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Original Article

Risk factors for and incidence of hospital-acquired infections after cardiac surgery in children with congenital heart disease: a single center experience

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ABSTRACT

Background. The epidemiology of hospital-acquired infections (HAIs) has been less well studied in critically ill children in pediatric cardiothoracic intensive care units. This study aimed to investigate independent risk factors for and incidence of HAIs after cardiac surgery in children with congenital heart disease (CHD).

Methods. Our study included 574 patients who underwent congenital heart surgery and were followed up in the cardiothoracic intensive care unit between September 2016 and December 2020. All patients were divided into four groups according to age: 0-1 months, 1-6 months, 6-12 months, and 1-18 years, and into two subgroups according to HAI development.

Results. The patients' median age and weight at surgery were 3.28 (interquartile range [IQR]): 0.43-8.1) months and 4.34 (IQR: 4.34-6.69) kg, respectively. HAIs and infection-related deaths were observed in 223 and 21 patients, respectively. Age at surgery, weight at surgery, concomitant syndromes and immunodeficiency status, presence of cyanotic heart disease, intubation, and use of antibiotics during hospitalization were statistically significant between the two groups with and without infection ($p<0.05$). In logistic regression analysis, surgical weight <5 kg (odds ratio [OR]: 2.55; 95% confidence interval [CI]: 1.56-4.17; $p<0.001$), preoperative mechanical ventilation (OR: 2.0; 95% CI: 1.26-3.12; p=0.003), complexity of cardiac surgery according to the risk-adjusted congenital heart surgery classification score 3 (OR: 3.13; 95% CI: 1.24-7.92; p=0.016), presence of an concomitant syndrome (OR: 1.56; 95% CI: 1.02-2.88; p=0.040), age (OR: 1.01; 95% CI: 1.01-1.04; p=0.044) were independent risk factors for HAIs after cardiac surgery in children with CHD.

Conclusions. In this study, younger age, presence of an associated syndrome, preoperative mechanical ventilation, and weight less than 5 kg were found to be independent risk factors for HAI after cardiac surgery in children with CHD.

Key words: congenital heart diseases, pediatric cardiac surgery, hospital-acquired infection.

Hospital-acquired infections (HAIs) are a well-defined problem in pediatric and neonatal intensive care units (ICUs). Individual HAI rates are higher in developing countries than in developed countries.[1] However, the epidemiology of HAIs in critically ill children in pediatric cardiothoracic ICUs has been less well studied.[1,2] More than 50% of patients treated in ICUs are affected by HAIs due to severe congenital heart disease (CHD), an immature immune system, and multiple invasive procedures.[3-5] HAIs impair the clinical outcome and may lead to mortality, morbidity, increased treatment costs, and prolonged hospital stay in pediatric patients undergoing cardiac surgery.[3,6] The incidence and severity of HAIs are higher in children after cardiac surgery. This is because impaired nutrition, pulmonary congestion, some forms of CHD with genetic abnormalities, or syndromes leading to some degree of immunosuppression increase susceptibility

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to infection.[1,3,4] In developing countries, the severity of HAIs is underestimated, mainly due to the lack of an effective surveillance system that requires expertise and resources.[7]

After cardiac surgery, HAIs in patients with CHD are influenced by several factors. Younger age, longer preoperative hospital stay, longer duration of surgery, open chest, congenital malformations, and postoperative complications are associated with HAIs in pediatric patients undergoing cardiac surgery.[1,6,8] In addition, pediatric cardiothoracic ICUs should identify their risk factors. It is important to identify the risk factors for each unit and take appropriate precautions. Therefore, identifying risk factors for infections in these patients would be beneficial. This study aimed to investigate the incidence of HAIs and their independent risk factors after cardiac surgery with or without cardiopulmonary bypass (CPB) in children with CHD based on age.

Material and Methods

This retrospective cohort study included children with CHD who underwent cardiac surgery and were treated in pediatric cardiovascular ICUs between September 2016 and December 2020. Data were collected from a digital database and immediately entered into detail. This retrospective observational study was approved by the Research Ethics Committee of Başkent University Hospital, and the need for individual informed consent was waived. Patients who underwent surgery and were transferred on the day of surgery, those who died within 24 hours of surgery, and preterm infants after ductal ligation were excluded from this study. All patients were divided into four groups according to age: 0-1 months, 1-6 months, 6-12 months, and 1-18 years, and into two subgroups according to HAI development. Patients were clinically examined daily for signs of HAIs until hospital discharge. Patients were evaluated for signs of infection by determining their daily blood count, C-reactive protein, and procalcitonin. Urine analysis and cultures (blood, urine, tracheal aspirate) were obtained from patients with signs of or suspected HAIs. The Centers for Disease Control and Prevention (CDC) criteria were used as standard definitions for HAIs.[9] Infections occurring 48-72 hours after hospitalization were considered HAIs. Culture specimens were collected only when clinical signs indicated HAIs. Postoperative infections were categorized as hospital-acquired bloodstream or catheter-associated bloodstream infections or sepsis, ventilator-associated pneumonia (VAP), urinary tract or catheter-associated urinary tract infections, and surgical site or wound infections. According to the criteria adopted at the International Sepsis Conference in 2001, the deaths of patients diagnosed with sepsis were considered infection-related deaths.[10] In patients with suspected immunodeficiency, a complete blood count and immunoglobulin levels were analyzed. Lymphocyte subset analysis by flow cytometric examination was performed in patients with lymphopenia and hypogammaglobulinemia to establish the diagnosis of immunodeficiency.[11] The degree of hypothermia was classified as mild (32 °C to 34 °C), moderate (26 °C to 31°C), severe (20 °C to 25 °C) hypothermia. For preoperative antibiotic prophylaxis, cefazolin sodium was administered to some patients, whereas ampicillin-gentamicin, vancomycin, and meropenem were administered to other patients. Antibiotic prophylaxis was administered for a maximum of 3 days, even in patients whose chest tube remained in place for >3 days. Antibiotic prophylaxis was discontinued in most patients on the day of chest tube removal. Culture samples were obtained and analyzed according to standard methods when clinical signs of infection appeared after surgery.

Age and weight at surgery, sex, type of open/closed heart surgery, duration of CPB, complexity of cardiac surgery according to the risk-adjusted classification for congenital heart surgery (RACHS-1)[12], preoperative mechanical ventilation and antibiotic use, concomitant syndromes, immune status, hypothermia classification, and length of hospital stay were considered independent variables for analysis.

Statistical analysis

Variables are presented as means ± standard deviations for continuous variables with normal distribution, medians with interquartile range (IQR) (25th-75th percentiles) for continuous data with abnormal distribution, or numbers and percentages for categorical variables. T-tests or Mann-Whitney U tests for continuous variables and chi-squared or Fisher's exact tests for categorical data were used for comparison between groups. Spearman or Pearson tests were performed for the correlations. Point biserial correlation coefficient was used to determine the relation between numerical variables and dichotomous variables. Multi-variate analysis was performed using logistic regression analysis to determine the independent risk factors for HAIs. All variables with a p-value <0.20 in univariate analysis were included in the multi-variate analysis. Hosmer– Lemeshow goodness-of-fit statistics was used to assess model fit. Statistical significance was set at a p value <0.05. Data input and statistical analyses were performed using IBM SPSS statistical software (version 25.0; IBM Corp. 25.0, Armonk, NY, United States)

Results

The study population was comprised of 574 patients (259 girls and 315 boys). Their median age and weight at surgery were 3.28 (IQR: 0.43-8.1) months and 4.34 (IQR: 3.3–6.69) kg, respectively. Complete correction was performed in 417 (72.6%) patients, and palliative surgery (pulmonary banding, Blalock–Taussig shunt, central shunt, bidirectional cavopulmonary anastomosis) was performed in 157 (27.4%) patients. In total, 72 (12.5%) and 502 (87.5%) patients had univentricular cardiac and biventricular physiologies, respectively. A total of 252 (43.9%) patients had cyanotic heart disease. Cardiac surgery was performed in 457 (79.6%) patients with CPB and in 117 (20.4%) patients without CPB. Patients were classified according to the RACHS-1 classification: RACHS-1 score 1, 53 (9.2%); RACHS-1 score 2, 192 (33.4%); RACHS-1 score 3, 211 (36.8%); RACHS-1 score 4, 110 (19.2%); and RACHS-1 score 6, 8 (1.4%). In total, 146 (25.4%) patients were administered alprostadil before cardiac surgery (121 with cyanotic heart disease and 25 with acyanotic heart disease). A total of 145 (25.3%) patients required mechanical ventilation preoperatively. Moreover, 148 (25.7%) patients (including 14 patients with DiGeorge syndrome; 70 with Down syndrome; one with Turner syndrome; five with trisomy 18, one with 9-12 chromosomal translocation; one with Alagille syndrome; one with Robinow syndrome; one with vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities anomaly; two with Williams syndrome and 52 with unclassified syndromes) were syndromic. In total, 42 (7.3%) patients were diagnosed with immunodeficiency. Postoperative infections and HAI-related deaths were observed in 223 (38.9%) and 21 (9.4%) patients, respectively. Age, CPB duration, duration of aortic cross-clamping, RACHS-1 classification, preoperative mechanical ventilation, preoperative antibiotic use, presence of associated syndrome, presence of immunodeficiency, and length of hospital stay differed between patients with and without infection. HAI-related deaths were observed in 21 (52.4% in <1 month, 42.9% between 1 and 6 months, and 4.76% in >1 year) patients. The demographic characteristics of patients with and without infection are shown in Table I and Table II. Preoperatively, 149 (26%) patients received antibiotic therapy (prophylaxis or treatment).

There was a moderate correlation between the RACHS-1 classification score and CPB duration (r=0.42, p<0.001). In addition, according to point-biserial correlation coefficient, the incidence of infections was found to increase with increasing aortic cross-clamping and CPB duration and RACHS-1classification score and with decreasing weight and age of patients at the time of surgery (Table III).

In our study, 223 (38.9%) patients had HAIs, including hospital-acquired bloodstream or

Table I. Demographic features of the group with and without HAIs (*significant *p* values).

	HAIs (+)		HAIs (-)		*p*
	n	%	n	%	
Patient (female/male)	223 (95/128)	38.9	351 (164/187)	61.1	0.35
Preoperative use of antibiotics	86	38.6	63	17.9	<0.001
Preoperative mechanical ventilation	87	39.0	58	16.5	<0.001
Presence of immune deficiency	26	11.6	16	4.6	0.003
Cyanotic heart disease	122	54.7	130	37.0	<0.001
Absent of thymus	12	5.4	18	5.1	0.71
Alprostadil adminastered	82	36.8	64	18.2	<0.001
Presence of open chest	15	6.7	27	7.7	0.74
Presence of accompanied syndrome	70	31.4	78	22.2	0.019*
Presence of umbilical line	39	17.5	39	11.1	0.033*
Weight at surgery <5 kg	179	80.3	163	46.4	<0.001* *
Type of surgical procedure (Complete correction/palliative)	141/82	63.2	276/75	78.6	<0.001*
Physiology of univentricular heart	34	15.2	38	10.8	0.123
Presence of CPB	165	73.9	292	83.2	0.011*
Ductus dependent heart disease	88	39.4	64	18.2	<0.001*
Classification of hypothermia					0.025*
Normal	67	30.0	80	22.8	
Mild	66	29.6	129	36.8	
Moderate	47	21.0	94	26.8	
Deep	43	19.3	48	13.6	
Classification of age group					<0.001*
<1 month	103	46.2	92	26.2	
1-6 months	85	38.1	116	33.0	
6- 12 months	20	9.0	59	16.8	
>1year	15	6.7	84	23.9	
Classification of RACHS-1					<0.001*
score 1	7	3.1	46	13.1	
score 2	58	26.0	134	38.2	
score 3	107	48.0	104	29.6	
score 4	48	21.5	62	17.7	
score 6	3	1.35	5	0.9	

CPB= cardiopulmonary bypass, HAIs=hospital-acquired infections, n: number of patients, RACHS-1= complexity of cardiac surgery according to the risk-adjusted classification for congenital heart surgery.

catheter-associated bloodstream infections or sepsis in 171 (76.6%), VAP in 12 (5.4%), surgical site or wound infections in 39 (17.4%), and urinary tract or catheter-associated urinary tract infections in one (0.4%) patient. A positive culture was observed in 99 (44.4%) patients. The isolated pathogens are listed in Table IV.

Logistic regression analysis identified surgical weight of <5 kg, preoperative mechanical ventilation, RACHS-1 classification score of 3, presence of a syndrome, and young age as independent risk factors for the development of infection (Table V).

Table II. Demographic features of the group with and without HAIs. Data are expressed as median (25th– 75th percentile).

	HAIs (+) n: 223	HAIs (-) n: 351	*p*
Length of stay in the hospital (day)	35(20-60)	23(7.6-40.5)	<0.001
Duration of CPB (minute)	112 (93-142)	103 (88-145)	<0.001
Duration of aortic clamping (minute)	44 (32-72)	38 (26-68.5)	<0.001

CPB=cardiopulmonary bypass, HAIs=hospital-acquired infections, n: number of patients.

Table III. Evaluation of variables affecting the development of infection with point-biserial correlation coefficient.

	r_{pb}	*p*
Weight (kg)	-0.334	<0.001
Classification of age group	-0.283	<0.001
CPB time, minute	0.265	<0.001
The length of the clamped aorta, minute	0.188	<0.001
Length of stay in the hospital, days	0.557	<0.001
RACHS-1 classification	0.190	<0.001

CPB= cardiopulmonary bypass, RACHS-1= complexity of cardiac surgery according to the risk-adjusted classification for congenital heart surgery, r_{pb}= point-biserial correlation coefficient.

Table IV. Pathogens isolated from the cultures.

	n (%)
Klebsiella pneumoniae	20 (20.2)
Coagulase (-) staphylococci	18 (18.1)
Enterobacter aerogenes	17 (17.1)
Escherichia coli	11 (11.1)
Enterococcus species	9 (9.09)
Staphylococcus aureus	9 (9.09)
Streptococcus species	5 (5.05)
Pseudomonas aeruginosa	3 (3.03)
Acinetobacter species	2 (2.02)
Klebsiella oxytoca	2 (2.02)
Serratia marcescens	1 (1.01)
Morganella morganii	1 (1.01)
Candida non-albicans	1 (1.01)

n: number of patients.

Table V. Independent risk factors for developing HAIs.

Risk factor	Odds ratio (95% confidence interval)	*p*
<5 kg	2.55 (1.56-4.17)	<0.001
Presence of syndrome	1.56 (1.02-2.88)	0.040
Age (months)	1.01 (1.01-1.04)	0.044
Preoperative mechanical ventilation	2.0 (1.26-3.12)	0.003
RACHS-1 score 3	3.13 (1.24-7.92)	0.016

RACHS-1= complexity of cardiac surgery according to the risk-adjusted classification for congenital heart surgery, HAIs=hospital-acquired infections.

Discussion

HAIs are a major cause of morbidity, mortality, and prolonged hospitalization in pediatric cardiac surgery units.[1,6,8] In these patients, incomplete maturation of the immune system, immunosuppression from CPB, multiple invasive procedures, deep hypothermia, and delayed complete enteral nutrition increase the propensity for HAIs, which also increase the length of hospital stay and antibiotic use.[3,4] Therefore, it is important to identify the risk factors in children undergoing cardiac surgery and take the necessary preventive measures to reduce the risk of HAIs. Each cardiology and cardiothoracic ICU should identify the risk factors in children specific to its department and take the necessary precautions. Accordingly, we studied the risk factors for HAI development in our department. In our study, it was found that the percentage of HAI was 38.9%, which is similar to the percentage in developing countries but higher than in developed countries owing to a smaller age distribution, complex cardiac anomalies, the use of preoperative antibiotics, and preoperative intubation. In a study conducted in developing countries, Sen et al.[13] reported that the incidence of HAIs was 6.9% in their study, which included 28 regions from 17 developing countries. Most patients in their study were aged >1 year (54.1%). Only 6.2% of the patients were aged <1 month. For RACHS-1 classification, 18.6%, 49.8%, and 23% of the patients had RACHS-1 classification scores of 1, 2, and 3, respectively. In contrast, in our study, 82.8% of the patients were aged <1 year, 34% were aged <1 month, and 57.4% had an RACHS-1 score of ≥3. In addition, most patients with severe complex heart disease were followed up in the ICU of an outside center and were referred to our hospital for surgery. As a result of these findings, the fact that our patients were younger and had more complex heart disease increased the incidence of HAIs. The age of the patients was one of the most important factors in our study. The incidence rates of HAIs were 46.2% in patients aged <1 month, 38.1% in those aged between 1 and 6 months, 9% in those aged between 6 and 12 months, and 6.7% in those aged >1 year. The incidence rate of HAIs increased with decreasing age and was higher in children aged <6 months, especially those aged <1 month, than other age groups. Therefore, age is considered one of the most important causes of increased susceptibility to infections.[3,8,14] The lack of trained personnel or new employees is also a major problem for the development of HAIs in developing countries, such as ours.

The incidence rates of HAIs in our study were 3.1% at RACHS-1 score 1, 26% at score 2, 48% at score 3, 21.5% at score 4, and 1.3% at score 6. The incidence rate of infection increases with the increasing complexity of cardiac surgery. According to the RACHS-1 classification, surgery itself is an important risk factor.[1,4,15,16] In our study, cardiac complexity was an independent risk factor for HAIs, and the risk of HAIs increased with increasing complexity; specifically, a threefold increase in this risk was observed with a RACHS-1 score of 3. Yu et al.[8] found similar results in a multicenter study in which increased cardiac complexity was an independent risk factor for HAIs. In addition, CPB duration was longer in the HAI group, which is consistent with the results of other studies.[8,14,16] A possible reason for this can be the risk of bacterial contamination, which increases with longer duration. In addition, it can also be hypothesized that the increased incidence of systemic inflammatory syndrome due to the impaired immune response and prolonged time contributes to an increased risk of HAIs.

There is an increased tendency for infection in immunodeficiency-concomitant syndromes.[17] In some syndromes, such as Down syndrome, the tendency for infection is higher with concomitant immunodeficiency. As expected, having a syndrome was found to be an independent risk factor in these patients owing to immunodeficiencies and developmental disorders.

VAP was observed in 12 (5.4%) patients. It was the second most common form of HAIs after bloodstream infections. In pediatric patients, the VAP incidence rate in the pediatric ICU setting ranged from 3 to 10% in mechanically ventilated children.[18] Preoperative mechanical ventilation was a risk factor in patients who were preoperatively intubated because of their unstable general condition or severe heart failure. Preoperative mechanical ventilation, cardiac surgery, and CPB increased the incidence of VAP and subsequent pulmonary infections. Moreover, CPB and cardiac surgery impair endogenous defense in children. The origin and pathogenesis of VAP remain unclear, although it is likely that VAP is the result of microaspirations rather than bloodstream-associated infiltration of the lungs. Bacterial invasion of the lungs may be directly facilitated by the endotracheal tube during separation from the ventilatory circuit, as most bacteria found in the endotracheal aspirates of patients with VAP are also found in the nasal and oropharyngeal passages, and even in gastric secretions.[19] The increased incidence of VAP in children after cardiac surgery may be due to several factors, including young age, lower body weight, heart failure, failure to thrive, and poor general condition. The current literature highlights the importance of strategies to prevent VAP, which contributes to prolonged hospital stays, increased costs, mortality, and morbidity.[3,19,20]

The incidence rate of HAIs increased with decreasing patient weight. Weight was an independent risk factor in our study, and an inverse relationship was found between weight and infection. Diet plays an important role in the immune system[21], and low protein status may increase the risk of infection due to low antibody production.[22] An optimal nutritional status is also important for the regulation of inflammatory and oxidative stress processes, all of which are related to the immune system.[23]

Children undergoing heart surgery are placed in a special type of intensive care unit. Many of these patients are infants and neonates who require CPB and invasive procedures. Therefore, pediatric patients undergoing cardiac surgery may have a significantly higher risk of infection. Central lines and invasive monitoring are common in postoperative children with cardiac disease, who are often infants or neonates requiring complex and high-risk cardiac surgery.[24] In our study, a bloodstream or catheter-related bloodstream infection or sepsis was detected in 76.6% of the patients. The combination of younger age and high-risk surgical category in our cohort may have increased this risk. The most common infectious agent in our study was gram-negative bacteria, which also occurred in infections after cardiac surgery.[7,25] The increased prevalence of gram-negative organisms can also be attributed to the current practice of using prophylactic antibiotics that cover mainly Gram-positive organisms in the postoperative period.[26]

As expected, the length of hospital stay was longer in our group of infected patients than in the group without infection. This result is consistent with the results of previous studies and suggests that as the length of hospital stay increases, the tendency to become infected also increases, which directly affects the length of hospital stay. Thus, HAIs are an important factor in prolonging the length of hospital stay.[2,6,24]

Although advancements in surgical experience and intensive care conditions over the years have led to earlier surgery for complex and critically ill patients, the incidence of postoperative infections remains high and multifactorial. Culture positivity is low owing to the high proportion of antibiotics started before surgery. Prevention strategies, such as optimization of surgical procedures, early nutrition, infection control measures, and experienced staff, can reduce the risk of postoperative infection. Although this study has limitations, such as its retrospective, single-center design and small sample size we believe it is important in identifying risk factors for HAI specific to pediatric cardiovascular ICUs. However, further studies are required to identify the contributing factors and prevention strategies. The results of this single-center study cannot be generalized, and a large prospective multicenter study is required to confirm these findings.

Ethical approval

This study was approved by Başkent University Institutional Review Board (Project no: KA21/234).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: NC, MG; data collection: NC, MG, MC, ACG; analysis and interpretation of results: NC, MG; draft manuscript preparation: NC. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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