# Are macrolides as effective as fluoroquinolones in *Legionella* pneumonia?: YES, but…

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*Legionella* pneumonia (LP) is a well-known cause of community-acquired pneumonia (CAP) in immunocompetent patients[1]. This intracellular pathogen is considered one of the "core microorganisms" of CAP and it is also a microorganism that can cause hospital-acquired pneumonia (HAP) either in individual cases or in the form of large-scale outbreaks[2]. Immunosuppressed patients have a higher risk of acquiring this infection, both in the community and in the hospital, for this reason LP has to be empirically covered and intensively searched for diagnosis[3]. Inadequate initial or delayed antibiotic treatments in LP are factors associated with a worse prognosis.

In the current guidelines for hospitalized CAP, quinolones and macrolides are the two antibiotic families recommended to treat LP[4]. However, according to observational studies and one meta-analysis, clinicians believe that the use of quinolones (particularly levofloxacin) achieves better outcomes[5]. The meta-analysis published in 2014 including 879 patients found that quinolones were associated with shorter hospital stay and trends towards reduced mortality, higher clinical cure rates, shorter time to apyrexia and fewer complications[6]. In this issue of CID, Jasper and colleagues[7] present a second meta-analysis comparing fluoroquinolones to macrolides for the treatment of LP. On this occasion, they included 21 publications and 3525 patients – three times more than the 2014 meta-analysis. They found no differences in the effectiveness of fluoroquinolones vs macrolides in reducing mortality (the primary end point) or other secondary end points such as clinical cure, time to apyrexia, length of stay, or complications. In addition, in post-hoc analyses they found no differences regarding the type of macrolide (clarithromycin vs azithromycin) or quinolone used (levofloxacin vs moxifloxacin), the presence or absence of

immunosuppression, or disease severity (defined as intensive care unit (ICU) admission/non-admission).

The very good news from this meta-analysis is that azithromycin and quinolones are equally effective for the treatment of LP in terms of crude mortality. This finding corroborates the recent recommendations of the ATS/IDSA guidelines for the empirical treatment of CAP[4]. Another important result was that they did not find differences between levofloxacin and moxifloxacin or between azithromycin or clarithromycin. This is an extremely positive finding because there is a huge difference in the availability of these four antibiotics all over the world; for example, in some countries azithromycin is not available.

However, we have to be cautious with regard to some of the other findings of this meta-analysis:

1- The authors did not find significant differences in clinical cure. However, this finding was based on only two studies with a pooled OR of 2.36 (95% CI: 0.33-16.92). Clinical cure is an important end point (EMEA) in CAP and it does not always coincide entirely with crude mortality.

2- Complications: The analysis of complications was based on only four studies which used heterogeneous definitions of the concept of "complication". The pooled OR for complications was 0.80, and was significantly lower for fluoroquinolones, but this was not statistically significant.

3- Immunosuppressed patients: The authors did not find differences in mortality, but immunosuppression was reported in only a few studies.

4- ICU vs. non-ICU: As in the point above, the absence of differences in mortality was based on only a few studies.

In addition to these four points, other important variables that could not be studied included the influence of treatment duration, relapses, and CAP vs. HAP.

I recognize that the findings of this meta-analysis are important because they are sufficiently convincing to persuade clinicians to follow the recommendations of the current CAP guidelines when covering LP for the initial treatment. However, with all the uncertainties mentioned above regarding clinical cure, immunosuppression, severity and nosocomial pneumonia, we cannot state definitively that macrolides are equally as effective as quinolones.

There are two points that deserve further consideration. The primary end-point was crude in-hospital mortality and not attributable mortality. In a study aiming to determine whether macrolides are as effective as quinolones, the analysis of attributable mortality would have been preferable. Probably only a meta-analysis of individual data could resolve this question.

The second point refers to treatment duration. The current meta-analysis cannot shed any light on this point. The recommendations in the guidelines are imprecise: in immunocompetent patients, the ATS/IDSA[4] and European guidelines[8] recommend eight days of fluoroquinolones but do not specify the duration of treatment for macrolides. Nor do they distinguish between severe and non-severe LP. Personally, I believe that LP in non-immunocompromised needs longer treatment than other forms of CAP and should be individualized according to the clinical response [9].

In immunocompromised patients the general consensus is that longer treatments are needed[3]. The French guidelines[10] recommend 10 days of azithromycin for non-severe LP and 21 days of a fluoroquinolone in case of severe pneumonia.

In summary, the present meta-analysis is a step forward in our knowledge of antibiotic treatment of LP. Overall it increases our confidence in using macrolides or quinolones for the empirical treatment of CAP. This is of particular importance in view of the global warning about the side effects of quinolones[11]. However, when LP is diagnosed we cannot yet say that both families of antibiotics are equally effective. An individual data meta-analysis might help to determine this issue once and for all.

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