Published in final edited form as:
Crit Care Med. 2012 August ; 40(8): 2310–2314. doi:10.1097/CCM.0b013e31825151a8.

Comparison of two guideline-concordant antimicrobial combinations in elderly patients hospitalized with severe community-acquired pneumonia

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Abstract

Objective—Two of the guideline-concordant therapies for severe community-acquired pneumonia are either a beta-lactam and fluoroquinolone or beta-lactam and macrolide. However it is unclear if there is a benefit for one vs. the other for elderly patients with severe community-acquired pneumonia.

Design—A retrospective population-based cohort study of patients with community-acquired pneumonia.

Setting—Patients admitted to an intensive care unit of any Department of Veterans Affairs hospital during 5-yr period.

Patients—We included only those patients >65 yrs of age admitted to the intensive care unit with community-acquired pneumonia who received either beta-lactam + fluoroquinolone or beta-lactam + macrolide antibiotic therapy for pneumonia.

Intervention—Not applicable.

Measurements—We used multilevel regression models to examine the effect of beta-lactam + fluoroquinolone vs. beta-lactam + macrolide on each of the outcomes after adjusting for potential confounders using propensity scores.

Main Results—The cohort consisted of 1,989 patients: 98.5% male and a mean age of 74 yrs. For treatment, 44% of subjects received beta-lactam + fluoroquinolone and 56% received beta-lactam + macrolide. Unadjusted 30-day mortality was 27% for beta-lactam + fluoroquinolone and 24% for beta-lactam + macrolide (p = .11). In the multilevel models, the use of beta-lactam + fluoroquinolone was not significantly associated with 30-day mortality (odds ratio 1.05, 95% confidence interval 0.85–1.30). However, the use of beta-lactam + fluoroquinolone was

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The remaining authors have not disclosed any potential conflicts of interest.

significantly associated with increased mean length of stay (incidence rate ratio 1.30, 95% confidence interval 1.27–1.33).

Conclusions—We found no significant difference for 30-day mortality but did demonstrate an association with increase in length of stay associated with the use of beta-lactam + fluoroquinolone. Randomized controlled trials are needed to determine the most effective antibiotics regimes for patients with severe pneumonia.

Keywords

antimicrobial therapy; length of stay; mortality; pneumonia

Pneumonia is the eighth leading cause of death in the United States and is the leading infectious cause of death. Although mortality dropped precipitously with the advent of antimicrobial therapy, since 1950 mortality has been relatively stable despite the development of other interventions. Today it remains a leading cause of mortality with >50,000 deaths annually (1).

In response to the major impact of pneumonia, a number of prominent organizations, including the American Thoracic Society and Infectious Diseases Society of America have published clinical practice guidelines for community-acquired pneumonia (2–7). Previous studies have suggested that the empiric use of beta-lactams alone is associated with increased mortality and that the use of macrolides for patients with community-acquired pneumonia, and no risk factors pneumonia due to *Pseudomonas aeruginosa* or methicillin resistant *Staphylococcus aureus*, is associated with improved outcomes (8–13). In addition, we previously demonstrated an association, for patients hospitalized with severe community acquired pneumonia, between the empiric use of a beta-lactam with a fluoroquinolone and increased 30-day mortality (14).

Despite this, there have been few published studies examining guideline-concordant therapy with the combination of a beta-lactam plus a fluoroquinolone (BL+F) as compared to guideline concordant therapy with a beta-lactam plus a macrolide (BL+M) for patients hospitalized with severe community-acquired pneumonia. Therefore, the aim of this study was to examine the association between these antibiotic treatment regimens and important clinical outcomes, including 30-day mortality and length of hospital stay for patients > 65 yrs of age hospitalized with severe, community-acquired pneumonia.

METHODS

We conducted a population-based cohort study utilizing the administrative databases of the Department of Veterans Affairs (VA). These VA databases are the repositories of clinical data from approximately 160 VA hospitals and 850 VA clinics. The University of Texas Health Science Center at San Antonio Institutional Review Board approved the parent study and waived the need for informed consent.

Inclusion/Exclusion Criteria

We identified all patients admitted to one of the study hospitals between fiscal year 2002 and fiscal year 2007 (October 1, 2001–September 30, 2007) with a primary discharge diagnosis of pneumonia (International Classification of Diseases-9 codes 480.0–483.99 or 485–487.0) or secondary discharge diagnosis of pneumonia with a primary diagnosis of respiratory failure (518.81) or sepsis (038.xx). Subjects were included if they met the following inclusion criteria:

1) Were ≥65 on the date of admission;

2) Had at least 1 yr of VA outpatient care prior to admission;

3) Required ICU level care during the first 48 hrs of hospitalization; and

4) Received at least 1 dose of antibiotics within 48 hrs of admission.

To restrict the study to patients with community-acquired pneumonia, patients were excluded if they met one of the following potential risk factors for healthcare associated pneumonia:

1) Were hospitalized in the previous 90 days;

2) Were a resident of a nursing home at the time of hospitalization;

3) Had prior use of antibiotics within 90 days of hospitalization; or

4) Had a history of immunosuppression (e.g., human immunodeficiency virus/ acquire immunodeficiency syndrome, chemotherapy).

Data Sources

These databases contain information gathered from the following VA administrative databases: National Patient Care Database (contains demographics, comorbid conditions, discharge diagnoses), Decision Support System database (utilization, laboratory test results), Pharmacy Benefits Management database (inpatient and outpatient medications), and vital status file (mortality data).

We obtained demographic information (age, sex, race, marital status) from inpatient and outpatient data. Race categories included white, black, Hispanic, and other/unknown. To infer current efforts at smoking use and/or cessation we identified International Classification of Diseases, -Ninth Edition codes for tobacco use (305.1, V15.82), smoking cessation clinic use, and/or use of medications for the treatment of nicotine dependence (Zyban, GlaxoSmithKline, Brentford, United Kingdom), nicotine replacement, or varenicline).

We also obtained information on comorbid conditions from inpatient and outpatient administrative data. We used Charlson's comorbidity methodology to classify other preexisting comorbid conditions, both individually and as a composite score (15, 16). Charlson's comorbidity system includes 19 comorbid conditions, which are classified using International Classification of Diseases, -Ninth Edition codes from prior outpatient and

inpatient encounters (17). For severity of illness we assessed the need for mechanical ventilation and/or vasopressors within 48 hrs of admission.

Antimicrobial Therapy

For this study, patients were included in the BL+F group if they received at least one beta-lactam and at least one fluoroquinolone, but did not receive any macrolides within 48 hrs of admission. Similarly, the BL+M cohort was made up of patients whom received at least one beta-lactam and at least one macrolide, but did not receive any fluoroquinolones. We excluded those patients who received both fluoroquinolones and macrolides within 48 hrs of admission. Appropriate beta-lactams included ampicillin, cefepime, cefotaxime, ceftriaxone, cefuroxime, imipenem, ertapenem, ampicillin sulbactam, ticarcillin-calvulanate, meropenem, and piperacillin/tazobactam. Fluoroquinolones included gatifloxacin, levofloxacin, and moxifloxacin. Macrolides included azithromycin, clarithromycin, and erythromycin.

Outcomes

Outcomes included 30-day mortality and length of hospital stay. We chose to examine mortality at 30-days, as previous research has demonstrated that 30-day mortality is due primarily to pneumonia rather than comorbid conditions (18, 19). Mortality was assessed through October 1, 2007, using the VA vital status file. Previous studies have demonstrated that this methodology has a sensitivity of ~98% for veterans' deaths (20). Length of stay is also of additional interest in that it may represent a potential indicator of both inpatient treatment costs and time to clinical stability (21).

Statistical Analysis

Statistical significance was defined as two-tailed $p \leq .05$. We examined univariate relationships using Student's *t* tests for the continuous variables, and chi-square tests for the binary variables.

A propensity score technique was used to balance covariates associated with antimicrobial therapy between groups. This propensity score was derived from a logistic regression model using the dichotomous treatment indicator as the predictor variable. We included those variables that were statistically signifi-cant in univariate analyses (two-tailed $p \leq .05$) or that we hypothesized *a priori* would be associated with outcomes or with the treatments of interest. The covariates used in the propensity score model were age, sex, race, marital status, comorbid conditions, priority group (a marker for socioeconomic status), current tobacco cessation attempts, alcohol or drug abuse, the number of primary care visits during the year prior to admission, the need for mechanical ventilation, and the need for vasopressors.

For our primary analyses, we used multilevel regression models (logistic or Poisson as appropriate) to examine the effect of BL+F vs. BL+M (reference group) on each of the outcomes after adjusting for an ordered categorical variable based on quintile stratification of the propensity score with admitting hospital as a second level variable. As a secondary

analysis, we included only those subjects who received antipseudomonal therapy and repeated the multilevel regression analysis.

Analyses were performed using STATA 10 (StataCorp LP, College Station, TX).

RESULTS

The cohort was composed of 1,989 subjects who met the inclusion and exclusion criteria with a mean age of 74 yrs (SD 6.5) and 98.5% were male. The majority of the cohort was white (81.5%), with black race and Hispanic ethnicity making up 12.2% and 5%, respectively. The most common comorbid conditions were diabetes (34%), congestive heart failure (27%), and malignant neoplasms (20%).

The study cohort had 30-day all-cause mortality of 25.6%. Table 1 shows factors by vital status at 30-days after admission. Those alive at 30 days had a lower mean age (73.6 vs. 75.3, $p < .001$), a lower rate of liver disease (0.5% vs. 2%, $p = .02$), and a lower rate of malignant neoplasms (19% vs. 23%, $p = .02$); but also a higher rate of smoking cessation efforts (37% vs. 29%). Survivors had a significantly lower rate of mechanical ventilation (35% vs. 51%, $p < .001$) and vasopressor use (20% vs. 35%, $p = .005$).

We also compared subjects by treatment type (Table 2). The clinical and demographic characteristics of the BL+F and BL+M groups were quite similar. Patients in the BL+F group had a slightly higher average age (74.6 yrs vs. 73.6 yrs, $p < .001$) and a lower rate of current attempts at smoking cessation (31% vs. 38%, $p = .003$). The BL+F group also had a lower percentage of white patients (78% vs. 84%, $p < .001$) and a higher percentage of black patients (15% vs. 10%, $p < .001$). Although mortality was similar between treatment types (27% for BL+F vs. 24% for BL+M, $p = .11$), patients treated with BL+F had a significantly longer length of hospital stay (21.0 days vs. 15.9 days, $p < .001$) (Table 2).

After adjusting for potential confounding factors (Table 3), 30-day mortality was similar between treatment groups (odds ratio 1.05, 95% confidence interval 0.85–1.30). However, BL+F use was significantly associated with longer length of hospital stay (incidence rate ratio 1.30, 95% confidence interval 1.27–1.33). When we restricted the analysis to only those who received antipseudomonal therapy (n = 813), results were similar with no significant difference in 30-day mortality (odds ratio 0.80, 95% confidence interval 0.62–1.04) but significantly longer length of hospital stay for the BL+F group (incidence rate ratio 1.20, 95% confidence interval 1.16–1.24).

DISCUSSION

In our study, the use of BL+F was associated with a longer average length of hospital stay compared to those treated with BL+M; however, there were no significant differences found in 30-day mortality. Clinical guidelines published by major medical societies represent valuable tools for maximizing the efficacy of medical interventions, and thus, reducing the complications associated with pneumonia (8, 19, 22). Despite this, our results support previous evidence demonstrating that treatment with BL+ M may be the more preferable choice (23). These results raise questions regarding the current recommendations that do not

specify which antibiotic combinations (BL+M or BL+F) are the more preferable treatment for severe community-acquired pneumonia. Therefore, there is a need for randomized controlled trials that assess the relative efficacy of the specific antimicrobial therapies recommended by these guidelines.

Several studies in the past have found that the use of a BL+M is significantly associated with lower mortality (8–10, 13). On the other hand, other studies have demonstrated that monotherapy with beta-lactam is associated with worse clinical outcomes (8, 10, 13, 24). There are a few studies that have compared the antibiotic combination of BL+F with antibiotic combination BL+M (9, 13, 14, 25), and there were no significant differences found, except for one study. However, many of these studies had significant limitations (i.e., the lack of multivariable analyses, or too few subjects) to be able to appropriately examine this antimicrobial combination.

It seems unlikely that the difference in length of hospital stay between the two antibiotic treatment combinations stems from a difference in bacterial coverage. One possible explanation for the improved outcomes associated with the use of macrolides may be due to their previously demonstrated anti-inflammatory activity (26–29). This is supported by the previously demonstrated role of cytokines as mediators of acute respiratory distress syndrome, sepsis, and a number of pneumonia's negative prognostic factors (30–35). Therefore, we hypothesize that an antibiotic regimen, which includes a macrolide, will be more potentially protective when compared to antibiotic regimens without a macrolide. Another potential explanation is that recent studies suggest that fluoroquinolone use in intensive care unit patients is associated with increased risk for hospital-acquired multidrug resistant pathogens, which may also increase mortality and length of stay (36, 37).

There are a number of limitations to our analysis. The largest limitation was reliance on administrative data. Therefore, information such as the Acute Physiology and Chronic Health Evaluation score, duration of mechanical information, and inhospital complications (e.g., Clostridium difficile infections) were not available. We feel confident that our inclusion criteria requiring intensive care unit level of care during the first 48 hrs of admission allowed us to identify subjects with comparable levels of illness. In addition, due to the design of the primary study, we did not have information regarding duration of antibiotic therapy nor subsequent antibiotic regimes. Also, <2% of the VA patient population is female, which limits its generalizability. Additionally, male veterans may not be representative of the population as a whole. Another limitation is the inability to adjust for microbiology and antimicrobial resistance patterns at each patient's place of treatment. While these factors could impact the efficacy of the two antibiotic regimes, the use of data from the entire VA healthcare system makes it likely that results represent the general population rather than the nuances of a specific institution. Lastly, another limitation was that we were unable to determine if the reason for the use of one antibiotic combination vs. the other was due to increased severity of illness. Furthermore, as with any nonrandomized study, we are unable to state conclusively that differences in length of stay are due to the antibiotic received and not differences in patient characteristics at baseline.

In conclusion, although we did not find a significant difference in mortality between patients treated with BL+F vs. BL+M, there were significant differences in length of hospital stay, which is potentially associated with higher costs of healthcare and resource utilization. Therefore, clinically appropriate clinicians should preferably use BL+M for the treatment of severe community-acquired pneumonia. Further research is needed to determine which antimicrobial regimens provide the best outcomes for patients with severe community-acquired pneumonia.

Acknowledgments

The project described was supported by Grant Number R01NR010828 from the National Institute of Nursing Research. Dr. Restrepo is supported by grant K23HL096054 from the National Heart, Lung, and Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Nursing Research or the National Institutes of Health. Dr. Marcos I. Restrepo participated in advisory boards for Theravan, Forest Laboratories, Johnson and Johnson, and Novartis and was a consultant for Trius, Theravan and Pfizer (Wyeth). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Department of Veterans Affairs and National Institutes of Health. This material is the result of work supported with resources and the use of facilities at the South Texas Veterans Health Care System. The funding agencies had no role in conducting the study, or role in the preparation, review, or approval of the manuscript.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

Drs. Restrepo and Mortensen received funding from the National Institute of Health K23HL096054.

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Table 1

Patient demographics and clinical characteristics by 30-day mortality

	30-day mortality N (%)		
Variable	**Alive (n = 1479)**	**Dead (n = 510)**	***p***
Demographics			
Age, mean (sd)	73.6 (6.5)	75.3 (6.6)	<.001
Male	1,456 (98)	510 (100)	.77
White	1,203 (81)	419 (82)	.69
Black	192 (13)	50 (10)	.06
Hispanic	78(5)	20(4)	.22
Married	771 (52)	262 (51)	.77
Pre-existing comorbid conditions			
Myocardial infarction	97(7)	33(7)	.95
Congestive heart failure	397 (27)	136 (27)	.94
Peripheral vascular disease	223 (15)	72 (14)	.60
Cerebrovascular disease	242 (16)	102 (20)	.07
Dementia	50(3)	21(4)	.45
Chronic obstructive pulmonary disease	812 (55)	263 (52)	.20
Rheumatologic disease	39(3)	15(3)	.72
Peptic ulcer	46 (3)	11 (2)	.26
Diabetes mellitus	506 (34)	166 (33)	.50
Diabetes w/complications	141 (10)	49 (10)	.97
Mild liver disease	8 (0.5)	9 (2)	.02
Hepatic failure	4 (0.3)	5 (1)	.06
Hemi/paraplegia	21 (1)	4 (1)	.25
Chronic renal disease	196 (13.3)	63 (12)	.61
Malignant neoplasm	275 (19)	119 (23)	.02
Multiple myeloma/leukemia	33 (2)	16 (3)	.27
Metastatic solid tumor	26 (2)	20 (4)	.007
Other characteristics			
Tobacco cessation attempt	548 (37)	150 (29)	.002
Alcohol abuse	71 (5)	19 (4)	.31
Drug abuse	19 (1)	5 (1)	.58
Primary care clinic visits during prior year, mean (sd)	4.50 (3.96)	4.31 (3.53)	.33
Severity of illness			
Use of mechanical ventilation	523 (35)	260 (51)	< .001
Use ofvasopressors	291 (20)	180 (35)	.005

Table 2

Patient demographics and clinical characteristics by treatment

Variable	Treatment N (%)		
	Beta-Lactam + Fluoroquinolone (n = 883)	Beta-Lactam + Macrolide (n = 1,106)	*p*
Demographics			
Age, mean (SD)	74.6 (6.5)	73.6 (6.6)	< .001
Male	868 (98)	1091 (99)	.53
White	688 (78)	934 (84)	< .001
Black	136 (15)	106 (10)	< .001
Hispanic	37(4)	61(6)	.17
Married	443 (50)	590 (53)	.005
Pre-existing comorbid conditions			
Myocardial infarction	52 (6)	78 (7)	.3
Congestive heart failure	248 (28)	285 (26)	.25
Peripheral vascular disease	135 (15)	160 (14)	.61
Cerebrovascular disease	154 (17)	190 (17)	.88
Dementia	35 (4)	36 (3)	.4
Chronic obstructive pulmonary disease	463 (52)	612 (55)	.20
Rheumatologic disease	22 (3)	32 (3)	.59
Peptic ulcer	25 (3)	32 (3)	.94
Diabetes mellitus	295 (33)	377 (34)	.75
Diabetes with complications	82 (9)	108 (10)	.72
Mild liver disease	11 (1)	6 (0.5)	.09
Hepatic failure	4 (0.5)	5 (0.5)	1.00
Hemi/paraplegia	15 (2)	10 (0.9)	.12
Chronic renal disease	110 (13)	149 (14)	.51
Malignant neoplasm	185 (21)	209 (19)	.25
Multiple myeloma/leukemia	30 (3)	19 (2)	.017
Metastatic solid tumor	24 (3)	22 (2)	.29
Other characteristics			
Tobacco cessation attempt	278 (31)	420 (38)	.003
Alcohol abuse	38 (4)	52 (5)	.68
Drug abuse	8 (0.9)	16 (1)	.27
Primary care clinic visits during prior year, mean (sd)	4.32 (3.82)	4.57 (3.87)	.33
Severity of illness			
Use of mechanical ventilation	378 (43)	405 (37)	.005
Use ofvasopressors	242 (27)	229 (20.7)	.005
Outcomes			
Length of stay, mean (sd)	21.0 (25)	15.9 (17)	< .001
30-day mortality	242 (27)	265 (24)	.11

Table 3

Results of multilevel regression analyses

Outcome	All (n = 1989)	Treatment N (%)		Adjusted Odds Ratio/ Incidence Rate Ratio (95% Confidence Interval)	*p*
		Beta-Lactam + Fluoroquinolone (n = 883)	Beta-Lactam + Macrolide (n = 1106)		
Mortality at 30 days	510 (25.6)	242 (27.4)	268 (24.2)	1.05 (0.85–1.30)	.11
Length of stay in days, mean (sd)	18.2 (20.9)	21.0 (24.7)	15.9 (16.9)	1.30 (1.27–1.33)	< .001