MAJOR ARTICLE

Hospital and Societal Costs of Antimicrobial-Resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship

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(See the editorial commentary by Zaoutis, on pages 1185–6.)

Background. Organisms resistant to antimicrobials continue to emerge and spread. This study was performed to measure the medical and societal cost attributable to antimicrobial-resistant infection (ARI).

Methods. A sample of high-risk hospitalized adult patients was selected. Measurements included ARI, total cost, duration of stay, comorbidities, acute pathophysiology, Acute Physiology and Chronic Health Evaluation III score, intensive care unit stay, surgery, health care–acquired infection, and mortality. Hospital services used and outcomes were abstracted from electronic and written medical records. Medical costs were measured from the hospital perspective. A sensitivity analysis including 3 study designs was conducted. Regression was used to adjust for potential confounding in the random sample and in the sample expanded with additional patients with ARI. Propensity scores were used to select matched control subjects for each patient with ARI for a comparison of mean cost for patients with and without ARI.

Results. In a sample of 1391 patients, 188 (13.5%) had ARI. The medical costs attributable to ARI ranged from $18,588 to $29,069 per patient in the sensitivity analysis. Excess duration of hospital stay was 6.4–12.7 days, and attributable mortality was 6.5%. The societal costs were $10.7–$15.0 million. Using the lowest estimates from the sensitivity analysis resulted in a total cost of $13.35 million in 2008 dollars in this patient cohort.

Conclusions. The attributable medical and societal costs of ARI are considerable. Data from this analysis could form the basis for a more comprehensive evaluation of the cost of resistance and the potential economic benefits of prevention programs.

The emergence of antimicrobial-resistant organisms is accelerating, and novel drug development is not keeping pace [1–9]. When infection control adherence falls short, transmission of antimicrobial-resistant organisms between patients can occur [1, 10–13]. Those who develop antimicrobial-resistant infection (ARI) experience the consequences of ineffective treatment, delayed recovery, recurrent infection, or even death [2, 10, 14–17]. Solutions currently debated include eliminating antibiotics from livestock feed and decreasing the use of antibiotics for human infections that are self-limited or likely to have been caused by viruses [1, 6, 10, 18–22]. Improved adherence to infection control guidelines has become a national priority for preventing health care–acquired infection (HAI) and ARI [23, 24].

Clinicians are obligated to treat each patient as effectively as possible; thus, as more reports of antimicrobial resistance emerge [1, 25], there may be a paradoxical effect, causing providers to leapfrog to the newest broad-spectrum agent to which resistance may

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be less common. There are time and cost constraints for obtaining microbiological cultures to guide treatment decisions, and empirical therapy is perceived to be more cost-effective, especially in ambulatory settings [10]. Moreover, most antimicrobial prescriptions are written by clinicians who are not infectious diseases specialists [10]. More than 132.7 million outpatient antimicrobial courses were prescribed in 2006, and 80% were written by primary care and emergency department clinicians. That same year, of 95.7 million upper respiratory and skin infections, 83% were treated in primary care or emergency departments [26].

We applied an economic approach to the analysis of antimicrobial resistance. Decisions on the best way to spend or invest current limited resources depend on whose point of view is considered [27–29]. In addition, decision alternatives for medical management are usually considered in the present. Hospitals consider expenses such as labor and pharmaceuticals to be a cost of providing health care. For third-party payors, reimbursement of hospital bills is the cost of doing business. For patients and society, loss of life, quality of life, and productivity are additional costs. We argue that the medical and societal costs of future ARI should be considered in the current cost of inappropriate antimicrobial use and infection control lapses.

This report describes an economic analysis of the Chicago Antimicrobial Resistant Project dataset. Our goal was to measure the cost attributable to ARI in hospitalized patients. The sample included health care–acquired and community-acquired ARI, hospital service, treatment setting, and resistant organism subgroups. The results could be used to balance the benefits of antimicrobial use for current patients against the costs to future patients from increased resistance.

METHODS

Overview. A random sample of patients hospitalized at our urban public teaching hospital in the year 2000 was selected. Selection criteria were age >17 years and >5 *International Classification of Diseases, 9th Edition, Clinical Modification* codes at discharge. Exclusion criteria were hospitalization for trauma, burn, or obstetrical care. This random sample was used to measure an overall cost of ARI. To increase the number of patients for the subgroup analysis, we returned to the same eligibility pool and selected all additional patients with microbiological susceptibilities demonstrating resistance. Potential bias was introduced by the additional patients, so the analytic plan included 3 methods and a sensitivity analysis. Patients were the unit of analysis, and each either had an ARI or did not. The major problem was the effect of confounders that are associated with ARI and with increased hospital cost and mortality risk. To measure the cost attributable to ARI, linear regression was used to control for confounding factors in the initial random sample. Next, the expanded sample was analyzed to estimate the attributable cost and mortality for ARI in general and for specific organism subgroups and treatment settings, also with use of regression models. Finally, to address the sampling bias, propensity scores were used to select matched control subjects for each patient with ARI in a case-control study [30–32]. Propensity scores were also used as cost adjusters in the regression models.

This study was deemed exempt from review by the institutional review boards of the study hospital and the Centers for Disease Control and Prevention (CDC).

Measurements. Medical costs were measured from the hospital perspective [27–29]. All patient resource use was abstracted from the electronic and paper medical records, including length of stay in all wards, number and type of laboratory and radiological tests received, specialty consultations, bedside procedures (eg, endoscopy), minutes of operating room time for surgical procedures, and treatments (eg, pharmaceuticals or blood products) [33–36]. Unit costs for each resource were calculated using the hospital expenditure report for the year 2000. To fully capture the cost of hospital care, all costs for hospital operation and management were allocated to patient services; this included all support costs related to administration, employees, buildings, utilities, equipment, vendor contracts, and variable costs for consumables, such as food and supplies. The multiple distribution method was used to allocate support costs to departments that provide directly measurable services to individual patients [27, 34–36]. For physician care, we included the salaries for faculty, residents, part-time providers, and overtime, along with physician support departments (eg, credentialing and the library). Total operating room minutes, clinic hours, and consultation and procedure times were estimated using clinic schedules, operating room and hospital administrative data, and effort reporting. This information was used to determine the proportion of total physician time and cost for providing care on inpatient wards and intensive care units (ICUs). The cost for time spent in institutional educational activities was distributed proportionally across the patient service activities [37].

The resultant total cost for patient service departments included labor, benefits, supplies, equipment used, and allocated administrative and support costs for employees and space occupied. This total was divided by the annual work-output to determine each service unit cost. The variable cost was measured directly for each medication and blood product an individual received. The total cost per patient was calculated by multiplying the quantity of each service used by its unit cost, then summing all costs.

Our previous work demonstrated that initial severity of illness, care in ICUs, surgical procedures, and development of HAI were factors that predict the total cost of care [34]. Severity

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Table 1. Patient Characteristics Stratified by Presence of Antimicrobial-Resistant Infection (ARI)

	Random sample			Expanded sample		
Characteristic	All patients	Patients with ARI[a]	Patients without ARI	All patients	Patients with ARI	Patients without ARI
All patients	1253	50 (4.0)	1203 (96)	1391	188 (13.5)	1203 (86.5)
Age, years	54.4 ± 14	52.3 ± 15	54.5 ± 14	54.3 ± 14	53.0 ± 16	54.5 ± 14
Male sex	721 (57.5)	34 (68.0)	687 (57.1)	809 (58.2)	122 (64.9)	687 (57.1)
APACHE III score[a]	40.4 ± 18	48.1 ± 17	40.1 ± 18	42.1 ± 20	54.8 ± 27	40.1 ± 18
Duration of stay, days[a]	8.8 ± 10	26.4 ± 26	8.0 ± 7	10.2 ± 12	24.2 ± 21	8.0 ± 7
HAI[a]	159 (12.7)	34 (68.0)	125 (10.4)	260 (18.7)	135 (71.8)	125 (10.4)
Cost per day, US[a]	1597 ± 556	1975 ± 761	1581 ± 540	1651 ± 634	2098 ± 937	1581 ± 540
Total cost, US$[a]	14,947 ± 21,637	56,745 ± 68,154	13,210 ± 14,919	19,267 ± 32,251	58,029 ± 67,485	13,210 ± 14,919
Death[a]	44 (3.5)	8 (16.0)	36 (3.0)	70 (5.0)	34 (18.1)	36 (3.0)
Hospital service						
Medical	1087	30 (2.8)	1057 (97.2)	1179	122 (10.4)	1057 (89.6)
Surgical[a]	166	20 (12.1)	146 (87.9)	212	66 (31.1)	146 (68.9)
Treatment setting						
Non-ICU	1041	21 (2.0)	1020 (98.0)	1110	90 (8.1)	1020 (91.9)
ICU[a]	212	29 (13.7)	183 (86.3)	281	98 (34.9)	183 (65.1)

NOTE. Data are no. (%) of patients or mean ± standard deviation. APACHE, Acute Physiology and Chronic Health Evaluation; HAI, health care–acquired infection; ICU, intensive care unit.

[a] $P < .001$.

of illness was measured using the highest Acute Physiology and Chronic Health Evaluation (APACHE) III score in the first 24 h of hospitalization [38]. Patients were categorized as treated on a medical or surgical service and in an ICU or non-ICU setting. Only persons initially hospitalized on surgical services were categorized as surgery patients; patients treated at any time in an ICU were categorized as ICU patients.

The HAI definitions used were developed by the CDC for the National Nosocomial Infection Surveillance program and were modified slightly for retrospective use [34, 39, 40]. The same clinical definitions were used to define community-acquired ARI. Drug-resistant organisms were condensed into 4 subgroups: (1) methicillin-resistant *Staphylococcus aureus*, (2) vancomycin-resistant enterococci, (3) *Escherichia coli* resistant to fluoroquinolones or third-generation cephalosporins or *Klebsiella* species resistant to third-generation cephalosporins (AREK), and (4) amikacin- or imipenem-resistant *Enterobacter, Pseudomonas,* or *Acinetobacter* species (AIR). Because individual patients were the unit of analysis, and because some patients had >1 drug-resistant infection, a multiple-ARI variable was created. Infections were further classified as health care acquired or community acquired and by infection site (pulmonary, bloodstream, urinary, surgical site, other, and multisite).

The APACHE III score includes points for age, acute pathophysiology abnormalities, and 7 comorbidities [38]. However, it scores only the single comorbidity with the highest points. To address the potential cost impact of multiple comorbidities, we captured all APACHE III comorbidities in an Expanded APACHE III Score (Ex-APACHE). We also recorded 13 additional comorbidities from the Charlson score that were expected to predict increased hospital cost [41]. To determine whether acute pathophysiology (AP) abnormalities on hospital admission might be an additional confounder, we introduced an AP-APACHE III score that included only that portion of the total APACHE III.

Data analysis and reporting. Descriptive data included demographic characteristics, mean APACHE III score, length of stay, cost per day, total cost, HAI rate, and deaths for those with and without ARI. The statistical significance of between group differences for noncontinuous variables was determined using the χ^2 test or the Fisher exact test. The Student *t* test was used for continuous variables. Three propensity scores for ARI

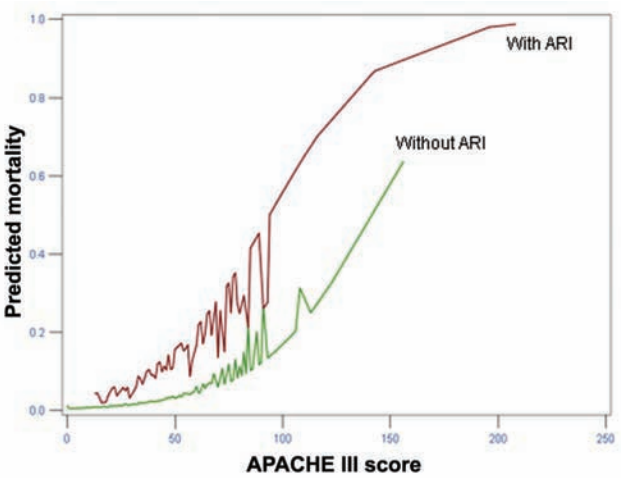

Figure 1. Predicted mortality for patients with and without antimicrobial-resistant infection (ARI). APACHE, Acute Physiology and Chronic Health Evaluation.

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Table 2 Comorbidities and Hospital Circumstances Used to Develop Propensity Score

Variable	No. (%) of patients			P
	All	With ARI	Without ARI	
Comorbidities				
Any renal disease	268 (19.3)	65 (34.6)	203 (16.9)	<.001
Renal failure (hemodialysis)	46 (3.3)	22 (11.7)	24 (2.0)	<.001
Acute myocardial infarction	78 (5.6)	12 (6.4)	66 (5.5)	NS
Congestive heart failure	321 (23.1)	37 (19.7)	284 (23.6)	NS
Peripheral vascular disease	88 (6.3)	24 (12.8)	64 (5.3)	<.001
Stroke	115 (8.3)	21 (11.2)	94 (7.8)	NS
Diabetes mellitus	466 (33.5)	57 (30.3)	409 (34.0)	NS
Diabetes mellitus with complications	106 (7.6)	28 (14.9)	78 (6.5)	<.001
Any liver disease	238 (17.1)	49 (26.1)	189 (15.7)	<.001
Cirrhosis	63 (4.5)	8 (4.3)	55 (4.6)	NS
Hepatic failure	86 (6.2)	13 (6.9)	73 (6.1)	NS
Dementia	52 (3.7)	17 (9.0)	35 (2.9)	<.001
Collagen vascular disease	35 (2.5)	6 (3.2)	29 (2.4)	NS
COPD	125 (9.0)	14 (7.5)	111 (9.2)	NS
Cancer	223 (16.0)	46 (24.5)	177 (14.7)	<.001
AIDS	206 (14.8)	39 (20.7)	167 (13.9)	<.05
Hospital circumstances				
ICU care	281 (20.2)	98 (52.1)	183 (15.2)	<.001
Surgery	212 (15.2)	66 (35.1)	146 (12.1)	<.001
HAI	260 (18.7)	135 (71.8)	125 (10.4)	<.001

NOTE. ARI, antimicrobial-resistant infection; COPD, chronic obstructive pulmonary disease; HAI, health care–acquired infection; ICU, intensive care unit; NS, not significant.

were calculated. The first (PS-1) used all measured comorbidities that were statistically significantly associated with ARI ($P < .05$). The second propensity score (PS-2) included surgery and ICU care as predictors. The third score (PS-3) added HAI.

In the initial random sample, attributable medical cost and length of stay were estimated only for ARI overall. Ordinary least-squares linear regression models were used to control for potential confounding. The sensitivity analysis for this sample included the base case, which adjusted for APACHE III score, ICU care, and surgery. Additional models sequentially introduced HAI, Ex-APACHE, Partial Charlson, and PS-1. The expanded sample was used to estimate cost and length of stay attributable to resistance subgroups and for specific treatment settings. The analysis of the expanded sample included 2 designs. Linear regression with progressive addition of confounders to the model was performed, with all patients included. In the last method, PS-2 and PS-3 were used to select 2 matched control groups for ARI patients. The statistical significance of between-group differences for these matched samples was compared using *t* tests. To estimate the total medical cost for the entire cohort, the number of drug-resistant cases was multiplied by our attributable costs for ARI.

Excess deaths attributable to ARI were estimated using the expanded sample. Logistic regression was used to measure the mortality risk associated with APACHE III score, ICU care, and concurrent HAI. The parameter estimates predicting death were used to calculate an adjusted mortality odds ratio for ARI alone. To estimate the societal costs for excess mortality, the number of deaths attributable to ARI was multiplied by the lost productivity cost (in 2000 US dollars) for death in the age group that included the sample mean age. The total mortality costs were calculated using both 0% ($768,015) and 3% discounted rates ($585,903) [42]. After subtracting the actual number of patients with ARI who died, the attributable length of stay for the remainder was multiplied by the daily cost for lost productivity in the year 2000 ($165) [42].

The totals were adjusted for general inflation to 2008 US dollars [43]. We did not use the higher medical inflation rates, because the medical costs used were from the hospital perspective. Hospital charges and third-party payor costs were not used, and no new medical technology implementation was assumed. Cost calculations and analyses included all patients and were completed using SAS software, version 9.2 (SAS Institute), and Excel, version 2002 (Microsoft).

RESULTS

In the year 2000, 23,904 patients were hospitalized, and 4944 (20.7%) met the eligibility criteria. The random sample of 1253 patients was expanded by 138 patients with ARI available from

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Table 3. Attributable Medical Costs and Length of Stay for Any Antimicrobial-Resistant Infection (ARI)

	Regression analysis			
	ARI cost		ARI length of stay	
Analysis	US$ ± SE	R^2	No. of days ± SE	R^2
Random sample regression analysis (n = 1253)				
Confounders used in regression				
Surgery, ICU, and APACHE III score	27,715 ± 2399	0.45	12.7 ± 1.2	0.34
Surgery, ICU, and Ex-APACHE III score[a]	27,574 ± 2402	0.45	12.6 ± 1.2	0.34
Surgery, ICU, Ex-APACHE III score,[a] and partial Charlson[b]	27,480 ± 2402	0.45	12.5 ± 1.2	0.34
Adjusted for HAI				
Surgery, ICU, APACHE III score, and HAI	21,018 ± 2380	0.49	9.3 ± 1.1	0.40
Surgery, ICU, Ex-APACHE III score,[a] and HAI	20,906 ± 2382	0.49	9.2 ± 1.1	0.40
Surgery, ICU, Ex-APACHE III score,[a] partial Charlson,[b] and HAI	20,840 ± 2383	0.49	9.2 ± 1.1	0.40
Expanded sample regression analysis (n = 1391)				
Confounders used in regression				
Surgery, ICU, and APACHE III score	27,216 ± 2009	0.46	10.5 ± 0.8	0.41
Surgery, ICU, and Ex-APACHE III score[a]	27,175 ± 2013	0.46	10.4 ± 0.8	0.41
Surgery, ICU, Ex-APACHE III score,[a] and partial Charlson[b]	27,076 ± 2019	0.46	10.3 ± 0.8	0.41
Surgery, ICU, and PS-1	25,871 ± 2054	0.47	10.0 ± 0.8	0.41
Surgery, ICU, PS-1, and AP-APACHE III score[c]	25,641 ± 2062	0.47	9.9 ± 0.8	0.42
Adjusted HAI				
Surgery, ICU, APACHE III score, and HAI	19,626 ± 2189	0.48	6.8 ± 0.8	0.45
Surgery, ICU, Ex-APACHE III score,[a] and HAI	19,623 ± 2191	0.48	6.7 ± 0.8	0.45
Surgery, ICU, PS-1, and HAI	18,767 ± 2213	0.49	6.5 ± 0.8	0.45
Surgery, ICU, PS-1, AP-APACHE III score,[c] and HAI	18,588 ± 2218	0.49	6.4 ± 0.8	0.46
Expanded sample subgroup regression analysis (n = 1391)				
Subgroups and confounders used in regression				
Medical patients (n = 1179)				
ICU and PS-1	18,974 ± 1708	0.39	8.1 ± 0.7	0.33
ICU, PS-1, and HAI	12,505 ± 1821	0.42	4.6 ± 0.8	0.39
Surgical patients (n = 212)				
ICU and PS-1	39,924 ± 7354	0.39	14.7 ± 2.5	0.29
ICU, PS-1, and HAI	31,289 ± 8044	0.40	11.3 ± 2.7	0.31
Non-ICU patients (n = 1110)				
Surgery and PS-1	7200 ± 870	0.35	5.7 ± 0.7	0.25
Surgery, PS-1, and HAI	3731 ± 902	0.40	3.3 ± 0.7	0.30
ICU patients (n = 281)				
Surgery and PS-1	47,727 ± 6391	0.33	15.7 ± 2.2	0.26
Surgery, PS-1, and HAI	35,726 ± 7016	0.36	10.5 ± 2.4	0.31

NOTE. All parameter estimates for cost and length of stay and all overall economic model significance tests and F statistics were significant at $P < .001$. APACHE, Acute Physiology and Chronic Health Evaluation; Ex-APACHE, expanded APACHE III; HAI, health care–acquired infection; ICU, intensive care unit; PS-1, propensity score 1; SE, standard error

[a] Includes all comorbidities in the APACHE III system.
[b] Charlson score for comorbidities not included in Ex-APACHE III.
[c] Includes scores for all abnormal acute pathophysiologic measures in APACHE III system.

the same eligibility group, resulting in a total of 1391 patients. Patients with ARI had significantly different APACHE III scores, HAI rates, and death rates, compared with those without ARI (Table 1). Among those with ARI, 34 (18.1%) died, compared with 36 (3.0%) of patients without ARI; ($P < .01$). The mortality odds ratio, adjusted for APACHE III, ICU care, and HAI, was 2.16, resulting in an attributable mortality rate of 6.5% or 12 excess deaths in the sample caused by ARI alone. Figure 1 illustrates that predicted mortality increased with APACHE III score, with higher increases among patients with ARI. There were 205 unique ARIs among 188 patients, and 260 patients had HAI. Among patients with ARI, 135 (71.8%) had concurrent HAI. Eleven patients (5.9%) were infected with >1 drug-resistant organism. Patients with ARI had significantly

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Table 4. Antimicrobial-Resistant Organism Subgroup Distribution, Mean Medical Costs, and Attributable Costs

Variable	R^2	Organism or infection					
		ARI	MRSA	VRE	AREK	AIR	Multiple ARIs[a]
Drug-resistant subgroup distribution (n = 1391)							
Individual patients							
No. (%) of patients	…	188	81 (43.1)	58 (30.9)	30 (16.0)	8 (4.3)	11 (5.9)
Total cost, mean US$ ± SD	…	…	46,236 ± 58,482	66,416 ± 70,747	26,549 ± 27,121	97,444 ± 47,237	157,835 ± 94,181
Community-acquired ARI							
No. (%) of patients	…	…	31 (47.7)	13 (20.0)	19 (29.2)	2 (3.1)	…
Total cost, Mean US$ ± SD	…	…	22,449 ± 18,429	41,963 ± 30,471	19,107 ± 14,817	56,588 ± 29,027	…
Health care–acquired ARI							
No. (%) of patients	…	…	50 (44.6)	45 (40.2)	11 (9.8)	6 (5.4)	…
Total cost, mean US$ ± SD	…	…	60,984 ± 69,254	73,481 ± 77,479	39,403 ± 38,091	111,062 ± 45,444	…
Individual infections							
No. (%) of infections	…	205	94 (45.9)	69 (33.7)	32 (15.6)	10 (4.9)	…
No. (%) of community-acquired ARIs	…	70 (34)	35 (50.0)	14 (20.0)	19 (27.1)	2 (2.9)	…
No. (%) of health care–acquired ARIs	…	135 (66)	59 (43.7)	55 (40.7)	13 (9.6)	8 (5.9)	…
Attributable medical costs, US$ ± SE							
Confounders used in regression							
Surgery, ICU, and APACHE III score	0.54	…	18,380 ± 2605	33,944 ± 3062	8241 ± 4075[b]	48,723 ± 8122	117,312 ± 6766
Surgery, ICU, Ex-APACHE III score[c]	0.54	…	18,303 ± 2612	33,920 ± 3064	8290 ± 4074[b]	49,138 ± 8074	117,210 ± 6769
Surgery, ICU, and PS-1	0.54	…	16,870 ± 2645	31,975 ± 3093	7190 ± 4063[d]	47,845 ± 7932	116,289 ± 6737
Surgery, ICU, PS-1, and AP-APACHE[e]	0.54	…	16,711 ± 2649	31,919 ± 3093	7066 ± 4065[d]	45,966 ± 8143	116,191 ± 6738
Adjusted for HAI							
Surgery, ICU, APACHE III score, HAI	0.55	…	11,842 ± 2693	25,543 ± 3196	3541 ± 4041[d]	42,190 ± 8005	109,110 ± 6716
Surgery, ICU, Ex-APACHE III score,[c] and HAI	0.55	…	11,803 ± 2698	25,545 ± 3197	3599 ± 4039[d]	42,625 ± 7958	109,054 ± 6719
Surgery, ICU, PS-1, and HAI	0.56	…	10,846 ± 2718	24,104 ± 3214	2768 ± 4030[d]	41,563 ± 7827	108,471 ± 6692
Surgery, ICU, PS-1, AP-APACHE III score,[e] HAI	0.56	…	10,732 ± 2722	24,080 ± 3214	2679 ± 4032[d]	40,033 ± 8029	108,413 ± 6693

NOTE. All parameter estimates for cost and all overall economic model significance tests and F statistics were significant at $P<.001$, unless otherwise indicated. AIR, amikacin or imipenem resistant *Enterobacter, Pseudomonas,* or *Acinetobacter* species; APACHE, Acute Physiology and Chronic Health Evaluation; AREK, *Escherichia coli* resistant to fluoroquinolones or third-generation cephalosporins or *Klebsiella* species resistant to third-generation cephalosporins; Ex-APACHE, expanded APACHE; HAI, health care–acquired infection; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* PS-1, propensity score 1; SD, standard deviation; SE, standard error; VRE, vancomycin-resistant enterococci.

[a] Patients infected with >1 antimicrobial-resistant organism.
[b] $P<.05$.
[c] Includes all comorbidities in the APACHE III system.
[d] P = not significant.
[e] Includes scores for all abnormal acute pathophysiologic measures in APACHE III system.

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Table 5. Mean Cost and Length of Stay for Patients with Antimicrobial-Resistant Infection (ARI), Compared with Matched Control Subjects

Propensity score	Patients with ARI	Patients without ARI	Mean difference	*P*
Propensity score 2[a]				
No. of patients	169	169	…	
Total cost, US$	53,863 ± 60,720	24,794 ± 23,231	29,069	<.001
Total length of stay, days	23.8 ± 20.3	12.8 ± 10.2	11.0	<.001
Propensity score 3[b]				
No. of patients	138	138	…	
Total cost, US$	52,211 ± 59,456	31,003 ± 26,325	21,208	<.001
Total length of stay, days	22.5 ± 20.1	15.9 ± 11.3	6.7	<.001

NOTE. Data are mean ± standard deviation, unless otherwise indicated.

[a] Comorbidities, surgery, and intensive care unit stay.

[b] Comorbidities, surgery, intensive care unit stay, and health care–acquired infection.

higher rates of comorbidities, surgery, ICU care, and HAI, demonstrating the need to control for confounding. Comorbidities associated with ARI were candidates for inclusion in the propensity scores (Table 2).

In the random sample of 1253 patients, the attributable cost of ARI (± standard error) in all patients was $27,715 ± $2399, and the attributable length of stay (± standard error) was 12.7 ± 1.2 days (Table 3). When adjusted to control for the effects of HAI, the attributable cost for ARI was $21,018 ± $2380, and the length of stay was 9.3 ± 1.1 days. In the sensitivity analysis, attributable costs ranged from $20,840 to $27,715. In the expanded sample of 1391 patients, costs ranged from $27,216 (base case) to $18,588 when adjusted for PS-1, AP-APACHE III, surgery, ICU care, and HAI. In the hospital service and treatment setting subgroup analysis, patients in the ICU subgroup incurred the highest costs, followed by those in the surgical group. When adjusted for surgery, ICU care, PS-1, and HAI, the attributable costs (± standard error) in the patient subgroups were as follows: ICU, $35,726 ± $7016; surgical ward, $31,289 ± $8044; medical ward, $12,505 ± $1821; and non-ICU, $3731 ± $902. Among all patients infected with only 1 organism, AIR infections were the most costly, followed by vancomycin-resistant enterococci and methicillin-resistant *S. aureus* infections (Table 4). When used to adjust for confounding, the PS-1 resulted in more robust parameter estimates than did the APACHE III score. Adding the Ex-APACHE III, the AP-APACHE, and Charlson additional comorbidities reduced the attributable cost but did not improve the significance of the regression coefficients. In the matched control analysis, the mean cost difference between ARI cases and matched controls was $29,069 ($P < .001$). (Table 5) This cost difference decreased to $21,208 when HAI was included in the propensity score.

The total attributable hospital and societal cost ranges for ARI in the expanded sample were as follows: hospital, $3.4–

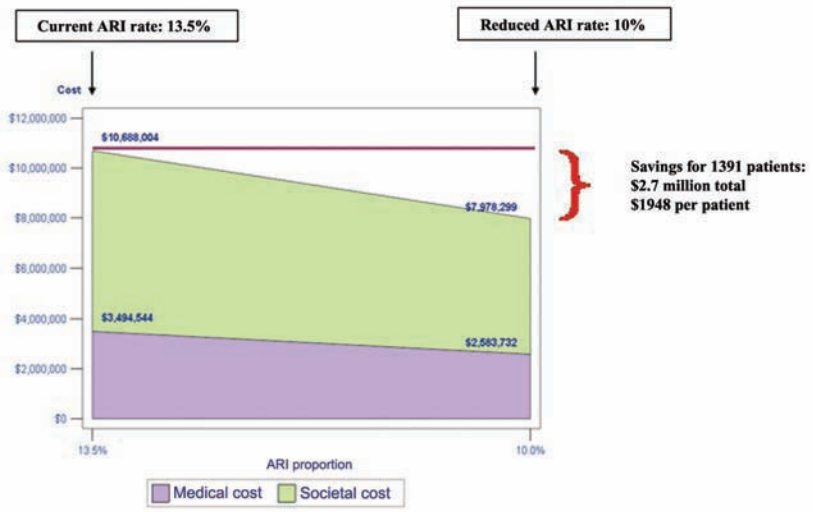

Figure 2. Projected cost savings if antimicrobial-resistant infection (ARI) rates were reduced from 13.5% to 10%.

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$5.4 million; mortality, $7.0–$9.2 million; lost productivity, $162,624–$322,707; and total, $10.7–$15.0 million. The total medical cost, if distributed to all sample patients, added $2512–$3929 (16.8%–26.3%) to the mean unadjusted hospital cost for all sample patients. Figure 2 illustrates the potential cost savings for the hospital and society if the ARI rate had been reduced by 3.5% in the cohort of 1391 patients. We used the lowest cost and length of stay figures from the sensitivity analysis to predict savings for this cohort if the ARI rate could have been held at 10%. The study hospital would have saved $910,812, and the societal savings for reduced mortality and lost productivity would have been $1.8 million. In 2008 US dollars, the total attributable medical and societal cost for ARI alone in 188 patients in a single hospital cost a minimum of $13.35 million. Use of our highest estimates resulted in total costs of $18.75 million.

DISCUSSION

Our study is unique in combining hospital treatment subgroups, a variety of resistant organisms, infection sites, and both healthcare and community-acquired infections. In this cohort, the occurrence of ARI was associated with an attributable cost of $21,018 per infected patient, after adjusting for cost confounding associated with initial severity of illness, ICU care, surgical procedures, and concurrent HAI. In the sensitivity analysis, cost estimates were $25,641–$29,069 without adjustment for HAI and $18,588–$21,208 with adjustment for HAI. The death rate was 2-fold higher among those with ARI, even after controlling for APACHE III scores, ICU care, and concurrent HAI. There was wide variation in the cost based on type of infecting organism, hospital service, and treatment setting.

Our findings indicate that significant health and economic benefits could be realized through effective interventions to reduce both ARI and HAI. A variety of programs have been developed to address antimicrobial resistance. They focus on prudent antimicrobial use, education, and infection control [1, 10, 19, 21, 44–48]. Ideally, future investigations will measure the independent effects of antimicrobial use and infection transmission on ARI rates and how they vary by organism, setting, and patient comorbidities. This approach will allow a more complete illustration of the contribution of ARI to total hospital and societal burden that can be used to estimate the potential value of future successful interventions.

There are several limitations to this work. All data are from a single hospital in a single year and did not include several important patient subgroups. Children and patients receiving obstetrical, trauma, and burn care were excluded because of their low numbers and unique infections. There may have been additional risks for high cost or death that we did not measure. Our costs and mortality rates were measured in a subset of hospital patients at high risk and severity of illness; therefore, these numbers cannot be applied to all patients with ARI in the community. In addition, the costs used to estimate lost productivity from hospitalization and death were national averages and may not apply to a sicker population. Reduction in the quality of life would be a more accurate measure of societal cost, but the retrospective design prevented access to that information. This would be an important future study direction. We adapted existing severity of illness scores to address the potential confounding in this study. Although these scores were originally developed for predicting mortality, both have more recently been used to predict cost and length of stay [41, 49] Infections categorized as community acquired may have actually been acquired during prior health care encounters that we were unable to measure, and "community-onset" ARIs are increasingly recognized as being health care associated. The projected savings from a 3.5% reduction in ARI rates assumed an equivalent reduction for all treatment subgroups and organisms.

A strength of our study was that we were able to measure costs with precision and to attribute them to specific subgroups, whereas other studies have had to rely on reported resistance through the use of *International Classification of Diseases, 9th Edition, Clinical Modification* VO9 codes, which indicate the presence of resistance but do not link it to a causative organism [50].

Although we might be critiqued for underestimating, our most conservative costs for ARI were still considerable. This detailed analysis of the cost of antibiotic resistance in a single large teaching hospital gives an indication of the magnitude of the burden imposed by resistance in the United States, and it should lead to increased efforts to control antibiotic resistance.

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Potential conflicts of interest. All authors: no conflicts.

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