Costs of Healthcare- and Community-Associated Infections With Antimicrobial-Resistant Versus Antimicrobial-Susceptible Organisms

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Objective. We compared differences in the hospital charges, length of hospital stay, and mortality between patients with healthcare- and community-associated bloodstream infections, urinary tract infections, and pneumonia due to antimicrobial-resistant versus -susceptible bacterial strains.

Methods. A retrospective analysis of an electronic database compiled from laboratory, pharmacy, surgery, financial, and patient location and device utilization sources was undertaken on 5699 inpatients who developed healthcare- or community-associated infections between 2006 and 2008 from 4 hospitals (1 community, 1 pediatric, 2 tertiary/quaternary care) in Manhattan. The main outcome measures were hospital charges, length of stay, and mortality among patients with antimicrobial-resistant and -susceptible infections caused by *Staphylococcus aureus*, *Enterococcus faecium*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.

Results. Controlling for multiple confounders using linear regression and nearest neighbor matching based on propensity score estimates, resistant healthcare- and community-associated infections, when compared with susceptible strains of the same organism, were associated with significantly higher charges ($15 626; confidence interval [CI], $4339–$26 913 and $25 573; CI, $9331–$41 816, respectively) and longer hospital stays for community-associated infections (3.3; CI, 1.5–5.4). Patients with resistant healthcare-associated infections also had a significantly higher death rate (0.04; CI, 0.01–0.08).

Conclusions. With careful matching of patients infected with the same organism, antimicrobial resistance was associated with higher charges, length of stay, and death rates. The difference in estimates after accounting for censoring for death highlight divergent social and hospital incentives in reducing patient risk for antimicrobial resistant infections.

Increasing rates of various resistant organisms associated with both healthcare-associated and community-onset infections are being reported worldwide [1–5]. For example, the US incidence of community-onset methicillin-resistant *Staphylococcus aureus* (MRSA) increased by >5-fold between 2000 and 2007 [6]. The costs of avoiding the spread of resistance are generally obvious and are directly and immediately incurred. The benefits, on the other hand, may be imprecise, require sustained, long-term efforts, and are frequently experienced by third parties who are unaware that they have benefited from an earlier costly decision. This externality may result in underinvestment in activities that reduce the spread of antimicrobial infection.

In a recent meta-analysis, we reviewed the incremental costs associated with antimicrobial-resistant

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infections compared with antimicrobial-susceptible strains, but studies varied widely in design, and cost estimates ranged from approximately −$27 000 to $127 000 [7]. Estimates varied in part because of small sample sizes, single site studies, and inadequate control for important confounders, such as severity of illness, device utilization, and length of hospital stay prior to infection.

This study aimed to estimate the additional hospital charges, length of stay, and mortality associated with healthcare-associated infections (HAIs) and community-associated infections (CAIs) among patients with antimicrobial-resistant versus -susceptible bacterial strains across a range of infections in a sample of >310 000 patient discharges from 4 hospitals. Death has a high societal cost, but does not increase costs incurred by a hospital. To address this possible divergence between social and hospital costs, we also estimated models that censor patients who die in the hospital.

METHODS

Data Collection

Data were extracted for 3 years (2006–2008) from various electronic databases from 4 sites in a large healthcare system in metropolitan New York City—the New York-Presbyterian Hospital (NYPH) System, which includes a community hospital, a pediatric hospital, and 2 tertiary/quaternary care hospitals that provide care to a diverse range of patients.

Data were compiled on (1) laboratory reports, including microbiologic results from blood, urine, and respiratory cultures; (2) patient location, including hospital unit and presence of roommates; (3) detailed accounts of medications administered and procedures performed; (4) financial information for each discharge, including total charges and itemized charges by date; and (5) device utilization. Patient information was linked across the multiple datasets using the patient's unique medical record number and date/time stamps associated with source data.

To define the type of infection, the causative organism, and its antimicrobial susceptibility pattern, a team of clinicians and researchers developed electronic algorithms to identify hospital stays with any of 3 types of infections: bloodstream infection (BSI), urinary tract infection (UTI), and pneumonia. We used the surveillance definitions from the Centers for Disease Control and Prevention National Healthcare Safety Network (http://www.cdc.gov/nhsn/about.html) for HAI to identify elements of infections that could be mapped to available electronic data. Recognizing the limitations of infection definitions utilizing electronic data only, we categorized patients into 3 groups: infected, noninfected, and uncertain (Supplementary Data), which allowed us to exclude patients with uncertain infection status to limit bias due to misclassification. We used a combination of microbiologic results, clinical symptoms, urine microscopy results, and *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis codes to identify patients with an infection with the causative organism [8, 9].

We focused our analysis on the following 6 organisms known to frequently cause antimicrobial-resistant infections in the United States [10, 11]: *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. We defined HAIs as those occurring after the patient's third day in the hospital, and CAIs as those occurring on or before the patient's third hospital day without a history of previous hospitalization in the previous 30 days. Because some HAIs can manifest for up to 30 days following exposure [12], patients with infections within the first few days of hospitalization who were hospitalized in the study institution within the previous 30 days were categorized as HAIs associated with the previous hospitalization. Definitions of antimicrobial resistance for each organism are summarized in Table 1. We aimed to capture a spectrum of antimicrobial resistance, from the more common to the less common, and encompassing resistance occurring in the community as well as in the hospital.

The availability of date and time stamps made it possible to separate time-varying factors into pre- and postinfection components. The dependent variables were hospital charges, length of stay, and death in the hospital, all measured postinfection. Covariates fell into 3 broad categories: patient demographics, factors present at admission, and factors arising during the hospital stay but prior to the onset of the infection. Factors present at admission included prior hospitalizations, diabetes, chronic dermatitis, trauma, wounds, burns, stay at a skilled nursing facility, renal failure, and history of substance abuse. *ICD-9-CM* diagnosis codes for conditions present on admission were used to calculate a weighted Charlson score as a measure of patients' health status. Measures of risk of mortality and severity of illness based on output from 3M's Grouper software was also included [13]. Factors arising during the hospital stay included medications, central venous catheterization, urinary catheterization, mechanical

Table 1. Antimicrobial Resistance in 6 Organisms

Organism	Antimicrobial Resistance
Staphylococcus aureus	Oxacillin
Enterococcus faecalis, *Enterococcus faecium*	Vancomycin
Klebsiella pneumoniae	Imipenem, meropenem
Pseudomonas aeruginosa	Levofloxacin
Acinetobacter baumannii	Ampicillin-sulbactam

ventilation, cardiac catheterization, catheter angiography, vascular stenting, dialysis, surgical procedure, general anesthesia, intubation, intensive care unit stay, and presence of roommates. We imputed data on central venous catheters, urinary catheters, and the administration of medication for a subset of approximately 10% of patients for whom such data were missing owing to the staggered rollout of the electronic health record used to record such events. We first imputed whether a patient received any of the 3 interventions by multiple imputation with chained equations, using all other available variables in the data set as predictors. We then imputed the start date and duration of these interventions by hotdeck imputation where "donors" had the same length of stay and similar predicted start day and duration [9].

Analysis

We conducted our analysis using multiple linear regression, with separate analyses for HAI and CAI. We separately regressed each of the dependent variables against an indicator variable for whether the organism causing infection was resistant or susceptible to antimicrobial drugs. All models controlled for patient demographics (sex and 5-year dummy variables for age), risk factors present at admission, and preinfection risk factors that arose during the hospital stay. Because CAIs by definition occur prior to hospitalization, we did not control for risk factors that arose during the hospital stay. We included indicator variables for each body site, each organism, each hospital, and each year-month (to control for seasonality), and controlled for the day number of the hospital stay on which the infection occurred.

Linear regression results may not reflect the full social costs of an infection, because patients with infections may die in the hospital, and charges and days in hospital do not accrue postmortem. Hence, we also estimated censored regression models that censored charges and length of stay for patients who died.

Although we controlled for a wide range of potential confounders, our regression models assumed a linear relationship between these variables and the outcomes. To allow for a more flexible relationship, we also performed nearest neighbor matching using propensity score estimates. To implement this, we obtained an estimate of the propensity score by estimating the probability that a patient acquired an infection using a discrete time hazard model that allowed for time-varying covariates and a flexible baseline hazard, where the unit of analysis was the patient-day. We included the same covariates in our linear regression model in the estimates of the propensity score. We then matched each patient with a resistant infection to a patient with a sensitive infection using the closest propensity score among those with the same organism of interest, body site, and day in hospital on which the infection occurred. Using the sample of matched resistant and sensitive observations, we performed the same linear and censored regressions. We clustered standard errors on the patient since multiple patients with a susceptible infection could be matched to the same patient with a resistant infection. An appendix (available upon request) describes this procedure in more detail and also shows diagnostic tests for assessing match quality, which was acceptable at high standards. All analyses were conducted using Stata software, version 12.0 (StataCorp, College Station, Texas).

RESULTS

Table 2 shows summary statistics for HAI and CAI, demonstrating that patients with resistant infections had considerably higher charges, days in the hospital, and likelihood of death compared to those with susceptible infections. However, patients with resistant infections also appeared to be higher-risk patients prior to the onset of the infection, as evidenced by higher Charlson comorbidity score, for example. Furthermore, patients with resistant HAI generally had more procedures done and higher charges prior to the onset of the infection, highlighting the importance of controlling for these risk factors.

Table 3 presents the main estimates of the difference in postinfection charges, length of stay, and death from having a resistant HAI relative to a sensitive HAI. In a simple mean comparison without adjusting for risk factors, patients with resistant infections experienced a statistically significant increase in charges of >$70 000, length of stay of 7 days, and probability of death of 0.11. These estimates, however, do not account for the fact that patients with more resistant infections may be more likely to experience worse outcomes for other reasons. The next column shows linear regression results that adjusted for the confounding variables described above; the estimates become much smaller and, in some cases, statistically insignificant. Patients with resistant infections experienced roughly $8000 more in charges and just over 1 extra day in the hospital, though these differences are not statistically significant. In the next column, which uses nearest neighbor matching based on the propensity score, estimates are slightly larger than those from the linear model, and now statistically significant for charges.

The results presented so far do not account for the fact that the outcomes of patients who die in the hospital are by definition censored. The next panel in Table 3 repeats the same set of results but using censored models, and the results become much larger and more likely to be statistically significant. For example, the linear regression results suggest that patients with resistant infections experienced charges that were >$15 000 higher and stayed almost 2 days longer than patients with sensitive infections, with both estimates statistically

Table 2. Characteristics of Patients With Healthcare-Associated and Community-Associated Infections

	Healthcare-Associated Infections			Community-Associated Infections		
	Total	Resistant	Susceptible	Total	Resistant	Susceptible
No.	3557	1240	2317	2142	579	1563
Characteristics prior to infection						
Age	64.1 (17.0)	64.0 (17.1)	64.1 (17.0)	66.7 (18.5)	65.7 (17.7)	67.1 (18.8)
Female sex	1830 (51%)	641 (52%)	1189 (51%)	1164 (54%)	286 (49%)	878 (56%)
1 hospital roommate	682 (19%)	248 (20%)	434 (19%)	…	…	…
>1 hospital roommate	2035 (57%)	684 (55%)	1351 (58%)	…	…	…
Charlson score	2.7 (2.5)	2.9 (2.5)	2.7 (2.5)	…	…	…
Preinfection charges ($1000)	104.6 (101.8)	123.7 (118.9)	94.4 (89.7)	…	…	…
Mechanical ventilation	903 (25%)	385 (31%)	518 (22%)	…	…	…
Major procedure[a]	1498 (42%)	490 (40%)	1008 (44%)	…	…	…
Urinary catheter	2790 (78%)	968 (78%)	1822 (79%)	…	…	…
Urinary catheter days[b]	21.8 (24.7)	26.4 (27.8)	19.3 (22.4)	…	…	…
CV line	1639 (46%)	660 (53%)	979 (42%)	…	…	…
CV line days[b]	22.6 (27.1)	25.8 (29.1)	20.4 (25.5)	…	…	…
ICU stay	2052 (58%)	763 (62%)	1289 (56%)	…	…	…
ICU stay days[b]	19.5 (25.3)	23.8 (27.2)	17.0 (23.8)	…	…	…
Infection and patient outcomes						
Day of infection	13.9 (13.3)	17.0 (15.2)	12.2 (11.9)	…	…	…
Bloodstream infection	715 (20%)	293 (24%)	422 (18%)	621 (29%)	171 (30%)	450 (29%)
Pneumonia	801 (23%)	311 (25%)	490 (21%)	182 (8%)	81 (14%)	101 (6%)
Urinary tract infection	2041 (57%)	636 (51%)	1405 (61%)	1339 (63%)	327 (56%)	1012 (65%)
Acinetobacter baumannii	124 (3%)	56 (5%)	68 (3%)	42 (2%)	11 (2%)	31 (2%)
Enterococcus faecalis, Enterococcus faecium	1270 (36%)	561 (45%)	709 (31%)	521 (24%)	92 (16%)	429 (27%)
Klebsiella pneumoniae	917 (26%)	173 (14%)	744 (32%)	720 (34%)	137 (24%)	583 (37%)
Pseudomonas aeruginosa	540 (15%)	118 (10%)	422 (18%)	214 (10%)	79 (14%)	135 (9%)
Staphylococcus aureus	671 (19%)	318 (26%)	353 (15%)	535 (25%)	240 (41%)	295 (19%)
Postinfection charges ($1000)	163.8 (270.7)	209.7 (308.0)	139.2 (245.0)	86.0 (126.2)	115.7 (162.5)	75.1 (107.8)
Postinfection days in hospital	18.4 (27.4)	23.0 (31.7)	16.0 (24.5)	12.2 (15.0)	15.7 (18.5)	10.9 (13.3)
Death	606 (17%)	303 (24%)	303 (13%)	227 (11%)	93 (16%)	134 (9%)

Data are mean (standard deviation) or No. (%).

Abbreviations: CV, central venous; ICU, intensive care unit.

[a] Operating room procedure lasting >30 minutes.

[b] The mean number of days is reported for cases where the number of days is positive.

significant. The propensity score estimates are again slightly larger than the linear regression estimates.

Table 4 shows the same set of results as Table 3 except it focuses on CAI. The results generally show a similar pattern as in Table 3, with adjusted estimates smaller than the unadjusted estimates, propensity score estimates slightly larger than the linear regression estimates (though estimates in the linear model are now statistically significant), and censored estimates larger than uncensored estimates. The impact of resistant infection on charges and length of stay is generally larger for CAI compared to HAI. For example, in the linear censored model, patients with resistant infections experienced additional charges of nearly $31 000 and slightly more than 3.5 extra days in the hospital, both roughly twice as large as the HAI estimates.

Table 5 shows estimates by type of organism and body site for HAIs, focusing only on the models that use linear adjustment for covariates. In the uncensored models, none of the resistant infections caused by specific organisms or body site were associated with significantly greater charges or length of stay, except for charges for vancomycin-resistant *Enterococcus* (VRE). Death rates were significantly higher for HAI caused by resistant *Enterococcus* species or *K. pneumoniae* as well as pneumonia and UTI. Estimates from censored models yield statistically significantly higher charges and length of stay for resistant infections for *Enterococcus* species, *K. pneumoniae*, pneumonia, and UTI.

Table 6 shows analogous results for CAI. Excess charges for CAI VRE infections were particularly high—$69 100 higher

Table 3. Regression Estimates of the Difference in Hospital Charges, Hospital Stay, and Death Between Those With Antimicrobial-Resistant and -Susceptible Healthcare-Associated Infections

	Uncensored Models			Models Censored for Death		
	Unadjusted	Linear	Matching	Unadjusted	Linear	Matching
Total No.	3557	3557	2167	3557	3557	2167
Resistant infection	1240	1240	1083	1240	1240	1083
Unique controls (sensitive infection)	2317	2317	692	2317	2317	692
Hospital charges, in $1000s (95% CI)	70.6 (50.7–90.4)[a]	8.2 (–.5 to 17.0)	15.6 (4.3–26.9)[a]	100.9 (79.6–122.1)[a]	15.2 (6.7–23.6)[a]	18.99 (9.1–28.9)[a]
R^2	0.015	0.854	0.854	0.002	0.152	0.154
Length of hospital stay, d (95% CI)	7.0 (5.0–9.0)[a]	1.1 (–.2 to 2.5)	1.6 (–.1 to 3.2)	10.4 (8.3–12.5)[a]	1.8 (.7–3.0)[a]	2.2 (.8–3.5)[a]
R^2	0.015	0.727	0.735	0.003	0.166	0.166
Probability of death (95% CI)	0.11 (.09–.14)[a]	0.05 (.02–.08)[a]	0.04 (.01–.08)[b]	…	…	…
R^2	0.021	0.253	0.287	…	…	…

Linear and matching models adjusted for sex; age 5 years; year and month of admission; hospital; organism; infection site; prior hospitalization; diabetes; chronic dermatitis; trauma; wounds; burns; prior stay in a skilled nursing facility; renal failure; history of substance abuse; having ≥1 hospital roommate; Clinical Classifications Software categories (Agency for Healthcare Research and Quality); use of and number of days of use of chemotherapeutic, immunosuppressive, and anti-inflammatory medications; mechanical ventilation; urinary, central venous, or cardiac catheterization; catheter angiography; vascular stenting; dialysis; surgical procedure; general anesthesia; intubation; intensive care unit stay; and day of hospital stay on which the infection occurred. Matching model uses nearest neighbor matching based on propensity score estimates with replacement after exact matching on organism of interest, body site, and day in hospital on which the infection occurred. Censored models using death as the censoring variable, hence probability of death models cannot be estimated. Healthcare-associated infections were defined as those diagnosed on third day in hospital or later.

Abbreviation: CI, confidence interval.

[a] $P < .01$.

[b] $P < .05$.

Table 4. Regression Estimates of the Difference in Hospital Charges, Hospital Stay, and Death Between Those With Antimicrobial-Resistant and -Susceptible Community-Acquired Infections

	Uncensored Models			Models Censored for Death		
	Unadjusted	Linear	Matching	Unadjusted	Linear	Matching
Total No.	2142	2142	1110	2142	2142	1110
Resistant infection	579	579	555	579	579	555
Unique controls (sensitive infection)	1563	1563	376	1563	1563	376
Hospital charges, in $1000s (95% CI)	40.7 (26.4–55.0)[a]	24.0 (10.1–37.8)[a]	25.6 (9.3–41.8)[a]	50.6 (37.7–63.6)[a]	30.9 (18.5–43.3)[a]	32.4 (17.1–47.6)[a]
R^2	0.020	0.199	0.212	0.002	0.024	0.027
Length of hospital stay, d (95% CI)	4.8 (3.2–6.5)[a]	2.8 (1.1–4.4)[a]	3.4 (1.5–5.3)[a]	6.1 (4.6–7.7)[a]	3.7 (2.2–5.2)[a]	4.2 (2.5–6.0)[a]
R^2	0.020	0.187	0.199	0.004	0.036	0.039
Probability of death (95% CI)	0.08 (.04–.11)[a]	0.04 (.01–.07)[b]	0.03 (–.02 to .08)	…	…	…
R^2	0.012	0.168	0.215	…	…	…

Linear and matching models adjusted for sex; age 5 years; year and month; hospital; organism infection site; prior hospitalization; diabetes; chronic dermatitis; trauma; wounds; burns; prior stay in a skilled nursing facility; renal failure; history of substance abuse; having ≥1 hospital roommate; Clinical Classifications Software categories (Agency for Healthcare Research and Quality); and day of hospital stay on which the infection occurred. Matching model uses nearest neighbor matching based on propensity score estimates with replacement after exact matching on organism of interest, body site, and day in hospital on which the infection occurred. Censored models using death as the censoring variable, hence probability of death models cannot be estimated. Community-associated infections were defined as those diagnosed within first 3 days of hospitalization in patients who had not been hospitalized in the previous 7 days.

Abbreviation: CI, confidence interval.

[a] $P < .01$.

[b] $P < .05$.

Table 5. Regression Estimates of the Difference in Hospital Charges, Hospital Stay, and Death Between Those With Antimicrobial-Resistant and -Susceptible Healthcare-Associated Infections by Type of Organism and Body Site

	Enterococcus faecalis/faecium	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	BSI	PNU	UTI
Total No.	1270	917	540	671	715	801	2041
Resistant infections	561	173	118	318	293	311	636
Unique controls (sensitive infection)	709	744	422	353	422	490	1405
A. Uncensored models							
Hospital charges, in $1000s (95% CI)	14.6 (.1–29.1)[a]	−1.7 (−21.7 to 18.3)	25.3 (−1.3 to 52.0)	−15.2 (−36.4 to 6.1)	19.6 (−.6 to 39.8)	−5.9 (−30.6 to 18.8)	9.0 (−.5 to 18.5)
R^2	0.871	0.883	0.910	0.846	0.878	0.892	0.815
Length of hospital stay, in days (95% CI)	0.46 (−1.92 to 2.84)	0.04 (−2.74 to 2.81)	2.43 (−.32 to 5.19)	0.16 (−2.77 to 3.08)	2.14 (−.77 to 5.04)	0.53 (−2.64 to 3.70)	0.65 (−.66 to 1.96)
R^2	0.721	0.808	0.896	0.730	0.784	0.824	0.667
Probability of death (95% CI)	0.05 (.01 to .09)[a]	0.07 (.01 to .14)[a]	0.02 (−.06 to .09)	−0.01 (−.07 to .06)	0.05 (−.03 to .12)	0.08 (.01–.15)[a]	0.04 (.01–.07)[a]
R^2	0.351	0.288	0.367	0.336	0.372	0.315	0.245
B. Models censored for death							
Hospital charges, in $1000s (95% CI)	16.9 (4.6–29.3)[b]	13.2 (−5.9 to 32.2)	31.4 (10.1–52.8)[b]	−16.0 (−36.9 to 4.8)	27.1 (6.0–48.2)[a]	4.3 (−20.3 to 28.8)	14.3 (5.5–23.2)[b]
R^2	0.169	0.170	0.179	0.145	0.162	0.164	0.140
Length of hospital stay, in days (95% CI)	0.85 (−.86 to 2.55)	1.63 (−.96 to 4.21)	3.30 (.87–5.73)[b]	0.42 (−2.29 to 3.13)	3.04 (.24–5.84)[a]	1.29 (−1.66 to 4.23)	1.37 (.13–2.62)[a]
R^2	0.169	0.198	0.258	0.161	0.187	0.201	0.144

See notes to Table 3. Results are based on linear adjustment for covariates.

Abbreviations: BSI, bloodstream infection; CI, confidence interval; PNU, pneumonia; UTI, urinary tract infection.

[a] $P < .05$.

[b] $P < .01$.

than sensitive *Enterococcus* infections. Patients with community-associated BSI or UTI with a resistant strain also had significantly higher charges. Length of stay was significantly longer for patients infected with resistant *Enterococcus* species, *P. aeruginosa*, and UTI as well, and probability of death was significantly higher for resistant BSI. Censored estimates are again considerably higher and more precise, though there is generally no difference in statistical significance.

DISCUSSION

While there is no paucity of research regarding the costs of antimicrobial resistance, and there is general agreement that resistance is often associated with higher utilization costs, longer hospital stays, and increased mortality [7, 14, 15], more robust methodologies and data are needed to better understand the health and economic consequences of resistance [16–18].

This current study adds to knowledge about costs of antimicrobial resistance in several important ways. We applied enhanced analytic strategies to improve the methodological rigor of the study. We developed a rich database using administrative data to account for a wide range of confounders including several risk indices and number of device days for central lines, urinary catheters, and mechanical ventilation; examined both CAI and HAI; and focused on several organisms. As Table 1 shows, subjects with resistant infections are more likely to have other risk factors that increase their charges, length of stay, and probability of death. Not surprisingly, the unadjusted models significantly overstate the impact of resistant infections. The adjusted models, which account for the fact that patients with resistant infections have more risk factors than patients with sensitive infections, yield considerably smaller estimates. We also used nearest neighbor propensity score matching to more flexibly control for confounders, but this did not change estimates appreciably. To our knowledge, we are also the first researchers to investigate censored charges and length of stay for those who died, which yielded considerably higher estimates since it also captures societal costs from resistant infections. Consistent with previous findings, our results from all models indicate that resistant infections lead to generally higher charges and length of stay for both HAIs and CAIs.

Adoption of cost-effective programs to reduce antimicrobial resistance has not reached an efficient level, perhaps because

Table 6. Regression Estimates of the Difference in Hospital Charges, Hospital Stay, and Death Between Those With Antimicrobial-Resistant and -Susceptible Community-Associated Infections by Type of Organism and Body Site

	Enterococcus faecalis/ faecium	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	BSI	PNU	UTI
Total No.	521	720	214	535	621	182	1339
Resistant infections	92	137	79	240	171	81	327
Unique controls (sensitive infection)	429	583	135	295	450	101	1012
A. Uncensored models							
Hospital charges, in $1000s (95% CI)	69.1 (36.9–101.4)[a]	8.2 (13.3–29.6)	14.4 (−7.8 to 36.6)	−1.3 (−23.2 to 20.6)	23.5 (.1–46.9)[b]	49.2 (−33.0 to 131.4)	19.0 (3.7–34.3)[b]
R^2	0.433	0.195	0.441	0.202	0.176	0.404	0.216
Length of hospital stay, in days (95% CI)	7.03 (3.10–10.96)[a]	1.81 (−1.06 to 4.68)	3.17 (.19–6.15)[b]	−0.94 (−3.56 to 1.67)	1.71 (−1.09 to 4.51)	6.65 (−1.77 to 15.08)	2.74 (.74–4.74)[a]
R^2	0.367	0.174	0.367	0.206	0.148	0.39	0.204
Probability of death (95% CI)	0.06 (−.02 to .14)	0.02 (−.05 to .08)	0.04 (−.02 to .11)	0.06 (−.00 to .11)	0.10 (.03–.17)[a]	−0.01 (−.12 to .10)	0.02 (−.02 to .06)
R^2	0.236	0.125	0.335	0.269	0.264	0.421	0.139
B. Models censored for death							
Hospital charges, in $1000s (95% CI)	80.8 (54.9–106.7)[a]	11.8 (−10.5 to 34.2)	5.3 (−18.1 to 28.6)	7.7 (−17.4 to 32.8)	43.2 (17.0–69.3)[a]	48.4 (−22.5 to 119.3)	21.6 (10.0–33.2)[a]
R^2	0.053	0.023	0.008	0.025	0.025	0.046	0
Length of hospital stay, in days (95% CI)	8.86 (5.72–11.99)[a]	2.34 (−.55 to 5.22)	0.13 (−3.16 to 3.43)	0.07 (−2.77 to 2.91)	4.37 (1.20–7.53)[a]	6.27 (−.85 to 13.38)[b]	3.11 (1.57–4.66)[a]
R^2	0.069	0.031	0.000	0.038	0.032	0.067	0.037

See notes toTable 4. Results are based on linear adjustment for covariates.

Abbreviations: BSI, bloodstream infection; CI, confidence interval; PNU, pneumonia; UTI, urinary tract infection.

[a] $P < .01$.

[b] $P < .05$.

of mismatches between private and social costs from infection: hospitals bear all the costs for these programs but may not accrue all of the benefits. One source of mismatch is the fact that a hospital only incurs costs while a patient is alive. Thus, although reducing infection-related death has a great benefit for patients, it can increase, rather than reduce, hospital costs. In this study, we found that patients with resistant infections were more likely to die in the hospital. These earlier deaths offset the higher costs hospitals incur to treat resistant cases while they are alive. Once we adjusted for this higher risk of death, the estimated impact of resistance increased costs by roughly 20%–60% compared with estimates that do not make this adjustment. Thus, the increased probability of death among patients with resistant infection dampens the financial incentive hospitals have to make costly investments aimed at avoiding resistance. This suggests that a hospital administration focused only on the bottom line would see few advantages to targeting resistant infection as a priority, even though our results also showed that these patients incur much higher costs while they are alive and are more likely to die.

Costs of Resistance by Organism and Body Site

Studies from the United States, the Netherlands, Spain, and Germany have reported that MRSA infection adds significant incremental hospital costs [19–24], but a small, single site study using propensity score matching reported that methicillin-resistant BSIs when compared with methicillin-susceptible *S. aureus* did not independently increase costs or length of stay [25]. Findings of significantly increased costs have been reported for VRE versus vancomycin-susceptible enterococcal BSIs [26] and for resistant *Escherichia coli* [27–29]. We find hospital charges and length of stay are generally driven by the organisms *Enterococcus* species and *P. aeruginosa* and by body sites BSI and UTI. Similar to the results combining organisms and body site, estimates again are considerably larger and

more likely to be statistically significant when estimating censored regression models.

Limitations

Although our regression models control for a wide range of risk factors, it is possible that residual confounding remains. Because the use of electronic health records limited the ability to obtain data on symptoms, our definitions were primarily based on laboratory results. Hence, it is also possible that some of our definitions reflected colonization rather than clinical infection; nevertheless, our cost estimates are likely to be conservative. Finally, some of our stratified analyses had smaller sample sizes, making Type II errors possible.

Next Steps

Despite the fact that cost estimates of resistance differ across studies, there is growing evidence that resistance causes a number of untoward effects, including increased costs and antimicrobial resistance. These costs are often borne by third-party payers, but changes in the reimbursement policies from the Centers for Medicaid and Medicare are likely to result in hospitals bearing a larger proportion of these costs [30]. Several strategies have been recommended to address this problem; the most common include antimicrobial stewardship programs [31–35] and active surveillance or screening for resistance at hospital admission or intermittently for patients at high risk of developing a resistant infection [36–38]. Results to date, however, have been equivocal and/or slow in coming [39–41], possibly because of failure to fully adhere to and implement these practices. Nevertheless, it may be prudent for each care setting to engage in more judicious antimicrobial prescribing to minimize the risk of resistance, and implement real-time barrier precautions to prevent cross-transmission once resistance has emerged.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Author contributions. M. J. N., analysis and interpretation of data; drafting of manuscript; critical revision of manuscript; administrative, technical, or material support. B. C., acquisition of data; drafting of manuscript; critical revision of manuscript; administrative, technical, or material support. Y. F., interpretation of data; drafting of manuscript; critical revision of manuscript; administrative, technical, or material support. J. H., analysis and interpretation of data; critical revision of manuscript. C. Y. J., analysis and interpretation of data; critical revision of manuscript. S. G., conception and design; obtaining funding; supervision; interpretation of data; critical revision of manuscript. E. L. L., conception and design; obtaining funding; supervision; acquisition of data; interpretation of data; supervision; administrative, technical, and material support; drafting of manuscript; critical revision of manuscript.

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