Combination Antibiotic Therapy for Patients Hospitalized with Community-Acquired Bacterial Pneumonia

S. Eapen, PhD;[1] C. J. Llop, BSc;[1] E. G. Tuttle, MBA[2]

[1] Analysis Group, Inc., Boston, MA

[2] Analysis Group, Inc., Menlo Park, CA

Disclosure: Research funding provided by Cempra, Inc.

Interscience Conference on Antimicrobial Agents and Chemotherapy
September 8 2014, Washington, DC

Background

- Community-acquired bacterial pneumonia (CAP)
  - Global community-acquired pneumonia incidence rate of 5–11 per 1,000 population[4]
  - A majority of cases involve bacterial infection[6]
  - Associated with considerable burden and frequent hospitalization (up to 68.8% of patients)[1–6]
- CAP commonly treated empirically
  - Rapid selection and initiation of appropriate antibiotic therapy associated with improved outcomes[6]
  - Timely microbiological identification typically not possible
  - Numerous treatment options with varying profiles for resistance and adverse events
- Combination antibiotic therapy is commonly used in cases of CAP requiring hospitalization, providing broad empirical pathogen coverage

1. Woodhead M: Community-acquired pneumonia in Europe: causative pathogens and resistance patterns. Eur Respir J Suppl 2002, 36:20s–27s.
2. Welte T: Risk factors and severity scores in hospitalized patients with community-acquired pneumonia: prediction of severity and mortality. *Eur J Clin Microbiol Infect Dis* 2012, 31:33–47.
3. Welte T, Kohnlein T: Global and local epidemiology of community-acquired pneumonia: the experience of the CAPNETZ Network. *Semin Respir Crit Care Med* 2009, 30:127–135.
4. Brar N, Niederman M: Management of community-acquired Pneumonia. *Ther Adv Resp Dis.* 2011, 5(1):61-78.
5. Capelastegui A, Espana PP, Bilbao A, Gamazo J, Medel F, Salgado J, Gorostiaga I, Esteban C, Altube L, Gorordo I, Quintana JM: Study of community-acquired pneumonia: incidence, patterns of care, and outcomes in primary and hospital care. *J Infect* 2010, 61:364–371.
6. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, Ortqvist A, Schaberg T, Torres A, van der Heijden G, Read R, Verheij TJ: Guidelines for the management of adult lower respiratory tract infections--full version. *Clin Microbiol Infect* 2011, 17(Suppl 6):E1–E59.

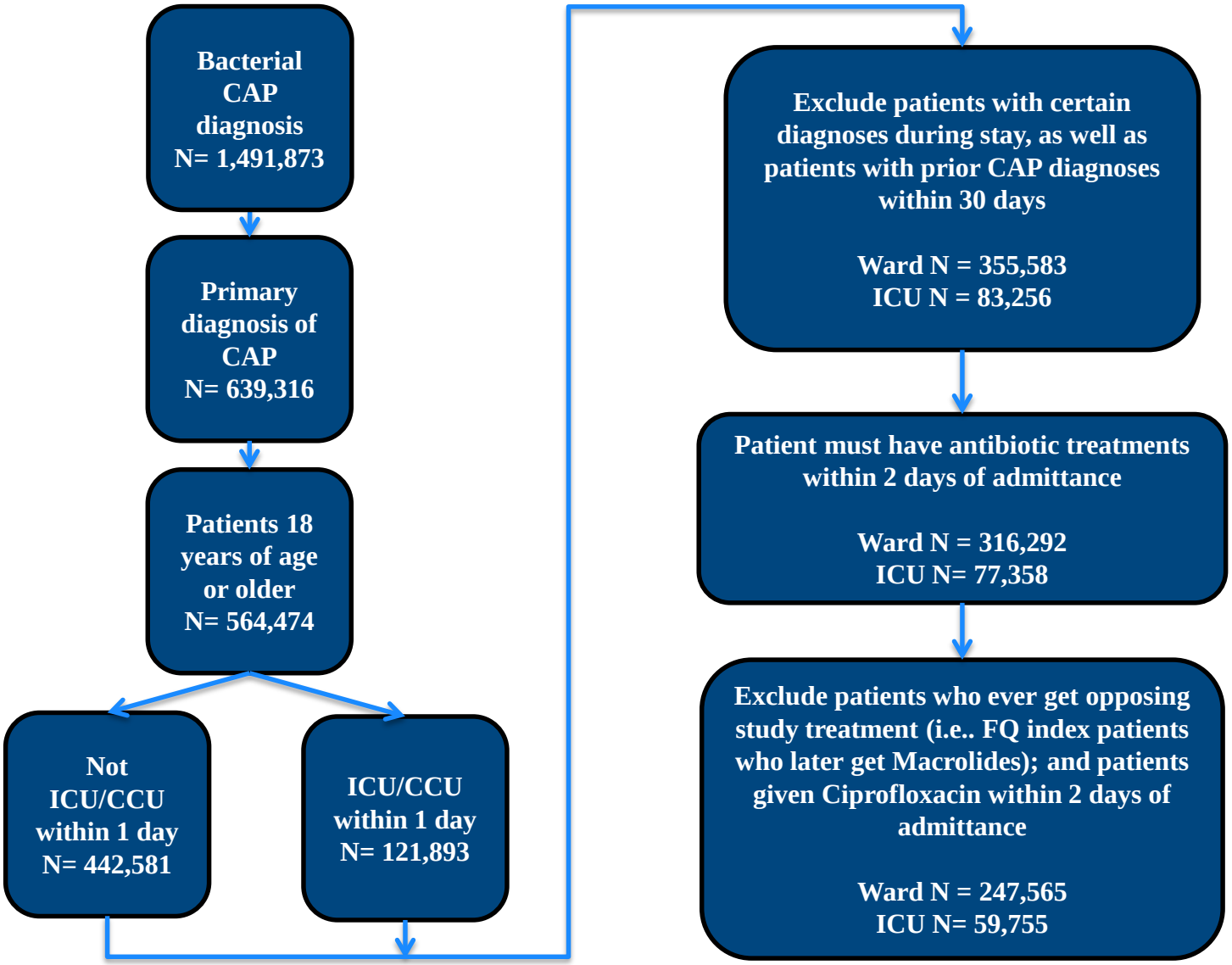
Study Objectives

1. Describe combination antibiotic treatment patterns for CAP patients in hospital general ward and ICU/CCU settings
2. Evaluate differences in outcomes among common treatment combinations including rates of in-hospital adverse events, mortality, and CAP-related re-hospitalizations at 30 days following index CAP episode

Data Source and Methods

- Retrospective cohort study using Truven Health MarketScan Hospital Drug Database
  - Including data from about 600 US-based hospitals (teaching and non-teaching)
  - Capturing in-patient information on demographic and clinical characteristics, and medical and pharmacy resource utilization
  - Covering January 2007 through December 2012
  - Final results differ slightly from those provided in the abstract due to the inclusion of additional ICU data from a larger group of hospitals
- Descriptive analysis of treatment patterns
  - Frequency counts and percentages used to summarize categorical variables; means and standard deviations reported for continuous variables
  - Categorical outcome variables compared, by type of initial antibiotic therapy, using Chi-Squared test and Wilcoxon Ranked-Sum test was used for continuous outcome variables
- Evaluation of differences in outcomes
  - Rates of adverse events, mortality, and re-hospitalization compared by type of initial antibiotic therapy using multivariate models controlling for age, gender, comorbidities, record of a chest x-ray, and length of hospital stay

Sample selection



Sample selection (cont.)

- This study compares the classes most frequently combined, macrolide/beta-lactam (M/BL) and fluoroquinolone/beta-lactam (F/BL)

	Ward	ICU/CCU	All
All Patients	247,565	59,755	307,320
Monotherapy	96,222 (39%)	21,034 (35%)	117,256 (38%)
Combination Therapy	151,343 (61%)	38,721 (65%)	190,064 (62%)
Combination Therapy	151,343	38,721	190,064
M/BL	81,171 (54%)	16,798 (43%)	97,969 (52%)
F/BL	26,200 (17%)	7,223 (19%)	33,423 (18%)
Other	43,972 (29%)	14,700 (38%)	58,672 (31%)

Key patient demographic and clinical characteristics

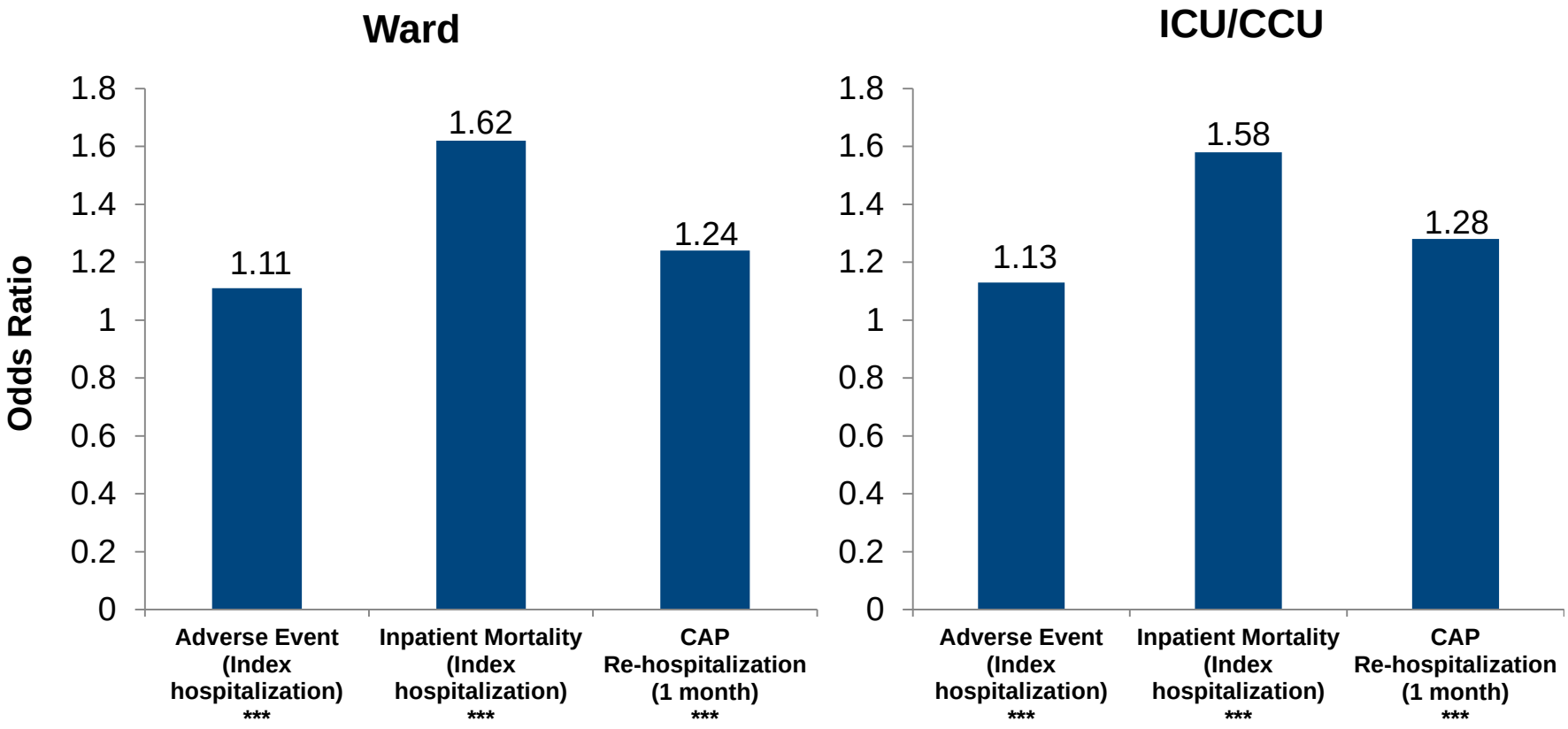
Ward Parameters	Macrolide + Beta-Lactam	Fluoroquinolone + Beta-Lactam
	N = 81,171	N = 26,200
Age (yrs), Mean ± SD***	66.0 ± 18.5	67.4 ± 17.5
Total Length of Stay (days), Mean ± SD***	4.3 ± 3.0	5.1 ± 3.8
Health Index, Mean ± SD***	1.6 ± 1.6	1.9 ± 1.8
Male, %	46.9%	46.6%

ICU/CCU Parameters	Macrolide + Beta-Lactam	Fluoroquinolone + Beta-Lactam
	N = 16,798	N = 7,223
Age (yrs), Mean ± SD***	67.8 ± 17.1	69.3 ± 16.3
Total Length of Stay (days), Mean ± SD***	4.6 ± 3.3	5.5 ± 4.1
Health Index, Mean ± SD***	1.8 ± 1.6	2.1 ± 1.8
Male, %	49.1%	49.3%

*P-value < 0.05 for starred analyses. ** P-value < 0.01 for double starred. *** P-value < 0.0001 for triple starred.

Health Index was calculated by evaluating the presence of the following diagnoses during index hospitalization: Myocardial Infarction, Congestive Heart Failure, Peripheral Vascular Disease, Cerebrovascular Disease, Dementia, Chronic Pulmonary Disease, Rheumatologic Disease, Peptic Ulcer Disease, Mild Liver, Mild to Moderate Diabetes, Chronic Diabetes, Hemiplegia, Renal Disease, Malignancy (including lymphoma and leukemia), Liver Disease, Metastatic Solid Tumor. Certain diagnoses were weighted to be more 'unhealthy' than others: HIV (*6), Metastatic Solid Tumor (*6), Liver Disease (*3), Malignancy (*2), Renal Disease (*2), Hemiplegia (*2), and Chronic Diabetes (*2). For specific ICD9 codes, please see the Appendix.

Adjusted outcomes – F/BL vs. M/BL*



*P-value < 0.05 for starred analyses. ** P-value < 0.01 for double starred. *** P-value < 0.0001 for triple starred.

Adjusted Odds Ratio calculated using logistic regression, adjusting for age, gender, health index, length of stay, and presence of a chest x-ray during the stay. A ratio above 1 indicates a greater risk attributed to the F/BL treatment.

Ward and ICU/CCU, adjusted outcomes F/BL vs. M/BL

Inpatient Analysis - Adverse Event Overview
Odds Ratio and 95% Confidence Intervals of F/BL vs. M/BL Treatment - Logistic Results

	Ward (F/BL vs. M/BL)		ICU (F/BL vs M/BL)	
	Odds (95% Inter.)	p-value	Odds (95% Inter.)	p-value
Any AE	1.11 (1.08-1.14)	<0.0001	1.13 (1.07-1.20)	<0.0001
Mortality	1.62 (1.43-1.83)	<0.0001	1.58 (1.25-1.98)	<0.0001
CAP Rehospitalization	1.24 (1.17-1.32)	<0.0001	1.28 (1.13-1.45)	<0.0001
Clostridium Difficile & Entercolitis	1.20 (1.00-1.44)	0.0499	1.58 (1.14-2.19)	0.0055
Peripheral Neuropathy	1.17 (1.05-1.32)	0.0065	0.95 (0.74-1.21)	0.6608
Tendonitis	1.20 (0.85-1.70)	0.3031	0.48 (0.16-1.47)	0.2003
Digestive Effects	1.13 (1.08-1.19)	<0.0001	1.12 (1.02-1.24)	0.0210
Centeral Nervous System Effects	0.99 (0.94-1.04)	0.6294	0.93 (0.84-1.03)	0.1511
Skin Reactions	0.98 (0.87-1.10)	0.7417	0.93 (0.73-1.19)	0.5642
Hepatotoxicity	1.06 (0.82-1.35)	0.6662	1.03 (0.62-1.69)	0.9227
Hematologic Toxicity	1.12 (1.08-1.16)	<0.0001	1.19 (1.12-1.27)	<0.0001
Total N	107,371		24,021	

Limitations

- It is difficult to rule out other potential drivers of the results. Particularly, since the database is derived from billing systems, it is difficult to account fully for disease severity
- Because the MarketScan dataset is made up of billing records from multiple hospitals, we are only able to track re-hospitalization if it occurs at the same hospital as the original index visit

Conclusions

- This study provides detailed, comprehensive data for examining hospital care, including drug utilization, among hospitalized CAP patients
  - 62% of the sample were treated with combination class therapy (61% Ward, 65% ICU)
  - Of these, 69% were treated with BL, either in combination with M or FQ

- In the combination therapy cohorts, M/BL and F/BL based regimens appear to be associated with differences in outcomes that persist even when patient differences are accounted for
  - In the Ward, CAP patients treated with F/BL had an increased risk of adverse events, including *Clostridium difficile* or enterocolitis, peripheral neuropathy, digestive effects, and hematologic toxicity; mortality; and 30-day CAP re-hospitalization when compared to patients treated with M/BL
  - In the ICU, CAP patients treated with F/BL had an increased risk of adverse events, including *Clostridium difficile* or enterocolitis, digestive effects, and hematologic toxicity; mortality; and 30 day CAP re-hospitalization when compared to patients treated with M/BL

Previous Results

- Previous research using Truven Health MarketScan Hospital Drug Database was presented in May 2014 at the 24th European Congress of Clinical Microbiology and Infectious Diseases
- This previous study only analyzed patients admitted to the ICU while the current research includes non-ICU as well as a larger sample of ICU inpatients
- A small number of ICU patients (n=732) receiving index ciprofloxacin were included in the F/BL groups in the earlier research but have been excluded in the current study due to that agent's profile against S. pneumoniae
- Results of the previous study in the ICU were comparable with this one: patients treated with F/BL in the ICU showed an increased risk of *Clostridium difficile* and hematologic toxicities, in-hospital mortality, and CAP related re-hospitalization within 30 days when compared to M/BL patients

Appendix

- Health Index was calculated by evaluating the presence of the following diagnoses during index hospitalization: Myocardial Infarction (410.xx, 412.xx), Congestive Heart Failure (402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.xx, 428.xx, 429.3x), Peripheral Vascular Disease (440.xx, 441.xx, 442.xx, 443.1x, 443.2x, 443.3x, 443.4x, 443.5x, 443.6x, 443.7x, 443.8x, 443.9x, 447.1x, 785.4x), Cerebrovascular Disease (362.34, 430.xx, 431.xx, 432.xx, 433.xx, 434.xx, 435.xx, 436.xx, 437.0x, 437.1x, 437.9x, 438.xx, 781.4x, 784.3x, 997.0x), Dementia (290.xx, 331.0x, 331.1x, 331.2x), Chronic Pulmonary Disease (415.0x, 416.8x, 416.9x, 491.xx, 492.xx, 493.xx, 494.xx, 496.xx), Rheumatologic Disease (710.xx, 714.xx), Peptic Ulcer Disease (531.xx, 532.xx, 533.xx, 534.xx), Mild Liver Disease (571.2x, 571.5x, 571.6x, 571.8x, 571.9x), Mild to Moderate Diabetes (250.0x, 250.1x, 250.2x, 250.3x), Chronic Diabetes (250.4x, 250.5x, 250.6x, 250.7x, 250.8x, 250.9x), Hemiplegia (342.xx, 344.xx), Renal Disease (585.xx, 586.xx, V42.0x, V45.1x, V56.xx), Malignancy (including lymphoma and leukemia) (14x.xx, 15x.xx, 16x.xx, 170.xx, 171.xx, 174.xx, 175.xx, 176.xx, 177.xx, 178.xx, 179.xx, 18x.xx, 190.xx, 191.xx, 192.xx, 193.xx, 194.xx, 195.xx, 200.xx, 201.xx, 202.xx, 203.xx, 204.xx, 205.xx, 206.xx, 207.xx, 208.xx, 273.0x, 273.3x, V10.46), Liver Disease (572.2x, 572.3x, 572.4x, 456.0x, 456.1x, 456.2x), Metastatic Solid Tumor (196.xx, 197.xx, 198.xx, 199.xx), and AIDS (042.xx, 043.xx, 044.xx). Certain diagnoses were weighted to be more ‘unhealthy’ than others: HIV (*6), Metastatic Solid Tumor (*6), Liver Disease (*3), Malignancy (*2), Renal Disease (*2), Hemiplegia (*2), and Chronic Diabetes (*2).