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ORIGINAL ARTICLE

Effect of Healthcare-Acquired Infection on Length of Hospital Stay and Cost

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OBJECTIVE. To estimate the independent effect of a single lower respiratory tract infection, urinary tract infection, or other healthcare-acquired infection on length-of-stay and variable costs and to demonstrate the bias from omitted variables that is present in previous estimates.

DESIGN. Prospective cohort study.

SETTING. A tertiary care referral hospital and regional district hospital in southeast Queensland, Australia.

PATIENTS. Adults aged 18 years or older with a minimum inpatient stay of 1 night who were admitted to selected clinical specialities.

RESULTS. Urinary tract infection was not associated with an increase in length of hospital stay or variable costs. Lower respiratory tract infection was associated with an increase of 2.58 days in the hospital and variable costs of AU\$24, whereas other types of infection were associated with an increased length of stay of 2.61 days but not with variable costs. Many other factors were found to be associated with increased length of stay and variable costs alongside healthcare-acquired infection. The exclusion of these variables caused a positive bias in the estimates of the costs of healthcare-acquired infection.

CONCLUSIONS. The existing literature may overstate the costs of healthcare-acquired infection because of bias, and the existing estimates of excess costs may not make intuitive sense to clinicians and policy makers. Accurate estimates of the costs of healthcare-acquired infection should be made and used in appropriately designed decision-analytic economic models (ie, cost-effectiveness models) that will make valid and believable predictions of the economic value of increased infection control.

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Healthcare-acquired infections (HAIs) are thought to generate substantial economic burdens. Patient morbidity and mortality risks are increased, hospital stay is prolonged, and additional cash costs arise for consumable items used to treat the infection.¹⁻³ The risk of acquiring an infection is also believed to increase with increased length of hospital stay.^{4,5} A recent review suggested that 10%-70% of HAIs are preventable⁶ with appropriate infection control. The decision to invest in additional infection control programs should be informed by the expected changes to both cost and health outcomes, and only efficient (ie, cost-effective) strategies should be used.⁷⁻¹⁰ Cost outcomes will change because of increased expenditure on infection control and the cost savings of avoided cases of HAI. Health outcomes will change (improve) because excess morbidity and mortality risks are reduced. Although economic arguments for additional infection control programs have been made, few data on the costs

and health benefits of these programs have been published.¹¹ These data are vital for decision makers who face an increasing pressure to tackle the problem of HAI from politicians and from journalists who regularly inform the public about the dangers of HAIs, especially those caused by methicillin-resistant *Staphylococcus aureus*.

Research-based models that describe the economics of additional infection control programs therefore rely on valid estimates of the independent effect of HAI on length of hospital stay and cost, but it is difficult to make bias-free estimates. An unadjusted comparison of the cost outcomes for patients with HAI and for those without HAI is not useful because of other differences, unrelated to HAI, between the two groups. For example, those with HAI might have more comorbid conditions and so might generate quite different (greater) cost outcomes regardless of the type of HAI. The challenge is to tease out the independent effect of HAI on

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cost outcomes by making allowances for all observable confounders. Haley¹ and Graves and Weinholt¹² review the existing methods of direct attribution and comparative attribution. Direct attribution requires an expert reviewer to assess the extra cost from HAI. This method has been criticized as being subjective and not reproducible,¹³ and comparative attribution studies have been preferred by the research community. Researchers undertaking comparative attribution studies use data collected from a cohort of hospitalized patients and either (1) select a subset of infected patients who are then matched with uninfected controls for variables thought likely to affect cost outcomes (eg, age, sex, and comorbidities) or (2) build multivariable statistical regression models that describe the relationship between HAI and cost outcomes, while controlling for other factors thought likely to affect cost outcomes.¹⁴ The disadvantage of matching is that infected patients can only be matched to uninfected controls for a limited number of variables. Matching more than, say, 5 or 6 variables requires a substantial increase in the size of the pool of controls, which makes the research process costly and inefficient. Matching too few variables might cause bias from “omitted variables” because important factors that explain the variation in cost outcomes are excluded. The source of the bias from omitted variables is described in Appendix A. The consequence of this bias is that the cost attributed to HAI is either overstated or understated, although our belief before performing the analysis was that the bias will be positive (ie, that the cost of HAI is overstated).¹⁵ If case patients are subsequently excluded from the study to match more variables (ie, to mitigate bias from omitted variables), then a selection bias arises because not all case patients have the same opportunity to be included in the comparison of cost outcomes. Those undertaking matched cohort studies are forced to trade bias from “omitted variables” with bias from the selection of individuals and cannot escape both sources of bias at the same time.

The use of statistical regression analysis for a cohort of patients can avoid selection bias completely and presents an opportunity to reduce bias from omitted variables. A correctly specified statistical regression model will summarize the association between the outcome variable (ie, length of stay or cost) and the independent variables (ie, HAI and other observable factors that might explain variation in outcomes). A statistical regression model might take the form of this equation:

$$\text{LOS} = f(\text{HAI, other controls}, u) ,$$

where LOS is the outcome we wish to explain (length of stay in the hospital), HAI is occurrence of an infection (1 = infection and 0 = no infection) and “other controls” represents all other factors (eg, age, sex, primary diagnosis, comorbidities, and underlying state of health) that we believe are associated with the variation in length of stay across the sample. The term u represents the “residuals” or “error terms”

that capture the residual variation in length of stay not explained by the independent variables (ie, HAI and “other controls”). An important requirement for regression analysis is that the residuals are evenly distributed around the fitted regression line (ie, error terms are homoskedastic), and the smaller the residuals, the better the model. A model like this will completely avoid selection bias, because every individual from the cohort can be included in the analysis, and it will reduce bias from omitted variables, because many independent variables can be included within the set called “other controls.” It is better to control for confounding in the analysis stage (regression analyses) than in the design stage (matching).

Another source of bias arises from the relationship between the variables HAI and LOS. Although we know that HAI increases the length of stay, there is good evidence^{4,5,16} that length of stay also increases the risk of HAI. This reverse causality, or feedback (LoS = HAI and HAI = LoS), induces a correlation between the error terms and the independent variables, leading to biased estimates and tests of hypotheses.¹⁷ This problem is called “endogenous variables bias” and has been discussed in the context of HAI.^{3,18} Graves and Weinholt^{12,19} describe the problem in detail and report preliminary attempts at a solution, using an instrumental variables method. Controlling bias from endogenous variables and interpreting the results of an unbiased model is a methodological challenge for future research.

The impact of different types of HAI on cost outcomes has been studied since the 1950s, when Clarke et al.²⁰ investigated whether *S. aureus* in surgical wounds extended the length of stay of patients admitted to an English hospital. Since then, studies using different methods of estimating costs have produced quite different results. Direct attribution methods have reported 3.7, 0.6, and 5.7 days of extra hospitalization due to lower respiratory tract infection (LRTI), urinary tract infection (UTI), and HAIs at other sites (hereafter, “other HAIs”), respectively,² and an extra cost of US \$589 for a case of UTI.²¹ Studies with a matched-cohort design have produced larger estimates, with 10 studies of LRTI reporting an increase in length of stay between 5.33 and 25.53 days,²²⁻³⁰ with a median increase of 9.35 days; 11 studies of UTI revealed a median increase of 3.6 days (range, 0.5-6 days)^{24,25,28,31-36}; and 2 studies of other infections reported increases of 0 days²⁴ and 2.5 and 7 days.² One study³⁷ that used statistical regression methods attributed 8.4, 5.1, and 12.4 extra days of hospital stay to the occurrence of LRTI, UTI, and other infections, respectively, whereas a second study³⁸ reported an unadjusted difference of 25 days in the hospital for each LRTI but used statistical regression to estimate an adjusted additional cost of US \$11,897 per LRTI.

The aim of the research reported here is to use statistical regression to estimate the independent effect of HAI on length-of-stay and cost outcomes in a cohort of hospitalized patients. The method will avoid selection bias completely and will address bias from omitted variables by including a com-

prehensive set of explanatory terms in a statistical regression model. We also aim to demonstrate that omitting important variables from the statistical model causes bias in the costs attributed to HAI. We conduct separate analyses for patients who received a diagnosis of LRTI, UTI, or other HAI. We do not, however, attempt to address the bias from endogenous variables.

METHODS

Study Sites and Participants

We recruited participants from a 712-bed tertiary care referral hospital and a 312-bed district hospital in southeast Queensland, Australia. Inclusion criteria were an age of 18 years or older and a minimum inpatient stay of 1 night for the clinical specialities listed in Table B1 in Appendix B. Patients were identified from a routinely generated list of all admissions, and patients with consecutive admissions were recruited from both hospitals between October 13, 2002, and January 16, 2003, by 5 registered research nurses who worked at the tertiary referral hospital and were seconded to collect the data from both hospitals.

Data Collection

All variables for data collection were selected on the basis of previous experience, expert opinion, and a review of the literature (the literature reviewed is listed in a Supplemental Reading List that is available in the online edition of the journal). Data collection tools were developed and then were tested during a 10-week pilot study, and criteria for selecting the values for all variables were established. This process involved the research nurses, a senior infectious diseases physician, the project coordinator, and an epidemiologist with a background in acute hospital services and infection control. The result was an extensive data dictionary that summarized definitions agreed to by the research team. This document was the reference for any decision to assign a value to a variable and is available from the authors on request. Demographic data were collected directly from the bedside by use of "personal digital assistants" that linked to a custom-designed Access database (Microsoft). After recruitment, data collection was completed by a review of the patient's medical record, the hospital-based corporate information systems, and the hospital pathology system, Auslab.³⁹ Variables were collected that described the demographic characteristics of the sample, including the primary or most recent occupation and education level, and a score of socioeconomic status was derived via an algorithm described by Jones and McMillan.⁴⁰ The length of hospital stay for each patient admitted was calculated, and data were collected that described the consumable items used by the patient. Market prices were then applied to estimate the variable costs incurred during the hospital stay. The type of admission (ie, elective, emergency, or transfer), admission to a clinical unit, and all diagnosis codes from the *International Classification of Diseases and Re-*

*lated Health Problems, 10th Revision, Australian Modification*⁴¹ were recorded. Any adverse events that occurred during the hospital stay that might extend the stay were recorded, as were all observable risk factors for HAI. Data cleaning was undertaken alongside data collection by a separate researcher. The data cleaner and research nurses worked together to ensure consistent application of definitions. All cases of HAI were diagnosed using the Centers for Disease Control and Prevention definitions modified for Australia⁴²; when ambiguity existed, the senior infectious diseases physician was consulted. The medical records of all patients with HAI and a length of stay greater than 40 days were reviewed to identify when, during the hospital stay, the infection was diagnosed, was treated, and had cleared.

Statistical Methods

We used the generalized linear modeling (GLM) approach, which employs maximum-likelihood estimation to summarize the relationship between HAI and cost outcomes. Model selection was based on testing whether the distributional assumptions fit the data and which approach yielded the best residuals; model selection is described in Appendix C. Six models were specified to describe the relationship between the 3 types of infection (UTI, LRTI, and other HAIs) and the 2 outcome variables (length of stay and variable costs). To model length-of-stay outcomes, we chose a gamma distribution to characterize the outcome and a log link function to specify the relationship with the explanatory variables. To model variable cost, we chose a gamma distribution with a square-root link function. The gamma distribution is similar in shape to the log-normal distribution⁴⁵ and is robust to the nonnormal distributions typical of length-of-stay and cost outcomes.⁴⁶⁻⁴⁷ All coefficients were retransformed back to the original units of length of stay (days) and variable costs (AU\$). We began with general models that included all available variables as explanatory terms, and variables were excluded because of multicollinearity, as assessed by nested auxiliary regression, where each variable in turn was dropped from the model and the R^2 values were compared with those of a complete model. We then sought a parsimonious specification for each model by further reducing the model, using backward stepwise regression with a 5% threshold for statistical significance. SEs were made heteroskedasticity consistent via the Huber-White covariance matrix, which was applied in all estimation procedures.⁴⁸ StataTM (Stata) was used for all analyses.

We undertook further analyses of the parsimonious models that described length-of-stay outcomes, to demonstrate the bias from omitted variables. We removed variables from each model, one by one, in no particular order, and compared the parsimonious model with each restricted model. The likelihood ratio (LR) test was used to assess the goodness of fit between the 2 models and to make an inference about whether the parsimonious model represented a better spec-

ification of the relationship between HAI and the length-of-stay outcome than did the artificially restricted models.

RESULTS

Overview of the Data

A total of 4,488 admissions were included in the study; 2,971 were admissions to the university teaching hospital, 1,640 were admissions for a surgical procedure, and 2,848 were admissions for nonsurgical specialties. The mean age of patients was 58 years (range, 18-100 years), and 51% were male. There were 228 cases of HAI diagnosed, giving an overall incidence rate of 5.08% for the 95 days during which patients were recruited. This included 37 LRTIs (incidence rate, 1.76%), 79 UTIs (incidence rate, 0.82%), and 49 other HAIs (6 in the digestive system, 2 in the ear, 6 in the mouth and/or esophagus, 1 in pleural fluid, 10 at an intravenous catheter insertion site), 18 involving skin, and 6 at an unknown site) (incidence rate, 1.09%). The remaining 63 cases of infection were excluded from the analyses and comprised surgical site infections, bloodstream infections, and multiple infections.

Patients with HAI and Length of Stay Greater Than 40 Days

Of the 4,488 patients, 98 (2.2%) had a length of stay greater than 40 days. Of these 98 patients, 10 received a diagnosis of LRTI, 20 received a diagnosis of UTI, and 8 received a diagnosis of other HAIs. For all but 1 of the patients with LRTI and 2 of the patients with UTI, the HAI cleared early in the stay (ie, within 12 days after admission), and other factors were found that caused the long stay in hospital. In particular, most of these patients were transferred to a rehabilitation facility within the hospital to wait for placement in a long-term residential care center; other reasons for long stay were community-acquired bacteremia, serious medical conditions, hypoxic brain injury, prolonged stay in the intensive care unit, and slow recovery after surgery. Because the extended hospital stay (>40 days) was unrelated to the episode of infection, those patients with a length of stay >40 days were excluded from the data set before the analyses were done.

Unadjusted Comparison of Patients With HAI and Patients Without

Patients without HAI were compared with patients with LRTI, UTI, and other infections for selected variables, and the results are presented in Table 1. A list of all variables available for analysis is included in Table B2 in Appendix B. Compared with patients without HAI, patients with HAI were older, stayed in the hospital longer, and incurred higher variable costs. Fewer of them were discharged home, had elective admissions, or were self-caring before hospital admission. A higher proportion died in the hospital, experienced an adverse event (eg, a fall, cardiac arrest, pressure ulcer, or gastrointestinal bleeding), presented with comorbidities (eg, anemia,

chronic obstructive pulmonary disease, congestive heart failure, diabetes, or underlying gastrointestinal or neurological disease), and required an invasive device or procedure (eg, catheterization, blood transfusion, oxygen therapy, or drainage tube).

Association Between HAI and Length of Hospital Stay, Controlling for Multiple Variables

Three general models were specified to describe the relationship between LRTI, UTI, and other HAIs and the length of hospital stay. Six variables were removed from the general models because of multicollinearity, which left 123 variables; further reductions via the stepwise procedure resulted in parsimonious models. In the UTI model, presence of UTI infection was not a significant predictor of length of stay ($P = .33$); however, LRTI and other HAIs retained their significance in the parsimonious models, indicating that they were associated with an increase in length of stay of 2.58 days (95% confidence interval [CI], 1.80-3.69) and 2.61 days (95% CI, 2.02-3.39), respectively. The Akaike information criterion (AIC) statistic was 4.98 for the LRTI model that included 44 variables and was 4.97 for the model of other HAIs that included 43 variables. The plot of the deviance residuals versus the predicted mean length of stay was not homoskedastic, suggesting that the Huber-White SEs were necessary for both models, and only 3 of the deviance residuals had values greater than 3. A summary of the other variables that remained significant in the parsimonious models and the estimates of the impact on length of stay are presented in Table 2. Many other factors alongside HAI were associated with increases in length of stay—in particular, if patients were transferred from another hospital or were admitted as emergency case patients, if they smoked in the past or required assistance for daily activities before admission, or if they were admitted to the geriatric unit. Adverse events, such as falls during the hospital stay, deep vein thrombosis, and anaphylactic reactions, also increased length of stay, as did the use of catheters, feeding devices, and drainage tubes. Underlying risk factors, such as obesity, diabetes, previous stroke, malignancy, and unresolved spinal injury, all increased length of stay, as did dyspnea during the hospital stay, community-acquired infection, fecal incontinence, and anemia.

Association Between HAI and Variable Costs, Controlling for Multiple Variables

Three models were specified to describe the relationship between variable costs and LRTI, UTI, and other HAIs. No variables were found to be multicollinear. The 3 general models included 129 variables that were reduced via the stepwise procedure to generate parsimonious models. Neither UTI ($P = .18$) nor other infections ($P = .11$) were significantly associated with variable costs in the parsimonious models. However, LRTI remained significant in the parsimonious model, with an estimated cost increase of AU\$24.04 (95%

TABLE 1. Differences Between the Groups with Lower Respiratory Tract Infection (LRTI), Urinary Tract Infection (UTI), or Other Healthcare-Acquired Infections (HAIs) and the Group Without HAI

Variable	Group without HAI (n = 4,230)	Group with LRTI (n = 27)	Group with UTI (n = 59)	Group with Other HAIs (n = 41)
Length of hospital stay, mean d ± SD	4.80 ± 5.01	15.19 ± 8.32	14.86 ± 10.52	15.49 ± 11.41
Cost outcomes, mean AU\$ ± SD				
Variable costs—drugs	100.61 ± 471.95	963.70 ± 1,842.56	139.29 ± 143.01	1,022.34 ± 3,380.29
Variable costs—other	21.21 ± 58.03	133.19 ± 209.23	37.66 ± 173.57	120.27 ± 284.21
Variable costs—total	121.77 ± 486.90	1,097.00 ± 1,887.51	176.93 ± 276.22	1,142.61 ± 3,395.30
Demographic and social characteristics				
Age at admission, mean y ± SD	56.90 ± 20.02	67.00 ± 14.04	71.59 ± 19.20	64.93 ± 18.49
Socioeconomic status score (range, 0-100), mean ± SD	37.23 ± 21.39	44.40 ± 24.92	32.33 ± 20.53	38.08 ± 25.39
Male	2,177 (51.47)	19 (70.37)	18 (30.51)	22 (53.66)
White	3,872 (91.55)	26 (95.83)	56 (94.55)	38 (91.89)
Current drinker	2,635 (62.30)	19 (70.83)	26 (44.06)	24 (58.61)
Current smoker	1,058 (25.01)	4 (13.15)	14 (22.96)	3 (6.97)
Self-caring before admission	3,024 (71.49)	15 (54.17)	23 (39.29)	24 (58.97)
Obese	3,164 (74.81)	24 (87.99)	49 (83.78)	33 (81.70)
Admission, hospital stay, and discharge characteristics				
Discharged to home	4,022 (95.08)	19 (70.37)	44 (74.58)	29 (70.73)
Died in hospital	88 (2.08)	6 (22.22)	8 (13.56)	7 (17.07)
Elective admission	1,833 (43.33)	8 (29.63)	19 (32.20)	14 (34.15)
Stay was in teaching hospital	2,763 (65.32)	25 (92.59)	42 (71.19)	30 (73.17)
Adverse events during hospital stay				
Fall	56 (1.32)	2 (7.41)	6 (10.17)	2 (4.88)
Cardiac arrest	105 (2.48)	6 (22.22)	8 (13.56)	7 (17.07)
Pulmonary embolus	5 (0.12)	2 (7.41)	1 (1.69)	0
Pressure ulcer	130 (3.07)	7 (25.93)	8 (13.56)	6 (14.63)
Gastrointestinal bleeding	187 (4.42)	7 (25.93)	4 (6.78)	6 (14.63)
Comorbidities				
Fecally incontinent	221 (5.22)	8 (29.63)	17 (28.81)	9 (21.95)
Anemic at admission	753 (17.80)	12 (44.44)	20 (33.90)	12 (29.27)
Anemic during hospital stay	1,603 (37.90)	25 (92.59)	42 (71.19)	29 (70.73)
Admitted with fracture or dislocation	225 (5.32)	4 (14.81)	10 (16.95)	2 (4.88)
Chronic obstructive pulmonary disease	447 (10.57)	7 (25.93)	12 (20.34)	5 (12.20)
Cirrhosis of the liver	48 (1.13)	1 (3.70)	0	3 (7.32)
Congestive heart failure	269 (6.36)	4 (14.81)	8 (13.56)	4 (9.76)
Coronary artery disease	585 (13.83)	3 (11.11)	6 (10.17)	6 (14.63)
Diabetes	668 (15.79)	9 (33.33)	20 (33.90)	7 (17.07)
Underlying gastrointestinal disease	1,273 (30.09)	14 (51.85)	26 (44.07)	13 (31.71)
Underlying neurological disease	446 (10.54)	7 (25.93)	27 (45.76)	12 (29.27)
Ever had a stroke	290 (6.86)	3 (11.11)	12 (20.34)	8 (19.51)
Hypertension	1,461 (34.54)	12 (44.44)	30 (50.85)	17 (41.46)
Dyspnea	1,047 (24.75)	18 (66.67)	22 (37.29)	15 (36.59)
Hyponatremic at admission	340 (8.04)	4 (14.81)	16 (27.12)	7 (17.07)
Multitrauma	6 (0.14)	0	0	1 (2.44)
Neurogenic bladder	12 (0.28)	1 (3.70)	1 (1.69)	1 (2.44)
Peripheral pulses absent	55 (1.30)	2 (7.41)	0	2 (4.88)
Device, procedure, and/or therapy received				
Urinary catheter	1,073 (25.37)	19 (70.37)	45 (76.27)	17 (41.46)
Arterial catheter	532 (12.58)	9 (33.33)	6 (10.17)	10 (24.39)
Central venous catheter	259 (6.12)	8 (29.63)	2 (3.39)	10 (24.39)
Epidural or intrathecal catheter	131 (3.10)	2 (7.41)	5 (8.47)	3 (7.32)
Indwelling or suprapubic urinary catheter	1,041 (24.61)	19 (70.37)	43 (72.88)	16 (39.02)
Instrumentation of bladder	144 (3.40)	1 (3.70)	4 (6.78)	0
Intracranial pressure monitor	5 (0.12)	1 (3.70)	1 (1.69)	1 (2.44)
Peripheral parenteral device	3,797 (89.76)	26 (96.30)	56 (94.92)	36 (87.80)
Transfusion of blood and/or blood products	394 (9.31)	11 (40.74)	14 (23.73)	19 (46.34)
Parenteral nutrition	10 (0.24)	0	0	4 (9.76)
Oxygen therapy	2,837 (67.07)	26 (96.30)	45 (76.27)	32 (78.05)
Nasogastric tube	317 (7.49)	13 (48.15)	12 (20.34)	12 (29.27)
Pleural drainage	692 (16.36)	8 (29.63)	11 (18.64)	16 (39.02)
Drain tube of any type	1,447 (34.21)	15 (55.56)	24 (40.68)	14 (34.15)
Anticoagulant therapy	480 (11.35)	8 (29.63)	4 (6.78)	6 (14.63)
Nonsteroid antiinflammatory therapy	1,584 (37.45)	11 (40.74)	30 (50.85)	16 (39.02)
Stress ulcer prophylaxis	1,287 (30.43)	21 (77.78)	26 (44.07)	22 (53.66)
Patient unable to protect airway from aspiration	1,530 (36.17)	17 (62.96)	25 (42.37)	20 (48.78)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

TABLE 2. Results of Generalized Linear Modeling Statistical Regression Models Under the Assumption of the Gamma Distribution That Describe the Association Between Length of Hospital Stay and Lower Respiratory Tract Infection (LRTI) and Other Healthcare-Acquired Infections (HAIs)

Variable	LRTI Coefficient ^a (95% CI), days	Other HAI Coefficient ^b (95% CI), days
HAI and general factors		
HAI (either LRTI or other)	2.58 (1.80-3.69)	2.61 (2.02-3.39)
Emergency admission	2.23 (1.90-2.61)	2.12 (1.81-2.48)
Interhospital transfer	2.57 (2.13-3.10)	2.48 (2.06-2.99)
Some assistance required before admission	2.24 (1.93-2.61)	2.19 (1.89-2.55)
Ex-smoker	1.76 (1.53-2.02)	1.72 (1.50-1.98)
Age (>55 y)	NS	2.05 (1.77-2.38)
Admitted to geriatric unit	0.97 (0.78-1.22)	0.91 (0.66-1.27)
Adverse events during hospital stay		
Any adverse event	2.90 (2.43-3.48)	2.78 (2.31-3.34)
Two falls	2.92 (1.80-4.76)	2.87 (1.74-4.74)
Deep vein thrombosis	2.81 (1.78-4.42)	2.83 (1.79-4.48)
Peripheral pulses absent	2.79 (2.12-3.67)	2.70 (2.06-3.55)
Anaphylactic reaction	0.98 (0.79-1.21)	1.02 (0.82-1.26)
Gastrointestinal bleeding	1.36 (1.09-1.70)	1.36 (1.09-1.70)
Devices, therapies, and/or interventions		
Central venous catheter in situ during hospital stay	2.41 (1.98-2.93)	2.33 (1.92-2.83)
Unable to protect airway from aspiration	NS	1.67 (1.42-1.96)
Indwelling or suprapubic urinary catheters during hospital stay	2.28 (1.96-2.66)	2.26 (1.94-2.63)
Parenteral nutrition during hospital stay	2.88 (1.99-4.16)	2.46 (1.75-3.45)
Received stress ulcer prophylaxis	2.14 (1.85-2.46)	2.10 (1.82-2.41)
Nasogastric tube in situ during hospital stay	2.36 (1.96-2.83)	2.35 (1.96-2.82)
Drain tube of any type during hospital stay	2.48 (2.10-2.91)	2.40 (2.05-2.82)
Nonsteroid antiinflammatory therapy	1.98 (1.72-2.29)	1.94 (1.69-2.24)
Anti-coagulant therapy during hospital stay	2.45 (2.08-2.89)	2.41 (2.05-2.84)
Intracranial pressure monitor in situ during hospital stay	1.24 (0.91-1.70)	1.18 (0.86-1.60)
Comorbid conditions (chronic)		
Unresolved spinal injury	1.19 (0.80-1.76)	1.19 (0.79-1.77)
History of stroke	2.24 (1.82-2.75)	2.19 (1.78-2.70)
Malignancy	2.03 (1.72-2.39)	2.00 (1.69-2.35)
Coronary artery disease	1.49 (1.27-1.75)	1.45 (1.23-1.70)
Obesity	1.74 (1.50-2.02)	1.71 (1.47-1.98)
Diabetes	1.98 (1.68-2.34) ^c	1.94 (1.65-2.29) ^c
Underlying urinary tract disease	2.02 (1.72-2.38)	1.98 (1.69-2.33)
History of organ transplant	1.55 (1.01-2.37) ^c	1.41 (0.96-2.08) ^c
Comorbid conditions (acute)		
Dyspnea during hospital stay	2.06 (1.78-2.38)	2.05 (1.77-2.37)
Admitted with fracture or dislocation	2.66 (2.10-3.38)	2.25 (1.71-2.97)
Community-acquired infection	2.27 (1.92-2.67)	2.21 (1.87-2.60)
Fecally incontinent during hospital stay	2.52 (2.06-3.09)	2.47 (2.02-3.02)
Anemic at admission	1.68 (1.42-1.99)	1.65 (1.40-1.95)
Anemic during hospital stay	2.63 (2.25-3.06)	2.55 (2.19-2.97)
ICD-10-AM disease classification		
Diseases of skin and subcutaneous tissue	2.53 (1.88-3.40)	2.54 (1.90-3.41)
Diseases of musculoskeletal system and connective tissue	2.14 (1.73-2.65)	2.19 (1.77-2.71)
Pregnancy, childbirth, and puerperium	2.22 (1.81-2.71)	2.21 (1.80-2.70)
Injury, poisoning, and external causes	NS	2.23 (1.79-2.78)
Endocrine, nutritional, and metabolic diseases	2.14 (1.71-2.67)	2.13 (1.71-2.66)
Diseases of the nervous system	2.41 (1.82-3.19)	2.39 (1.80-3.16)
Diseases of ear and mastoid process	1.22 (0.89-1.67)	1.24 (0.91-1.70)
Constant in model	3.46 (2.90-4.14)	3.30 (2.76-3.94)

NOTE. The outcome variable was length of hospital stay, in days. Data were significant at the 5% level unless indicated otherwise. AIC, Akaike information criterion; BIC, Bayesian information criterion; *ICD-10-AM*, *International Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification*; NS, variable was not significant at 5% and removed during stepwise variable selection process.

^a No. of observations = 3,833; deviance = 1,656; AIC = 4.98; BIC = -29,599.

^b No. of observations = 3,833; deviance = 1,644; AIC = 4.97; BIC = -29,603.

^c Data were significant at the 10% level.

TABLE 3. Results of Generalized Linear Modeling Statistical Regression Models Under the Assumption of the Gamma Distribution That Describe the Association Between Variable Costs and Lower Respiratory Tract Infection (LRTI)

Variable	LRTI Coefficient ^a (95% CI), \$
Infection and general characteristics	
LRTI	24.04 (10.15-43.46) ^b
Obesity	6.46 (4.69-8.47) ^b
Current smoker	6.72 (4.08-9.90)
Ex-smoker	6.97 (4.46-9.95)
Current drinker	5.92 (3.58-8.75)
More than 1 admission in data set	5.43 (3.25-8.06) ^b
Torres Straight Islander	5.46 (1.88-10.47)
Full assistance required before admission	4.38 (1.55-8.24) ^b
Patient admitted to 1 of study hospitals in previous 12 mo	7.40 (4.83-10.45) ^b
Adverse events	
One fall during hospital stay	12.95 (7.85-19.21) ^b
Two falls during hospital stay	17.75 (9.62-28.18) ^b
Three or more falls during hospital stay	20.83 (8.60-38.01) ^b
Deep vein thrombosis during hospital stay	11.79 (5.60-20.03) ^b
Anaphylactic reaction during hospital stay	19.35 (14.01-25.50) ^b
Peripheral circulation compromised as a result of pulmonary embolus	10.19 (4.63-17.64) ^c
Cardiac arrest during hospital stay	9.79 (5.44-15.25) ^b
Epilepsy or any seizure of unknown origin	7.71 (4.46-11.71) ^c
Devices, therapies, and/or interventions	
Drain tube of any type during hospital stay	8.43 (5.83-11.46) ^b
Transfusion of blood and/or blood products	15.80 (10.14-22.62) ^b
Oxygen therapy during hospital stay	6.52 (3.80-9.84)
Nasogastric tube in situ during hospital stay	6.87 (4.22-10.06)
Peripheral parenteral device in situ during hospital stay	10.86 (7.31-15.05) ^b
Intracranial pressure monitor in situ during hospital stay	15.13 (8.84-22.97) ^b
Arterial catheter in situ during hospital stay	9.68 (6.05-14.06) ^b
Central venous catheter in situ during hospital stay	10.80 (7.21-15.05) ^b
Epidural or intrathecal catheter in situ during hospital stay	9.27 (6.26-12.80) ^b
Nonsteroid antiinflammatory drugs (eg, aspirin) received during hospital stay	7.76 (5.19-10.77) ^b
Received stress ulcer prophylaxis (eg, Ranitidine)	6.85 (4.43-9.71)
Anticoagulant therapy during hospital stay	7.16 (4.30-10.63)
Patient unable to protect airway from aspiration	6.49 (3.98-9.52)
Comorbid condition (chronic)	
Cirrhosis of the liver	3.71 (0.97-7.64) ^b
Comorbid conditions (acute)	
Anemic at admission	5.12 (2.88-7.87) ^b
Community-acquired infection	8.26 (5.59-11.40) ^b
Anemic during hospital stay	7.60 (5.04-10.62) ^b
Dyspnea during hospital stay	7.17 (4.38-10.54)
ICD-10-AM disease classification	
Disease of digestive system	5.27 (3.07-7.93) ^b
Diseases of skin and subcutaneous tissue	8.01 (4.09-13.04)
Diseases of genitourinary system	4.10 (2.02-6.72) ^b
Pregnancy, childbirth, and puerperium	1.65 (0.02-4.03) ^b
Symptoms, signs, and abnormal clinical and/or laboratory findings	2.88 (0.96-5.46) ^b
Neoplasms	4.83 (2.60-7.60)
Factors influencing health status	5.08 (2.40-8.54) ^c
Constant	28.50 (21.62-36.29)

NOTE. The outcome variable was costs in AU\$. AIC, Akaike information criterion; CI, confidence interval; ICD-10-AM, *International Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification*.

^a No. of observations = 3, 795; deviance = 5,155; AIC = 11.10.

^b Data were significant at the 5% level.

^c Data were significant at the 10% level.

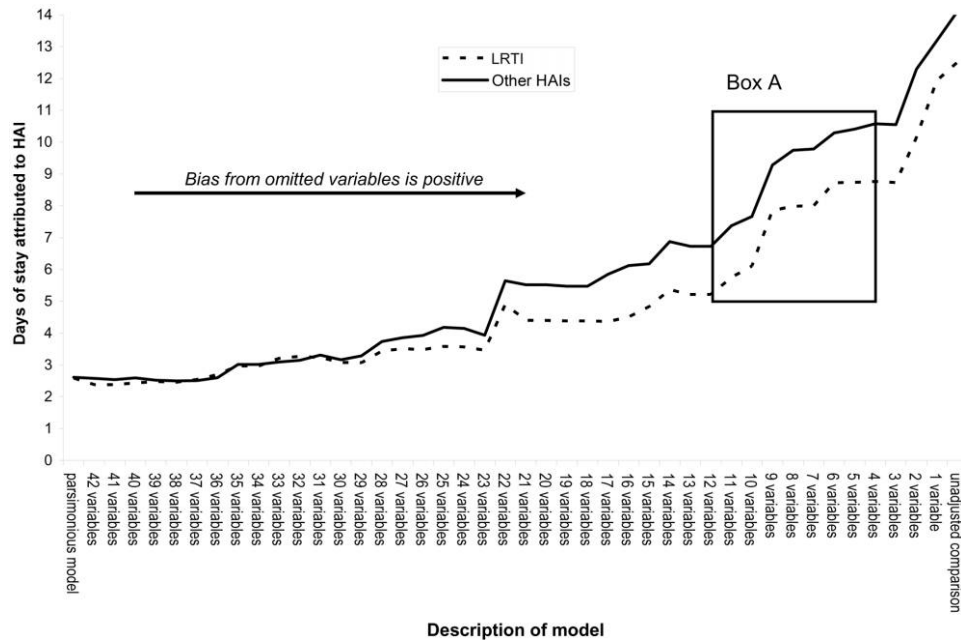


FIGURE 1. An illustration of bias from omitted variables in models that describe the relationship between lower respiratory tract infection (LRTI) or other healthcare-acquired infections (HAIs) and additional length of hospital stay.

CI, \$10.15-\$43.46) per LRTI (approximately US \$17.58 [95% CI, \$7.42-\$31.79]). The AIC statistic was 11.1 for the model that included 45 variables. The plot of the deviance residuals versus the predicted mean length of stay was not homoskedastic, suggesting that the Huber-White SEs were necessary, and 41 of the deviance residuals had values greater than 3. A summary of the variables that remained significant in the parsimonious model for LRTI, along with their estimated effect on variable costs, is presented in Table 3. Many other factors alongside LRTI were associated with increased variable costs.

Bias from Omitted Variables and Length of Stay Outcomes

To explore what might happen if information on a smaller number of confounders was available for the analyses, we removed variables related to length of stay from the models for LRTI and for other HAIs. As variables were removed, the fit of the models deteriorated. When the parsimonious model for LRTI was compared with a restricted model that had 1 variable omitted, the result of the LR test showed that the omitted variable made a valid contribution to the explanatory power of the model (LR $\chi^2(1 \text{ df}) = 3.54$; $P = .0598$), indicating at the 5% significance threshold that there was marginal evidence for the restricted model (ie, the model with 1 omitted variable). The interpretation is that the unrestricted, or parsimonious, model provides a superior description of the relationship between LRTI and length of stay. When the parsimonious model for other HAIs was compared with a restricted model with 1 variable omitted, the same conclusion

was drawn (LR $\chi^2(1 \text{ df}) = 3.38$; $P = .0660$). As more variables were omitted, the χ^2 statistic increased, suggesting that the model specifications continued to deteriorate. The coefficient for LRTI and other HAIs increased as more variables were removed, suggesting a positive bias from omitted variables. The extent of the bias is illustrated in Figure 1, where the number of variables included in the model is plotted along the X-axis and the length of stay attributable to LRTI and other HAIs, as estimated by the model, is plotted along the Y-axis.

DISCUSSION

These data suggest that patients who developed an HAI stayed longer in the hospital and incurred greater variable costs. This is no great surprise, because the patients with HAI were older, sicker, and required more clinical interventions; more of them were unable to care for themselves before admission; more of them died in the hospital; and more of them did not return to their own homes after discharge. After controlling for a comprehensive set of confounders, we found that LRTI is associated with an increase in length of stay of 2.58 days and with variable costs of AU\$24 (approximately US \$17), whereas other HAIs are associated with an increase in length of stay of 2.61 days but no increase in variable costs. UTI did not increase length of hospital stay or variable costs. We found many other variables that were important for explaining the relationship between HAI and cost outcomes, and the omission of these variables causes a positive bias in the estimated length of stay attributed to HAI.

Although these results contradict those reported in the existing literature, we believe they are less biased. The first part of our argument is that we specified a good statistical model. The method avoided selection bias by controlling for confounding in the analysis stage rather than in the design stage and reduced bias from omitted variables by including a comprehensive set of control variables. We also suggest that the GLM model using a log link function is more appropriate than an ordinary least squares regression on a log-transformed outcome, and we provide a review of model selection in Appendix C. The second part of our argument is that these results are clinically intuitive. In our experience, few hospital physicians believe that a single UTI independently increases length of hospital stay and that patients with HAI often demonstrate multiple health problems that predispose them to a longer stay regardless of the type of HAI. The third part of our argument is that, when variables were excluded from the parsimonious model, the quality of the model deteriorated and the estimates of length of stay attributable to HAI increased and were biased. Box A marked in Figure 1 summarizes the characteristics of the existing published research that used 4-12 control variables and estimated outcomes at 5-11 days of stay due to HAI. The existing studies are superior to an unadjusted comparison, which estimates attributable length of stay at 12.5 days for LRTI and 14 days for other HAIs, but we demonstrate that inclusion of a comprehensive set of control variables produces a lower estimate of attributable length of stay.

We believe that length of stay and variable costs are the appropriate outcomes to describe the economic cost of HAI. The reasons have been discussed elsewhere,⁹ but we review the argument here. Between 80% and 90% of the costs of running a hospital are fixed in the short term,^{49,50} and the short term is generally the time frame in which decisions about investments in infection control are made. The financial expenditures made for fixed costs, as recorded by the hospital's cost accountants, are important for those who manage the cash flow and financial viability of the hospital. However, they are largely irrelevant for economic analysis and decision making in the short term, because these expenditures for fixed costs will not change with rates of HAI. A more useful measure on which to base decisions about additional investment in infection control is the number of bed-days used for HAIs, and the monetary value of these bed-days depends on their value for alternate uses (ie, the revenue from providing treatment to newly admitted patients). In contrast, expenditures for variable costs, such as dressings, drugs, fluids, gloves, gowns, and other consumables used by HAI, will change with rates of HAI; however, these items are much lower in value compared with the high fixed overheads typical of healthcare organizations.⁵¹⁻⁵³ Because the main reason we wish to understand the cost of HAI is to demonstrate how costs will change with increased investments in infection control, we should concentrate on measuring the cost outcomes that change rather than those that do not; therefore,

data from the cost-accounting department of a hospital that describe expenditures for fixed costs are not useful. Length-of-stay data and expenditure for variable costs are more useful, as well as easier to procure and interpret.

There are weaknesses of this study; for example, we did not address any possible interactions between control variables, nor did we address the problem of bias from endogenous variables. We do not believe, however, that the inclusion of interaction terms will make substantial improvements on the parsimonious model, and the complexities of bias from endogenous variables are probably best dealt with in separate analyses.

Our estimates of the cost of HAI are lower than those reported in the existing literature. We encourage other research groups to collect data to test the predictors in our models and either validate or refute our findings. We sincerely hope that these results are received with interest and enthusiasm by the infection control community. A perception that this work is anti-infection control and is an attempt to downplay the size of the problem represented by HAI is incorrect; our intention is the polar opposite. Biased and inflated estimates of the costs of HAI might have short-term impact, but, when decision makers undertake a critical examination of the research and find methods that may lead to bias and subsequently to results that do not make intuitive sense, then the infection control community risks the loss of credibility. Furthermore, the likelihood of further investments in infection control may diminish as a result. More useful are valid estimates of the cost of HAI that are then applied in appropriately designed decision-analytic economic models that will make valid and believable predictions of the economic value of infection control. There is no doubt that existing infection control is an essential activity and that more infection control than current levels is likely to return a favorable ratio of cost to benefit, compared with other investments in healthcare services. However, the economic arguments must be made properly with good quality data, and the results should be targeted at key decision makers at the local, state, and federal levels. This should be the aim of those who lobby for increases in investments in infection control.

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APPENDIX A

Description of Bias From Omitted Variables

If the true model is $Y_t = \alpha_0 + \alpha_1 X_t + \alpha_2 Z_t + u$ and the model $Y_t = \beta_0 + \beta_1 X_t + u$ is estimated, then the omitted variable can be thought of as a function of X in an auxiliary regression, $Z_t = \gamma_0 + \gamma_1 X_t + w_t$. So, it has been estimated that $Y_t = \beta_0 + \beta_1 X_t + \beta_2(\gamma_0 + \gamma_1 X_t + w_t) + u_t$, or

$$Y_t = (\beta_0 + \beta_2 \gamma_0) + (\beta_1 + \gamma_1 \beta_2) X_t + (\beta_2 w_t + u_t)$$

$$Y_t = \delta_0 + \delta_1 X_t + \varepsilon_t .$$

So, unless $\beta_2 = E(\hat{\beta}_1) \neq 0$,

$$E(\hat{\beta}_1) = \beta_1 + \beta_2 \left(\frac{\sum x_t z_t}{\sum x_t^2} \right).$$

There will be a bias as the coefficient of X picks up part of the influence of Z that was correlated with X , and it can be concluded that (1) the coefficient estimate can have a positive or negative bias, (2) its standard error will also be biased positively, and (3) the bias on the coefficient can either cancel or reinforce the bias in the standard error when a t test is done.

The source of the material presented in Appendix A is the Applied Research in Economics Group (<http://carecon.org.uk/>) at the University of the West of England in Bristol, United Kingdom.

APPENDIX B

TABLE B1. Clinical Specialties From Which Patients Were Recruited

Breast endocrine and thoracic
Cardiac surgical unit
Cardiology
Colorectal
Diabetes/endocrine
Ear nose and throat
Gastroenterology
General medicine
Geriatric
Gynecology
Hepato-pancreato-biliary
Infectious diseases
Intensive care unit
Medical stroke unit
Neurology
Orthopedic
Respiratory
Rheumatology
General surgical unit
Upper gastrointestinal and soft tissue
Urology
Vascular
Women's and children's health

TABLE B2. All Variables Included in the Data Collection and Available for Analyses

This table is available in its entirety in the online edition of *Infection Control and Hospital Epidemiology*.

APPENDIX C

Notes on Model Selection: GLM Versus $\ln(y)$ Ordinary Least Squares

In Figure C1, we present the plot of the residuals versus fitted values with Lowess smoother of $\ln(y)$ with ordinary least squares. This suggests heteroskedasticity and implies either the implementation of a suitable GLM model or retransformation by estimation of the log-scale variance function $\nu(x)$. The log-scale residuals were slightly leptokurtic (coefficient of kurtosis, 3.20). Because the log-scale residuals were heteroskedastic and somewhat leptokurtic, the performance of the GLM and $\ln(y)$ ordinary least squares with heteroskedasticity transformation were compared for precision. The modified Park test was used to determine the relationship between the raw-scale mean and the raw-scale variance for a suitable GLM model. The ordinary least squares version of the modified Park test is described by Manning and Mullahy⁴³; $\ln(y_i - \hat{y}_i)^2 = \lambda_0 + \lambda_1 \ln(\hat{y}_i) + \nu_p$, where $\hat{y}_i = \exp(x_i\beta)$ from the GLM specification. The estimate of the coefficient λ_1 on the log of the raw-scale prediction indicated the type of GLM to be employed. The coefficient $\lambda_1 = 1.93$ supported the gamma family because λ_1 was not significantly different from 2, $\chi^2(1) = 0.64$ ($P = .42$). The data in Figure C2 demonstrate that the SEs of the gamma GLM (median, 0.09 [range, 0.00-0.45]) and the $\ln(y)$ ordinary least squares (median, 0.08 [range, 0.04-0.49]) were very similar, with a median difference of .008 in favor of the marginally more precise $\ln(y)$ ordinary least squares. However, the gamma GLM with log link was preferred because of the ease of expressing the expected outcome, $E(y|x)$; the difficulty in retransforming the $\ln(y)$ ordinary least squares to account for heteroskedasticity is described by Willard Manning.⁴⁴

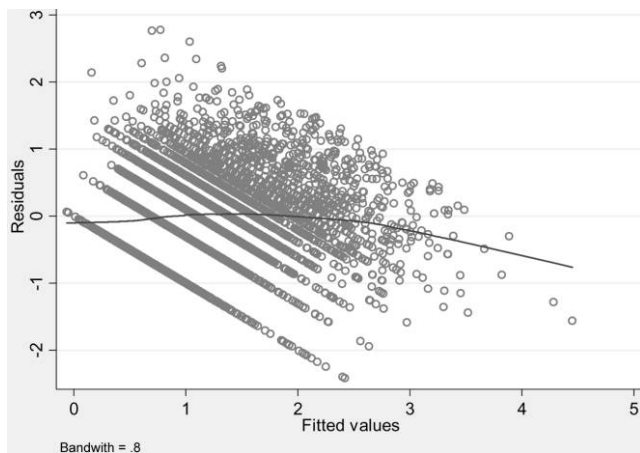


FIGURE C1. Plot of the residuals versus the fitted values with Lowess smoother of $\ln(y)$ ordinary least squares.

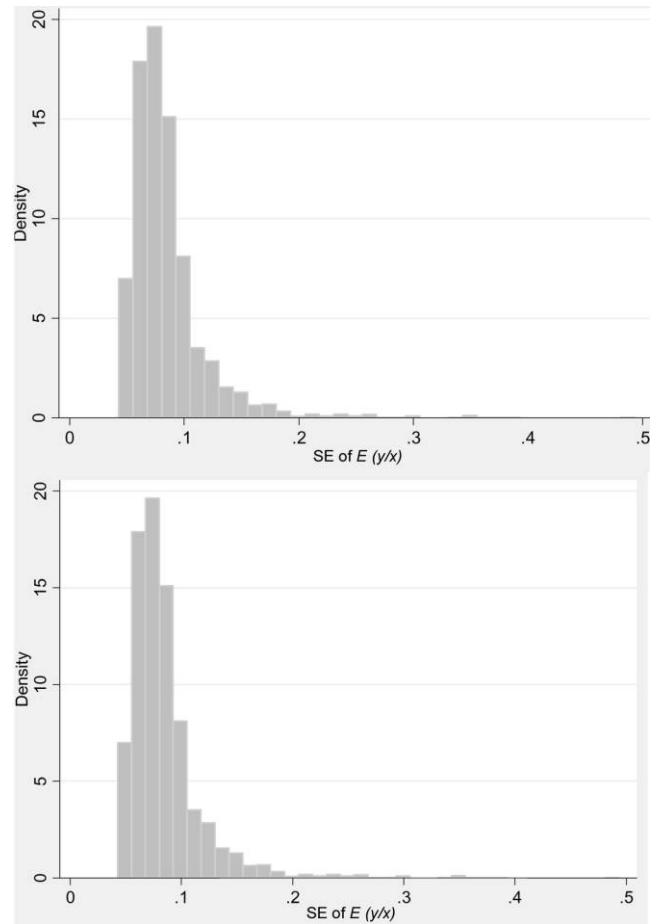


FIGURE C2. SEs of $E(y|x)$ from gamma GLM with log link and $E(y|x)$ from $\ln(y)$ ordinary least squares.

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A Supplemental Reading List appears in the online version of this article, immediately after the References.

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