Guideline-Based Antibiotics and Mortality in Healthcare-Associated Pneumonia

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BACKGROUND: Guidelines recommend administration of antibiotics with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* for treatment of healthcare-associated pneumonia (HCAP). It is unclear if this therapy improves outcomes for patients with HCAP.

OBJECTIVE: To determine if administration of guideline-similar therapy (GST) was associated with a reduction in 30-day mortality for HCAP.

DESIGN: Multi-center retrospective study.

PARTICIPANTS: Thirteen hundred and eleven admissions for HCAP in six Veterans Affairs Medical Centers.

INTERVENTIONS: Each admission was classified as receiving GST, anti-MRSA or anti-pseudomonal components of GST, or other non-HCAP therapy initiated within 48 hours of hospitalization. Association between 30-day mortality and GST was estimated with a logistic regression model that included GST, propensity to receive GST, probability of recovering an organism from culture resistant to antibiotics traditionally used to treat community-acquired pneumonia (CAP-resistance), and a GST by CAP-resistance probability interaction.

MAIN MEASURES: Odds ratios and 95% confidence intervals [OR (95% CI)] of 30-day mortality for patients treated with GST and predicted probability of recovering a CAP-resistant organism, and ratio of odds ratios [ROR (95% CI)] for treatment by CAP-resistance probability interaction.

KEY RESULTS: Receipt of GST was associated with increased odds of 30-day mortality [OR=2.11 (1.11, 4.04), $P=0.02$] as was the predicted probability of recovering a CAP-resistant organism [OR=1.67 (1.26, 2.20), $P<0.001$ for a 25% increase in probability]. An interaction between predicted probability of recovering a CAP-resistant organism and receipt of GST demonstrated lower mortality with GST at high probability of CAP resistance [ROR=0.71 (≤ 1.00) for a 25% increase in probability, $P=0.05$].

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CONCLUSIONS: For HCAP patients with high probability of CAP-resistant organisms, GST was associated with lower mortality. Consideration of the magnitude of patient-specific risk for CAP-resistant organisms should be considered when selecting HCAP therapy.

KEY WORDS: pneumonia; anti-bacterial agents; guideline; methicillin-resistant *Staphylococcus aureus*; *Pseudomonas aeruginosa*; healthcare-associated infection.

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INTRODUCTION

Healthcare-associated pneumonia (HCAP) is defined as pneumonia that is present upon admission, and occurs in patients that have recently been hospitalized, reside in a nursing home, or have other recent healthcare exposures. In 2005, guidelines for the diagnosis and treatment of HCAP were published by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA).¹ A premise of the guidelines is that recent healthcare exposure places patients at risk for infection by multi-drug resistant (MDR) pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*. The guidelines recommend empirical antibiotic therapy with activity against these pathogens. However, there is disagreement about whether current HCAP criteria clearly identify patients at risk for MDR, and concerns that over-treatment with broad-spectrum antibiotics may produce selection pressure for MDR.^{2–4} Recently, an intervention to improve guideline-based treatment of patients with possible MDR pneumonia including HCAP, found that guideline-adherent therapy was associated with increased mortality.⁵ Therefore, it is unclear if guideline-based therapy improves outcomes for patients with HCAP. The primary objective was to compare the 30-day mortality of patients that received guideline-based therapy to those that received alternative therapy. A secondary objective was to determine if patients with a high probability of

culturing bacteria resistant to community-acquired pneumonia antibiotic therapy with either ceftriaxone or moxifloxacin (CAP-resistance) derive benefit from guideline-based therapies relative to those less likely to have CAP-resistant bacteria.

MATERIALS AND METHODS

Patients admitted between January 1, 2003 and December 31, 2008 to six Veterans Affairs Medical Centers (VAMC) in the Northwest U.S. were included in this study. HCAP admissions were identified utilizing medical records data extracted from the Veterans Integrated Service Network (VISN20) Data Warehouse.⁶ This research complies with all U.S. Federal guidelines and VAMC policies relative to human subjects and clinical research, and was approved by the Puget Sound VA Healthcare System Human Subjects committee.

Pneumonia admissions were identified by discharge International Classification of Diseases (ICD-9 CM) codes: 1) primary diagnosis of 480–483; 485–487.0 (pneumonia); or 2) a primary diagnosis of 507.0 (pneumonitis), 518.8 (respiratory failure), or 0.38 (septicemia) combined with a secondary diagnosis of pneumonia (ICD-9 480–483; 485–487.0).⁷ Prior to study initiation, accuracy of the ICD-9 CM based algorithm to identify pneumonia was assessed. During a two-month period, all pneumonia cases (N=56) at one VAMC were identified by reviewing all patient discharges using the VA Computerized Patient Records System. Pneumonia was confirmed by a review of the chief complaint, radiology reports, progress notes, medication histories, and discharge summaries as described by Aronskey et al.⁸ In addition, HCAP risk factors obtained through the data warehouse were compared to chart data. The sensitivity of the algorithm to detect pneumonia was 90.7%, and sensitivity of the data warehouse to detect HCAP risk factors in pneumonia cases was 89.7%. Cohort eligibility required that patients meet any of the following HCAP criteria: 1) hospitalization ≥ 2 days during the preceding 90 days; 2) admission from a nursing home; 3) outpatient or home wound care or infusion therapy, or 4) chronic hemodialysis.¹ Patients were required to receive antibiotic therapy within 24 hours of admission. Direct transfers from other hospitals or patients admitted within 24 hours of prior discharge were excluded.

The guidelines define three categories of antibiotics for treatment of HCAP: A) anti-pseudomonal β -lactams such as a cephalosporin (cefepime, ceftazidime), carbapenem (imipenem, meropenem), or β -lactamase inhibitor (piperacillin/tazobactam); B) other anti-pseudomonal antibiotics such as a fluoroquinolone (ciprofloxacin, levofloxacin), or aminoglycoside (gentamicin, tobramycin); and C) anti-MRSA therapy (vancomycin, linezolid).¹ The guidelines recommend one antibiotic from each category for treatment of HCAP. Pilot data determined that few admissions received anti-pseudomonal double coverage (categories A+B). Because the

guidelines emphasize the importance of treating both MRSA and *Pseudomonas aeruginosa*, the primary variable of interest was guideline-similar therapy (GST), which was defined as treatment with an antibiotic from Category C combined with at least one antibiotic from Category A or B. Secondary analyses focused on guideline-based antibiotic categories (A, B, etc.). Classification of therapy into categories was based on antibiotic administration initiated within 48 hours of hospitalization that was continued for >24 hours (i.e. ≥ 2 doses of a q24 or ≥ 3 doses of a q12 hour antibiotic). If short courses of an antibiotic were administered (usually a single dose of CAP therapy), but therapy was changed to an alternative antibiotic for a longer duration within 48 hours of admission, the longer duration therapy was selected. Admissions that received other antibiotics in addition to Category A, B, or C antibiotics were classified based on their receipt of anti-MRSA and/or anti-pseudomonal therapy. Admissions with changes to therapy after 48 hours remained in their initial treatment group.

Non-antibiotic covariates included: age; primary diagnoses; guideline-specified healthcare exposure criteria; vital signs; admitting ward; chronic diagnoses defined in the Charlson Index; mechanical ventilation; electrolyte, renal function, and white blood count results; microbial cultures; chronic outpatient immunosuppressive and acid suppressive medications; facility, and time.^{9, 10}

Association between 30-day mortality and GST was estimated with a logistic generalized estimating equation (GEE) model that included a binary indicator for GST (X_1), predicted probability of recovering a CAP-resistant organism from culture (X_2), their interaction ($X_3 = X_1X_2$), and, to adjust for selection bias, propensity to have received GST (X_4).¹¹ The model of expected 30-day mortality was:

$$\text{Logit}(\text{Mortality}) = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_4$$

with GEE correction for repeat admissions. To test whether patients most likely to have a CAP-resistant infection benefitted from GST; a lower one-sided test for the interaction (β_3) was evaluated. β_3 was exponentiated to create a ratio of odds ratios (ROR): the odds ratio (OR) comparing GST to non-GST at an elevated probability of CAP-resistance divided by the OR comparing GST to non-GST at a reference-level probability of CAP-resistance. A value less than one indicates that the relative benefit of GST increases with increasing probability of CAP resistance.

The model used to predict CAP-resistance from culture-positive patients in this cohort was developed and validated in an earlier study.¹⁰ The model was based on variables associated with CAP-resistance including: prior MRSA positive culture, nursing home residence, recent intravenous therapy, ICU admission, diabetes, and prior cephalosporin exposure. This model significantly improved prediction of culture-positive patients with CAP-resistance relative to HCAP guideline criteria. For this study, this model provided a predicted probability of recovering a CAP-resistant

organism from admission cultures for each admission in the full cohort (i.e., X_2).

Propensity to have received GST (propensity score) was estimated from a logistic GEE model that included all covariates significantly associated (0.05 level) with 30-day mortality (i.e., potential confounders of GST).¹²

Associations between 30-day mortality and guideline-based antibiotic categories were estimated in the same manner. In each case, a therapy-specific propensity score model was estimated and used to adjust for selection bias in the outcome model.

Because of concern that adjustment for selection bias could not be fully accomplished with a propensity score, we also conducted an ecological study to test whether facility-level monthly use of GST was associated with 30-day mortality (online appendix).

All statistical analyses were performed using R version 2.10.0. GEE models were fit with R package geepack.¹³

RESULTS

The cohort was comprised of 356 admissions that received GST and 955 admissions that received alternative therapy

(Table 1). In general, GST recipients were more likely to be acutely ill, have more prior healthcare and antibiotic exposures, and greater co-morbidity. In addition, patients receiving GST were more likely to have prior MRSA or *Pseudomonas aeruginosa* positive cultures in the past year, and have cultures obtained within 48 hours of admission.

Only 17.7% of patients that received GST (4.8% of the entire cohort) were treated with concordant guideline concordant care with one antibiotic from all three guideline recommended categories (Table 2). Of patients receiving GST, the combination of piperacillin/tazobactam and vancomycin was the most common treatment regimen. For patients not receiving GST, the most commonly prescribed antibiotics included agents utilized in the treatment of CAP. However, 38.2% received anti-pseudomonal coverage, and 7.0% received anti-MRSA coverage, without receiving both therapies in combination (GST). As the study included admissions from two years before and four years after guideline publication, the annual percentage of patients that received GST increased throughout the study (+7.9% per study year, $P<0.001$), primarily due to increased utilization of anti-MRSA antibiotics (+9.0% per study year, $P=0.001$).

Table 1. Cohort Demographics of Patients with HCAP

Characteristics	Guideline Similar Therapy (n=356)	Non-Guideline Similar Therapy (n=955)	P-value
Demographics			
Age (Mean/S.D.)	71.3(11.3)	72.1(12.1)	0.26
Gender (% Male)	97.8	97.3	0.40
Primary Inclusion Diagnosis (%)			
Pneumonia	71.9	85.6	<0.001
Aspiration pneumonitis	14.0	10.3	0.08
Septicemia	7.9	2.3	<0.001
Respiratory failure	6.2	1.8	<0.001
HCAP inclusion criteria (%)			
Nursing Home Residence	45.5	35.7	0.002
Hospitalization >2 d in last 90 d	75.0	66.9	0.005
Intravenous Therapy in last 30 d	23.9	23.2	0.43
Wound care in last 30 d	3.4	3.2	0.52
Chronic dialysis in last 30 d	3.1	2.5	0.34
Other risk for antibiotic resistance (%)			
Antibiotics in last 90 days	73.0	59.8	<0.001
Prior administration of anti-pseudomonal antibiotic	71.5	51.5	<0.001
Prior administration of anti-MRSA antibiotic	39.0	15.3	<0.001
<i>P. aeruginosa</i> cultured within last 365 d	12.1	6.0	<0.001
MRSA cultured within last 365 d	19.4	8.7	<0.001
Recent Immunosuppression	19.4	20.0	0.37
Severity of Illness			
Admitted to ICU (%)	44.9	20.8	<0.001
Mechanical ventilation (%)	15.4	4.4	<0.001
CPAP during hospitalization (%)	12.1	6.5	<0.001
Blood urea nitrogen (mg/dl)	31.4(22.1)	27.5(16.8)	0.05
Sodium (meq/dl)	135.9(5.1)	135.4(5.9)	0.12
Glucose (meq/dl)	140.6(59.0)	136.8(61.1)	0.31
WBC (cells/mm ³)	14.9(17.5)	13.2 (10.1)	0.04
Comorbidity			
Charlson score (mean±S.D.)	5.0 (3.1)	4.1 (2.9)	<0.01
Acute substance use upon admit (%)	9.3	10.2	0.26
Microbial cultures obtained (%)			
Blood culture obtained	94.1	77.5	<0.001
Sputum culture obtained	54.8	41.8	<0.001
MRSA surveillance culture obtained	30.6	10.4	<0.001
Culture-positive (quality sputum or blood)	35.4	21.8	<0.001
Culture-positive (blood)	12.9	8.3	0.02

Table 2. Initial Antibiotic Treatments for Patients with HCAP[†]

Antibiotic Group	Guideline Similar Therapy (n=356)	Non-Guideline Similar Therapy (n=955)	P-value
Category A (anti-Pseudomonal β-lactam)	94.1	31.8	<0.001
Beta-lactamase inhibitor (piperacillin/tazo., ticarcillin/clav.)	77.0	23.4	<0.001
Carbapenem (imipenem, meropenem)	8.4	3.4	<0.001
Cephalosporin (cefepime, ceftazidime)	12.6	6.3	<0.001
Aztreonam	1.7	0.1	0.002
Category B (other anti-pseudomonal antibiotics)	23.6	10.8	<0.001
Anti-pseudomonal fluoroquinolone (ciprofloxacin, levofloxacin)	23.3	10.0	<0.001
Aminoglycoside (gentamicin, tobramycin, amikacin)	1.1	1.2	>0.999
Category C (anti-MRSA antibiotics)	100.0	7.0	<0.001
Vancomycin	97.9	6.8	<0.001
Linezolid	2.1	0.3	0.006
A+C category	76.0	0.0	<0.001
B+C category	5.3	0.0	<0.001
A+B+C category	17.7	0.0	<0.001
CAP antibiotics	7.9	60.8	<0.001
3 rd generation cephalosporins (ceftriaxone, cefotaxime)	2.0	36.9	<0.001
8-methoxy fluoroquinolones (moxifloxacin, gatifloxacin)	6.2	15.4	<0.001
Ampicillin/sulbactam	0.8	8.5	<0.001
Macrolide or tetracycline antibiotics	18.8	43.2	<0.001
Azithromycin, erythromycin, clarithromycin	18.5	42.9	<0.001
Doxycycline, tetracycline	0.3	0.8	0.25
Other antibiotics	16.0	24.9	<0.001
Anti-anaerobes (clindamycin, metronidazole)	13.5	13.5	0.51
Miscellaneous (other cephalosporins, sulfonamides, etc.)	2.5	7.4	<0.001

[†]Results are represented as a percentage of admissions in the GST or non-GST groups that received the particular antibiotic

Twenty-three covariates associated with 30-day mortality were included in the GST propensity score model (Table 3). Covariates significantly associated with GST use included: acute illness indicators (ICU admission and mechanical ventilation), and select HCAP guideline risk factors for MDR (admission from a nursing home, recent IV therapy, and prior antibiotic exposure), uremia, blood culture collection, and time. GST was prescribed at different rates across facilities with less frequent use at smaller facilities.

Among patients that received non-GST, the probability of recovering a CAP-resistant organism from culture was significantly associated [OR (95% CI)] with 30-day mortality [1.67 (1.26, 2.20) for a 25% increase in predicted probability, $P<0.001$] (Table 4). Among patients that received GST, the predicted probability of CAP-resistance was not significantly associated with 30-day mortality [1.18 (0.86, 1.64) for a 25% increase in predicted probability, $P=0.30$]. The interaction between the predicted probability of CAP-resistance and receipt of GST suggested that GST was

Table 3. Propensity Score Model to Receive Guideline-Similar Therapy (GST)

Variable	OR	95% CI	P-value
Mechanical ventilation during hospitalization	3.52	(2.05, 6.06)	<0.001
Nursing home residence or recent (≤ 180 d) nursing home residence	2.09	(1.49, 2.93)	<0.001
Blood culture obtained within 2 d of hospitalization	1.89	(1.06, 3.38)	0.03
Direct ICU admission upon hospitalization	1.86	(1.30, 2.67)	<0.001
Continuous positive airway pressure (CPAP) during hospitalization	1.86	(1.16, 2.97)	0.01
Prior IV infusion ≤ 30 d	1.75	(1.20, 2.58)	0.004
Prior antibiotic therapy ≤ 90 d	1.66	(1.14, 2.40)	0.01
Prior MRSA therapy ≤ 365 d	1.61	(1.09, 2.39)	0.02
Prior positive culture for MRSA ≤ 365 d	1.52	(0.94, 2.47)	0.09
Co-diagnosis of shock, sepsis, or septicemia during hospitalization	1.39	(0.87, 2.24)	0.17
Prior <i>P. aeruginosa</i> therapy ≤ 365 d	1.38	(0.98, 1.96)	0.07
Prior positive culture for <i>P. aeruginosa</i> ≤ 365 d	1.13	(0.63, 2.02)	0.68
Co-diagnosis of pneumonitis during hospitalization	1.10	(0.80, 1.51)	0.55
Blood Urea Nitrogen (mg./dl.)	1.01	(1.00, 1.02)	0.01
Charlson score	1.01	(0.96, 1.07)	0.68
Total days of hospitalization within ≤ 90 d	1.01	(1.00, 1.02)	0.28
Age (y)	1.00	(0.98, 1.01)	0.46
Co-diagnosis of acute substance use during hospitalization	0.98	(0.59, 1.62)	0.94
Co-diagnosis of metastatic cancer during hospitalization	0.70	(0.40, 1.22)	0.21
Receipt of loop diuretics during hospitalization	0.66	(0.47, 0.94)	0.02
Time to first antibiotic dose (d)	0.33	(0.16, 0.64)	0.001
Date of admission from study initiation(d)	1.00	(1.00, 1.00)	<0.001
Third largest facility compared to largest facility*	1.01	(0.69, 1.47)	0.97
Second largest facility compared to largest facility*	0.52	(0.34, 0.80)	0.003
Three smallest facilities (combined) compared to largest facility*	0.12	(0.06, 0.23)	<0.001

Table 4. Logistic GEE Regression Model to Predict 30-Day Mortality by the Interaction Between GST and Predicted Probability of CAP-Resistance while Adjusting for Propensity to Receive GST

Variable	$\hat{\beta}$	SE($\hat{\beta}$)	OR	95% CI	P-value
Propensity score to receive GST	0.22	0.34	1.24	0.64, 2.43	0.52
Predicted probability of CAP-resistance (Pr(CAP-resistance)) [†] *	0.51	0.14	1.67	1.26, 2.20	<0.001
(Guideline Similar Therapy (GST)) [†]	0.75	0.33	2.11	1.11, 4.04	0.02
Pr(CAP-resistance) x GST Interaction [‡]	-0.34	0.21	0.71 [§]	≤ 1.00	0.05

*The estimated OR is for patients who did not receive GST.

[†]The estimated OR is for patients with a low probability of CAP resistance (Pr(CAP-resistance)=0).

[‡]The Pr(CAP-resistance) odds ratio is expressed for a 25% absolute increase in probability.

[§]The exponentiated regression coefficient for the interaction (0.71) is a ratio of odds ratios. More specifically, it is the mortality odds ratio comparing GST to non-GST at an elevated probability of CAP-resistance divided by the mortality odds ratio comparing GST to non-GST at a reference-level probability of CAP-resistance. A value less than one is evidence that the relative benefit of GST increases with probability of CAP-resistance.

relatively beneficial at higher probabilities of CAP-resistance [ROR=1.18/1.67=0.71 (≤ 1.00) for a 25% increase in predicted probability, $P=0.05$]. Expected mortality with GST was lower than with non-GST for a predicted probability of CAP-resistance greater than 0.6 (Fig. 1). Illustrating the estimated relative benefit of GST, the curve relating mortality with CAP-resistance probability for the GST group is less steep than that for the non-GST group. Receipt of GST in patients with low probability of CAP-resistance was also associated with increased mortality [2.11 (1.11, 4.04) at predicted probability of CAP-resistance=0, $P=0.02$]. As GST recipients were more severely ill, it is not clear whether this finding suggests that GST is harmful in patients with low probability of CAP-resistance or if incomplete adjustment for selection bias accounts for this finding.

Interactions between the predicted probability of recovering a CAP-resistant organism from culture and select guideline-based antibiotic components for all cohort patients are represented in Table 5. The interaction between CAP-resistance and anti-Pseudomonal β -lactam therapy

combined with anti-MRSA therapy was protective [ROR=0.68 (≤ -0.96), $P=0.03$] and similar to the interaction involving GST. Triple combination therapy (categories A+B+C) as recommended by the guidelines was not significantly protective.

Visual inspection of aggregate GST utilization and 30-day mortality over time suggested a potential relationship between the increased utilization of GST and a reduction in the 30-day mortality rate (Figure, [online appendix](#)). The ecological study results parallel the finding of a protective GST interaction in the patient-level analysis. The GST administration rate was associated with a decreased 30-day mortality rate after adjustment for non-antibiotic covariates (negative binomial regression $\hat{\beta} = -0.0092$, $P = 0.02$), whereas utilization of non-GST antibiotics was not associated with a reduction in the 30-day mortality rate.¹³ In both studies, the combination of an anti-pseudomonal β -lactam and anti-MRSA therapy appeared to be the most beneficial component of GST. In contrast to the patient-level analysis where GST was associated with higher mortality at low probability of CAP-resistance, in the ecological analysis, GST was associated with a general reduction in the 30-day mortality rate.

DISCUSSION

In this cohort, few patients received triple combination therapy as recommended by the guidelines consisting of double coverage against *Pseudomonas aeruginosa* and MRSA coverage. However, approximately 30% received GST directed against both of these pathogens. Utilization of GST to empirically treat HCAP was uncommon prior to guideline release but increased throughout the study. However, the mean utilization of anti-pseudomonal therapy was 56% prior to guideline publication, suggesting a pre-existing awareness of *Pseudomonas aeruginosa* as a potential pathogen. The increased utilization of GST was largely driven by increased vancomycin use.

Although all patients met criteria for HCAP, less than 30% were directly admitted to the ICU indicating a broad

Figure 1. Relationship between patient-level probability of 30-day mortality and probability of recovering an organism resistant to community-acquired pneumonia antibiotics (CAP-resistance) from culture for healthcare-associated pneumonia patients. Interaction between therapy and probability of CAP-resistance suggests guideline-similar therapy (GST) was beneficial at higher probabilities of CAP-resistance.

Table 5. Logistic GEE Regression Models to Predict 30-Day Mortality by the Interaction Between GST-based Components and Predicted Probability of CAP-resistance (Pr(CAP-resistance)) while Adjusting for Propensity to Receive GST-based Components

Variable	β	SE(β)	P-value	OR	95% CI
Therapy: Category A (anti-Pseudomonal β-lactam)					
Propensity score to receive Category A antibiotics	1.70	0.38	<0.001	5.49	2.59, 11.63
Pr(CAP-resistance)*	0.38	0.18	0.04	1.47	1.02, 2.10
Category A antibiotics	0.52	0.33	0.11	1.67	0.89, 3.17
Pr(CAP-resistance) x Category A antibiotics Interaction*	-0.33	0.22	0.06	0.72 [†]	≤1.03
Therapy: Category B (other anti-pseudomonal antibiotics)					
Propensity score to receive Category B antibiotics	1.93	0.84	0.02	6.86	1.31, 35.88
Pr(CAP-resistance)*	0.34	0.12	0.003	1.41	1.12, 1.77
Category B antibiotics	0.40	0.41	0.33	1.49	0.66, 3.34
Pr(CAP-resistance) x Category B antibiotics Interaction*	-0.10	0.25	0.35	0.91 [†]	≤1.38
Therapy: Category C (anti-MRSA antibiotics)					
Propensity score to receive Category C antibiotics	-0.04	0.34	0.90	0.96	0.49, 1.88
Pr(CAP-resistance)*	0.54	0.15	<0.001	1.72	1.28, 2.32
Category C antibiotics	0.70	0.32	0.03	2.01	1.07, 3.79
Pr(CAP-resistance) x Category C antibiotics Interaction*	-0.29	0.20	0.08	0.75 [†]	≤1.05
Therapy: Category A+C antibiotics					
Propensity score to receive Category A+C antibiotics	0.22	0.34	0.52	1.24	0.64, 2.43
Pr(CAP-resistance)*	0.54	0.13	<0.001	1.72	1.32, 2.24
Category A+C antibiotics	0.71	0.35	0.04	2.03	1.03, 4.01
Pr(CAP-resistance) x Category A+C antibiotics Interaction*	-0.39	0.21	0.03	0.68 [†]	≤0.96
Therapy: Category A+B+C antibiotics[‡]					
Propensity score to receive Category A+B+C antibiotics	0.18	0.89	0.84	1.20	0.21, 6.93
Pr(CAP-resistance)*	0.42	0.11	<0.001	1.52	1.22, 1.89
Category A+B+C antibiotics	0.37	0.67	0.58	1.45	0.39, 5.43
Pr(CAP-resistance) x Category A+B+C antibiotics Interaction*	-0.05	0.37	0.44	0.95 [†]	≤1.73

*The Pr(CAP-resistance) odds ratio is expressed for a 25% absolute increase in probability.

[†]The exponentiated regression coefficient for the interaction is a ratio of odds ratios.

[‡]Guideline recommended therapy for HCAP.

range of illness severity. However, patients that received GST were more likely to be acutely ill, have greater comorbidity, and at greater risk for antibiotic resistant pathogens due to increased prior health care and antibiotic exposures. Patients that received GST were also more likely to have microbial cultures obtained and have potential pneumonia pathogens identified from culture.

Consistent with this observation, 30-day mortality was positively associated with probability of identifying a CAP-resistant organism and receipt of GST. However, the interaction between treatment and probability of CAP-resistance suggests that for patients with a relatively high probability of recovering these organisms, GST was beneficial. A similar interaction term between the combination of anti-Pseudomonal β -lactam and anti-MRSA therapy and the probability of CAP-resistance was also protective. Triple combination therapy was not significantly protective; although the power to detect a true interaction was limited. While other temporal factors (e.g. improved quality of pneumonia care over time) may explain the reduction in mortality observed in the population-level analysis, these results provide further evidence that use of GST may be associated with improved outcome, particularly the combination of an anti-pseudomonal β -lactam and anti-MRSA antibiotic.

While several studies have reported on outcomes of HCAP, few have addressed impact of guideline-recommended therapy on outcome.^{5, 14–19} El Sohl et. al retrospectively stratified 344 nursing home patients based on treatment with HCAP or CAP guideline concordant therapy.¹⁵ After

adjustment for selection bias and covariates, concordant treatment with either the HCAP or CAP guidelines was not predictive of mortality (30-day mortality 16.8%). A prospective observational study conducted in Italy described the epidemiology and outcome of CAP and HCAP.¹⁶ Patients with HCAP had a 17.8% mortality rate, and receipt of empirical therapy not consistent with international guidelines was a risk factor for in-hospital mortality. Details regarding specific antibiotic therapies were not reported. Similar to these studies, we found a relatively small proportion of patients that received guideline-concordant triple therapy, and a comparable overall 30-day mortality rate of 17.3%.

Recently, a cohort study of guideline implementation in ICU patients at risk for MDR pneumonia found that although compliance with antibiotic recommendations increased, there was an increased risk of mortality among patients receiving HCAP guideline concordant therapy.^{5, 19} Guideline concordant therapy was defined as triple coverage with both anti-MRSA and two anti-pseudomonal antibiotics which is different than our study. Similarly, we did not establish benefit with triple therapy in the interaction between CAP-resistance and treatment or in the ecological analysis. Although antibiotic-related complications may explain the increased mortality in both patient-level studies, a more likely possibility is inadequate adjustment for disease severity.²⁰

The divergence in outcomes observed between studies may be explained by differences in study populations and definitions for guideline recommended treatment. In our study utilization of anti-pseudomonal therapy or anti-MRSA therapy alone was negatively, but not significantly,

associated with a reduction in the 30-day mortality rate. A prospective study of non-ICU HCAP and HAP patients that excluded patients at high risk for *Pseudomonas* or MRSA found no difference in outcome between cefepime or ertapenem, and recent studies report that culture-negative HCAP patients may be successfully de-escalated to antibiotics without anti-MRSA or anti-pseudomonal therapy.^{21–23} These studies highlight the need to consider differences in study criteria when applying results to specific HCAP populations.

Study strengths include the VISN20 Data Warehouse that provided a detailed integrated outpatient and inpatient medical record, permitting identification of prior healthcare exposures, and both antibiotic and non-antibiotic variables. Additionally, the ability to adjust for the probability of recovering CAP-resistant organisms from culture allowed for assessment of therapy based upon a patient's potential to benefit from GST. A final strength is that dual patient-level and population-level analyses were conducted which allowed for comparison of findings between methods. While inference of findings identified in ecological studies to individual patients may pose problems, complete correction for selection bias in retrospective patient-level studies is frequently difficult. The findings from the two analyses are more similar than divergent and supportive of the relative benefit of GST in HCAP.

Study limitations include the use of administrative data to establish a pneumonia diagnosis. However, an enhanced ICD-9 based algorithm demonstrated to be superior to other claims-based definitions of pneumonia was utilized.^{7, 8} While the sensitivity and specificity to identify pneumonia cases approached 90%, diagnoses were only validated at one facility and a possibility is that we underestimated pneumonia cases. Further, some patients could have developed HAP during hospitalization as opposed to HCAP upon admission; however, inclusion of admissions that received antibiotic therapy within 24 hours, and exclusion of direct transfers from other hospitals minimize this possibility. While antibiotic group designations were based on therapy initiated within 48 hours of admission it was not possible to determine if concomitant infectious conditions were considered in selecting antibiotic therapy. The cohort was comprised primarily of elderly males, and these results may not generalize to other populations.

Future studies should involve confirmation of our findings. In addition, prediction of which patients are most at risk for MDR is sub-optimal for selection of empirical therapy.^{24–26} Further work on predicting which patients should receive empirical therapy directed at MDR is needed. Finally, prospective randomized trials should be conducted in carefully selected HCAP populations that compare regimens with and without single and double coverage for *Pseudomonas aeruginosa*.

In conclusion, the combination of anti-MRSA and anti-pseudomonal antibiotics consistent with guideline

recommendations has increased over time. We identified an interaction between the predicted probability of recovering an organism resistant to antibiotics traditionally used to treat community-acquired pneumonia from culture and receipt of GST in which patients with a high probability of recovering CAP-resistant organisms had reduced 30-day mortality compared to non-GST patients. As GST recipients had increased severity of illness it is not possible to determine if GST is harmful in patients with a low probability of CAP-resistance, or if incomplete correction for selection bias accounts for this finding. Consideration of the magnitude of patient-specific risk of CAP-resistant organisms should be considered when selecting HCAP therapy as to provide appropriately broad coverage for patients with high MDR risk while preventing overtreatment for patients with lesser risk.

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