Funding

The authors declare that they have not received funding for this work.

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Dual Antibiotic Therapy for Outpatient Management of Community-acquired Pneumonia?

¿Tratamiento antibiótico dual en el manejo ambulatorio de la neumonía adquirida en la comunidad?

Dear Editor:

In the updated 2020 guideline on community-acquired pneumonia, Menéndez et al.[1] still consider dual antibiotic therapy in all patients with community-acquired pneumonia (CAP), and also for outpatients. Recommendations for CAP therapy should be different, depending on whether patients require hospitalisation, are admitted to intensive units or are treated as outpatients. In line with the different recommendations published in other European countries, Spanish guidelines in primary care recommend beta-lactam therapy in monotherapy as empirical treatment.[2]

Despite citing articles highlighting the little beneficial effect of macrolides in the treatment of outpatients with CAP, Menéndez et al. conclude that in the absence of randomised clinical trials and based on clinical evidence from observational studies, the combination of a macrolide and a beta-lactam should constitute the empirical outpatient treatment regimen in patients with CAP or consider the administration of a quinolone in monotherapy. However, a recent systematic review and meta-analysis published by Horita et al.,[3] showed based on mostly observational studies that, compared with beta-lactam monotherapy, combination therapy with a beta-lactam plus macrolide may decrease all-cause mortality only in severe CAP, with an odds ratio (OR) of 0.75 (95% CI, 0.65–0.86), but not in mild to moderate CAP (OR 1.12, 95% CI, 0.87–1.45). However, this pooled OR for mild to moderate CAP comes from only three studies: two randomised clinical trials with patients with a median pneumonia severity index of 3 and one observational study (outpatients with a low severity, with a median CRB65 of 1). No randomised clinical trials comparing beta-lactam with a combination of beta-lactam and macrolides have been published in primary care. Extrapolation of the results of the group of mild to moderate CAP from this meta-analysis to patients managed in primary care might, therefore, not be straightforward. However, this is currently the only information available from patients with lower CAP severity. The authors of this meta-analysis also found significantly more adverse events in the group receiving a combination of antibiotics.[3]

Between two-thirds and 80% of patients with CAP are treated as outpatients, with a low therapeutic failure and a mortality rate of less than 1%, both in patients discharged from the emergency department or directly assessed in the primary care setting.[4] There is compelling evidence that increasing consumption of antibiotics is associated with the development of antibiotic resistance, both at the individual and the community level, and increases the likelihood of adverse events, as shown in the previous meta-analysis. Therefore, prudent antibiotic stewardship strategies, aiming to ensure the judicious use of antimicrobials by preventing their unnecessary use, should be encouraged. In addition, in the absence of a superiority of broad-spectrum antibiotic regimens, narrowing the spectrum of coverage of empirical treatments as well as shortening the duration of therapies are preferable to reduce the emergence of resistance and adverse effects.

We agree with the authors that more high quality randomised clinical trials comparing beta-lactam monotherapy with dual antibiotic regimens should be carried out in primary care. However, recommendations should be based on high quality clinical studies, not on observational analyses.[5] The few randomised clinical trials published so far do not show a clear benefit of adding macrolides to beta-lactams for the treatment of mild to moderate CAP. Therefore, we propose further studies in ambulatory CAP that allow us to reaffirm our idea that beta-lactam monotherapy should be the first line in outpatients and reserve respiratory fluoroquinolone or the combination of a macrolide and a beta-lactam if there is a documented allergy to β lactams (in this case use of fluoroquinolone), presence of significant comorbidities, therapeutic failure, or in areas with high suspicion of prevalence of highly resistant pneumococci. All this in order to reduce the antibiotic spectrum and therefore the risk of generating resistance.

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https://doi.org/10.1016/j.arbres.2020.05.016

Reply to "Dual antibiotic therapy for outpatient management of community-acquired pneumonia?"☆

Respuesta a «Dual antibiotic therapy for outpatient management of community-acquired pneumonia?»

To the Editor:

One of the most controversial topics in the recommendations and consensus documents on antibiotic treatment in respiratory infections is the choice of outpatient treatment of pneumonia. The debate between monotherapy with a beta-lactam or combination with a macrolide leads to differences of opinion among clinicians, and even among scientific societies.[1,2] There is some logic to the arguments, and several reasons to justify both approaches in the treatment of mild pneumonia. The first and most important is that no randomized trials with sufficient patient numbers have been conducted in different geographical areas and over long periods that include different seasons, comparing the use of a beta-lactam alone versus the combination of a beta-lactam with a macrolide. The few studies in non-hospitalized patients use mortality as a study variable, which is unhelpful since death rates are very low in this setting, and it is unlikely that significant differences will be detected. Other outcomes, such as therapeutic failure, complications or need for later admission, would be of greater interest. Secondly, because microbiological studies are not performed, there is a shortage of etiological information in mild pneumonia, so the percentage of intracellular microorganisms in which macrolides play an obvious role is unknown. The few studies that use microbiological molecular diagnostic techniques show that the prevalence of these intracellular bacteria, in particular *Legionella pneumophila*, is underestimated. Moreover, in the early stages of infection, urinary antigen testing for *Legionella pneumophila* may give false negatives, and this technique also only recognizes serotype 1. In Spain, *Legionella pneumophila* occurs in up to 6% of cases in the outpatient setting and a beta-lactam in monotherapy is insufficient.[3] Microbiological point-of-care testing in the outpatient setting that covers a range of bacteria and viruses would be very useful for improving etiological information; however, we are aware that these services are not available in standard practice and conventional microbiological studies are not recommended in the guidelines. The third factor is the possibility of pneumonia caused by mixed etiologies such as pneumococcus and intracellular bacteria or the possibility of bacteremia in mild pneumonias.[4] For all these reasons, the therapeutic approach to mild pneumonias should always include a regimen offering complete cover that always includes pneumococcus and intracellular bacteria, in order to reduce the chance of failure. Efforts must be made to avoid continuing the macrolide for more than 3 or 5 days if the response is good.

Horita et al. published a meta-analysis[5] analyzing the impact of the combination of beta-lactams and macrolides on mortality, but only 3 studies were included in the mild/moderate pneumonia subgroup. This is insufficient to properly address mortality, and the authors recognize the shortage of randomized and observational studies in their paper. Asadi et al.,[6] in an observational study of 2,845 patients, compared macrolides with quinolones, and found fewer hospital admissions and lower mortality (0.2 vs. 3.0%, p = 0.02) in the macrolide group. In fact, macrolides have even shown good outcomes in patients with risk factors for pneumococcal resistance.[7]

When the decision has to be made between using fewer antibiotics or offering complete coverage of the most common microorganisms of mild pneumonia, the SEPAR update of the CAP guidelines leans towards the second option. We agree that a very large, well-designed randomized trial may provide an answer to this unresolved issue.

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☆ Please cite this article as: Menéndez R, Méndez R, Torres A. Respuesta a «Dual antibiotic therapy for outpatient management of community-acquired pneumonia?». Arch Bronconeumol. 2020;56:766–767.