Guideline-Recommended Antibiotics in Community-Acquired Pneumonia

Not Perfect, but Good

COMMUNITY-ACQUIRED PNEUMONIA (CAP) is a common, morbid, and mortal disease, and appropriate antibiotic therapy remains the cornerstone of management. Patients hospitalized with CAP can be infected with both typical and atypical bacterial organisms.1 Most evidence indicates that clinical features (signs and symptoms) at presentation are not specific enough to consistently predict the causative agent.1 Therefore, absent unique epidemiologic characteristics, the overwhelming majority of patients must be treated empirically. To improve the quality of care and decrease practice variability, professional societies have published guidelines for the management of CAP, including recommending specific empirical antibiotic regimens.

See also pages 1515 and 1525

For patients outside of the intensive care unit, most of these guidelines, including the most recent Infectious Diseases Society of America and American Thoracic Society (IDSA/ATS) consensus guidelines,1 recommend either a β-lactam plus a macrolide or a respiratory fluoroquinolone. The guideline recommendations were derived from multiple large retrospective cohort studies that showed decreased mortality associated with the above regimens.2-3 Despite these published guidelines and adherence to the guidelines being used as a measure of quality in the treatment of community-acquired pneumonia,1 controversy exists in the literature regarding the most appropriate initial empirical antibiotics for patients hospitalized with CAP.

EVIDENCE SUPPORTING GUIDELINE-RECOMMENDED REGIMENS

In the last 5 years, a growing body of evidence supports the use of empirical regimens to target both typical and atypical organisms. Many published articles have been observational, documenting improved outcomes in hospitalized patients with CAP who receive guideline-concordant antibiotics—that is, in those who are treated with antibiotics in accordance with the available published guidelines. Three retrospective cohort studies involving in total more than 5000 patients in different settings (community, tertiary academic, and international hospitals) reported that patients who received guideline-concordant antibiotic regimens had decreased inhospital or 30-day mortality.4-6 Two large Medicare databases of elderly patients (65 years or older) admitted with CAP were analyzed and also revealed lower 30-day mortality in patients treated with antibiotic regimens compliant with pneumonia guidelines.7,8 Given the retrospective nature of all of these studies, attempts were made to control for potential confounding factors, which might have affected the outcomes. These factors included patient characteristics,4-8 degree of illness using the Pneumonia Severity Index,2,4-7 and other process-of-care measures (eg, time to antibiotic treatment initiation, blood cultures performed within 24 hours of admission, and other measures).2,4-7 Overall, the mortality benefits were significant: the absolute risk reduction ranged from 1.3% to 15.5%, with an average of approximately 5%.2,4-8 This risk reduction corresponds to a number needed to treat of 20—that is, only 20 patients hospitalized with pneumonia would have to be given guideline-concordant antibiotics to save 1 life. The evidence is not perfect by any means, but it is good.

CONTROVERSY PERSISTS

Other researchers strongly disagree with the guideline-recommended regimens on the basis of 2 issues. Many argue that the retrospective and cohort nature of the evidence makes it impossible to control for possible confounders.7,9 The primary concern raised has been confounding by indication—that is, patients who are given treatment for atypical organisms (in accordance with the guidelines) in a nonrandomized fashion may be different than those treated with a β-lactam alone or treated with other regimens. In a prospective observational study of patients hospitalized with CAP, which adjusted for the likelihood of receiving atypical coverage through a propensity analysis, no benefit was found for the addition of a macrolide to a β-lactam in a CAP regimen.9 In addition, those who question the guidelines for CAP point to a meta-analysis and systematic review of randomized-controlled trials comparing regimens with atypical coverage to regimens without, neither of which revealed a difference in mortality or clinical response.10,11 Based on these arguments and with concurrent concerns about increasing resistance, medication adverse effects, and cost to the health care system, some researchers contend that adding atypical coverage to the management of CAP in the hospital should not be routine.9,11
NEW CONTRIBUTIONS

Two articles in this issue of the Archives add to the literature regarding appropriate empirical antibiotic regimens in CAP and augment the evidence in support of the current guidelines.12,13 The articles provide not only additional data for consideration but are methodologically sound, use different data sources, and examine unique and varied patient populations hospitalized with CAP.

Arnold et al12 performed a secondary analysis of an international database (the Community-Acquired Pneumonia Organization international cohort) of patients 65 years or older and hospitalized with CAP. For the 1725 patients, the authors compared outcomes between those who were given antibiotics in accordance with the 2007 IDSA/ATS consensus guidelines1 and those who were not. Possible confounders were controlled for, including disease severity (by Pneumonia Severity Index), clinical features, and processes of care (including time to antibiotic treatment initiation and blood cultures taken within 24 hours of admission). Patients who received guideline-concordant antibiotic regimens had decreased time to clinical stability, shorter hospital length of stay (LOS), and lower in-hospital and CAP-related mortality. The overall absolute risk reduction in mortality in the hospital was 9.9%, with a number needed to treat of 10.

These results are consistent with the prior research involving elderly patients (65 years or older) with CAP.2,7,8 but are unique in a number of ways. The study by Arnold et al12 involved a broad international group of patients, strictly evaluated each patient for the diagnosis of CAP, controlled for potential confounding factors, and showed a benefit not only in LOS and mortality but also in time to clinical stability. As the authors point out, time to clinical stability as a short-term outcome may be strongly linked to processes of care in the management of pneumonia (including antibiotic selection). To my knowledge, this result was reported in only 2 previous studies.4,5

In the companion article, McCabe et al13 analyze data from a large database of 54,620 patients with International Classification of Diseases, Ninth Revision (ICD-9) diagnoses of pneumonia from 113 hospitals (both community and teaching) in the United States. Similar to Arnold et al.,12 the authors compare outcomes in patients who were treated with guideline-concordant antibiotic regimens with those who were not. After controlling for severity of illness and other patient characteristics, McCabe et al13 found that there was a statistically significant decrease in in-hospital mortality (odds ratio, 0.70; 95% confidence interval, 0.63-0.77) and LOS (by 0.6 days) (P < .001) in those patients treated in accordance with the 2007 IDSA/ATS guidelines.3 These patients also had an improvement in short-term outcomes, including decreased sepsis and renal failure and earlier switch to oral therapy. The improved outcomes were linked specifically to the addition of macrolide agents to β-lactam regimens or the use of fluoroquinolones. Although McCabe et al13 were somewhat limited in their ability to control for confounders, the results expand prior research: the study involved a large database in urban and rural settings, included both community and tertiary hospitals, and showed improvement in both clinical outcomes and resource utilization.

IMPLICATIONS FOR RESEARCHERS AND CLINICIANS

Direction for Researchers

What are the implications of these 2 publications12,13 in the context of the broader controversy surrounding guideline-recommended antibiotic regimens for CAP? It seems that there are messages for both researchers and clinicians. For researchers, these articles direct future research and raise a series of intriguing issues. First and foremost, we need a large, multicenter, randomized controlled trial comparing β-lactam monotherapy with β-lactam plus a macrolide in patients hospitalized with CAP. Many of the experts in the field have called, often loudly, for this research.2,3,6,9,11

Second, if the results of these studies are valid, what is the cause of the benefit in the use of fluoroquinolones or the addition of macrolides to β-lactam CAP regimens? Arnold et al12 and McCabe et al13 postulate that it may be related to targeted therapy for atypical pathogens, especially Legionella species.12,13 A recent international study revealed that atypical agents are relatively common and causative in up to 28% of all cases of nonsevere CAP.9 Others have postulated that any benefit might be a result of the recognized anti-inflammatory or immunomodulatory effects of macrolides.3,4,12,13

Third, can we identify which patients are most likely to benefit from atypical coverage? Future studies of patients with CAP should focus on rapid bedside testing to determine the etiologic agent, or the development of clinical prediction rules to allow for early identification of those patients most likely to benefit from guideline-concordant therapy.

Finally, the impact of health care–associated pneumonia (HCAP) on the prior research is unclear. Recent evidence suggests HCAP is associated with increased mortality and worse clinical outcomes when compared with CAP and patients with HCAP may require broader spectrum antibiotics.14 HCAP was only recently recognized as a distinct clinical entity and therefore the articles by Arnold et al and McCabe et al as well as most of the retrospective studies described herein included patients from nursing homes and did not specifically exclude patients with other risk factors for HCAP. Future research on the treatment of CAP must actively exclude this patient population.

Clinical Ramifications

For clinicians, these 2 articles12,13 add to the growing body of robust evidence supporting guideline-recommended antibiotic regimens in patients hospitalized with CAP. Notably, to my knowledge, none of the prior research in this area, retrospective or otherwise, has documented any clear negative consequences to these regimens: at this point any adverse effects remain hypothetical in the face of a potentially substantial mortality benefit. In addition, while it is possible that the results of the 2 articles...
in the present issue of the Archives and other cohort studies can be explained by unmeasured confounders, it is unlikely. As McCabe et al state, this would require the presence of an unrecognized or uncontrolled confounder with an impact as large as the mortality benefit documented (a relative risk reduction of 30%-40% in these 2 studies); it is difficult to imagine what such a confounder might be.

Therefore, while we await further research, patients hospitalized with CAP should receive treatment with guideline-concordant antibiotic regimens covering both typical and atypical organisms. Health care systems should act to standardize treatment for all patients with CAP based on the current guidelines through whatever means are available: education, reminders, clinical pathways, or information technology. To paraphrase Voltaire, we should not let the perfect be the enemy of the good. The data supporting guideline-recommended therapies are not perfect, but they are good. They were made even better with the addition of the articles by Arnold et al and McCabe et al.

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REFERENCES