

EDITORIAL

Empirical treatment of nonsevere community-acquired pneumonia: still a difficult issue

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Empirical treatment of community-acquired pneumonia (CAP) continues to be a challenge to the physician [1]. The proof of this statement is that recently at least two important institutions (British Thoracic Society (BTS) and American Thoracic Society (ATS)) have elaborated documents to direct the initial management of community-acquired pneumonia [2, 3]. Whilst the BTS still recommends the use of penicillins for the initial treatment of noncomplicated pneumonias, the ATS recommends macrolides for this indication. These important differences between guidelines are just an example of the difficulty in reaching agreement among physicians concerning this apparently simple subject.

In our opinion, the ideal empirical treatment of noncomplicated CAP has to accomplish the following requisites: 1) to cover *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*, if endemic; 2) to use a single oral antibiotic if possible; and 3) to take into account resistances of microorganisms to antibiotics which vary from country to country. In addition, seasonal variations in the epidemiology of CAP should be known and taken into account. Regarding the first point, in industrialized countries, *S. pneumoniae* and *M. pneumoniae* are the two most frequent causal microbial agents in the population under 60 yrs of age, and not requiring hospitalization. Severe clinical presentations can be caused mainly by both *S. pneumoniae* and *L. pneumophila*, and even by *M. pneumoniae* [4, 5]. Thus, it would be reasonable to cover all these microorganisms empirically, particularly in severe cases. The ability to cover this spectrum with a single antibiotic would be advisable.

S. pneumoniae resistant to penicillins and macrolides is one of the major problems in the decision making concerning empirical treatment for CAP. The occurrence has been reported with increasing frequency since the first multiresistant strain was isolated in 1977 [6, 7]. The highest incidence rates of pneumococcal resistance to penicillins have been reported from South Africa, Spain and Hungary; although resistant strains have been identified worldwide [7–11]. On the other hand, the increasing use of macrolides during the last decade as an empirical treatment of CAP has been associated with the appearance of resistance to erythromycin [12]. The lowest rates of

erythromycin resistance (<5%) in Europe are reported from Switzerland, Germany and the UK. In 1979, Spain had <1% of resistance to erythromycin but this progressively increased to 15–17% in 1994. Other European countries, such as France, Belgium or Hungary, have exceeded 25% resistance rates [6, 12]. In most countries, an association between the local prevalence of pneumococcal resistance to penicillin and macrolides has been observed. In Spain, in particular, the macrolide resistance rate of penicillin-susceptible strains is around 5%, whilst this rate increases to 20% in partially resistant pneumococci (minimal inhibitory concentrations (MICs)=0.2–1 mg·L⁻¹) to 25% in totally resistant strains (MICs ≥2 mg·L⁻¹) [13].

If the resistance of *S. pneumoniae* to penicillin is particularly worrisome, then the resistance to macrolides implies that great care is needed when using these drugs as the first-line empirical treatment against nonsevere and nonhospitalized CAP patients [7, 14, 15]. Although no prospective studies have been published, clinical experience suggests that mild-to-moderate pneumonia caused by penicillin-resistant pneumococci can be treated with high doses of oral amoxicillin [7, 15]. In addition, penicillin and amoxicillin have higher bactericidal activity than cephalosporins [16]; this being a further argument to continue to use the former in cases of partially resistant pneumococci. Concerning macrolides, it is important to point out that strains of *S. pneumoniae* are either very susceptible (modal MIC 0.1–0.2 mg·L⁻¹) or highly resistant to erythromycin (modal MIC ≥64 mg·L⁻¹). The high erythromycin resistance caused by the action of ermAM gene indicates additional resistance to all macrolides (e.g. clarythromycin, azithromycin, roxithromycin or dirithromycin) and also lincosamides [12]. Thus, the treatment decision in CAP patients is difficult: to use penicillins at high dosage without initially covering *M. pneumoniae* and *L. pneumophila*; or to use macrolides alone with the risk of the existence of totally resistant *S. pneumoniae* in some cases. Which is the better policy? Since *S. pneumoniae* is by far the most common microbial agent causing CAP [1], the risk of not covering microorganisms is probably reduced when using penicillins at high doses instead of using macrolides.

Meanwhile some newly available antibiotics can apparently overcome these problems. Furthermore, they can be administered alone at a single daily dose. The most promising are the new fluoroquinolones, such as sparfloxacin,

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that presents much better activity against *S. pneumoniae* than does ciprofloxacin (modal MIC 0.2 mg·L⁻¹), and may, therefore, be useful against borderline ciprofloxacin-resistant strains (MIC 2–4 mg·L⁻¹). However, sparfloxacin is not effective against *S. pneumoniae* with high resistance to ciprofloxacin [17–19]. Moreover, sparfloxacin has shown greater *in vitro* activity than currently marketed quinolones against other common pathogens causing CAP (*M. pneumoniae*, *C. pneumoniae*, *Haemophilus influenzae*, *L. pneumophila*, and other Gram-positive and Gram-negative microorganisms) [18, 19]. Additional advantages of this antibiotic are its prolonged half-life (20 h), which allows single daily doses, and its high penetration characteristics that persist for at least 24 h after oral administration [17].

In the present issue of The Journal, LODE *et al.* [20] report the efficacy and safety of sparfloxacin compared to amoxicillin/clavulanate or erythromycin for the empirical treatment of nonsevere CAP. In this multicentre study, the approach used to evaluate sparfloxacin was remarkable: double-blind (triple placebo technique), double-dummy and randomized. The sample size of 808 patients was enough to draw unequivocal conclusions. The principal analysis of efficacy concerned the population of evaluable patients and was expressed as overall success or failure according to predefined classification rules using a one-sided equivalence analysis. The results of the study showed similar rates of efficacy for sparfloxacin and erythromycin (87 and 85%) and a nonsignificant trend to lower efficacy for amoxicillin/clavulanate. Similar comments can be applied for the evaluable population at follow-up and when examining the efficacy in relation to different microorganisms. The percentage of failures during the first week was lower with sparfloxacin (5.5%) or erythromycin (5.8%) when compared to amoxicillin/clavulanate (12%).

However, there are some findings that deserve particular comment. Firstly, the incidence rate of *S. pneumoniae* partially (6.9%) or totally (4.3%) resistant to penicillins or erythromycin (4.3%) was not impressive. Secondly, almost all cases (11 of 12) of *M. pneumoniae* were cured in the group treated with amoxicillin/clavulanate, meaning that these infections resolved spontaneously. Thirdly, most of Legionella cases were aberrantly randomized to the erythromycin group (seven cases) proving difficult to evaluate efficacy against *L. pneumophila*. Fourthly, 12 cases considered as a failure during the first week in the erythromycin group were due to digestive intolerance to this drug and not real failures. Lastly, as regarding adverse effects, although very similar in the three groups diarrhoea was more frequent in the amoxicillin/clavulanate group and vomiting and nausea in the erythromycin group compared to sparfloxacin.

Taking into account all these considerations, the results of this outstanding study show that sparfloxacin is as efficacious as amoxicillin/clavulanate or erythromycin in the initial empirical treatment of nonsevere CAP. Although, in this study, the cost-effectiveness of sparfloxacin for CAP treatment was not evaluated, others [21] have found that its overall cost for a CAP treatment was similar (1211 FF) when compared to amoxicillin/

clavulanate (1294 FF), and lower when compared to roxithromycin (1475 FF). However, the exclusive cost of sparfloxacin as a first-line antimicrobial drug was higher when compared to the latter antibiotics (460 vs 227 vs 179 FF respectively) [21].

The new quinolones represent a major step in the development of antimicrobial compounds. Specifically, sparfloxacin is a reliable antibiotic for the initial treatment of nonsevere CAP, with the great advantage of a single daily dose administration. However, its inappropriate and extensive prescription can lead to the reduction of its value in the treatment of bacterial infections [22]. Old antibiotics, particularly penicillins, are still highly efficacious against nonsevere CAP. There is no sufficiently strong reason to withdraw these drugs from our first-line antibiotic armamentarium.

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