Commentary

Lessons learned from 2 decades of CAP therapy data: ways to improve patient management

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Community-acquired pneumonia (CAP) is the leading cause of death from infectious disease in North America, accounting for over 60,000 deaths in the United States in 2005 (1). CAP encompasses a wide range of clinical presentations resulting in variable clinical outcomes. While mild forms lead to mortality in less than 5% and may be safely treated in outpatient settings, more severe forms necessitate intensive care unit (ICU) admission and are associated with mortality rates exceeding 30% (2).

In their recent review published in *The Journal of American Medical Association*, Lee *et al.* (3), surveyed two decades [1995–2015] of CAP literature investigating optimal antibiotic choice, time to antibiotic initiation, and criteria guiding the transition from intravenous to oral antibiotics. The authors concluded that for patients with radiographically confirmed pneumonia, who do not require ICU admission, a lower adjusted short-term mortality rate results when CAP treatment, with either a β-lactam plus macrolide combination regimen or a fluoroquinolone alone, is started within 4–8 hours of hospital arrival.

This conclusion is consistent with the treatment goals in the 2007 IDSA/ATS CAP consensus guidelines (4), in which the authors recommended starting antibiotic therapy in the emergency department, as soon as the diagnosis of pneumonia is confirmed, but not within a specific time frame.

The time to initiation of antibiotic therapy is an important variable, and Lee *et al.* identified eight observational studies looking at the relationship between mortality and the time to start therapy, concluding that initiation of therapy within 4–8 hours of arrival was associated with a reduction in either in-hospital or 30-day mortality. The data supporting this conclusion are controversial, since evidence in favor of earlier use tends to be stronger in retrospective studies (in which the diagnosis of CAP is known), than in prospective studies. In the latter case, many patients without confirmed CAP may be inappropriately treated with antibiotics, exposing some to adverse events without providing significant benefits. With today's focus on processes of care, it is important not to conflate the goal of delivering timely therapy in an organized and efficient manner with direct improvement in patient outcomes. One recent prospective study of 13,725 patients with CAP in the United Kingdom (5) found that the majority of the study population (63%) received antibiotics within 4 hours, and that this group had a reduced 30-day inpatient mortality, compared to those treated later. However, the authors could not determine if initiation of therapy was a quality measure itself or a marker of other beneficial processes of care. Conversely, it is plausible that delayed therapy in cases of CAP may be the result of CAP's indistinct clinical presentation, which hinders prompt recognition. The resulting diagnostic delay, rather than a delay in therapy itself, could be the factor associated with poor CAP outcomes.

While the 4–8 hours initiation time period is reasonable for patients with CAP treated outside of the ICU, we advocate for expedited antibiotic delivery, particularly for those who are critically ill, after the history, physical examination, and appropriate imaging studies are obtained, with or without supporting microbiological data. However, a focus on timing should not prevent a careful consideration of alternative diagnoses such as non-bacterial forms of lung infection, tracheobronchitis, pulmonary embolism, congestive heart failure, and autoimmune or drug-related pneumonitis. In the past, complications of antibiotic therapy, including drug-induced colitis, have been

documented when there has been an excessive focus on timing, and not on carefully evaluating for the presence of pneumonia (6).

In their evaluation of antibiotic selection, Lee *et al.* concluded that a β-lactam plus macrolide combination or fluoroquinolone monotherapy are preferable to β-lactam monotherapy. However, they identified only two "high-quality" randomized controlled trials (7,8) among the 11 trials reviewed in their analysis. These two studies deserve special scrutiny, especially because they highlight recent debate regarding the role of macrolides in the treatment of CAP. The CAP-START study by Postma *et al.* (7) used a cluster-randomized trial to investigate outcomes, including mortality, associated with different antibiotic strategies, assigning patients during distinct 4 month-time intervals to β-lactam monotherapy (n=656), β-lactam plus macrolide combination therapy (n=739), or fluoroquinolone monotherapy (n=888). A non-statistically significant trend towards lower 90-day mortality was associated with fluoroquinolone and β-lactam monotherapy (8.8% and 9.0%, respectively) compared with the β-lactam plus macrolide combination therapy (11.1%). The authors concluded that β-lactam monotherapy was non-inferior to β-lactam plus macrolide combination therapy. A number of aspects of this trial make this conclusion uncertain, including: (I) atypical pathogens accounted for an unusually small number of infections (2.1%) in the study population, whereas these organisms were responsible for 6.1% of infections encountered in hospitalized patients treated outside of the ICU in one large observational trial (9); (II) 38.7% of the patients treated in the β-lactam group ultimately received antibiotics directed against atypical organisms during the trial; (III) CAP was not confirmed radiographically in 25% of the study population; (IV) the study excluded patients managed in ICU settings, skewing the cohort towards those with low severity of illness; (V) adherence to the β-lactam plus macrolide combination therapy regimen was lower than adherence to the monotherapy regimen; (VI) Although the number of patients with severe illness was small, in this group, mortality was not higher in the combination therapy group. These limitations, in our estimation, make it difficult to conclude that the combination of a β-lactam plus a macrolide is not better than monotherapy with a β-lactam for hospitalized patients with CAP. Looking at a wealth of data from other studies, there may be some question of the value of adding a macrolide in patients without severe illness, but in those who are admitted to the hospital or ICU, combination therapy seems superior to monotherapy, with mortality and clinical response as the endpoints.

In contrast to the CAP-START trial, the study by Garin *et al.* did not find β-lactam monotherapy to be non-inferior to β-lactam plus macrolide combination therapy for the endpoint of time to clinical stability after 7 days of treatment, in hospitalized patients with moderately severe CAP (8). Specifically, the authors found that 41.2% of the patients in the monotherapy group did not reach clinical stability compared with 33.6% of patients in the combination group, with an absolute difference of 7.6%. Therefore the authors could not conclude non-inferiority of monotherapy compared with combination therapy. Of note, patients infected with atypical pathogens (HR, 0.33; 95% CI: 0.13–0.85) or with Pneumonia Severity Index (PSI) category IV pneumonia (HR, 0.81; 95% CI: 0.59–1.10) were not only less likely to reach clinical stability with monotherapy, but also had more 30-day readmissions with monotherapy, compared to combination therapy (7.9% *vs.* 3.1%, P=0.01).

While the review by Lee *et al.* is comprehensive, many other studies show the unique benefits of macrolide therapy in treating various forms of CAP. Indeed, macrolides as a class possess anti-inflammatory properties, and a number of related non-antibiotic macrolides, such as tacrolimus and sirolimus, are used as immunosuppressive therapy in transplant patients (10). Macrolides exert their antibacterial effects by inhibiting RNA synthesis and thus bacterial protein and biofilm production, while also attenuating bacterial virulence factors. Macrolide antibiotics also inhibit host cell cytokine production and release, and promote macrophage phagocytosis of apoptotic cells, reduce T-cell mediated inflammation, and limit neutrophil chemotaxis, survival, and oxidative burst (11). Therefore, the beneficial effects of macrolide antibiotics in CAP are thought to be pleiotropic, which is supported by the findings from a number of clinical trials.

A meta-analysis of 28 observational studies by Sligl *et al.* (12), including 9,850 patients with severe CAP, found that mortality risk was significantly lower when patients received macrolide therapy (risk ratio, 0.82; 95% CI: 0.70–0.97, P=0.02), compared to those not receiving such therapy. However, it is important to remember that all ICU patients should receive combination therapy, and never monotherapy, even with a fluoroquinolone. Interestingly, a trend towards lower mortality was observed in the β-lactam plus macrolide combination group compared with the β-lactam plus fluoroquinolone group in those with

Table 1 Lessons learned from 2 decades of data about CAP therapy

A β-lactam plus macrolide combination regimen, or fluoroquinolone monotherapy, are recommended for patients with CAP treated outside of the ICU
Macrolides play an important role in treating more severe forms of the disease, particularly for patients in the ICU
The benefits of macrolides may come from their non-antibiotic effects
Early initiation of antibiotic therapy, after clinical and radiographic evaluation is performed, and alternative diagnoses are excluded, ensures optimal CAP outcome
Timely therapy is especially valuable for severely ill patients, but a focus on timing should not lead to indiscriminate antibiotic use
Objective measures of clinical stability can promote rapid transition from intravenous to oral antibiotic therapy, without compromising morbidity, mortality, and readmissions, while decreasing hospital length of stay
The transition is optimized if there is an implementation plan in place, and not simply a guideline

severe CAP (risk ratio, 0.83; 95% CI: 0.67–1.03, P=0.09), suggesting that some of the benefit of macrolide therapy is not due to its antimicrobial properties, but to other effects. Another prospective, observational, multicenter trial of 218 critically ill patients with CAP requiring mechanical ventilation (nearly 76% meeting criteria for severe sepsis and septic shock) concluded that combination regimens containing a macrolide improved survival over regimens containing a quinolone (13). Interestingly, a study by Brown *et al.* (14) found improved 30-day survival when macrolides were added to quinolones, compared with quinolone monotherapy (2.91% *vs.* 4.94%, P<0.05), underlining the possibility that macrolide therapy added benefits beyond simply acting against atypical pathogens. Lastly, even in situations when the infecting organism is resistant to macrolide therapy (15), the addition of a macrolide to the treatment regimen decreased mortality. These findings should spur efforts to develop new macrolide compounds with primarily anti-inflammatory properties, for use in the future in patients with CAP.

Critics of macrolide therapy often refer to data linking them to increased cardiovascular adverse events (16). However, a recent retrospective study of 73,690 patients admitted to acute care Veterans Affairs hospitals found significantly lower 90-day mortality in patients treated with azithromycin compared to matched controls (17.4% *vs.* 22.3%) (17). Although a slight increased risk of myocardial infarction was discovered (5.1% *vs.* 4.4%), there were no differences in the rates of arrhythmia and congestive heart failure. These new data suggest that the cardiac effects of azithromycin are mitigated by the overall favorable impact on pneumonia outcome.

Finally, in their review, Lee *et al.* advocate for the use of objective criteria to guide conversion from intravenous to oral treatment in CAP. They identified one well-designed randomized controlled trial (18), which showed that when objective criteria were met, intravenous antibiotics could be safely transitioned to oral antibiotics approximately 3.5 days earlier, without significant differences in the composite endpoint of death, continued hospitalization at day 28, or clinical deterioration. Criteria for switching to oral therapy include: (I) respiratory rate <25 breaths/minute; (II) oxygen saturation >90% or arterial oxygen partial pressure >55 mmHg; (III) hemodynamic stability; (IV) greater than 1 °C decrease in temperature in patients with fever; (V) absence of mental confusion and (VI) ability to tolerate oral medications. By using such objective criteria, investigators were able to reduce hospital length of stay by almost 2 days, confirming other studies showing the benefit of using objective criteria to guide both the switch from intravenous to oral antibiotics (19,20), as well as the discharge decision (21,22). However, to optimize this transition from intravenous to oral therapy, a guideline itself is not sufficient and results are best when an implementation strategy for switch therapy is present (23).

We believe that the systematic review by Lee *et al.* points to a number of ways to improve CAP outcome, that are supported by data from a large number of studies (*Table 1*). The recommendations from their analysis apply not only to severely ill patients but also to other hospitalized CAP patients. The available data support the importance of macrolide therapy as part of a CAP regimen, compared to monotherapy with a β-lactam. The data also demonstrate the importance of early antibiotic initiation after prompt

recognition of CAP. These findings continue to build upon current evidence to safely transition CAP patients' antibiotics to oral therapy after an appropriately sustained clinical response, a beneficial intervention that does not add to morbidity, mortality, or readmission.

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Footnote

Conflicts of Interest: Dr. MS Niederman has consulted for Pfizer and Cempra related to macrolide therapy. Dr. MT Bender has no conflicts of interest to declare.

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