Antibiotic Administration in Community-Acquired Pneumonia

To the Editor:

Silber et al (November 2003) performed an observational study of 409 hospitalizations for community-acquired pneumonia (CAP). They were unable to detect an association between the administration of antimicrobial agents within 4 h of hospital presentation and the shorter time to clinical stability (TCS), and thus concluded that clinicians should not be held to a door-to-needle time of < 8 h. They expressed concern that there was insufficient evidence to support the measurement of a “door-to-needle time” of 4 h made by the Medicare National Pneumonia Project (MNPP), because it had not been linked with reduced in-hospital mortality, TCS, or length of stay. As collaborators in the development of the MNPP, we appreciate the opportunity to describe the rationale for reducing its timing measure from 8 to 4 h and to comment on the authors’ results.

The foundation of the use of antimicrobial timing as a pneumonia performance measure can be found in the work by Meehan et al. They studied 14,069 Medicare pneumonia hospitalizations from 1994 to 1995, and found that door-to-needle times as short as 3 h were associated with a lower 30-day mortality rate and that the association became statistically significant at 8 h. They reported a stronger association when the analysis was limited to patients who had not received therapy with antimicrobial agents before hospital presentation, but they did not report additional results for this restricted cohort. As a result, from 1999 through mid-2002 the MNPP promoted the administration of antimicrobial agents within 8 h after arrival at the hospital.

We examined an additional 13,771 Medicare CAP hospitalizations from 1998 to 1999. Analysis was stratified by prehospital antimicrobial treatment, and was adjusted for disease severity, demographics, and whether the initial antimicrobial regimen was consistent with published guidelines. Among the > 75% of patients with no evidence of prehospital treatment, a door-to-needle time of ≤ 4 h was associated with a lower mortality rate in the hospital (adjusted odds ratio, 0.85; 95% confidence interval, 0.74 to 0.98) and within 30 days of hospital admission (odds ratio, 0.85; 95% confidence interval, 0.76 to 0.95). Similar associations were observed for times as short as 3 h and for Pneumonia Patient Outcomes Research Team risk classes II/III and IV/V. The mean length of stay was significantly shorter among patients who were treated within 4 h. No timing-mortality association was demonstrated among patients who had evidence of any prehospital treatment. Portions of our preliminary findings were presented at the American College of Emergency Physicians Research Forum in October 2001 and in a letter to the editor in April 2002. In April 2003, a manuscript with the full study results was accepted for publication. The Infectious Diseases Society of America reviewed our results and included a 4-h timing recommendation in its recent update of CAP treatment guidelines.

Based on the data obtained from 1998 to 1999 and from 1994 to 1995, we reduced the MNPP antimicrobial timing target to 4 h in 2002. An important consideration was our projection that a modest improvement in attaining 4-h door-to-needle times could prevent > 1,200 deaths each year among Medicare pneumonia patients who are hospitalized without prior treatment. Limiting the promotion of such timing to previously untreated patients was judged to be impractical. Given all of the evidence, we thought that it would have been unjustified and unethical for us to delay the implementation of the more aggressive timing target until the full results of our work appeared in print.

We think that the conclusion of Silber et al has very limited applicability to the MNPP timing measure. Small differences in TCS are of little importance to hospitalized patients when compared to clinical success measured by survival. Hence, an inability to link reduced TCS with 4-h timing should not determine whether that process is promoted, particularly when it has, in fact, been associated with improved survival.

We also have concerns about the statistical methods used by the authors. The inclusion of cases with prehospital oral antimicrobial treatment and the exclusion of cases in which patients did not reach clinical stability (the outcome of interest) may have seriously affected the results. It would have been more appropriate to use survival analysis and to treat the latter such cases as censored observations at the time of death or hospital discharge. It is also unclear why the sample size calculation was based on geometric means when it appears that only arithmetic means were reported. It would require > 900 patients per group to detect a difference of ≥ 0.5 days in the arithmetic mean TCS using the one-tailed t test, if one sets α at 0.05, power at 0.80, and the assumed TCS SD at 4 days (as reported). Finally, while there were substantial differences in patient demographics across the three groups, it appears that multivariate analyses were not performed to control for the confounding that is common in observational studies. Although “multiple” linear regression was mentioned in the methods, it appears that only univariate linear regressions (ie, 1:1 variable correlation) were reported.

The change in the MNPP antimicrobial timing measure to 4 h was based on a sample with adequate statistical power and was associated by sound analysis with a clinical outcome that is highly relevant to patients. Had we delayed this change until our results were published, we would have failed our responsibility to promote the most effective care for Medicare beneficiaries. We did not have the freedom to ignore the information that we possessed or to postpone the action that it appeared to demand.

Peter M. Houck, MD
Centers for Medicare & Medicaid Services
Seattle, WA

Dale W. Bratzler, DO, MPH
Wato Nsu, MD, PhD
Oklahoma Foundation for Medical Quality
Oklahoma City, OK

John G. Bartlett, MD
Johns Hopkins University School of Medicine
Baltimore, MD

REFERENCES
1 Silber SH, Garrett C, Singh R, et al. Early administration of antibiotics does not shorten time to clinical stability in...

Anti-inflammatory Effect of Pentoxifylline

To the Editor:

We read with great interest the recent in vitro study by Tong and colleagues.¹ We have some comments. First, the authors implicated the possibility of pentoxifylline as a therapeutic option for pulmonary sarcoidosis. A study² has described that pentoxifylline has no severe side effects as compared with dexamethasone. However, as Tong et al³ introduced in their discussion, pentoxifylline has no significant suppression of interleukin-1β and interferon-γ, T-helper type 1-derived cytokines.³ T-cells play a central role in cell-mediated immune responses through the production of type 1 cytokines, such as interferon-γ and interleukin-2. It has been reported that the suppression of T-helper type 1 function damages the host response to fungi.⁴ We should give careful consideration when using the agent, especially its long-term use in clinical stages, because it may lead to mycosis in patients.

In addition, we wonder if dexamethasone could not inhibit lipopolysaccharide-induced interleukin-1β expression in alveolar macrophages in the experiment by Tong et al.¹ Glucocorticoids are potent inhibitors of immune response, inflammation, and endotoxic shock. This occurs, at least partly, through an inhibition of the synthesis of proinflammatory cytokines and chemokines.⁵–⁷

One of the target enzymes of glucocorticoids inhibition is interleukin-1β. Dexamethasone (10 nmol/L to 10 μmol/L) inhibits interleukin-1 messenger RNA in lipopolysaccharide-stimulated human monocytes in a dose-dependent fashion.⁸ Also, dexamethasone suppresses interleukin-1β gene expression in lipopolysaccharide-stimulated RAW 264.7 cells through the inhibition of the activation of transcription factors related to endotoxin such as nuclear factor-κB and activator protein-1.⁹ Other mechanisms may be present in lipopolysaccharide-induced interleukin-1 production in alveolar macrophages of patients with sarcoidosis.

Ken-ichiro Inoue, MD
Hirolisa Takano, MD, PhD
Rie Yamao, MD
Miki Sakurai, MD
National Institute for Environmental Studies
Tsukuba, Japan

References
2 Ward A, Clissold SP. Pentoxifylline: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. Drugs 1987; 34:50–97
7 Lee SW, Tsou AP, Chan H, et al. Glucocorticoids selectively inhibit the transcription of the interleukin 1β gene and decrease the stability of interleukin 1β mRNA. Proc Natl Acad Sci U S A 1988; 85:1204–1208