Attributable Cost and Length of Stay Associated with Nosocomial Gram-Negative Bacterial Cultures

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ABSTRACT Few studies have estimated the excess inpatient costs due to nosocomial cultures of Gram-negative bacteria (GNB), and those that do are often subject to time-dependent bias. Our objective was to generate estimates of the attributable costs of the underlying infections associated with nosocomial cultures by using a unique inpatient cost data set from the U.S. Department of Veterans Affairs that allowed us to reduce time-dependent bias. Our study included data from inpatient admissions between 1 October 2007 and 30 November 2010. Nosocomial GNB-positive cultures were defined as clinical cultures positive for *Acinetobacter*, *Pseudomonas*, or *Enterobacteriaceae* between 48 h after admission and discharge. Positive cultures were further classified by site and level of resistance. We conducted analyses using both a conventional approach and an approach aimed at reducing the impact of time-dependent bias. In both instances, we used multivariable generalized linear models to compare the inpatient costs and length of stay for patients with and without a nosocomial GNB culture. Of the 404,652 patients included in the conventional analysis, 12,356 had a nosocomial GNB-positive culture. The excess costs of nosocomial GNB-positive cultures were significant, regardless of specific pathogen, site, or resistance level. Estimates generated using the conventional analysis approach were 32.0% to 131.2% greater than those generated using the approach to reduce time-dependent bias. These results are important because they underscore the large financial burden attributable to these infections and provide a baseline that can be used to assess the impact of improvements in infection control.

KEYWORDS Gram-negative bacteria, antimicrobial resistance, burden, cost, health care-associated infections, length of stay

Health care-associated infections (HAIs) are an important safety threat to hospitalized patients but often are preventable (1). Nearly one-third of all HAIs and more than one-half of HAIs that occur in intensive care units (ICUs) are caused by Gram-negative bacteria (GNB) (2–4). The resistance profiles of GNB can determine the types of treatments that are available to combat these organisms; like other bacteria, GNB have developed resistance to many available antibiotics (5, 6).

A number of infection control strategies exist for the prevention of transmission of GNB in hospitals. A recent systematic review and meta-analysis found that adding antimicrobial stewardship, environmental cleaning, and source control to standard care significantly decreased the rates of acquisition of extended-spectrum β -lactamase (ESBL)-producing *Enterobacteriaceae* and multidrug-resistant (MDR) *Acinetobacter*, compared to standard care alone (7). It is important to perform health economic evaluations of these infection control strategies and to ensure that scarce resources are being used in the most efficient manner possible. Such analyses can be performed only with

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accurate estimates of the cost and length-of-stay (LOS) consequences of HAIs due to the relevant pathogens. However, little is known regarding the attributable costs and hospital LOS associated with these infections. In addition, most estimates of the attributable costs of HAIs are inflated due to time-dependent bias, because most inpatient cost data sets do not differentiate between inpatient costs that occur prior to a HAI and those that occur after the HAI (8).

The purpose of this study was to estimate the costs and LOS associated with nosocomial GNB-positive cultures (specifically, *Acinetobacter*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*), relative to a control group of patients without positive cultures, in more than 100 Veterans Affairs (VA) hospitals in the United States. We overcame the issue of time-dependent bias using a unique inpatient cost data set (9). Finally, we also examined differences in cost and LOS estimates according to the level of resistance of the organisms.

RESULTS

Patient characteristics. A total of 404,652 and 117,829 patients were included in the conventional (Table 1) and post-HAI (Table 2) analyses, respectively. Of the patients included in the conventional analysis, 3.2% had a nosocomial GNB-positive culture, compared with only 0.4% in the post-HAI analysis. In general, patients with GNB HAIs were older and more likely to have had surgery, to have been admitted to the ICU, to have undergone mechanical ventilation, and to have received hemodialysis during the first 2 days of their inpatient stays, compared to those in the noninfected control group.

Cost and LOS outcomes. The unadjusted mean per-patient total costs, variable costs, and LOS for patients with or without a nosocomial GNB-positive culture are shown in Fig. 1 for each of the analysis strategies. Mean costs and LOS were higher among patients with HAIs, compared to those without HAIs, in both the conventional and post-positive-culture analyses. In most cases, the mean costs and LOS were considerably lower in the post-positive-culture analysis than in the conventional analysis.

Results from model 1 for both the conventional and post-positive-culture analysis strategies are presented in Table 3. Table 3 presents the adjusted mean differences in costs and LOS between patients with nosocomial GNB-positive cultures of each level of resistance, compared to the reference category of no nosocomial GNB-positive culture. MDR infections were associated with an increase in total inpatient costs of \$26,492 (95% confidence interval [CI], \$25,775 to \$27,209), slightly higher than the \$25,948 (95% CI, \$24,072 to \$27,825) and \$19,344 (95% CI, \$18,779 to \$19,909) increases in total inpatient costs associated with drug-resistant (DR) and susceptible nosocomial GNB-positive cultures, respectively. Similarly, attributable variable costs were \$14,576 (95% CI, \$14,163 to \$14,989), \$14,544 (95% CI, \$13,466 to \$15,623), and \$10,700 (95% CI, \$10,375 to \$11,025) with MDR, DR, and susceptible nosocomial GNB-positive cultures, respectively. A similar pattern was seen in the LOS results.

Using the post-positive-culture analysis approach, nosocomial GNB-positive cultures were associated with significant increases in total costs, variable costs, and LOS, although the magnitudes of those estimates were considerably smaller than the magnitudes of the estimates obtained through the conventional analysis. The results obtained through the conventional estimation approach ranged from 32.9% (for LOS for nosocomial MDR GNB-positive cultures) to 131.2% (for variable costs for nosocomial DR GNB-positive cultures) higher than those from the post-positive-culture approach.

Figures 2 to 4 contain results from multivariable cost and LOS regressions for models 2 to 4. Overall, these results indicate that GNB-positive cultures, regardless of resistance level, site, or pathogen, are associated with increased costs and LOS in the hospital. The sizes of these effects varied slightly based on the different characteristics of the cultures but, in general, higher resistance levels and sterile sites were associated with larger attributable cost and LOS estimates.

TABLE 1 Patient characteristics in the conventional analysis

Characteristic	No nosocomial GNB-positive culture	Nosocomial MDR GNB-positive culture	<i>P</i> ^a	Nosocomial DR GNB-positive culture	<i>P</i> ^a	Nosocomial susceptible GNB-positive culture	<i>P</i> ^a
Total no. of patients	392,296	4,571		601		7,184	
Age (mean ± SD) (yr)	63.9 ± 13.8	70.3 ± 11.6	<0.0001	68.9 ± 11.4	<0.0001	70.2 ± 12.1	<0.0001
Insurance (no. [%])							
No insurance	95,685 (24.4)	1,152 (25.2)	<0.0001	143 (23.8)	0.318	1,674 (23.3)	<0.0001
Insurance	209,621 (53.4)	2,526 (55.3)		338 (56.2)		4,099 (57.1)	
Missing data	86,990 (22.2)	893 (19.5)		120 (20.0)		1,411 (19.6)	
Sex (no. [%])							
Female	18,685 (4.8)	120 (2.6)	<0.0001	11 (1.8)	0.003	334 (4.6)	0.746
Male	373,377 (95.2)	4,450 (97.4)		590 (98.2)		6,847 (95.3)	
Missing data	234 (0.1)	1 (0.0)		0 (0.0)		3 (0.0)	
Race/ethnicity (no. [%])							
White	272,549 (69.5)	2,933 (64.2)	<0.0001	429 (71.4)	0.139	4,936 (68.7)	0.033
Black	76,304 (19.5)	843 (18.4)		109 (18.1)		1,430 (19.9)	
Other	25,829 (6.6)	559 (12.2)		29 (4.8)		450 (6.3)	
Unknown/missing data	17,614 (4.5)	236 (5.2)		34 (5.7)		368 (5.1)	
Marital status (no. [%])							
Married	159,824 (40.7)	1,951 (42.7)	<0.0001	273 (45.4)	0.008	2,965 (41.3)	<0.0001
Never married	46,969 (12.0)	452 (9.9)		61 (10.1)		691 (9.6)	
Divorced	115,888 (29.5)	1,158 (25.3)		152 (25.3)		1,905 (26.5)	
Separated	17,044 (4.3)	178 (3.9)		18 (3.0)		253 (3.5)	
Widowed	42,109 (10.7)	647 (14.2)		74 (12.3)		1,089 (15.2)	
Unknown/missing data	10,462 (2.7)	185 (4.0)		23 (3.8)		281 (3.9)	
BMI (no. [%])							
<18.5 kg/m ²	9,158 (2.3)	220 (4.8)	<0.0001	37 (6.2)	<0.0001	313 (4.4)	<0.0001
18.5–25 kg/m ²	102,174 (26.0)	1,480 (32.4)		199 (33.1)		2,263 (31.5)	
25–30 kg/m ²	131,455 (33.5)	1,395 (30.5)		158 (26.3)		2,237 (31.1)	
30–35 kg/m ²	84,590 (21.6)	744 (16.3)		98 (16.3)		1,318 (18.3)	
>35 kg/m ²	57,775 (14.7)	557 (12.2)		80 (13.3)		805 (11.2)	
Unknown/missing data	7,144 (1.8)	175 (3.8)		29 (4.8)		248 (3.5)	
Surgery ^b (no. [%])							
Abdominal/pelvic	21,807 (5.6)	673 (14.7)	<0.0001	89 (14.8)	<0.0001	1,043 (14.5)	<0.0001
Cardiovascular	11,199 (2.9)	293 (6.4)	<0.0001	25 (4.2)	0.055	433 (6.0)	<0.0001
Head/neck/back	5,667 (1.4)	99 (2.2)	<0.0001	8 (1.3)	0.816	149 (2.1)	<0.0001
Orthopedic	24,324 (6.2)	293 (6.4)	0.559	29 (4.8)	0.162	485 (6.8)	0.055
Other	23,638 (6.0)	543 (11.9)	<0.0001	57 (9.5)	<0.0001	752 (10.5)	<0.0001
ICU ^b (no. [%])	33,706 (8.6)	857 (18.7)	<0.0001	125 (20.8)	<0.0001	1,031 (14.4)	<0.0001
Mechanical ventilation ^b (no. [%])	5,001 (1.3)	632 (13.8)	<0.0001	78 (13.0)	<0.0001	544 (7.6)	<0.0001
Hemodialysis ^b (no. [%])	3,076 (0.8)	104 (2.3)	<0.0001	14 (2.3)	<0.0001	102 (1.4)	<0.0001
Comorbidity index (mean ± SD)	1.3 ± 1.8	1.6 ± 2.0	<0.0001	1.6 ± 1.9	0.000	1.5 ± 1.9	<0.0001
Outpatient costs ^c (mean ± SD) (\$)	9,604 ± 11,869	10,795 ± 12,722	<0.0001	10,458 ± 9,943	0.078	10,710 ± 12,108	<0.0001

^aCompared to no nosocomial GNB-positive culture.^bDuring the first 2 days of admission.^cDuring the 365 days prior to admission.

DISCUSSION

Using a large data set that included data for more than 7,000 patients with nosocomial GNB-positive cultures and control patients without nosocomial GNB-positive cultures, we found that the nosocomial cultures were associated with significant increases in inpatient costs and LOS; this was true for both cultures from sterile sites, which are likely to be true infections, and cultures from nonsterile sites, which may represent infections or colonization. In addition, while the magnitude of this effect was greatest for organisms that were resistant to ≥ 3 antibiotic drug classes, the increases in costs due to infections from organisms that were resistant to 1 or 2 drug classes or were susceptible to all drug classes were still substantial. The increased costs

TABLE 2 Patient characteristics in the post-positive-culture analysis

Characteristic	No nosocomial GNB-positive culture	Nosocomial MDR GNB-positive culture	<i>P</i> ^a	Nosocomial DR GNB-positive culture	<i>P</i> ^a	Nosocomial susceptible GNB-positive culture	<i>P</i> ^a
Total no. of patients	117,398	149		26		256	
Age (mean ± SD) (yr)	63.6 ± 14.2	70.3 ± 13.2	<0.0001	70.0 ± 13.0	0.024	70.7 ± 11.3	<0.0001
Insurance (no. [%])							
No insurance	30,425 (25.9)	36 (24.2)	0.847	7 (26.9)	0.988	71 (27.7)	0.085
Insurance	60,434 (51.5)	80 (53.7)		13 (50.0)		142 (55.5)	
Missing data	26,539 (22.6)	33 (22.1)		6 (23.1)		43 (16.8)	
Sex (no. [%])							
Female	5,192 (4.4)	8 (5.4)	0.821	2 (7.7)	0.715	10 (3.9)	0.860
Male	112,142 (95.5)	141 (94.6)		24 (92.3)		246 (96.1)	
Missing data	64 (0.1)	0 (0.0)		0 (0.0)		0 (0.0)	
Race/ethnicity (no. [%])							
White	79,830 (68.0)	93 (62.4)	0.003	18 (69.2)	0.165	186 (72.7)	0.089
Black	24,840 (21.2)	27 (18.1)		5 (19.2)		49 (19.1)	
Other	7,788 (6.6)	21 (14.1)		0 (0.0)		8 (3.1)	
Unknown/missing data	4,940 (4.2)	8 (5.4)		3 (11.5)		13 (5.1)	
Marital status (no. [%])							
Married	43,855 (37.4)	73 (49.0)	0.030	9 (34.6)	0.668	100 (39.1)	0.249
Never married	16,356 (13.9)	11 (7.4)		5 (19.2)		23 (9.0)	
Divorced	35,867 (30.6)	38 (25.5)		6 (23.1)		86 (33.6)	
Separated	5,285 (4.5)	5 (3.4)		1 (3.8)		11 (4.3)	
Widowed	12,675 (10.8)	16 (10.7)		3 (11.5)		31 (12.1)	
Unknown/missing data	3,360 (2.9)	6 (4.0)		2 (7.7)		5 (2.0)	
BMI (no. [%])							
<18.5 kg/m ²	3,063 (2.6)	8 (5.4)	0.008	1 (3.8)	0.234	13 (5.1)	0.001
18.5–25 kg/m ²	32,342 (27.5)	50 (33.6)		8 (30.8)		77 (30.1)	
25–30 kg/m ²	39,489 (33.6)	48 (32.2)		6 (23.1)		87 (34.0)	
30–35 kg/m ²	24,324 (20.7)	27 (18.1)		7 (26.9)		39 (15.2)	
>35 kg/m ²	15,943 (13.6)	10 (6.7)		2 (7.7)		28 (10.9)	
Unknown/missing data	2,237 (1.9)	6 (4.0)		2 (7.7)		12 (4.7)	
Surgery ^b (no. [%])							
Abdominal/pelvic	6,166 (5.3)	27 (18.1)	<0.0001	5 (19.2)	0.001	41 (16.0)	<0.0001
Cardiovascular	3,734 (3.2)	6 (4.0)	0.556	0 (0.0)	0.355	15 (5.9)	0.015
Head/neck/back	1,444 (1.2)	5 (3.4)	0.019	1 (3.8)	0.226	1 (0.4)	0.223
Orthopedic	6,932 (5.9)	12 (8.1)	0.266	3 (11.5)	0.223	18 (7.0)	0.445
Other	6,600 (5.6)	16 (10.7)	0.007	3 (11.5)	0.190	21 (8.2)	0.073
ICU ^b (no. [%])	9,982 (8.5)	29 (19.5)	<0.0001	5 (19.2)	0.050	45 (17.6)	<0.0001
Mechanical ventilation ^b	2,519 (2.1)	22 (14.8)	<0.0001	5 (19.2)	<0.0001	25 (9.8)	<0.0001
Hemodialysis ^b	966 (0.8)	6 (4.0)	<0.0001	0 (0.0)	0.642	6 (2.3)	0.007
Comorbidity index (mean ± SD)	1.3 ± 1.7	1.8 ± 2.2	0.001	1.5 ± 2.1	0.605	1.6 ± 2.0	0.007
Outpatient costs ^c (mean ± SD) (\$)	9,649 ± 13,025	12,496 ± 15,352	0.008	8,726 ± 9,283	0.718	10,836 ± 11,603	0.145

^aCompared to no nosocomial GNB-positive culture.^bDuring the first 2 days of admission.^cDuring the 365 days prior to admission.

and LOS were significant and substantial across all 3 pathogen groups in our study, with slightly greater effects among patients with positive cultures from sterile sites versus nonsterile sites. We found that nosocomial GNB-positive cultures were associated with higher total and variable costs. It is likely that the variable costs represent additional medications, fluids, testing, gloves, gowns, and other consumables (10, 11).

Using a unique inpatient cost data set from the VA, we were able to isolate the costs that patients incurred after a GNB-positive culture from the total costs across the entire inpatient stay. This allowed us to generate estimates of the attributable costs of nosocomial GNB-positive cultures that were not inflated due to time-dependent bias. These analyses resulted in estimates that were 32.0% to 131.2% lower than those generated using conventional methods. Our approach, which uses observations from

FIG 1 Unadjusted mean total cost, variable cost, and LOS by infection status.

inpatient cost data that are unique to a calendar month, can be used to estimate the attributable costs and LOS associated with nosocomial positive cultures that occur on the first day of a calendar month. Because only ~1 of every 30 nosocomial positive cultures can be used with this method, the sample of nosocomial positive cultures was too small to apply this method to subcategories of infections, such as those involving specific sites or specific pathogens. However, the estimates of the amount of inflation from our primary analysis can be used to adjust the site- and pathogen-specific estimates for time-dependent bias.

These results are important because they underscore the large financial burden attributable to these events and provide a baseline that can be used to assess the impact of improvements in infection control, such as methods to improve hand hygiene adherence, improved surveillance and patient isolation techniques, or antimicrobial stewardship programs. Evaluations of the effectiveness of these interventions should include economic evaluations of both the costs of the resources required to undertake the interventions and the benefits of prevented deaths and morbidity. While much of the focus of the efforts of the infection control community is on limiting the spread of MDR organisms, we found that even susceptible strains of these pathogens

TABLE 3 Results from multivariable generalized linear models in conventional and post-positive-culture analyses^a

Infection definition	Difference in total costs (mean [95% CI]) (\$)	P	Difference in variable costs (mean [95% CI]) (\$)	P	Difference in LOS (mean [95% CI]) (days)	P
Conventional method ^b						
Nosocomial MDR GNB-positive culture	26,492 (25,775–27,209)	<0.0001	14,576 (14,163–14,989)	<0.0001	10.458 (10.397–10.518)	<0.0001
Nosocomial DR GNB-positive culture	25,948 (24,072–27,825)	<0.0001	14,544 (13,466–15,623)	<0.0001	9.929 (9.764–10.094)	<0.0001
Nosocomial susceptible GNB-positive culture	19,344 (18,779–19,909)	<0.0001	10,700 (10,375–11,025)	<0.0001	7.940 (7.885–7.995)	<0.0001
Post-positive-culture method ^b						
Nosocomial MDR GNB-positive culture	13,744 (9,535–17,953)	<0.0001	7,232 (4,936–9,527)	<0.0001	7.870 (7.422–8.317)	<0.0001
Nosocomial DR GNB-positive culture	12,050 (2,000–22,099)	0.019	6,291 (811–11,770)	0.024	5.871 (4.686–7.056)	<0.0001
Nosocomial susceptible GNB-positive culture	12,293 (9,074–15,511)	<0.0001	6,535 (4,779–8,290)	<0.0001	4.330 (3.933–4.726)	<0.0001

^aRegression models controlled for demographic characteristics (age, race, marital status, insurance status, BMI, and sex); outpatient health care costs in the 365 days prior to admission; an indicator for surgery, an ICU admission, mechanical ventilation, or hemodialysis during the first 48 h of the inpatient admission; the primary diagnosis at admission; and comorbidities during the 365 days prior to admission. Additionally, post-positive-culture regressions controlled for LOS during the first calendar month of the inpatient stay.

^bThe reference was no nosocomial GNB-positive culture.

FIG 2 Results from multivariable generalized linear models for total cost outcomes using conventional methods. Regression models controlled for demographic characteristics (age, race, marital status, insurance status, BMI, and sex); outpatient health care costs in the 365 days prior to admission; an indicator for surgery, an ICU admission, mechanical ventilation, or hemodialysis during the first 48 h of the inpatient admission; the primary diagnosis on admission; and comorbidities during the 365 days prior to admission.

can lead to significant costs. These results indicate that infection control efforts that can have an effect on multiple pathogens across the resistance spectrum may yield important gains. However, even infection control strategies that target just one pathogen may have spillover effects on other pathogens. For example, through the national VA methicillin-resistant *Staphylococcus aureus* (MRSA) initiative, VA facilities practiced active surveillance for MRSA carriage, with isolation of patients who tested positive. While the incidence of MRSA HAIs declined following implementation of the program (12), so did the incidence of GNB HAIs (13). An economic evaluation focusing just on the impact on MRSA infections found that this program was cost-effective (14). The results from this analysis can be used as input parameters for an updated version of the analysis, in which the spillover effects on other pathogens are considered.

To our knowledge, only two previously published studies have estimated the direct medical costs attributable to nosocomial GNB infections. Wilson et al. found that the direct medical costs for patients in a burn unit with nosocomial MDR *Acinetobacter* infections were \$128,797 (in 2016 U.S. dollars) greater than those for control patients in the same unit without infections (15). This estimate is substantially higher than ours because that analysis did not control for confounders, did not take into account time-dependent bias, and was conducted with a subpopulation of sicker inpatients. Eagye et al. compared the costs for inpatients with nosocomial resistant *Pseudomonas* infections with those incurred by control patients without infections, in a single-center study (16). Controlling only for the time at risk for infection and not adjusting for time-dependent bias, the authors estimated that the median cost difference was \$65,253 (in 2016 U.S. dollars). No previous studies have estimated the costs associated with nosocomial infections due to *Enterobacteriaceae*.

FIG 3 Results from multivariable generalized linear models for variable cost outcomes using conventional methods. Regression models controlled for demographic characteristics (age, race, marital status, insurance status, BMI, and sex); outpatient health care costs in the 365 days prior to admission; an indicator for surgery, an ICU admission, mechanical ventilation, or hemodialysis during the first 48 h of the inpatient admission; the primary diagnosis on admission; and comorbidities during the 365 days prior to admission.

It is important to note several limitations to this study. First, our exposure of interest was a clinical culture positive for one of several organisms. While the cultures may not all be indicative of true infections, we determined whether the cultures were obtained from a site that is usually considered sterile (blood, bone, bone marrow, cerebrospinal fluid, pleural fluid, synovial fluid, or lymph node) or nonsterile. Positive cultures from sterile sites are much more likely to be infections. Second, our analyses used administrative and clinical data from the VA system. These data were produced not for the purposes of research but in the process of providing care to patients in the VA system. This means that, to the extent that differences exist among patients and health care delivery systems, these results may not be generalizable to other settings. Finally, while we included many observable patient characteristics as covariates in our multivariable regression models, there might be residual confounding that we were unable to control for using administrative data.

Our study has a number of strengths. First, this is the largest study to estimate the attributable costs and LOS associated with HAIs due to nosocomial GNB-positive cultures, with patients from >100 hospitals in the United States. Second, we examined the influence of time-dependent bias on our results by comparing estimates obtained using conventional analyses and an approach that takes into account the time-varying nature of HAIs (17). Third, using detailed microbiology and resistance data, we were able to generate estimates of the attributable costs and LOS associated with nosocomial positive cultures for multiple pathogens (*Acinetobacter*, *Pseudomonas*, and *Enterobacteriaceae*), from multiple sites (sterile or nonsterile), and with multiple levels of resistance (resistant to ≥ 3 drug classes, resistant to 1 or 2 drug classes, or susceptible to all drug classes).

FIG 4 Results from multivariable generalized linear models for LOS outcomes using conventional methods. Regression models controlled for demographic characteristics (age, race, marital status, insurance status, BMI, and sex); outpatient health care costs in the 365 days prior to admission; an indicator for surgery, an ICU admission, mechanical ventilation, or hemodialysis during the first 48 h of the inpatient admission; the primary diagnosis on admission; and comorbidities during the 365 days prior to admission.

In conclusion, using clinical and administrative data from the VA system, we identified significant and substantial cost and LOS increases attributable to nosocomial positive cultures due to 3 different pathogens with Gram-negative classification, regardless of susceptibility to antibiotics and whether the organisms were detected in cultures from sterile versus nonsterile sites. Future work should use these results to evaluate interventions to prevent transmission of these bacteria within the hospital.

MATERIALS AND METHODS

Study design, population, and data. Using a historical cohort study design and data from the national VA health care system, the largest integrated health care system in the United States (18), we constructed a cohort of patients admitted to any of 114 VA hospitals in the United States between 1 October 2007 and 30 September 2010.

Although patients might have been hospitalized multiple times during our study time frame, we included only the first hospitalization in our analysis. Because our study was focused on nosocomial positive cultures, which potentially could be avoided with additional infection prevention efforts, we excluded patients with a positive culture for MRSA, *Acinetobacter*, *Pseudomonas aeruginosa*, or *Enterobacteriaceae* at admission or during the first 48 h after admission. Finally, we excluded patients who died within the first 48 h after admission, those whose LOS was >90 days, and those who did not have at least 365 days of observation in the VA system prior to the hospital admission.

The results of microbiological tests performed in VA facilities are entered into a patient's electronic medical record in the form of free text. Our team developed a natural-language-processing system that extracts microorganisms and antibiotic susceptibilities mentioned in these reports, allowing us to identify the specific organisms causing the infections and the drug classes to which they were susceptible, at all VA hospitals (19).

Health care cost data were obtained from the VA managerial cost accounting (MCA) system (20), which is an activity-based accounting system. Physicians and managers report their activities, which are then used to distribute costs from the VA payroll and general ledger (21). These personnel costs are combined with the costs of intermediate goods, such as X-rays, units of blood, or days in the ICU, to

generate the costs of inpatient and outpatient encounters. Inpatient cost data from the MCA system are available for each calendar month of a patient's hospital stay (21). In other words, if a patient is admitted to the hospital during one month (e.g., 25 October) and is discharged during the following month (e.g., 5 November), then we would see separate records for the costs that occurred on the days of that patient's hospital stay that occurred during the first month (October) and during the second month (November). As described in more detail below, we used this characteristic of the data to separate costs that occurred prior to a nosocomial positive culture from those that occurred after a nosocomial positive culture.

We conducted our analyses using two different analysis strategies. In our first analysis strategy (conventional analysis), we compared the costs over the entire inpatient stay for patients with a nosocomial GNB-positive culture at some point during their stay with those for patients who did not have a nosocomial GNB-positive culture at any point during their stay. This approach, which has been commonly employed in the published literature, results in inaccurate estimates of the attributable costs of nosocomial positive cultures due to time-dependent bias, because the costs that occurred during the days prior to the positive culture are incorrectly attributed to the positive culture (22, 23).

Time-dependent bias occurs when a time-varying exposure is treated as if it were time fixed. Strategies for avoiding this bias include longitudinal analysis in which the exposure is appropriately treated as time varying and analysis in which the index date is shifted to the exposure date and outcomes are analyzed only over the postexposure time period (17). We took the latter approach in our second analysis strategy ("post-positive-culture" analysis), by shifting the index date from the day of hospital admission to the first day of the second calendar month of the patient's stay. As a result of this redefinition of the index date, we excluded from the post-positive-culture analysis patients whose inpatient stay did not span at least 2 calendar months (since those patients had been discharged prior to the new index date) and patients whose nosocomial GNB-positive culture occurred during the first calendar month (since those patients had the exposure of interest prior to the new index date). In addition, our dependent variable in this analysis was confined to the inpatient costs that occurred from the start of the second calendar month on. We employed this post-positive-culture approach in a previous study that focused on outcomes associated with MRSA HAIs (9).

Outcome variables. VA MCA data allow inpatient costs to be separated into fixed and variable costs, a distinction that is important for the estimation of costs attributable to a nosocomial positive culture (10). Fixed costs are those that are associated with long-term obligations and are difficult to change in the short term. Examples of fixed costs in health care include contractual commitments, such as staff employment and lease agreements for diagnostic devices, and physical commitments, such as investments in buildings and infrastructure. Variable costs, such as costs of drugs and consumables, can be avoided in the short term and therefore represent expenditures that could be saved if a HAI is prevented. We report results for total and variable inpatient costs. Finally, we also included inpatient LOS as a dependent variable.

Independent variables. The key independent variable in our model was a categorical variable for a nosocomial GNB-positive culture. This was defined as a clinical culture positive for *Acinetobacter*, *Pseudomonas aeruginosa*, or *Enterobacteriaceae* during hospitalization, between 48 h after admission and discharge. Using the historical Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) surveillance definition for hospital-onset infections, we considered positive cultures that were identified >48 h after hospital admission (24). We used four models for each of our three outcomes, with each model having a different amount of detail regarding the positive cultures. In model 1, organisms could be classified as MDR if they were resistant to ≥ 3 drug classes, as DR if they were resistant to 1 or 2 drug classes, and as susceptible if they were resistant to no drug classes. Antibiotic drug classes are listed in Table S1 in the supplemental material.

The GNB-positive cultures that we identified might have been evidence of true infections or might simply represent non-infection-related colonization. Because positive cultures taken from a sterile site are more likely to represent true infections, in model 2 we further categorized positive cultures based on whether the site from which they were obtained is typically a sterile site. We classified a sterile site as any of the following: blood, bone, bone marrow, cerebrospinal fluid, pleural fluid, synovial fluid, or lymph node; all other sites were considered nonsterile. For patients with positive cultures from both a sterile site and a nonsterile site, we considered only the culture from the sterile site when the cultures were obtained within 7 days of each other. Otherwise, we considered only a patient's first positive culture. Similarly, if a patient had positive cultures in more than one resistance category, then we considered only the culture with the highest resistance level when the cultures were obtained within 7 days of each other.

In order to investigate differences in the magnitudes of our estimates with specific pathogens, in model 3 our key independent variable was a categorical variable that characterized the level of resistance (MDR, DR, or susceptible) and the specific pathogen (*Acinetobacter*, *Pseudomonas aeruginosa*, or *Enterobacteriaceae*). Finally, in model 4 our key independent variables included the level of resistance, the specific pathogen, and whether the culture was taken from a sterile or nonsterile site.

In addition to these key independent variables, our multivariable regressions controlled for demographic characteristics (age, race, marital status, insurance status, body mass index [BMI], and sex); outpatient health care costs in the 365 days prior to admission; an indicator for surgery, an ICU admission, mechanical ventilation, or hemodialysis during the first 48 h of the inpatient admission; the primary diagnosis on admission; and comorbidities during the 365 days prior to admission. Comorbidities were included in the model through a risk score that combines conditions in the Charlson and Elixhauser measures and has been shown to perform better than either individual measure (25). The post-positive-

culture analyses also included the LOS during the first calendar month of the inpatient stay as an additional independent variable.

Statistical models. For each analysis, we estimated the positive-culture-attributable outcomes using a generalized linear model, a commonly used regression method for skewed data (26). Using a modified Park test, we identified gamma and Poisson as the most appropriate distributions for the dependent variables of costs and LOS, respectively. Model 1 was analyzed using both the conventional and post-positive-culture approaches outlined above. However, because of the small sample size in each of the cells as we subdivided the positive cultures into different classifications in models 2 to 4, those analyses were conducted only using the conventional methods.

All analyses were performed using SAS 9.2 and Stata 12. All relevant ethical safeguards were met in relation to patient and subject protection. Institutional review board approval for this study was obtained through the University of Utah institutional review board and the VA Office of Research and Development, and this study was performed in accordance with the ethical standards contained in the 1964 Declaration of Helsinki and its later amendments.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at <https://doi.org/10.1128/AAC.00462-18>.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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