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Epidemiology and outcome of major postoperative infections following cardiac surgery: Risk factors and impact of pathogen type

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Abstract

Background—Major postoperative infections (MPIs) are poorly understood complications of cardiac surgery. We examined the epidemiology, microbiology, and outcome of MPIs occurring after cardiac surgery.

Methods—The study cohort was drawn from the Society of Thoracic Surgeon National Cardiac Database and comprised adults who underwent cardiac surgery at 5 tertiary hospitals between 2000 and 2004. We studied the incidence, microbiology, and risk factors of MPI (bloodstream or chest wound infections within 30 days after surgery), as well as 30-day mortality. We used multivariate regression analyses to evaluate the risk of MPI and mortality.

Results—MPI was identified in 341 of 10,522 patients (3.2%). Staphylococci were found in 52.5% of these patients, gram-negative bacilli (GNB) in 24.3%, and other pathogens in 23.2%. High body mass index, previous coronary bypass surgery, emergency surgery, renal impairment,

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immunosuppression, cardiac failure, and peripheral/cerebrovascular disease were associated with the development of MPI. Median postoperative duration of hospitalization (15 days vs 6 days) and mortality (8.5% vs 2.2%) were higher in patients with MPIs. Compared with uninfected individuals, odds of mortality were higher in patients with *S aureus* MPIs (adjusted odds ratio, 3.7) and GNB MPIs (adjusted odds ratio, 3.0).

Conclusions—Staphylococci accounted for the majority of MPIs after cardiac surgery. Mortality was higher in patients with *Staphylococcus aureus*- and GNB-related MPIs than in patients with MPIs caused by other pathogens and uninfected patients. Preventive strategies should target likely pathogens and high-risk patients undergoing cardiac surgery.

Keywords

Wound infection; Sepsis; Cardiac surgical procedures; Morbidity; Mortality

Major postoperative infections (MPIs), including bloodstream infections (BSIs) and surgical site infections (SSIs), occur in up to 5% of patients after cardiac surgery.^{1–3} These infections have a devastating impact on patient outcomes and entail high health care costs.^{4,5} The frequency of MPIs is likely to climb, given the growing demand for complex cardiac surgical procedures in older and high-risk patients.^{6,7}

The epidemiology of MPIs after cardiac procedures remains incompletely understood. The literature contains scant information on the collective burden of SSIs and BSIs after cardiac surgery. In addition, whether specific pathogens can adversely affect outcome in patients with MPIs is unknown.^{8,9} Research examining the association of pathogen type and outcome of MPIs may inform future preventive and therapeutic efforts, including the use of preoperative screening, decolonization of pathogens, selection and timing of antibiotic prophylaxis, and use of empiric antibiotic therapy in the management of patients with MPIs.^{10,11}

In the present study, we examined the epidemiology, microbiology, and risk factors for the development of MPIs after cardiac surgery and mortality within 30 days after surgery. We also evaluated the impact of pathogen type on the outcome of patients who developed MPIs.

METHODS

This multicenter retrospective cohort study evaluated combined clinical and microbiology data from 5 US medical centers. These patient-specific clinical data were prospectively collected for the Society for Thoracic Surgery (STS) National Cardiac Database.

The STS database was established in 1989 to collect surgical outcomes after cardiothoracic procedures.¹² It currently receives clinical data from more than half of all US medical centers that perform adult cardiac surgery, including data for almost two-thirds of all coronary bypass procedures performed in the country. Participating centers send data semiannually to the STS Data Warehouse and Analysis Center at the Duke Clinical Research Institute. The data in the STS database have been validated and shown to be highly accurate.^{13,14} For the current study, complete patient-specific microbiological data were available from 5 tertiary care medical centers participating in STS database. The microbiological data were combined with clinical data (STS case report form, versions 2.35, 2.41, and 2.52) at these 5 participating sites and then transferred to the Duke Clinical Research Institute to create a final study database.

Study population

We enrolled patients aged 18 years who underwent a cardiac surgical procedure at a participating hospital between January 2000 and December 2004. A patient record was excluded if it lacked details related to age, sex, urgency level of surgery, or predicted mortality risk index.¹⁵ Only the first eligible surgical procedure was included in the study. Definitions used for major clinical risk factors are available from the STS Web site.¹⁶

Definitions

The primary endpoint was development of MPI, defined as the presence of either BSI or SSI, including mediastinitis, within 30 days after cardiac surgery. An episode of BSI was defined as the presence of at least one positive blood culture yielding one or more pathogens. Blood cultures growing coagulase-negative staphylococci (CoNS) and other common skin contaminants were not considered BSIs unless the same organism was isolated from at least 2 consecutive blood cultures. An SSI was considered present if one or more pathogens was isolated from culture of a chest wound (superficial or deep).¹⁷ Secondary endpoints included mortality within 30 days of surgery and postoperative length of hospital stay (LOS).

Statistical analysis

SAS version 9 (SAS Institute, Cary, NC) was used for all statistical analyses. The incidence of MPIs, microbiology of infections, and mortality were described as counts and proportions. Univariate analyses were used to estimate associations between variables and outcomes of interest (presented as unadjusted odds ratio [OR] with 95% confidence interval [CI]). Hypothesis testing was performed on nonmissing data. The χ^2 test was used to compare categorical variables, and the Wilcoxon rank-sum test was used for continuous data. A 2-tailed *P* value of .05 was considered significant. A *P* value of .05 was required to include or keep a dependent variable in the backward selection process of determining the final parsimonious multivariate model.

Preoperative predictors of MPI

We developed a model to determine preoperative predictors for the development of MPI. Candidate variables were chosen based on univariate analyses and previously identified risk factors.¹⁷ We assessed predictors of 30-day mortality of cardiac surgeries as follows:

1. Simple logistic regression to verify that the development of MPIs was significantly associated with 30-day mortality compared with no MPIs,
2. Multivariate logistic regression to determine whether MPIs caused by different bacterial pathogens were independently associated with 30-day mortality. For this analysis, we included the logit value of predicted mortality from a previously published STS mortality model,¹⁵ as well as the following candidate factors: type of MPI, type of pathogen, urgency of cardiac surgery, and interaction terms between infection type and pathogen type. Including the logit value of the STS-predicted mortality provided 3 distinct advantages during modeling: the ability to include data from the predicted mortality in a single composite variable, the ability to account for predicted mortality and to determine any excess risk of mortality attributable to MPIs, and the avoidance of overfitting the model with excessive factors.¹⁵ We constructed two parsimonious models using different study populations and reference groups to examine whether MPIs due to specific types of pathogens were associated with mortality. One model included all enrolled surgical patients and used patients without MPI as the reference group, whereas the other

model included only patients with MPIs and used patients with MPIs due to CoNS as the reference group.

RESULTS

A total of 10,522 patients underwent cardiac surgery at 5 participating medical centers during the study period (Table 1). Of these, 7,460 (71%) were male and 9,208 (88%) were Caucasian. The mean patient age was 65 ± 11.3 years. A total of 8,112 patients (77.1%) underwent coronary artery bypass graft (CABG) surgery, 1,309 (12.4%) underwent cardiac valve surgery, and 1,101 (10.5%) underwent both CABG and valve surgery. A total of 225 patients (2.1%) underwent an emergent surgical procedure.

Incidence of MPI

Overall, 341 out of 10,522 patients developed an MPI within 30 days of cardiac surgery (overall rate, 3.2 per 100 procedures). Of these 341 patients, 186 (55%) had a BSI, 124 (36%) had an SSI, and 31 (9%) had both a BSI and an SSI. The overall incidence of MPI decreased over the study period, from 5.4 per 100 procedures in 2000 to 2.6 per 100 procedures by the end of 2004 ($P < .001$).

Epidemiology of pathogens associated with MPI

Of the 341 MPIs identified, 302 (89%) were monomicrobial. The 341 MPIs included 179 (52.5%) caused by staphylococci, 83 (24.3%) caused by gram-negative bacilli (GNB), and 79 (23.2%) caused by other pathogens. Of the 179 staphylococcal MPIs, CoNS was found in 92 (51.4%) cases, and *S aureus* as a single species accounted for the other 87 cases (48.6%). Almost half (48.3%) of the *S aureus* MPIs were due to methicillin-resistant *S aureus* (MRSA).

The most common GNBs associated with MPI were Enter-obacteriaceae (67%), followed by organisms designated “other” GNBs (21%). *Pseudomonas* spp were the least common GNB, accounting for only 12% of GNB MPIs. Other miscellaneous pathogens associated with MPI included streptococci, enterococci, other gram-positive cocci, and fungi.

Both categories of staphylococci, *S aureus* (25.5%) and CoNS (27.0%), were closely associated with the development of MPIs. In addition, *S aureus* was a frequent pathogen in MPIs that simultaneously involved BSIs and sternal SSIs (48.4%). GNB were the most common pathogens associated with BSIs, found in 59 of 186 cases (32%). CoNS was the most common pathogen associated with SSIs (35%).

Table 2 presents the characteristics of patients with MPI stratified by organism. Patients with MPI due to GNB had a higher rate of comorbidities, such as cerebrovascular disease, peripheral vascular disease, renal failure, and immunosuppressive therapy.

Outcomes of patients with MPIs

The overall 30-day mortality for patients in the study was 2.4%. Mortality varied substantially by the presence of MPI and the type of causative pathogen. Specific 30-day mortality was 8.5% in patients with MPI and only 2.2% in those without MPI ($P < .0001$) (Table 1). Unadjusted pathogen-specific 30-day mortality was significantly higher ($P < .0001$) for patients with MPIs due to GNB (10 of 83; 12.1%) and patients with MPIs due to *S aureus* (10 of 87; 11.5%) compared with either CoNS (3 of 92; 3.3%) or other pathogens (6 of 79; 7.6%) (Table 2).

The median LOS for the study patients was 6 days (interquartile range [IQR], 5–8 days). The presence of an MPI extended the median LOS to 15 days, compared with 6 days for patients without MPI ($P < .0001$). The median LOS was 22 days for patients with MPIs due to GNB, the longest compared with MPIs due to other organisms ($P < .0001$) (Table 2).

Preoperative factors associated with MPI

Several preoperative factors were associated with the development of MPI on univariate analysis (Table 1). For example, patients with MPI were more likely to have a body mass index (BMI) >40 kg/m² (OR, 2.5; 95% CI, 1.7–3.7), to be receiving hemodialysis (OR, 3.2; 95% CI, 1.9–5.3), to have undergone emergency surgery (OR, 2.2; 95% CI, 1.3–3.7), or to have heart failure (OR, 1.8; 95% CI, 1.4–2.3) or a history of vascular disease. Table 1 also shows the adjusted OR (aOR) for variables that were included in the multivariate logistic regression for MPI (C index, 0.690). Specifically, the following factors were statistically significantly associated with the development of MPI: BMI ≥ 30 kg/m², emergent surgery, renal impairment, immunosuppressed state, and cardiac failure.

Modeling predictors of 30-day mortality after cardiac surgery

Impact of MPI on 30-day mortality—Logistic regression demonstrated that the development of MPI was significantly associated with 2.1-fold greater odds of death within 30 days of cardiac surgery compared with patients without MPI (95% CI, 1.4- to 3.2-fold; $P < .001$).

Impact of pathogen-specific MPI on 30-day mortality—We constructed logistic regression models to identify the impact of pathogen-specific MPI on 30-day mortality on patients in the cohort who underwent cardiac surgery and in patients diagnosed with an MPI. In the first model, which included the entire study cohort, patients with MPI due to CoNS had similar 30-day mortality as the reference group of uninfected individuals (aOR, 0.8; 95% CI, 0.2–2.6) (Table 3). In contrast, MPIs due to GNB (aOR, 3.0; 95% CI, 1.5–6.2) or *S aureus* (aOR, 3.7; 95% CI, 1.7–7.7) were independently associated with 30-day mortality.

In the second model, we included only enrolled patients with MPI and compared their odds of 30-day mortality by pathogen type. We used patients with CoNS MPI as the reference group. We found that MPI due to *S aureus* was independently associated with 30-day mortality compared with MPI due to other pathogens (aOR, 4.7; 95% CI, 1.2–18.5; $P = .027$) (Table 3).

DISCUSSION

In this study, we made several key observations. First, we found an overall rate of MPI of 3.2 per 100 procedures, a rate consistent with previous estimates from the STS database.² Second, we identified and confirmed several preoperative characteristics as predictors for the development of MPI. Unfortunately, many of these factors are not easily modified; however, patients at high risk for the development of MPI may be offered specific and intensive prophylaxis measures before elective cardiac surgical procedures. Third, we found that the type of pathogen associated with MPI, particularly *S aureus*, had a significant impact on 30-day mortality.

Our data demonstrate that MPIs are devastating complications of cardiac surgery, associated with an average LOS of 15 days after surgery and a 30-day mortality of 8.5%, approximately 4 times greater than that in patients without MPI. This high mortality is likely due in large part to *S aureus*, for several reasons. First, *S aureus* was associated with more than one-quarter of all MPIs and accounted for the highest combined burden of different

types of MPI. Second, the high mortality rate of uncontrolled or poorly treated *S aureus* infections is well recognized,¹⁸ and patients with *S aureus* MPI had the highest adjusted odds of 30-day mortality of any subgroup in this study. Finally, almost one-half of all *S aureus* MPIs in our cohort were due to MRSA, which is particularly difficult to treat.¹⁹

We found a significant decrease in the incidence of MPIs during the 5-year study period. In this period, the rate of MPI at the participating sites decreased by half, from 5.4 per 100 procedures in 2000 to 2.6 per 100 procedures by the end of 2004. This finding is consistent with previous reports.^{20,21} This decrease may be attributed in part to other preventative measures implemented by all 5 sites during the study period, including the Surgical Improvement Project/Surgical Care Improvement Project²² and central line “bundle” practices.²³

We have identified several preoperative risk factors for the development of MPIs. Obesity (BMI ≥ 30 kg/m²), emergent surgical procedure, immunosuppressed state, and such comorbidities as diabetes, renal impairment, and history of vascular disease were all significantly associated with subsequent development of MPI. Among these factors, obesity deserves special mention because it is a well-recognized risk factor for surgery and has a multitude of implications for the development of infection after many types of surgery.² Our findings reveal a direct relationship between the severity of obesity and the odds of developing MPI after cardiac surgery. BMI is a good marker for obesity and has been included in several new risk indices designed to predict risk of infections after cardiothoracic surgery.^{2,24,25} In addition to increasing the risk of infection, obesity also affects the dosing of antimicrobial prophylaxis for surgical procedures. Obese patients undergoing cardiac surgery may require higher doses of antibiotics to achieve the same tissue drug levels to prevent infections as nonobese patients, and thus perioperative antibiotic dosages should be calculated based on patient weight.

Almost half of the *S aureus*-associated MPIs in this study were MRSA. This finding has profound implications. First, it implies that cefazolin, the antibiotic usually recommended for prophylaxis before cardiac surgery, will have no efficacy in half of the cases of *S aureus* MPI. Instead, vancomycin or another anti-MRSA agent may be given for surgical prophylaxis in settings of high MRSA prevalence. If vancomycin is used for surgical prophylaxis, the infusion must be started within 2 hours of the incision, and another antibiotic with gram-negative coverage should be given as well. Finally, the high observed rate of MRSA-related MPI also suggests that empiric therapy for patients with MPI after cardiac surgery should include coverage for MRSA.

GNB were the next most common causative organisms in MPIs, especially BSIs. Interestingly, gram-negative MPIs were associated with prolonged hospitalization, but not with increased risk of mortality in the adjusted model. The *P* value for GNB MPI in the model was 0.10, in the context of very few deaths occurring during the study period. In a larger study population, GNB MPIs also might have been statistically significantly associated with 30-day mortality. In any case, we hypothesize that patients with GNB MPI had a prolonged LOS because of the greater complexity of their care. Indeed, patients with MPI due to GNB had high rates of renal failure, vascular disease, myocardial infarction, immunosuppressive therapy, and redo cardiac surgery. In contrast, MPI associated with CoNS was not associated with prolonged hospitalization or excess mortality compared with uninfected individuals. This finding also may reflect the relatively low virulence capacity of CoNS.

Our results underscore the significance and the burden of *S aureus* infections after cardiac surgery. *S aureus* is one of the leading causes of MPI, and MPI due to *S aureus* is associated

with significantly worse clinical outcomes compared with MPI due to other pathogens. This combination of poor outcome and high frequency emphasizes the need for *S aureus*-specific management and prevention. Such strategies might include decolonization, appropriate antibiotic prophylaxis, and future interventions such as vaccines²⁶ and monoclonal antibodies.²⁷ The potential utility of chlorhexidine-based decontamination strategies to prevent postoperative infections has been reported.^{10,11,28,29}

This study has some limitations. First, the SSIs in this study were categorized differently than the surveillance definitions used by the National Healthcare Safety Network.^{30,31} More specifically, our definition is based only on a positive wound culture from the chest, which might have led to an underestimation of the true incidence of SSIs (eg, culture-negative wound infection or wound infections where cultures were not obtained). However, our classification of SSIs remained clinically useful and allowed us to observe important trends in mortality and LOS. Second, we were unable to include infections involving secondary wounds, such as saphenous vein harvest sites.³² Such infections also increase morbidity and potentially prolong LOS. Omitting these nonchest wound infections would have resulted in further underestimation of the impact of infections on patients undergoing cardiac surgery.

Other study limitations include the inability to obtain details involving type, timing, and dosage of antibiotic prophylaxis (unavailable from the STS database). Thus, we were not able to assess adherence to Surgical Improvement Project guidelines. In addition, data for the present study came from only 5 reasonably large tertiary care medical centers that submitted patient-specific microbiological data. The dataset did not include any community hospitals in the dataset. Thus, our results might not be generalizable to patient populations in other settings. Finally, we used patients with MPI due to CoNS as a reference group in the second multivariate logistic regression, because a sensitivity analysis to ensure detection of MPIs due to bacterial pathogens had a specific impact on 30-day mortality. This reference group was chosen because of the generally held belief that CoNS is of lower virulence; however, this choice was arbitrary and may be of little clinical relevance.

Despite these limitations, this study is the largest investigation of the microbiological epidemiology of major infections after cardiac surgery published to date, and it has yielded several important observations. Critically, we demonstrated that microbiology influences the scope and severity of MPI. We found that presence of a *S aureus*-related MPI was the most dominant risk factor in 30-day mortality. In addition, we confirmed several preoperative risk factors, including obesity, for the development of MPIs. Future studies should examine the effects of eliminating identified risk factors, optimizing prophylaxis, and implementing decolonization strategies as well as pathogen-specific measures, such as a vaccine against *S aureus*, on reducing the incidence and impact of MPI after cardiac surgery.

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Table 1

Risk factors and outcomes of MPI

Variable	Major infection (n = 341)	No major infection (n = 10,181)	Unadjusted OR (95% CI)	P value	aOR (95% CI)	P value
Risk factors						
Caucasian	278 (81.5)	8,930 (87.7)	0.6 (0.5–0.8)	.0007	0.73 (0.54–0.97)	.03
BMI, kg/m²*						
30 and <40	120 (35.2)	3,267 (32.1)	1.3 (1.0–1.6)		1.31 (1.03–1.66)	.028
40	32 (9.4)	437 (4.3)	2.5 (1.7–3.7)		2.48 (1.66–3.71)	<.0001
Emergent surgery	15 (4.4)	210 (2.1)	2.2 (1.3–3.7)	.0034	1.99 (1.13–3.48)	.017
Diabetes	154 (45.2)	3,481 (34.2)	1.6 (1.3–2.0)	<.0001	1.25 (1.00–1.58)	.063
Renal failure	54 (15.8)	550 (5.4)	3.3 (2.4–4.5)	<.0001	2.25 (1.54–3.28)	<.0001
Chronic lung disease					0.73 (0.55–0.97)	.029
Cerebrovascular accident	49 (14.4)	807 (7.9)	2.0 (1.4–2.7)	<.0001	1.57 (1.14–2.17)	.006
Peripheral vascular disease	88 (25.8)	1,640 (16.1)	1.8 (1.4–2.3)	<.0001	1.47 (1.13–1.92)	.004
Immunosuppressive treatment	22 (6.5)	284 (2.8)	2.4 (1.5–3.8)	<.0001	1.97 (1.23–3.13)	.005
Previous CABG	41 (12.0)	747 (7.3)	1.7 (1.2–2.4)	.0012	1.72 (1.22–2.43)	.002
Congestive heart failure	108 (31.7)	2,094 (20.6)	1.8 (1.4–2.3)	<.0001	1.30 (1.01–1.67)	.043
NYHA class IV	121 (35.5)	2,702 (26.5)	1.5 (1.2–1.9)	.0002	1.38 (1.09–1.74)	.007
Outcomes						
30-day mortality, n (%)	29 (8.5)	227 (2.2)		<.0001		
Postoperative LOS, days, median	15.0	6.0		<.0001		

CABG, coronary artery bypass graft surgery; NYHA, New York Heart Association.

* Reference group was BMI <30 kg/m².

Table 2

Baseline characteristics and outcomes of MPI by pathogen type

Variable	Any <i>S aureus</i> (n = 87)	Any gram-negative bacteria (no <i>S aureus</i> infection) (n = 83)	CoNS only (n = 92)	Other pathogens (n = 79)	P value
Risk factors, n (%)					
BMI, kg/m ² *					
30 and <40	32 (36.8)	32 (38.6)	35 (38.0)	21 (26.6)	<.0001
40	8 (9.2)	5 (6.0)	12 (13.0)	7 (8.9)	
Emergent procedure	3 (3.5)	5 (6.0)	7 (7.6)	0 (0.0)	.0002
Diabetes	42 (48.3)	35 (42.2)	44 (47.8)	33 (41.8)	.0008
Renal failure	13 (14.9)	19 (22.9)	14 (15.2)	8 (10.1)	<.0001
Cerebrovascular accident	12 (13.9)	14 (16.9)	13 (14.1)	10 (12.7)	.0007
Peripheral vascular disease	20 (23.0)	25 (30.1)	24 (26.1)	19 (24.1)	<.0001
Immunosuppressive treatment	2 (2.3)	10 (12.1)	5 (5.4)	5 (6.3)	<.0001
Previous CABG	9 (10.3)	16 (19.3)	12 (13.0)	4 (5.1)	.0001
Myocardial infarction	47 (54.0)	50 (60.2)	50 (54.4)	41 (51.9)	<.0001
Congestive heart failure	21 (24.1)	30 (36.1)	31 (33.7)	26 (32.9)	<.0001
NYHA class IV	28 (32.2)	34 (41.0)	31 (33.7)	28 (35.4)	.0040
30-day infection type (infected patients), n (%)					
SSI only	36 (41.4)	15 (18.1)	43 (46.7)	30 (38.0)	<.0001
BSI only	36 (41.4)	59 (71.1)	47 (51.1)	44 (55.7)	
SSI and BSI	15 (17.2)	9 (10.8)	2 (2.2)	5 (6.3)	
Outcomes					
30-day mortality, n (%)	10 (11.5)	10 (12.1)	3 (3.3)	6 (7.6)	<.0001
Postoperative LOS, days, median	11.0	22.0	14.0	13.0	<.0001

CABG, coronary artery bypass graft surgery; NYHA, New York Heart Association.

* Reference group was BMI <30 kg/m².

Table 3

Association between pathogen-specific MPI and 30-day mortality

	<u>Odds for 30 day-mortality</u>		
	aOR	95% CI	P value
Final model 1: includes all enrolled patients			
Uninfected individuals	1.00	Reference	
MPI due to <i>S aureus</i>	3.67	1.74–7.74	<.001
MPI due to any gram-negative bacillus	3.00	1.45–6.24	.003
MPI due to other pathogens	2.51	1.04–6.08	.040
MPI due to CoNSz	0.79	0.24–2.63	.698
Final model 2: includes only enrolled patients with MPI			
MPI due to CoNS	1.00	Reference	
MPI due to <i>S aureus</i>	4.70	1.19–18.5	.027
MPI due to any gram-negative bacillus	3.12	0.80–12.2	.10
MPI due to other pathogens	2.63	0.62–11.3	.19