Editorial

Shorter antibiotic courses in community-acquired pneumonia—ready for prime time

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Pneumonia causes a significant burden of disease in the world, second only to ischaemic heart disease (1). Whilst the major burden of pneumonia is felt in low and middle income countries, it is, importantly, the leading cause of death from infection in the United States (2). Hence the global impact of community-acquired pneumonia (CAP), especially its mortality and morbidity, is often cited as an important reason for improving care in these patients. The economic burden of CAP is considerable and often overlooked and interventions that might decrease costs, including shortening the length of hospital stay and the duration of antibiotic treatment, also need to be considered. There are other potential benefits of shortening antibiotic courses, including better patient compliance and fewer adverse events. Probably the most important benefit of shorter courses would be to decrease the risk of antibiotic resistance.

It is felt by some that the rapid increase in organisms resistant to antibiotics could be the greatest challenge facing modern medicine, and doomsayers have predicted a future as bleak as the pre-antibiotic era (3). There are few new novel antibiotics in the pipeline and we therefore need to start to use the antibiotics we have in cunning and intelligent ways. This includes taking full advantage of the pharmacokinetic/pharmacodynamic (PK/PD) properties of the different antibiotic classes, using the highest possible doses to improve bacterial killing and possibly using prolonged/continuous infusions (4). This will aid in shortening antibiotic courses and hence the exposure of the bug to the antibiotic, which may decrease the pressures for antibiotic resistance development

Initially CAP was treated for about 5 days; some studies in the 60's and 70's even showed that a single dose of penicillin G procaine was curative (5,6). The standard duration of treatment later evolved to 5 to 7 days. Even though numerous studies comparing these longer treatment durations against shorted courses showed no benefit for the longer treatment, clinicians gradually increased the treatment duration to 10–14 days (7).

The most recent Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults, published in 2007 recommend that patients with CAP should be treated for a minimum of 5 days, should be afebrile for 48–72 h, and should have no more than one CAP-associated sign of clinical instability before discontinuation of therapy (8). These recommendations were made based on level 1 or 2 evidence. A further recommendation, only based on level 3 evidence, was that a longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection, such as meningitis or endocarditis (8). It is interesting to note that even though these guidelines where published in 2007, a

study performed over a 1-year period from July 2011 until June 2012 at a Veterans Affairs Medical Centre in Houston looking at CAP patients demonstrated average antibiotic courses lasting a mean of 13 days (IQR 10–15 days) (9).

The British Thoracic Society (BTS) guidelines recommend for patients managed in the community and for most patients admitted to hospital with low or moderate severity and uncomplicated CAP the use of 7 days of appropriate antibiotics (10). The guideline statement grade was however only a grade C, meaning based on a formal combination of expert views. For those with high severity microbiologically-undefined pneumonia the BTS recommends 7–10 days of treatment (10).

It is for these reasons that Uranga *et al*. performed a multicentre non-inferiority randomised study in Spanish hospitals (11). This study, published in JAMA Internal Medicine in September 2016, was designed to evaluate if shorter courses of antibiotics (≤5 days) were non-inferior to standard clinician decided longer courses (>5 days). The planned initial primary outcome was to be all-cause mortality or major complications, as well as clinical cure; however they subsequently considered that since too few of these events typically occur this primary outcome would not be a good choice. They therefore chose the clinical success rate at day 10 and day 30 since admission as the new primary outcome. The sample size calculation was based on this clinical recovery outcome. This outcome was defined as resolution or improvement in signs and symptoms related to pneumonia without further antibiotics and the administration of the 18 item CAP symptom questionnaire (12,13). Non-inferiority was defined as a difference in the CAP symptom questionnaire score of ≤3 points. Stratification of the primary outcome according to the Pneumonia Severity Index (PSI), antibiotic group and hospital where treatment was received were also planned. This primary outcome is clinically relevant and straight forward to implement. It requires clinical examination and a questionnaire and not expensive investigations such as culture or biomarkers. Other interesting secondary outcomes included length of hospital stay, duration of antibiotic treatment, time to normal activity, in hospital mortality and number of days with adverse events.

Standard pneumonia diagnostics were used for inclusion criteria, with CAP being defined as a new pulmonary infiltrate on chest radiograph plus at least one compatible symptom, such as cough, fever, dyspnoea and chest pain. The exclusion criteria were well thought out so as to exclude hospital-acquired infection or pneumonias in the immunocompromised host, to keep data clear, with few confounders.

Recruited patients were randomised on day 5. Those in the control group had their antibiotic decisions made by the clinician managing their case, whilst those in the intervention group were treated for a minimum of 5 days and antibiotics were stopped once their temperature was below 37.8 ℃ for 48 hours and they had no more than one CAP-associated sign of clinical instability, defined as systolic blood pressure <90 mmHg, heart rate >100/min, respiratory rate >24/min, arterial oxygen saturation <90%, or PaO_2 <60 mmHg in room air. The choice of antibiotic used was decided by the treating doctor and this makes the results applicable to the real world.

The clinical success rate (primary outcome) at day 10 was 48.6% (71 of 150) in the control group and 56.3% (90 of 162) in the intervention group (P=0.18) in the intent-to-treat analysis and 50.4% (67 of 137) in the control group and 59.7% (86 of 146) in the intervention group (P=0.12) in the per-protocol analysis. At day 30, the clinical success rate improved to 88.6% (132 of 150) and 91.9% (147 of 162) in the control and intervention groups, respectively, in the intent-to treat analysis (P=0.33) and to 92.7% (126 of 137) and 94.4% (136 of 146) in the control and intervention groups, respectively, in the per-protocol analysis (P=0.54). The CAP symptom questionnaire scores were similar in the two groups on day 5 (24.7 and 27.2 in the control and intervention groups, respectively; P=0.10 in the intent to-treat analysis; and 24.3 and 26.6 in the control and intervention groups, respectively; P=0.16 in the per protocol analysis). At day 10, the CAP symptom questionnaire scores decreased in both groups (18.6 and 17.9 in the control and intervention groups, respectively; P=0.69 in the intent-to-treat analysis; and 18.1 and 17.6 in the control and intervention groups, respectively, P=0.81 in the per protocol analysis). These results demonstrate the non-inferiority of the shorter courses of antibiotics over the standard longer courses and support the Infectious Diseases Society of America/American Thoracic Society guidelines for length of treatment of CAP. In the stratification according to pneumonia severity, in the intent-to treat analysis, it was found that the patients with more severe disease, those in PSI classes IV and V, achieved clinical success at day 30 more frequently in the intervention group than in the control group, 93.1% (54/58) *vs*. 80.3% (49/61) respectively, P=0.04. No significant differences were observed in the per-protocol analysis. Whilst the study wasn't powered to make comments about the more severe patients, this finding does add confidence when using the shorter durations.

Therefore it appears safe to choose the shorter (≤5 days) courses in all severity groups if the patient demonstrates clinical improvement and stability for 48 hours.

As this study was open-label, it could be argued that the exposure to recruitment might result in shorter antibiotic times in the control group as clinicians were made more aware of the duration of treatment. Whilst this may have added some bias, the results still showed a significantly shorter duration of treatment in the intervention arm. The median time patients received antibiotic treatment was 5 days (interquartile range, 5–6.5 days) in the intervention arm and 10 days in the control group (interquartile range, 10–11 days; P<0.001).

Other interesting secondary outcomes to note were that the length of hospital stay, and the in-hospital and 30-day mortality were similar in the two arms. Readmission at 30 days was surprisingly more common in the control group (longer antibiotic duration) than the intervention arm [9 (6.6%) *vs.* 2 (1.4%); P=0.02]. All recruited patients were given a telephone number to call for any queries or problems and the intervention arm made more use of the telephone number to call in than the control arm [58 (39.7%) *vs.* 38 (27.7%); P=0.03]. The authors postulated that this might be the reason there were fewer readmissions in the intervention arm.

An interesting result to note is the type of antibiotics used in the study. Overall 79% (119/150) in the control group and 79% (128/162) in the intervention arm were treated with fluoroquinolones; 7% (11/150) *vs.* 8% (13/162) received beta-lactams plus macrolides, and 13% (20/150) *vs.* 12% (19/162) received only beta-lactams (data available from the eTable 3 of the Supplementary Online Content). The authors did comment on this, explaining that there is a high rate of fluoroquinolone prescription for CAP in Spain, which may be different from that in other countries. For example, the United Kingdom and South Africa use beta-lactams as the back-bone of their CAP guidelines (10,14). It is especially relevant when one considers the special pharmacodynamics of the fluoroquinolones, which have a type 1 pattern of activity. In other words they have concentration-dependant killing and a prolonged persistent effect, which may be ideally suited to shorter courses of treatment (15). However, while different antibiotic classes may therefore be better suited for short course therapy, if one view the supplemental data there do not appear to be differences between the clinical success of the different antibiotic groups; however we must be cautious in extrapolating this data as the study was not powered to detect differences between the different antibiotic classes.

This is the first study comparing a shortened antibiotic course to the usual standard of care, in a setting where the clinician could choose the antibiotic. It is however not the first study to show efficacy of short-course antibiotic regimes for CAP. In fact there have been two meta-analyses reviewing the studies. Li *et al*, publishing in 2007 in the American Journal of Medicine included studies that compared short-course (7 days or less) *vs*. long-course (>7 days) antibiotic monotherapy for CAP in adults and concluded that antibiotic regimes of 7 days or less could safely and effectively treat mild to moderate CAP in adults (16). Dimopoulos *et al*. published their meta-analysis in Drugs in 2008 (17). They included randomised control trials and also found no difference in the effectiveness and safety of short- *vs*. long-course antimicrobial treatment of adult and paediatric patients with CAP of mild to moderate severity. Uranga and colleagues had made an important contribution to this topic, especially by including a group of more severely ill patients.

Finally, there is a growing body of evidence that shorter courses of antibiotics are equivalent and perhaps better than prolonged courses in many different infections such as ventilator-associated pneumonia (18), intra-abdominal sepsis (19), pyelonephritis and urinary tract infection (20), and uncomplicated cellulitis (21). Uranga *et al*.'s study has added to this growing trend of "less being more" and hopefully clinicians will feel confident to use shorter courses of antibiotics in their treatment of patients with CAP and place these recommendations in the guidelines.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2163-96.
2. Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the

20th century. JAMA 1999;281:61-6.
3. Mendelson M, Whitelaw A, Nicol M, et al. Wake up South Africa! The antibiotic 'horse' has bolted. S Afr Med J 2012;102:607-8.
4. MacVane SH, Kuti JL, Nicolau DP. Prolonging β-lactam infusion: a review of the rationale and evidence, and guidance for implementation. Int J Antimicrob Agents 2014;43:105-13.
5. Townsend EH Jr, Decancq HG Jr. Pneumococcic segmental (lobar) pneumonia. Its treatment with a single injection of procaine penicillin G. Clin Pediatr (Phila) 1965:117-22.
6. Sutton DR, Wicks AC, Davidson L. One-day treatment for lobar pneumonia. Thorax 1970;25:241-4.
7. Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med 2014;371:1619-28.
8. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44 Suppl 2:S27-72.
9. Afzal Z, Minard CG, Stager CE, et al. Clinical Diagnosis, Viral PCR, and Antibiotic Utilization in Community-Acquired Pneumonia. Am J Ther 2016;23:e766-72.
10. Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax 2009;64 Suppl 3:iii1-55.
11. Uranga A, España PP, Bilbao A, et al. Duration of Antibiotic Treatment in Community-Acquired Pneumonia: A Multicenter Randomized Clinical Trial. JAMA Intern Med 2016;176:1257-65.
12. Lamping DL, Schroter S, Marquis P, et al. The community-acquired pneumonia symptom questionnaire: a new, patient-based outcome measure to evaluate symptoms in patients with community-acquired pneumonia. Chest 2002;122:920-9.
13. Chow AW, Hall CB, Klein JO, et al. Evaluation of new anti-infective drugs for the treatment of respiratory tract infections. Infectious Diseases Society of America and the Food and Drug Administration. Clin Infect Dis 1992;15 Suppl 1:S62-88.
14. Working Group of the South African Thoracic Society. Management of community-acquired pneumonia in adults. S Afr Med J 2007;97:1296-306.
15. Oliphant CM, Green GM. Quinolones: a comprehensive review. Am Fam Physician 2002;65:455-64.
16. Li JZ, Winston LG, Moore DH, et al. Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. Am J Med 2007;120:783-90.
17. Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, et al. Short- versus long-course antibacterial therapy for community-acquired pneumonia : a meta-analysis. Drugs 2008;68:1841-54.
18. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003;290:2588-98.
19. Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med 2015;372:1996-2005.
20. Eliakim-Raz N, Yahav D, Paul M, et al. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection-- 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother 2013;68:2183-91.
21. Hepburn MJ, Dooley DP, Skidmore PJ, et al. Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. Arch Intern Med 2004;164:1669-74.

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