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ORIGINAL ARTICLE

# Perioperative blood transfusion is associated with post-operative infectious complications in patients with Crohn's disease

Nan Lan[1], Luca Stocchi[2], Yi Li[2], Bo Shen[1,*]

[1]Center for Inflammatory Bowel Disease, and Digestive Disease and Surgery Institute, The Cleveland Clinic Foundation, Cleveland, OH, USA and [2]Department of Colorectal Surgery, Digestive Disease and Surgery Institute, The Cleveland Clinic Foundation, Cleveland, OH, USA

*Corresponding author. Center for Inflammatory Bowel Diseases, Digestive Disease and Surgery Institute-A31, The Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195, USA. Tel: +1–216–444–9252; Fax: +1–216–444–6305; Email: shenb@ccf.org

## Abstract

**Background:** We have previously demonstrated that blood transfusion (BT) was associated with post-operative complications in patients undergoing surgery for Crohn's disease (CD), based on our institutional data registry. The aim of this study was to verify the association between perioperative BT and infectious complications in CD patients enrolled in the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database.
**Methods:** All CD patients undergoing surgery between 2005 and 2013 were identified from NSQIP. Variables were defined according to the ACS NSQIP guidelines. The primary outcome was infectious complications, including superficial, deep and organ/space surgical site infection, wound dehiscence, urinary tract infection, pneumonia, systemic sepsis and septic shock. Multivariate analyses were performed to assess the risk factors for post-operative infections.
**Results:** All 10 100 eligible patients were included and 611 (6.0%) received perioperative BT. BT patients were older, lighter in weight and more likely to be functionally dependent. BT patients were more likely to have post-operative infectious complications than those without BT, including superficial surgical site infection (SSI) (10.8% *vs* 7.4%, $p=0.002$), deep SSI (3.3% *vs* 1.6%, $p=0.003$), organ/space SSI (14.2% *vs* 5.4%, $p<0.001$), pneumonia (3.8% *vs* 1.3%, $p<0.001$), urinary tract infection (3.9% *vs* 2.2%, $p=0.006$), sepsis (11.5% *vs* 4.5%, $p<0.001$) and sepsis shock (3.1% *vs* 0.8%, $p<0.001$). Multivariate analysis showed that *intra*- and/or *post*-operative BT was an independent risk factor for post-operative infectious complications (odds ratio [OR] = 2.2; 95% confidence interval [CI]: 1.8–2.7; $p<0.001$) and the risk increased with each administered unit of red blood cell (OR = 1.3, 95% CI: 1.2–1.5). Other independent factors were history of smoking, chronic heart disease, diabetes, hypertension and the use of corticosteroids. *Pre*-operative BT, however, was not found to be a risk factor to post-operative infections.
**Conclusions:** *Intra*- and/or *post*-operative, not *pre*-operative, BT was found to be associated with an increased risk for post-operative infectious complications in this CD cohort. Therefore, the timing and risks and benefits of BT should be carefully balanced.

**Key words:** blood transfusion; Crohn's disease; infectious complications; surgical outcomes

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## Introduction

The clinical course of Crohn's disease (CD) is often unpredictable. Most patients do require surgery, sometimes repeatedly, to correct or reduce clinical symptoms and improve patient's quality of life (QOL) [1]. Investigators have attempted to identify the risk factors associated with post-operative adverse outcomes, such as infection and anastomotic leak, believing that risk factor modification could result in reduced morbidity, length of hospital stay and mortality, and improved patient's QOL [2]. Purported risk factors for post-operative infections include weight loss and the use of corticosteroids or anti-tumor necrosis factor (TNF) biological agents [3–5]. Blood transfusion (BT), on the other hand, has been also found to be associated with multiple adverse surgical outcomes such as venous thrombosis, infections and increased 5-year mortality [6–8]. Purported mechanisms include the disruption of coagulation factors, altered balance between anti- and pro-inflammatory factors [9] and the release of cytokines from apoptic white blood cell (WBC) in allogeneic blood [10]. Biological factors in the blood may also influence the innate immunity making patients susceptible to infections [11]. It appears that BT carries a significant risk for infections and profound immunosuppression [12–14].

BT is still a common practice for patients with severe anemia [12,15]. While aiming to correct patient's anemic state, the effect BT might have on possible consequent surgery is often overlooked. The actual risk of BT remains controversial [16–19], even though extensive research has been conducted in some major operations such as cardiac surgery [6,20] as well as cancer-related surgery [10,21–23]. As for CD surgical patients, BT has been reported to be associated with an increased risk of post-operative endoscopic and surgical recurrence of CD [24,25] as well as septic complications [26]. Our previous institutional, registry-based study showed that BT was associated with both infectious and noninfectious outcomes [27]. These studies, however, were mostly conducted in a single institution and they usually combine all perioperative (*pre*-, *intra*- and *post*-) transfusion for analysis. Since CD patients are inherently susceptible to postsurgical complications, it would be important to clarify the possible and specific risk factors that might lead to an unsatisfying surgical outcome on a larger scale. Therefore the aims of this study were: (i) to identify the rate of transfusion among CD patients undergoing surgery and adverse outcomes associated with BT and (ii) to assess the risk factors, including perioperative BT, for post-operative infectious complications, by using the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP).

## Patients and methods

### Data sources

The ACS NSQIP is a national database prospectively collecting data from hundreds of centers voluntarily participating in the program across the USA. The data were collected by an assigned trained Surgical Clinical Reviewer on randomly assigned patients per database protocol. The number and types of variables collected will differ from hospital to hospital, depending on the hospital size, patient population and quality improvement focus. The data include demographic, clinical and laboratory information, along with surgical outcome variables including 30-day post-operative complications. Patients with the diagnosis of CD were extracted between 2005 and 2013. This study was approved by the Cleveland Clinic Institutional Review Board.

### Inclusion and exclusion criteria

All patients with CD were identified by using the International Classification of Disease, 9th revision (ICD-9) via ICD-9=555.XXX. All surgical procedures related to CD were included in this study. Exclusion criteria were: (i) patients without complete data on BT and post-operative follow-up and (ii) patients with ongoing infection(s) upon admission that included pneumonia, wound infection and sepsis.

### Data collection

According to the ACS NSQIP guideline descriptions, there were three variables in the database that concerned transfusion: (i) transfusion of more than four units of red blood cell (RBC) within 72 hours before surgery, (ii) the number of RBC units given *intra*-operatively and (iii) occurrence of transfusion for bleeding. Transfusion of four units or more RBC in 72 hours before surgery was regarded as *pre*-operative BT for analysis. The number of RBC units given *intra*-operatively was an old variable recorded in a limited number of patients before 2009 and was the only quantified BT-related variable available in the database. The occurrence of transfusion for bleeding, which was defined as any transfusion given from the time patients enter the operating room (*intra*-operative) up to 72 hours post-operatively (*post*-operative), was regarded as *intra*- and/or *post*-operative BT for analysis. No variables were documented in the database for transfusions occurring outside the 72-hour range before and after surgery.

Demographic information, including age, gender, height and weight, were extracted from the database. Height and weight were used to calculate the body mass index (BMI) for each patient. The ethnicity of the patients was classified into the following categories according to the NSQIP guideline: African American, American Indian or Alaska Native, Asian, Hawaiian or Pacific Islander, White and unknown. Functional health status was defined as the patient's ability to perform daily activities with or without the help of others. Daily activities include: bathing, feeding, dressing, toileting and mobility. Patients who required assistant with some or all daily activities were regarded as functionally dependent and patients who did not require assistance from another person for any daily activities were regarded as functionally independent. The American Society of Anesthesiology (ASA) Physical Status Classification of the patient's present physical condition was also extracted. It was rated on a scale from 1 to 5, 1 being normal healthy patients and 5 being a moribund patient who might not survive without the operation. Patients' clinical histories were also extracted from the data, along with previous surgical history and medication history.

### Outcome measurements

The primary outcome was infectious event after surgery, which includes superficial, deep and organ/space surgical site infection (SSI), wound dehiscence, urinary tract infection (UTI), pneumonia, systemic sepsis and septic shock. Secondary outcome included other post-operative adverse outcomes such as the length of hospital stay, unplanned tracheal intubation, ventilator usage exceeding 48 hours, acute renal failure, cardiac arrest

that required cardiopulmonary resuscitation (CPR), any thromboembolic events and unplanned return to the operation room for surgical exploration.

### Statistical analysis

Categorical variables were summarized as percentages. Quantitative variables were summarized as mean ± standard deviation. Tests for association between groups and categorical variables were performed using the chi-square method and Fisher's exact test. For quantitative variables, the means were compared by Student's *t*-tests or Wilcoxon rank sum tests. $P<0.05$ was accepted as statistically significant. Comparisons of infection rates were conducted between those with any BT and those without. Along with BT, other factors were also evaluated by univariate and multivariate analyses to identify whether BT was an independent risk factor for infection-related outcome. The relationship between the number of units of packed-RBC transfused and infection was also be examined by logistic analysis.

## Results

### Demographic and clinical data

A total of 10 100 patients were extracted from the ACS NSQIP database and 611 (6.0%) of them underwent perioperative BT. The mean age for the whole cohort was 42.0±15.2 years and patients with BT were older than those without BT (46.3±16.5 *vs* 41.7±15.1 years, $p<0.001$). BMI was 23.9±6.1 kg/m$^2$ in patients with BT and 24.9±6.7 kg/m$^2$ in those without BT ($p<0.001$). Of the whole cohort, 27 (4.4%) patients with BT and 124 (1.3%) patients without BT were functionally dependent ($p<0.001$). Regarding the ASA Classification, patients without BT were more often found to be classified into Levels 1 and 2, while patients with BT were more often found to be Levels 3 and 4 (Table 1).

### Adverse outcomes

Patients with BT had a longer mean total surgery time than controls (214±115 *vs* 159±95 minutes, $p<0.001$). Transfused patients had a longer total hospital stay than controls (12.4±12.1 *vs* 7.6±7.0 days, $p<0.001$). Patients with BT were associated with an increased rate of superficial SSI (10.8% *vs* 7.4%, $p=0.002$), deep SSI (3.3% *vs* 1.6%, $p=0.003$), organ space SSI (14.2% *vs* 5.4%, $p<0.001$), pneumonia (3.8% *vs* 1.3%, $p<0.001$), UTI (3.9% *vs* 2.2%, $p=0.006$), sepsis (11.5% *vs* 4.5%, $p<0.001$) and sepsis shock (3.1% *vs* 0.8%, $p<0.001$), as compared with those without BT (Table 1). The rate for wound disruption, however, was comparable between the two groups (1.6% *vs* 1.0%, $p=0.103$). In addition, patients with transfusion were also at risk of suffering thromboembolic complications such as pulmonary embolism (1.3% *vs* 0.4%, $p=0.003$) and deep vein thrombosis (3.1% *vs* 0.8%, $p<0.001$). A higher risk for respiratory dysfunction was also found in those with BT. Patients with BT were more likely to undergo unplanned tracheal intubation (3.3% *vs* 0.7%, $p<0.001$) and to have ventilators for more than 48 hours (3.6% *vs* 0.6%, $p<0.001$) (Table 1).

### Risk factors for post-operative infections

In the whole cohort, 1850 patients (18.3%) were found to have post-operative infections. The infection rate in patients with *pre*-operative BT was 30.3% (23/76), while it was 32.9% (187/568) in patients with *intra*-/*post*-operative BT. Possible variables associated with post-operative infections were analysed (Table 2). A significant difference was found in the history of chronic illnesses, such as diabetes (27.9% *vs* 18.0%, $p<0.001$), chronic obstructive pulmonary diseases (25.9% *vs* 18.2%, $p=0.02$), chronic heart diseases (63.6% *vs* 18.3%, $p=0.001$) and hypertension (22.0% *vs* 17.6%, $p<0.001$). Patients being dependent on overall health status (32.5% *vs* 18.1%, $p<0.001$), having a weight loss of more than 10% (21.3% *vs* 18.1%, $p=0.02$), higher ASA level (8.0% *vs* 16.3% *vs* 23.2% *vs* 23.0% *vs* 0.0%, $p<0.001$) or worse wound classification (11.2% *vs* 16.7% *vs* 21.4% *vs* 23.1%, $p<0.001$) were also more susceptible to infection. In addition, the use of corticosteroids (19.9% *vs* 17.2%, $p=0.001$), smoking (22.3% *vs* 16.9%, $p<0.001$), peripheral vascular disease (40.9% *vs* 18.3%, $p=0.01$) and bleeding disorders (24.7% *vs* 18.2%, $p=0.02$) were also found to be more common in patients with post-operative infections. Laboratory results showed significant differences in hypoalbuminemia (21.3% *vs* 18.0%, $p=0.001$), low hematocrit (19.1% *vs* 17.5%, $p=0.04$) and high alkaline phosphatase (23.7% *vs* 18.4%, $p<0.001$). Both emergency surgery (22.4% *vs* 18.1%, $p=0.03$) and open surgery (20.8% *vs* 14.0%, $p<0.001$) were more susceptible to post-operative infection.

Multivariate analysis was conducted with the inclusion of all variables that were found to be statistically significant in the univariate analysis (Table 3). The results showed that *intra*-/*post*-operative BT was independently related to infections with an odds ratio (OR) of 2.1 and 95% confidence interval (CI) of 1.7–2.6. *Pre*-operative transfusion, on the other hand, was not found to be a risk factor (OR=1.1, 95% CI: 0.7–2.0). Other risk factors were a history of smoking (OR=1.4, 95% CI: 1.2–1.6), chronic heart diseases (OR=4.7, 95% CI: 1.0–21.3), diabetes (OR=1.7; 95% CI: 1.2–2.3), the use of corticosteroids (OR=1.2, 95% CI: 1.1–1.4) and a dependent health status (OR=1.8, 95% CI: 1.2–2.6). Laparoscopic surgery (OR=0.7, 95% CI: 0.6–0.8) was found to be a protective factor.

### Assessment of dose-dependency between BT and post-operative infectious complications

The above data showed that *intra*- and/or *post*-operative transfusion had an adverse impact on infectious complication of CD surgery. The only quantified variable available in the database was the number of RBC infused *intra*-operatively which could be found in 3648 cases. There were a total of 218 patients that received *intra*-operative transfusion (Table 4). After assessing all BT data available with logistic regression, we found that the overall OR for infection was 1.3 (95% CI: 1.2–1.5) for each increase in units of blood infused *intra*-operatively, suggesting that the adverse effect on the infectious complication was dose-dependent.

## Discussion

The prospectively maintained national database has provided a powerful tool to sort out the controversy in the association between BT and post-operative infectious complications. This is especially important in patients with CD, as those patients are prone to the development of those complications. We found that patients with BT were older and more likely to have a lower BMI. Those with concomitant chronic illness were more likely to need BT as well. BT patients seemed to have a longer operative time and a longer total hospital stay. BT itself was found to be significantly associated with infectious outcome along with thromboembolism, respiratory failure, renal failure and cardiac arrest. In multivariate analysis, we confirmed that *intra*-/*post*-operative BT was an independent risk factor and the association of *intra*- and/or

**Table 1.** Comparison of demographic and post-operative complications between patients with and without BT

| | Total (*n*=10 100) | Patients with transfusion (*n*=611) | Patients without transfusion (*n*=9489) | *P*-value |
|---|---|---|---|---|
| **Age, years** | 42.0±15.2 | 46.3±16.5 | 41.7±15.1 | <0.001 |
| **Female, *n* (%)** | 5473 (54.2) | 326 (53.4) | 5147 (54.3) | 0.67 |
| **Body mass index, kg/m$^2$** | 24.9±6.7 | 23.9±6.1 | 24.9±6.7 | <0.001 |
| **Ethnicity, *n* (%)** | | | | <0.001 |
| American Indian or Alaska Native | 23 (0.2) | 3 (0.5) | 20 (0.2) | |
| Asian | 62 (0.6) | 6 (1.0) | 56 (0.6) | |
| African American | 789 (7.8) | 80 (13.1) | 709 (7.5) | |
| Native Hawaiian or Pacific Islanders | 15 (0.1) | 0 (0.0) | 15 (0.2) | |
| Caucasian | 8368 (82.9) | 468 (76.6) | 7900 (83.3) | |
| Unknown | 843 (8.3) | 54 (8.8) | 789 (8.3) | |
| **Diabetes, *n* (%)** | 308 (3.0) | 35 (5.7) | 273 (2.9) | <0.001 |
| **History of smoking, *n* (%)** | 2600 (25.7) | 132 (21.6) | 2468 (26.0) | 0.016 |
| **Alcohol use, *n* (%)** | 63 (0.6) | 2 (0.3) | 61 (0.6) | 0.59 |
| **Dependent functional health status, *n* (%)** | 151 (1.5) | 27 (4.4) | 124 (1.3) | <0.001 |
| **ASA classification at time of surgery, *n* (%)** | | | | <0.001 |
| 1—No disturb | 251 (2.5) | 5 (0.8) | 246 (2.6) | |
| 2—Mild disturb | 6619 (65.5) | 272 (44.5) | 6347 (66.9) | |
| 3—Severe disturb | 3139 (31.1) | 316 (51.7) | 2823 (29.7) | |
| 4—Life threat | 74 (0.8) | 16 (2.6) | 58 (0.7) | |
| 5—Moribund | 3 (0.0) | 1 (0.1) | 2 (0.0) | |
| **Location of Crohn's disease, *n* (%)** | | | | <0.001 |
| Large bowel | 1434 (14.2) | 103 (16.9) | 1331 (14.0) | |
| Small bowel | 1968 (19.5) | 62 (10.1) | 1906 (20.1) | |
| Both | 1669 (16.5) | 80 (13.1) | 1589 (16.7) | |
| Unspecific | 2390 (23.7) | 121 (19.8) | 2269 (23.9) | |
| **Emergency surgery, *n* (%)** | 397 (3.9) | 34 (5.6) | 363 (3.8) | 0.032 |
| **Laparoscopy surgery, *n* (%)** | 3647 (36.1) | 153 (25.0) | 3494 (36.8) | <0.001 |
| **Wound classification, *n* (%)** | | | | <0.001 |
| 1—Clean | 116 (1.1) | 5 (0.8) | 111 (11.2) | |
| 2—Clean/contaminated | 6775 (67.1) | 333 (54.5) | 6442 (67.9) | |
| 3—Contaminated | 2109 (20.9) | 175 (28.6) | 1934 (20.4) | |
| 4—Dirty/infected | 1100 (10.9) | 98 (16.0) | 1002 (10.6) | |
| **Length of surgery, minutes** | 162.4±88.0 | 214.4±115.0 | 159.0±95.0 | <0.001 |
| **Length of hospital stay, days** | 7.9±7.5 | 12.4±12.1 | 7.6±7.0 | <0.001 |
| **Infectious complications, *n* (%)** | | | | |
| Superficial surgical site infection | 772 (7.6) | 66 (10.8) | 706 (7.4) | 0.002 |
| Deep surgical site infection | 175 (1.7) | 20 (3.3) | 155 (1.6) | 0.003 |
| Organ space surgical site infection | 596 (5.9) | 87 (14.2) | 509 (5.4) | <0.001 |
| Wound disrupt | 101 (1.0) | 10 (1.6) | 91 (1.0) | 0.103 |
| Pneumonia | 144 (1.4) | 23 (3.8) | 121 (1.3) | <0.001 |
| Urinary tract infection | 234 (2.3) | 24 (3.9) | 210 (2.2) | 0.006 |
| Sepsis | 501 (5.0) | 70 (11.5) | 431 (4.5) | <0.001 |
| Sepsis shock | 97 (1.0) | 19 (3.1) | 78 (0.8) | <0.001 |
| **Other complications, *n* (%)** | | | | |
| Deep vein thrombosis | 101 (0.1) | 19 (3.1) | 82 (0.8) | <0.001 |
| Pulmonary embolism | 42 (0.4) | 8 (1.3) | 34 (0.4) | 0.003 |
| Unplanned intubation | 88 (0.9) | 20 (3.3) | 68 (0.7) | <0.001 |
| Ventilator >48 hours | 83 (0.8) | 22 (3.6) | 61 (0.6) | <0.001 |
| Acute renal failure | 20 (0.2) | 5 (0.8) | 15 (0.2) | 0.006 |
| Cardiac arrest that requires cardiopulmonary resuscitation | 11 (0.1) | 5 (0.8) | 6 (0.1) | <0.001 |
| Return to the operation room | 584 (5.8) | 87 (14.2) | 497 (5.2) | <0.001 |

*post*-operative infection appeared to be dose-dependent. *Pre*-operative BT, however, was not found to be a risk factor.

CD patients were susceptible to post-operative infections. There were many known risk factors that could further increase the odds. In general, patients with penetrating disease or with unfavorable biochemistry parameters such as hypoalbuminemia and anemia were often at risk of developing infections after surgery [4,28–30]. Furthermore, pre-operative medications such as corticosteroids, biologics and even narcotic use were cited to increase the incidence of infectious complications [4,5,28,30]. Complex surgery and a longer duration of surgery were all relevant factors that might lead to infection [2,3,5].

In addition, previously published data suggest that BT was also related to post-operative infectious complications, longer hospital stay and overall higher morbidity and mortality in surgical non-CD patients [31–33]. On the other hand, the frequency of BT has still

**Table 2.** Univariate analysis of risk factors for post-operative infections in Crohn's disease

| | No. of patients | Post-operative infection, *n* (%) | *P*-value |
|---|---|---|---|
| **Gender** | | | 0.16 |
| Female | 5473 | 1030 (18.8) | |
| Male | 4627 | 820 (17.7) | |
| **Ethnicity** | | | 0.30 |
| American Indians or Alaska native | 23 | 4 (17.4) | |
| Asian | 62 | 8 (12.9) | |
| African American | 789 | 159 (8.6) | |
| Native Hawaiian or Pacific Islander | 15 | 5 (33.3) | |
| Caucasian | 8368 | 1531 (18.3) | |
| Unknown | 843 | 143 (7.7) | |
| **Diabetes** | | | <0.001 |
| Yes | 308 | 86 (27.9) | |
| No | 9792 | 1764 (18.0) | |
| **History of smoking** | | | <0.001 |
| Yes | 2600 | 579 (22.3) | |
| No | 7500 | 1271 (16.9) | |
| **History of alcohol use** | | | 0.62 |
| Yes | 63 | 10 (15.9) | |
| No | 10 037 | 1840 (18.3) | |
| **Functional health status** | | | <0.001 |
| Dependent | 151 | 49 (32.5) | |
| Independent | 9949 | 1801 (18.1) | |
| **Chronic obstructive pulmonary disease** | | | 0.02 |
| Yes | 143 | 37 (25.9) | |
| No | 9957 | 1813 (18.2) | |
| **History of ascites** | | | 0.33 |
| Yes | 37 | 9 (24.3) | |
| No | 10 063 | 1841 (18.3) | |
| **Chronic heart disease** | | | 0.001 |
| Yes | 11 | 7 (63.6) | |
| No | 10 089 | 1843 (18.3) | |
| **Hypertension** | | | <0.001 |
| Yes | 1626 | 358 (22.0) | |
| No | 8474 | 1492 (17.6) | |
| **Corticosteroid use** | | | 0.001 |
| Yes | 4101 | 816 (19.9) | |
| No | 5999 | 1034 (17.2) | |
| **Bleeding disorder** | | | 0.02 |
| Yes | 194 | 48 (24.7) | |
| No | 9906 | 1802 (18.2) | |
| **Weight loss >10%** | | | 0.02 |
| Yes | 792 | 169 (21.3) | |
| No | 9308 | 1681 (18.1) | |
| **Percutaneous coronary intervention** | | | 0.05 |
| Yes | 74 | 20 (27.0) | |
| No | 10 026 | 1830 (18.3) | |
| **Previous cardiac surgery** | | | 0.25 |
| Yes | 58 | 14 (24.1) | |
| No | 10 042 | 1836 (18.3) | |
| **Peripheral vascular disease** | | | 0.01 |
| Yes | 22 | 9 (40.9) | |
| No | 10 078 | 1841 (18.3) | |
| **Transient ischemic attack** | | | 0.44 |
| Yes | 39 | 9 (23.1) | |
| No | 10 061 | 1841 (18.3) | |
| **Stroke with neurological damage** | | | 0.13 |
| Yes | 27 | 8 (29.6) | |
| No | 10 073 | 1842 (18.3) | |
| **Stroke without neurological damage** | | | 0.88 |
| Yes | 31 | 6 (19.4) | |
| No | 10 069 | 1844 (18.3) | |

(continued)

Table 2. Continued

| | No. of patients | Post-operative infection, *n* (%) | *P*-value |
|---|---|---|---|
| **ASA classification at time of surgery** | | | <0.001 |
| 1—No disturb | 251 | 20 (8.0) | |
| 2—Mild disturb | 6619 | 1079 (16.3) | |
| 3—Severe disturb | 3139 | 729 (23.2) | |
| 4—Life threat | 74 | 17 (23.0) | |
| 5—Moribund | 3 | 0 (0.0) | |
| **Pre-operative transfusion** | | | 0.008 |
| Yes | 76 | 23 (30.3) | |
| No | 10 024 | 1827 (18.2) | |
| **Pre-operative serum albumin** | | | 0.001 |
| Normal | 5158 | 929 (18.0) | |
| Hypoalbuminemia | 2095 | 447 (21.3) | |
| **Pre-operative creatinine** | | | 0.35 |
| Normal | 8911 | 1646 (18.5) | |
| High | 286 | 59 (20.6) | |
| **Pre-operative aspartate aminotransferase** | | | 0.42 |
| Normal | 452 | 92 (20.4) | |
| High | 6709 | 1262 (18.8) | |
| **Pre-operative bilirubin** | | | 0.52 |
| Normal | 6724 | 1285 (19.1) | |
| High | 500 | 89 (17.8) | |
| **Pre-operative alkaline phosphatase** | | | <0.001 |
| Normal | 6483 | 1192 (18.4) | |
| High | 775 | 184 (23.7) | |
| **Pre-operative hematocrit** | | | 0.04 |
| Normal | 4482 | 785 (17.5) | |
| Low | 5110 | 9878 (19.1) | |
| **Emergency surgery** | | | 0.03 |
| Yes | 397 | 89 (22.4) | |
| No | 9703. | 1761 (18.1) | |
| **Laparoscopic surgery** | | | <0.001 |
| Yes | 3647 | 510 (14.0) | |
| Open | 6453 | 1340 (20.8) | |
| **Wound classification** | | | <0.001 |
| 1—Clean | 116 | 13 (11.2) | |
| 2—Clean/contaminated | 6775 | 1132 (16.7) | |
| 3—Contaminated | 2109 | 451 (21.4) | |
| 4—Dirty/infected | 1100 | 254 (23.1) | |
| ***Intra*- and/or *post*-operative transfusion** | | | <0.001 |
| Yes | 568 | 187 (32.9) | |
| No | 9532 | 1663 (17.4) | |

**Table 3.** Multivariate analysis of risk factors for post-operative infectious complication in Crohn's disease

| | OR (95% CI) | *P*-value |
|---|---|---|
| *Intra*- and/or *post*-operative transfusion | 2.1 (1.7–2.6) | <0.001 |
| Functional health status | 1.8 (1.2–2.6) | 0.004 |
| History of smoking | 1.4 (1.2–1.6) | <0.001 |
| Chronic heart disease | 4.7 (1.0–21.3) | 0.04 |
| Diabetes | 1.7 (1.2–2.3) | 0.001 |
| Corticosteroid use | 1.2 (1.1–1.4) | 0.001 |
| Laparoscopic surgery | 0.7 (0.6–0.8) | <0.001 |
| Pre-operative transfusion | 1.1 (0.7–2.0) | 0.65 |

remained high among surgical non-CD patients [34–36]. Since pre-operative anemia and perioperative bleeding complications could lead to adverse outcomes, they were often managed by BT. A recent study conducted among hepatopancreaticobiliary surgery reported an average triggering level for transfusion in anemic patients was hemoglobin (Hb) of 7.7 g/dL and the average target was 9.3 g/dL. They suggested that, by using a restricted transfusion policy (Hb<8 g/dL), BT would be avoided in about 20–25% patients without increasing the risk for morbidity [37]. Another study from the same group that consisted of cardiothoracic and gastrointestinal procedures also pointed out that patients with restricted perioperative transfusion strategy (Hb<7 g/dL, mean target Hb was 9.1 g/dL) did not increase risk for ischemic complications, as compared with a more liberal triggering level (Hb $\geq$ 7 g/dL, mean target Hb was 9.3 g/dL). Therefore, due to frequent complications seen in transfused patients, a more restrictive transfusion practice may be safe and efficient [38]. Most publications agreed that patients undergoing BT were more likely to experience complications and that the triggering level of Hb and target of transfusion should be restricted. However, not many studies were conducted in CD surgical patients.

The results of our study were mostly consistent with previously published data in non-CD patients, except that the CD patients had a relatively lower BT rate (6%) than other diseases [34–38]. Our study confirms that the overall post-operative infection rate in CD patients undergoing surgery was higher in the

**Table 4.** Intra-operative transfusion units and post-operative infections

| Number of red blood cells given | No. of patients | Without infection, *n* (%) | With infection, *n* (%) | OR relative to transfusion unit=0 (95% CI) | *P*-value |
|---|---|---|---|---|---|
| 0 | 3430 | 2793 (81.4) | 637 (18.6) | | |
| 1 | 86 | 58 (67.4) | 28 (32.6) | 2.1 (1.3–3.4) | 0.001 |
| 2 | 91 | 68 (74.7) | 23 (25.3) | 1.5 (0.9–2.4) | 0.1 |
| 3 | 23 | 11 (47.8) | 12 (52.2) | 4.7 (2.1–10.9) | <0.001 |
| 4 | 15 | 8 (52.3) | 7 (46.7) | 3.8 (1.4–10.6) | 0.01 |
| 6 | 2 | 2 (100.0) | 0 (0.0) | 0 | 1.0 |
| 8 | 1 | 0 (0.0) | 1 (100.0) | 0 | 1.0 |

BT group than in the non-BT group. Although many studies have shown the association between BT and overall infection, there is scant literature on the association between BT and specific infections. Our study showed that the association extended to each infection subgroup, including local infections like SSI as well as systemic infections like pneumonia, UTI, sepsis and sepsis shock. The results suggest that the impact of BT was systematic. Bernard *et al*. showed that BT of two units as compared with to that of one unit further increased the odds for 30-day mortality, morbidity, pneumonia and sepsis/shock [39]. Our study also showed an increase in the risk of infections with increased units of blood transfused *intra*-operatively, delineating a dose–response relationship. But, differently from the previous studies, we included all perioperative infections for analysis. In addition, we analysed *pre*-operative and *intra*- and/or *post*-operative BT separately. Our results showed that *intra*- and/or *post*-operative BT, not *pre*-operative BT, was an independent risk factor for the adverse complications. One possible explanation is that the purpose of *pre*-operative BT in the majority of patients was to correct anemia, which might have improved the patient's overall health status and better prepared them for surgery. The patients requiring pre-operative transfusion were also those who tended to have a more severe disease presentation and were therefore prone to having a worse outcome. In this way, pre-operative transfusion may be a confounding factor that might result from the patient's overall worse health status.

The mechanism of transfusion-associated post-operative infection remains to be clarified. The most commonly cited is transfusion-induced immunosuppression [40]. In surgical patients, interleukin (IL)-6 and IL-6 soluble receptor are highly up-regulated when they receive BT, suggesting that BT may enhance IL-6 along with IL-2 response [12,40]. The role of allogeneic leukocytes in the immunomodulation and in the development of post-operative infectious complications has also been investigated. Despite careful process and separation, transfused RBC may not be completely free of WBC or WBC products [41]. However, the results of several randomized trials of WBC-depleted transfusions were inconclusive in this aspect [42,43]. CD patients are often in an immunosuppressive state, from the underlying disease and concurrent use of immunosuppressive agents [12], which makes them even more susceptible to transfusion-related post-operative infections.

The findings of this study have clinical implications. This was the largest study to date for the evaluation of the effect of BT on post-operative infectious complications in CD patients. The ACS NSQIP has provided a national perspective on the outcomes of these patients. We demonstrated that *intra*- and/or *post*-operative BT was a risk factor for infectious complications after the surgery for CD. The risks and benefits of transfusions *intra*- and/or *post*-operatively should be carefully balanced, especially in the current era of extensive use of biological agents in CD. On the other hand, the benefits of correcting anemia with *pre*-operative BT may be justified.

There are several limitations to the study. The database only tracked patients up to 30 days post-operatively and the available number of variables was limited. Many long-term consequences, such as post-operative recurrence of CD, which could have been associated with BT, were not documented in the database. Second, the units of RBC transfused in the perioperative period were only found in some patients before 2009 in the database, resulting in a much smaller sample size for this particular endpoint. Third, there was no documentation on whether the blood was autogenic or allogeneic. Patients' low Hb level that triggered transfusion and the target Hb were not included. Other factors that might have contributed to post-operative infectious complications, such as the use of anti-TNF or narcotics, were not included in the database.

In conclusion, BT was shown to be associated with multiple adverse outcomes, especially infections. As patients with CD undergoing surgery are prone to the development of post-operative infectious complications, the risks and benefits of *intra*- and/or *post*-operative BT should be carefully balanced.

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