Allogeneic Blood Transfusion Increases the Risk of Postoperative Bacterial Infection: A Meta-analysis

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Background: **Immunosuppression is a consequence of allogeneic (homologous) blood transfusion (ABT) in humans and is associated with an increased risk in cancer recurrence rates after potentially curative surgery as well as an increase in the frequency of postoperative bacterial infections. Although a meta-analysis has been reported demonstrating the relationship between ABT and colon cancer recurrence, no meta-analysis has been reported demonstrating the relationship of ABT to postoperative bacterial infection.**

Methods: **Twenty peer-reviewed articles published from 1986 to 2000 were included in a meta-analysis. Criteria for inclusion included a clearly defined control group (nontransfused) compared with a treated (transfused) group and statistical analysis of accumulated data that included stepwise multivariate logistic regression analysis. In addition, a subgroup of publications that included only the traumatically injured patient was included in a separate meta-analysis. A fixed effects analysis was conducted with odds ratios obtained by using the conditional maximum likelihood method and 95% confidence intervals on the obtained odds ratios were determined using the mid-*p* technique.**

Results: **The total number of subjects included in this meta-analysis was 13,152 (5,215 in the transfused group and 7,937 in the nontransfused group). The common odds ratio for all articles included in this meta-analysis evaluating the association of ABT to the incidence of postoperative bacterial infection was 3.45 (range, 1.43–15.15), with 17 of the 20 studies demonstrating a value of $p \leq 0.05$. These results provide overwhelming evidence that ABT is associated with a significantly increased risk of postoperative bacterial infection in the surgical patient. The common odds ratio of the subgroup of trauma patients was 5.263 (range, 5.03–5.43), with all studies showing a value of $p < 0.05$ (0.005–0.0001). These results demonstrate that ABT is associated with a greater risk of postoperative bacterial infection in the trauma patient when compared with those patients receiving ABT during or after elective surgery.**

Conclusion: **These results demonstrate that ABT is an associated and apparently significant and frequently overlooked risk factor for the development of postoperative bacterial infection in the surgical patient. Allogeneic blood transfusion is a greater risk factor in the traumatically injured patient when compared with the elective surgical patient for the development of postoperative bacterial infection.**

Key Words: **Meta-analysis, Blood transfusion, Immunosuppression, Postoperative infection, Trauma.**

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Postoperative bacterial infections remain a serious problem in the surgical patient, causing increased morbidity and mortality, total hospital costs, and total length of hospital stay. Although allogeneic (homologous) blood transfusion (ABT) may be essential in the management of the surgical patient, several investigators have reported increased infection rates after ABT. The increased risk of postoperative bacterial infection is dose related, that is, as the number of transfused units increases, the risk of infection increases.[1,2]

Immunosuppression is a known consequence of ABT and increases the cancer recurrence and mortality rates after potentially curative surgery in addition to increasing postoperative bacterial infection rates.[3] A meta-analysis on the existing literature evaluating the relationship between ABT and colorectal cancer recurrence rates after potentially curative surgery has previously been reported.[3] The primary strength of a meta-analysis is the potential to increase statistical power by combining the number of experimental subjects from individual studies into an inclusive overall analysis and thereby increasing statistical confidence. To date, no meta-analysis of the currently existing literature evaluating the relationship of ABT to the incidence of postoperative bacterial infections has been reported.

PATIENTS AND METHODS

Our goal was to identify all relevant prospective controlled human clinical trials available for review and published by October 2001. A prospective controlled clinical trial was defined as a trial in which the included subjects received one of two (or more) interventions and, in this case, were separated into a clearly defined treated (transfusion) group and an untreated control (nontransfused or placebo) group. A MEDLINE literature search of peer-reviewed publications was performed by hand using the key words "blood transfusion," "postoperative infection," "immunosuppression," and

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"trauma." In addition, only articles including stepwise multivariate logistic regression analysis as a portion of their statistical evaluation of collected data were included. Standard medical criteria were used to determine the presence of postoperative bacterial infection in each study. All studies in this meta-analysis used standard laboratory-determined crossmatched human allogeneic blood for transfusion therapy.

Statistical Analysis

For the analysis, the odds ratio was defined as the odds of the transfusion (treated) group divided by those of the nontransfused (placebo) group. A fixed effects analysis was conducted, with the point estimates of the odds ratios obtained by using the conditional maximum likelihood method.[4] Ninety-five percent confidence intervals on the odds ratios were computed using the mid-p technique.[5] The Breslow-Day test[6] was used to determine homogeneity of the individual odds ratios. Least squares regression was used to investigate possible linear relationships of odds ratio estimates to sample size, chronologic ordering, and observed risk in the groups of patients that did not undergo a transfusion.[7] A funnel plot as described by Egger and Smith[8] was constructed to determine whether selection, publication, citation, multiple publication, or inclusion bias was present in article selection. Implementation was carried out with the StatXact and S-Plus software packages. Values of $p \leq 0.05$ were considered significant.

RESULTS

Twenty articles published between 1986 and 2000 met the criteria for inclusion.[9–28] The total number of subjects included in this meta-analysis was 13,152 (overall n = 13,152, with 5,215 included in the transfusion group and 7,937 in the nontransfused group (Table 1). The odds ratios ranged from 1.43 to 15.15, with a common odds ratio of 3.45. Seventeen of the 20 studies evaluated had accompanying values of $p \leq 0.05$. All point estimates of the odds ratios were greater than unity and the lower boundary of most confidence intervals were not less than 1 (Fig. 1).

In the subset of trauma patients (three articles included), the total number of subjects was 5,993 (1,571 in the transfusion group and 4,422 in the nontransfused group). The common odds ratio was 5.263 (range, 5.03–5.43), and all studies in the trauma subgroup had accompanying values of $p < 0.05$ (0.005–0.0001) (Fig. 2). The Breslow-Day test[6] did not reject the null hypothesis of common odds ($p = 0.99$), thereby demonstrating that the individual odds ratios were homogenous in the trauma subgroup. Therefore, the reporting of a common odds ratio as a single summary statistic for the trauma subgroup meets the requirement of validity as suggested by Brand and Kragt.[7]

For the complete meta-analysis of all 20 studies, the Breslow-Day test statistic was highly significant ($p < 0.0001$), thus rejecting the hypothesis that there was an underlying common odds ratio for all 20 studies (i.e., the individual odds ratios were nonhomogenous). A subsequent investigation revealed that the odds ratios decreased as the observed baseline risk increased in the nontransfused (placebo) group ($p = 0.001$), resulting in a nonhorizontal regression line (Fig. 3). Therefore, reporting of a common odds ratio for the full meta-analysis of all 20 publications may be

Table 1 Summary of Randomized Trials Comparing a Control (Nontransfused) Group to a Group Receiving Allogeneic Blood Transfusion Evaluating the Incidence of Postoperative Bacterial Infections

Reference	Critical Illness	Total No. of Subjects	No. Transfused	Infection (%)	No. Nontransfused	Infection (%)
Dawes et al., 1986[9]	Trauma	143	91	30	52	7.5
Tartter, 1988[10]	Colon cancer	343	134	25	209	9
Van Pabst et al., 1988[11]	Colon cancer	164	117	26	47	17
Wobbes et al., 1990[12]	Various	548	260	40	288	29
Murphy et al., 1991[13]	Total hip replacement	84	50	32	34	3
Trivlzi et al., 1992[14]	Spinal fusion	109	24	21	85	4
Fernandez et al., 1992[15]	Orthopedics	376	254	7	122	5
Johnson et al., 1992[16]	Colon cancer	217	138	16	79	9
Doersten et al., 1992[17]	Head/neck Cancer	104	51	47	53	27
Jensen et al., 1992[18]	Colon surgery	197	104	13	93	2
Edna and Bjerkeset, 1992[19]	Trauma	484	125	22	359	5
Ford et al., 1993[20]	Colon cancer	1123	778	8.6	345	2
Agarwal et al., 1993[21]	Trauma	5366	1,355	34	4,011	9
Heiss et al., 1993[22]	Colon cancer	120	58	27	62	12
Houbiers et al., 1999[23]	Colon cancer	697	446	30	251	23
Vignali et al., 1995[24]	Colon cancer	123	48	33	75	9
Koual et al., 1997[25]	Hip fracture	687	395	27	292	16
Houbiers et al., 1997[26]	Colon cancer	697	446	39	251	24
Tartter et al., 1998[27]	Various GI	221	59	44	162	11
Chang et al., 2000[28]	Colon surgery	1349	282	26	1,067	14

GI, gastrointestinal.

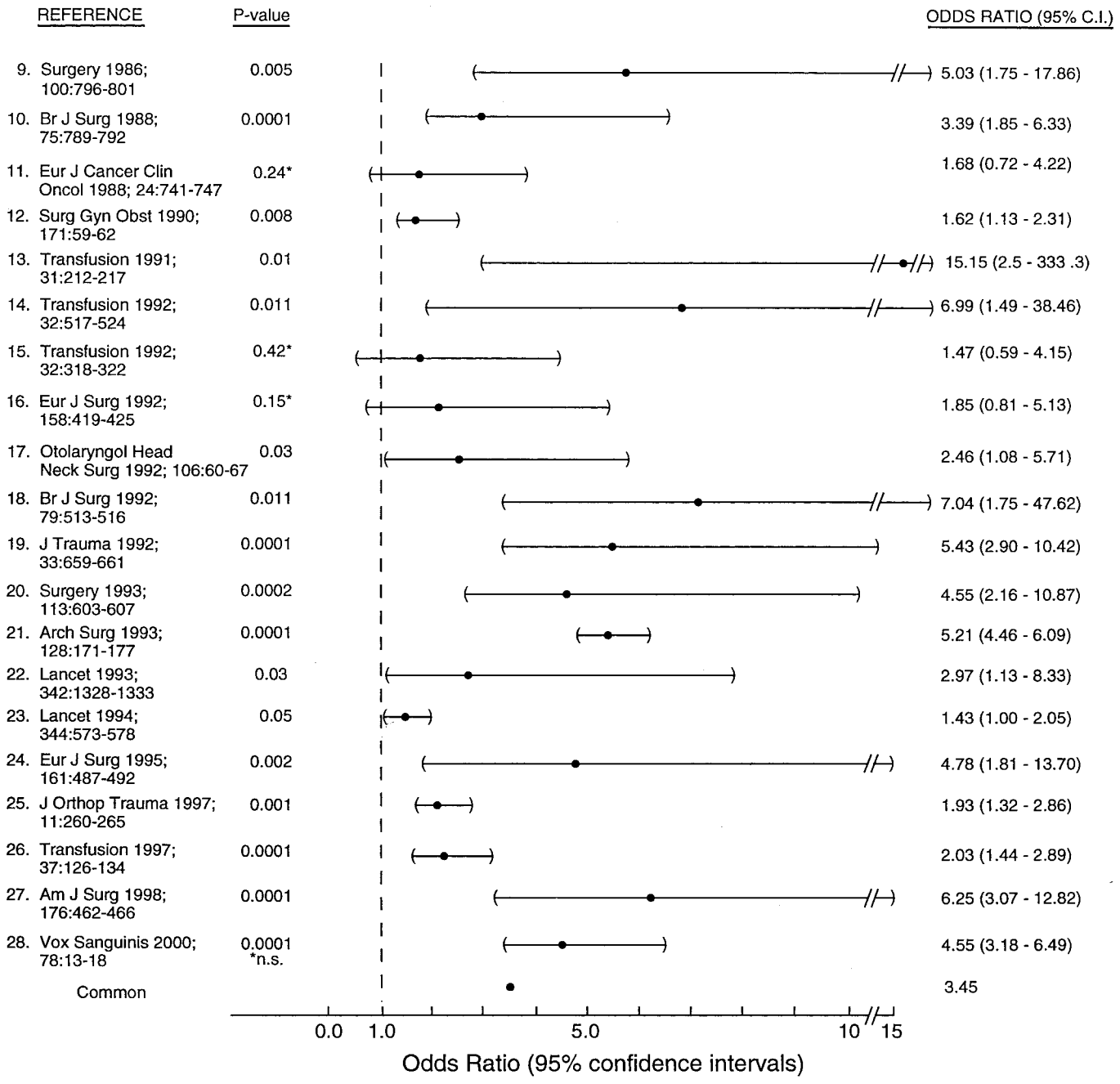

Fig. 1. *Odds ratios (●) of postoperative bacterial infection (95% confidence intervals) occurring after allogeneic blood transfusion.* Broken vertical line *represents an odds ratio of 1.0 (no increased risk). References are numbered sequentially in the order of analysis and as in the References section. Values of* $p \leq 0.05$ *were considered significant (*n.s., not significant).*

misleading as a single summary statistic as defined by Brand and Kragt[7] (see Discussion section for more detail concerning this issue).

A funnel plot was constructed and plotted as log sample size against the respective odds ratio. The resulting funnel plot demonstrated no asymmetry and therefore met the criteria for lack of bias in article selection as described by Egger and Smith[8] (Fig. 4).

DISCUSSION

All point estimates of the individual odds ratios were greater than unity (1.0, or the odds ratio at which there is no increased risk of an event occurring), providing overwhelming evidence that undergoing ABT is associated with a significantly increased risk of postoperative bacterial infection. The common odds ratio for all publications included in this

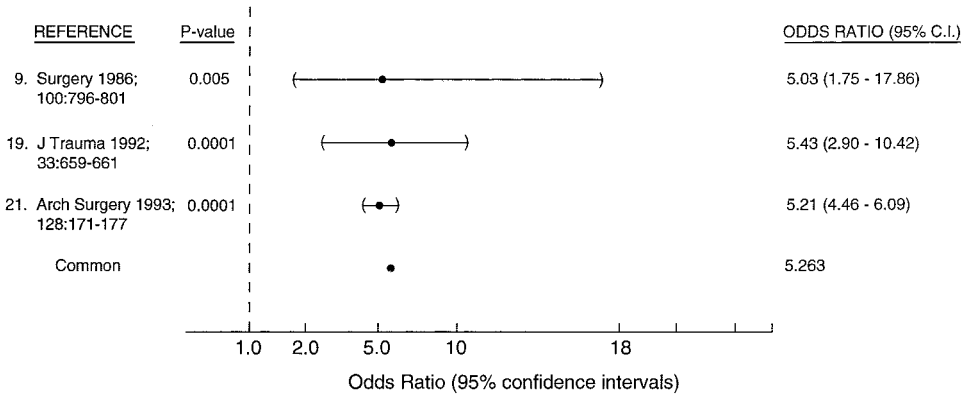

Fig. 2. *Odds ratios (●) of postoperative bacterial infection (95% confidence intervals) occurring after allogeneic blood transfusion in the subset of trauma patients.* Broken vertical line *represents an odds ratio of 1.0 (no increased risk). References are numbered as in the complete meta-analysis (see Fig. 1). Values of* $p \leq 0.05$ *were considered significant.*

meta-analysis supports the understanding that ABT significantly increases the risk of postoperative bacterial infection in the surgical patient. Of interest is the finding that this risk is higher in the subset of reports that evaluated only trauma patients, suggesting that ABT may be an additive and frequently overlooked factor in the immunosuppression commonly reported in the postoperative trauma victim.[2,9]

An important issue in the reporting of a meta-analysis is the validity of a common odds ratio. The terms common, cumulative, combined, or overall have been used interchangeably by different authors to define this value. Brand and Kragt[7] suggested that unless a test for homogeneity is performed, a common odds ratio reported as a single summary statistic is misleading. When the Breslow-Day test[6] was used for this determination of homogeneity, the hypothesis that a common odds ratio may be present for all 20 studies was rejected. This is demonstrated by the finding that the odds ratios decreased as the observed risk of postoperative infection increased in the placebo (nontransfused or untreated control) group. This is noted in Figure 3 by a nonhorizontal line of regression (a horizontal regression line would demonstrate homogeneity of the individual odds ratios). If a test

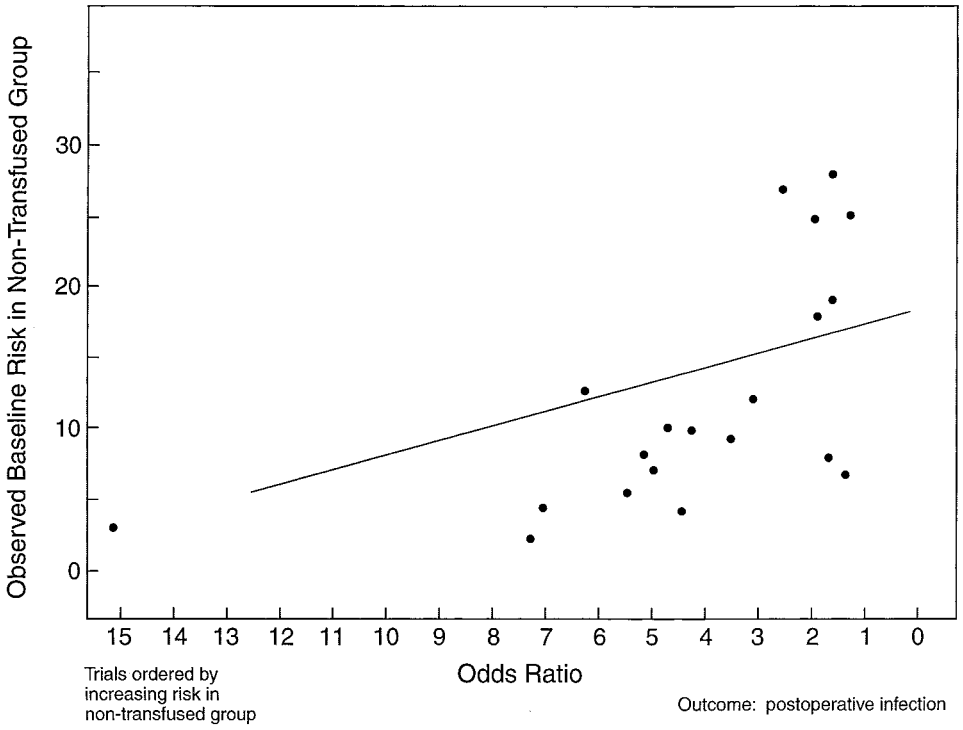

Fig. 3. *Graph demonstrating lack of homogeneity of individual odds ratios constructed by plotting the odds ratios against the observed baseline risk of postoperative infection in the nontransfused group. See Discussion section for details.*

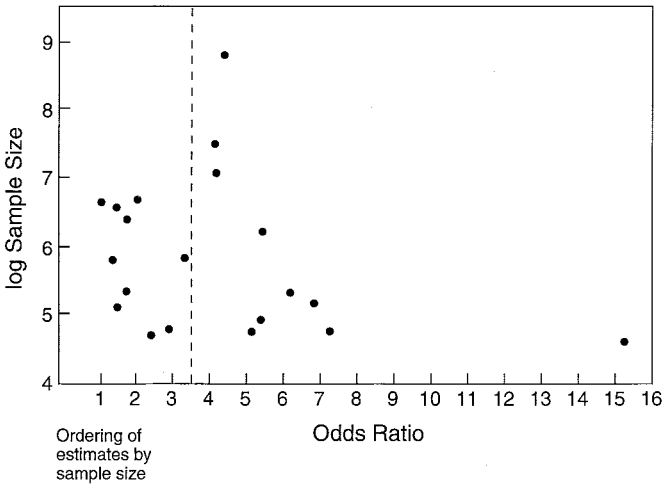

Fig. 4. *A funnel plot obtained by plotting individual odds ratios against their respective log study sample size. Each dot (●) represents one study. See Results section for details.*

for individual odds ratio homogeneity is rejected (as in this case), Brand and Kragt[7] suggested that only individual odds ratios with accompanying *p* values be reported (Fig. 1). However, we elected to report a common odds ratio because it is customary to do so in meta-analyses of clinical studies and also to give the reader a definitive overall numeric impression of the impact of ABT on the incidence of postoperative bacterial infection. Conversely, when the Breslow-Day test[6] was performed on the subset of trauma patients, the individual odds ratios were demonstrated to be homogenous (Fig. 2). Therefore, the reporting of a common odds ratio for this subset of trauma patients would be valid as defined by Brand and Kragt.[7] In contrast to the complete meta-analysis, the individual *p* values found in the trauma subgroup were uniformly and highly significant (Fig. 2). Therefore, the understanding that ABT is of greater significance in causing immune hyporesponsiveness resulting in higher postoperative bacterial infection rates in the trauma victim when compared with the elective surgical patient is supported by the findings of this study.

Also of importance in the findings of this meta-analysis is the mechanism for the additive effect of ABT with trauma on the frequency of postoperative bacterial infections. Isolated hemorrhage (without tissue injury) causes immunosuppression as demonstrated by a post–bacterial challenge mortality rate of 100% in hemorrhaged mice when compared with a 58% mortality rate in unhemorrhaged controls.[29] This model of hemorrhage without tissue trauma[29] demonstrated evidence of reduced cellular (lymphocyte) immune function, and others[30] similarly report reduced response to bacterial infection caused by hemorrhage alone. Bowel bacterial translocation resulting in systemic bacteremia occurs after hemorrhagic shock in both animal models and humans.[31] Other studies report reduced immune response to a bacterial challenge after ABT in animal models.[32] In addition, humans demonstrate reduced natural killer cell function after multiple ABT.[33] These[29–33] and other reports demonstrate the potential additive effects of hemorrhage together with ABT in causing immune hyporesponsiveness in humans. Hemorrhage, hypotension, and traumatic tissue injury combined with ABT resulting in altered T-lymphocyte function[34] may be responsible for the frequently described postoperative immunosuppression reported in the trauma victim,[34,35] resulting in an increased risk of postoperative bacterial infection in this patient group.[3,19,21]

Logistic regression analysis has been used to define the relationship between ABT and infection while taking into consideration other frequently confounding variables, including age, shock, and wound contamination. This approach has been used by Tartter[10] for patients undergoing colon cancer surgery and has demonstrated a consistent highly significant relationship between ABT and postoperative bacterial infection rates. Other studies using similar statistical approaches also report that when additional confounding variables, including gender, Injury Severity Scores, length of surgery, and admission hematocrit are considered, ABT continued to be a significant independent predictor of an increased risk of postoperative infection in a dose-dependent fashion.[19] Other publications[1,2] report this dose-dependent effect of ABT on infection rates in humans, but because these studies[1,2] did not include a well-defined untreated control (nontransfused) group, they were not included in this meta-analysis. Although logistic regression analysis is a well-recognized statistical technique, clinical circumstances dictate that it is impossible to state with certainty that patients receiving ABT are in all respects similar to a nontransfused control group. Thus, these statistical results allow the statement to be made that ABT is associated with an increased risk of postoperative bacterial infection and may or may not be a primary causative factor.

The immunosuppressive effects of ABT may be long-standing. Evidence of immune dysfunction (reduced lymphocyte function,[36] reduced natural killer cell cytotoxicity scores, and helper/suppressor cell ratios[37]) after prior blood transfusions has been reported to be demonstrable for several years. Other investigators report reduced T-cell and total lymphocyte counts in a transfused group when compared with a nontransfused group 18 months after transfusion.[38]

The causative factor(s) responsible for ABT-induced immunosuppression remains undefined. Some investigators have implicated leukocytes,[39] whereas others have implicated the plasma component of blood.[40] Gianotti et al.[41] reported transfused white blood cells to be the blood component responsible for the reduced resistance to *Escherichia coli* bacterial infection and the subsequent mortality rate after burn injury in mice. Regardless of the mechanism, this immunosuppressive effect of blood transfusion is not seen with autologous blood transfusions.[13,22] Although dextran preparations[42] and albumin[43] are reported to cause immune hyporesponsiveness, hydroxyethyl starch[44] is reported to

have minimal antigenicity and little effect on immune function. This effect of human serum albumin preparations on the immune system may explain the increased mortality rate after albumin therapy in humans.[45] No study evaluating the relationship between artificial blood substitute preparations and the immune system in human subjects has been reported.

In summary, this meta-analysis demonstrates that ABT is associated with a significantly increased risk of postoperative bacterial infection in humans. This effect of ABT is of greater significance in the trauma patient and may be an additive factor in the immune hyporesponsiveness demonstrated by this group of patients. Less immunosuppression after the restrictive use of ABT may explain reduced mortality rates in the critically ill patient when lower hemoglobin concentrations are accepted.[46] This untoward effect of ABT can be avoided by autologous blood transfusion,[13,22] and currently is the only clinically available technique to increase hemoglobin concentration without unwanted immunosuppressive effects.

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