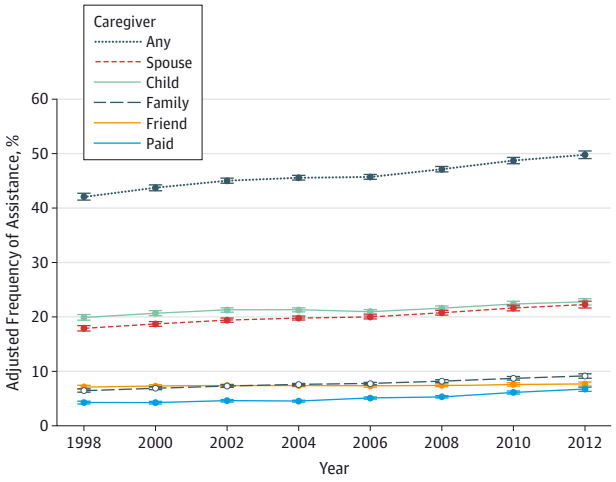
Figure. Adjusted Frequency of Caregiver Assistance for Homebound Functionally Disabled People Older Than 55 Years, 1998-2012



Error bars indicate 95% CIs.

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COMMENT & RESPONSE

Management of Community-Acquired Pneumonia

To the Editor Dr Lee and colleagues[1] addressed several important questions in their review of the management of community-acquired pneumonia. We have concerns about the analysis of time to first antibiotic dose and the conclusions inferred from the use of observational studies.

For the time to first antibiotic dose, the authors found only observational studies and included only those adjusting the mortality analysis for other risk factors. Exclusion of studies that did not report an adjusted association estimate disregards studies in which there was no association between time to antibiotic initiation and mortality in the bivariable analysis and therefore did not enter the variable into the adjusted analysis. Another analysis including such studies showed no association between time to first antibiotic dose and mortality.[2]

In the systematic review, large studies found an association between early initiation and survival, whereas small studies did not. Rather than the study size, clinical and methodological variables explaining the discrepant results of different studies would have been more interesting. One such variable is whether community-acquired pneumonia was defined by admission or discharge diagnosis. In other words, was the analysis limited to patients with documented community-acquired pneumonia (answers a pathophysiological question) or to all patients suspected of community-acquired pneumonia in the emergency department (answers a clinical and practical question).

The larger studies were retrospective and based on discharge diagnosis, whereas the smaller studies investigated the real-life consequences of starting antibiotics in the emergency department for patients suspected of having community-acquired pneumonia. Adopting the recommendation of 4 to 8 hours to the first antibiotic dose can lead to overdiagnosis of pneumonia and increase unnecessary use of antibiotics.[3,4]

The review claimed to provide "an evidence-based assessment of" antibiotic therapy for adults with community-acquired pneumonia. Evidence-based medicine relies mainly on randomized clinical trials and high-quality observational studies. However, all of the studies assessing time to antibiotic initiation were observational and of low quality.

The Cochrane Collaboration is trying to promote careful wording of conclusions based on quality of evidence assessment.[5] Therefore, the conclusion that "Antibiotic therapy should be initiated within 4 to 8 hours of hospital arrival" is too definitive. We believe that a better conclusion would have been that there is no or insufficient evidence for many basic interventions in the management of community-acquired pneumonia and that well-conducted randomized clinical trials are needed.

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To the Editor A systematic review concluded that "antibiotic therapy should be initiated within 4 to 8 hours of hospital arrival for patients with radiographically confirmed pneumonia and moderate to high levels of illness severity at presentation."[1] It is unclear from the included studies that this time to antibiotic therapy initiation is applicable to patients with moderate to severe community-acquired pneumonia.

The reviewed studies that showed the benefit of time to antibiotic initiation within 4 to 8 hours of presentation either did not adjust for severity of community-acquired pneumonia by pneumonia severity index (PSI) or demonstrated the benefit in the whole cohort of patients, not in the subgroup with moderate to severe pneumonia.[2-5] These studies included many older patients (aged ≥65 years) with comorbid conditions, who are expected to have an elevated PSI score.

In 1 of the studies, Lee and colleagues[2] showed a decrease in annual mortality for patients with pneumonia due mainly to a decrease in mortality in patients not in the intensive care unit. Appropriate antibiotics were selected for 59.7% to 76.5% of patients in the intensive care unit and for 88.1% to 94.5% of patients outside the intensive care unit. Appropriate antibiotic selection had a stronger association with improved mortality than time to antibiotic initiation within 6 hours of presentation.

Meehan and colleagues[3] found the benefit of time of antibiotic initiation within 8 hours of hospital arrival in the whole cohort of patients with community-acquired pneumonia with PSI scores of II to V, but not specifically in patients with PSI scores of IV and V (at high risk). Houck and colleagues[4] adjusted for the severity of pneumonia using the PSI score in a study in which 71% of the included patients had PSI scores of IV and V. They found that antibiotic administration within 4 hours was associated with decreased 30-day mortality and reduced length of hospital stay in both low-risk (PSI scores of II and III) and high-risk patients.

In addition, Arnold and colleagues[5] used the PSI score to adjust for the severity of community-acquired pneumonia. They found improved mortality with administration of either an atypical or typical antimicrobial regimen within 8 hours of admission in the whole cohort that included patients with PSI scores of I to V, but not specifically in patients with PSI scores of IV and V.

Despite the recommendation to start antibiotic therapy within 4 to 8 hours of hospital presentation for patients with moderate to severe community-acquired pneumonia, strong evidence for this recommendation does not yet exist.

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To the Editor Dr Lee and colleagues[1] systematically reviewed the literature on empirical antibiotic treatment for patients with community-acquired pneumonia requiring admission to the hospital and concluded that β-lactam plus macrolide combination therapy or fluoroquinolone monotherapy is superior to β-lactam monotherapy. The authors mainly based their conclusion on observational studies, which are prone to residual confounding and usually overestimate treatment effects.[2] For the comparison of β-lactam monotherapy with β-lactam plus macrolide combination therapy, the 2 high-quality trials provide evidence for the opposite conclusion.

One study was a noninferiority trial with individual randomization in selected patients with community-acquired pneumonia, yielding a nonsignificant increase in 30-day mortality of 1.4% (P = .42) in the β-lactam monotherapy group vs the combination group; clinical stability criteria were reached more rapidly with combination therapy (4.5 days) vs monotherapy (5 days).[3] The other was a cluster randomized clinical trial comparing different empirical treatment strategies among patients receiving antibiotics for presumed community-acquired pneumonia. In this study, 90-day mortality for radiologically confirmed community-acquired pneumonia was 2.5% (90% CI, −0.6% to 5.2%) higher with β-lactam plus macrolide combination therapy compared with β-lactam monotherapy, but the result was not statistically significant.[4] Thus, both results are in line with the hypothesis of no difference.

Noninferiority for survival was also demonstrated in the comparison between β-lactam and fluoroquinolone monotherapy.[4] For that comparison, the 3% noninferiority criterion was not met for the subgroup with radiologically confirmed community-acquired pneumonia, but that does not mean that the trial supports the superiority of fluoroquinolone monotherapy. Because this was a subgroup analysis, the smaller sample size reduced statistical precision. Yet despite the wider confidence interval, the point estimate remained −0.7% (90% CI, −3.4% to 1.8%). Moreover, other

outcome measures, such as length of stay, were not different between the groups. Furthermore, although the authors noted that antibiotics covering atypical pathogens were still used in 27% of patients in the β-lactam monotherapy group, they failed to acknowledge that there was a reduction in use of these antibiotics by 57% to 62% compared with the other 2 strategies.

The beneficial effects of β-lactam plus macrolide combination therapy or fluoroquinolone treatment must be clearly demonstrated on relevant outcomes before these strategies, known to increase antibiotic selective pressure, are widely recommended as first-line treatment for community-acquired pneumonia in hospitalized patients. Findings from the only high-quality studies in the review do not support such a recommendation.

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In Reply Dr Paul and colleagues question our decision to exclude observational studies that did not perform statistical adjustment for illness severity or comorbidity when assessing the association between time to initiate antibiotic therapy and mortality. All studies meeting eligibility for this question were observational in design and had a high likelihood of confounding by indication (ie, patients who were more severely ill would be more likely to have antibiotic therapy initiated rapidly). Therefore, we considered it imperative to focus the review on studies with adjustment for such confounding.

We concur that distinguishing patients with radiographically confirmed and clinically suspected community-acquired pneumonia is clinically important and that the use of these disparate study populations could help answer distinct questions regarding the benefits and risks of more rapid initiation of antibiotic therapy. Because our goal was to evaluate patients with radiographically confirmed community-acquired pneumonia and we limited the review to studies meeting this criterion, we do not believe the timing of diagnosis (ie, on admission or discharge) affects the interpretation of these studies.

We agree with the stated concern for unintended consequences of antibiotic overuse driven by premature, rapid initiation of antibiotic therapy in inconclusively diagnosed patients. Consequently, we made our recommendation for timely initiation of antibiotic therapy for patients with radiographically confirmed pneumonia. In addition, the current low-quality evidence base for time to antibiotic initiation is unlikely to be supplemented by higher-quality randomized clinical trials. Therefore, we based our conclusions on the available observational, severity-adjusted studies.

Dr Bader questions the limitation of our recommendation for time to initiate antibiotic therapy to patients with moderate to severe illness severity at presentation. The majority of studies demonstrating a benefit for more rapid antibiotic initiation comprised older patients (aged ≥65 years) with half or more classified as moderate to high risk when assessed using the PSI. Rather than concluding that antibiotic therapy should be initiated within 4 to 8 hours of hospital arrival in all hospitalized patients, we more conservatively recommended such therapy in patients with moderate to severe illness severity, both reflecting the composition of the study populations and balancing the benefits of early initiation with the potential harms of antibiotic overuse.

Dr van Werkhoven and colleagues draw attention to our interpretation of the 2 randomized clinical trials addressing the selection of empirical antibiotic therapy for community-acquired pneumonia. The trial by Garin and colleagues[1] failed to demonstrate noninferiority of β-lactam monotherapy vs β-lactam plus macrolide combination therapy using attainment of clinical stability on hospital day 7 as the primary outcome. Although there was no statistically significant difference in mortality between the 2 groups in this study, the trial was not powered for this outcome.

To maintain consistency in study populations across clinical questions, we limited our review to patients with radiographically confirmed community-acquired pneumonia. We concede that results from the study by Postma and colleagues[2] do not support the superiority of fluoroquinolone monotherapy, but neither do they clearly support noninferiority of β-lactam monotherapy for this more targeted population.

Because our conclusions regarding antibiotic selection were informed by a larger body of observational than experimental evidence, we support the need for additional randomized clinical trials to assess the optimal choice of empirical antibiotic therapy for patients with community-acquired pneumonia.

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Hospitalization After a Return Visit to the Emergency Department

To the Editor In an investigation on outcomes and resource use of adult patients hospitalized during return visits to the emergency department (ED), Dr Sabbatini and colleagues[1] reported that compared with patients hospitalized during index ED visits without subsequent ED return, patient admissions during return to the ED were associated with lower inpatient mortality, intensive care unit admission rates, and costs.

The analysis was based on data obtained by linking hospital discharge records from the Healthcare Cost and Utilization Project (HCUP) databases for New York and Florida and used rigorous regression techniques, including logit models for binomial outcomes (mortality and intensive care unit admission rates), a log-link model with a negative binomial distribution for modeling length of stay, and a log-link model with a γ distribution for modeling cost, while accounting for within-hospital correlation.

Despite the robust analysis accounting for the design of the HCUP databases, the authors' findings should be interpreted with caution. The missing data in the HCUP data sets for certain exposures included in the case-mix adjustments (such as age, race, sex, and primary payer) may introduce bias in the absence of a model-based multiple imputation approach. To mitigate potential confounding, matched imputed cohorts should have been used, balancing covariates using appropriate propensity score matching algorithms and assessing intervariable improvements in standardized differences.

Iterating propensity-adjusted models, with no missing values for exposures, and exploring the relationship of the primary exposure of interest (ED return admission vs no return visit) with outcomes as part of a sensitivity analysis would have been an interesting analysis of the data. Certain unobserved confounders known to affect readmission rates and possibly outcomes in such patients include socioeconomic status,[2] area of residence,[3] level of education, marital status, mode of transport, emergency medical services arrival time, neurological status, hospital and physician volume, and hospital characteristics,[4] albeit unaccounted for in the current analysis.

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In Reply Dr Kalakoti and colleagues raise 2 important questions about our analysis of outcomes among patients hospitalized during an ED return visit. The first is the effect of missing data in the HCUP data sets and the second is the potential for unadjusted confounding to bias the results of the study.

First, the amount of missing data for the variables used in our regression models was low in HCUP data sets, amounting to less than 0.01% for age, sex, and primary payer. In the Florida State Inpatient Database, race was missing in approximately 1% of cases, whereas in New York, race was missing in less than 0.01% of cases. These low amounts of missing data are unlikely to have systematically affected the assessment of outcomes in the study and the use of multiple imputation, as suggested, would have added little value.

The effect of missing data on Elixhauser comorbidities is more challenging. The HCUP comorbidity software uses an algorithm that runs through *International Classification of Diseases, Ninth Revision,* codes and assigns an indicator for the presence or absence of each comorbidity. As a result, there are no missing data for any of the Elixhauser comorbidities in the HCUP databases.

However, the accuracy of assigning comorbidities depends on the quality and completeness of the administrative data reported by state agencies to HCUP, as well as the completeness of hospital coding of patient comorbidities in the medical record. This is a well-known limitation of using administrative data for outcomes analysis, and we agree that it is likely that there is some level of incomplete coding of patient comorbidities by hospitals that cannot be addressed by statistical techniques. Nevertheless, it is unlikely that incomplete coding of comorbidities was systematically biased in any of the revisit cohorts across the large sample of hospitals that were included in the study.

Second, Kalakoti and colleagues raise the suggestion of using propensity scores to compare outcomes among the revisit cohorts. Although propensity matching generally produces a stronger comparative analysis, in this case, in which only a small number of covariates with good overlap in values across the cohorts was used, propensity matching has