Commentary

Community-acquired pneumonia: the elusive quest for the best treatment strategy

Nicolas Garin[1,2], Christophe Marti[1]

[1]Division of General Internal Medicine, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland; [2]Division of Internal Medicine, Regional Hospital Riviera-Chablais, Monthey, Switzerland

Correspondence to: Nicolas Garin, MD. Division of Internal Medicine, Hôpital Riviera-Chablais, Route de Morgins 54, 1870 Monthey, Switzerland. Email: Nicolas.Garin@hopitalrivierachablais.ch; Christophe Marti, MD. Division of General Internal Medicine, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, 1211 Genève 14 , Switzerland. Email: christophe.marti@hcuge.ch.

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Introduction

Community-acquired pneumonia (CAP) is a frequent disease which can be fatal and has a heavy impact on resources use. The introduction of penicillin more than seventy years ago led to an impressive drop in the mortality rate in severe disease. A diminution of mortality in milder disease is less apparent, but appropriate antibiotics lead to a reduction of symptoms duration and of hospital resources use, which are important outcomes on a patient and societal perspective. However, despite previous works, some aspects of antibiotic treatment for this common condition remain unsettled.

In their systematic search recently issued in the *JAMA* (1), Lee *et al*. aimed to summarize current knowledge on three key questions: does earlier antibiotic treatment lead to beneficial outcomes; is empiric coverage of typical and atypical pathogens through use of a betalactam and macrolide combination (BLM) or a fluoroquinolone monotherapy (FQ) better than a betalactam monotherapy (BL); and how can clinicians assess that a patient is ready to switch to oral treatment. They included randomized controlled trials (RCT) and observational studies recruiting predominantly patients hospitalized on the ward and in which antibiotics included in the 2007 American Thoracic Society (ATS)/ Infectious Diseases Society of America (IDSA) guidelines were used (2). To be included, observational studies had to provide outcomes adjusted for severity of the disease or for age and co-morbidities.

Optimal time to antibiotic initiation

Diagnosing pneumonia is not straightforward, as neither clinical findings nor blood tests are specific. Even chest radiography is probably an imperfect gold standard (3). Clinicians must balance between the delay needed to secure the diagnosis, and early administration of antibiotics for prognostic reasons. In 2003, the IDSA recommended early (<4 hours) administration of antibiotics in CAP (4), and this process of care has been adopted as an indicator of quality of care in North America. Nevertheless, further studies failed to confirm the association between early antibiotic administration and 30-day mortality and suggested that the prognostic advantage described in earlier studies was potentially due to residual confounding (5,6). Lee *et al*. identified eight studies reporting the association between the time to initiate antibiotics and patient outcomes. Four out of five retrospective studies reported statistically significant associations between the time to initiate antibiotics and short-term mortality with a 5% to 46% relative risk reduction (7-10). However, these studies were limited by their retrospective design based on medical records limiting the number of variables available for adjustment. In the largest retrospective study, early antibiotic administration was associated with a 5% relative risk reduction of 30-day mortality, while smoking cessation counseling, pneumococcal vaccination and influenza vaccination were all associated with a relative risk reduction of 30-day mortality over 20% (8). The biological plausibility of these latter associations and their causal relation are

unlikely. The three prospective studies failed to show a significant association between early antibiotic treatment and patient outcomes (5,6,11). These results might stem from a lack of power due to their smaller sample size or from more accurate adjustment for confounding factors. For instance, in one of these studies (11), altered mental status or atypical presentation were strongly associated both with late administration of antibiotics and 30-day mortality and may represent residual sources of confounding in retrospective studies.

In conclusion, the relationship between the time to antibiotic administration and patient outcomes in CAP is probably complex, since delayed administration of antibiotics is probably an indicator of patient characteristics, illness presentation, and quality of care. The evidence supporting a causal relation between time to antibiotic administration and patient outcomes is low and the potential benefit of early antibiotic treatment may be balanced by an increase in CAP misdiagnosis and antibiotic overuse (12,13). These uncertainties have led the IDSA to de-emphasize the importance of the time to antibiotic administration in their more recent guidelines and to recommend the administration of the first antibiotic dose while the patient is still in the emergency department, without time specification (2).

Initial antibiotic selection

Multiple pathogens, including typical bacterias, atypical intracellular bacterias, and virus, can cause CAP. However, they cannot be differentiated on clinical ground; mixed infections including more than one pathogen do occur; and point of care testing is available for a limited number of pathogens. Consequently, the initial treatment is most often empiric. As CAP is a common condition, the choice of the initial treatment can have large repercussions on the societal level, through the selection pressure exerted by antibiotic prescription.

The authors identified two RCTs and nine observational studies. The latter included patients from 1993 to 2011 and were conducted quasi exclusively in European countries and in the United States. The two RCTs were conducted in Europe. For the comparison between BLM and BL, all observational studies except one found an adjusted odd ratio for short-term mortality in favor of BLM. The two RCTs diverged in their results, one favoring BLM and the other BL, though results of both studies were not statistically significant. Results were more consistent for studies comparing FQ and BL. Three observational studies were in favor of FQ, as was the only RCT including a FQ arm, though results for the latter were not statistically significant. Based principally on the results of the observational studies, and considering the discordant results of the two RCTs, the authors of the systematic review recommended that a combination of a macrolide with a betalactam, or a fluoroquinolone monotherapy should be preferred as empirical options for CAP.

The quality of the review conducted by Lee *et al*. is excellent, and their conclusions are coherent with the data presented. However, some considerations should prevent us to reject definitely the betalactam monotherapy as an empiric treatment option in patients with CAP.

First, the inferiority of betalactam monotherapy is inferred predominantly from observational studies. Inclusion of observational studies in systematic reviews of interventions is acceptable if confounding by indication can be controlled, i.e., potential confounders are well identified and adequately measured, allowing adjustment for imbalances between arms (14). Compared with patients treated with combination therapy or with a fluoroquinolone, patients treated with a monotherapy of betalactam are generally older, come more frequently from nursing homes, and have more co-morbidities (15-17). Mortality in CAP is also highly correlated with functional status (18,19), a characteristic that is rarely documented in observational studies. As none of the cited observational studies could adjust for this important variable, residual confounding could still be present.

Secondly, none of the observational studies reported on side effects of the different treatments. One of the RCTs found a higher incidence of adverse events in the BLM arm. Cardiac toxicity has been reported with macrolides and fluoroquinolones, a matter of concern as patients hospitalized for CAP are often older people with cardiac comorbidity, and pneumonia itself is a trigger for cardiac events (20). Thirdly, the impact on the selection of resistant pathogens of BLM and FQ is probably higher than for BL. Macrolides select for multidrug resistant *Streptococcus pneumoniae* (21) and Fluoroquinolones for extended-spectrum betalactamase-producing bacteria (22,23). Finally, all the available evidence on this topic comes from Europe and the United States. Whether the results are directly applicable in other parts of the world where distribution of pathogens and resistance patterns differ remains hypothetic (24).

Criteria for the transition from intravenous to oral therapy

For patients admitted to the hospital, the antibiotic treatment is most of the time delivered intravenously. The decision to switch to oral therapy is important to minimize hospital stay. Lee *et al*. focused on trials comparing step-down to oral therapy based on objective criteria with fixed 7 to 10 days duration of intravenous treatment. In one single high quality RCT, switching to oral therapy at day 3 if patients were clinically stable was equivalent to a full course of IV antibiotics. Patients in the oral switch arm had a shorter length of stay (mean difference 1.9 days).

As few clinicians nowadays would use the intravenous route for the full length of the treatment, the size of the benefit is somehow artificially inflated. However, the message is important and timely switch to oral therapy guided by normalization of vital parameters can decrease considerably length of stay and hospital costs even in routine contemporary practice (25).

Conclusions

Early administration of antibiotics in CAP is associated with a lower mortality in low-quality observational studies. Respiratory fluoroquinolones or combination of a betalactam with a macrolide seem superior to betalactam monotherapy as empiric treatment strategies, but this conclusion is based predominantly on low quality evidence. More research focusing on toxicity of the different treatments and selection of resistant pathogens is needed; large studies should be conducted to determine the impact of the empiric antibiotic strategies outside Europe and the United States. Early switch to oral therapy is safe in patients with clinical stability and leads to shorter hospital stay.

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Footnote

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