

## Association of guideline-based antimicrobial therapy and outcomes in healthcare-associated pneumonia

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Received 17 September 2014; returned 10 October 2014; revised 14 November 2014; accepted 30 November 2014

**Objectives:** Guidelines for treatment of healthcare-associated pneumonia (HCAP) recommend empirical therapy with broad-spectrum antimicrobials. Our objective was to examine the association between guideline-based therapy (GBT) and outcomes for patients with HCAP.

**Patients and methods:** We conducted a pharmacoepidemiological cohort study at 346 US hospitals. We included adults hospitalized between July 2007 and June 2010 for HCAP, defined as patients admitted from a nursing home, with end-stage renal disease or immunosuppression, or discharged from a hospital in the previous 90 days. Outcome measures included in-hospital mortality, length of stay and costs.

**Results:** Of 85 097 patients at 346 hospitals, 31 949 (37.5%) received GBT (one agent against MRSA and at least one against *Pseudomonas*). Compared with patients who received non-GBT, those who received GBT had a heavier burden of chronic disease and more severe pneumonia. GBT was associated with higher mortality (17.1% versus 7.7%,  $P < 0.001$ ). Adjustment for demographics, comorbidities, propensity for treatment with GBT and initial severity of disease decreased, but did not eliminate, the association (OR 1.39, 95% CI 1.32–1.47). Using an adaptation of an instrumental variable analysis, GBT was not associated with higher mortality (OR 0.93, 95% CI 0.75–1.16). Adjusted length of stay and costs were also higher with GBT.

**Conclusions:** Among patients who met HCAP criteria, GBT was not associated with lower adjusted mortality, length of stay or costs in any analyses. Better criteria are needed to identify patients at risk for MDR infections who might benefit from broad-spectrum antimicrobial coverage.

**Keywords:** cohort studies, healthcare-associated infections, mortality

### Introduction

Pneumonia is a common reason for hospital admission in the USA and a leading cause of death.<sup>1</sup> Patients who have frequent contact with the healthcare system have pneumonia outcomes that are worse than patients without such exposures,<sup>2,3</sup> a finding thought to be associated with their increased risk for harbouring resistant organisms. Inadequate antibiotic therapy has been associated with higher mortality,<sup>4,5</sup> and small observational studies in healthcare-associated pneumonia (HCAP) have demonstrated improved outcomes with administration of broad-spectrum antimicrobials.<sup>6,7</sup>

Consequently, the American Thoracic Society (ATS) and IDSA guidelines recommend that initial treatment of HCAP include combination therapy consisting of one agent with activity against MRSA and two agents with activity against *Pseudomonas aeruginosa*.<sup>8</sup> However, these guidelines are not followed routinely.<sup>9</sup> Moreover, several observational studies have noted increased mortality among patients who received guideline-concordant therapy.<sup>10</sup>

In a large population of HCAP patients, we aimed to evaluate the effectiveness of guideline-based therapy (GBT) compared with other antimicrobial regimens and to identify subgroups of patients with HCAP who received the greatest benefit from GBT.

## Patients and methods

### Setting and patients

We identified patients discharged between July 2007 and June 2010 from 346 US hospitals that participated in the Premier Alliance.<sup>11</sup> Member hospitals represent all geographical regions and generally reflect US hospitals overall. The Premier database contains sociodemographic information, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes, and hospital and physician information. It also includes a date-stamped log of billed items and services, including diagnostic tests, medications and other treatments. Because the data do not contain identifiable information, the Institutional Review Board at Baystate Medical Center determined that this study did not constitute human subjects research.

We included all patients aged  $\geq 18$  years with a principal ICD-9-CM diagnosis of pneumonia or a secondary diagnosis of pneumonia paired with a principal diagnosis of respiratory failure, acute respiratory distress syndrome, respiratory arrest, sepsis or influenza (Figure S1, available as Supplementary data at JAC Online). We excluded: transfer patients, because we could not assess initial severity or outcomes; those with length of stay of  $\leq 1$  day; patients with cystic fibrosis; those whose attending physician was in a specialty not expected to treat pneumonia (e.g. psychiatry); those with a diagnosis related group inconsistent with pneumonia or a code indicating that the pneumonia was not present on admission; and any patient who did not have a chest radiograph and begin antimicrobials within 48 h of admission. For patients with multiple admissions, one admission was randomly selected.

Patients were designated as having HCAP if they had a diagnosis of end-stage renal disease or haemodialysis in the first 2 hospital days, if they were admitted from a skilled nursing facility or had been discharged from hospital in the past 90 days. We also included patients taking immunosuppressant drugs.

### Data elements

For each patient, we extracted age, sex, race, marital and insurance status, comorbidities, tests, medications and treatments associated with severity of illness, as well as the specialty of the attending physician. Comorbidities were identified using Healthcare Cost and Utilization Project Comorbidity Software, version 3.1, based on the work of Elixhauser et al.,<sup>12</sup> and by use of medications in the first 2 days of hospitalization. Hospitals were categorized by region (north-east, south, mid-west or west), bed size, setting (urban versus rural) and teaching status.

### Antimicrobial treatment and outcome variables

GBT, our main predictor variable, was defined as treatment with an antimicrobial regimen similar to those recommended by the ATS-IDSA guidelines (Table 1) begun on hospital day 1 or 2. The guidelines stress the importance of adequate coverage for MRSA and *Pseudomonas*, but the necessity of routinely using two agents with activity against *Pseudomonas* is debated.<sup>13</sup> Therefore, patients receiving one antimicrobial active against MRSA and any agent against *Pseudomonas* were classified as receiving GBT. All others were classified as receiving non-GBT.

Our primary outcome was in-hospital mortality. Secondary outcomes included 7 day mortality, initiation of mechanical ventilation or admission to the ICU after hospital day 2, readmission to hospital within 30 days, cost, length of stay and *Clostridium difficile* infection (CDI). The latter was defined by ICD-9 code, treatment with metronidazole or oral vancomycin begun after hospital day 3 or readmission within 30 days for *C. difficile*.

### Statistical analysis

Summary statistics are presented as frequencies and proportions for categorical variables and medians with IQRs for continuous variables.

Associations between GBT and patient characteristics were assessed using  $\chi^2$  tests for categorical variables and using Kruskal–Wallis tests for continuous variables.

We developed a hierarchical logistic regression model for treatment to produce propensity scores for GBT versus non-GBT. The model produced a predicted probability, or propensity for treatment, for each patient. It included all patient and hospital characteristics as well as the individual's predicted mortality based on a previously published mortality model.<sup>14</sup>

Multivariable hierarchical regression models<sup>15</sup> were developed to assess the effect of GBT on mortality, all-cause readmission within 30 days, admission to ICU on or after hospital day 3, length of stay, costs and adverse events adjusted for patient characteristics, other early treatments, propensity score and hospital characteristics.

Models with length of stay and costs were trimmed at three standard deviations above mean and natural log-transformed values were modelled to account for extreme skew. SAS software procedure GLIMMIX was used to account for the hierarchical nature of the data (patients clustered within hospital with hospital as a random effect). Logit link models were used for binary outcomes and identity link models were used for continuous outcomes. In addition, we evaluated log-binomial models, Poisson and negative binomial models due to concern that the OR would overestimate the risk ratio for frequent outcomes. Risk ratios were close to ORs; hence we present ORs only.

In additional analyses, we matched each GBT patient based on propensity for GBT with a non-GBT patient. Using conditional logistic regression, we assessed the association between treatment and outcomes, adjusting for factors unbalanced between groups ( $P < 0.05$ ). Stratified analyses assessed outcomes among quintiles of predicted mortality and for each subcategory of HCAP patient.

Finally, we developed grouped treatment models, an adaptation of instrumental variable analysis,<sup>16</sup> to address the threat of residual confounding by indication. Each patient was assigned a group rate of GBT at the hospital where they were treated. We then applied hierarchical models as described above.

A sensitivity analysis was conducted to explore the effect of a hypothetical unmeasured confounder associated with both GBT and mortality. We varied the prevalence of the unmeasured confounder and hypothesized a range of ORs for mortality for the unmeasured confounder between 1.5 and 3.0, within the range of factors found in our data. Using a method proposed by Lin et al.,<sup>17</sup> we explored the combination of prevalence and effect sizes that would be necessary to find that GBT reduced mortality relative to non-GBT.

All tests were two-sided with a significance level of 0.05. All analyses were performed using the Statistical Analysis System (version 9.3, SAS Institute Inc., Cary, NC, USA) and STATA (StataCorp. 2011, Stata Statistical Software: Release 12, College Station, TX, USA: StataCorp LP).

## Results

Our final sample included 85 097 patients from 346 hospitals; 31 949 (37.5%) patients received GBT. Of those not receiving GBT, 82% received standard therapy for community-acquired pneumonia. Patient characteristics appear in Table 1 and Table S1. Compared with patients who received non-GBT, those who received GBT were younger and more likely to be male. They had a heavier burden of chronic diseases such as weight loss (10.2% versus 7.0%) or metastatic cancer (4.3% versus 3.4%) and presented with more severe pneumonia as evidenced by more frequent treatment with mechanical ventilation (23.9% versus 7.6%) or vasopressors (25.2% versus 6.5%) in the first 2 hospital days.

Those who received GBT had higher mortality than those who received non-GBT (17.1% versus 7.7%,  $P < 0.001$ ). Adjustment for patient characteristics (including demographics, comorbidities,

**Table 1.** Characteristics of patients receiving GBT and non-GBT for HCAP

Description	Total, n=85 097 (100%)	GBT, n=31 949 (37.5%)	Non-GBT, n=53 148 (62.5%)	P (two-sided)
Age (years), median (IQR)	73 (61–83)	72 (60–81)	75 (62–83)	<0.0001
Gender, n (%)				<0.0001
female	44 086 (51.8)	15 699 (49.1)	28 387 (53.4)	
male	41 011 (48.2)	16 250 (50.9)	24 761 (46.6)	
Race/ethnicity, n (%)				<0.0001
white	57 571 (67.7)	20 895 (65.4)	36 676 (69.0)	
black	10 925 (12.8)	4 769 (14.9)	6 156 (11.6)	
Hispanic	3 900 (4.6)	1 565 (4.9)	2 335 (4.4)	
other	12 701 (14.9)	4 720 (14.8)	7 981 (15.0)	
Insurance payer, n (%)				<0.0001
Medicare	64 307 (75.6)	23 614 (73.9)	40 693 (76.6)	
Medicaid	6 807 (8)	2 896 (9.1)	3 911 (7.4)	
managed care	8 465 (10.0)	3 434 (10.7)	5 031 (9.5)	
commercial indemnity	2 455 (2.9)	834 (2.6)	1 621 (3.0)	
other	3 063 (3.6)	1 171 (3.7)	1 892 (3.6)	
HCAP individual components, n (%)				<0.0001
admission source is SNF/ICF	8 299 (9.8)	3 119 (9.8)	5 180 (9.7)	
haemodialysis	5 296 (6.2)	2 119 (6.6)	3 177 (6.0)	
admission in previous 90 days	34 677 (40.8)	11 002 (34.4)	23 675 (44.5)	
immunosuppressed	15 456 (18.2)	5 092 (15.9)	10 364 (19.5)	
two or more components	21 369 (25.1)	10 617 (33.2)	10 752 (20.2)	
Comorbidities, n (%)				
congestive heart failure	20 851 (24.5)	7 349 (23)	13 502 (25.4)	<0.0001
valvular disease	7 504 (8.8)	2 188 (6.8)	5 316 (10.0)	<0.0001
hypertension	38 314 (45.0)	12 593 (39.4)	25 721 (48.4)	<0.0001
paralysis	2 814 (3.3)	1 305 (4.1)	1 509 (2.8)	<0.0001
other neurological disorders	9 698 (11.4)	3 667 (11.5)	6 031 (11.3)	0.563
chronic pulmonary disease	40 719 (47.85)	14 526 (45.5)	26 193 (49.3)	<0.0001
diabetes	21 146 (24.9)	7 562 (23.7)	13 584 (25.6)	<0.0001
hypothyroidism	9 883 (11.6)	3 179 (10.0)	6 704 (12.6)	<0.0001
metastatic cancer	3 186 (3.7)	1 370 (4.3)	1 816 (3.4)	<0.0001
weight loss	6 972 (8.2)	3 258 (10.2)	3 714 (7.0)	<0.0001
depression	8 709 (10.2)	2 835 (8.9)	5 874 (11.1)	<0.0001
chronic kidney disease	15 069 (17.7)	6 048 (18.9)	9 021 (17.0)	<0.0001
Principal diagnosis, n (%)				<0.0001
pneumonia/influenza	53 284 (62.6)	14 287 (44.7)	38 997 (73.4)	
sepsis	23 374 (27.5)	14 189 (44.4)	9 185 (17.3)	
respiratory failure/arrest	8 439 (9.9)	3 473 (10.9)	4 966 (9.3)	
Admission to ICU, n (%)				
ICU	20 891 (24.6)	12 897 (40.4)	7 994 (15.0)	<0.0001
cardiac ICU	4 348 (5.1)	2 394 (7.5)	1 954 (3.7)	<0.0001
intermediate care (step down)	1 668 (2.0)	721 (2.3)	947 (1.8)	<0.0001
Measures of severity of illness, <sup>a</sup> n (%)				
any oral medications	74 753 (87.8)	26 503 (83.0)	48 250 (90.8)	<0.0001
calcium (intravenous)	4 018 (4.7)	2 691 (8.4)	1 327 (2.5)	<0.0001
Foley catheter	12 662 (14.9)	6 215 (19.5)	6 447 (12.1)	<0.0001
bicarbonate	4 613 (5.4)	3 023 (9.5)	1 590 (3.0)	<0.0001
vasopressors	11 496 (13.5)	8 044 (25.2)	3 452 (6.5)	<0.0001
benzodiazepines	12 379 (14.6)	6 584 (20.6)	5 795 (10.9)	<0.0001
insulin	27 699 (32.6)	12 418 (38.9)	15 281 (28.8)	<0.0001

Continued

**Table 1.** Continued

Description	Total, n=85 097 (100%)	GBT, n=31 949 (37.5%)	Non-GBT, n=53 148 (62.5%)	P (two-sided)
arterial and venous blood gas	36 817 (43.3)	18 304 (57.3)	18 513 (34.8)	<0.0001
blood cultures	77 282 (90.8)	30 492 (95.4)	46 790 (88.0)	<0.0001
blood lactate	19 982 (23.5)	12 172 (38.1)	7 810 (14.7)	<0.0001
non-invasive ventilation	8 604 (10.1)	4 235 (13.3)	4 369 (8.2)	<0.0001
invasive mechanical ventilation	11 683 (13.7)	7 637 (23.9)	4 046 (7.6)	<0.0001
central line	3 294 (3.9)	2 262 (7.1)	1 032 (1.9)	<0.0001
Hospital characteristics				
bed size, n (%)				<0.0001
≤200 beds	13 953 (16.4)	4 026 (12.6)	9 927 (18.7)	
201–400 beds	32 986 (38.8)	11 124 (34.8)	21 862 (41.1)	
>400 beds	38 158 (44.8)	16 799 (52.6)	21 359 (40.2)	
rural/urban status, n (%)				<0.0001
urban	74 498 (87.5)	29 194 (91.4)	45 304 (85.2)	
rural	10 599 (12.5)	2 755 (8.6)	7 844 (14.8)	
teaching status, n (%)				<0.0001
non-teaching	52 801 (62.0)	17 654 (55.3)	35 147 (66.1)	
teaching	32 296 (38.0)	14 295 (44.7)	18 001 (33.9)	
region, n (%)				<0.0001
north-east	15 192 (17.9)	5 717 (17.9)	9 475 (17.8)	
mid-west	20 459 (24.0)	7 304 (22.9)	13 155 (24.8)	
west	13 233 (15.6)	4 453 (13.9)	8 780 (16.5)	
south	36 213 (42.6)	14 475 (45.3)	21 738 (40.9)	
Outcomes				
inpatient mortality, n (%)	9 575 (11.3)	5 470 (17.1)	4 105 (7.7)	<0.0001
7 day mortality, <sup>b</sup> n (%)	4 966 (5.8)	2 888 (9.0)	2 078 (3.9)	<0.0001
length of stay (days), median (IQR)	6 (4–10)	7 (5–12)	5 (3–8)	<0.0001
cost (\$), median (IQR)	9 846 (5 993–17 979)	13 978 (8 321–25 263)	8 123 (5 224–13 919)	<0.0001

<sup>a</sup>In first 2 hospital days.

<sup>b</sup>Patients discharged alive within 7 days were assumed to survive.

propensity for treatment and treatments in the first 2 hospital days that reflect initial severity of disease) decreased, but did not eliminate, this difference in mortality, with the OR falling from 2.61 to 1.40 (Figure 1). We successfully matched 65.7% of GBT patients with non-GBT patients based on propensity score. Matching balanced all covariates except for minimal differences in peripheral vascular disease and early use of dobutamine and antipsychotics (Table S2). In the matched analysis, adjusted for unbalanced covariates, GBT was still associated with higher mortality. Odds of mortality were increased across all quintiles of predicted mortality, but the higher the predicted mortality, the smaller the increased odds of mortality.

Hospital rates of GBT ranged from 0% to 87%. In the grouped treatment model, in which the hospital's rate of GBT was used in place of the actual therapy received, the odds of mortality with GBT versus non-GBT therapy fell to 0.93 (0.75–1.16). Results for 7 day mortality were almost identical (Table 2). Readmissions followed a pattern similar to mortality for all models, but the magnitude of the effect was smaller. Late ICU admission was slightly higher among the GBT group, even in the grouped treatment model. Adjusted costs and length of stay were also higher with GBT.

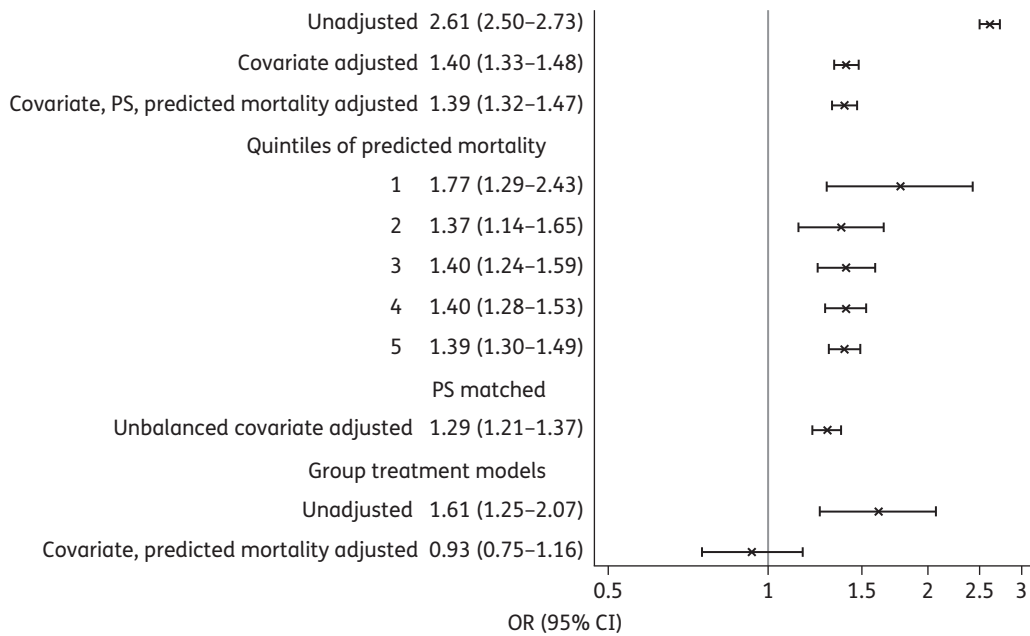
Figure 2 shows the association between mortality and GBT across HCAP subgroups. The association was strongest for immunosuppressed patients and weakest for patients from skilled nursing facilities or on haemodialysis. The magnitude of the association between mortality and GBT declined with each additional HCAP risk factor.

Patients who received GBT were slightly more likely than those receiving non-GBT to experience CDI, but this result was not statistically significant, OR (95% CI) 1.15 (0.98–1.35).

Lastly, we assessed how strong a confounder would be necessary to produce the results we observed if concordant therapy actually reduced mortality. A single potential confounder would have to be present in 30% of the GBT patients (and none of the non-GBT patients) and have an OR of 3.0 in order to find a statistically significant benefit to GBT.

## Discussion

In this large observational study of patients with HCAP, we found that patients receiving initial therapy based on HCAP guidelines had higher unadjusted mortality than those receiving other antimicrobial combinations. After adjustment for patient factors,



**Figure 1.** In-hospital mortality with GBT versus non-GBT. PS, propensity score.

**Table 2.** Outcomes of patients receiving GBT and non-GBT for HCAP, OR (95% CI)

Outcome	Unadjusted	Covariate adjusted	Propensity matched <sup>a</sup>	Group treatment <sup>a</sup>
7 day mortality <sup>b</sup>	2.53 (2.39–2.69)	1.49 (1.39–1.60)	1.41 (1.30–1.53)	0.90 (0.70–1.16)
All-cause readmission	1.28 (1.22–1.33)	1.17 (1.11–1.23)	1.14 (1.06–1.21)	1.01 (0.98–1.03)
Late ICU admission <sup>c</sup>	1.61 (1.49–1.75)	1.18 (1.08–1.28)	1.16 (1.03–1.30)	1.05 (1.00–1.11)
CDI	1.87 (1.63–2.15)	1.24 (1.07–1.44)	1.09 (0.91–1.30)	1.01 (1.00–1.02)
Ln length of stay	1.31 (1.30–1.33)	1.10 (1.09–1.11)	1.10 (1.08–1.11)	
Ln cost	1.62 (1.60–1.64)	1.17 (1.16–1.18)	1.15 (1.14–1.17)	

<sup>a</sup>Adjusted for unbalanced covariates.

<sup>b</sup>Patients discharged alive within 7 days were assumed to survive.

<sup>c</sup>Patients admitted to ICU on hospital day 1 or 2 were excluded from this analysis.

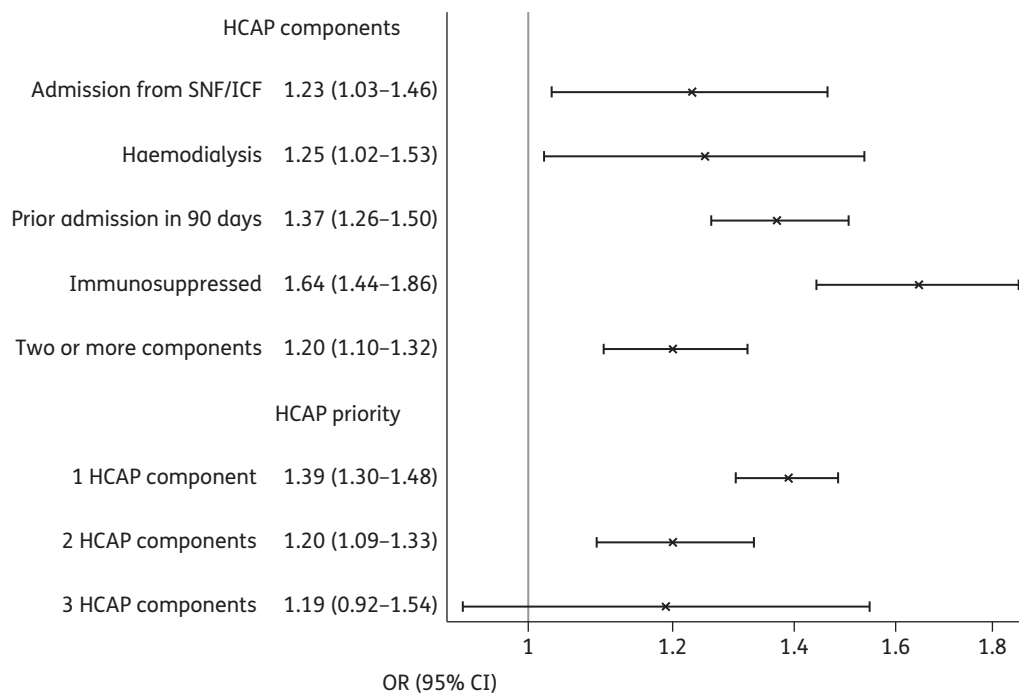
propensity adjustment and propensity matching, the difference between GBT and non-GBT was diminished, but remained. In contrast, a grouped treatment analysis yielded a non-significant 7% mortality reduction associated with GBT. The same pattern occurred for each subgroup of HCAP patients, regardless of HCAP risk factor.

To date, there have been no randomized trials of GBT for HCAP. Several retrospective studies have examined the association between GBT and mortality. The largest examined 15071 non-critically ill HCAP patients from 150 Veterans' Administration hospitals.<sup>18</sup> In a propensity-adjusted analysis, GBT was associated with increased mortality. Of five smaller studies,<sup>19–23</sup> only one found that GBT was associated with reduced mortality.<sup>20</sup> One additional study observed increased mortality associated with GBT, but for patients with a probability of a resistant organism >60%, mortality was reduced.<sup>7</sup> Finally, a quality improvement collaborative aimed at increasing GBT in ICUs also found that GBT was associated with increased

mortality, although overall mortality did not change significantly after implementation of the collaborative (from 24% to 27%,  $P=0.46$ ) despite an increase in GBT from 33% to 47% of cases.<sup>24</sup>

We observed that mortality was more than double among patients receiving GBT. One explanation is selection bias due to unmeasured confounders, with physicians reserving GBT for the sickest patients. Indeed, physicians were much more likely to prescribe GBT for critically ill patients. Our grouped treatment model, in which the hospital rate of GBT serves as an instrumental variable, supports this hypothesis, as higher hospital levels of GBT were associated with lower mortality, albeit not statistically so. An alternative explanation is that GBT might harm some patients. Others have postulated that the use of broad-spectrum antimicrobials among patients without MDR pathogens could lead to unnecessary complications, including adverse drug events, development of antimicrobial resistance, superinfections, CDIs and complications of intravenous therapy or prolonged hospital





**Figure 2.** In-hospital mortality for GBT versus non-GBT among HCAP groups (all models adjusted for propensity score). SNF/ICF, skilled nursing facility/intermediate care facility.

stays.<sup>10,24</sup> However, it seems unlikely that these factors could explain the 30% higher adjusted mortality that we observed among patients receiving GBT.

Our findings call into question the necessity of treating all HCAP patients with GBT. The guidelines do not differentiate among HCAP patients, but physicians in our study apparently did, reserving broad-spectrum antimicrobials for those at greatest risk. Most patients received non-GBT and had low mortality nonetheless. While inadequate antimicrobial therapy is a risk factor for mortality among severely ill patients,<sup>4,5,25,26</sup> in Europe MDR Gram-negative infections are rare,<sup>13</sup> and additional antimicrobials may not affect outcomes.<sup>27,28</sup> Rather than identifying exposure to the healthcare system as a risk for MDR organisms, more precise models for identifying at-risk patients could reduce prescribing and improve patient outcomes.<sup>29</sup>

Our study has several strengths. First, our sample was more than five times as large as all HCAP studies combined, allowing us to assess the impact of GBT in different subpopulations. We found the same pattern regardless of whether patients had been hospitalized, resided in a nursing home or received haemodialysis.

Our study also has limitations. First, its observational nature precludes demonstration of cause and effect. Second, we worked solely with administrative data and could have missed important confounders. Nevertheless, our results were robust. An unmeasured confounder with a strong association with mortality (i.e. similar to admission to ICU) would have had to be present 30% more often, in absolute terms, among patients treated with GBT to produce the observed differences. ICU admission was present 25% more often, so an unobserved confounder with the properties of ICU admission could not account for the observed differences. Third, we lacked microbiology data and therefore cannot

comment on the causative organisms or local resistance patterns. Fourth, we did not strictly speaking evaluate the ATS-IDSA guidelines because patients who received a single agent against *Pseudomonas* were considered to have received GBT. However, patient characteristics and outcomes were similar between those receiving one or two agents. Additionally, we studied in-hospital mortality; results may have been different with 30 day mortality. Finally, in order to increase specificity, we identified patients based on discharge diagnosis rather than admitting diagnosis. Additional patients may have mistakenly received GBT before a correct diagnosis was made.

Eight years after the appearance of published guidelines for treatment of HCAP, physician compliance remains low. As late as 2010, only 40% of patients with HCAP received GBT. Physicians appeared to reserve GBT for patients at highest risk of mortality and most patients who received non-GBT did well. Overall, we found no evidence that GBT reduced mortality. These findings argue for a more nuanced approach to HCAP, with better tools to identify those patients most likely to benefit from broad-spectrum antimicrobial coverage.

## Funding

This study was supported by grant # R01HS018723 from the Agency for Healthcare Research and Quality. The funder had no role in the design and conduct of the study, no role in the collection, management, analysis and interpretation of the data, no role in the preparation, review or approval of the manuscript and no role in the decision to submit the manuscript for publication.

T. L. is supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number K01HL114745.

## Transparency declarations

M. D. Z. has received research funding from and has served as a consultant for Pfizer, Astellas, Cubist, Forest, Theravance and Tetrphase. All other authors: none to declare.

## Supplementary data

Figure S1, Table S1 and Table S2 are available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

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