Review

Infectious and immunologic consequences of blood transfusion

E Patchen Dellinger[1] and Daniel A Anaya[2]

[1]Professor and Vice-Chairman, Department of Surgery, Chief, Division of General Surgery, University of Washington Medical Center, Seattle, Washington, USA
[2]Resident in Surgery, University of Washington School of Medicine, Seattle, Washington, USA

Correspondence: E Patchen Dellinger, patch@u.washington.edu

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Abstract

Blood transfusions remain common practice in the critical care and surgical settings. Transfusions carry significant risks, including risks for transmission of infectious agents and immune suppression. Transmission of bacterial infections, although rare, is the most common adverse event with transfusion. The risk for transmission of viral infections has decreased over time, clearly because tests are becoming more sensitive in detecting certain viral infections such as hepatitis B, hepatitis C, and HIV. Several immunomodulatory effects are thought to be related to transfusions, and these can result in cancer recurrence, mortality, and postoperative infections. Numerous studies have been performed to examine the role of leukoreduction in decreasing these transfusion-related complications but results remain contradictory. We review the infectious risks associated with blood transfusion and the most recent data on its immunologic effects, specifically on cancer recurrence, mortality, and postoperative infections in surgical patients. We also review the use of leukoreduction in blood transfusion and its role in preventing transfusion-transmitted infections and immunomodulatory complications.

Keywords blood, immune suppression, infection, leukoreduction, mortality, transfusion

Introduction

Blood transfusion remains a common event in current medical practice. Between 10 and 14 million units of blood are donated annually in the USA, and 3–4 million people receive blood transfusions every year [1,2]. Transfusion administration in surgical and critical care settings is particularly frequent and, although they vary substantially, primarily according to the specific surgical population studied, series show that transfusion is used in 30–100% of patients [3]. Despite a general trend toward a decreased number of transfusions per year, operations in older patients and those with more comorbidities ensures that blood transfusion will frequently be used in these surgical settings.

Blood transfusions carry significant risks. Among these, transmission of infectious organisms (e.g. viral or bacterial) remains one of the most feared complications. Also, studies from the 1970s proved that blood transfusion can cause immune suppression, as evidenced by a reduced immunologic response and improved outcome in kidney transplant recipients who had previously been transfused [4]. More recently, specific studies looking at the immunosuppressive effect of blood transfusion have raised new questions for the practice of transfusion in today's medicine.

This article reviews the infectious risks associated with blood transfusion and analyzes the most recent data on its immunologic effects, specifically on cancer recurrence, mortality, and postoperative infections in surgical patients. We also review the use of leukoreduction in blood transfusion and its role in preventing transfusion-transmitted infections and immunomodulatory complications.

Infectious risks of blood transfusion

Any intravenously administered fluid can transmit infection, but blood is a uniquely nutritious medium and is seemingly an excellent means for transmitting infection. In fact, any pathogen that is capable of existing in blood can be transmit-

CMV = cytomegalovirus; FNHTR = febrile nonhemolytic transfusion reaction; nvCJD = new variant Creutzfeldt–Jakob disease; RBC = red blood cell; WBC = white blood cell; SSI = surgical site infection; TRIM = transfusion-related immune modulation.

ted in this manner. It is a tribute to modern blood banking procedures that transfusion-transmitted infection is actually quite rare. Blood-borne parasites can be transmitted with transfusion, and a handful of cases of malaria, babesiosis, Chagas' disease, trypanosomiasis, and toxoplasmosis have been reported. The primary means of preventing these infections is through careful screening of donors, especially those who have traveled to areas that are endemic for these diseases [5]. Syphilis can be transmitted by blood transfusion but no cases have been reported since 1969; it is generally thought that the practice of refrigerating blood, which kills spirochetes within 1–2 days, is responsible for this.

Bacterial contamination is the second most frequently reported cause of blood transfusion-related death after hemolytic reactions, and it accounts for more than 10% of transfusion-associated deaths in the USA [6]. The Assessment of the Frequency of Blood Component Bacterial Contamination Associated with Transfusion Reaction Study (BaCon), which was implemented by the US Centers for Disease Control and Prevention, was the first study to look at specific characteristics related to bacterial contamination of blood products [7]. Results from data collected between 1998 and 2000 showed that the risk for transfusion-transmitted bacteremia is 1 in 100,000 units of platelets and 1 in 500,000 units of red blood cells (RBCs), and that the estimated risk for death from bacterial transfusion-transmitted causes is 1 in 500,000 units of platelets and 1 in 8 million units of RBCs. Contamination with Gram-positive bacteria was more common; however, Gram-negative contamination was independently associated with increased risk for death. Rigors, fever, or tachycardia within 4 hours of transfusion were present in at least 75% of the cases, and haziness or discoloration of the blood product was present in 24% of the contaminated units [7].

Previous reports of small case series showed that Gram-negative bacteria appeared to be the most common source of blood component contamination. However, as shown by the BaCon study, this is not true and these reports might have been biased by the fact that Gram-negative bacteria are more frequently associated with death and hence are reported more often. Actually, Gram-positive bacteria, including *Staphylococcus* and *Streptococcus* spp., as well as Gram-negative bacteria including *Escherichia coli*, and *Serratia*, *Enterobacter,* and *Yersinia* spp.*,* have all been implicated in blood contamination. In general, if bacteremia or endotoxemia is suspected after transfusion of a unit of blood or platelets, then the remaining blood/platelets in the bag and/or tubing should be examined by stain and cultured. In addition, the recipient's blood should also be cultured.

Unlike bacterial infections, viral infections are not immediately evident. Hepatitis B was once the most serious transfusion risk, but the development many years ago of a sensitive and specific test for hepatitis B has led to a dramatic reduction in the transmission of this infection via transfusion. After the introduction of tests for hepatitis B antigen and antibody, non-A/non-B hepatitis became the most prevalent form of transfusion-transmitted infection. For a period, the risk for developing non-A/non-B hepatitis was estimated to be approximately 7% for recipients of volunteer-donated blood and 28% for recipients of commercial blood [8,9]. The availability of increasingly sensitive and specific tests for hepatitis C has greatly reduced this risk as well.

The spread of HIV in the 1980s introduced a new risk for viral infection into the equation for blood transfusion. Again, increasingly sensitive and specific tests have become available, and the absolute risk for acquiring transfusion-associated HIV infection has become quite low, accounting for fewer deaths in the current era than post-transfusion hepatitis. However, the possibility of transfusion-associated HIV is still much more frightening to most patients and many practitioners. Prevention of transfusion-associated HIV infection is accomplished first through careful screening of all potential donors to eliminate those at high risk for having the infection, and second by screening all donated units for antibodies to HIV. It has been estimated that predonation screening is 98% effective in preventing the donation of positive units and that antibody testing is 95% effective, providing a combined effectiveness of approximately 99.9% [10]. Using these techniques only, between 1985 and 1988 – a time when the overall prevalence of HIV infection in the USA was increasing – post-transfusion HIV infections were reduced by 76%.

The only remaining real risk for acquiring HIV through blood transfusion comes from the small possibility that blood could be donated during the so-called window of sero-negativity between the time when HIV infection occurs and detectable antibodies develop. The average window is estimated to be about 8 weeks [10]. The incidence of positive units of blood discovered through postdonation screening has been steadily decreasing. The risk for blood being sero-negative but virus-positive is assumed to be proportional to the number of sero-positive units discovered through post-transfusion antibody screening. In one study [11] conducted at five blood centers across the USA, 2,318,356 units of blood derived from 586,507 donors were tested between 1991 and 1993. In that study, the risk for acquiring an HIV infection from a unit of blood was 1 in 493,000, the risk for hepatitis C was 1 in 103,000, and the risk for hepatitis B was 1 in 63,000. The combined risk for acquiring any type of viral infection was 1 in 34,000, and 88% of that risk was derived from hepatitis B and C.

Current risks with improved, more sensitive tests are considered to be even lower (Table 1). Busch and colleagues [12] reported that risk estimates are now based on mathematical models. These model-based estimates indicate that the current risk for HIV is 1 in 1,800,000, for hepatitis C it is 1 in 1,600,000, and for hepatitis B it is 1 in 220,000. Using the newest nucleic acid technology screening techniques, the

Table 1

Infectious transmission risks with blood transfusion

Agent transmitted	Estimated risk
Bacterial	1 in 100,000-500,000
Hepatitis B	1 in 220,000
Hepatitis C	1 in 1,600,000
HIV	1 in 1,800,000

Data from Kuehnert and coworkers [7] and Busch and coworkers [12].

window during which infection is not detectable in a donated unit of blood has decreased to 11 days for HIV and 8–10 days for hepatitis C virus [12]. The risk for a fatal hemolytic transfusion reaction is estimated to be 1 in 100,000 [13]. Thus, it can be seen that after transfusion the risk for death from hepatitis B or C, or from a hemolytic transfusion reaction, is greater than the risk for dying from transfusion-associated HIV.

One of the most recent potential infectious agents in blood transfusion to be proposed is the prion agent of the new variant Creutzfeldt–Jakob disease (nvCJD). To date, no evidence of transfusion-mediated transmission of classic CJD has been found. However, the disease has been transmitted through corneal transplants, human growth hormone derived from human pituitary glands, dura mater transplants, and inadequately sterilized depth electrodes used in the brain during the work-up and treatment of epilepsy. Because experience with nvCJD is so limited and because it appears to have previously unreported modes of transmission, some authorities have enacted precautionary donor exclusion regulations [14,15] and some countries have even changed their practice to universal leukoreduction [16].

More recently, transfusion-transmitted West Nile Virus was confirmed within the USA. Since screening began in June 2003, 163 highly reactive units were removed from a total of 1.1 million units screened during a 2-month period. The investigations into West Nile Virus transmission, as well as the fast implementation of a screening test and preventive strategies, are all examples of the significant advances in blood transfusion medicine and highlight the need for a multidisciplinary approach to prevent transfusion-mediated infectious complications [17,18].

On the whole, transfusion is a very safe treatment modality. For those patients and physicians who wish to keep the risk for transfusion-associated infection to a minimum, the primary response should be to limit unnecessary transfusion. Another response has been to increase donation of autologous blood for transfusion. Although the practice of autologous blood donation appears to have reached a plateau over the past 10 years, analysis of transfusion practices in the USA has revealed that the number of autologous units donated increased more than 30-fold from 1980 to 1992 [1,19,20].

Immunologic consequences of blood transfusion

Since the early 1970s, transfusion of blood and blood products has been linked to immune suppression [4]. Specific immunomodulatory effects thought to be related to transfusions include increased cancer recurrence, increased mortality, increased postoperative bacterial infections, decreased recurrence rate of Crohn's disease, and decreased risk for recurrent spontaneous abortion. This whole constellation of immune effects associated with transfusion has been referred to as the 'TRIM' effect (transfusion-related immune modulation).

A unit of donated blood is usually fractionated into its different components. When fractionated, it can be separated into RBCs, buffy coat (containing white blood cells [WBCs] and platelets) and plasma, or into RBCs (with buffy coat) and plasma. Buffy-coat-free RBCs (a technique mostly used in European countries) have a 75% reduction in WBCs, resulting in approximately 10^9 leukocytes/unit. To reduce effectively the number of leukocytes in order to prevent alloimmunization and transmission of viruses, leukocyte filters are used, which remove 99.9% of WBCs, resulting in approximately 10^6 leukocytes/unit in a RBC suspension.

Particular interest has been directed toward the role of WBCs in allogeneic blood and the risk of the TRIM complications [21]. The specific mechanism by which this occurs remains elusive, although multiple hypotheses have been formulated, including allogeneic WBC apoptosis with cytokine release and immunologically active allogeneic WBCs, among others. Studies performed to evaluate the effect of WBCs present in allogeneic blood traditionally compare transfusions with either RBCs or buffy-coat depleted RBCs (common in Europe) with transfusion of autologous RBCs or WBC depleted RBCs, which are considered to be equally non-immunogenic, for this purpose.

Various studies have looked at cancer recurrence and blood transfusion. Three randomized clinical trials comparing buffy-coat reduced RBCs versus autologous whole blood [22], WBC-reduced RBCs [23], or autologous RBCs [24] in patients with colorectal cancer, and two recent meta-analyses [3,25] showed independently that there was no difference in risk for recurrence between the WBC reduced group and the other groups studied. The fact that the three studies were very homogeneous with regard to patient population and recurrence rates makes these results even more reliable. However, it is not known whether there might be a difference in recurrence rate between WBC reduced RBCs and RBCs with buffy coat, as some experimental studies have suggested [26], which would be more relevant to practice standards in the USA.

Mortality has also been compared between patients receiving transfusions of allogeneic blood and those receiving WBC reduced blood. In a study of patients undergoing cardiac

surgery in which infection rates were compared between buffy-coat reduced RBCs and WBC reduced RBCs, Van de Watering and coworkers [27] found an increased risk for mortality not related to infections in patients with non-WBC-reduced blood. Two other similar studies [23,28] also showed a trend toward increased mortality with the use of non-WBC-reduced blood. However, these studies were not initially designed to evaluate differences in mortality, and prognostic factors may not have been distributed equally in the different groups or confounding factors may not have been included for this analysis.

Recently, Hebert and colleagues published the results of a retrospective cohort study conducted to evaluate experience in Canada following adoption of universal leukoreduction. The results show a reduction in mortality from the period before implementation of leukoreduction to current practice [29]. However, similar studies have yielded conflicting results. Dzik and coworkers [30] showed no significant difference in mortality between patients receiving non-leukoreduced blood and those receiving leukoreduced blood. Similarly, Baron and coworkers [31] found no difference in mortality in their study, in which a before-and-after study design was used to evaluate the impact of leukoreduction on patients undergoing abdominal aortic surgery. More recently, Vamvakas [32] reported a meta-analysis that included 14 randomized controlled trials evaluating mortality in patients receiving WBC-reduced and non-WBC-reduced transfusions. Although no mortality difference was found, a subgroup analysis revealed that non-WBC-reduced transfusion was associated with increased short-term mortality in patients undergoing open heart surgery. Overall, there does not appear to be an association between allogeneic non-WBC-reduced transfusions and mortality, but further studies must be done to address this question specifically for subsets of patients.

Surgical site infection (SSI) remains the most common infectious complication in surgical patients and is associated with significant morbidity, mortality, and resource utilization. SSI is a measurable common complication in surgical patients and is a surrogate for other postoperative infections. Transfusion has traditionally been considered a risk factor for SSI [33]. Observational studies [34,35] have shown this association over time and more recent studies (including a meta-analysis) [36–39], with greater numbers of patients followed, continue to corroborate this relationship.

At least 12 randomized controlled trials and two meta-analyses have been reported that evaluated the role of allogeneic versus WBC reduced blood in postoperative infections [3,22–24,27,31,40–49]. The results are conflicting and meta-analyses are not applicable, given the heterogeneous characteristics of the different studies regarding patient population, infections definitions, study design, infection rates, and other factors.

Most of the studies show either a small increase or no significant difference in infection risk with non-WBC-reduced transfusion. Two studies, however, conducted by Jensen and coworkers [40,41] showed a significantly increased risk for postoperative infection with non-WBC-reduced blood transfusion. They evaluated the rate of SSI in patients undergoing colorectal surgery. In one of the studies [41], one group of patients received buffy-coat depleted RBCs (control group) and was compared with another group that received WBC reduced RBCs. Patients who received WBC reduced transfusions had no SSIs whereas the control group developed significantly more infectious complications (18.3%). This was a prospective and randomized study; however, it has been criticized for having uncontrolled confounding factors, giving non-leukoreduction an implausible cause–effect association in the risk for SSI.

Moreover, other well designed studies have not been able to show a significant association between the use of non-WBC-reduced blood transfusions and risk for postoperative infections. Wallis and coworkers [47] conducted a prospective, randomized controlled trial that compared postoperative infection rates in patients undergoing coronary or heart valve surgery. Patients were randomly assigned to receive plasma reduced, buffy-coat reduced, or WBC reduced blood. Postoperative infections overall were more common in patients with plasma reduced blood transfusion. However, when urinary tract infections were excluded, no significant difference was seen across the three groups.

Results from the two published meta-analyses [3,49], from which the studies by Jensen and coworkers were excluded, indicate no significant differences in postoperative infections between the WBC reduced group and the control group. Nevertheless, some very well designed studies [27] show a statistically significant decrease in postoperative infections with the use of WBC reduced blood, and more well designed and comparable randomized, controlled trials must be done to elucidate this question.

Leukoreduction practices in blood transfusion

There is enough evidence to support the contention that transfusion of WBC depleted allogeneic blood decreases the risk for febrile nonhemolytic transfusion reactions (FNHTRs), cytomegalovirus (CMV) transmission, and platelet refractoriness due to HLA alloimmunization. In 1999, the UK, Ireland, and Portugal implemented universal leukoreduction of all blood components with the goal of preventing the theoretical risk for nvCJD transmission. At the same time, France and Canada also implemented leukoreduction, just as means of making blood transfusion a safer practice [16].

In the USA, the Advisory Committee on Blood Safety and Availability to the US Food and Drug Administration has recommended universal leukoreduction and has noted that its use is justified from a benefit-to-risk perspective [50]. However,

multiple experts in the area have expressed disagreement with this view when justified only by current data [51]. The role of leukoreduction in preventing nvCJD is not supported by the literature, and if universal leukoreduction is to be implemented for reasons beyond its three proven benefits (FNHTRs, CMV transmission, and platelet refractoriness) then it will probably be based on its immunomodulatory effects. It has not been shown that cancer recurrence is decreased by leukoreduction practices. Mortality and postoperative infections still remain the most attractive reasons to implement this practice, but to date there is not enough evidence to support this practice when based solely on those two effects and further studies are needed.

Conclusion

Overall, blood transfusion is a safe treatment option. Increased donor selection criteria and increased screening of donated blood have led to a decrease in the rate of transfusion-related infections. However, unnecessary transfusion should be avoided to further reduce the risk for infection and other complications. Several studies have looked at immune effects associated with transfusion. These studies compare different blood preparations to examine the role that WBCs have in the development of certain complications. Universal leukoreduction has been instituted in many countries and has been recommended by an advisory committee to the US Food and Drug Administration in the USA. It decreases the rate of FNHTRs, the risk of CMV transmission, and the unresponsiveness of platelet transfusion after previous alloimmunization. However, leukoreduction does not appear to play a role in risk for cancer recurrence, and further studies must be done to better determine its role in mortality and postoperative infections, particularly in specific subsets of surgical patients. The practice of universal leukoreduction based on a cost-effectiveness perspective is still debated, and the variability of results when studying its effects on mortality and postoperative infections calls for future and better designed studies.

Competing interests

None declared.

References

1. Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP: **Transfusion medicine. First of two parts–blood transfusion.** *N Engl J Med* 1999, **340:**438-447.
2. Ratko TA, Cummings JP, Oberman HA, Crookston KP, DeChristopher PJ, Eastlund DT, Godwin JE, Sacher RA, Yawn DH, Matuszewski KA: **Evidence-based recommendations for the use of WBC-reduced cellular blood components.** *Transfusion* 2001, **41:**1310-1319.
3. 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.** *Br J Surg* 1998, **85:**171-178.
4. Opelz G, Sengar DP, Mickey MR, Terasaki PI: **Effect of blood transfusions on subsequent kidney transplants.** *Transplant Proc* 1973, **5:**253-259.
5. Kahn RA: **Diseases transmitted by blood transfusion.** *Hum Pathol* 1983, **14:**241-247.
6. US Department of Health and Human Services: *Workshop on Bacterial Contamination of Platelets*. Bethesda: FDA, Center for Biologics Evaluation and Research; 24 September 1999. [http://www.fda.gov/cber/minutes/bact092499.pdf]
7. Kuehnert MJ, Roth VR, Haley NR, Gregory KR, Elder KV, Schreiber GB, Arduino MJ, Holt SC, Carson LA, Banerjee SN, Jarvis WR: **Transfusion-transmitted bacterial infection in the United States, 1998 through 2000.** *Transfusion* 2001, **41:**1493-1499.
8. Aach RD, Kahn RA: **Post-transfusion hepatitis: current perspectives.** *Ann Intern Med* 1980, **92:**539-546.
9. Shorey J: **Southwestern internal medicine conference: the current status of Non-A, Non-B hepatitis.** *Am J Med Sci* 1985, **289:**251-261.
10. Cumming PD, Wallace EL, Schorr JB, Dodd RY: **Exposure of patients to human immunodeficiency virus through the transfusion of blood components that test antibody-negative.** *N Engl J Med* 1989, **321:**941-946.
11. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ: **The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study.** *N Engl J Med* 1996, **334:**1685-1690.
12. Busch MP, Kleinman SH, Nemo GJ: **Current and emerging infectious risks of blood transfusions.** *JAMA* 2003, **289:**959-962.
13. Menitove JE: **Current risk of transfusion-associated human immunodeficiency virus infection.** *Arch Pathol Lab Med* 1990, **114:**330-334.
14. Budka H: **Prions and transfusion medicine.** *Vox Sang* 2000, **Suppl 2:**231-238.
15. Alter M: **How is Creutzfeldt–Jakob disease acquired?** *Neuroepidemiology* 2000, **19:**55-61.
16. Vamvakas EC, Blajchman MA: **Universal WBC reduction: the case for and against.** *Transfusion* 2001, **41:**691-712.
17. Centers for Disease Control: **West Nile virus infection in organ donor and transplant recipients: Georgia and Florida, 2002.** *MMWR Morb Mortal Wkly Rep* 2002, **51:**790-791.
18. Dodd RY: **Emerging infections, transfusion safety, and epidemiology.** *N Engl J Med* 2003, **349:**1205-1206.
19. Surgenor DM, Wallace EL, Hao SH, Chapman RH: **Collection and transfusion of blood in the United States, 1982-1988.** *N Engl J Med* 1990, **322:**1646-1651.
20. Wallace EL, Churchill WH, Surgenor DM, An J, Cho G, McGurk S, Murphy L: **Collection and transfusion of blood and blood components in the United States, 1992.** *Transfusion* 1995, **35:**802-812.
21. Blajchman MA: **Allogeneic blood transfusion, immunomodulation, and postoperative bacterial infection: do we have the answers yet?** *Transfusion* 1997, **37:**121-125.
22. Busch ORC, Hop WCJ, Hoynck van Papendrecht MAW, Marquet RL, Jeekel J: **Blood transfusions and prognosis in colorectal cancer.** *N Engl J Med* 1993, **329:**1354-1356.
23. Houbiers JGA, Brand A, van de Watering LMG, Hermans J, Verwey PJM, Bijnen AB, Pahlplatz P, Schattenkerk ME, Wobbes T, de Vries JE, Klementschitsch P, van de Maas AHM, van de Velde CJH: **Randomised controlled trial comparing transfusion of leucocyte-depleted or buffy-coat-depleted blood in surgery for colorectal cancer.** *Lancet* 1994, **344:**573-578.
24. Heiss MM, Mempel W, Delanoff C, Jauch K-W, Gabka C, Mempel M, Dieterich H-J, Eissner H-J, Schildberg F-W: **Blood transfusion-modulated tumor recurrence: first results of a randomized study of autologous versus allogeneic blood transfusion in colorectal cancer surgery.** *J Clin Oncol* 1994, **12:**1859-1867.
25. Vamvakas EC: **Transfusion-associated cancer recurrence and postoperative infection: meta-analysis of randomized, controlled clinical trials.** *Transfusion* 1996, **36:**175-186.
26. Blajchman MA: **Immunomodulatory effects of allogeneic blood transfusions: clinical manifestations and mechanisms.** *Vox Sang* 1998, **Suppl 2:**315-319.
27. van de Watering LMG, Hermans J, Houbiers JGA, van den Broek PJ, Bouter H, Boer F, Harvey MS, Huysmans HA, Brand A: **Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery: a randomized clinical trial.** *Circulation* 1998, **97:**562-568.
28. Blajchman MA, Dzik S, Vamvakas EC, Sweeney J, Snyder EL: **Clinical and molecular basis of transfusion-induced immunomodulation: summary of the proceedings of a state-of-the-art conference.** *Transfus Med Rev* 2001, **15:**108-135.
29. Hebert PC, Fergusson D, Blajchman MA, Wells GA, Kmetic A, Coyle D, Heddle N, Germain M, Goldman M, Toye B, Schweitzer I,

vanWalraven C, Devine D, Sher GD: **Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions.** *JAMA* 2003, **289:**1941-1949.
30. Dzik WH, Anderson JK, O'Neill EM, Assmann SF, Kalish LA, Stowell CP: **A prospective, randomized clinical trial of universal WBC reduction.** *Transfusion* 2002, **42:**1114-1122.
31. Baron JF, Gourdin M, Bertrand M, Mercadier A, Delort J, Kieffer E, Coriat P: **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:** 529-537.
32. Vamvakas EC: **WBC-containing allogeneic blood transfusion and mortality: a meta-analysis of randomized controlled trials.** *Transfusion* 2003, **43:**963-973.
33. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR, Hospital Infection Control Practices Advisory Committee: **Guideline for prevention of surgical site infection, 1999.** *Infect Control Hosp Epidemiol* 1999, **20:**250-278.
34. Agarwal N, Murphy JG, Cayten CG, Stahl WM: **Blood transfusion increases the risk of infection after trauma.** *Arch Surg* 1993, **128:**171-176.
35. Dellinger EP, Oreskovich MR, Wertz MJ, Hamasaki V, Lennard ES: **Risk of infection following laparotomy for penetrating abdominal injury.** *Arch Surg* 1984, **119:**20-27.
36. Olsen MA, Sundt TM, Lawton JS, Damiano RJ Jr, Hopkins-Broyles D, Lock-Buckley P, Fraser VJ: **Risk factors for leg harvest surgical site infections after coronary artery bypass graft surgery.** *J Thorac Cardiovasc Surg* 2003, **126:**992-999.
37. Tang R, Chen HH, Wang YL, Changchien CR, Chen JS, Hsu KC, Chiang JM, Wang JY: **Risk factors for surgical site infection after elective resection of the colon and rectum: a single-center prospective study of 2,809 consecutive patients.** *Ann Surg* 2001, **234:**181-189.
38. Ikuta S, Miki C, Hatada T, Inoue Y, Araki T, Tanaka K, Tonouchi H, Kusunoki M: **Allogenic blood transfusion is an independent risk factor for infective complications after less invasive gastrointestinal surgery.** *Am J Surg* 2003, **185:**188-193.
39. Hill GE, Frawley WH, Griffith KE, Forestner JE, Minei JP: **Allogeneic blood transfusion increases the risk of postoperative bacterial infection: a meta-analysis.** *J Trauma* 2003, **54:**908-914.
40. Jensen LS, Andersen AJ, Christiansen PM, Hokland P, Juhl CO, Madsen G, Mortensen J, Moller-Nielsen C, Hanberg-Sorensen F, Hokland M: **Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colorectal surgery.** *Br J Surg* 1992, **79:**513-516.
41. Jensen LS, Kissmeyer-Nielsen P, Wolff B, Qvist N: **Randomised comparison of leucocyte-depleted versus buffy-coat-poor blood transfusion and complications after colorectal surgery.** *Lancet* 1996, **348:**841-845.
42. Thomas D, Wareham K, Cohen D, Hutchings H: **Autologous blood transfusion in total knee replacement surgery.** *Br J Anaesth* 2001, **86:**669-673.
43. Wong JC, Torella F, Haynes SL, Dalrymple K, Mortimer AJ, McCollum CN: **Autologous versus allogeneic transfusion in aortic surgery: a multicenter randomized clinical trial.** *Ann Surg* 2002, **235:**145-151.
44. Farrer A, Spark JI, Scott DJ: **Autologous blood transfusion: the benefits to the patient undergoing abdominal aortic aneurysm repair.** *J Vasc Nurs* 1997, **15:**111-115.
45. Newman JH, Bowers M, Murphy J: **The clinical advantages of autologous transfusion. A randomized, controlled study after knee replacement.** *J Bone Joint Surg Br* 1997, **79:**630-632.
46. Titlestad IL, Ebbesen LS, Ainsworth AP, Lillevang ST, Qvist N, Georgsen J: **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:**147-153.
47. Wallis JP, Chapman CE, Orr KE, Clark SC, Forty JR: **Effect of WBC reduction of transfused RBCs on postoperative infection rates in cardiac surgery.** *Transfusion* 2002, **42:**1127-1134.
48. Tartter PI, Mohandas K, Azar P, Endres J, Kaplan J, Spivack M: **Randomized trial comparing packed red cell blood transfusion with and without leukocyte depletion for gastrointestinal surgery.** *Am J Surg* 1998, **176:**462-466.
49. 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:**304-314.
50. US Department of Health and Human Services Advisory Committee on Blood Safety and Availability. *Blood Safety Resolution: January 2001.* [http://www.hhs.gov/bloodsafety/resolutions/resjan01.html]
51. Corwin HL, AuBuchon JP: **Is leukoreduction of blood components for everyone?** *JAMA* 2003, **289:**1993-1955.