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Allogeneic Red Blood Cell Transfusion and Infectious Complications Following Pediatric Spinal Fusion

NSQIP-P Analysis

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Background: Substantial bleeding occurs during spinal fusion surgery in the pediatric population, and many patients receive allogeneic red blood cell transfusion (ARBT) for the treatment of resulting perioperative anemia. ARBT is thought to increase vulnerability to postoperative infections following major surgical procedures, but studies of this relationship in children undergoing spinal fusion have yielded conflicting results.

Methods: Patients who underwent spinal fusion before the age of 18 years were identified from the National Surgical Quality Improvement Program-Pediatric (NSQIP-P) 2016 to 2019 databases, along with patient and procedure-specific characteristics, transfusion events and volumes, and postoperative infectious complications such as wound-related infection, pneumonia, urinary tract infection (UTI), and sepsis. Multivariable logistic regression analyses provided adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the association between ARBT and each infection outcome and the overall risk of infection.

Results: Among 19,159 patients studied, 714 (3.7%) developed a total of 931 episodes of postoperative infection. In multivariable logistic regression analyses, perioperative ARBT was independently associated with postoperative pneumonia (aOR = 1.93, 95% CI = 1.40 to 2.68), UTI (aOR = 1.80, 95% CI = 1.19 to 2.73), sepsis (aOR = 1.58, 95% CI = 1.10 to 2.28), and the overall risk of infection (aOR = 1.40, 95% CI = 1.20 to 1.64). The risk of any postoperative infection increased in a dose-response fashion with transfusion volume.

Conclusions: ARBT in pediatric spinal fusion is associated with significantly increased risks of postoperative pneumonia, UTI, and sepsis. The overall risk of postoperative infection increases with the volume transfused. Enhanced efforts to minimize perioperative anemia and ARBT should be considered as a means of improving patient outcomes.

Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

Spinal fusion is one of the most commonly performed pediatric orthopaedic surgical procedures in North America, and postoperative infection is a common complication[1]. Reported rates of surgical site infection (SSI) range from 1% to 13% and vary depending on the type of spinal deformity (e.g., neuromuscular, idiopathic)[2]. Other infectious complications among these patients include pneumonia (occurring in 0.6% to 4.0% of patients), urinary tract infection (UTI) (0.4% to 2.8%), and sepsis (0.3% to 2.4%)[2-6]. Postoperative infections are associated with increased morbidity and hospital length of stay in children and adolescents treated with spinal fusion[3,4]. These clinical outcomes may be improved by the mitigation of specific risk factors for postoperative infections[7].

There is growing evidence that allogeneic red blood cell transfusion (ARBT) is associated with infections following orthopaedic and other major surgical procedures[8-17]. The authors of several analyses have described this relationship as dose-dependent[13,18]. ARBT may confer vulnerability to infection via transfusion-related immunomodulation (TRIM), although definitive mechanism(s) for immunosuppression have yet to be confirmed[19,20]. In addition, red blood cell units can be damaged by routine refrigerated storage, and the damaged cells have been shown to undergo rapid hemolysis on transfusion into both healthy volunteers and critically ill children[21-24]. Hemolysis releases iron into the circulation and, following transfusion of a sufficient quantity of storage-damaged red blood cells, the

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amount of iron released can overwhelm the capacity of transferrin (the physiologic transporter of iron in the circulation) to bind iron, leading to the presence of a pathologic form of iron, termed *non-transferrin-bound iron*[21-24]. Non-transferrin-bound iron has been shown to contribute to the proliferation of pathogenic bacteria both in vitro and in vivo[24-27]. Red blood cells obtained from intraoperative cell salvage (e.g., with a Cell Saver [Haemonetics]) appear to be of higher quality than those of ARBT, and transfusion of those units has not been associated with an increased risk of postoperative infectious complications[28-31].

Children undergoing spinal fusion experience a median blood loss of 21% of their estimated blood volume, largely as a result of extensive soft-tissue exposure and bone resection[32,33]. The rate of allogeneic blood transfusion ranges from 17.8% for idiopathic scoliosis to 57% for neuromuscular scoliosis[34,35]. Observational studies examining the association between ARBT and postoperative infections in this population have shown conflicting results[36-38]. Inconsistent findings may have resulted from methodologic limitations, such as small sample size and inadequate bias control[37,39]. Numerous studies have focused on SSI while failing to examine other types of postoperative infections, such as pneumonia and UTI[4]. In the present study, we used a large database to evaluate the association between ARBT and postoperative infections with the goal of improving our understanding of the risk-benefit balance between ARBT and clinical outcomes after spinal fusion in children[40].

Materials and Methods

Overview

This study was deemed exempt from review under Title 45 Code of Federal Regulations Part 46 by the Columbia University institutional review board. The approach and findings are reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement reporting guidelines[41].

Data Source

The American College of Surgeons National Surgical Quality Improvement Program-Pediatric (NSQIP-P) database is a surgical outcomes database sampling from major surgical procedures at participating children's hospitals in North America. Clinical reviewers at >100 participating sites record roughly 90 data elements, including patient characteristics, preoperative conditions, and outcomes up to 30 days following a procedure[42].

Study Design and Study Participants

According to NSQIP-P, 19,470 patients <18 years old underwent spinal fusion from 2016 to 2019. Urgent or emergency cases (n = 195) and patients receiving a preoperative blood transfusion (n = 34) were excluded. In a data cleaning step, those with implausible biometric data as defined by the World Health Organization (WHO) (n = 82) were removed as data entry errors[43]. A final analytic sample of 19,159 was available for further study.

Variables

The NSQIP-P database indicates volumes of ARBT given intraoperatively and up to 72 hours after surgery. In this study, any non-zero total volume constituted an ARBT (yes/no), while total volumes were also categorized as 0 mL/kg (reference group), >0 and ≤10 mL/kg, >10 and ≤20 mL/kg, and >20 mL/kg. Covariates predictive of transfusion in previous work and/or deemed by 2 attending physicians (L.E., L.G.L.) to contribute to infectious outcomes were included in the analysis[44,45]. Patient age, sex, race, year of procedure, transfer status, American Society of Anesthesiologists (ASA) physical status classification, structural pulmonary abnormality, steroid use, nutritional support (enteral feeding or total parenteral nutrition), neuromuscular spinal deformity, hematological disorder, surgical duration, surgical extent (number of levels fused), cardiac risk factors, and application of antibiotics to the wound were available directly from the NSQIP-P data set. Weight below the third percentile for the patient's age, determined from weight and age data by sex based on a WHO algorithm (z-score), was considered a marker of poor nutritional status and has been previously identified as a predictor of transfusion[43,46]. Continuous variables (age, operative time) were categorized based on prior research, and complex categorical variables (e.g., ASA status, number of levels fused) were reduced to fewer categories to simplify analyses[44,47,48]. Preoperative anemia was defined based on hematocrit, using an algorithm for age- and sex-specific thresholds[47].

Postoperative infectious outcomes included wound-related infections (superficial SSI, deep SSI, organ/space infection, or wound dehiscence), pneumonia, UTI, and sepsis (systemic sepsis or septic shock). Binary composite variables were created (e.g., wound-related complication, septic complication, and any infection). To account for the occurrence of outcome clustering in some patients, we also treated the 4 binary outcomes (i.e., wound-related infection, pneumonia, UTI, and sepsis) as a multivariate composite outcome per patient[49].

Statistical Methods

Frequency distributions of various postoperative infections were tabulated according to ARBT status. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were computed for each type of postoperative infection and ARBT status. In addition, the Pearson chi-square test was used to compare characteristics between patients with and those without infection.

Logistic regression models were used to estimate adjusted ORs (aORs) and 95% CIs for the 4 main types of infections (and the multivariate composite outcome) associated with perioperative ARBT and other patient and procedure-related characteristics, including covariates that were found in unadjusted analyses to be associated with postoperative infection. For the multivariate composite outcome, generalized estimating equations with a log link and robust variance were used to account for correlation within subjects, such that exponentiated coefficients represent the ORs and 95% CIs for the overall risk of infection associated with each characteristic and accounting for clustering of the outcomes in individual patients[49].

Sensitivity analyses employed 2 sets of conditional logistic regression modeling based on all-case and complete-case propensity score matching. Propensity scores were calculated using logistic regression for the outcome of ARBT, using all available

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covariates examined in the unadjusted analyses. Balance was achieved using 1:1 nearest-neighbor matching across all complete cases using the MatchIt package provided in R (R Foundation for Statistical Computing). Furthermore, post-match examination of the standardized mean difference was used to confirm balance between groups in the matched samples[45]. All data analyses were conducted in R (2021). Significance was set at $p < 0.05$ for 2-tailed tests.

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Results

The overall rate of ARBT was 21.4% (n = 4098); 931 postoperative infections occurred in 3.7% of the patients (n = 714). In the overall series, 2.1% (n = 400) of the patients developed wound infection; 1.1% (n = 201), pneumonia; 0.6% (n = 120), UTI; 0.8% (n = 157), sepsis; and 3.7% (n = 714), an infection of any type. We found that 0.3% of the patients (n = 53) experienced >1 wound-related infection, and 0.86% (n = 164) experienced >1 type of infection.

Crude ORs and 95% CIs reached significance for the associations between perioperative ARBT and all infectious outcomes except for superficial SSI (Table I). Patient characteristics according to postoperative infection status are summarized in Table II. Younger age, male sex, weight below the third percentile, higher ASA score, neuromuscular deformity, greater surgical extent as reflected by the planned number of levels fused, and longer surgical duration were among the variables that were significantly associated with postoperative infection. The rate of postoperative infection did not vary according to the year of the procedure or with application of antibiotics to the surgical site/wound.

An analytic sample of complete cases for use in logistic regression procedures consisted of 13,929 patients, following removal of 5230 patients who were missing data for ≥1 of the covariates (Table II). After adjusting for other significant predictors of infection (Table II), ARBT was independently associated with postoperative pneumonia, UTI, sepsis, and the multivariate outcome including 4 types of infection (Fig. 1). A similar analysis was performed using ARBT volume, which showed that the overall risk of infection increased in a dose-response fashion with transfusion volume (Fig. 2). A dose-response effect was additionally observed for outcomes of pneumonia and sepsis (see Appendix Supplement Table 1).

The full list of covariates (shown in Table II) was then used to assign a propensity score for the likelihood of perioperative ARBT. The overall range and spread of the estimated probability of ARBT was well-matched between patients who did and did not receive ARBT (see Appendix Supplement Fig. 1), and propensity score-matching was achieved for 2959 pairs of complete cases[50]. A significant reduction of the standardized mean differences was observed in the matched sample, with balanced matching defined as all differences less than the upper limit of 0.10[51]. When the propensity-score-matched pairs were compared, perioperative ARBT was again shown to be associated with many types of postoperative infection as well as the composite of all infection types (Table III).

Bias introduced by the absence of certain types of data was examined through propensity score matching of all cases. We found aORs and 95% CIs to be consistent overall in identifying perioperative ARBT as an independent predictor

TABLE I Frequency of Postoperative Infections According to Perioperative Allogeneic Red Blood Cell Transfusion Status in NSQIP-P 2016-2019

		Transfusion		
Infection Outcome	Total (N = 19,159) *(no. [%])*	Yes (N = 4098) *(no. [%])*	No (N = 15,061) *(no. [%])*	Crude OR (95% CI)
Wound-related infection*	400 (2.09)	150 (3.66)	250 (1.66)	2.25 (1.83, 2.76)
Superficial SSI	143 (0.75)	40 (0.98)	103 (0.68)	1.43 (0.98, 2.05)
Deep SSI	154 (0.80)	67 (1.63)	87 (0.58)	2.86 (2.07, 3.94)
Organ/space SSI	61 (0.32)	32 (0.78)	29 (0.19)	4.08 (2.46, 6.78)
Wound dehiscence	95 (0.50)	36 (0.88)	59 (0.39)	2.25 (1.47, 3.40)
Pneumonia	201 (1.05)	111 (2.71)	90 (0.60)	4.63 (3.50, 6.14)
Urinary tract infection	120 (0.63)	66 (1.61)	54 (0.36)	4.55 (3.17, 6.55)
Sepsis				
Total	157 (0.82)	88 (2.15)	69 (0.46)	4.77 (3.48, 6.56)
Systemic sepsis	128 (0.67)	69 (1.68)	59 (0.39)	4.35 (3.07, 6.19)
Septic shock	29 (0.15)	19 (0.46)	10 (0.07)	7.01 (3.33, 15.71)
Any infection†	714 (3.73)	320 (7.81)	394 (2.62)	3.15 (2.71, 3.67)

*Fifty-three patients had >1 wound-related infection. SSI = surgical site infection. †One hundred and sixty-four patients had >1 type of infection outcome.

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TABLE II Characteristics of Patients Experiencing Postoperative Infections in NSQIP-P 2016-19

Characteristics	Total (N = 19,159) *(no. [%])*	Any Infection		P Value
		Yes* (N = 714 *(no. [%])*	No† (N = 18,445) *(no. [%])*	
Age				<0.001
1-11 yr	3635 (19.00)	230 (32.21)	3405 (18.46)	
12-17 yr	15,524 (81.00)	484 (67.79)	15,040 (81.54)	
Sex				<0.001
Female	13,172 (68.75)	416 (58.26)	12,756 (69.16)	
Male	5987 (31.25)	298 (41.74)	5689 (30.84)	
Race				0.3518
White	12,869 (77.63)	455 (76.73)	12,414 (77.66)	
Black	3058 (18.45)	108 (18.21)	2950 (18.45)	
Other	651 (3.93)	30 (5.06)	621 (3.88)	
Year				0.5542
2019	6083 (31.75)	239 (33.47)	5844 (31.68)	
2018	5263 (27.47)	182 (25.49)	5081 (27.55)	
2017	4180 (21.82)	152 (21.29)	4028 (21.84)	
2016	3633 (18.96)	141 (19.75)	3492 (18.93)	
Transfer status				0.0390
Home/clinic/emergency dept.	18,681 (97.51)	702 (98.32)	17,979 (97.47)	
Other	478 (2.49)	12 (1.68)	466 (2.53)	
ASA score				<0.001
1-2	12,777 (66.83)	205 (28.75)	12,572 (68.31)	
3	5872 (30.71)	447 (62.69)	5425 (29.48)	
4	469 (2.45)	61 (8.56)	408 (2.22)	
Structural pulmonary abnormality				<0.001
No	17,873 (93.29)	578 (89.95)	17,295 (93.77)	
Yes	1286 (6.71)	136 (19.05)	1150 (6.23)	
Steroid use				<0.001
No	18,970 (99.01)	694 (97.20)	18,276 (99.08)	
Yes	189 (0.99)	20 (2.80)	169 (0.92)	
Nutritional support				<0.001
No	17,504 (91.36)	486 (68.07)	17,018 (92.26)	
Yes	1655 (8.64)	228 (31.93)	1427 (7.74)	
Anemia				0.6512
No	13,842 (87.25)	499 (86.63)	13,343 (87.27)	
Yes	2023 (12.75)	77 (13.37)	1946 (12.73)	
Neuromuscular spinal deformity				<0.001
No	15,419 (80.48)	323 (45.24)	15,096 (81.84)	
Yes	3740 (19.52)	391 (54.76)	3349 (18.16)	
No. of levels fused				<0.001
1-6	2087 (11.20)	78 (11.32)	2009 (11.19)	
7-12	9771 (52.42)	173 (25.11)	9598 (53.46)	
≥13	6783 (36.39)	438 (63.57)	6345 (35.34)	
Weight in <3rd percentile				<0.001
No	16,288 (85.01)	488 (68.35)	15,800 (85.66)	
Yes	2871 (14.99)	226 (31.65)	2645 (14.34)	

continued

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TABLE II (*continued*)

Characteristics	Total (N = 19,159) *(no. [%])*	Any Infection		P Value
		Yes* (N = 714 *(no. [%])*	No† (N = 18,445) *(no. [%])*	
Hematological disorder				<0.001
No	18,671 (97.45)	666 (93.28)	18,005 (97.61)	
Yes	488 (2.55)	48 (6.72)	440 (2.39)	
Cardiac risk factors				<0.001
None	17,313 (90.37)	586 (82.07)	16,727 (90.69)	
Minor	923 (4.82)	66 (9.24)	857 (4.65)	
Major	922 (4.81)	62 (8.68)	860 (4.66)	
Surgical duration				<0.001
<300 min.	11,917 (62.21)	321 (44.96)	11,596 (62.88)	
≥300 min.	7238 (37.79)	393 (55.04)	6845 (37.12)	
Antibiotics applied to wound				0.1594
No	3508 (18.31)	145 (20.31)	3363 (18.23)	
Yes	15,651 (81.69)	569 (79.69)	15,082 (81.77)	

*Among the patients with any infection, 121 had missing data on race; 1, on ASA score; 138, on anemia; and 25, on number of levels fused.
†Among the patients without any infection, 2460 had missing data on race; 40, on ASA score; 3156, on anemia; 493, on number of levels fused; 1, on cardiac risk factors; and 4, on surgical duration.

of a variety of postoperative infections as well as the composite of all infection types (Table III).

Discussion

This multicenter study examined the association between ARBT and postoperative infections in children treated with spinal fusion. The observed frequencies of transfusion and postoperative infection align with published findings in this patient population[34-36,52-54]. Our analysis was also consistent with prior studies in identifying several risk factors for postoperative infection, including age, sex, ASA status, neuromuscular spinal deformity, operative time, number of spinal levels fused, and ARBT[36,55].

Our primary analysis demonstrated that ARBT increased the odds of postoperative pneumonia by 93%, UTI by 80%, sepsis by 58%, and a composite of postoperative infections by 40%. The association between ARBT and infection following spinal fusion in children emphasizes the need for hemoglobin optimization, intraoperative blood salvage, and postoperative management to obviate transfusions during and after these surgical procedures.

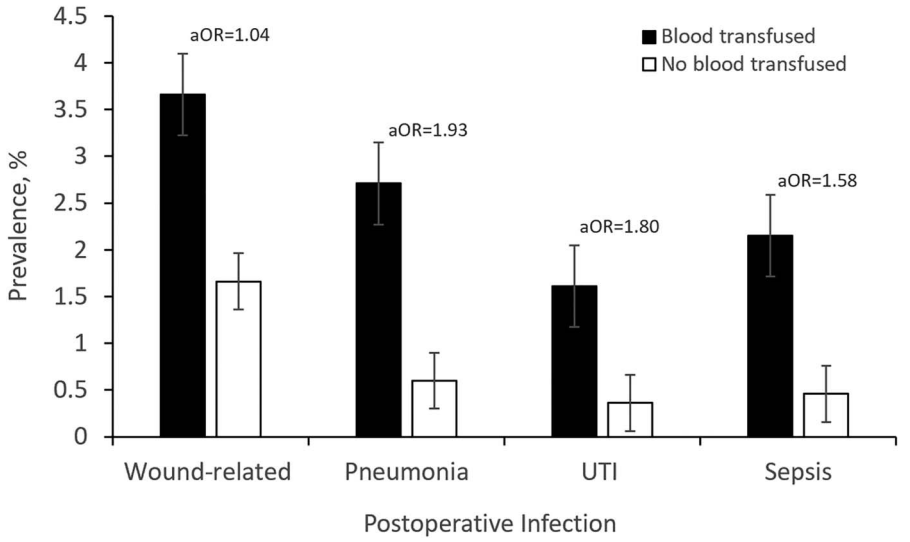

Fig. 1
Prevalences of postoperative infections, with adjusted odds ratios (aORs) for the association with perioperative allogeneic red blood cell transfusion. The whiskers indicate the 95% confidence interval.

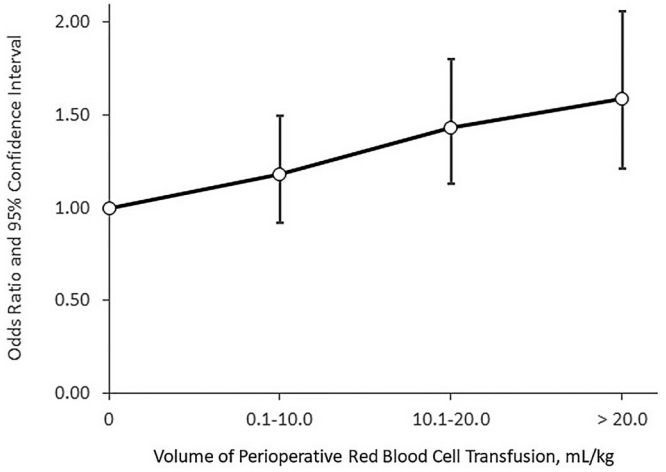

Fig. 2

Estimated adjusted odds ratios and 95% confidence intervals for overall risk of postoperative infection(s) associated with volume of perioperative allogeneic red blood cell transfusion.

A significant independent association between ARBT and postoperative wound-related infection was not observed in our primary analysis but was seen in our secondary analysis of a propensity-score-matched complete case cohort. Although it is difficult to fully explain this discrepancy, it is possible that propensity-score methods, by adjusting for both exposure and outcome risk factors, are more effective at addressing unmeasured confounding[50]. Furthermore, there is evidence that when examining the relationship between a common exposure such as blood transfusion and a rare outcome such as infection, or when many covariates are interrelated, ORs can be estimated more precisely using propensity score methods[56]. For this reason, we find the propensity-score-matched analysis to be a robust approach, providing corroborative evidence and enhancing the validity of the finding that perioperative ARBT is associated with an increased rate of postoperative infections.

We found that transfusion volume was independently associated with postoperative infections, with modest doses increasing the odds of infection by 43% and the highest doses increasing it by almost 60% compared with the infection rate in patients not receiving a transfusion. A previous NSQIP-P-based study of children who had undergone non-cardiac surgery also demonstrated that the odds of postoperative infection increased with transfusion volume; however, in that study the exposure included totals of allogeneic and autologous blood without distinguishing between the two[13]. Both that analysis and ours would have benefited from context that was not available, such as the volume and rate of surgical blood loss, whether patients had perioperative hemodynamic instability requiring vasopressors, and whether metabolic derangements had occurred in the setting of higher-dose blood transfusions, which may confound the relationship with infection[57]. Therefore, although our dose-response finding enhances empirical evidence for the relationship between ARBT and infection, particularly as it applies to larger doses, we cannot yet infer that restricting volume below a particular threshold would necessarily provide better outcomes for this population.

Transfusion may contribute to infection risk through the hemolysis-mediated release of iron, and other immunomodulatory mechanisms have also been described[19,58,59]. The published literature also identifies organisms that are the likely mediators between transfusion and postoperative infections. The largest effects observed throughout our primary and secondary analyses were for postoperative pneumonia, UTI, and sepsis. These are infections in which gram-negative organisms dominate, in contrast to the gram-positive organisms implicated in many SSIs and wound-related infections[60-64]. Murine studies have previously identified an increased vulnerability to infection with gram-negative organisms, in particular, following transfusion[26,27,59]. This may explain why evidence of an association between transfusion and wound infection tends to be weaker[37]. While application of antibiotics to the wound did not impact the overall rate of postoperative infectious complications and has not yet been proven to be clearly effective at reducing SSIs after spinal fusion in a pediatric population, it is possible that the widespread use of this intervention (in 82% of all patients) played a role in mitigating the adverse effects of

TABLE III Multivariable Logistic Regression and Propensity-Score-Matched Odds Ratios and 95% Confidence Intervals for Postoperative Infections Associated with Perioperative Allogeneic Red Blood Cell Transfusion in NSQIP-P 2016-2019

	OR (95% CI)				
Model	Wound-Related Infection	Pneumonia	Urinary Tract Infection	Sepsis	Overall Infection*
Multivariable logistic regression	1.04 (0.82, 1.32)	1.93 (1.40, 2.68)	1.80 (1.19, 2.73)	1.58 (1.10, 2.28)	1.40 (1.20, 1.64)
Conditional logistic regression: complete-case propensity score matching	1.39 (1.05, 1.85)	2.52 (1.64, 3.87)	1.52 (0.92, 2.52)	2.07 (1.33, 3.22)	1.72 (1.42, 2.09)
Conditional logistic regression: all-case propensity score matching	1.26 (0.99, 1.61)	2.24 (1.60, 3.14)	1.67 (1.12, 2.48)	1.91 (1.34, 2.73)	1.64 (1.40, 1.92)

*Obtained from a generalized estimating equation accounting for the correlation between the 4 types of infection.

ARBT on the risk of postoperative SSI in this population. The incorporation of microbiological data in future studies may help to further subcategorize infections associated with ARBT while informing the design of interventions such as targeted antimicrobial therapy in patients requiring perioperative transfusion.

Based on our prior work[44] demonstrating that anemia is an independent predictor of ARBT rate, and the observed association between ARBT and infections, we expected to find a stronger relationship between anemia and infection in our unadjusted analysis. However, we previously showed the impact of anemia on ARBT to be less pronounced in younger patients and in those with neuromuscular scoliosis[44], groups found in the present study to be at the greatest risk of postoperative infection. Studying a heterogeneous group with disparate risks of infection dictated in large part by deformity type may have thus minimized any impact of preoperative anemia.

By including a wide array of potential confounders, we aimed to minimize biases resulting from differences in demographic and clinical characteristics that are likely to exist between those who did and those who did not receive a transfusion. However, unmeasured confounding and residual bias must still be considered when interpreting our findings. NSQIP-P does not stratify cases by location, social/environmental factors, or health insurance status, which are all known contributors to overall morbidity. The appropriateness of either giving or withholding a transfusion may impact postoperative outcomes, and this information cannot be inferred from the available data. Numerous risk factors specifically for SSI were not included, which may have biased these results. For example, medical optimization, microbiological surveillance, surgical techniques (e.g., plastic surgical closure), tissue oxygenation, glycemic control, and appropriate preoperative and perioperative administration of antibiotics are critical to prevent SSI[37,65]. In addition, although the duration of the storage of the packed red blood cells was not recorded in the database, transfusion with blood stored for >28 days during spine surgery has been observed to increase the odds of perioperative morbidity[66]. Finally, misclassification and underreporting of outcomes in this large database study may have introduced additional bias. Despite these limitations, the current analysis includes the most comprehensive list of covariates to date, gleaned across many institutions by trained research staff, so it is better positioned than most to evaluate the association of interest.

Lastly, missing data on ≥1 of the covariates reduced the number of evaluable patients in our analytic sample prior to the adjusted analyses. However, the consistency of the results observed in the logistic regression and propensity-score-matching analyses, dose-response analysis, and a sensitivity analysis including cases with missing data substantially reduces the likelihood that this was a source of bias. Smaller, single-center studies are likely to be more prone to bias, whereas our survey of >100 hospitals has greater generalizability.

Conclusions

These findings strengthen evidence for an association between ARBT and postoperative infections in children treated with spinal fusion. To the extent that the need for ARBT may be reduced through risk stratification and targeted preventive measures, including the treatment of preoperative anemia and other blood conservation strategies, we hope that further study can contribute to a reduction in postoperative infections and associated morbidity[40,44].

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJSOA/A428). ■

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