et al. Major sternal wound infection after open-heart surgery: a multivariate analysis of

risk factors in 2,579 consecutive operative procedures. Ann Thorac Surg 1987;44:173-9.
6. Murphy PJ, Connery C, Hicks GL, et al. Homologous blood transfusion as a risk factor for postoperative infection after coronary artery bypass graft operations. J Thorac Cardiovasc Surg 1992;104:1092-9.
7. Vamvakas EC, Blajchman MA. Deleterious clinical effects of transfusion-associated immunomodulation: fact or fiction? Blood 2001;97:1180-95.
8. Van Prooijen HC, Aarts-Riemens MI, van Oostendorp WR, et al. Prevention of donor-specific T-cell unresponsiveness after buffy-coat-depleted blood transfusion. Br J Haematol 1995;91:219-23.
9. Vamvakas EC. Perioperative blood transfusion and cancer recurrence: meta-analysis for explanation. Transfusion 1995;35:760-8.
10. Vamvakas EC. Transfusion-associated cancer recurrence and postoperative infection: meta-analysis of randomized, controlled clinical trials. Transfusion 1996;36:175-86.
11. Vamvakas EC. Meta-analysis of randomized controlled trials investigating the risk of postoperative infection in association with white blood cell-containing allogeneic blood transfusion: the effects of the type of transfused red blood cell product and surgical setting. Transfus Med Rev 2002; 16:304-14.
12. Wallis JP, Chapman CE, Orr KE, et al. Effect of WBC reduction of transfused RBCs on postoperative infection rates in cardiac surgery. Transfusion 2002;42:1127-34.
13. Dzik WH, Anderson JK, O'Neill EM, et al. A prospective, randomized clinical trial of universal WBC reduction. Transfusion 2002;42:1114-22.
14. Hébert PC, Fergusson D, Blajchman MA, et al. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. JAMA 2003;289:1941-9.
15. Blumberg N, Heal JM, Gettings KF. WBC reduction of RBC transfusions is associated with a decreased incidence of RBC alloimmunization. Transfusion 2003;43:945-52.
16. Bilgin YM, van de Watering LMG, Lorinser JE, et al. The effects of prestorage leukocyte-depletion of erythrocyte concentrates in cardiac surgery: a double-blind randomized clinical trial (abstract). Blood 2001;98(Suppl):828a-9a.
17. Fergusson D, Hébert PC, Lee SK, et al. Clinical outcomes following institution of universal leukoreduction of blood transfusions for premature infants. JAMA 2003;289: 1950-6.
18. Jensen LS, Andersen AJ, Christiansen PM, et al. Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colorectal surgery. Br J Surg 1992;79:513-6.
19. Heiss MM, Mempel W, Jauch KW, et al. Beneficial effect of autologous blood transfusion on infectious complications after colorectal cancer surgery. Lancet 1993;342:1328-33.
20. Jensen LS, Kissmeyer-Nielsen P, Wolff B, et al. Randomised comparison of leucocyte-depleted versus buffy-coat poor blood transfusion and complications after colorectal surgery. Lancet 1996;348:841-5.
21. Van de Watering LM, Hermans J, Houbiers JG, et al. Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery: a randomized clinical trial. Circulation 1998;97: 562-8.
22. Busch OR, Hop WC, Hoynck van Papendrecht MA, et al. Blood transfusions and prognosis in colorectal cancer. N Engl J Med 1993;328:1372-6.
23. Houbiers JG, Brand A, van de Watering LM, et al. Randomised controlled trial comparing transfusion of leucocyte-depleted or buffy-coat-depleted blood in surgery for colorectal cancer. Lancet 1994;344:573-8.
24. Titlestad IL, Ebbesen LS, Ainsworth AP, et al. Leukocyte-depletion of blood components does not significantly reduce the risk of infectious complications: results of a double-blinded, randomized study. Int J Colorectal Dis 2001;16:147-53.
25. Tartter PI, Mohandas K, Azar P, et al. Randomized trial comparing packed red cell blood transfusion with and without leukocyte depletion for gastrointestinal surgery. Am J Surg 1998;176:462-6.
26. Whitehouse JD, Friedman ND, Kirkland KB, et al. The impact of surgical-site infections following orthopedic surgery at a community hospital and a university hospital: adverse quality of life, excess length of stay, and extra cost. Infect Control Hosp Epidemiol 2002;23:183-9.
27. Orsi GB, Di Stefano L, Noah N. Hospital-acquired, laboratory-confirmed bloodstream infection: increased hospital stay and direct costs. Infect Control Hosp Epidemiol 2002;23:190-7.
28. Guidelines on the clinical use of leucocyte-depleted blood components. British Committee for Standards in Haematology, Blood Transfusion Task Force. Transfus Med 1998;8: 59-71.
29. Dumont LJ, Dzik WH, Rebulla P, Brandwein H. Practical guidelines for process validation and process control of white cell-reduced blood components: report of the Biomedical Excellence for Safer Transfusion (BEST) Working Party of the International Society of Blood Transfusion (ISBT). Transfusion 1996;36:11-20.
30. Reference Costs 2000 (Internet). London: The Department of Health; c2000. Available from: http://www.doh.gov.uk/nhsexec/refcosts/refcosts2000.pdf.
31. Llewelyn CA, Amin M, Ballard S, et al. Transfusion medicine epidemiology pilot survey (abstract). Br J Haematol 2002; 117(Suppl):77.
32. Baron JF, Gourdin M, Bertrand M, et al. The effect of universal leukodepletion of packed red blood cells on postoperative infections in high-risk patients undergoing abdominal aortic surgery. Anesth Analg 2002;94: 529-37.
33. Vamvakas EC, Carven JH. Exposure to allogeneic plasma and risk of postoperative pneumonia and/or wound infection in

coronary artery bypass graft surgery. Transfusion 2002; 42:107-13.
34. Klein HG. Getting older is not necessarily getting better. Anesthesiology 2003;98:807-8.
35. Leal-Noval SR, Jara-López I, Garcia-Garmendia JL, et al. Influence of erythrocyte concentrate storage time on postsurgical morbidity in cardiac surgery patients. Anesethesiology 2003;98:815-22.
36. Vamvakas EC. WBC-containing allogeneic blood transfusion and mortality: a meta-analysis of randomized controlled trials. Transfusion 2003;43:963-73.
37. Keogh BE, Kinsman R. Compilers. National adult cardiac surgical database report 2000-2001. London: The Society of Cardiothoracic Surgeons of Great Britain and Ireland and Dendrite Clinical Systems; 2002.
38. Vamvakas EC. Transfusion of buffy-coat-depleted blood components and risk of postoperative infection in orthopedic patients. Transfusion 2000;40:381.
39. Volkova N, Klapper E, Pepkowitz SH, et al. A case-control study of the impact of WBC reduction on the cost of hospital care for patients undergoing coronary artery bypass graft surgery. Transfusion 2002;42:1123-6.