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實 EVIDENCE 証

Hospital Authority Head Office
Medical Services Development Division

Clinical Effectiveness Unit
Issue No. 10, 2000

TRANSFUSION THRESHOLD, AUTOLOGOUS TRANSFUSION & RISKS of IMMUNOMODULATION in ALLOGENEIC TRANSFUSION

Invited commentary from Dr HW Liu, Consultant (Haematopathology), Hospital Authority

Blood and blood derived products, like all other therapeutic agents, are not completely safe. Their risks have been very much reduced in recent years as a result of improvements in donor screening and regulatory standards enforced upon the blood establishments and fractionation industry. Nevertheless, heightened awareness of the problems of disease transmission, particularly of the human immunodeficiency virus (HIV), hepatitis C virus (HCV) and possibly transmissible spongiform encephelopathy (TSE), and adverse reactions and immunomodulation associated with transfusion has seriously tainted the public confidence in blood and its products. The traditional belief that allogeneic blood is an effective and safe therapy with minimal risk is no longer convincing.

Considering the associated risks, the escalating cost and our capacity to maintain an adequate supply of blood and its products for an ever-expanding aging patient load, it becomes obvious that blood must be used even more judiciously than before. It is both necessary and desirable for the healthcare providers to regard conservation as an integral part of a comprehensive transfusion program. It would appear to be self-evident that elective allogeneic blood transfusion should be avoided as far as practicable, but one has yet to define the appropriate use of blood in different clinical settings. Until recently, there were scanty randomised controlled trials (RCTs) on the use of blood and the different **AUTOLOGOUS TRANSFUSION** strategies, namely preoperative autologous blood deposit (PABD), acute normovolaemic haemodilution (ANH) & intraoperative cell salvage (ICS).

It is surprising to note that the use of such a commonly prescribed "drug" - blood and its products - are more influenced by conventional practice, originating from level III/IV evidence (observational studies & expert committee reports or opinions) than by good evidence based on clinical trials (ideally, RCTs). Our lack of understanding in blood usage prevented an evidence-based approach in transfusion medicine. Doctors are prone to swing back and forth between over-usage and avoidance, without the assurance of anchorage provided by robust evidence.

This issue of " 實 **EVIDENCE** 証 " has put forth some very exciting evidence that helps to put us in better perspectives. The paper by Hebert PC, et al. demonstrated that it is feasible to study different transfusion strategies by means of a RCT and its results compel us to rethink about the **TRANSFUSION THRESHOLD**. Similarly, recently published level I evidence on effects of **IMMUNOMODULATION in ALLOGENEIC TRANSFUSION** (cancer recurrence, postoperative infection) produced results at variance to earlier claims from lower level of evidence. In the case of cell salvage, it seems to depend on the type of surgery performed. Perhaps it is still too early to refute our traditional practice and guidelines but the recently available high level evidence should certainly compel us to rethink the basis of our actions. I believe it is the right direction to study transfusion practices and blood conservation techniques by means of RCT. In the Hospital Authority, with our annual red cells/whole blood transfusion rate exceeding 160,000 U, we can contribute much to the scientific knowledge bases on this important subject in the future.

[***Editorial Note:*** An expert panel will be convened to put the evidence in HA context, and to identify appropriate actions to benefit our patients. Look out for "**實 EVIDENCE 証 in CONTEXT**" on '**TRANSFUSION THRESHOLD, AUTOLOGOUS TRANSFUSION & RISKS of IMMUNOMODULATION in ALLOGENEIC TRANSFUSION**'.]

▪ Transfusion threshold

A prospective multicenter randomised controlled trial of transfusion requirements in critical care compared different transfusion strategies. The restrictive strategy resulted in less transfusion, both in the total amount of blood received and the number of patients requiring transfusion.

Transfusion strategy	Transfusion threshold (g/dl)	Target range Hb (g/dl)	Mean Hb (g/dl)	Actual blood transfused (U)	Patients without transfusion (%)
Restrictive	≤ 7.0	7.0 to 9.0	8.5 ± 0.7	2.6 ± 4.1	33%
Liberal	≤ 10.0	10.0 to 12.0	10.7 ± 0.7	5.6 ± 5.3	0%

There is no statistical difference in the 30-day mortality (primary outcome indicator) between the 2 groups:

	Restrictive (n = 418)	Liberal (n = 420)	Absolute difference	95% CI	p value
All patients	18.7%	23.3%	4.7%	-0.84% to 10.2%	0.11

Subsequent subgroup analysis revealed that the restrictive transfusion strategy was associated with significant reductions in 30-day mortality in patients < 55 yrs of age and/or less acutely ill:

	Restrictive	Liberal	Absolute difference	95% CI	p value
Patients with clinically significant cardiac disease	20.5% (n = 207)	22.9% (n = 217)	2.4%	-6.7% to 11.3%	0.69
Less acutely ill patients (acute physiology and chronic health evaluation II score of ≤ 20)*	8.7% (n = 137)	16.1% (n = 161)	7.4%	1.0% to 13.6%	0.03
Patients < 55 years*	5.7% (n = 137)	13.0% (n = 161)	7.3%	1.1% to 13.5%	0.02

*No significant difference in baseline characteristics

[Source: Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Eng J Med 1999 Feb 11;340(6):409-17].

[***Editorial note***: Notwithstanding the limited validity of sub-group analysis, the statistically significant difference in 30-day mortality between liberal and restrictive transfusion strategy in younger or less acutely ill patients deserve further study. From the study observation, the NNT to avoid one death is only 13 for a restrictive strategy, or conversely, the NNH for one more death is also 13 for a liberal strategy. We shall pursue this in our "實 **EVIDENCE** 証 in CONTEXT".]

▪ Preoperative Autologous Blood Deposit (PABD)

The Royal College of Physicians of Edinburgh's conference on autologous transfusion (Nov 1998) reconfirmed an earlier statement - that PABD should be available for use in appropriate selected patients. The panel of experts held the opinion that evidence for the value and safety of recombinant human erythropoietin in PABD remained unclear.

[Source: Update statement from the conference 'Autologous transfusion, 3 years on - what is new? what has happened?' held at the Royal College of Physicians of Edinburgh, 10-11 November 1998. Brit J Haematology 1999;104:640]

▪ Acute normovolaemic haemodilution (ANH)

From the same conference as above, the consensus was that there was still no good evidence that ANH is effective in reducing allogeneic red cell transfusion. A recent meta-analysis intended to answer the role of ANH identified 24 RCTs (1218 patients in total). With all data poled, ANH reduced the likelihood of exposure to allogeneic blood (OR 0.31, 95% CI 0.15 to 0.62) and the total units of allogeneic blood transfused (weighted mean difference –22.2 U, 95% CI –3.57 to 0.86). There was marked heterogeneity of the results and closer examination suggested that the reduction in blood exposure might be due to flaw in study design. ANH was effective in cardiac and miscellaneous procedures but not in orthopaedic surgery. ANH reduced likelihood of transfusion to statistical significance only when the volume of blood withdrawn exceeded 1000ml, or when a pre-defined transfusion protocol was absent. The authors concluded that the review remained inconclusive.

[Source: Bryson GL, Laupacis A, Wells GA. Does acute normovolemic hemodilution reduce perioperative allogeneic transfusion? A meta-analysis. Anesth & Analg 1998 Jan;86(1):9-15.]

- **Comparing PABD & ANH**

Several small randomized, prospective studies demonstrated no significant difference in the need for allogeneic blood transfusion between the use of ANH or PABD in patients undergoing radical prostatectomy or total joint arthoplasty. ANH, however, is more convenient, economic and could eliminate the possibility of administrative error compared to PABD.

Type of surgery and study	No. enrolled			No. received allogeneic blood		
	ANH	PABD	No autologous donation	ANH	PABD	No autologous donation
Prostatectomy						
• Ness et al. [1]	30	30	-	0	1	-
• Monk et al. [2]	26	26	-	0	4	-
Orthopaedic surgery						
• Lorentz et al. [3]	16	16	15	1	2	8
• Goodnough et al. [4]	15	17	-	7	4	-
• White et al. [5]	25	23	-	3	3	-

[Source: (1) Ness PM, Bourke DL, Walsh PC. A randomized trial of perioperative hemodilution versus transfusion of preoperatively deposited autologous blood in elective surgery. Transfusion 1992;32:226-30.

(2) Monk TG, Goodnough LT, Brecher ME, Colberg JW, Andriole GL, Catalona WJ. A prospective randomized comparison of three blood conservation strategies for radical prostatectomy. Anaesthesiology 1999 Jul;91(1):24-33

(3) Lorentz A, Osswald PM, Schilling M, Jani L. Vergleich autologer Transfusionsverfahren in der Huftgelenkchirurgie. Anaesthesist 1991;40:205-13.

(4) Goodnough LT, Monk TG, Despotis GJ, Merkel K. A randomized trial of acute normovolemic hemodilution compared to preoperative autologous blood donation in total knee arthoplasty. Vox Sang 1999;77(1):11-6.

(5) White KL, Goodnough LT, Merkel K, Davis MH, Monk TG. A comparison of autologous blood procurement techniques for total hip replacement surgery. Anesth Analg 1997;84-Suppl:S58 (abstract).]

- **Intraoperative cell salvage (ICS)**

Consensus of the Royal College of Physicians of Edinburgh (1998)

"The use of ICS has increased since 1995 and evidence has accumulated that it is practical and safe. It also appears to be relatively inexpensive and may even be cost saving, although this has not been conclusively demonstrated. The case for routinely considering the use of intraoperative cell salvage in appropriate circumstances, seen as strong in 1995, has strengthened."

[Source: Update statement from the conference 'Autologous transfusion, 3 years on - what is new? what has happened?' held at the Royal College of Physicians of Edinburgh, 10-11 November 1998. Brit J Haematology 1999 Mar;104(3):640]

Non-randomized (observational) studies

Author	Source	Study characteristics	Outcomes
Keeling et al.[1]	Ann Surg 1983	648 patients vs 100 historical controls. Cardiovascular procedures	Average 1.97U of bank blood was utilised per open heart procedure (historical control) compared to 0.75U with use of Cell Saver ($p<0.0001$).
Cutler BS. [2]	Surgery 1984	106 autotransfused patients vs 32 historical controls. Aortic reconstructive operations	Elective procedures required an average of 1.65U & ruptured aneuryms 9.63U of homologous blood. Autotransfusion saved 1.54U for elective operations and 0.87U for ruptured aneuryms. On the whole, transfusion was avoided in 42.6% of elective reconstruction & 8.3% of emergency procedure.
Stanton et al. [3]	South Med J 1987	50 prospective patients (group 2) vs 50 historic controls (group 1). Major aortic reconstructive procedures.	The estimated blood loss for group 1 & 2 were 1700 & 1900ml per operation. Autologous transfusion accounted for approximately 75% of all transfusion in group 2, tremendously reducing blood bank requirements. However, the study did not compare the percentage of patients who did not require allogeneic blood. The degree of blood loss replaced also differed between the 2 groups.

Author	Source	Study characteristics	Outcomes
Hallett et al. [4]	J Vasc Surg 1987	50 patients received ICS prospectively (group 1) vs 50 matched patients who received allogeneic blood (group 2). Abdominal aortic surgery	96% of control (group 2) received allogeneic blood whereas 68% of patients in group 1, did not require allogeneic transfusion.
Ouriel et al. [5]	J Vasc Surg 1993	100 patients received reinfusion of unwashed filtered shed blood vs 100 patients with allogeneic transfusion. Aortic reconstructive procedures.	The amount of blood salvaged & reinfused averaged 1729 ± 68 ml in the autotransfusion group. Autotransfused patients received a mean of 0.6 ± 0.1 units of banked blood, compared with 3.4 ± 0.1 units in the control group ($p<0.001$).
Goodnough LT et al. [6]	J Vasc Surg 1996	165 suprarenal and 19 infrarenal abdominal aortic aneurysm repairs. No control.	87% of patients still required allogeneic blood in significant amounts (3.5 ± 2.0 units per patient) despite ICS. There were no differences in likelihood of allogeneic transfusion when patients were stratified according to estimated blood loss (EBL) or cell salvage volume. The percentage of patients who had EBL ≥1000ml and who received allogeneic RBCs was not different from the percentage of patients who had EBL <1000ml who received allogeneic RBCs (85% vs 89%, $p=0.26$). Overall, 53 (38%) of the 138 patients who had EBL >1000ml benefited from ICS with reduced need of allogeneic RBCs.

[Source: (1) Keeling MM, Gray LA Jr, Brink MA, Hillerich VK, Bland KI. Intraoperative autotransfusion. Experience in 725 consecutive cases. Ann Surg 1983 May;197(5):536-41.

(2) Cutler BS. Avoidance of homologous transfusion in aortic operations: The role of autotransfusion, hemodilution, and surgical technique. Surgery 1984 Jun;95(6):717-23.

(3) Stanton PE Jr, Shannon J, Rosenthal D, Clark M, Lamis PA, Grover W. Intraoperative autologous transfusion during major aortic reconstructive procedures. South Med J 1987 Mar;80(3):315-9.

(4) Hallett JW Jr, Popovsky M, Ilstrup D. Minimizing blood transfusions during abdominal aortic surgery: Recent advances in rapid autotransfusion. J Vasc Surg 1987 Apr;5(4):601-6.

(5) Ouriel K, Shortell CK, Green RM, DeWeese JA. Intraoperative autotransfusion in aortic surgery. J Vasc Surg 1993 Jul;18(1):16-22.

(6) Goodnough LT, Monk TG, Sicard G, Satterfield SA, Allen B, Anderson CB et al. Intraoperative salvage in patients undergoing elective abdominal aortic aneurysm repair: An anaylsis of cost and benefit. J Vasc Surg 1996 Aug; 24(2):213-8]

Randomized Controlled Trials

i) A prospective, randomized trial of 100 patients undergoing elective abdominal aortic aneurysm (AAA) repair or aortofemoral bypass (AFB) for occlusive disease found that intraoperative cell salvaged & reinfusion had no advantage over control.

Primary outcome: Allogeneic blood transfusion

	Patients randomized to IAT			*Control patients*		
	All (n = 50)	*AAA (n = 25)*	*AFB (n = 25)*	*All (n = 50)*	*AAA (n = 25)*	*AFB (n = 25)*
EBL (mL)	981 ± 983	1418 ± 1192*	544 ± 389	1000 ± 787	1346 ± 920*	654 ± 417
A-PRBCs (U), intraoperative	0.8 ± 1.2	0.9 ± 1.5	0.6 ± 1.0	1.0 ± 1.5	1.2 ± 1.5	0.8 ± 1.5
A-PRBCs (U), postoperative	1.3 ± 1.7	1.6 ± 1.9	1.1 ± 1.4	1.3 ± 1.4	1.2 ± 1.4	1.4 ± 1.4
A-PRBCs (U), total	2.1 ± 2.1	2.5 ± 2.5	1.7 ± 1.6	2.3 ± 2.1	2.4 ± 2.2	2.1 ± 2.1
Number (proportion) not given A-PRBCs	17 (34%)	8 (32%)	9 (36%)	14 (28%)	6 (24%)	8 (32%)
Number (proportion) given IAT-PRBCs	37 (74%)	24 (96%)*	13 (52%)	—	—	—
IAT-PRBCs (mL)	435 ± 301	500 ± 322	315 ± 220	—	—	—

IAT, Intraoperative autotransfusion; *AAA,* abdominal aortic aneurysm; *AFB,* aortofemoral bypass; *EBL,* estimated blood loss; *A-PRBCs,* allogeneic packed red blood cells; *IAT-PRBCs,* intraoperative autotransfusion packed red blood cells.
*$P < .001$, AAA vs. AFB.

"There were no significant differences between patients randomized to IAT [intraoperative autotransfusion] and control patients in estimated blood loss (EBL), allogeneic blood transfusion (units administered intraoperatively, postoperatively, and total), proportion of patients receiving allogeneic blood (34% of patients randomised to IAT and 28% of control patients), postoperative hemoglobin/hematocrit levels, and complications." The authors concluded that "no net benefit of IAT in patients undergoing elective, infrarenal aortic surgery."

[Source: Clagett GP, Valetine RJ, Jackson MR, Mathison C, Kakish HB, Bengtson TD. A randomized trial of intraoperative autotransfusion during aortic surgery. J Vasc Surg 1999 Jan;29(1):22-31.]

ii) Meta-analysis of RCTs on cell salvage in elective cardiac and orthopaedic surgeries.

a) A meta-analysis of 7 RCTs on intraoperative cell salvage that washed salvaged blood considerably decreased the need for allogeneic blood in orthopaedic surgery: RR = 0.39, 95%CI = 0.31-0.51. Statistically significant heterogeneity exist among studies ($p<0.05$).

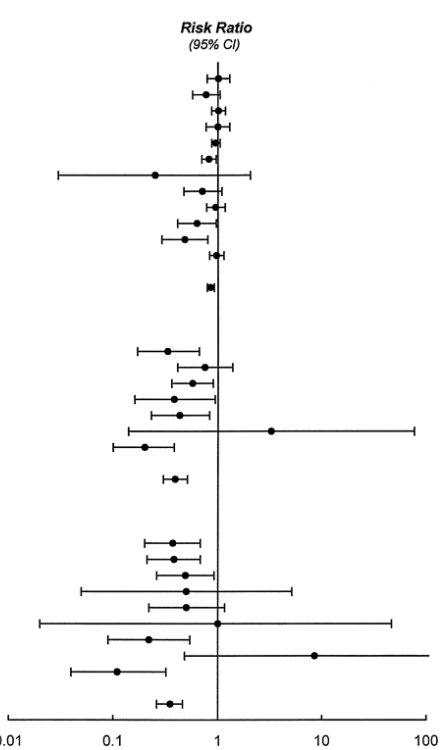
b) A meta-analysis of 9 RCTs on intraoperative cell salvage that did not wash salvaged blood considerably decreased the need for allogeneic blood in orthopaedic surgery: RR = 0.35, 95%CI = 0.26-0.46. Statistically significant heterogeneity exist among studies ($p<0.01$).

c) A meta-analysis of 12 RCTs on postoperative cell salvage that did not wash salvaged blood were marginally effective in reducing need of allogeneic transfusion in cardiac surgery: relative risk [RR] = 0.85, 95% CI = 0.79-0.92.

d) Cell salvage did not appear to increase the frequency of adverse events, although side effects were inconsistently reported and the number of patients studied was relatively small.

The authors cautioned that the small sample size involved (n=2061) and the difficulty in blinding the practitioners might affect their transfusion behaviours.

Study	Year	Treatment Transfused/Total (%)	Control Transfused/Total (%)	Risk Ratio	95% CI Lower	95% CI Upper
Cardiac Unwashed						
Thurer et al. (71)	1979	37/54 (69)	40/59 (68)	1.01	0.79	1.30
Dietrich et al. (49)	1989	17/25 (68)	22/25 (88)	0.77	0.57	1.05
Page et al. (62)	1989	42/48 (88)	45/52 (87)	1.01	0.87	1.18
Eng et al. (51)	1990	17/20 (85)	17/20 (85)	1.00	0.77	1.30
Shirvani (69)	1991	20/21 (95)	21/21 (100)	0.95	0.87	1.05
Lepore and Radegran (56)	1992	50/67 (75)	62/68 (91)	0.82	0.70	0.96
Schonberger et al. (67)	1993	1/20 (5)	4/20 (20)	0.25	0.03	2.05
Axford et al. (46)	1994	10/16 (63)	14/16 (88)	0.71	0.47	1.09
Bouboulis et al. (48)	1994	34/42 (81)	28/33 (85)	0.95	0.78	1.17
Fragnito et al. (52)	1995	17/41 (41)	27/41 (66)	0.63	0.41	0.96
Schmidt et al. (66)	1996	15/60 (25)	31/60 (52)	0.48	0.29	0.80
Unsworth-White et al. (72)	1996	32/36 (89)	31/34 (91)	0.97	0.83	1.14
	Overall	292/450 (65)	342/449 (76)	0.85	0.79	0.92
Orthopedic Washed						
Elawad et al. (50)	1991	6/20 (30)	18/20 (90)	0.33	0.17	0.66
Lorentz et al. (57)	1991	8/16 (50)	10/15 (67)	0.75	0.41	1.38
Menges et al. (60)	1992	8/14 (57)	12/12 (100)	0.57	0.36	0.90
Koopman-van Gemert (55)	1993	5/30 (17)	13/30 (43)	0.38	0.16	0.94
Mah et al. (58)	1995	9/44 (20)	26/55 (47)	0.43	0.23	0.83
Rollo 1 et al. (64)	1995	1/35 (3)	0/38 (0)	3.25	0.14	77.25
Shenolikar et al. (59)	1997	8/50 (16)	40/50 (80)	0.20	0.10	0.38
	Overall	45/209 (22)	119/220 (54)	0.39	0.30	0.51
Orthopedic Unwashed						
Majkowski et al. (65)	1991	7/20 (35)	19/20 (95)	0.37	0.20	0.68
Heddle et al. (54)	1992	10/40 (25)	27/41 (66)	0.38	0.21	0.68
Healy et al. (53)	1994	14/84 (17)	15/44 (34)	0.49	0.26	0.92
Riou et al. (63)	1994	1/25 (4)	2/25 (8)	0.50	0.05	5.17
Rosencher et al. (65)	1994	6/20 (30)	6/10 (60)	0.50	0.22	1.16
Simpson et al. (70)	1994	0/12 (0)	0/12 (0)	1.00	0.02	46.70
Ayers et al. (47)	1995	5/103 (5)	29/129 (22)	0.22	0.09	0.54
Rollo 2 et al. (64)	1995	4/40 (10)	0/38 (0)	8.56	0.48	153.83
Newman et al. (61)	1997	3/35 (9)	28/35 (80)	0.11	0.04	0.32
	Overall	50/379 (13)	126/354 (36)	0.35	0.26	0.46



Summary of the risk ratios associated with cell salvage, all studies. CI = confidence interval.

[Source: Huet C, Salami LR, Fergusson D, Koopman-van Gemert AW, Rubens F, Laupacis A. A meta-analysis of the effectiveness of cell salvage to minimize perioperative allogeneic blood transfusion in cardiac and orthopedic surgery. Anaes Analg 1999 Oct;89(4):861-9]

[***Editorial note***: It is apparent that the amount of estimated blood loss, blood salvaged and transfusion requirements are important parameters in defining the value of ICS in specific practice. This will be further discussed in our "實 **EVIDENCE** 証 in CONTEXT".]

- **Transfusion-associated immunomodulation - cancer recurrence and postoperative infection?**

A meta-analysis of observational studies

Cancer sites	No. of studies	Q statistics*	Summary RR	95% CI for RR
Colorectal	28	62.2($p<0.001$)	1.49	1.23-1.79
Breast	8	2.8 ($p=0.9$)	1.06	0.90-1.24
Head and neck	7	3.8($p>0.75$)	3.62	2.15-6.09)
Lung	6	3.9($p>0.50$)	1.30	1.02-1.66
Prostate	6	6.0($p=0.25$)	1.51	1.13-2.01
Gastric	5	11.2($p=0.025$)	2.44	1.60-3.71

*Test statistic testing the hypothesis of homogenity of effects reported from individual studies. If $p<0.05$, the hypothesis of homogenity is rejected.

28 observational studies on the effect of transfusion and postoperative cancer recurrence were reviewed. "Before any adjustment for the effect of confounding, computed crude summary RRs [relative risk ratio] suggested a significant ($p<0.05$) deleterious transfusion effect in all cancer sites, except for breast. The RR of an adverse outcome was 1.49 in colorectal cancer (95%CI, 1.23-1.79) and ranged from 1.06 in breast cancers to 3.62 in head and neck cancers. The disagreements among published studies were most marked in the case of colorectal and gastric cancers. These discrepancies could be explained, in part, by study design, because prospective investigations had not produced a significant unadjusted transfusion (RR = 1.18; 95%CI 0.93-1.51 in the case of colorectal cancer).

[Source: Vamvakas EC. Perioperative blood transfusion and cancer recurrence: meta-analysis for explanation. Transfusion 1995;35(9);760-8.]

A meta-analysis of randomized controlled trials

5 RCTs comparing (1) allogeneic blood (standard or buffy-coat removed) and (2) autologous or leuco-depleted (by filtration) allogeneic blood did not demonstrate any difference in cancer recurrence or postoperative infection. Noting, however, that given the statistical power of the analysis, an effect smaller than 33% increase in risk cannot be ruled out.

	Summary Risk Ratio	95%CI	p (Q test statistic)*
Cancer recurrence	1.04	0.81-1.35	>0.10
Death due to cancer recurrence	0.98	0.76-1.26	>0.10
Postoperative bacterial infection	1.03	0.81-1.30	>0.10

* Test statistic testing the hypothesis of homogenity of effects reported from individual studies. If $p<0.05$, the hypothesis of homogenity is rejected.

[Source: Vamvakas EC. Transfusion-associated cancer recurrence and postoperative infection: meta-analysis of randomized, controlled clinical trials. Transfusion 1996;36;175-86.]

In 1998, McAlister et al performed a meta-analysis in the same topic and revealed no significant additional new evidence, comparing with Vamvakas report in 1996.

[Source: McAlister FA, Clark HD, Wells PS, Laupacis A. Perioperative allogeneic blood transfusion does not cause adverse sequelae in patients with cancer: a meta-analysis of unconfounded studies Brit J Surg 1998 Feb;85(2):171-8.]

*[**Editorial note**: In this particular topic, we observe decreasing support for the previously perceived risk of immunomodulation from allogeneic transfusion as we demand for a more stringent (i.e. higher level) evidence basis. More simply put, high level robust evidence for increased risk of cancer recurrence and post-operative infection from perioperative allogeneic transfusion is (still) NOT available.]*

Review Panel for this issue: Dr Dickson Chang, Dr S P Lim & Dr H W Liu