Pneumonia after cardiac surgery: Experience of the National Institutes of Health/Canadian Institutes of Health Research Cardiothoracic Surgical Trials Network

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ABSTRACT

Rationale: Pneumonia remains the most common major infection after cardiac surgery despite numerous preventive measures.

Objectives: To prospectively examine the timing, pathogens, and risk factors, including modifiable management practices, for postoperative pneumonia and estimate its impact on clinical outcomes.

Methods: A total of 5158 adult cardiac surgery patients were enrolled prospectively in a cohort study across 10 centers. All infections were adjudicated by an independent committee. Competing risk models were used to assess the association of patient characteristics and management practices with pneumonia within 65 days of surgery. Mortality was assessed by Cox proportional hazards model and length of stay by a multistate model.

Measurements and Main Results: The cumulative incidence of pneumonia was 2.4%, 33% of which occurred after discharge. Older age, lower hemoglobin level, chronic obstructive pulmonary disease, steroid use, operative time, and left ventricular assist device/heart transplant were risk factors. Ventilation time (24–48 vs ≤ 24 hours; hazard ratio [HR], 2.83; 95% confidence interval [95% CI], 1.72–4.66; >48 hours HR, 4.67; 95% CI, 2.70–8.08), nasogastric tubes (HR, 1.80; 95% CI, 1.10–2.94), and each unit of blood cells transfused (HR, 1.16; 95% CI, 1.08–1.26) increased the risk of pneumonia. Prophylactic use of second-generation cephalosporins (HR, 0.66; 95% CI, 0.45–0.97) and platelet transfusions (HR, 0.49, 95% CI, 0.30–0.79) were protective. Pneumonia was associated with a marked increase in mortality (HR, 8.89; 95% CI, 5.02–15.75) and longer length of stay of 13.55 ± 1.95 days (bootstrap 95% CI, 10.31–16.58).

Conclusions: Pneumonia continues to impose a major impact on the health of patients after cardiac surgery. After we adjusted for baseline risk, several specific management practices were associated with pneumonia, which offer targets for quality improvement and further research. (J Thorac Cardiovasc Surg 2017;153:1384–91)

Cumulative incidence of pneumonia over 65 days.

Central Message

Pneumonia is the most common infection after cardiac surgery. Several specific modifiable management practices were associated with pneumonia, which offer targets for quality improvement.

Perspective

Pneumonia is a common complication after cardiac surgery, and previous studies have identified several patient-specific risk factors. Ours, however, is the first multicenter, prospective study of both risk factors and management practices on the risk of pneumonia. This analysis provides knowledge and targets for future quality improvement initiatives.

See Editorial Commentary page 1392.

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Abbreviations and Acronyms

CI	= confidence interval
COPD	= chronic obstructive pulmonary disease
CTSN	= Cardiothoracic Surgical Trials Network
HAI	= healthcare-associated infection
HR	= hazard ratio
LOS	= length of stay
NG	= nasogastric
SCIP	= Surgical Care Improvement Project

Scanning this QR code will take you to the online appendices for this article.

Healthcare-associated infections (HAIs) represent the leading cause of noncardiac morbidity after cardiac surgery,¹ and pneumonia particularly is common and responsible for adverse patient outcomes.²⁻⁴ Moreover, pneumonia frequently is cited as among the most costly and resource-intensive of all HAIs.⁵⁻⁷

Patients undergoing cardiac surgery are highly susceptible to pneumonia. Many patients present with cardiac symptoms requiring hospitalization before urgent surgery, predisposing them to pathogens. Common risk factors among cardiac surgery patients, such as chronic obstructive pulmonary disease (COPD), heart failure, and advanced age, result in a greater risk profile for pneumonia. Moreover, cardiopulmonary bypass, with its effect on systemic inflammatory mediators and its potential for lung injury, may further contribute to the risk of developing pneumonia.⁸ Significant fluid shifts in the perioperative setting often leading to pulmonary edema, combined with the frequent need for transfusion of blood products, may affect a patient's risk for pneumonia.⁹ Any prolonged use of mechanical ventilation also places patients at increased risk for pneumonia.^{10,11} Finally, postoperative pain due to sternotomy or thoracotomy can affect pulmonary mechanics. Variations in management practices, such as fluid administration and ventilator management, are likely to affect the incidence of pneumonia,^{12,13} but few insights exist about the relationship between these "process of care" variables and pneumonia.

The purpose of this study was to examine the time course, pathogens, and risk factors, including modifiable management practices, for postoperative pneumonia in patients undergoing cardiac surgery. This study is a substudy of a larger prospective cohort study conducted within centers participating in the Cardiothoracic Surgical Trials Network (CTSN), looking at all serious postoperative infections.¹⁴

PATIENTS AND METHODS**Study Design and Patients**

The primary objective of this CTSN observational study was to identify management practices associated with the risk of infection after cardiac surgery. This study was conducted in 10 centers from the CTSN. The patient population included all adults receiving cardiac surgical interventions, excluding those with active systemic infections, including endocarditis.

We targeted a minimum sample size of 5000 patients to obtain at least 200 patients with major infections. This sample size was based not on explicit statistical criteria but on acquiring an adequate number of events (at least 10 per variable) to ensure stability of coefficient estimates in our models.^{15,16} Patients were followed for up to 60 ± 5 days after surgery, with 2 planned postdischarge assessments at 30 and 60 days after surgery; the last date of follow-up was November 29, 2010. We collected data on patient characteristics (demographics, baseline laboratory values, comorbidities), surgery-related factors (such as previous intra-aortic balloon pump, surgery time, operative procedure), and management practices (such as antimicrobial prophylaxis, glycemic control, line management) (see [Appendix E1](#)). Data were transmitted from sites electronically to a secure server administered by the Data Coordinating Center. Participating institutional review boards approved the protocol (see [Appendix E2](#) for participating sites), and the study was overseen by a National Heart, Lung, and Blood Institute–appointed Data Safety and Monitoring Board. All patients provided written informed consent to participate and release their medical information.

Endpoints

The primary endpoint for this analysis was pneumonia within 65 days of the index cardiac surgery. Pneumonia was classified according to definitions from the Centers for Disease Control and the National Healthcare Safety Network surveillance (see [Appendix E1](#)). Other secondary endpoints included all-cause mortality, reoperation, and hospital readmissions. All pneumonias were reviewed by an independent event adjudication committee. The date of final event adjudication was June 2011.

Data Analysis

We used the proportional subdistribution hazards model,¹⁷ a variant of the Cox proportional hazards model, to account for death as a competing event when assessing the effect of baseline characteristics and management practices on pneumonia. Model building proceeded in 2 stages. We first identified patient- and procedure-related risk factors that were associated individually (at $P < .10$) with pneumonia and remained significant (at $P < .05$) in the multivariable model using a backward selection procedure. We then evaluated the additional contribution of management practices used before the first pneumonia (see [Appendix E1](#) for details), except for postoperative transfusions, where the exact timing could not always be ascertained. Management practices that were associated individually with pneumonia (at $P < .10$) were placed in a multivariable model that contained all the patient- and procedure-specific variables in the first stage. With the use of a backward selection approach, the final competing risk model for pneumonia consisted of only management practices with a $P < .05$, adjusting for all the first stage baseline risk factors.

The standard Cox proportional hazards model was applied to the mortality analysis, with pneumonia treated as a time-dependent covariate. Patient characteristics that are known risk factors for mortality in the elderly cardiac surgery population and that were significant in our model were controlled for in the analysis.

To estimate the incremental length of stay (LOS) due to pneumonia, we used a multistate approach that treats pneumonia as a time-dependent exposure and mortality as a competing risk.¹⁸ LOS was defined as the time from index procedure to hospital discharge or death. The model assumed a time-inhomogeneous Markov process with 1 initial state (index surgery), 1 intermediate state (pneumonia), and 2 absorbing states (death and discharged

alive). All patients started in the initial state and could transition to the other states. Patients who developed pneumonia could have had a previous or subsequent infection, and patients who did not develop pneumonia could have had other infections. A bootstrap standard error and 95% confidence interval (CI) was computed for the additional LOS due to pneumonia based on 1000 bootstrap samples. All analyses were done in SAS statistical software (SAS v9.4; SAS Institute, Cary, NC) and R 3.1.1.^{19,20}

RESULTS

Patients Characteristics

Among the patients enrolled (n = 5158), the mean age was 64.4 ± 13.2 years, the median body mass index was 28.2 kg/m^2 , and the proportion of women was 33% (n = 1708; Table 1). Diabetes was present in 23% (n = 1169) of patients, 29% (n = 1505) had heart failure, and 14% (n = 746) had COPD of mild or greater severity. Nineteen percent (n = 958) of patients had undergone previous cardiac surgery. The most common procedures were isolated coronary artery bypass grafting (33%, n = 1677) and isolated valve surgery (36%, n = 1878).

Frequency and Timing of Pneumonia and Microorganisms

A total of 123 patients experienced 125 pneumonia events (crude cumulative incidence 2.4%, Figure 1, A), accounting for 41.5% of all major infections (n = 301) in this cohort (Figure 1, A). The initial diagnosis was made during the index hospitalization in 67% (n = 82) of patients who developed pneumonia, nearly one half of which (n = 58) occurred during the first week after surgery. The mean time to the first episode of pneumonia was 14.4 days, with a median time of 8 days (range 1-62). Of the 123 patients who experienced pneumonia, 106 (86%) contracted it within 30 days after cardiac surgery.

The distribution of microorganisms isolated from patients who developed pneumonia is shown in Figure 2. The 3 most common isolates were *Pseudomonas aeruginosa* (15.8%, n = 15), *Klebsiella pneumonia* (11.6%, n = 11), and *Enterobacter cloacae* (10.5%, n = 10).

Baseline Risk Factors Related to Pneumonia

Preoperative patient characteristics that were associated with a greater risk of pneumonia in multivariable analysis included older age (hazard ratio [HR], 1.02; 95% CI, 1.00-1.03; $P = .05$), presence of COPD (HR, 2.17; 95% CI, 1.47-3.21; $P < .001$), and recent steroid use (HR, 1.91; 95% CI, 1.01-3.59; $P = .05$). Greater hemoglobin levels at baseline were protective (HR, 0.88; 95% CI, 0.79-0.97; $P = .01$) (Table 2). Smoking history did not increase the risk of pneumonia in the multivariable model. Approximately 50% of patients were admitted on the same day of

TABLE 1. Patient and operative characteristics*

Baseline and operative characteristics	Overall (N = 5158)
Demographics	
Age, mean (SD)	64.4 (13.2)
Male	3450 (66.9)
White	4322 (83.9)
BMI	28.2 (25.1-32.3)
Insurance	
Medicaid	233 (4.5)
Medicare	1928 (37.5)
Government (other)	626 (12.2)
Private	2099 (40.8)
None/self	260 (5.1)
Baseline laboratory values	
WBC, $\times 10^3/\text{mL}$	7.0 (5.7-8.4)
Creatinine, mg/dL	1.0 (0.8-1.2)
Hemoglobin, g/dL	13.4 (12.0-14.5)
Cardiac morbidity	
Heart failure	1505 (29.2)
Ejection fraction	55.0 (48.0-60.0)
Previous cardiac surgery	958 (18.6)
Noncardiac morbidity	
Corticosteroids	176 (3.4)
Diabetes†	1169 (22.7)
COPD	
None	4412 (85.5)
Mild or moderate	644 (12.5)
Severe	102 (2.0)
Operative	
Surgery time, h	4.2 (3.3-5.2)
Bypass time, min‡	105.0 (78.0-140.0)
Sternotomy	4669 (90.5)
Surgery type	
Elective	3806 (73.8)
Urgent	1214 (23.5)
Emergent	138 (2.7)
Procedure	
Isolated CABG	1677 (32.5)
Isolated valve	1878 (36.4)
CABG + valve	692 (13.4)
LVAD/Tx	122 (2.4)
Thoracic aortic	428 (8.3)
Other§	361 (7.0)

SD, Standard deviation; BMI, body mass index; WBC, white blood cells; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting; LVAD/Tx, left ventricular assist device or heart transplant surgery. *Continuous variables are expressed as median (interquartile range) and categorical variables as count (%). †Insulin or oral medications. ‡A total of 91.1% of patients had on-pump surgical procedures. §Other: ventricular septal defect repairs, atrial septal defect repairs, aneurysmectomies, patent foramen ovale closures, ablations, septal myectomies, excision of cardiac tumors, pericardiectomies, and limited other procedures.

surgery, and the majority of the other patients were admitted within 1 week before surgery. Preoperative LOS was not associated with the development of pneumonia after we accounted for other risk factors. Operative

FIGURE 1. A, Cumulative incidence function with 95% confidence intervals for pneumonia with death as a competing risk. B, Extended Kaplan-Meier curve with 95% confidence intervals for mortality based on method of Snappin and colleagues.²⁰

variables associated with greater pneumonia risk included left ventricular assist device implantation or heart transplantation (HR, 2.79; 95% CI, 1.50-5.17; $P = .001$), and longer operative time (HR, 1.38; 95% CI, 1.25-1.53; $P < .001$).

Management Practices Related to Pneumonia

When we controlled for baseline risk factors, management practices that were associated with an increased risk of pneumonia included the use of a nasogastric (NG) tube postoperatively (HR, 1.80; 95% CI, 1.10-2.94; $P = .02$), and transfusion of packed red blood cells (for each unit: HR, 1.16; 95% CI, 1.08-1.26; $P < .001$; Table 3). Platelet transfusion, however, was protective (HR, 0.49, 95% CI, 0.30-0.79, $P = .004$). Compared with postoperative ventilation of 24 hours or less, an intubation time of 24 to 48 hours was associated with more than double the risk of pneumonia (HR, 2.83; 95% CI, 1.72-4.66; $P < .001$) and ventilation exceeding 48 hours was associated with more than a 4-fold greater risk (HR, 4.67; 95% CI, 2.70-8.08; $P < .001$). Perioperative second-generation cephalosporins (cefuroxime, cefoxitin, with or without concomitant vancomycin), which were used in 47% of patients, reduced the risk of pneumonia by more than 30% (HR, 0.66; 95% CI, 0.45-0.97; $P = .04$). There was consistent use of head of

bed elevation and secretion management postoperatively and thus, neither affected pneumonia risk. Placement of femoral lines, number of central lines, and hyperglycemia were not significant predictors in the multivariable model.

LOS and Readmissions

The observed mean LOS after the initial surgical procedure was 32.4 ± 22.6 days for patients with pneumonia during the index hospitalization compared with 8.9 ± 6.5 days for those without it. After their index surgery, patients who developed pneumonia stayed in the hospital for nearly 2 weeks longer (excess LOS: 13.55 ± 1.95 days; bootstrap 95% CI, 10.31-16.58). In the overall parent cohort study, the readmission rate was 19% ($n = 945$). Infection was the most common reason for readmission (16% of all readmissions) and pneumonia constituted 21.3% of this group.

Pneumonia and Mortality

Ninety-seven patients (1.9%) died during follow-up, with one half of the deaths occurring within 19 days of index surgery. Figure 1, B depicts the unadjusted time-varying effect of pneumonia on mortality. Pneumonia was associated with a markedly greater risk of death (HR, 8.89; 95% CI, 5.02-15.75; $P < .001$), after we adjusted for patient's age, sex, comorbidities (diabetes and

FIGURE 2. Distribution of identified microorganisms among patients developing pneumonia organism data was available for 62% of pneumonia cases. Up to different 3 organisms was recorded for each event. Other categories: *Neisseria sicca*, *Alcaligenes xylosoxidans*, *Corynebacterium pseudodiphtheriticum*, *Morganella morganii*, and *Serratia plymuthica*.

congestive heart failure), and baseline hemoglobin and creatinine levels (Table 4). The 65-day mortality rates (per 100 patient-months) for patients with and without pneumonia were 6 and 0.8, respectively.

COMMENT

In this large, multicenter, prospective cohort study, postoperative pneumonia was the most common infection that occurred within 65 days, with more than 30% of first events diagnosed after discharge from the index hospitalization.¹⁴ Older age, COPD, steroid use, lower hemoglobin levels, left ventricular assist device/heart transplants, and longer

duration of surgery were significantly associated with risk of pneumonia. Importantly, the use of second-generation cephalosporins for perioperative prophylaxis, shorter ventilation time (<24 hours), avoidance of NG tube use, fewer packed red blood cell transfusions, and receipt of platelet transfusions were all associated with a decreased risk of postoperative pneumonia. Ultimately, postoperative pneumonia was associated with a nearly 9-fold increase in mortality and an additional 2 weeks of index hospital stay.

Impact of Pneumonia in Cardiac Surgery

Traditionally, surgical-site infections have been perceived as the most common infection after cardiac surgery. Our study reveals pneumonia to be the most common serious infection after cardiac surgery, and this finding is supported by other contemporary studies.^{14,21} In a recent analysis of more than 19,000 patients, pneumonia was the most common postoperative infection (6%) whereas deep surgical-site infections occurred in just 1%.²² In the present study, pneumonia was associated with an 8.9-fold increased risk of mortality even after we adjusted for baseline patient characteristics and resulted in a 65-day pneumonia mortality rate of 6 per 100 patient-months.

TABLE 2. Patient and procedure characteristics associated with pneumonia

Baseline variable	HR (95% CI)	P value
Age, y	1.02 (1.00-1.03)	.05
COPD, yes/no	2.17 (1.47-3.21)	<.001
Corticosteroids, yes/no	1.91 (1.01-3.59)	.05
Hemoglobin, g/dL	0.88 (0.79-0.97)	.01
LVAD/Tx, yes/no	2.79 (1.50-5.17)	.001
Duration of surgery, h	1.38 (1.25-1.53)	<.001

HR, Hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LVAD/Tx, left ventricular assist device or heart transplant surgery.

TABLE 3. Management practices associated with pneumonia

Management practice*	HR (95% CI)	P value
Second-generation CEPH, yes/no	0.66 (0.45-0.97)	.04
Ventilation (vs ≤ 24 h)		
24-48 h	2.83 (1.72-4.66)	<.001
>48 h	4.67 (2.70-8.08)	<.001
NG tube, yes/no	1.80 (1.10-2.94)	.02
PRBC, unit	1.16 (1.08-1.26)	<.001
Platelet, yes/no	0.49 (0.30-0.79)	.004

HR, Hazard ratio; CI, confidence interval; CEPH, cephalosporin; NG, nasogastric tube; PRBC, packed red blood cells. *Model adjusted for baseline risk factors in Table 2.

In addition to the effect on morbidity and mortality, pneumonia represents a significant burden on resource use. Our group has estimated the incremental cost associated with a major HAI to be \$38,000, with infection-related readmissions costing 3 times that of readmissions that were unrelated to infection.²³ There have been few publications that focus on the economic impact of pneumonia (compared with undefined pneumonitis) in the cardiac surgery population. A recent analysis that used the Nationwide Inpatient Sample in patients undergoing isolated mitral valve surgery estimated an average net increase in hospital cost of \$29,692 for the 5.5% of individuals with postoperative pneumonia and an increase in the median LOS of 10 days.²⁴ Thus, postoperative pneumonia represents not only a significant risk factor for morbidity and mortality but also a significant driver of resource use.

Timing of Pneumonia

In comparison with the published literature, which focuses mostly on the index hospitalization or on 30-day follow-up, patients in this study were followed for up to 65 days after the index operation. As such, this study revealed that a substantial proportion of first pneumonia events (more than 30%) occurred after the index hospitalization, and 14% more than 30 days postsurgery.

Although it would be expected that the majority of cases of pneumonia would manifest early in the postoperative setting due to postoperative pain, need for narcotics, and

fluid shifts, there are some potential reasons why pneumonia may develop later. Because the average LOS for many routine cardiac operations is 5 to 7 days, retrospective studies may underestimate the true prevalence of pneumonia. It is likely that the intensive pulmonary care that occurs in the hospital is not maintained after discharge. Also, many “late” pneumonias (after the first week) in our study occurred in patients with prolonged hospitalizations and/or difficult postoperative courses with multiple complications.

Modifiable Processes of Care

Given the significant association with mortality and increased resource use, there has been a strong effort during the past decade to reduce HAIs through improvements in management practices. This prospective study was the first to our knowledge to investigate the relationship between processes of care and the incidence of postoperative pneumonia after cardiac operations. National guidelines have been developed and implemented to avert infections, and among these is the Surgical Care Improvement Project (SCIP).²⁵ The SCIP guidelines include standardizing perioperative antibiotic use to decrease postoperative surgical-site infections. Specific SCIP measures addressing the risk of infection include (1) the administration of appropriate antibiotics within 60 minutes of incision, (2) discontinuation of antibiotics within 48 hours after cardiac surgery, and (3) controlled blood glucose (<200 mg/dL) at 6 AM postoperative day one. The Society of Thoracic Surgeons also has published practice guidelines related to antibiotic prophylaxis.²⁶ In these guidelines, first- or second-generation cephalosporins are considered first-line therapy for prophylaxis with no clear data supporting first-generation over second-generation cephalosporins. In patients with significant allergy to β -lactam antibiotics, vancomycin with or without an aminoglycoside is recommended. In multivariable analysis, the use of second-generation cephalosporins with broader Gram-negative coverage was associated with a lower risk of pneumonia; however, neither first- nor second-generation cephalosporins have activity against *Pseudomonas*, which was the most common organism observed in patients with pneumonia. Therefore, consideration might be given to optimizing perioperative antibiotic regimens for patients who may be high risk for developing postoperative pneumonia, although any recommendation of this type needs to be balanced carefully against the risk of promoting the emergence of multidrug-resistant nosocomial organisms.

Numerous studies have shown that prolonged intubation affects postoperative pneumonia, LOS, and complications. As such, early extubation after surgery has been a prominent focus of cardiac surgical quality improvement for

TABLE 4. Impact of pneumonia on mortality

Variable	HR (95% CI)	P value
Pneumonia	8.89 (5.02-15.75)	<.001
Age, y	1.03 (1.01-1.05)	<.001
Male	0.60 (0.39-0.91)	.02
Diabetes,* yes/no	1.57 (1.03-2.41)	.04
Heart failure, yes/no	1.86 (1.24-2.80)	.003
Creatinine, mg/dL	1.17 (1.06-1.30)	.002
Hemoglobin, g/dL	0.85 (0.75-0.95)	.005

HR, Hazard ratio; CI, confidence interval. *Insulin or oral medications.

several years, often with reimbursement linked to postoperative extubation time. The present study reinforces the importance of timely postoperative extubation, with patients intubated between 24 and 48 hours or >48 hours having 2.83- and 4.67-fold increased risk of pneumonia, respectively, compared with patients who are extubated within 24 hours. Likewise, we have demonstrated previously the dose-dependent association between red blood cell transfusion and risk of postoperative infections and, as such, efforts need to continue to improve blood conservation in cardiac surgery.²⁷

The use of a NG tube was associated with risk of pneumonia. Previous reports have supported this finding. A randomized study comparing the use of an NG tube to no NG tube after cardiac surgery demonstrated no benefit to routine NG use.²⁸ Another study identified the use of an NG tube to be the strongest risk factor for developing nosocomial pneumonia (odds ratio, 6.48 [95% CI, 2.11-19.82]) in patients intubated longer than 72 hours.²⁹ The fact that many of the organisms cultured in our study were enteral flora supports this observation. It is possible that some patients who received an NG tube were ill for a long period of time postoperatively and, therefore, the NG tube was a marker of illness severity and not the dominant predisposing factor. Nonetheless, it was surprising that 73% of all patients in this study had an NG tube after surgery; NG tube management may be an important target for process improvement investigations.

Limitations

We identified the timing of infections and included in the analysis only those management practices that were used before the diagnosis of pneumonia, except transfusions, the timing of which was sometimes unavailable. We cannot definitively exclude practices that were used on the basis of a suspicion of infection. Absence of an association between pneumonia and head elevation and secretion management reflects the fact that there was nearly uniform adoption of these practices across sites. Randomized trials are challenging to conduct in this area. However, the standardization of infection definitions and data collection procedures, as well as site monitoring and adjudication of infections by an expert committee, improve the validity of this observational study. Finally, although we were able to garner much insight from these 123 patients with pneumonia, the relatively low number of outcome events limits our ability to assess more precisely the impact of all measured process of care variables.

CONCLUSION AND IMPLICATIONS

In this observational study of cardiac surgical patients, pneumonia was the most prevalent infection and had a significant, deleterious impact on LOS and mortality. We identified various processes of care measures that were

associated independently with the development of pneumonia, including choice of antibiotic prophylaxis, the use of an NG tube, length of mechanical ventilation after surgery, and the use of red blood cell and platelet transfusions. Despite substantial efforts to reduce the incidence of surgery-associated pneumonia, gaps remain in the application of quality improvement strategies. Given the high incidence of postdischarge pneumonia, efforts also should be directed towards identifying high risk patients and developing and evaluating transitional programs to address this issue.

Conflict of Interest Statement

Dr Gillinov reports personal fees from Edwards Lifesciences, personal fees from Medtronic, personal fees from On-X, grants and personal fees from St Jude Medical, personal fees from Abbott, personal fees and other from AtriCure, and personal fees from ClearFlow, outside the submitted work. Dr Alexander reports grants from National Institutes of Health/NHLBI, during the conduct of the study. Dr Smith reports grants from NIH/CTSN, during the conduct of the study, personal fees from Abbott Vascular, personal fees from Edwards Lifesciences, grants from Edwards Lifesciences, personal fees from St Jude, outside the submitted work. All other authors have nothing to disclose with regard to commercial support.

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Key Words: pneumonia, infections, cardiac surgery, outcomes, quality improvement

APPENDIX E1. PRIMARY ENDPOINT DEFINITION AND VARIABLES FOR COX REGRESSION

Definition of Pneumonia

To be classified as pneumonia, the following criteria must have been met (adapted from the Centers for Disease Control and Prevention/National Healthcare Safety Network guidelines for the clinical diagnosis of pneumonia):

- At least one or more chest radiographs no earlier than 2 days after surgery with at least 1 of the following: (a) new or progressive and persistent infiltrate, (b) consolidation, or (c) cavitation.
- Patient has at least 1 of the following signs or symptoms: fever ($>38^{\circ}\text{C}$) with no other recognized cause, leukopenia (<4000 white blood cells/ mm^3) or leukocytosis ($\geq 12,000$ white blood cells/ mm^3), or altered mental status with no other recognized cause (for patients ≥ 70 years old) and at least 2 of the following: (a) new onset of purulent sputum or change in character or sputum or increased respiratory secretions or increased suctioning requirements; (b) new onset or worsening cough, or dyspnea, or tachypnea; (c) rales or bronchial breath sounds; (d) worsening gas exchange (eg, oxygen desaturations, increased oxygen requirements, or increased ventilator demand)

Variables tested in the Stage 1 baseline risk model and their crude association with pneumonia

Baseline and operative characteristics	Pneumonia, n (%)	Unadjusted HR (95% CI)	P value*
Demographics			
Age, y		1.02 (1.00-1.03)	.02
Sex		1.07 (0.73-1.56)	.73
Male	84 (2.4)		
Female	39 (2.3)		
Race		0.56 (0.38-0.85)	.01
White	92 (2.1)		
Nonwhite	31 (3.7)		
BMI, kg/m^2		1.00 (0.96-1.03)	.83
Insurance			.59
Medicaid	8 (3.4)	1.79 (0.73-4.38)	
Medicare	51 (2.6)	1.38 (0.74-2.59)	
Government (other)	12 (1.9)	1.00 (ref)	
Private	45 (2.1)	1.12 (0.59-2.11)	
None/self	7 (2.7)	1.41 (0.55-3.59)	
Baseline laboratory values			
WBC, $\times 10^3/\text{mL}$		1.03 (0.99-1.07)	.19
Creatinine, mg/dL		1.14 (1.07-1.22)	<.001
Hemoglobin, g/dL		0.80 (0.73-0.88)	<.001
Cardiac morbidity			
Hypertension		1.60 (1.01-2.54)	.04
Yes	101 (2.6)		
No	22 (1.7)		

(Continued)

(Continued)

Baseline and operative characteristics	Pneumonia, n (%)	Unadjusted HR (95% CI)	P value*
Heart failure		2.19 (1.53-3.11)	<.001
Yes	58 (3.9)		
No	65 (1.8)		
Previous cardiac surgery		1.98 (1.35-2.89)	<.001
Yes	38 (4.0)		
No	85 (2.0)		
Noncardiac morbidity			
Corticosteroids		2.82 (1.52-5.21)	.001
Yes	11 (6.3)		
No	112 (2.3)		
Diabetes†		1.05 (0.69-1.60)	.81
Yes	29 (2.5)		
No	94 (2.4)		
History of smoking			.06
No	52 (1.9)	1.00 (ref)	
Current	23 (3.4)	1.76 (1.08-2.88)	
Former	47 (2.7)	1.38 (0.93-2.05)	
COPD		2.58 (1.75-3.78)	<.001
Yes	37 (5.0)		
No	86 (1.9)		
Cerebrovascular accident		1.06 (0.59-1.88)	.85
Yes	13 (2.5)		
No	110 (2.4)		
Peripheral vascular disease		1.59 (0.97-2.59)	.06
Yes	19 (3.6)		
No	104 (2.2)		
Operative			
Surgery time, hours		1.44 (1.31-1.58)	<.001
Bypass		1.10 (0.58-2.11)	.77
Yes	113 (2.4)		
No	10 (2.2)		
Circulatory arrest		2.19 (1.21-3.97)	.01
Yes	12 (4.9)		
No	111 (2.3)		
Sternotomy		0.78 (0.46-1.32)	.35
Full	107 (2.5)		
Not full	16 (1.9)		
Surgery type			.08
Elective	80 (2.1)	1.00 (ref)	
Urgent	38 (3.1)	1.50 (1.02-2.20)	
Emergent	5 (3.6)	1.72 (0.70-4.22)	
Procedure		4.99 (2.84-8.78)	<.001
LVAD/Tx	13 (10.7)		
All others	110 (2.2)		
Previous IABP		1.51 (0.55-4.10)	.42
Yes	4 (3.5)		
No	119 (2.4)		

Variables not used because of small cell counts: The sternum was not closed for 16 patients, only 1 of whom developed pneumonia. Variables not used because of excessive missing data: ejection fraction. HR, Hazard ratio; CI, confidence interval; BMI, body mass index; WBC, white blood cell; COPD, chronic obstructive pulmonary disease; LVAD/Tx, left ventricular assist device or heart transplant surgery; IABP, intra-aortic balloon pump. *Based on competing risk model with time to pneumonia as outcome, baseline factors as covariates, and death as competing risk. †Insulin or oral medications.

Variables tested in the Stage 2 process of care model and their crude association with pneumonia

Management practice	Pneumonia, n (%)	Unadjusted HR (95% CI)	P value*
Correct timing of preoperative antibiotics before surgery		0.76 (0.48-1.22)	.26
Yes	102 (2.3)		
No	21 (3.0)		
Nasopharyngeal decontamination		0.80 (0.56-1.15)	.24
Yes	51 (2.1)		
No	71 (2.6)		
Scrubbing of surgical site			.01
No	5 (6.4)	1.00 (ref)	
Yes with chlorhexidine	106 (2.6)	0.39 (0.16-0.96)	
Yes without chlorhexidine	12 (1.3)	0.20 (0.07-0.55)	
Appropriate dosing of intraoperative antibiotics		0.47 (0.21-1.06)	.07
Yes	117 (2.3)		
No	6 (4.9)		
Postoperative antibiotics duration			<.001
≤24 h	48 (1.8)	1.16 (0.75-1.79)	
24-48 h	34 (1.6)	1.00 (ref)	
>48 h	41 (9.4)	6.09 (3.87-9.59)	
Second-generation CEPH		0.68 (0.47, 0.98)	.04
Yes	46 (1.9)		
No	77 (2.8)		
Ventilation			<.001
≤24 h	46 (1.1)	1.00 (ref)	
24-48 h	32 (4.7)	4.25 (2.71-6.68)	
>48 h	43 (11.1)	10.36 (6.84-15.67)	
NG tube		1.84 (1.15-2.94)	.01
Yes	102 (2.7)		
No	21 (1.5)		
Femoral line		3.58 (1.13-11.32)	.03
Yes	3 (8.1)		
No	120 (2.3)		
More than 1 central line		2.39 (1.56-3.67)	<.001
Yes	27 (4.9)		
No	96 (2.1)		
Glucose management		1.21 (0.85-1.73)	.30
Hyperglycemic	58 (2.6)		
Nonhyperglycemic	63 (2.2)		
PRBC, unit		1.30 (1.24-1.36)	<.001
Platelet		2.13 (1.50-3.04)	<.001
Yes	60 (3.7)		
No	63 (1.8)		

Variable not used because of small cell counts: (1) Elevation of head of bed: Among the 18 patients who did not have elevation of head of bed, only 1 developed pneumonia. (2) Aspiration of secretions: Among the 201 patients who did not have aspiration of secretions, only 1 developed pneumonia. HR, Hazard ratio; CI, confidence interval; CEPH, cephalosporin; NG, nasogastric tube; PRBC, packed red blood cells. *Based on competing risk model with time to pneumonia as outcome, management practices as covariates, and death as competing risk.

APPENDIX E2. CTSN MEMBERS

The members of the Cardiothoracic Surgical Trials Network (CTSN) involved in this study were as follows:

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