Azithromycin and Survival In Streptrococcus pneumoniae Pneumonia: A Retrospective Study

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Azithromycin and Survival In *Streptrococcus pneumoniae* Pneumonia: A Retrospective Study

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ARTICLE SUMMARY

Article focus

-To determine the impact of azithromycin co-therapy on outcomes in *Streptococcus pneumoniae* pneumonia

Key messages

-Azithromycin co-therapy in pneumonia due to *S. pneumoniae* is associated with improved short-term survivial

-This finding is independent of multiple potential confounders including timeliness of antibiotic treatment

Strengths and limitations of this study

-Strengths: large sample of pure *S. pneunmoniae* pneumonia

-Limitations: Data derive from a single center and the study's retrospective design

ABSTRACT

Objective: *S. pneumoniae* (SP) represents a major pathogen in pneumonia. The impact of azithromycin on mortality in SP pneumonia remains unclear. Recent safety concerns regarding azithromycin have raised alarm about this agent's role with pneumonia. We sought to clarify the relationship between survival and azithromycin use in SP pneumonia.

Design: Retrospective cohort.

Setting: Urban, academic hospital.

Participants: Adults with a diagnosis of SP pneumonia (Jan-Dec 2010). The diagnosis of pneumonia required a compatible clinical syndrome and radiographic evidence of an infiltrate.

Intervention: None

Primary and secondary outcome measures: Hospital mortality served as the primary endpoint, and we compared subjects given azithromycin to those not treated with this. Co-variates of interest included demographics, severity of illness, comorbidities, and infection related characteristics (eg, appropriateness of initial treatment, bacteremia). We employed logistic regression to assess the independent impact of azithromycin on hospital mortality.

Results: The cohort included 187 subjects (mean age: 67.0 ± 8.2 years, 50.3% male, 5.9% admitted to the ICU). The most frequently utilized non-macrolide antibiotics included: ceftriaxone (n=111), cefipeme (n=31), and moxifloxacin (n=22). Approximately 2/3rds of the cohort received azithromycin. Crude mortality was lower in persons given azithromycin (5.6% vs. 23.6%, $p<0.01$). The final survival model included four variables: age, need for mechanical ventilation, initial appropriate therapy, and azithromycin use. The adjusted odds ratio for mortality associated with azithromycin equaled 0.26 (95% confidence interval: 0.08-0.80, p=0.018).

Conclusions: SP pneumonia generally remains associated with substantial mortality while azithromycin treatment is associated with significantly higher survival rates. The impact of azithromycin is independent of multiple potential confounders.

INTRODUCTION

Pneumonia remains a leading cause of morbidity and mortality. Annually more than 1.3 million patients present to the hospital with pneumonia and require admission.[1] Direct costs related to pneumonia exceed several billion each year in the United States.1 Because of this burden, multiple efforts have focused on improving the care of patient with pneumonia and attempted to address means for enhancing outcomes in this disease and hospitalists often care for and design hospital pathways for those admitted with pneumonia.

Concurrent with these quality efforts, the microbiology of pneumonia presenting to the hospital has evolved. Over the last decade, pathogens traditionally thought confined to the hospital, such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, now are implicated in non-nosocomial pneumonia.[2,3] This epidemiologic trend led to the creation of the concept of healthcare-associated pneumonia (HCAP).[2,3] At the same time, rates of pneumonia in adults due to *Streptococcus pneumoniae* have diminished, in part due to the effects of herd immunity arising from the use of the newer vaccines in children.[4] Nonetheless, *S. pneumoniae* remains a leading pathogen in non-nosocomial pneumonia, whether it be CAP or HCAP and whether it results in mild disease or more severe illness necessitating admission to the intensive care unit (ICU).[5,6] Furthermore, current treatment guidelines for HCAP do not suggest consideration of adjunctive macrolide antibiotics, despite the fact that *S. pneumoniae* can still be seen in this syndrome.[3,5,7] Surveillance studies and epidemiologic reports presently indicate that *S. pneumoniae* often represents either the second or third most frequent pathogen recovered from subjects admitted with pneumonia via the ED.[5,6] Thus, despite it being less prevalent than in prior years, *S. pneumoniae* continues to lead to a disproportionate burden on the healthcare system.

Macrolide antibiotics, particularly azithromycin, are unique as anti-infective agents in that they appear to have potent anti-inflammatory properties.[8] Earlier analyses suggest that azithromycin exposure may confer a mortality advantage in CAP, irrespective of the causative pathogen.[9,10] This

observation has resulted in treatment guidelines recommending utilization of macrolides in CAP and their continuation even if the patient is concurrently being treated with another in vitro active antimicrobial as one potential approach.[11] Many of the reports supporting a survival benefit related to macrolide use in CAP, though, have been limited because they either were conducted in an era before HCAP became a concern or because they often did not account for issues related to rates of initially appropriate antimicrobial administration. These reports have also explored CAP as a syndrome, regardless of the pathogen, and not specifically addressed *S. pneumoniae*. Recent descriptions of potential cardiovascular toxicities arising with azithromycin reinforce the need to elucidate if this agent alters mortality.[12] A potential survival benefit related to azithromycin in *S. pneumoniae* pneumonia would indicate that the risk/benefit calculus favors utilization of this agent not withstanding concerns about rhythm disturbances.

We hypothesized that co-treatment with azithromycin would improve mortality in pneumonia due to *S. pneumoniae* and that this effect would be independent of confounding arising from failure to administer appropriate initial antibiotic therapy. To explore our hypothesis, we conducted a retrospective analysis of all subjects with either CAP or HCAP admitted with evidence of infection related to *S. pneumoniae*.

METHODS

Study Overview and Subjects

We retrospectively identified all adult (age > 18 years) patients admitted with a clinical diagnosis of pneumonia between January 1, 2010 and December 31, 2010. All patients were required to have initially presented to the ED. We defined pneumonia based on both signs and symptoms of infection (ie, elevated white blood cell count or > 10% band forms, fever or hypothermia). We further required compatible chest imaging documenting an infiltrate(s). One investigator (MHK), blinded to the clinical and microbiologic information adjudicated the chest imaging. Identification of *S. pneumoniae* was based on the results of cultures from either blood, pleural fluid, sputum, or the lower airways. A positive urinary antigen for *S. pneumoniae* also was used to document infection with this pathogen. The patients

described in this report have been previously included in an earlier analysis validating the concept of HCAP.[3] The Washington University School of Medicine Human Studies Committee approved the study (# 201205194). As this was a retrospective analysis, there was no requirement for informed consent.

Endpoints and Co-variates

Hospital mortality represented the primary endpoint. We compared persons with pneumococcal pneumonia initially treated with azithromycin to those not given this agent. During the observation period, this was the only macrolide available for treatment of pneumonia at the study hospital. There were no subjects given clarithromycin. Co-variates of interest included patient demographics, severity of illness, and infection related variables. For demographic factors we noted age, gender, and race. With respect to co-morbidities, we recorded if the subject was residing in a nursing home or long-term care facility, was recently hospitalized in the last 90 days, had received antimicrobials in the last 30 days, suffered from end stage renal disease requiring hemodialysis, or was immunosuppressed. We defined immunosuppression based on the presence of either acquired-immunodeficiency syndrome (AIDS), active malignancy undergoing chemotherapy, or treatment with immunosuppressants (ie, 10 mg prednisone or equivalent daily for at least 30 days or alternate agents such as methotrexate). To assess disease severity we calculated the CURB-65 score along with recording if there was a need for either ICU care or mechanical ventilation (MV).[13] With respect to infection-related variables we determined if bacteremia complicated the pneumonia and the initial antibiotic regimen. We classified the initial antibiotic regimen as appropriate if a non-macrolide antibiotic that was *in vitro* active against the *S. pneumoniae* isolate was administered within 6 hours of presentation. At the host institution, antibiotic administration is protocolized such that all subjects received a non-macrolide anti-infective with activity against pneumoccocus. Therefore, appropriateness of antibiotics was a reflection of the timeliness of administration. Additionally, by convention, patients given combination treatment including azithromycin received these drugs concurrently.

Statistics

We completed univariate analyses with either the Fisher's exact test or Student's t-test as appropriate. Continuous, non-parametrically distributed data was compared via the Mann-Whitney U test. All analyses were two tailed, and a p value of < 0.05 was assumed to represent statistical significance. To determine independent factors associated with mortality, we employed logistic regression. Variables significant at $P<0.10$ level in univariate analyses were entered into model. To arrive at the most parsimonious model we utilized a step-wise backward elimination approach. Co-linearity was explored with correlation matrices. Adjusted odds ratios (AORs) and ninety-five percent confidence intervals (CIs) are reported where appropriate. The model's goodness-of-fit was assessed via calculation of the R^2 value and the Hosmer-Lemeshow c-statistic. All analyses were performed with SPSS 19.0 (SPSS, Chicago, IL).

RESULTS

During the study period 977 persons were admitted via the ED with evidence of bacterial pneumonia. Of these patients, 187 were infected with *S. pneumoniae*. The mean age of these subjects was 57.0 +/- 8.2 years and approximately half were male. The crude hospital mortality in *S. pneumoniae* pneumonia equaled 11.2% while the mean hospital length of stay measured 8.2 +/- 5.0 days. The most commonly utilized non-azithromycin antibiotics were ceftriaxone (n=111), cefipeme (n= 31), and moxifloxacin (n=22).

Table 1 reveals the differences in baseline characteristics between subjects dying while hospitalized and those surviving to discharge. Those who died were older but there were no other differences in demographics. Patients dying were more severely ill based on all measures used to assess this. Specifically, survivors had lower CURB-65 scores as compared to decedents (median CURB-65 class 4 vs 2, p=0.025). More than a quarter of those dying received MV while fewer than 5% of those discharged alive required MV (p=0.001). The distribution of criteria defining HCAP did not differ

between groups. Approximately 11% of all patients resided in nursing homes prior to admission and the rate of admission from nursing homes did not correlate with hospital mortality. Immunosuppression was prevalent in the study population but this also did not differ between those dying and survivors.

With respect to infection-related characteristics, the frequency of bacteremia was similar between the two groups. Compared to those who survived, however, those who died were more likely to have been given delayed antibiotic therapy (61.9% vs. 91.0%, p=0.001). In all instances, inappropriate therapy occurred not because of the use of an *in vitro* inactive agent but because of a delay in the initiation of antibiotics.

Hospital mortality rates were significantly lower in persons treated with azithromycin. Of patients given the macrolide, only 5.6% expired in the hospital as opposed to 23.6% of persons not treated with such an agent (Figure 1). The odds ratio (OR) for death with a macrolide was 0.20 (94% CI: 0.08-0.52).

In the logistic regression, four variables remained independently associated with mortality (Table 2). Mortality increased with increasing age (AOR 1.05, 95% CI: 1.01-1.09, p=0.018) and with the need for MV (AOR 8.82, 95% CI: 2.74-28.46, <0.001). Timely antibiotic therapy resulted in lower in-hospital death rates (AOR, 0.13, 95% CI: 0.03-0.46, p=0.002). Finally, treatment with azithromycin correlated with enhanced survival. Azithromycin exposure was independently associated with a reduced risk for death by nearly 75% (AOR 0.26, 95% CI: 0.08-0.90, p=0.018). Neither being classified as HCAP nor any of the individual criteria defining HCAP stayed in the final model. The model had excellent fit with an R^2 value of 0.42 and a C-statistic of 0.991.

DISCUSSION

This retrospective analysis of a cohort of patients with microbiologically confirmed pneumococcal pneumonia indicates that co-administration of azithromycin is associated with significant reductions in short-term mortality. This effect is independent of multiple potential confounders such as

severity of illness and the timeliness and activity of initial antimicrobial therapy. The positive impact of azithromycin was also independent of whether bacteremia was present.

Prior efforts evaluating the significance of macrolide therapy on outcomes in CAP have reached conflicting conclusions. Some large case series indicate a survival benefit in persons given macrolides while others have failed to detect such an impact. For example, Martin-Loeches and colleagues observed that macrolide use reduced the risk for mortality in intubated patients with CAP.[9] Tessemer et al. in a large observational German trial also noted that macrolide exposure improved cure rates and short-term mortality.[10] In pneumococcal bacteremia complicating pneumonia, Metersky conclude that macrolide use improved 30 day readmission and mortality rates [14]. On the other hand, Asadi and co-workers reported that mortality rates were similar among 3000 patients treated with either monotherapy with a fluroquinolone as opposed to a beta-lactam /macrolide combination.[15] Wilson et al additionally determined that inclusion of a macrolide in the antibiotic regimen failed to enhance survival in elderly patients with CAP.[16] Meta-analyses are similarly conflicting in their assessments. One recent meta-analysis including 16 randomized controlled trials (RCTs) evaluating fluroquinolones against beta-lactam/macrolide combinations calculated that there was no difference in mortality between these regimens.[17] Another group of investigators, though, included both observational reports and RCTs and determined that macrolide administration offered a small but statistically significant mortality benefit.[18]

Our findings add to this debate and are novel in several respects. First, one potential limitation of the above-mentioned studies is that they tend to pool all subjects with CAP, irrespective of culture findings. In contrast, we restricted our evaluation to patients with confirmed *S. pneumoniae* infection whether they had CAP or risk factors for HCAP. Including subjects with either syndrome serves to underscore the need to focus on the pathogen rather than the infectious syndrome. Treatment guidelines currently stratify persons in to two cohorts based on their risk factors for infection with resistant pathogens.[7,11] This scheme ignores the point that pneumococcal infection occurs in both CAP and HCAP. Our results suggest that revision of the guidelines may be appropriate as we noted a mortality benefit with azithromycin even after controlling for factors and co-morbidities which define HCAP.

Furthermore, some of the subjects in earlier reports failed to have either evidence of bacterial infection or were infected with a pathogen other than *S. pneumoniae*. In some instances, only administrative coding data rather than actual culture results facilitated subject identification. This distinction is important in that the immunomodulatory effects of azithromycin have been most clearly elucidated as it relates to infection with *S. pneumoniae*. Although broadly anti-inflammatory in a number of ways, the strongest biologic evidence of a potential means for an impact in pulmonary infection relates to investigations in *S. pneumoniae*. More importantly these effects of macrolides alter both cellular and humoral immunity. *In vitro*, azithromycin, for instance, prevents apoptosis of human polymorphonuclear lymphocytes and may reduce interleukin (IL)-8 production.[19,20] Exposure to azithromycin, furthermore, reduces pneumolysin from both macrolide-susceptible and resistant strains of *S. pneumoniae*.[21] Azithromycin may also reduce production of tumor necrosis alpha and IL-1 alpha in human monocytes and down regulate natural killer cell production with an ensuing alteration in various cytokines.[22] Therefore, by focusing on a specific organism where the nexus with the theoretical mechanisms of immune modulation are better established, our observations help to clarify the discordant findings of others. Our results, in turn, suggest that the benefit of macrolide co-treatment may be restricted to persons with pneumococcal infection

We also specifically controlled for the timeliness of initial therapy. Initially appropriate and timely antibiotic treatment is a key determinant of survival in a number of severe infections ranging from bacteremia to septic shock.[23,24] Many prior studies did not address modification effect related to the prescribing of initial antimicrobial therapy. In most RCTs, adjudicating the coverage and timeliness of initial therapy is clouded by the time window allowed to enroll patients in the specific clinical trial. Some observational reports have failed to explore the importance of this issue in their analytic approaches. Others have simply determined whether an antibiotic regimen was concordant with formal treatment guidelines was given. This constitutes only a surrogate means for evaluating the true appropriateness of antimicrobial treatment as it does not examine specific *in vitro* susceptibilities or the timing of the

antibiotic administration. We, however, specifically sought to rectify and address this limitation by applying specific and clear criteria.

Our overall patient outcomes suggest that our data are broadly generalizable. The crude hospital mortality rate was approximately 10%, as was the prevalence of bacteremia, reflecting what has been noted in multiple epidemiologic analyses.[1] Likewise, the average LOS in our cohort parallels the general LOS for this syndrome described in large analyses of US hospital discharge data. The goodness of fit of our final mortality prediction model was also excellent indicating that there is at most moderate unmeasured residual confounding. Many earlier analyses of case series data have not described either if or how well their modeling of outcomes fits their observations.

Ray and co-workers have sparked concern regarding macrolides and reported potential cardiovascular toxicity associated with azithromycin.[13] In a review of Medicaid claims data from Tennessee, these authors state that deaths due to cardiovascular causes were higher in subjects given azithromycin as compared to either no antibiotic or amoxicillin. This study has led to calls to re-evaluate our utilization of azithromycin.[25] The potential for a mortality benefit accruing with use of this drug in pneumococcal pneumonia should give pause to efforts to reflexively and broadly restrict access to azithromycin. The burden and prevalence of pneumococcal pneumonia suggest that it would be inappropriate for policy makers to mix all types of *S. pneumoniae* infection into one group as they make decisions regarding the availability of this agent. Our results suggest that a measured risk-benefit analysis is still required at the individual patient level.

The present study has several significant limitations. First, its retrospective nature exposes it to several forms of bias. However, there is little potential for ascertainment bias in our primary endpoint of mortality. Second, the data represent the experience from a single center and thus may not be indicative of the experience of others. Likewise we only studied inpatients and so our results do not apply to patients not requiring admission. Third, given the constraints of modern microbiology and culture techniques there are certainly cases of pneumococcal pneumonia we missed. Fourth, only 5% of the population required ICU admission. As such, our results most reflect the experience of less severely ill

subjects and the significance of azithromycin in critically ill persons may be different. These, though, are the patients most often cared for by hospitalists. Finally, the sample size precluded us from examining several important variables such as the exact timing of anti-infective administration (eg, by hour delay from presentation). Sample size also likely explains why some variables were not significant in our final model. That the CURB-65 score failed to represent a correlate of mortality probably arose because other factors associated with survival (eg, need for MV) proved more strongly linked with mortality. With a larger cohort, CURB-65 may have remained in our final model.

In conclusion, co-administration of azithromycin appears to reduce mortality in persons admitted to the hospital with pneumoniae due to *S. pneumoniae*. This affect persists after adjusting for other important variables known to correlate with survival in this syndrome. Given the safety issues that have arisen with azithromycin along with the possible positive impact of this drug on hospital mortality, a randomized trial exploring the role for adjunctive azithromycin relative to placebo in CAP appears not only warranted but urgently needed.

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Dr. Shorr had full access to the data and takes responsibility for the content of the paper including all analyses.

Author contributions

Study concept and design: AFS, MDZ, JH, JK, STM, MHK

Acquisition of data: JH, JK, STM

Analysis and interpretation of data: AFS, MDZ, STM, MHK

Drafting the manuscript: AFS, MDZ, MHK

Critical revision of the manuscript for important intellectual content: AFS, MDZ, JH, JK, STM, MHK

Statistical expertise: AFS, MDZ

Obtained funding: MHK

Study supervision: AFS,MHK

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Data sharing: There are no additional unpublished data available from this study.

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Baseline Characteristics

Table 1.

	Hospital Death (n=21)	Hospital Survival (n=166)	p
Demographics			
-Age, mean±SD, years	66.8±18.23	55.7±15.0	0.002
-Male, %	47.6%	50.6%	0.821
-Race			
Caucasian, %	47.6%	52.4%	0.767
African-American,%	52.4%	46.5%	
Other,%	0. %	1.2%	
Severity of Illness			
-CURB 65 Score, median	4	2	0.025
-ICU Admission, %	22.9%	3.4%	0.001
-Mechanical Ventilation,%	27.8%	4.5%	0.001
Comorbidities			
-LTC admission, %	11.1%	11.2%	0.999
-HD, %	0%	2.4%	0.999
-Immunosuppression, %	33.3%	22.9%	0.289
-Prior antibiotics, %	33.3%	24.1%	0.423
-Recent hospitalization, %	14.1%	8.8%	0.353
Infection-related Characteristics			
-Bacteremia, %	13.7%	8.2%	0.256
-Delay in appropriate antibiotics, %*	61.9%	91.0%	0.001

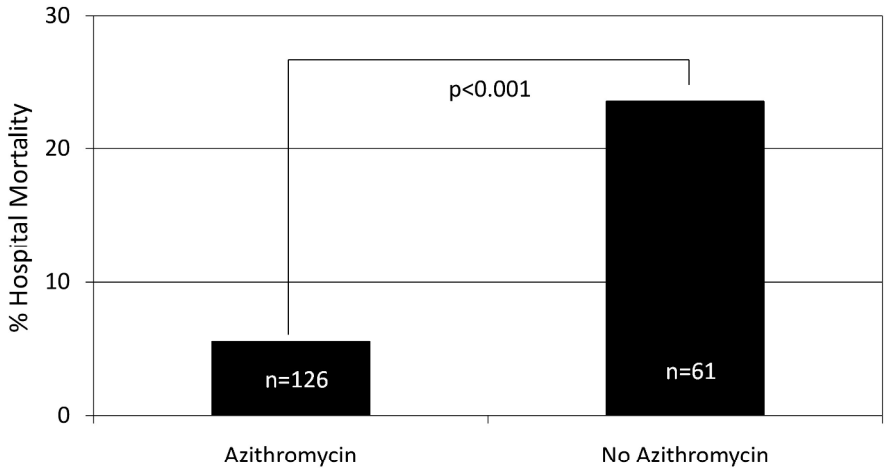
Variables Associated with Hospital Mortality

Table 2

	Adjusted Odds Ratio	95% Confidence Interval	p
-Age, per year	1.05	1.01-1.09	0.018
-Need for MV	8.82	2.74-28.46	0.001
-Appropriate therapy	0.13	0.03-0.47	0.002
-Use of Azithromycin	0.26	0.08-0.80	0.018

Hospital Mortality and Azithromycin Treatment

Figure 1.



Odds Ratio for Death with Azithromycin: 0.20 (94% CI: 0.08-0.52)

1058x793mm (72 x 72 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, Table
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Azithromycin and Survival In Streptrococcus pneumoniae Pneumonia: A Retrospective Study

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Azithromycin and Survival In *Streptrococcus pneumoniae* Pneumonia: A Retrospective Study

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ARTICLE SUMMARY

Article focus

-To determine the impact of azithromycin co-therapy on outcomes in *Streptococcus pneumoniae* pneumonia

Key messages

-Azithromycin co-therapy in pneumonia due to *S. pneumoniae* is associated with improved short-term survivial

-This finding is independent of multiple potential confounders including timeliness of antibiotic treatment

Strengths and limitations of this study

-Strengths: large sample of pure *S. pneunmoniae* pneumonia

-Limitations: Data derive from a single center and the study's retrospective design

ABSTRACT

Objective: *S. pneumoniae* (SP) represents a major pathogen in pneumonia. The impact of azithromycin on mortality in SP pneumonia remains unclear. Recent safety concerns regarding azithromycin have raised alarm about this agent's role with pneumonia. We sought to clarify the relationship between survival and azithromycin use in SP pneumonia.

Design: Retrospective cohort.

Setting: Urban, academic hospital.

Participants: Adults with a diagnosis of SP pneumonia (Jan-Dec 2010). The diagnosis of pneumonia required a compatible clinical syndrome and radiographic evidence of an infiltrate.

Intervention: None

Primary and secondary outcome measures: Hospital mortality served as the primary endpoint, and we compared subjects given azithromycin to those not treated with this. Co-variates of interest included demographics, severity of illness, comorbidities, and infection related characteristics (eg, appropriateness of initial treatment, bacteremia). We employed logistic regression to assess the independent impact of azithromycin on hospital mortality.

Results: The cohort included 187 subjects (mean age: 67.0 ± 8.2 years, 50.3% male, 5.9% admitted to the ICU). The most frequently utilized non-macrolide antibiotics included: ceftriaxone (n=111), cefipeme (n=31), and moxifloxacin (n=22). Approximately 2/3rds of the cohort received azithromycin. Crude mortality was lower in persons given azithromycin (5.6% vs. 23.6%, $p<0.01$). The final survival model included four variables: age, need for mechanical ventilation, initial appropriate therapy, and azithromycin use. The adjusted odds ratio for mortality associated with azithromycin equaled 0.26 (95% confidence interval: 0.08-0.80, p=0.018).

Conclusions: SP pneumonia generally remains associated with substantial mortality while azithromycin treatment is associated with significantly higher survival rates. The impact of azithromycin is independent of multiple potential confounders.

INTRODUCTION

Pneumonia remains a leading cause of morbidity and mortality. Annually more than 1.3 million patients in the United States (US) present to the hospital with pneumonia and require admission.[1] Direct costs related to pneumonia exceed several billion each year in the US.[1] Because of this burden, multiple efforts have focused on improving the care of patient with pneumonia and attempted to address means for enhancing outcomes in this disease and hospitalists often care for and design hospital pathways for those admitted with pneumonia.

Concurrent with these quality efforts, the microbiology of pneumonia presenting to the hospital has evolved. Over the last decade, pathogens traditionally thought confined to the hospital, such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, now are implicated in non-nosocomial pneumonia.[2,3] This epidemiologic trend led to the creation of the concept of healthcare-associated pneumonia (HCAP).[2,3] At the same time, rates of pneumonia in adults due to *Streptococcus pneumoniae* have diminished, in part due to the effects of herd immunity arising from the use of the newer vaccines in children.[4] Nonetheless, *S. pneumoniae* remains a leading pathogen in non-nosocomial pneumonia, whether it be CAP or HCAP and whether it results in mild disease or more severe illness necessitating admission to the intensive care unit (ICU).[5,6] Furthermore, current treatment guidelines for HCAP do not suggest consideration of adjunctive macrolide antibiotics, despite the fact that *S. pneumoniae* can still be seen in this syndrome.[3,5,7] While some surveillance studies indicate that *S. pneumoniae* remains the most prevalent pathogen in patients admitted with pneumonia via the ED, other studies suggest that *S. pneumoniae* often represents either the second or third most frequent pathogen in this setting.[5,6,8] Thus, despite it potentially being less prevalent than in prior years, *S. pneumoniae* continues to lead to a disproportionate burden on the healthcare system.

Macrolide antibiotics, particularly azithromycin, are unique as anti-infective agents in that they appear to have potent anti-inflammatory properties.[9] Earlier analyses suggest that azithromycin exposure may confer a mortality advantage in CAP, irrespective of the causative pathogen.[10,11] This

observation has resulted in treatment guidelines recommending utilization of macrolides in CAP and their continuation even if the patient is concurrently being treated with another in vitro active antimicrobial as one potential approach.[12] Many of the reports supporting a survival benefit related to macrolide use in CAP, though, have been limited because they either were conducted in an era before HCAP became a concern or because they often did not account for issues related to rates of initially appropriate antimicrobial administration. These reports have also explored CAP as a syndrome, regardless of the pathogen, and not specifically addressed *S. pneumoniae*. Recent descriptions of potential cardiovascular toxicities arising with azithromycin reinforce the need to elucidate if this agent alters mortality.[13] A potential survival benefit related to azithromycin in *S. pneumoniae* pneumonia would indicate that the risk/benefit calculus favors utilization of this agent not withstanding concerns about rhythm disturbances.

We hypothesized that co-treatment with azithromycin would improve mortality in pneumonia due to *S. pneumoniae* and that this effect would be independent of confounding arising from failure to administer appropriate initial antibiotic therapy. To explore our hypothesis, we conducted a retrospective analysis of all subjects with either CAP or HCAP admitted with evidence of infection related to *S. pneumoniae*.

METHODS

Study Overview and Subjects

We retrospectively identified all adult (age > 18 years) patients admitted with a clinical diagnosis of pneumonia between January 1, 2010 and December 31, 2010. All patients were required to have initially presented to the ED. We defined pneumonia based on both signs and symptoms of infection (ie, elevated white blood cell count or > 10% band forms, fever or hypothermia). We further required compatible chest imaging documenting an infiltrate(s). One investigator (MHK), blinded to the clinical and microbiologic information adjudicated the chest imaging. Identification of *S. pneumoniae* was based on the results of cultures from either blood, pleural fluid, sputum, or the lower airways. A positive urinary antigen for *S. pneumoniae* also was used to document infection with this pathogen. The patients

described in this report have been previously included in an earlier analysis validating the concept of HCAP.[3] The Washington University School of Medicine Human Studies Committee approved the study (# 201205194). As this was a retrospective analysis, there was no requirement for informed consent.

Endpoints and Co-variates

Hospital mortality represented the primary endpoint. We compared persons with pneumococcal pneumonia initially treated with azithromycin to those not given this agent. During the observation period, this was the only macrolide available for treatment of pneumonia at the study hospital. There were no subjects given clarithromycin. Co-variates of interest included patient demographics, severity of illness, and infection related variables. For demographic factors we noted age, gender, and race. With respect to co-morbidities, we recorded if the subject was residing in a nursing home or long-term care facility, was recently hospitalized in the last 90 days, had received antimicrobials in the last 30 days, suffered from end stage renal disease requiring hemodialysis, or was immunosuppressed. We defined immunosuppression based on the presence of either acquired-immunodeficiency syndrome (AIDS), active malignancy undergoing chemotherapy, or treatment with immunosuppressants (ie, 10 mg prednisone or equivalent daily for at least 30 days or alternate agents such as methotrexate). To assess disease severity we calculated the CURB-65 score along with recording if there was a need for either ICU care or mechanical ventilation (MV).[14] With respect to infection-related variables we determined if bacteremia complicated the pneumonia and the initial antibiotic regimen. We classified the initial antibiotic regimen as appropriate if a non-macrolide antibiotic that was *in vitro* active against the *S. pneumoniae* isolate was administered within 4 hours of presentation. [15] At the host institution, antibiotic administration is protocolized such that all subjects received a non-macrolide anti-infective with activity against pneumoccocus. Therefore, appropriateness of antibiotics was a reflection of the timeliness of administration. Additionally, by convention, patients given combination treatment including azithromycin received these drugs concurrently.

Statistics

We completed univariate analyses with either the Fisher's exact test or Student's t-test as appropriate. Continuous, non-parametrically distributed data was compared via the Mann-Whitney U test. All analyses were two tailed, and a p value of < 0.05 was assumed to represent statistical significance. To determine independent factors associated with mortality, we employed logistic regression. Variables significant at $P<0.10$ level in univariate analyses were entered into model. We utilized an enter approach for the regression. Co-linearity was explored with correlation matrices. Adjusted odds ratios (AORs) and ninety-five percent confidence intervals (CIs) are reported where appropriate. The model's goodness-of-fit was assessed via calculation of the R^2 value and the Hosmer-Lemeshow c-statistic. All analyses were performed with SPSS 19.0 (SPSS, Chicago, IL).

RESULTS

During the study period 977 persons were admitted via the ED with evidence of bacterial pneumonia. Of these patients, 187 were infected with *S. pneumoniae*. The mean age of these subjects was 57.0 +/- 8.2 years and approximately half were male. The crude hospital mortality in *S. pneumoniae* pneumonia equaled 11.2% while the mean hospital length of stay measured 8.2 +/- 5.0 days. The most commonly utilized non-azithromycin antibiotics were ceftriaxone (n=111), cefipeme (n= 31), and moxifloxacin (n=22).

Table 1 reveals the differences in baseline characteristics between subjects dying while hospitalized and those surviving to discharge. Those who died were older but there were no other differences in demographics. Patients dying were more severely ill based on all measures used to assess this. Specifically, survivors had lower CURB-65 scores as compared to decedents (median CURB-65 class 4 vs 2, p=0.025). More than a quarter of those dying received MV while fewer than 5% of those discharged alive required MV (p=0.001). The distribution of criteria defining HCAP did not differ between groups. Approximately 11% of all patients resided in nursing homes prior to admission and the

rate of admission from nursing homes did not correlate with hospital mortality. Immunosuppression was prevalent in the study population but this also did not differ between those dying and survivors.

With respect to infection-related characteristics, the frequency of bacteremia was similar between the two groups. Compared to those who survived, however, those who died were more likely to have been given delayed antibiotic therapy (61.9% vs. 91.0%, p=0.001). In all instances, inappropriate therapy occurred not because of the use of an *in vitro* inactive agent but because of a delay in the initiation of antibiotics. All isolates were susceptible to the agents actually administered.

Hospital mortality rates were significantly lower in persons treated with azithromycin. Of patients given the macrolide, only 5.6% expired in the hospital as opposed to 23.6% of persons not treated with such an agent (Figure 1). The odds ratio (OR) for death with a macrolide was 0.20 (94% CI: 0.08-0.52).

In the logistic regression, four variables remained independently associated with mortality (Table 2a). Mortality increased with increasing age (AOR 1.05, 95% CI: 1.01-1.09, p=0.018) and with the need for MV (AOR 8.82, 95% CI: 2.74-28.46, <0.001). Timely antibiotic therapy resulted in lower in-hospital death rates (AOR, 0.13, 95% CI: 0.03-0.46, p=0.002). Finally, treatment with azithromycin correlated with enhanced survival. Azithromycin exposure was independently associated with a reduced risk for death by nearly 75% (AOR 0.26, 95% CI: 0.08-0.90, p=0.018). Neither being classified as HCAP nor any of the individual criteria defining HCAP stayed in the final model. The model had excellent fit with an R^2 value of 0.42 and a C-statistic of 0.991. In a sensitivity analysis (Table 2b) where CURB 65 score was employed as a marker for severity of illness rather than either need for MV or ICU admission, treatment with azithromycin remained associated with a lower probability for mortality (AOR 0.34, 95% CI: 0.11-0.88).

DISCUSSION

This retrospective analysis of a cohort of patients with microbiologically confirmed pneumococcal pneumonia indicates that co-administration of azithromycin is associated with significant reductions in short-term mortality. This effect is independent of multiple potential confounders such as severity of illness and the timeliness and activity of initial antimicrobial therapy. The positive impact of azithromycin was also independent of whether bacteremia was present.

Prior efforts evaluating the significance of macrolide therapy on outcomes in CAP have reached conflicting conclusions. Some large case series indicate a survival benefit in persons given macrolides while others have failed to detect such an impact. For example, Martin-Loeches and colleagues observed that macrolide use reduced the risk for mortality in intubated patients with CAP.[10] Tessemer et al. in a large observational German study also noted that macrolide exposure improved cure rates and short-term mortality.[11] In pneumococcal bacteremia complicating pneumonia, Metersky conclude that macrolide use improved 30 day readmission and mortality rates [15]. On the other hand, Asadi and co-workers reported that mortality rates were similar among 3000 patients treated with either monotherapy with a fluroquinolone as opposed to a beta-lactam /macrolide combination.[17] Wilson et al additionally determined that inclusion of a macrolide in the antibiotic regimen failed to enhance survival in elderly patients with CAP.[18] Meta-analyses are similarly conflicting in their assessments. One recent meta-analysis including 16 randomized controlled trials (RCTs) evaluating fluroquinolones against beta-lactam/macrolide combinations calculated that there was no difference in mortality between these regimens.[19] Another group of investigators, though, included both observational reports and RCTs and determined that macrolide administration offered a small but statistically significant mortality benefit.[20]

Our findings add to this debate and are novel in several respects. First, one potential limitation of the above-mentioned studies is that they tend to pool all subjects with CAP, irrespective of culture findings. In contrast, we restricted our evaluation to patients with confirmed *S. pneumoniae* infection whether they had CAP or risk factors for HCAP. Including subjects with either syndrome serves to underscore the need to focus on the pathogen rather than the infectious syndrome. Treatment guidelines

currently stratify persons in to two cohorts based on their risk factors for infection with resistant pathogens.[7,12] This scheme ignores the point that pneumococcal infection occurs in both CAP and HCAP. Our results suggest that revision of the guidelines may be appropriate as we noted a mortality benefit with azithromycin even after controlling for factors and co-morbidities which define HCAP.

Furthermore, some of the subjects in earlier reports failed to have either evidence of bacterial infection or were infected with a pathogen other than *S. pneumoniae*. In some instances, only administrative coding data rather than actual culture results facilitated subject identification. This distinction is important in that the immunomodulatory effects of azithromycin have been most clearly elucidated as it relates to infection with *S. pneumoniae*. Although broadly anti-inflammatory in a number of ways, the strongest biologic evidence of a potential means for an impact in pulmonary infection relates to investigations in *S. pneumoniae*. More importantly these effects of macrolides alter both cellular and humoral immunity. *In vitro*, azithromycin, for instance, prevents apoptosis of human polymorphonuclear lymphocytes and may reduce interleukin (IL)-8 production.[21,22] Exposure to azithromycin, furthermore, reduces pneumolysin from both macrolide-susceptible and resistant strains of *S. pneumoniae*.[23] Azithromycin may also reduce production of tumor necrosis alpha and IL-1 alpha in human monocytes and down regulate natural killer cell production with an ensuing alteration in various cytokines.[24] Therefore, by focusing on a specific organism where the nexus with the theoretical mechanisms of immune modulation are better established, our observations help to clarify the discordant findings of others. Our results, in turn, suggest that the benefit of macrolide co-treatment may be restricted to persons with pneumococcal infection

We also specifically controlled for the timeliness of initial therapy. Initially appropriate and timely antibiotic treatment is a key determinant of survival in a number of severe infections ranging from bacteremia to septic shock.[25,26] Many prior studies of macrolides and *S. pneumoniae* pneumonia simply did not address the timing of initial antimicrobial therapy. In most RCTs, adjudicating the coverage and timeliness of initial therapy is clouded by the time window allowed to enroll patients in the specific clinical trial. Some observational reports have failed to explore the importance of this issue in

their analytic approaches. Others have simply determined whether an antibiotic regimen was concordant with formal treatment guidelines was given. This constitutes only a surrogate means for evaluating the true appropriateness of antimicrobial treatment as it does not examine specific *in vitro* susceptibilities or the timing of the antibiotic administration. We, however, specifically sought to rectify and address this limitation by applying specific and clear criteria.

Our overall patient outcomes suggest that our data are broadly generalizable. The crude hospital mortality rate was approximately 10%, as was the prevalence of bacteremia, reflecting what has been noted in multiple epidemiologic analyses.[1] Likewise, the average LOS in our cohort parallels the general LOS for this syndrome described in large analyses of US hospital discharge data. The goodness of fit of our final mortality prediction model was also excellent indicating that there is at most moderate unmeasured residual confounding. Many earlier analyses of case series data have not described either if or how well their modeling of outcomes fits their observations.

Ray and co-workers have sparked concern regarding macrolides and reported potential cardiovascular toxicity associated with azithromycin.[13] In a review of Medicaid claims data from Tennessee, these authors state that deaths due to cardiovascular causes were higher in subjects given azithromycin as compared to either no antibiotic or amoxicillin. This study has led to calls to re-evaluate our utilization of azithromycin.[27] The potential for a mortality benefit accruing with use of this drug in pneumococcal pneumonia should give pause to efforts to reflexively and broadly restrict access to azithromycin. The burden and prevalence of pneumococcal pneumonia suggest that it would be inappropriate for policy makers to mix all types of *S. pneumoniae* infection into one group as they make decisions regarding the availability of this agent. Our results suggest that a measured risk-benefit analysis is still required at the individual patient level.

The present study has several significant limitations. First, its retrospective nature exposes it to several forms of bias. However, unlike clinical cure, there is little potential for bias in determining at patient's vital status. Confounding by indication is a similar concern. If such confounding were present, though, we would expect this to bias our data towards the absence of an impact of azithromycin on

mortality, while we observed precisely the opposite. Second, the data represent the experience from a single center and thus may not be indicative of the experience of others. Likewise we only studied inpatients and so our results do not apply to patients not requiring admission. Third, given the constraints of modern microbiology and culture techniques there are certainly cases of pneumococcal pneumonia we missed. Fourth, only 5% of the population required ICU admission. As such, our results most reflect the experience of less severely ill subjects and the significance of azithromycin in critically ill persons may be different. These, though, are the patients most often cared for by hospitalists. Fifth we lacked information on certain co-variates that might have affected mortality, specifically underlying pulmonary and liver disease. Finally, the sample size precluded us from examining several important variables such as the exact timing of anti-infective administration (eg, by hour delay from presentation). Sample size also likely explains why some variables were not significant in our final model. That the CURB-65 score failed to represent a correlate of mortality in our initial model probably arose because other factors associated with survival (eg, need for MV) proved more strongly linked with mortality. Likewise, the vast majority of persons given azithromycin also were given a beta-lactam. As a result, few patients received either azithromycin alone or with moxifloxacin. Hence, we cannot exclude the possibility that the benefit with the macrolide is either a surrogate for exposure to a beta-lactam agent or a function of the combined use of azithromycin with this class of antibiotics.

In conclusion, co-administration of azithromycin appears to reduce mortality in persons admitted to the hospital with pneumoniae due to *S. pneumoniae*. This affect persists after adjusting for other important variables known to correlate with survival in this syndrome. Given the safety issues that have arisen with azithromycin along with the possible positive impact of this drug on hospital mortality, a randomized trial exploring the role for adjunctive azithromycin relative to placebo in CAP appears not only warranted but urgently needed.

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Dr. Shorr had full access to the data and takes responsibility for the content of the paper including all analyses.

Author contributions

Study concept and design: AFS, MDZ, JH, JK, STM, MHK

Acquisition of data: JH, JK, STM

Analysis and interpretation of data: AFS, MDZ, STM, MHK

Drafting the manuscript: AFS, MDZ, MHK

Critical revision of the manuscript for important intellectual content: AFS, MDZ, JH, JK, STM, MHK

Statistical expertise: AFS, MDZ

Obtained funding: MHK

Study supervision: AFS,MHK

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Baseline Characteristics

Table 1.

	Hospital Death (n=21)	Hospital Survival (n=166)	p
Demographics			
-Age, mean±SD, years	66.8±18.23	55.7±15.0	0.002
-Male, n,%	10, 47.6%	84, 50.6%	0.821
-Race			
Caucasian, n,%	10, 47.6%	87, 52.4%	0.767
African-American, n,%	11, 52.4%	77, 46.5%	
Other, n,%	0, 0. %	2, 1.2%	
Severity of Illness			
-CURB 65 Score, median	4	2	0.025
-CURB score distribution			--
0, n,%	0, 0%	28, 16.9%	
1, n,%	2, 9.5%	51, 30.7%	
2, n,%	0, 0%	28, 16.9%	
3, n,%	6, 28.6%	29, 17.5%	
4, n,%	10, 47.6%	25, 15.1%	
5 n,%	3, 14.3%	5, 3%	
-ICU Admission, n,%	5, 22.9%	6, 3.6%	0.001
-Mechanical Ventilation, n,%	6, 27.8%	8, 4.8%	0.001
Comorbidities			
-LTC admission, n,%	2, 11.1%	19, 11.4%	0.999

-HD, n,%	0%	4, 2.4%	0.999
-Immunosuppression, n,%	7, 33.3%	38, 22.9%	0.289
-Prior antibiotics, n,%	7, 33.3%	40, 24.1%	0.423
-Recent hospitalization, n,%	3, 14.1%	15, 9.0%	0.353
Infection-related Characteristics			
-Bacteremia, n,%	3, 14.1%	13, 7.8%	0.256
-Delay in appropriate antibiotics, %*	13, 61.9%	151, 91.0%	0.001
Non-azithromycin Antibiotic therapy			0.099
-Ceftriaxone, n,%	7, 33.3%	104, 62.7%	
-Cefipeme, n,%	8, 38.1%	23, 13.9%	
-Moxifloxacin, n, %	1, 4.8%	21, 12.7%	
-Piperacillin/tazobactam, n, %	2, 9.5%	8, 4.8%	
-Other, n, %	3, 14.3%	10, 6.0%	

Variables Associated with Hospital Mortality

Table 2a

	Unadjusted Odds Ratio	Adjusted Odds Ratio (AOR)	95% Confidence Interval for AOR	P for AOR
-Age, per year	--	1.05	1.01-1.09	0.018
-Need for MV	8.14	8.82	2.74-28.46	0.001
-Appropriate therapy	0.16	0.13	0.03-0.47	0.002
-Use of Azithromycin	0.20	0.26	0.08-0.80	0.018

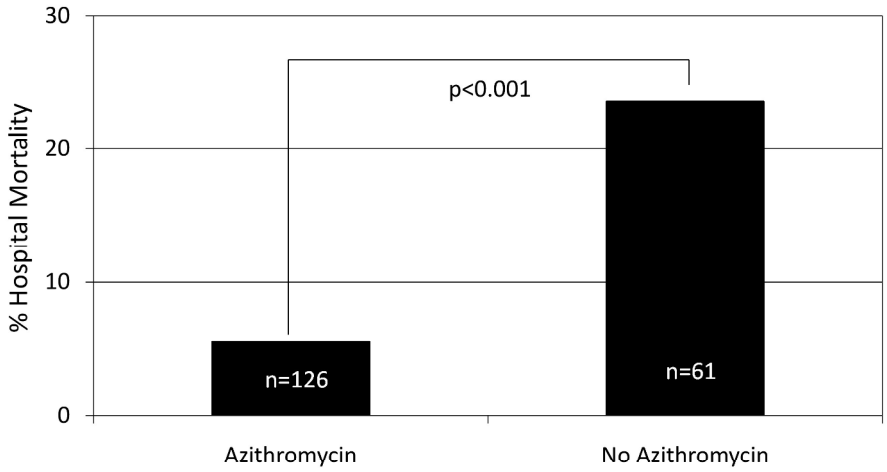
Sensitivity Analysis for Mortality

Table 2b

	Unadjusted Odds Ratio	Adjusted Odds Ratio (AOR)	95% Confidence Interval for AOR	P for AOR
-Age, per year	--	1.02	0.98-1.05	0.368
-CURB-65 score, per point increase	--	2.07	1.32-3.25	0.001
-Appropriate therapy	0.16	0.12	0.03-0.42	0.001
-Use of Azithromycin	0.20	0.34	0.11-0.88	0.041

Hospital Mortality and Azithromycin Treatment

Figure 1.



Odds Ratio for Death with Azithromycin: 0.20 (94% CI: 0.08-0.52)

1058x793mm (72 x 72 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, Table
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Azithromycin and Survival In *Streptrococcus pneumoniae* Pneumonia: A Retrospective Study

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Key words: Azithromycin, pneumonia, *S. pneumoniae*, survival

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ARTICLE SUMMARY

Article focus

-To determine the impact of azithromycin co-therapy on outcomes in *Streptococcus pneumoniae* pneumonia

Key messages

-Azithromycin co-therapy in pneumonia due to *S. pneumoniae* is associated with improved short-term survivial

-This finding is independent of multiple potential confounders including timeliness of antibiotic treatment

Strengths and limitations of this study

-Strengths: large sample of pure *S. pneunmoniae* pneumonia

-Limitations: Data derive from a single center and the study's retrospective design

ABSTRACT

Objective: *S. pneumoniae* (SP) represents a major pathogen in pneumonia. The impact of azithromycin on mortality in SP pneumonia remains unclear. Recent safety concerns regarding azithromycin have raised alarm about this agent's role with pneumonia. We sought to clarify the relationship between survival and azithromycin use in SP pneumonia.

Design: Retrospective cohort.

Setting: Urban, academic hospital.

Participants: Adults with a diagnosis of SP pneumonia (Jan-Dec 2010). The diagnosis of pneumonia required a compatible clinical syndrome and radiographic evidence of an infiltrate.

Intervention: None

Primary and secondary outcome measures: Hospital mortality served as the primary endpoint, and we compared subjects given azithromycin to those not treated with this. Co-variates of interest included demographics, severity of illness, comorbidities, and infection related characteristics (eg, appropriateness of initial treatment, bacteremia). We employed logistic regression to assess the independent impact of azithromycin on hospital mortality.

Results: The cohort included 187 subjects (mean age: 67.0 ± 8.2 years, 50.3% male, 5.9% admitted to the ICU). The most frequently utilized non-macrolide antibiotics included: ceftriaxone (n=111), cefipeme (n=31), and moxifloxacin (n=22). Approximately 2/3rds of the cohort received azithromycin. Crude mortality was lower in persons given azithromycin (5.6% vs. 23.6%, $p<0.01$). The final survival model included four variables: age, need for mechanical ventilation, initial appropriate therapy, and azithromycin use. The adjusted odds ratio for mortality associated with azithromycin equaled 0.26 (95% confidence interval: 0.08-0.80, p=0.018).

Conclusions: SP pneumonia generally remains associated with substantial mortality while azithromycin treatment is associated with significantly higher survival rates. The impact of azithromycin is independent of multiple potential confounders.

INTRODUCTION

Pneumonia remains a leading cause of morbidity and mortality. Annually more than 1.3 million patients in the United States (US) present to the hospital with pneumonia and require admission.[1] Direct costs related to pneumonia exceed several billion each year in the US.[1] Because of this burden, multiple efforts have focused on improving the care of patient with pneumonia and attempted to address means for enhancing outcomes in this disease and hospitalists often care for and design hospital pathways for those admitted with pneumonia.

Concurrent with these quality efforts, the microbiology of pneumonia presenting to the hospital has evolved. Over the last decade, pathogens traditionally thought confined to the hospital, such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, now are implicated in non-nosocomial pneumonia.[2,3] This epidemiologic trend led to the creation of the concept of healthcare-associated pneumonia (HCAP).[2,3] At the same time, rates of pneumonia in adults due to *Streptococcus pneumoniae* have diminished, in part due to the effects of herd immunity arising from the use of the newer vaccines in children.[4] Nonetheless, *S. pneumoniae* remains a leading pathogen in non-nosocomial pneumonia, whether it be CAP or HCAP and whether it results in mild disease or more severe illness necessitating admission to the intensive care unit (ICU).[5,6] Furthermore, current treatment guidelines for HCAP do not suggest consideration of adjunctive macrolide antibiotics, despite the fact that *S. pneumoniae* can still be seen in this syndrome.[3,5,7] While some surveillance studies indicate that *S. pneumoniae* remains the most prevalent pathogen in patients admitted with pneumonia via the ED, other studies suggest that *S. pneumoniae* often represents either the second or third most frequent pathogen in this setting.[5,6,8] Thus, despite it potentially being less prevalent than in prior years, *S. pneumoniae* continues to lead to a disproportionate burden on the healthcare system.

Macrolide antibiotics, particularly azithromycin, are unique as anti-infective agents in that they appear to have potent anti-inflammatory properties.[9] Earlier analyses suggest that azithromycin exposure may confer a mortality advantage in CAP, irrespective of the causative pathogen.[10,11] This

observation has resulted in treatment guidelines recommending utilization of macrolides in CAP and their continuation even if the patient is concurrently being treated with another in vitro active antimicrobial as one potential approach.[12] Many of the reports supporting a survival benefit related to macrolide use in CAP, though, have been limited because they either were conducted in an era before HCAP became a concern or because they often did not account for issues related to rates of initially appropriate antimicrobial administration. These reports have also explored CAP as a syndrome, regardless of the pathogen, and not specifically addressed *S. pneumoniae*. Recent descriptions of potential cardiovascular toxicities arising with azithromycin reinforce the need to elucidate if this agent alters mortality.[13] A potential survival benefit related to azithromycin in *S. pneumoniae* pneumonia would indicate that the risk/benefit calculus favors utilization of this agent not withstanding concerns about rhythm disturbances.

We hypothesized that co-treatment with azithromycin would improve mortality in pneumonia due to *S. pneumoniae* and that this effect would be independent of confounding arising from failure to administer appropriate initial antibiotic therapy. To explore our hypothesis, we conducted a retrospective analysis of all subjects with either CAP or HCAP admitted with evidence of infection related to *S. pneumoniae*.

METHODS

Study Overview and Subjects

We retrospectively identified all adult (age > 18 years) patients admitted with a clinical diagnosis of pneumonia between January 1, 2010 and December 31, 2010. All patients were required to have initially presented to the ED. We defined pneumonia based on both signs and symptoms of infection (ie, elevated white blood cell count or > 10% band forms, fever or hypothermia). We further required compatible chest imaging documenting an infiltrate(s). One investigator (MHK), blinded to the clinical and microbiologic information adjudicated the chest imaging. Identification of *S. pneumoniae* was based on the results of cultures from either blood, pleural fluid, sputum, or the lower airways. A positive urinary antigen for *S. pneumoniae* also was used to document infection with this pathogen. The patients

described in this report have been previously included in an earlier analysis validating the concept of HCAP.[3] The Washington University School of Medicine Human Studies Committee approved the study (# 201205194). As this was a retrospective analysis, there was no requirement for informed consent.

Endpoints and Co-variates

Hospital mortality represented the primary endpoint. We compared persons with pneumococcal pneumonia initially treated with azithromycin to those not given this agent. During the observation period, this was the only macrolide available for treatment of pneumonia at the study hospital. There were no subjects given clarithromycin. Co-variates of interest included patient demographics, severity of illness, and infection related variables. For demographic factors we noted age, gender, and race. With respect to co-morbidities, we recorded if the subject was residing in a nursing home or long-term care facility, was recently hospitalized in the last 90 days, had received antimicrobials in the last 30 days, suffered from end stage renal disease requiring hemodialysis, or was immunosuppressed. We defined immunosuppression based on the presence of either acquired-immunodeficiency syndrome (AIDS), active malignancy undergoing chemotherapy, or treatment with immunosuppressants (ie, 10 mg prednisone or equivalent daily for at least 30 days or alternate agents such as methotrexate). To assess disease severity we calculated the CURB-65 score along with recording if there was a need for either ICU care or mechanical ventilation (MV).[14] With respect to infection-related variables we determined if bacteremia complicated the pneumonia and the initial antibiotic regimen. We classified the initial antibiotic regimen as appropriate if a non-macrolide antibiotic that was *in vitro* active against the *S. pneumoniae* isolate was administered within 4 hours of presentation. [15] At the host institution, antibiotic administration is protocolized such that all subjects received a non-macrolide anti-infective with activity against pneumoccocus. Therefore, appropriateness of antibiotics was a reflection of the timeliness of administration. Additionally, by convention, patients given combination treatment including azithromycin received these drugs concurrently.

Statistics

We completed univariate analyses with either the Fisher's exact test or Student's t-test as appropriate. Continuous, non-parametrically distributed data was compared via the Mann-Whitney U test. All analyses were two tailed, and a p value of < 0.05 was assumed to represent statistical significance. To determine independent factors associated with mortality, we employed logistic regression. Variables significant at $P<0.10$ level in univariate analyses were entered into model. We utilized an enter approach for the regression. Co-linearity was explored with correlation matrices. Adjusted odds ratios (AORs) and ninety-five percent confidence intervals (CIs) are reported where appropriate. The model's goodness-of-fit was assessed via calculation of the R^2 value and the Hosmer-Lemeshow c-statistic. All analyses were performed with SPSS 19.0 (SPSS, Chicago, IL).

RESULTS

During the study period 977 persons were admitted via the ED with evidence of bacterial pneumonia. Of these patients, 187 were infected with *S. pneumoniae*. The mean age of these subjects was 57.0 +/- 8.2 years and approximately half were male. The crude hospital mortality in *S. pneumoniae* pneumonia equaled 11.2% while the mean hospital length of stay measured 8.2 +/- 5.0 days. The most commonly utilized non-azithromycin antibiotics were ceftriaxone (n=111), cefipeme (n= 31), and moxifloxacin (n=22).

Table 1 reveals the differences in baseline characteristics between subjects dying while hospitalized and those surviving to discharge. Those who died were older but there were no other differences in demographics. Patients dying were more severely ill based on all measures used to assess this. Specifically, survivors had lower CURB-65 scores as compared to decedents (median CURB-65 class 4 vs 2, p=0.025). More than a quarter of those dying received MV while fewer than 5% of those discharged alive required MV (p=0.001). The distribution of criteria defining HCAP did not differ between groups. Approximately 11% of all patients resided in nursing homes prior to admission and the

rate of admission from nursing homes did not correlate with hospital mortality. Immunosuppression was prevalent in the study population but this also did not differ between those dying and survivors.

With respect to infection-related characteristics, the frequency of bacteremia was similar between the two groups. Compared to those who survived, however, those who died were more likely to have been given delayed antibiotic therapy (61.9% vs. 91.0%, p=0.001). In all instances, inappropriate therapy occurred not because of the use of an *in vitro* inactive agent but because of a delay in the initiation of antibiotics. All isolates were susceptible to the agents actually administered.

Hospital mortality rates were significantly lower in persons treated with azithromycin. Of patients given the macrolide, only 5.6% expired in the hospital as opposed to 23.6% of persons not treated with such an agent (Figure 1). The odds ratio (OR) for death with a macrolide was 0.20 (94% CI: 0.08-0.52).

In the logistic regression, four variables remained independently associated with mortality (Table 2a). Mortality increased with increasing age (AOR 1.05, 95% CI: 1.01-1.09, p=0.018) and with the need for MV (AOR 8.82, 95% CI: 2.74-28.46, <0.001). Timely antibiotic therapy resulted in lower in-hospital death rates (AOR, 0.13, 95% CI: 0.03-0.46, p=0.002). Finally, treatment with azithromycin correlated with enhanced survival. Azithromycin exposure was independently associated with a reduced risk for death by nearly 75% (AOR 0.26, 95% CI: 0.08-0.90, p=0.018). Neither being classified as HCAP nor any of the individual criteria defining HCAP stayed in the final model. The model had excellent fit with an R^2 value of 0.42 and a C-statistic of 0.991. In a sensitivity analysis (Table 2b) where CURB 65 score was employed as a marker for severity of illness rather than either need for MV or ICU admission, treatment with azithromycin remained associated with a lower probability for mortality (AOR 0.34, 95% CI: 0.11-0.88).

DISCUSSION

This retrospective analysis of a cohort of patients with microbiologically confirmed pneumococcal pneumonia indicates that co-administration of azithromycin is associated with significant reductions in short-term mortality. This effect is independent of multiple potential confounders such as severity of illness and the timeliness and activity of initial antimicrobial therapy. The positive impact of azithromycin was also independent of whether bacteremia was present.

Prior efforts evaluating the significance of macrolide therapy on outcomes in CAP have reached conflicting conclusions. Some large case series indicate a survival benefit in persons given macrolides while others have failed to detect such an impact. For example, Martin-Loeches and colleagues observed that macrolide use reduced the risk for mortality in intubated patients with CAP.[10] Tessemer et al. in a large observational German study also noted that macrolide exposure improved cure rates and short-term mortality.[11] In pneumococcal bacteremia complicating pneumonia, Metersky conclude that macrolide use improved 30 day readmission and mortality rates [15]. On the other hand, Asadi and co-workers reported that mortality rates were similar among 3000 patients treated with either monotherapy with a fluroquinolone as opposed to a beta-lactam /macrolide combination.[17] Wilson et al additionally determined that inclusion of a macrolide in the antibiotic regimen failed to enhance survival in elderly patients with CAP.[18] Meta-analyses are similarly conflicting in their assessments. One recent meta-analysis including 16 randomized controlled trials (RCTs) evaluating fluroquinolones against beta-lactam/macrolide combinations calculated that there was no difference in mortality between these regimens.[19] Another group of investigators, though, included both observational reports and RCTs and determined that macrolide administration offered a small but statistically significant mortality benefit.[20]

Our findings add to this debate and are novel in several respects. First, one potential limitation of the above-mentioned studies is that they tend to pool all subjects with CAP, irrespective of culture findings. In contrast, we restricted our evaluation to patients with confirmed *S. pneumoniae* infection whether they had CAP or risk factors for HCAP. Including subjects with either syndrome serves to underscore the need to focus on the pathogen rather than the infectious syndrome. Treatment guidelines

currently stratify persons in to two cohorts based on their risk factors for infection with resistant pathogens.[7,12] This scheme ignores the point that pneumococcal infection occurs in both CAP and HCAP. Our results suggest that revision of the guidelines may be appropriate as we noted a mortality benefit with azithromycin even after controlling for factors and co-morbidities which define HCAP.

Furthermore, some of the subjects in earlier reports failed to have either evidence of bacterial infection or were infected with a pathogen other than *S. pneumoniae*. In some instances, only administrative coding data rather than actual culture results facilitated subject identification. This distinction is important in that the immunomodulatory effects of azithromycin have been most clearly elucidated as it relates to infection with *S. pneumoniae*. Although broadly anti-inflammatory in a number of ways, the strongest biologic evidence of a potential means for an impact in pulmonary infection relates to investigations in *S. pneumoniae*. More importantly these effects of macrolides alter both cellular and humoral immunity. *In vitro*, azithromycin, for instance, prevents apoptosis of human polymorphonuclear lymphocytes and may reduce interleukin (IL)-8 production.[21,22] Exposure to azithromycin, furthermore, reduces pneumolysin from both macrolide-susceptible and resistant strains of *S. pneumoniae*.[23] Azithromycin may also reduce production of tumor necrosis alpha and IL-1 alpha in human monocytes and down regulate natural killer cell production with an ensuing alteration in various cytokines.[24] Therefore, by focusing on a specific organism where the nexus with the theoretical mechanisms of immune modulation are better established, our observations help to clarify the discordant findings of others. Our results, in turn, suggest that the benefit of macrolide co-treatment may be restricted to persons with pneumococcal infection

We also specifically controlled for the timeliness of initial therapy. Initially appropriate and timely antibiotic treatment is a key determinant of survival in a number of severe infections ranging from bacteremia to septic shock.[25,26] Many prior studies of macrolides and *S. pneumoniae* pneumonia simply did not address the timing of initial antimicrobial therapy. In most RCTs, adjudicating the coverage and timeliness of initial therapy is clouded by the time window allowed to enroll patients in the specific clinical trial. Some observational reports have failed to explore the importance of this issue in

their analytic approaches. Others have simply determined whether an antibiotic regimen was concordant with formal treatment guidelines was given. This constitutes only a surrogate means for evaluating the true appropriateness of antimicrobial treatment as it does not examine specific *in vitro* susceptibilities or the timing of the antibiotic administration. We, however, specifically sought to rectify and address this limitation by applying specific and clear criteria.

Our overall patient outcomes suggest that our data are broadly generalizable. The crude hospital mortality rate was approximately 10%, as was the prevalence of bacteremia, reflecting what has been noted in multiple epidemiologic analyses.[1] Likewise, the average LOS in our cohort parallels the general LOS for this syndrome described in large analyses of US hospital discharge data. The goodness of fit of our final mortality prediction model was also excellent indicating that there is at most moderate unmeasured residual confounding. Many earlier analyses of case series data have not described either if or how well their modeling of outcomes fits their observations.

Ray and co-workers have sparked concern regarding macrolides and reported potential cardiovascular toxicity associated with azithromycin.[13] In a review of Medicaid claims data from Tennessee, these authors state that deaths due to cardiovascular causes were higher in subjects given azithromycin as compared to either no antibiotic or amoxicillin. This study has led to calls to re-evaluate our utilization of azithromycin.[27] The potential for a mortality benefit accruing with use of this drug in pneumococcal pneumonia should give pause to efforts to reflexively and broadly restrict access to azithromycin. The burden and prevalence of pneumococcal pneumonia suggest that it would be inappropriate for policy makers to mix all types of *S. pneumoniae* infection into one group as they make decisions regarding the availability of this agent. Our results suggest that a measured risk-benefit analysis is still required at the individual patient level.

The present study has several significant limitations. First, its retrospective nature exposes it to several forms of bias. However, unlike clinical cure, there is little potential for bias in determining at patient's vital status. Confounding by indication is a similar concern. If such confounding were present, though, we would expect this to bias our data towards the absence of an impact of azithromycin on

mortality, while we observed precisely the opposite. Second, the data represent the experience from a single center and thus may not be indicative of the experience of others. Likewise we only studied inpatients and so our results do not apply to patients not requiring admission. Third, given the constraints of modern microbiology and culture techniques there are certainly cases of pneumococcal pneumonia we missed. Fourth, only 5% of the population required ICU admission. As such, our results most reflect the experience of less severely ill subjects and the significance of azithromycin in critically ill persons may be different. These, though, are the patients most often cared for by hospitalists. Fifth we lacked information on certain co-variates that might have affected mortality, specifically underlying pulmonary and liver disease. Finally, the sample size precluded us from examining several important variables such as the exact timing of anti-infective administration (eg, by hour delay from presentation). Sample size also likely explains why some variables were not significant in our final model. That the CURB-65 score failed to represent a correlate of mortality in our initial model probably arose because other factors associated with survival (eg, need for MV) proved more strongly linked with mortality. Likewise, the vast majority of persons given azithromycin also were given a beta-lactam. As a result, few patients received either azithromycin alone or with moxifloxacin. Hence, we cannot exclude the possibility that the benefit with the macrolide is either a surrogate for exposure to a beta-lactam agent or a function of the combined use of azithromycin with this class of antibiotics.

In conclusion, co-administration of azithromycin appears to reduce mortality in persons admitted to the hospital with pneumoniae due to *S. pneumoniae*. This affect persists after adjusting for other important variables known to correlate with survival in this syndrome. Given the safety issues that have arisen with azithromycin along with the possible positive impact of this drug on hospital mortality, a randomized trial exploring the role for adjunctive azithromycin relative to placebo in CAP appears not only warranted but urgently needed.

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Dr. Shorr had full access to the data and takes responsibility for the content of the paper including all analyses.

Author contributions

Study concept and design: AFS, MDZ, JH, JK, STM, MHK

Acquisition of data: JH, JK, STM

Analysis and interpretation of data: AFS, MDZ, STM, MHK

Drafting the manuscript: AFS, MDZ, MHK

Critical revision of the manuscript for important intellectual content: AFS, MDZ, JH, JK, STM, MHK

Statistical expertise: AFS, MDZ

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Study supervision: AFS,MHK

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Baseline Characteristics

Table 1.

	Hospital Death (n=21)	Hospital Survival (n=166)	p
Demographics			
-Age, mean±SD, years	66.8±18.23	55.7±15.0	0.002
-Male, n,%	10, 47.6%	84, 50.6%	0.821
-Race			
Caucasian, n,%	10, 47.6%	87, 52.4%	0.767
African-American, n,%	11, 52.4%	77, 46.5%	
Other, n,%	0, 0. %	2, 1.2%	
Severity of Illness			
-CURB 65 Score, median	4	2	0.025
-CURB score distribution			--
0, n,%	0, 0%	28, 16.9%	
1, n,%	2, 9.5%	51, 30.7%	
2, n,%	0, 0%	28, 16.9%	
3, n,%	6, 28.6%	29, 17.5%	
4, n,%	10, 47.6%	25, 15.1%	
5 n,%	3, 14.3%	5, 3%	
-ICU Admission, n,%	5, 22.9%	6, 3.6%	0.001
-Mechanical Ventilation, n,%	6, 27.8%	8, 4.8%	0.001
Comorbidities			
-LTC admission, n,%	2, 11.1%	19, 11.4%	0.999

-HD, n,%	0%	4, 2.4%	0.999
-Immunosuppression, n,%	7, 33.3%	38, 22.9%	0.289
-Prior antibiotics, n,%	7, 33.3%	40, 24.1%	0.423
-Recent hospitalization, n,%	3, 14.1%	15, 9.0%	0.353
Infection-related Characteristics			
-Bacteremia, n,%	3, 14.1%	13, 7.8%	0.256
-Delay in appropriate antibiotics, %*	13, 61.9%	151, 91.0%	0.001
Non-azithromycin Antibiotic therapy			0.099
-Ceftriaxone, n,%	7, 33.3%	104, 62.7%	
-Cefipeme, n,%	8, 38.1%	23, 13.9%	
-Moxifloxacin, n, %	1, 4.8%	21, 12.7%	
-Piperacillin/tazobactam, n, %	2, 9.5%	8, 4.8%	
-Other, n, %	3, 14.3%	10, 6.0%	

Variables Associated with Hospital Mortality

Table 2a

	Unadjusted Odds Ratio	Adjusted Odds Ratio (AOR)	95% Confidence Interval for AOR	P for AOR
-Age, per year	--	1.05	1.01-1.09	0.018
-Need for MV	8.14	8.82	2.74-28.46	0.001
-Appropriate therapy	0.16	0.13	0.03-0.47	0.002
-Use of Azithromycin	0.20	0.26	0.08-0.80	0.018

Sensitivity Analysis for Mortality

Table 2b

	Unadjusted Odds Ratio	Adjusted Odds Ratio (AOR)	95% Confidence Interval for AOR	P for AOR
-Age, per year	--	1.02	0.98-1.05	0.368
-CURB-65 score, per point increase	--	2.07	1.32-3.25	0.001
-Appropriate therapy	0.16	0.12	0.03-0.42	0.001
-Use of Azithromycin	0.20	0.34	0.11-0.88	0.041

Azithromycin and Survival In Streptrococcus pneumoniae Pneumonia: A Retrospective Study

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Azithromycin and Survival In *Streptrococcus pneumoniae* Pneumonia: A Retrospective Study

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ARTICLE SUMMARY

Article focus

-To determine the impact of azithromycin co-therapy on outcomes in *Streptococcus pneumoniae* pneumonia

Key messages

-Azithromycin co-therapy in pneumonia due to *S. pneumoniae* is associated with improved short-term survivial

-This finding is independent of multiple potential confounders including timeliness of antibiotic treatment

Strengths and limitations of this study

-Strengths: large sample of pure *S. pneunmoniae* pneumonia

-Limitations: Data derive from a single center and the study's retrospective design

ABSTRACT

Objective: *S. pneumoniae* (SP) represents a major pathogen in pneumonia. The impact of azithromycin on mortality in SP pneumonia remains unclear. Recent safety concerns regarding azithromycin have raised alarm about this agent's role with pneumonia. We sought to clarify the relationship between survival and azithromycin use in SP pneumonia.

Design: Retrospective cohort.

Setting: Urban, academic hospital.

Participants: Adults with a diagnosis of SP pneumonia (Jan-Dec 2010). The diagnosis of pneumonia required a compatible clinical syndrome and radiographic evidence of an infiltrate.

Intervention: None

Primary and secondary outcome measures: Hospital mortality served as the primary endpoint, and we compared subjects given azithromycin to those not treated with this. Co-variates of interest included demographics, severity of illness, comorbidities, and infection related characteristics (eg, appropriateness of initial treatment, bacteremia). We employed logistic regression to assess the independent impact of azithromycin on hospital mortality.

Results: The cohort included 187 subjects (mean age: 67.0 ± 8.2 years, 50.3% male, 5.9% admitted to the ICU). The most frequently utilized non-macrolide antibiotics included: ceftriaxone (n=111), cefipeme (n=31), and moxifloxacin (n=22). Approximately 2/3rds of the cohort received azithromycin. Crude mortality was lower in persons given azithromycin (5.6% vs. 23.6%, $p<0.01$). The final survival model included four variables: age, need for mechanical ventilation, initial appropriate therapy, and azithromycin use. The adjusted odds ratio for mortality associated with azithromycin equaled 0.26 (95% confidence interval: 0.08-0.80, p=0.018).

Conclusions: SP pneumonia generally remains associated with substantial mortality while azithromycin treatment is associated with significantly higher survival rates. The impact of azithromycin is independent of multiple potential confounders.

INTRODUCTION

Pneumonia remains a leading cause of morbidity and mortality. Annually more than 1.3 million patients in the United States (US) present to the hospital with pneumonia and require admission.[1] Direct costs related to pneumonia exceed several billion each year in the US.[1] Because of this burden, multiple efforts have focused on improving the care of patient with pneumonia and attempted to address means for enhancing outcomes in this disease and hospitalists often care for and design hospital pathways for those admitted with pneumonia.

Concurrent with these quality efforts, the microbiology of pneumonia presenting to the hospital has evolved. Over the last decade, pathogens traditionally thought confined to the hospital, such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, now are implicated in non-nosocomial pneumonia.[2,3] This epidemiologic trend led to the creation of the concept of healthcare-associated pneumonia (HCAP).[2,3] At the same time, rates of pneumonia in adults due to *Streptococcus pneumoniae* have diminished, in part due to the effects of herd immunity arising from the use of the newer vaccines in children.[4] Nonetheless, *S. pneumoniae* remains a leading pathogen in non-nosocomial pneumonia, whether it be CAP or HCAP and whether it results in mild disease or more severe illness necessitating admission to the intensive care unit (ICU).[5,6] Furthermore, current treatment guidelines for HCAP do not suggest consideration of adjunctive macrolide antibiotics, despite the fact that *S. pneumoniae* can still be seen in this syndrome.[3,5,7] While some surveillance studies indicate that *S. pneumoniae* remains the most prevalent pathogen in patients admitted with pneumonia via the ED, other studies suggest that *S. pneumoniae* often represents either the second or third most frequent pathogen in this setting.[5,6,8] Thus, despite it potentially being less prevalent than in prior years, *S. pneumoniae* continues to lead to a disproportionate burden on the healthcare system.

Macrolide antibiotics, particularly azithromycin, are unique as anti-infective agents in that they appear to have potent anti-inflammatory properties.[9] Earlier analyses suggest that azithromycin exposure may confer a mortality advantage in CAP, irrespective of the causative pathogen.[10,11] This

observation has resulted in treatment guidelines recommending utilization of macrolides in CAP and their continuation even if the patient is concurrently being treated with another in vitro active antimicrobial as one potential approach.[12] Many of the reports supporting a survival benefit related to macrolide use in CAP, though, have been limited because they either were conducted in an era before HCAP became a concern or because they often did not account for issues related to rates of initially appropriate antimicrobial administration. These reports have also explored CAP as a syndrome, regardless of the pathogen, and not specifically addressed *S. pneumoniae*. Recent descriptions of potential cardiovascular toxicities arising with azithromycin reinforce the need to elucidate if this agent alters mortality.[13] A potential survival benefit related to azithromycin in *S. pneumoniae* pneumonia would indicate that the risk/benefit calculus favors utilization of this agent not withstanding concerns about rhythm disturbances.

We hypothesized that co-treatment with azithromycin would improve mortality in pneumonia due to *S. pneumoniae* and that this effect would be independent of confounding arising from failure to administer appropriate initial antibiotic therapy. To explore our hypothesis, we conducted a retrospective analysis of all subjects with either CAP or HCAP admitted with evidence of infection related to *S. pneumoniae*.

METHODS

Study Overview and Subjects

We retrospectively identified all adult (age > 18 years) patients admitted with a clinical diagnosis of pneumonia between January 1, 2010 and December 31, 2010. All patients were required to have initially presented to the ED. We defined pneumonia based on both signs and symptoms of infection (ie, elevated white blood cell count or > 10% band forms, fever or hypothermia). We further required compatible chest imaging documenting an infiltrate(s). One investigator (MHK), blinded to the clinical and microbiologic information adjudicated the chest imaging. Identification of *S. pneumoniae* was based on the results of cultures from either blood, pleural fluid, sputum, or the lower airways. A positive urinary antigen for *S. pneumoniae* also was used to document infection with this pathogen. The patients

described in this report have been previously included in an earlier analysis validating the concept of HCAP.[3] The Washington University School of Medicine Human Studies Committee approved the study (# 201205194). As this was a retrospective analysis, there was no requirement for informed consent.

Endpoints and Co-variates

Hospital mortality represented the primary endpoint. We compared persons with pneumococcal pneumonia initially treated with azithromycin to those not given this agent. During the observation period, this was the only macrolide available for treatment of pneumonia at the study hospital. There were no subjects given clarithromycin. Co-variates of interest included patient demographics, severity of illness, and infection related variables. For demographic factors we noted age, gender, and race. With respect to co-morbidities, we recorded if the subject was residing in a nursing home or long-term care facility, was recently hospitalized in the last 90 days, had received antimicrobials in the last 30 days, suffered from end stage renal disease requiring hemodialysis, or was immunosuppressed. We defined immunosuppression based on the presence of either acquired-immunodeficiency syndrome (AIDS), active malignancy undergoing chemotherapy, or treatment with immunosuppressants (ie, 10 mg prednisone or equivalent daily for at least 30 days or alternate agents such as methotrexate). To assess disease severity we calculated the CURB-65 score along with recording if there was a need for either ICU care or mechanical ventilation (MV).[14] With respect to infection-related variables we determined if bacteremia complicated the pneumonia and the initial antibiotic regimen. We classified the initial antibiotic regimen as appropriate if a non-macrolide antibiotic that was *in vitro* active against the *S. pneumoniae* isolate was administered within 4 hours of presentation. [15] At the host institution, antibiotic administration is protocolized such that all subjects received a non-macrolide anti-infective with activity against pneumoccocus. Therefore, appropriateness of antibiotics was a reflection of the timeliness of administration. Additionally, by convention, patients given combination treatment including azithromycin received these drugs concurrently.

Statistics

We completed univariate analyses with either the Fisher's exact test or Student's t-test as appropriate. Continuous, non-parametrically distributed data was compared via the Mann-Whitney U test. All analyses were two tailed, and a p value of < 0.05 was assumed to represent statistical significance. To determine independent factors associated with mortality, we employed logistic regression. Variables significant at $P<0.10$ level in univariate analyses were entered into model. We utilized an enter approach for the regression. Co-linearity was explored with correlation matrices. Adjusted odds ratios (AORs) and ninety-five percent confidence intervals (CIs) are reported where appropriate. The model's goodness-of-fit was assessed via calculation of the R^2 value and the Hosmer-Lemeshow c-statistic. All analyses were performed with SPSS 19.0 (SPSS, Chicago, IL).

RESULTS

During the study period 977 persons were admitted via the ED with evidence of bacterial pneumonia. Of these patients, 187 were infected with *S. pneumoniae*. The mean age of these subjects was 57.0 +/- 8.2 years and approximately half were male. The crude hospital mortality in *S. pneumoniae* pneumonia equaled 11.2% while the mean hospital length of stay measured 8.2 +/- 5.0 days. The most commonly utilized non-azithromycin antibiotics were ceftriaxone (n=111), cefipeme (n= 31), and moxifloxacin (n=22).

Table 1 reveals the differences in baseline characteristics between subjects dying while hospitalized and those surviving to discharge. Those who died were older but there were no other differences in demographics. Patients dying were more severely ill based on all measures used to assess this. Specifically, survivors had lower CURB-65 scores as compared to decedents (median CURB-65 class 4 vs 2, p=0.025). More than a quarter of those dying received MV while fewer than 5% of those discharged alive required MV (p=0.001). The distribution of criteria defining HCAP did not differ between groups. Approximately 11% of all patients resided in nursing homes prior to admission and the

rate of admission from nursing homes did not correlate with hospital mortality. Immunosuppression was prevalent in the study population but this also did not differ between those dying and survivors.

With respect to infection-related characteristics, the frequency of bacteremia was similar between the two groups. Compared to those who survived, however, those who died were more likely to have been given delayed antibiotic therapy (38.1% vs. 9.0%, p=0.001). In all instances, inappropriate therapy occurred not because of the use of an *in vitro* inactive agent but because of a delay in the initiation of antibiotics. All isolates were susceptible to the agents actually administered.

Hospital mortality rates were significantly lower in persons treated with azithromycin. Of patients given the macrolide, only 5.4% expired in the hospital as opposed to 23.8% of persons not treated with such an agent (Figure 1). The odds ratio (OR) for death with a macrolide was 0.20 (94% CI: 0.08-0.52).

In the logistic regression, four variables remained independently associated with mortality (Table 2a). Mortality increased with increasing age (AOR 1.05, 95% CI: 1.01-1.09, p=0.018) and with the need for MV (AOR 8.82, 95% CI: 2.74-28.46, <0.001). Timely antibiotic therapy resulted in lower in-hospital death rates (AOR, 0.13, 95% CI: 0.03-0.46, p=0.002). Finally, treatment with azithromycin correlated with enhanced survival. Azithromycin exposure was independently associated with a reduced risk for death by nearly 75% (AOR 0.26, 95% CI: 0.08-0.90, p=0.018). Neither being classified as HCAP nor any of the individual criteria defining HCAP stayed in the final model. The model had excellent fit with an R^2 value of 0.42 and a C-statistic of 0.991. In a sensitivity analysis (Table 2b) where CURB 65 score was employed as a marker for severity of illness rather than either need for MV or ICU admission, treatment with azithromycin remained associated with a lower probability for mortality (AOR 0.34, 95% CI: 0.11-0.88).

DISCUSSION

This retrospective analysis of a cohort of patients with microbiologically confirmed pneumococcal pneumonia indicates that co-administration of azithromycin is associated with significant reductions in short-term mortality. This effect is independent of multiple potential confounders such as severity of illness and the timeliness and activity of initial antimicrobial therapy. The positive impact of azithromycin was also independent of whether bacteremia was present.

Prior efforts evaluating the significance of macrolide therapy on outcomes in CAP have reached conflicting conclusions. Some large case series indicate a survival benefit in persons given macrolides while others have failed to detect such an impact. For example, Martin-Loeches and colleagues observed that macrolide use reduced the risk for mortality in intubated patients with CAP.[10] Tessemer et al. in a large observational German study also noted that macrolide exposure improved cure rates and short-term mortality.[11] In pneumococcal bacteremia complicating pneumonia, Metersky conclude that macrolide use improved 30 day readmission and mortality rates [15]. On the other hand, Asadi and co-workers reported that mortality rates were similar among 3000 patients treated with either monotherapy with a fluroquinolone as opposed to a beta-lactam /macrolide combination.[17] Wilson et al additionally determined that inclusion of a macrolide in the antibiotic regimen failed to enhance survival in elderly patients with CAP.[18] Meta-analyses are similarly conflicting in their assessments. One recent meta-analysis including 16 randomized controlled trials (RCTs) evaluating fluroquinolones against beta-lactam/macrolide combinations calculated that there was no difference in mortality between these regimens.[19] Another group of investigators, though, included both observational reports and RCTs and determined that macrolide administration offered a small but statistically significant mortality benefit.[20]

Our findings add to this debate and are novel in several respects. First, one potential limitation of the above-mentioned studies is that they tend to pool all subjects with CAP, irrespective of culture findings. In contrast, we restricted our evaluation to patients with confirmed *S. pneumoniae* infection whether they had CAP or risk factors for HCAP. Including subjects with either syndrome serves to underscore the need to focus on the pathogen rather than the infectious syndrome. Treatment guidelines

currently stratify persons in to two cohorts based on their risk factors for infection with resistant pathogens.[7,12] This scheme ignores the point that pneumococcal infection occurs in both CAP and HCAP. Our results suggest that revision of the guidelines may be appropriate as we noted a mortality benefit with azithromycin even after controlling for factors and co-morbidities which define HCAP.

Furthermore, some of the subjects in earlier reports failed to have either evidence of bacterial infection or were infected with a pathogen other than *S. pneumoniae*. In some instances, only administrative coding data rather than actual culture results facilitated subject identification. This distinction is important in that the immunomodulatory effects of azithromycin have been most clearly elucidated as it relates to infection with *S. pneumoniae*. Although broadly anti-inflammatory in a number of ways, the strongest biologic evidence of a potential means for an impact in pulmonary infection relates to investigations in *S. pneumoniae*. More importantly these effects of macrolides alter both cellular and humoral immunity. *In vitro*, azithromycin, for instance, prevents apoptosis of human polymorphonuclear lymphocytes and may reduce interleukin (IL)-8 production.[21,22] Exposure to azithromycin, furthermore, reduces pneumolysin from both macrolide-susceptible and resistant strains of *S. pneumoniae*.[23] Azithromycin may also reduce production of tumor necrosis alpha and IL-1 alpha in human monocytes and down regulate natural killer cell production with an ensuing alteration in various cytokines.[24] Therefore, by focusing on a specific organism where the nexus with the theoretical mechanisms of immune modulation are better established, our observations help to clarify the discordant findings of others. Our results, in turn, suggest that the benefit of macrolide co-treatment may be restricted to persons with pneumococcal infection

We also specifically controlled for the timeliness of initial therapy. Initially appropriate and timely antibiotic treatment is a key determinant of survival in a number of severe infections ranging from bacteremia to septic shock.[25,26] Many prior studies of macrolides and *S. pneumoniae* pneumonia simply did not address the timing of initial antimicrobial therapy. In most RCTs, adjudicating the coverage and timeliness of initial therapy is clouded by the time window allowed to enroll patients in the specific clinical trial. Some observational reports have failed to explore the importance of this issue in

their analytic approaches. Others have simply determined whether an antibiotic regimen was concordant with formal treatment guidelines was given. This constitutes only a surrogate means for evaluating the true appropriateness of antimicrobial treatment as it does not examine specific *in vitro* susceptibilities or the timing of the antibiotic administration. We, however, specifically sought to rectify and address this limitation by applying specific and clear criteria.

Our overall patient outcomes suggest that our data are broadly generalizable. The crude hospital mortality rate was approximately 10%, as was the prevalence of bacteremia, reflecting what has been noted in multiple epidemiologic analyses.[1] Likewise, the average LOS in our cohort parallels the general LOS for this syndrome described in large analyses of US hospital discharge data. The goodness of fit of our final mortality prediction model was also excellent indicating that there is at most moderate unmeasured residual confounding. Many earlier analyses of case series data have not described either if or how well their modeling of outcomes fits their observations.

Ray and co-workers have sparked concern regarding macrolides and reported potential cardiovascular toxicity associated with azithromycin.[13] In a review of Medicaid claims data from Tennessee, these authors state that deaths due to cardiovascular causes were higher in subjects given azithromycin as compared to either no antibiotic or amoxicillin. This study has led to calls to re-evaluate our utilization of azithromycin.[27] The potential for a mortality benefit accruing with use of this drug in pneumococcal pneumonia should give pause to efforts to reflexively and broadly restrict access to azithromycin. The burden and prevalence of pneumococcal pneumonia suggest that it would be inappropriate for policy makers to mix all types of *S. pneumoniae* infection into one group as they make decisions regarding the availability of this agent. Our results suggest that a measured risk-benefit analysis is still required at the individual patient level.

The present study has several significant limitations. First, its retrospective nature exposes it to several forms of bias. However, unlike clinical cure, there is little potential for bias in determining at patient's vital status. Confounding by indication is a similar concern. If such confounding were present, though, we would expect this to bias our data towards the absence of an impact of azithromycin on

mortality, while we observed precisely the opposite. Second, the data represent the experience from a single center and thus may not be indicative of the experience of others. Likewise we only studied inpatients and so our results do not apply to patients not requiring admission. Third, given the constraints of modern microbiology and culture techniques there are certainly cases of pneumococcal pneumonia we missed. Fourth, only 5% of the population required ICU admission. As such, our results most reflect the experience of less severely ill subjects and the significance of azithromycin in critically ill persons may be different. These, though, are the patients most often cared for by hospitalists. Fifth we lacked information on certain co-variates that might have affected mortality, specifically underlying pulmonary and liver disease. Finally, the sample size precluded us from examining several important variables such as the exact timing of anti-infective administration (eg, by hour delay from presentation). Sample size also likely explains why some variables were not significant in our final model. That the CURB-65 score failed to represent a correlate of mortality in our initial model probably arose because other factors associated with survival (eg, need for MV) proved more strongly linked with mortality. Likewise, the vast majority of persons given azithromycin also were given a beta-lactam. As a result, few patients received either azithromycin alone or with moxifloxacin. Hence, we cannot exclude the possibility that the benefit with the macrolide is either a surrogate for exposure to a beta-lactam agent or a function of the combined use of azithromycin with this class of antibiotics.

In conclusion, co-administration of azithromycin appears to reduce mortality in persons admitted to the hospital with pneumoniae due to *S. pneumoniae*. This affect persists after adjusting for other important variables known to correlate with survival in this syndrome. Given the safety issues that have arisen with azithromycin along with the possible positive impact of this drug on hospital mortality, a randomized trial exploring the role for adjunctive azithromycin relative to placebo in CAP appears not only warranted but urgently needed.

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Dr. Shorr had full access to the data and takes responsibility for the content of the paper including all analyses.

Author contributions

Study concept and design: AFS, MDZ, JH, JK, STM, MHK

Acquisition of data: JH, JK, STM

Analysis and interpretation of data: AFS, MDZ, STM, MHK

Drafting the manuscript: AFS, MDZ, MHK

Critical revision of the manuscript for important intellectual content: AFS, MDZ, JH, JK, STM, MHK

Statistical expertise: AFS, MDZ

Obtained funding: MHK

Study supervision: AFS,MHK

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Baseline Characteristics

Table 1.

	Hospital Death (n=21)	Hospital Survival (n=166)	p
Demographics			
-Age, mean±SD, years	66.8±18.23	55.7±15.0	0.002
-Male, n,%	10, 47.6%	84, 50.6%	0.821
-Race			
Caucasian, n,%	10, 47.6%	87, 52.4%	0.767
African-American, n,%	11, 52.4%	77, 46.5%	
Other, n,%	0, 0. %	2, 1.2%	
Severity of Illness			
-CURB 65 Score, median	4	2	0.025
-CURB score distribution			--
0, n,%	0, 0%	28, 16.9%	
1, n,%	2, 9.5%	51, 30.7%	
2, n,%	0, 0%	28, 16.9%	
3, n,%	6, 28.6%	29, 17.5%	
4, n,%	10, 47.6%	25, 15.1%	
5 n,%	3, 14.3%	5, 3%	
-ICU Admission, n,%	5, 22.9%	6, 3.6%	0.001
-MV, n,%	6, 27.8%	8, 4.8%	0.001
Comorbidities			
-LTC admission, n,%	2, 11.1%	19, 11.4%	0.999

-HD, n,%	0%	4, 2.4%	0.999
-Immunosuppression, n,%	7, 33.3%	38, 22.9%	0.289
-Prior antibiotics, n,%	7, 33.3%	40, 24.1%	0.423
-Recent hospitalization, n,%	3, 14.1%	15, 9.0%	0.353
Infection-related Characteristics			
-Bacteremia, n,%	3, 14.1%	13, 7.8%	0.256
-Delay in appropriate antibiotics, %*	8, 38.1%	15, 9.0%	0.001
Antibiotic therapy			0.099
-Ceftriaxone, n,%	7, 33.3%	104, 62.7%	
-Cefipeme, n,%	8, 38.1%	23, 13.9%	
-Moxifloxacin, n, %	1, 4.8%	21, 12.7%	
-Piperacillin/tazobactam, n, %	2, 9.5%	8, 4.8%	
-Other, n, %	3, 14.3%	10, 6.0%	
-Any beta-lactam/cephalosporin	17, 81.0%	135, 81.8%	0.999
-Azithromycin	5, 23.8%	9, 5.4%	

Abbreviations: HD – hemodialysis; ICU – intensive care unit; LTC – long-term care; MV—Mechanical ventilation.

Variables Associated with Hospital Mortality

Table 2a

	Unadjusted Odds Ratio	Adjusted Odds Ratio (AOR)	95% Confidence Interval for AOR	P for AOR
-Age, per year	1.04	1.05	1.01-1.09	0.018
-Need for MV	8.14	8.82	2.74-28.46	0.001
-Appropriate therapy	0.16	0.13	0.03-0.47	0.002
-Use of Azithromycin	0.20	0.26	0.08-0.80	0.018

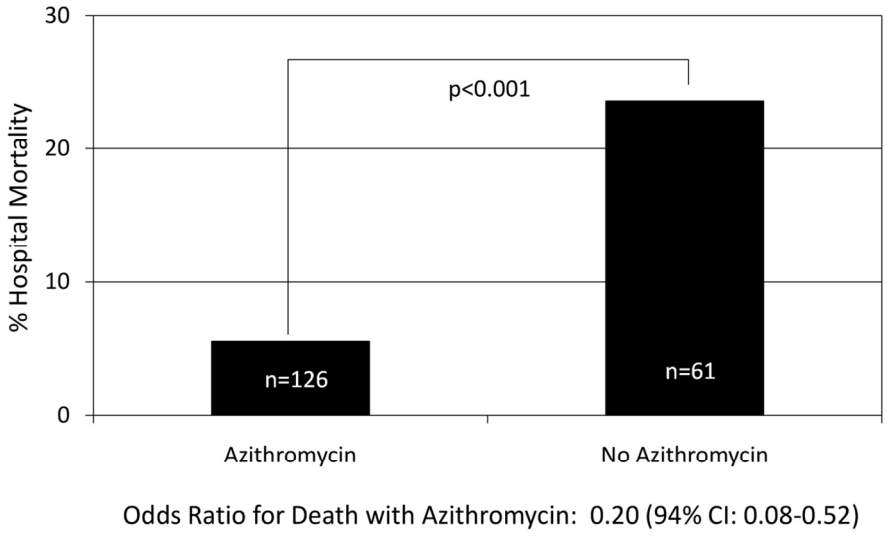
Abbreviations: MV – mechanical ventilation.

Sensitivity Analysis for Mortality

Table 2b

	Unadjusted Odds Ratio	Adjusted Odds Ratio (AOR)	95% Confidence Interval for AOR	P for AOR
-Age, per year	1.05	1.02	0.98-1.05	0.368
-CURB-65 score, per point increase	2.43	2.07	1.32-3.25	0.001
-Appropriate therapy	0.16	0.12	0.03-0.42	0.001
-Use of Azithromycin	0.20	0.34	0.11-0.88	0.041

Hospital Mortality and Azithromycin Treatment
Figure 1.



Odds Ratio for Death with Azithromycin: 0.20 (94% CI: 0.08-0.52)

119x90mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, Table
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Azithromycin and Survival In *Streptrococcus pneumoniae* Pneumonia: A Retrospective Study

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ARTICLE SUMMARY

Article focus

-To determine the impact of azithromycin co-therapy on outcomes in *Streptococcus pneumoniae* pneumonia

Key messages

-Azithromycin co-therapy in pneumonia due to *S. pneumoniae* is associated with improved short-term survivial

-This finding is independent of multiple potential confounders including timeliness of antibiotic treatment

Strengths and limitations of this study

-Strengths: large sample of pure *S. pneunmoniae* pneumonia

-Limitations: Data derive from a single center and the study's retrospective design

ABSTRACT

Objective: *S. pneumoniae* (SP) represents a major pathogen in pneumonia. The impact of azithromycin on mortality in SP pneumonia remains unclear. Recent safety concerns regarding azithromycin have raised alarm about this agent's role with pneumonia. We sought to clarify the relationship between survival and azithromycin use in SP pneumonia.

Design: Retrospective cohort.

Setting: Urban, academic hospital.

Participants: Adults with a diagnosis of SP pneumonia (Jan-Dec 2010). The diagnosis of pneumonia required a compatible clinical syndrome and radiographic evidence of an infiltrate.

Intervention: None

Primary and secondary outcome measures: Hospital mortality served as the primary endpoint, and we compared subjects given azithromycin to those not treated with this. Co-variates of interest included demographics, severity of illness, comorbidities, and infection related characteristics (eg, appropriateness of initial treatment, bacteremia). We employed logistic regression to assess the independent impact of azithromycin on hospital mortality.

Results: The cohort included 187 subjects (mean age: 67.0 ± 8.2 years, 50.3% male, 5.9% admitted to the ICU). The most frequently utilized non-macrolide antibiotics included: ceftriaxone (n=111), cefipeme (n=31), and moxifloxacin (n=22). Approximately 2/3rds of the cohort received azithromycin. Crude mortality was lower in persons given azithromycin (5.6% vs. 23.6%, $p<0.01$). The final survival model included four variables: age, need for mechanical ventilation, initial appropriate therapy, and azithromycin use. The adjusted odds ratio for mortality associated with azithromycin equaled 0.26 (95% confidence interval: 0.08-0.80, p=0.018).

Conclusions: SP pneumonia generally remains associated with substantial mortality while azithromycin treatment is associated with significantly higher survival rates. The impact of azithromycin is independent of multiple potential confounders.

INTRODUCTION

Pneumonia remains a leading cause of morbidity and mortality. Annually more than 1.3 million patients in the United States (US) present to the hospital with pneumonia and require admission.[1] Direct costs related to pneumonia exceed several billion each year in the US.[1] Because of this burden, multiple efforts have focused on improving the care of patient with pneumonia and attempted to address means for enhancing outcomes in this disease and hospitalists often care for and design hospital pathways for those admitted with pneumonia.

Concurrent with these quality efforts, the microbiology of pneumonia presenting to the hospital has evolved. Over the last decade, pathogens traditionally thought confined to the hospital, such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, now are implicated in non-nosocomial pneumonia.[2,3] This epidemiologic trend led to the creation of the concept of healthcare-associated pneumonia (HCAP).[2,3] At the same time, rates of pneumonia in adults due to *Streptococcus pneumoniae* have diminished, in part due to the effects of herd immunity arising from the use of the newer vaccines in children.[4] Nonetheless, *S. pneumoniae* remains a leading pathogen in non-nosocomial pneumonia, whether it be CAP or HCAP and whether it results in mild disease or more severe illness necessitating admission to the intensive care unit (ICU).[5,6] Furthermore, current treatment guidelines for HCAP do not suggest consideration of adjunctive macrolide antibiotics, despite the fact that *S. pneumoniae* can still be seen in this syndrome.[3,5,7] While some surveillance studies indicate that *S. pneumoniae* remains the most prevalent pathogen in patients admitted with pneumonia via the ED, other studies suggest that *S. pneumoniae* often represents either the second or third most frequent pathogen in this setting.[5,6,8] Thus, despite it potentially being less prevalent than in prior years, *S. pneumoniae* continues to lead to a disproportionate burden on the healthcare system.

Macrolide antibiotics, particularly azithromycin, are unique as anti-infective agents in that they appear to have potent anti-inflammatory properties.[9] Earlier analyses suggest that azithromycin exposure may confer a mortality advantage in CAP, irrespective of the causative pathogen.[10,11] This

observation has resulted in treatment guidelines recommending utilization of macrolides in CAP and their continuation even if the patient is concurrently being treated with another in vitro active antimicrobial as one potential approach.[12] Many of the reports supporting a survival benefit related to macrolide use in CAP, though, have been limited because they either were conducted in an era before HCAP became a concern or because they often did not account for issues related to rates of initially appropriate antimicrobial administration. These reports have also explored CAP as a syndrome, regardless of the pathogen, and not specifically addressed *S. pneumoniae*. Recent descriptions of potential cardiovascular toxicities arising with azithromycin reinforce the need to elucidate if this agent alters mortality.[13] A potential survival benefit related to azithromycin in *S. pneumoniae* pneumonia would indicate that the risk/benefit calculus favors utilization of this agent not withstanding concerns about rhythm disturbances.

We hypothesized that co-treatment with azithromycin would improve mortality in pneumonia due to *S. pneumoniae* and that this effect would be independent of confounding arising from failure to administer appropriate initial antibiotic therapy. To explore our hypothesis, we conducted a retrospective analysis of all subjects with either CAP or HCAP admitted with evidence of infection related to *S. pneumoniae*.

METHODS

Study Overview and Subjects

We retrospectively identified all adult (age > 18 years) patients admitted with a clinical diagnosis of pneumonia between January 1, 2010 and December 31, 2010. All patients were required to have initially presented to the ED. We defined pneumonia based on both signs and symptoms of infection (ie, elevated white blood cell count or > 10% band forms, fever or hypothermia). We further required compatible chest imaging documenting an infiltrate(s). One investigator (MHK), blinded to the clinical and microbiologic information adjudicated the chest imaging. Identification of *S. pneumoniae* was based on the results of cultures from either blood, pleural fluid, sputum, or the lower airways. A positive urinary antigen for *S. pneumoniae* also was used to document infection with this pathogen. The patients

described in this report have been previously included in an earlier analysis validating the concept of HCAP.[3] The Washington University School of Medicine Human Studies Committee approved the study (# 201205194). As this was a retrospective analysis, there was no requirement for informed consent.

Endpoints and Co-variates

Hospital mortality represented the primary endpoint. We compared persons with pneumococcal pneumonia initially treated with azithromycin to those not given this agent. During the observation period, this was the only macrolide available for treatment of pneumonia at the study hospital. There were no subjects given clarithromycin. Co-variates of interest included patient demographics, severity of illness, and infection related variables. For demographic factors we noted age, gender, and race. With respect to co-morbidities, we recorded if the subject was residing in a nursing home or long-term care facility, was recently hospitalized in the last 90 days, had received antimicrobials in the last 30 days, suffered from end stage renal disease requiring hemodialysis, or was immunosuppressed. We defined immunosuppression based on the presence of either acquired-immunodeficiency syndrome (AIDS), active malignancy undergoing chemotherapy, or treatment with immunosuppressants (ie, 10 mg prednisone or equivalent daily for at least 30 days or alternate agents such as methotrexate). To assess disease severity we calculated the CURB-65 score along with recording if there was a need for either ICU care or mechanical ventilation (MV).[14] With respect to infection-related variables we determined if bacteremia complicated the pneumonia and the initial antibiotic regimen. We classified the initial antibiotic regimen as appropriate if a non-macrolide antibiotic that was *in vitro* active against the *S. pneumoniae* isolate was administered within 4 hours of presentation. [15] At the host institution, antibiotic administration is protocolized such that all subjects received a non-macrolide anti-infective with activity against pneumoccocus. Therefore, appropriateness of antibiotics was a reflection of the timeliness of administration. Additionally, by convention, patients given combination treatment including azithromycin received these drugs concurrently.

Statistics

We completed univariate analyses with either the Fisher's exact test or Student's t-test as appropriate. Continuous, non-parametrically distributed data was compared via the Mann-Whitney U test. All analyses were two tailed, and a p value of < 0.05 was assumed to represent statistical significance. To determine independent factors associated with mortality, we employed logistic regression. Variables significant at $P<0.10$ level in univariate analyses were entered into model. We utilized an enter approach for the regression. Co-linearity was explored with correlation matrices. Adjusted odds ratios (AORs) and ninety-five percent confidence intervals (CIs) are reported where appropriate. The model's goodness-of-fit was assessed via calculation of the R^2 value and the Hosmer-Lemeshow c-statistic. All analyses were performed with SPSS 19.0 (SPSS, Chicago, IL).

RESULTS

During the study period 977 persons were admitted via the ED with evidence of bacterial pneumonia. Of these patients, 187 were infected with *S. pneumoniae*. The mean age of these subjects was 57.0 +/- 8.2 years and approximately half were male. The crude hospital mortality in *S. pneumoniae* pneumonia equaled 11.2% while the mean hospital length of stay measured 8.2 +/- 5.0 days. The most commonly utilized non-azithromycin antibiotics were ceftriaxone (n=111), cefipeme (n= 31), and moxifloxacin (n=22).

Table 1 reveals the differences in baseline characteristics between subjects dying while hospitalized and those surviving to discharge. Those who died were older but there were no other differences in demographics. Patients dying were more severely ill based on all measures used to assess this. Specifically, survivors had lower CURB-65 scores as compared to decedents (median CURB-65 class 4 vs 2, p=0.025). More than a quarter of those dying received MV while fewer than 5% of those discharged alive required MV (p=0.001). The distribution of criteria defining HCAP did not differ between groups. Approximately 11% of all patients resided in nursing homes prior to admission and the

rate of admission from nursing homes did not correlate with hospital mortality. Immunosuppression was prevalent in the study population but this also did not differ between those dying and survivors.

With respect to infection-related characteristics, the frequency of bacteremia was similar between the two groups. Compared to those who survived, however, those who died were more likely to have been given delayed antibiotic therapy (38.1% vs. 9.0%, ~~61.9% vs. 91.0%;~~ p=0.001). In all instances, inappropriate therapy occurred not because of the use of an *in vitro* inactive agent but because of a delay in the initiation of antibiotics. All isolates were susceptible to the agents actually administered.

Hospital mortality rates were significantly lower in persons treated with azithromycin. Of patients given the macrolide, only 5.4% expired in the hospital as opposed to 23.8% of persons not treated with such an agent (Figure 1). The odds ratio (OR) for death with a macrolide was 0.20 (94% CI: 0.08-0.52).

In the logistic regression, four variables remained independently associated with mortality (Table 2a). Mortality increased with increasing age (AOR 1.05, 95% CI: 1.01-1.09, p=0.018) and with the need for MV (AOR 8.82, 95% CI: 2.74-28.46, <0.001). Timely antibiotic therapy resulted in lower in-hospital death rates (AOR, 0.13, 95% CI: 0.03-0.46, p=0.002). Finally, treatment with azithromycin correlated with enhanced survival. Azithromycin exposure was independently associated with a reduced risk for death by nearly 75% (AOR 0.26, 95% CI: 0.08-0.90, p=0.018). Neither being classified as HCAP nor any of the individual criteria defining HCAP stayed in the final model. The model had excellent fit with an R^2 value of 0.42 and a C-statistic of 0.991. In a sensitivity analysis (Table 2b) where CURB 65 score was employed as a marker for severity of illness rather than either need for MV or ICU admission, treatment with azithromycin remained associated with a lower probability for mortality (AOR 0.34, 95% CI: 0.11-0.88).

DISCUSSION

This retrospective analysis of a cohort of patients with microbiologically confirmed pneumococcal pneumonia indicates that co-administration of azithromycin is associated with significant reductions in short-term mortality. This effect is independent of multiple potential confounders such as severity of illness and the timeliness and activity of initial antimicrobial therapy. The positive impact of azithromycin was also independent of whether bacteremia was present.

Prior efforts evaluating the significance of macrolide therapy on outcomes in CAP have reached conflicting conclusions. Some large case series indicate a survival benefit in persons given macrolides while others have failed to detect such an impact. For example, Martin-Loeches and colleagues observed that macrolide use reduced the risk for mortality in intubated patients with CAP.[10] Tessemer et al. in a large observational German study also noted that macrolide exposure improved cure rates and short-term mortality.[11] In pneumococcal bacteremia complicating pneumonia, Metersky conclude that macrolide use improved 30 day readmission and mortality rates [15]. On the other hand, Asadi and co-workers reported that mortality rates were similar among 3000 patients treated with either monotherapy with a fluroquinolone as opposed to a beta-lactam /macrolide combination.[17] Wilson et al additionally determined that inclusion of a macrolide in the antibiotic regimen failed to enhance survival in elderly patients with CAP.[18] Meta-analyses are similarly conflicting in their assessments. One recent meta-analysis including 16 randomized controlled trials (RCTs) evaluating fluroquinolones against beta-lactam/macrolide combinations calculated that there was no difference in mortality between these regimens.[19] Another group of investigators, though, included both observational reports and RCTs and determined that macrolide administration offered a small but statistically significant mortality benefit.[20]

Our findings add to this debate and are novel in several respects. First, one potential limitation of the above-mentioned studies is that they tend to pool all subjects with CAP, irrespective of culture findings. In contrast, we restricted our evaluation to patients with confirmed *S. pneumoniae* infection whether they had CAP or risk factors for HCAP. Including subjects with either syndrome serves to underscore the need to focus on the pathogen rather than the infectious syndrome. Treatment guidelines

currently stratify persons in to two cohorts based on their risk factors for infection with resistant pathogens.[7,12] This scheme ignores the point that pneumococcal infection occurs in both CAP and HCAP. Our results suggest that revision of the guidelines may be appropriate as we noted a mortality benefit with azithromycin even after controlling for factors and co-morbidities which define HCAP.

Furthermore, some of the subjects in earlier reports failed to have either evidence of bacterial infection or were infected with a pathogen other than *S. pneumoniae*. In some instances, only administrative coding data rather than actual culture results facilitated subject identification. This distinction is important in that the immunomodulatory effects of azithromycin have been most clearly elucidated as it relates to infection with *S. pneumoniae*. Although broadly anti-inflammatory in a number of ways, the strongest biologic evidence of a potential means for an impact in pulmonary infection relates to investigations in *S. pneumoniae*. More importantly these effects of macrolides alter both cellular and humoral immunity. *In vitro*, azithromycin, for instance, prevents apoptosis of human polymorphonuclear lymphocytes and may reduce interleukin (IL)-8 production.[21,22] Exposure to azithromycin, furthermore, reduces pneumolysin from both macrolide-susceptible and resistant strains of *S. pneumoniae*.[23] Azithromycin may also reduce production of tumor necrosis alpha and IL-1 alpha in human monocytes and down regulate natural killer cell production with an ensuing alteration in various cytokines.[24] Therefore, by focusing on a specific organism where the nexus with the theoretical mechanisms of immune modulation are better established, our observations help to clarify the discordant findings of others. Our results, in turn, suggest that the benefit of macrolide co-treatment may be restricted to persons with pneumococcal infection

We also specifically controlled for the timeliness of initial therapy. Initially appropriate and timely antibiotic treatment is a key determinant of survival in a number of severe infections ranging from bacteremia to septic shock.[25,26] Many prior studies of macrolides and *S. pneumoniae* pneumonia simply did not address the timing of initial antimicrobial therapy. In most RCTs, adjudicating the coverage and timeliness of initial therapy is clouded by the time window allowed to enroll patients in the specific clinical trial. Some observational reports have failed to explore the importance of this issue in

their analytic approaches. Others have simply determined whether an antibiotic regimen was concordant with formal treatment guidelines was given. This constitutes only a surrogate means for evaluating the true appropriateness of antimicrobial treatment as it does not examine specific *in vitro* susceptibilities or the timing of the antibiotic administration. We, however, specifically sought to rectify and address this limitation by applying specific and clear criteria.

Our overall patient outcomes suggest that our data are broadly generalizable. The crude hospital mortality rate was approximately 10%, as was the prevalence of bacteremia, reflecting what has been noted in multiple epidemiologic analyses.[1] Likewise, the average LOS in our cohort parallels the general LOS for this syndrome described in large analyses of US hospital discharge data. The goodness of fit of our final mortality prediction model was also excellent indicating that there is at most moderate unmeasured residual confounding. Many earlier analyses of case series data have not described either if or how well their modeling of outcomes fits their observations.

Ray and co-workers have sparked concern regarding macrolides and reported potential cardiovascular toxicity associated with azithromycin.[13] In a review of Medicaid claims data from Tennessee, these authors state that deaths due to cardiovascular causes were higher in subjects given azithromycin as compared to either no antibiotic or amoxicillin. This study has led to calls to re-evaluate our utilization of azithromycin.[27] The potential for a mortality benefit accruing with use of this drug in pneumococcal pneumonia should give pause to efforts to reflexively and broadly restrict access to azithromycin. The burden and prevalence of pneumococcal pneumonia suggest that it would be inappropriate for policy makers to mix all types of *S. pneumoniae* infection into one group as they make decisions regarding the availability of this agent. Our results suggest that a measured risk-benefit analysis is still required at the individual patient level.

The present study has several significant limitations. First, its retrospective nature exposes it to several forms of bias. However, unlike clinical cure, there is little potential for bias in determining at patient's vital status. Confounding by indication is a similar concern. If such confounding were present, though, we would expect this to bias our data towards the absence of an impact of azithromycin on

mortality, while we observed precisely the opposite. Second, the data represent the experience from a single center and thus may not be indicative of the experience of others. Likewise we only studied inpatients and so our results do not apply to patients not requiring admission. Third, given the constraints of modern microbiology and culture techniques there are certainly cases of pneumococcal pneumonia we missed. Fourth, only 5% of the population required ICU admission. As such, our results most reflect the experience of less severely ill subjects and the significance of azithromycin in critically ill persons may be different. These, though, are the patients most often cared for by hospitalists. Fifth we lacked information on certain co-variates that might have affected mortality, specifically underlying pulmonary and liver disease. Finally, the sample size precluded us from examining several important variables such as the exact timing of anti-infective administration (eg, by hour delay from presentation). Sample size also likely explains why some variables were not significant in our final model. That the CURB-65 score failed to represent a correlate of mortality in our initial model probably arose because other factors associated with survival (eg, need for MV) proved more strongly linked with mortality. Likewise, the vast majority of persons given azithromycin also were given a beta-lactam. As a result, few patients received either azithromycin alone or with moxifloxacin. Hence, we cannot exclude the possibility that the benefit with the macrolide is either a surrogate for exposure to a beta-lactam agent or a function of the combined use of azithromycin with this class of antibiotics.

In conclusion, co-administration of azithromycin appears to reduce mortality in persons admitted to the hospital with pneumoniae due to *S. pneumoniae*. This affect persists after adjusting for other important variables known to correlate with survival in this syndrome. Given the safety issues that have arisen with azithromycin along with the possible positive impact of this drug on hospital mortality, a randomized trial exploring the role for adjunctive azithromycin relative to placebo in CAP appears not only warranted but urgently needed.

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Dr. Shorr had full access to the data and takes responsibility for the content of the paper including all analyses.

Author contributions

Study concept and design: AFS, MDZ, JH, JK, STM, MHK

Acquisition of data: JH, JK, STM

Analysis and interpretation of data: AFS, MDZ, STM, MHK

Drafting the manuscript: AFS, MDZ, MHK

Critical revision of the manuscript for important intellectual content: AFS, MDZ, JH, JK, STM, MHK

Statistical expertise: AFS, MDZ

Obtained funding: MHK

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Baseline Characteristics

Table 1.

	Hospital Death (n=21)	Hospital Survival (n=166)	p
Demographics			
-Age, mean±SD, years	66.8±18.23	55.7±15.0	0.002
-Male, n,%	10, 47.6%	84, 50.6%	0.821
-Race			
Caucasian, n,%	10, 47.6%	87, 52.4%	0.767
African-American, n,%	11, 52.4%	77, 46.5%	
Other, n,%	0, 0. %	2, 1.2%	
Severity of Illness			
-CURB 65 Score, median	4	2	0.025
-CURB score distribution			--
0, n,%	0, 0%	28, 16.9%	
1, n,%	2, 9.5%	51, 30.7%	
2, n,%	0, 0%	28, 16.9%	
3, n,%	6, 28.6%	29, 17.5%	
4, n,%	10, 47.6%	25, 15.1%	
5 n,%	3, 14.3%	5, 3%	
-ICU Admission, n,%	5, 22.9%	6, 3.6%	0.001
-MV, n,%	6, 27.8%	8, 4.8%	0.001
Comorbidities			
-LTC admission, n,%	2, 11.1%	19, 11.4%	0.999

-HD, n,%	0%	4, 2.4%	0.999
-Immunosuppression, n,%	7, 33.3%	38, 22.9%	0.289
-Prior antibiotics, n,%	7, 33.3%	40, 24.1%	0.423
-Recent hospitalization, n,%	3, 14.1%	15, 9.0%	0.353
Infection-related Characteristics			
-Bacteremia, n,%	3, 14.1%	13, 7.8%	0.256
-Delay in appropriate antibiotics, %*	8, 38.1%	15, 9.0%	0.001
Antibiotic therapy			0.099
-Ceftriaxone, n,%	7, 33.3%	104, 62.7%	
-Cefipeme, n,%	8, 38.1%	23, 13.9%	
-Moxifloxacin, n, %	1, 4.8%	21, 12.7%	
-Piperacillin/tazobactam, n, %	2, 9.5%	8, 4.8%	
-Other, n, %	3, 14.3%	10, 6.0%	
-Any beta-lactam/cephalosporin	17, 81.0%	135, 81.8%	0.999
-Azithromycin	5, 23.8%	9, 5.4%	

Abbreviations: HD – hemodialysis; ICU – intensive care unit; LTC – long-term care; MV—Mechanical ventilation.

Variables Associated with Hospital Mortality

Table 2a

	Unadjusted Odds Ratio	Adjusted Odds Ratio (AOR)	95% Confidence Interval for AOR	P for AOR
-Age, per year	1.04	1.05	1.01-1.09	0.018
-Need for MV	8.14	8.82	2.74-28.46	0.001
-Appropriate therapy	0.16	0.13	0.03-0.47	0.002
-Use of Azithromycin	0.20	0.26	0.08-0.80	0.018

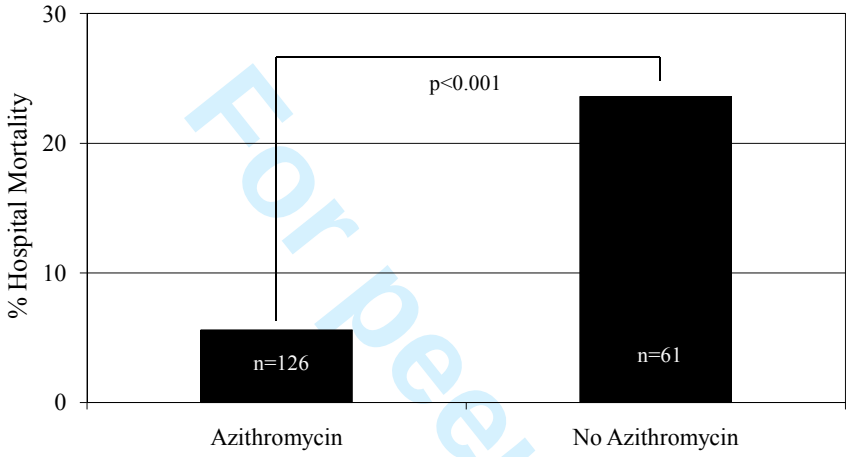
Abbreviations: MV – mechanical ventilation.

Sensitivity Analysis for Mortality

Table 2b

	Unadjusted Odds Ratio	Adjusted Odds Ratio (AOR)	95% Confidence Interval for AOR	P for AOR
-Age, per year	1.05	1.02	0.98-1.05	0.368
-CURB-65 score, per point increase	2.43	2.07	1.32-3.25	0.001
-Appropriate therapy	0.16	0.12	0.03-0.42	0.001
-Use of Azithromycin	0.20	0.34	0.11-0.88	0.041

Hospital Mortality and Azithromycin Treatment
Figure 1.



Odds Ratio for Death with Azithromycin: 0.20 (94% CI: 0.08-0.52)