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Are macrolides now obligatory in severe community-acquired pneumonia?

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In this issue of Intensive Care Medicine, Martin-Loeches and colleagues [1] present an analysis of a cohort of 218 patients with community-acquired pneumonia requiring mechanical ventilation enrolled into a larger, observational, multi-center European study. The major finding of the study in this issue was that the 42 patients who received a macrolide antibiotic had half the mortality rate of other patients after adjusting for severity of illness at presentation.

That macrolide antibiotics appear to confer a significant survival advantage in patients with severe community-acquired pneumonia is not a new concept, with multiple observational and retrospective studies demonstrating substantial mortality benefits [2–7]. However, as has been pointed out in many editorials and reviews, none of these studies are prospective, randomized controlled trials. In the absence of scientifically irrefutable evidence, at what point does the weight of data in favor of using macrolides become so overwhelming that their use is obligatory?

If we look at the potential downsides of making macrolides obligatory, then there is an obvious economic cost if they are not needed. However, relative to most costs in

health care, the economic burden is trivial. Unnecessary macrolide use could perceivably contribute to increased antibiotic resistance to this class of antibiotics in the community, but the reality is that patients hospitalized with community-acquired pneumonia account for a minute portion of total antibiotic use, and this is not a sustainable argument given the already widespread use of this class of agents in the outpatient setting for upper and lower respiratory tract infections. Overuse of macrolides, like any antibiotic, could theoretically lead to selection for multi-resistant pathogens. However, the risk of this seems to be smaller than for broad-spectrum beta-lactams, third-generation cephalosporins and fluoroquinolones, which all have well-documented track records of this adverse side effect. As with all antibiotics, drug reactions can occur, but macrolides are generally a very safe class of antibiotics. An increased incidence of arrhythmias has been reported with macrolides because of prolongation of the Q-T interval, but overall the risk is no greater than that associated with fluoroquinolones [8].

If there is no major downside to adding a macrolide, the next question is whether these are the best agents or whether other antibiotics or antibiotic combinations have an equivalent or greater beneficial effect. One of the proposed (and I think the least likely) potential explanations for the benefit of macrolides is covering unrecognized ‘atypical’ pathogens (such as *Legionella* spp. or *Mycoplasma*). If this were the mechanism, then there should be equivalent benefit from fluoroquinolones and tetracyclines. However, just as previous observational studies have shown [9, 10], the current study by Martin-Loeches and colleagues [1] also clearly demonstrates that fluoroquinolones do not give the same apparent protective effect as macrolides. Although much more limited, there are also some data suggesting that tetracyclines are also not as efficacious as macrolides [10].

That the benefit of macrolides is almost certainly not driven by undiagnosed atypical pathogens invalidates the

argument that physicians do not need to use them if they have a low prevalence of atypical pathogens in their region. There is substantive evidence for macrolides having an immunomodulating effect on the host immune response [11], and this may be a key factor in their apparent clinical benefit. However, the recent demonstration that most patients with community-acquired pneumonia and sepsis-related organ dysfunction have high systemic pneumococcal bacterial loads [12] suggests to me that the now well-recognized anti-toxin effects of macrolides, even in macrolide-resistant organisms [13], also play a key role. Importantly, neither fluoroquinolones nor tetracyclines were observed to have anti-pneumolysin effects in pneumococci [13].

Clearly not all patients admitted to hospital with community-acquired pneumonia will die with or without a macrolide, so can we select those who will benefit? The research group reporting in this journal had previously suggested that the most benefit may be for patients with shock [6]; however, their current analysis clearly extends the indication to patients requiring mechanical ventilation [1]. Unfortunately, while it is straight forward if patients require inotropic support or mechanical ventilation at the time of presentation, our ability to predict patients who

will deteriorate over the first 24 h after admission remains more limited. As the proposed mechanisms by which macrolides improve outcome may clearly be more effective prior to significant organ failure being established, it would seem prudent to give a macrolide to any patient with significant physiological compromise. Better predictive tools, such as quantitative systemic bacterial load [12], may help improve the selection of at-risk patients in the future.

Given the overwhelming weight of data, I believe that macrolides should be obligatory in all cases of severe community-acquired pneumonia. With odds ratios for death ranging from two to six times greater in non-macrolide-treated patients [1, 3, 4, 7], and given the low risk and cost of such treatment, refusal to do so out of scepticism of the data is unjustifiable. We would all like the definitive prospective trial, but that is unlikely to occur for financial, logistic and even ethical reasons. Hopefully, the growing animal [14, 15] and human data [16] suggesting macrolides are of benefit in sepsis due to many causes other than community-acquired pneumonia will be extended into prospective randomized, controlled trials, and then the issue of not having this data in community-acquired pneumonia will become moot.

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