Blood Transfusion and Infection After Cardiac Surgery

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Cardiac surgery is the largest consumer of blood products in medicine; although believed life saving, transfusion carries substantial adverse risks. This study characterizes the relationship between transfusion and risk of major infection after cardiac surgery. In all, 5,158 adults were prospectively enrolled to assess infections after cardiac surgery. The most common procedures were isolated coronary artery bypass graft surgery (31%) and isolated valve surgery (30%); 19% were reoperations. Infections were adjudicated by independent infectious disease experts. Multivariable Cox modeling was used to assess the independent effect of blood and platelet transfusions on major infections within 60 ± 5 days of surgery. Red blood cells (RBC) and platelets were transfused in 48% and 31% of patients, respectively. Each RBC unit transfused was associated with a 29% increase in crude risk of major infection (p < 0.001). Among RBC recipients, the most common infections were pneumonia (3.6%) and bloodstream infections (2%). Risk factors for infection included postoperative RBC units transfused, longer duration of surgery, and transplant or ventricular assist device implantation, in addition to chronic obstructive pulmonary disease, heart failure, and elevated preoperative creatinine. Platelet transfusion decreased the risk of infection (p = 0.02). Greater attention to management practices that limit RBC use, including cell salvage, small priming volumes, vacuum-assisted venous return with rapid autologous priming, and ultrafiltration, and preoperative and intraoperative measures to elevate hematocrit could potentially reduce occurrence of major postoperative infections.

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Cardiac morbidity

Demographics management practices associated with risk for infections. Health Research. Its overall objective was to identify national Institutes of Health and Canadian Institutes of the United States and Canada was funded by the National Study Design and Patients

This observational study of postoperative infections occurring up to 65 days after cardiac surgery. The Cardiothoracic Surgical Trials Network has conducted a unique prospective multiinstitutional observational study, with an overall aim to identify modifiable management practices, such as transfusion, associated with infections occurring up to 65 days after cardiac surgery. The primary objectives of the present study were (1) to investigate the association of RBC transfusion and postoperative infection, including type and microbiology; and (2) to identify patient and operative risk factors for infection, including use of RBC and platelets, cell salvage, and timing of transfusion (intraoperative versus postoperative).

Patients and Methods

Study Design and Patients

This observational study of postoperative infections among adults undergoing cardiac surgery at 10 centers in the United States and Canada was funded by the National Institutes of Health and Canadian Institutes of Health Research. Its overall objective was to identify management practices associated with risk for infections. Inclusion criteria were a clinical indication for a cardiac surgical intervention and age 18 years or older. Patients with active systemic infection at enrollment (most commonly hospital transfer patients and those with long preoperative length of stay) were excluded.

The study sample size was not predetermined; rather, enrollment continued until a prespecified minimum of 200 patients with a major infection were identified. This is the number needed to make valid inferences about 20 risk factors for infection based on reliable multivariable models. Data were transmitted from sites using a Web-based electronic data capture system to a secure server administered by the Data Coordinating Center (DCC). Each study site and the DCC received Institutional Review Board approval for the registry. All patients provided written informed consent to participate in the study and to release their medical information during this time frame.

From February 2010 through September 2010, 5,158 consecutive adult cardiac surgery patients were prospectively enrolled in the study. Patients were followed for 65 days after surgery with two planned postdischarge assessments at 30 and 60 days after surgery. The last date of follow-up was November 29, 2010.

Patients had a mean age of 64 ± 13 years and preoperative hemoglobin of 13 ± 1.8 g/dL; 33% were women and 19% had undergone prior cardiac surgery (Table 1). The most common procedures were isolated coronary artery bypass grafting (CABG), 31%, and isolated valve surgery, 30% (Table 1).

Endpoints

All infections were reviewed by an independent event adjudication committee consisting of three infectious disease experts. The final date of event adjudication for this manuscript was April 28, 2011. Infections were classified according to definitions from the Centers for Disease Control and the National Healthcare Safety Network (CDC/NHSN) surveillance [12]. These definitions were slightly revised to accommodate the clinical characteristics of cardiac surgery patients (Appendix).

This study focused on major infections, which included (1) deep incisional surgical site infection occurring at the primary chest incision site; (2) deep incisional surgical site infection occurring at a secondary incision site (e.g., saphenous harvest site, groin cannulation site); (3) mediastinitis; (4) infectious myocarditis or pericarditis; (5) endocarditis; (6) cardiac device infection; (7) pneumonia; (8) empyema; (9) Clostridium difficile colitis; and (10) bloodstream infection.

Data Analysis

Categorical variables were summarized by frequencies and percentages, and continuous variables by means and standard deviations, or medians and interquartile ranges if their distributions were skewed. Because infection occurred in a time-related fashion, time from surgery to infection was described using Kaplan-Meier curves. We recognized there would be a strong association between type of procedure, risk of infection, and risk of transfusion. Consequently, the case mix of our institutions
affects distribution of infection among sites. Therefore, our strategy was to adjust for patient-level characteristics in the multivariable analysis, but not site. Adjusting for site runs the risk of obscuring variation in transfusion practices that is central to the question addressed in the current study.

We used Cox proportional hazards regression to identify the association of blood product utilization with risk of infection after adjusting for patient-level risk factors for major infection and those that would affect clinical decision making about transfusion. Variables tested included demographics, baseline laboratory values, comorbidities, surgical procedure, and surgery time. After performing the analysis using this strategy, we performed a secondary analysis that took into account patient clustering within sites using a marginal Cox proportional hazards model. Results were consistent with the primary analysis reported. All tests were conducted at the two-sided 0.05 significance level. All analyses used SAS version 9.2 statistical software (SAS Institute, Cary, NC).

Results

Infections After Cardiac Surgery

Overall, 5,158 patients experienced 298 major infections (5.8%). The most commonly occurring major infections were pneumonia, C difficile colitis, and bloodstream infections. Surgical site infections were uncommon (Table 2). More than 40% of major infections occurred after hospital discharge.

Prevalence of Transfusion

Overall, 2,481 patients (48%) received at least 1 unit RBC, with close to half of transfused patients receiving 1 or 2 units (48%). Although percentage of patients transfused ranged from 33% to 74%, practice was relatively homogeneous across sites. Median number of units transfused was 2 at 8 sites and 3 at 2. Of patients transfused RBC, 27% (n = 1,385) received them only in the operating room, 38% (n = 1,941) only postoperatively, and 35% (n = 1,805) both intraoperatively and postoperatively (Fig 1).

For patients transfused, median number of RBC units transfused was 3 (interquartile range, 2 to 5). The highest volume of RBC was given during transplant, left ventricular assist device implantation, and thoracic aorta procedures (Table 3). Timing of transfusion (see Fig 1) was strongly related to volume of units given, with the majority of patients receiving intraoperative RBC receiving only 1 to 2 units. Platelets were administered to 31% of patients, and 85% received cell salvage blood. In this latter group, 38% received cell salvage blood only.

Transfusion and Infection

There was a dose-related association between quantity of RBCs transfused and risk of infection, with crude risk increasing by an average of 29% with each RBC unit (p < 0.001; Fig 2). Although in univariate analysis, platelet transfusion was associated with a greater risk of infection, once adjusted for quantity of transfused RBC units, platelet transfusion was protective (Fig 3). Specifically, lower risk of infection was observed when platelets were transfused with more than 4 units of RBCs.

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<tr>
<th>Table 2. Infections and Transfusions</th>
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<td>Pneumonia</td>
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<td>Bloodstream</td>
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<td>Clostridium difficile colitis</td>
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<td>Deep incision surgical site (chest)</td>
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<td>Myocarditis or pericarditis</td>
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<th>Table 3. Procedure and Transfusion</th>
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<td>Procedure</td>
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<td>Isolated CABG</td>
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<td>CABG + valve</td>
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<td>Transplant or LVAD</td>
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<td>Thoracic aorta</td>
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<td>Other</td>
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<td>Overall</td>
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* Median units among patients transfused (n = 2,481).

CABG = coronary artery bypass grafting; LVAD = left ventricular assist device.
In addition to patient characteristics such as chronic obstructive pulmonary disease, heart failure, and elevated preoperative serum creatinine, other relevant risk factors for major infection included longer duration of surgery and whether patients received a transplant or left ventricular assist device (Table 4). However, risk did not appear to be increased after reoperations nor after postoperative reoperations for bleeding. Use of cell salvage was not associated with increased risk of infection. Interestingly, diabetes mellitus (even when restricting patients to those receiving insulin or oral medications) and body mass index were among the baseline characteristics that were not predictive of infection.

The association of RBC transfusion with infection differed depending on type of infection observed. Thus, although transfused patients had a higher risk of any type of infection, the relationship was particularly strong for pneumonia and bacteremia (see Table 2).

Comment

Principal Findings

This unique contemporary multiinstitutional study of infections occurring up to 65 days after a variety of cardiac surgical operations, with well-adjudicated events, revealed that RBC transfusion, particularly postoperative transfusion, was strongly associated with major postoperative infections in a dose-related fashion. Use of platelets appeared to have a mitigating effect, especially for patients receiving higher numbers of RBC units. The association between RBC transfusion and infection was particularly strong for pneumonia and bacteremia.


Transfusion and Infection

There is more than a 20-year history with over 200 reports of mostly observational studies demonstrating a relationship between transfusion and postoperative infection [13–20]. This finding is not unique to cardiac surgery, as demonstrated by the meta-analysis of Hill and colleagues [21] in trauma and elective general surgery patients. However, there have been some notable exceptions. Ali and colleagues [22], for example, did not find such a relation and suggested that “clinicians should reconsider withholding blood transfusion in patients solely owing to concerns of predisposition to infection.” Vamvakas and Moore [5] reviewed the evidence reported up to 1994 and concluded that a causal pathway was not established and that there were multiple confounders that could render transfusion merely a surrogate marker for infection and other adverse outcomes. These include extent of surgical trauma, which itself is an immune modulator, surgical bleeding and factors leading to coagulopathy, reoperation for bleeding, and unanalyzed patient and operative factors. In studies before 2004, the effect of transfusions may have been in part related to low-dose bacterial contamination from the phlebotomy site and methods of blood handling and storage [23]. Yet, studies since then continue to demonstrate this association, including our contemporary multiinstitutional study.

Several mechanisms have been proposed to explain this association. The most frequently cited is immune modulation [24]. This is proposed as the mechanism for transfusion-related acute lung injury and transfusion-associated circulatory overload. However, as Koch and colleagues [25] demonstrate, a large proportion of patients after cardiopulmonary bypass—which renders the lungs relatively ischemic—meet qualitative criteria for transfusion-related acute lung injury, whether they are transfused or not. There is some controversy as to whether immune modulation is mediated by white blood cells (WBC) contained in the transfusion, with demonstrated reduction in natural killer cell function. The several randomized trials of WBC-depleted transfusions are inconclusive [13, 26]. In addition, bactericidal permeability-increasing protein increases during blood storage, indicating presence of activated WBCs, and in transfused patients in the 1990s, this serum biomarker was substantially increased along with other inflammatory mediators known to promote infection [27]. White blood cell-depleted and irradiated blood transfusion is now routinely practiced throughout the world, but not necessarily in the United States. The sites in our network, however, all used leukocyte-reduced blood, and most sites used irradiated blood for special patient categories such as transplants. Therefore, this mechanism is not likely to play a role in our observations.

The most recent theory relates to circulating non-transferrin-bound iron, which promotes proliferation of pathogenic bacteria [28, 29]. The longer blood is stored before transfusion, the higher the serum iron concentration and transferrin saturation after transfusion of human volunteers [30]. Further, growth of Escherichia coli is enhanced when exposed to serum samples of volunteers with elevated non–transferrin-bound iron. The increase in iron is correlated with elevation in bilirubin levels, indicating that the mechanism for transferrin saturation is likely more rapid destruction of erythrocytes from older stored blood [31].

Attenuation of the relationship of transfused blood to infection was seen after administration of platelets. This observation has been reported by others [19]. Banbury and colleagues [32] speculated that this phenomenon
may be related to cotransfusion of immunoglobulin with platelet-rich plasma, which has been demonstrated in other settings to reduce postoperative infections. Although an increase in infections may itself explain the relation between RBC transfusion and prolonged postoperative length of stay and increased mortality, it also has been demonstrated that the number of transfusions given during and after cardiac surgery appears to be associated with not only increased early mortality, but also a substantial increase in late risk of death [14, 16, 18, 33, 34].

Study Limitations
Because this is an observational hypothesis-generating study, the reported associations cannot be considered causal. Participating institutions were generally high-volume tertiary referral centers performing a substantial number of complex operations leading to heterogeneity of procedures and patients. Surgeon-specific data for each procedure were not recorded. Moreover, we do not know the exact timing of transfusion in relation to postoperative infection; most transfusions are given intraoperatively and in the intensive care unit after surgery. Generally, infections are not manifest by that time, with many infections occurring after hospital discharge. We also do not know the age of transfused units, which may affect the relationship to infection [31], nor if the units came from a male or female donor. Transfused units were not independently audited. Finally, we also do not know the clinical triggers or reasons for transfusion; indeed, no attempt was made to control transfusion or any other institutional behaviors. We simply focused on transfusion risks, and cannot address the important clinical dilemma of when to transfuse to realize benefits of transfusion that outweigh the risks of anemia.

Clinical Implications
Even recent guidelines advocating blood conservation continue to stress resource utilization and blood-borne viruses, without much consideration given to elevation of postoperative morbidity such as infections [7]. All risks, and benefits, of transfusion must be weighed against the risks of anemia, which itself is associated with adverse outcomes [10]. Given the high prevalence of preoperative antiplatelet therapy, particularly for patients with coronary artery disease, surgeons can take some solace in the relative safety of administering platelets.

There are a number of process measures that can be employed to avoid transfusion [7, 35]. These include use of cell salvage (which in our study was not associated with increased risk of infection), use of small priming volume cardiopulmonary bypass circuits, minimizing he-modilution by crystalloid fluids, use of vacuum-assisted venous return [36, 37] with rapid autologous priming [38], increase in hematocrit by modified ultrafiltration [39], elevation of preoperative hematocrit in elective cases by iron and B-complex vitamin administration, and possibly, the selective use of erythropoetin, although not approved by the Food and Drug Administration for this indication [40, 41]. In addition, attention to intraoperative hemostasis, establishment of protocols for transfusion and reoperation for bleeding, use of antifibrinolytic drugs, and a tolerance for mild-to-moderate anemia are reasonable means to reduce use of a scarce resource [35].

References
20. Koch CG, Li L, Duncan AJ, et al. Morbidity and mortality risk associated with red blood cell and blood-component trans-

Appendix

Infection Definitions

Deep Incisional Surgical Site Infection (SSI), Primary (DIP)
A surgical site infection (SSI) that is identified in the primary chest incision and meets all of the following criteria:
1. Infection occurs within 60 days after the operative intervention
2. Infection involves deep soft tissues (eg, fascial and muscle layers)
3. Patient has at least one of the following:
   a. Purulent discharge from the deep incision, but not from the organ/space component of the surgical site
   b. A deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture positive, or not cultured, when the patient has at least one of the following: fever >38°C, localized pain or tenderness
   c. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination
   d. Diagnosis of deep incisional SSI by the surgeon or attending physician

Deep Incisional Surgical Site Infection, Secondary (DIS)
An SSI that is identified in the secondary incision (eg, donor site [leg] incision for CABG) in a patient who has had an operation with one or more incisions and meets all of the following criteria:
1. Infection occurs within 60 days after the operative intervention
2. Infection involves deep soft tissues (eg, fascial and muscle layers)
3. Patient has at least 1 of the following:
   a. Purulent discharge from the deep incision, but not from the organ/space component of the surgical site
   b. A deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture positive, or not cultured, when the patient has at least 1 of the following: fever >38°C, localized pain or tenderness
   c. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination
   d. Diagnosis of deep incisional SSI by the surgeon or attending physician

Empyema

Pyothorax (empyema thoracis) is the accumulation of pus within the pleural cavity. Empyema can occur in the setting of thoracic surgery, instrumentation of the pleural space (thoracentesis, chest tube placement), and suppurative lung disease (ie, pneumonia, lung abscess, bronchiectasis). Empyema is characterized by bacterial organisms seen on gram stain or the aspiration of pus on thoracentesis. A positive culture is not required for diagnosis since there are several reasons why bacteria may not be cultured from an empyema: anaerobic organisms are difficult to culture; sampling is often performed after a patient has received antibiotics; and sterile inflammatory fluid can be aspirated adjacent to an infection.

(Continued)
Appendix. Continued

**Endocarditis (ENDO)**

Endocarditis of a natural or prosthetic heart valve must meet at least one of the following criteria:

1. Direct evidence of endocarditis based on histological findings
2. Positive gram stain results or cultures of specimens obtained from surgery or autopsy
3. Two major clinical criteria
4. One major and any three minor clinical criteria
5. Four minor clinical criteria

**Major Clinical Criteria**

1. Positive blood cultures
   a. Typical microorganism for infective endocarditis from two separate blood cultures
   b. Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from blood cultures drawn more than 12 hours apart or all of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 hour apart
   c. Single positive blood culture for Coxiella burnetii or anti-phase I immunoglobulin G antibody titer >1:800
2. Evidence of endocardial involvement
   a. Positive echocardiogram for infective endocarditis
   b. New valvar regurgitation

**Minor Clinical Criteria**

1. Predisposition
   a. Heart condition
   b. Intravenous drug use
2. Fever >38°C
3. Vascular phenomena
   a. Major arterial emboli
   b. Septic pulmonary infarcts
   c. Myotic aneurysm
   d. Intracranial hemorrhage
   e. Conjunctival hemorrhages
   f. Janeway lesions
4. Immunologic phenomena
   a. Glomerulonephritis
   b. Osler’s nodes
   c. Roth spots
   d. Rheumatoid factor
5. Microbiologic evidence
   a. Positive blood culture, but not meeting major criteria as noted previously
   b. Serologic evidence of active infection with organism consistent with infective endocarditis
6. Echocardiographic minor criteria eliminated

**Infectious Myocarditis or Pericarditis (CARD)**

Infectious myocarditis or pericarditis must meet at least one of the following criteria:

1. Patient has organisms cultured from pericardial tissue or fluid obtained by needle aspiration or during a surgical operation
2. Patient has at least two of the following signs or symptoms with no other recognized cause: fever >38°C, chest pain, paradoxical pulse, or increased heart size, and at least one of the following:
   a. Abnormal electrocardiogram consistent with myocarditis or pericarditis
   b. Positive antigen test on blood (eg, H influenzae, S pneumoniae)
   c. Evidence of myocarditis or pericarditis on histologic examination of heart tissue
   d. Fourfold rise in type-specific antibody with or without isolation of virus from pharynx or feces
   e. Pericardial effusion identified by echocardiogram, computed tomography scan, magnetic resonance imaging, or angiography

**Mediastinitis (MED)**

Mediastinitis must meet at least one of the following criteria:

1. Patient has organisms cultured from mediastinal tissue or fluid obtained during a surgical operation or needle aspiration
2. Patient has evidence of mediastinitis seen during a surgical operation or histopathologic examination
3. Patient has at least one of the following signs or symptoms with no other recognized cause: fever >38°C, chest pain, or sternal instability, and at least one of the following:
   a. Purulent discharge from mediastinal area
   b. Organisms cultured from blood or discharge from mediastinal area

**Pneumonia (PNEU)**

Clinically defined pneumonia must meet all of the following criteria:

1. At least one or more chest radiographs no earlier than 2 days after surgery, with at least one of the following:
   a. New or progressive and persistent infiltrate
   b. Consolidation
   c. Cavitation
2. Patient has at least one of the following signs or symptoms with no other recognized cause: fever >38°C, chills, or hypotension, and signs and symptoms noted previously
3. Infection of blood-contacting surfaces of a left ventricular assist device documented by positive site culture