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Original Article

Nasal Methicillin-Resistant S. Aureus is a Major Risk for Mediastinitis in Pediatric Cardiac Surgery

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Background: Mediastinitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is a serious complication after pediatric cardiac surgery. An outbreak of surgical site infections (SSIs) provided the motivation to implement SSI prevention measures in our institution.
Methods: Subjects comprised 174 pediatric patients who underwent open-heart surgery after undergoing preoperative nasal culture screening. The incidence of SSIs and mediastinitis was compared between an early group, who underwent surgery before SSI measures (Group E, n = 73), and a recent group, who underwent surgery after these measures (Group R, n = 101), and factors contributing to the occurrence of mediastinitis were investigated.
Results: The incidence of both SSIs and Mediastinitis has significantly decreased after SSI measures. With regard to factors that significantly affected mediastinitis, preoperative factors were "duration of preoperative hospitalization" and "preoperative MRSA colonization," intraoperative factors were "Aristotle basic complexity score," "operation time," "cardiopulmonary bypass circuit volume" and "lowest rectal temperature." And postoperative factor was "blood transfusion volume." Patients whose preoperative nasal cultures were MRSA-positive suggested higher risk of MRSA mediastinitis.
Conclusions: SSI prevention measures significantly reduced the occurrence of SSIs and mediastinitis. Preoperative MRSA colonization should be a serious risk factor for mediastinitis following pediatric cardiac surgeries.

Keywords: mediastinitis, surgical site infection, pediatric cardiac surgery, cardiopulmonary bypass, antibiotic prophylaxis

Introduction

Surgical site infections (SSIs) are a type of postoperative complication that cannot be disregarded, and SSI prevention measures have been emphasized at each institution since the Centers for Disease Control (CDC) released its guidelines.[1,2] SSIs prolong time spent in hospital, increase medical costs and reduce patient satisfaction.[3,4] The field of cardiovascular surgery in particular entails not only massive surgical invasion of the heart and lungs, but also the unavoidable implantation of artificial materials and the adverse effects of the use of extracorporeal circulation on the body's defense mechanisms, increasing the risk of postoperative infection. Postoperative mediastinitis remains a serious SSI that affects prognosis. At our hospital (Toho University Omori Medical Center, Tokyo), we experienced an outbreak of postoperative mediastinitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA) that required the urgent introduction of SSI prevention measures. We introduced

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comprehensive SSI prevention measures in collaboration with the Department of Infection Control.

Although some studies have referred to the importance of preoperative nasal culture in pediatric cardiac surgery,[5] we have been unable to locate any reports focusing on MRSA in particular. We therefore investigated the effectiveness of SSI prevention measures, and used logistic regression analysis to carry out a retrospective investigation of the preoperative, intraoperative and postoperative factors that are associated with the occurrence of mediastinitis.

Patients and Methods

This clinical study was approved by the Ethics Committee of our hospital (screening number: 21–25). The National Nosocomial Surveillance System (NNIS) definitions were used to classify SSI as superficial wound infections, deep incisional infections, or organ space infections (Mediastinitis).[6] The definitions are fully compatible with the cases of SSI in this study.

Subjects were patients aged ≤15 years who underwent pediatric open-heart surgery between October 2002 and October 2010. During this period, because we experienced an outbreak of postoperative mediastinitis caused by MRSA, comprehensive SSI prevention measures were introduced in September 2005 comprising: (1) reduction in duration of preoperative hospitalization (patients scheduled to undergo surgery were admitted on the day prior to surgery whenever possible); (2) more thorough implementation of standard precautions;[1] (3) preoperative nasal cultures to check for MRSA colonization, and treatment of those who tested positive with preoperative application of mupirocin ointment to the nasal cavity and prophylactic administration of vancomycin from immediately before surgery until day 2 after surgery, as well as postoperative zoning in private intensive care unit (ICU) rooms; and (4) reduction of the duration of general prophylactic administration of antibiotics other than vancomycin.

Subjects were 174 patients who underwent preoperative nasal culture screening during the period described above. They were divided into an early group, who underwent surgery before SSI prevention measures were introduced (Group E, n = 73), and a recent group, who underwent surgery after these measures were introduced (Group R; n = 101). Cases of operative death and patients for whom even one of the four SSI prevention measures was not implemented, i.e., those who underwent surgery during the transition period, were excluded.

Anesthesia and cardiopulmonary bypass (CPB)

All patients received modified neurolepto-anesthesia and analgesia, including fentanyl, midazolam and vecuronium bromide or rocuronium bromide as a neuromuscular agent. CPB was provided with perfusion via ascending aorta and bicaval venous drainage. Extracorporeal circulation was accomplished using a MAQUET HL-30® (MAQUET Holding GmbH & Co. KG, Rastatt, Germany) with pulsatile flow control. Surgery proceeded under systemic hypothermia with antegrade intermittent cold cardioplegia. A pump flow rate of 2.8 L/m^2 per minute was maintained. During bypass, dilutional ultrafiltration (DUF) or DUF with modified ultrafiltration (MUF) were performed.

Patient backgrounds were compared between the two groups using Wilcoxon's rank sum test, and the incidence of SSIs and mediastinitis was compared using a χ^2 test. Logistic regression analysis was also used to investigate the following preoperative, intraoperative, and postoperative factors to evaluate risk factors affecting the occurrence of postoperative mediastinitis in all patients (n = 174).

Preoperative factors: Height, weight, body surface area, gender, age at time of surgery, preoperative hemoglobin (Hb) level, duration of preoperative hospitalization, MRSA colonization in nasal culture

Intraoperative factors: Complexity of surgical procedure, operation time, CPB time, CPB-circuit volume, lowest rectal temperature, amount of water removed during DUF/MUF.

Postoperative factors: perioperative packed red blood cell transfusion volume, duration of postoperative intubation, duration of prophylactic antibiotic administration, duration of postoperative stay in ICU, duration of drainage tube insertion

Statistical significance was set at $p < 0.05$, and SPSS for Windows was used as statistical analysis software.

Results

Table 1 shows the attributes of patients in Groups E and R. Height, weight, body surface area (BSA), age and preoperative hemoglobin levels were all lower in Group R when compared with Group E, but there was no significant differences in Aristotle basic complexity (ABC) score,[7] which was derived by consensus of an international surgeon panel to facilitate assessment of the surgical performances

Table 1 Preoperative patient characteristics by group

	Group E (n = 73)	Group R (n = 101)	
Height (cm)	88.4 ± 29.7	77.4 ± 22.5	p <0.05
Weight (kg)	14.6 ± 13.6	10.1 ± 8.7	p <0.05
BSA (m^2)	0.6 ± 0.3	0.4 ± 0.2	p <0.05
Age (year)	3.4 ± 3.9	2.2 ± 3.7	p <0.05
Hb (g/dl)	13.4 ± 2.0	12.6 ± 1.8	p <0.05
Hospitalization (day)	2.7 ± 2.0	1.7 ± 2.2	p <0.05
ABC score	6.1 ± 2.2	6.3 ± 2.0	p = 0.52
Surgical procedures			p = 0.13
ASD ICR (%)	26	18	
VSD ICR (%)	30	45	
TOF ICR (%)	11	8	
Fontan (%)	7	1	
Palliation (%)	5	6	
Others (%)	21	22	

Group E: Early group, before SSI measures n = 73. Group R: Recent group, after SSI measures n = 101. ABC: Aristotle Basic Complexity; ASD: atrial septal defect; BSA: body surface Area; Hb: hemoglobin; ICR: intracardiac repair; SSI: surgical site infections; TOF: tetralogy of Fallot; VSD: ventricular septal defect

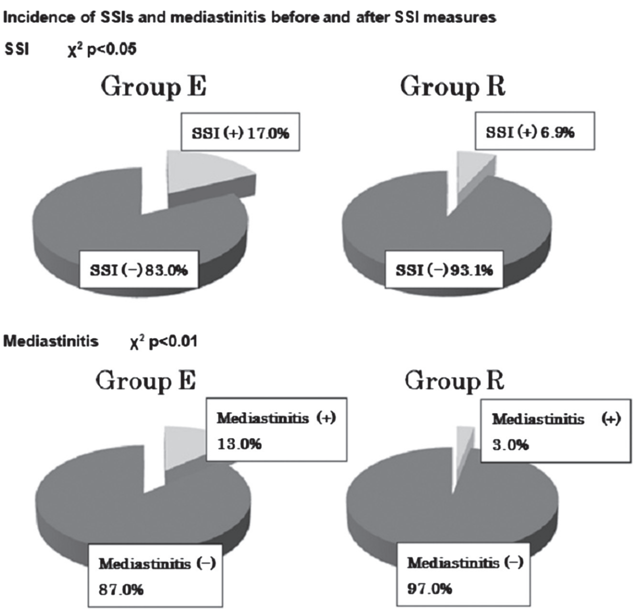

Fig. 1 Group E: Early group, before SSI measures n = 73. Group R: Recent group, after SSI measures n = 101. SSI: surgical site infections.

and the degree of each procedure difficulty in congenital heart surgery.

Table 1 shows the breakdown of surgical procedures. There were no significant differences between the two groups. The incidence of SSIs was 17.0% in Group E and 6.9% in Group R, and the incidence of mediastinitis was 13.0% in Group E and 3.0% in Group R, with a significant decrease after the introduction of SSI prevention measures ($p < 0.05$) **(Fig. 1)**.

Table 2 shows factors with the potential to affect the occurrence of postoperative mediastinitis for all subjects. Significant preoperative factors were "duration of preoperative hospitalization" and "preoperative MRSA colonization" (odds ratios 1.01 and 7.14, respectively; both p = 0.03). Significant intraoperative factors were "ABC score," "operation time," "CPB-circuit volume," and "lowest rectal temperature" (odds ratios 1.35, 1.27, 1.34 and 0.78, respectively; p = 0.04, <0.01, <0.01, and <0.01, respectively), and the one significant postoperative factor was "blood transfusion volume" (odds ratio 1.27, $p < 0.01$).

An investigation of the correlation between the duration of preoperative hospitalization and preoperative MRSA nasal colonization found that prolonged preoperative hospitalization significantly increased the rate of MRSA-positive preoperative nasal culture (odds ratio of 1.01; $p < 0.01$) (**Table 3**). Preoperative MRSA nasal colonization was also an extremely significant risk factor for postoperative mediastinitis caused by MRSA (odds ratio of 16.30; $p < 0.01$) (**Table 4**).

Discussion

The reported incidence of SSIs in pediatric cardiovascular surgery is 1.7–8.0%.[3,8-13] At our hospital, because we experienced an outbreak of SSIs caused by MRSA, the incidence of SSIs prior to the introduction of SSI prevention measures was remarkably high, at 17.0%, and mediastinitis accounted for 70% of cases. SSI prevention measures were therefore an urgent issue, and we collab-

Table 2 Univariate risk factors for mediastinitis

Variable	Odds ratio	(95% CI)	p value
Preoperative factors			
BSA (m^2)	0.56	(0.07–4.62)	0.59
Male	0.98	(0.31–3.06)	0.97
Age (year)	0.98	(0.85–1.15)	0.89
Preoperative-Hb (g/dl)	1.16	(0.89–1.48)	0.26
Preoperative Hospitalization (day)	1.01	(1.00–1.02)	0.03
Positive nasal culture of MRSA	7.14	(1.18–43.36)	0.03
Intraoperative factors			
ABC score	1.35	(1.01–1.80)	0.04
RACHS-1	1.92	(0.97–3.81)	0.06
Operation time (hour)	1.27	(1.06–1.52)	<0.01
CPB circuit volume (dl/m^2)	1.33	(1.11–1.62)	<0.01
CPB time (hour)	1.45	(0.99–2.13)	0.05
Lowest rectal temperature (°C)	0.78	(0.62–0.95)	0.01
DUF ± MUF (dl/m^2)	1.01	(0.98–1.02)	0.77
Postoperative factors			
Blood transfusion	1.27	(1.13–1.43)	<0.01
Mechanical ventilation (hour)	1.06	(0.99–1.13)	0.09
Chest tube duration (day)	1.11	(0.95–1.28)	0.19
ICU stay (day)	1.06	(0.99–1.14)	0.09
Antimicrobial Prophylaxis (day)	1.03	(0.97–1.08)	0.35

ABC: Aristotle Basic Complexity; BSA: Body Surface Area; CI: Confidence interval; CPB: Cardiopulmonary Bypass; DUF: Dilutional Ultrafiltration; Hb: Hemoglobin; ICU: Intensive Care Unit; MUF: Modified Ultrafiltration; MRSA: Methicillin-resistant *Staphylococcus aureus;* RACHS: Risk Adjustment in Congenital Heart Surgery

Table 3 Risk factors for positive nasal culture of MRSA on univariate analysis

Variable	Odds ratio	(95% CI)	p Value
BSA (m^2)	0.01	(0.01–4.10)	0.11
Male	0.56	(0.10–3.16)	0.51
Age (year)	0.49	(0.17–1.44)	0.19
Preoperative-Hb (g/dl)	0.66	(0.41–1.10)	0.09
Preoperative Hospitalization (day)	1.01	(1.01–1.02)	<0.01

BSA: Body Surface Area; CI: Confidence Interval; Hb: Hemoglobin; MRSA: Methicillin-resistant *Staphylococcus aureus*

orated with the Department of Infection Control to introduce comprehensive SSI prevention measures. Doctors, nurses and other medical professionals underwent thorough retraining on infection, including standard precautions,[1,2] and efforts were also made to improve the hospital environment and make it more hygienic. As a result, the incidence of both SSIs and mediastinitis decreased significantly in Group R (the recent group) when compared with Group E (the early group).

Some of the preoperative factors that are generally believed to affect SSIs include newborns aged <1 month, infants aged <1 year, duration of preoperative hospitalization ≥48 h, and genetic syndromes.[8,12,14,15] In terms of the preoperative attributes of the patients in this study, patients in Group R were younger than those in Group E, with significantly lower height, weight and body surface area **(Table 1)**. Despite this, the occurrence of SSIs and mediastinitis was reduced in Group R. This indicates that the efficacy of our SSI prevention measures outweighed the disadvantage of small body size.

One important point about this study was the use of preoperative nasal culture. Nasal colonization with MRSA was shown to be a significant factor affecting postoperative mediastinitis. Nasal carriage of MRSA is considered to constitute a risk factor for SSIs in the fields of adult cardiac surgery.[16–21] In this study, the incidence of

Table 4 Univariate risk factors for MRSA–mediastinitis

Variable	Odds ratio	(95% CI)	p Value
Preoperative factors			
BSA (m^2)	0.82	(0.07–10.44)	0.88
Male	0.85	(0.19–3.95)	0.84
Age (year)	1.02	(0.85–1.22)	0.85
Preoperative-Hb (g/dl)	1.12	(0.79–1.57)	0.52
Preoperative Hospitalization (day)	1.02	(1.01–1.02)	0.01
Nasal cavity culture (MRSA)	16.30	(2.39–110.81)	<0.01
Intraoperative factors			
ABC score	1.22	(0.83–1.76)	0.31
RACHS-1	0.97	(0.34–2.76)	0.96
Operation time (hour)	1.17	(0.92–1.49)	0.19
CPB circuit volume (dl/m^2)	1.23	(0.96–1.58)	0.09
CPB time (hour)	1.29	(0.76–2.17)	0.34
Lowest rectal temperature (°C)	0.81	(0.63–1.05)	0.12
DUF ± MUF (dl/m^2)	1.00	(1.00–1.00)	0.94
Postoperative factors			
Blood transfusion	1.27	(1.10–1.46)	<0.01
Mechanical ventilation (hour)	1.01	(0.99–1.01)	0.19
Chest tube duration (day)	1.08	(0.88–1.32)	0.46
ICU stay (day)	1.06	(0.95–1.17)	0.28
Antimicrobial Prophylaxis (day)	0.99	(0.89–1.12)	0.95

ABC: Aristotle Basic Complexity; BSA: Body Surface Area; CI: Confidence Interval; CPB: Cardiopulmonary Bypass; DUF: Dilutional Ultrafiltration; Hb: Hemoglobin; ICU: Intensive Care Unit; MUF: Modified Ultrafiltration; MRSA: Methicillin-resistant *Staphylococcus aureus;* RACHS: Risk Adjustment in Congenital Heart Surgery

postoperative mediastinitis for patients with MRSA-positive nasal cultures was much higher when compared with that for MRSA-negative patients, with an odds ratio of 16.3. Few studies have found that preoperative nasal colonization is a risk for postoperative SSIs in pediatric cardiac surgery.[5)] We have been unable to find any reports focusing on MRSA in particular. As far as we have been able to determine from a search of the literature, our study is the first to report that those pediatric cardiac surgery patients who were found to be MRSA carriers during preoperative MRSA nasal culture screening were at significantly higher risk of developing postoperative MRSA mediastinitis.

Chang, et al. used the polymerase chain reaction (PCR) method to investigate the rate of contamination of the skin and surroundings of MRSA nasal carriers, and found that MRSA was detected from the skin of 38 of 74 carriers (51%) and from the surroundings of 37 of 83 carriers (45%). However, the relationship between MRSA in the nasal cavity and MRSA in the mediastinum is still unclear, as is the route by which the bacteria invade the mediastinum. Jakob, et al. carried out nasal cultures for 376 adult heart surgery patients, and used deoxyribonucleic acid (DNA) fingerprint analysis to distinguish whether deep sternal wound infections were caused by endogenous or exogenous pathways.[22)] DNA fingerprint analysis also showed that the DNA patterns of *S. aureus* from the nasal cavity and sternum were identical, demonstrating that the endogenous infection pathway is the major route for deep sternal wound infection. They therefore insisted that the preoperative eradication of locally colonized *S. aureus* is important in terms of preventing serious SSIs and mediastinitis.

In our own hospital, we now treat the nasal cavities of patients in whom MRSA is detected from preoperative nasal culture with mupirocin ointment. Kluytmans, et al. also reported that patients who underwent nasal treatment with mupirocin ointment to eradicate *S. aureus* from the nasal cavity during the perioperative period had a significantly lower incidence of SSIs.[19)] This study suggests that mupirocin treatment is an effective tool. Since our hospital introduced SSI prevention measures, we have also administered the anti-MRSA drug vancomycin as antibiotic prophylaxis from the day of surgery until day 2 after surgery for all patients from whom MRSA was detected in preoperative nasal culture. Although the optimum duration of vancomycin administration remains unclear, our period of administration is almost the same as that reported by Finkelstein, et al.[23]

The second important point in this study is that the duration of preoperative hospitalization was a significant factor affecting postoperative mediastinitis. The major route of infection for in-hospital MRSA transmission is believed to be via the hands of hospital staff.[24] Shortening the duration of preoperative hospitalization reduces opportunities for exposure to MRSA and other bacteria. The duration of preoperative hospitalization is therefore important in preventing SSIs.

Surgical complexity, operation time, lowest rectal temperature, and CPB-circuit volume were significant intraoperative factors for the development of mediastinitis. Surgical complexity can be graded according to ABC score or Risk Adjustment in Congenital Heart Surgery (RACHS-1) score.[25] In this study, procedures with a high ABC score were a significant factor for postoperative mediastinitis ($p = 0.04$), and the incidence of mediastinitis also tended to increase for procedures with a high RACHS-1 score ($p = 0.06$). Sarvikivi, et al. indicated that procedures with high American Society of Anesthesiologists (ASA) score,[26] and high RACHS-1 score were SSI risk factors, stating that highly complex surgical procedures were risk factors for SSIs,[12] a result that agrees with our own observations. Numerous studies in cardiac surgery have shown that operation time is a risk factor for SSIs.[8,9,12,13] This supports the results in this study. Low body temperature during surgery was also found to be a risk factor for SSIs by McAnally, et al.[27] Our results also showed that lowest rectal temperature was a significant factor affecting mediastinitis. In patients undergoing highly complex procedures, however, minimum rectal temperature is frequently lowered intentionally to preserve organs. Low body temperature may be unavoidable for highly complex procedures.

In this study, we also found that CPB-circuit volume was a risk factor for SSIs. Activation of the coagulation and fibrinolytic system and the complement system caused by contact between blood components and the inner surface of CPB-circuit as a foreign body, as well as systemic inflammatory responses (SIR) have been reported to be lower when CPB-circuit is smaller.[28–30] CPB-circuit volume should be an indirect risk factor for SSIs from the immunological perspective. As cytokines were not measured, we were unable to verify the hypothesis that mediastinitis and other SSIs were induced by immunosuppression. This was a limitation of this study.

Blood transfusion volume was also shown to be a risk factor for mediastinitis. Blood transfusions reportedly decrease natural killer cell function, causing incomplete antigen presentation and reducing cellular immunity,[31] meaning they constitute a risk factor for postoperative infection.[14] These reports also support our findings.

SSIs after heart surgery in adults have been addressed by a comparatively greater number of studies, in contrast to the small number of reports on SSIs after heart surgery in children. In the present study, we have shown that prolonging the duration of preoperative hospitalization increases the opportunities for children to be exposed to MRSA, ultimately causing them to become MRSA carriers, and these children then undergo highly invasive heart surgery with a high degree of complexity that requires a long period of extracorporeal circulation and massive blood transfusions, creating a vicious circle that means they develop postoperative mediastinitis. Patients before open heart surgery should therefore undergo nasal culture screening as early as possible to check for MRSA colonization, and stringent measures to eliminate MRSA should be implemented for carriers. Other advances should include improving the hospital environment and making it more hygienic, as well as reminding medical professionals of the importance of standard precautions.[1,2]

Conclusion

The comprehensive SSI prevention measures implemented in our hospital were successful in significantly reducing the occurrence of postoperative mediastinitis. Shortening durations of preoperative hospitalization and surgery, and reducing CPB-circuit volume were important factors in preventing postoperative mediastinitis. MRSA carriers, patients undergoing complex procedures, those with low body temperature during CPB, and those requiring large blood transfusions are at high risk of developing mediastinitis, and the groundwork to prevent SSI from the preoperative period is essential.

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Disclosure Statement

Tomoyuki Katayanagi has no conflict of interest.

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