CRITICAL CARE

COMMENTARY

Macrolides and community-acquired pneumonia: is quorum sensing the key?

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Abstract

Combination therapy with two antimicrobial agents is superior to monotherapy in severe community-acquired pneumonia, and recent data suggest that addition of a macrolide as the second antibiotic might be superior to other combinations. This observation requires confirmation in a randomised control trial, but this group of antibiotics have pleiotropic effects that extend beyond bacterial killing. Macrolides inhibit bacterial cell-to-cell communication or quorum sensing, which not only might be an important mechanism of action for these drugs in severe infections but may also provide a novel target for the development of new anti-infective drugs.

Outcome in community-acquired pneumonia (CAP) is adversely affected by increasing severity of illness, co-morbidity and age. Organisational factors such as timely administration of appropriate antibiotics, prompt admission to critical care and adherence to antibiotic policies, however, are also important in influencing outcome [1-3]. Combination therapy with two antimicrobial agents seems superior to monotherapy in severe CAP, and this approach is recommended by a number of organisations [4,5]. The Infectious Diseases Society of America/American Thoracic Society guidelines suggest therapy with a β-lactam antibiotic, with the addition of either a macrolide or fluoroquinolone antibiotic [4], whilst the British Thoracic Society recommends initiating a β-lactam/macrolide antibiotic combination [5].

Martin-Loeches and colleagues recently conducted a prospective, observational cohort, multicentre study involving 218 mechanically ventilated CAP patients to see what effect different antibiotic combinations had on mortality [6]. These investigators reported that the addition of a macrolide, but not a fluoroquinolone, to standard antibiotic therapy was associated with reduced mortality in patients admitted to critical care with CAP. Death in critical care occurred in 26.1% of individuals receiving combination therapy with a macrolide, compared with 46.3% in those receiving fluoroquinolones [6]. These results support data from other observational studies that suggest β-lactam/macrolide combinations offer a survival advantage in severe CAP. This body of data is not scientifically robust enough, however, to adequately answer the question of whether adding a macrolide to a β-lactam confers a survival advantage – this will only be satisfactorily addressed by a large prospective randomised control trial.

In addition to activity against atypical bacteria, macrolides have ubiquitous immunomodulatory effects. Speculating how this group of drugs might offer a survival advantage when added to a β-lactam is therefore of interest, and several plausible mechanisms exist. Treatment of undiagnosed atypical pneumonia could occur since 53% of patients in the reported study had no microbiological diagnosis [6]; however, this seems unlikely as one might expect fluoroquinolones to be equally effective [7]. Moreover, studies limited to pneumococcal disease demonstrate that addition of a macrolide improves survival [8]. It also seems improbable that synergistic killing is responsible, as equivalency with fluoroquinolones would be expected.

Many researchers have focused on the pleiotropic immunomodulatory effects [9] observed with macrolides as the reason why these agents may be beneficial in CAP. Macrolides, at doses lower than those required for antibacterial activity, alter the production of cytokines and chemokines, and reduce cellular infiltrates and mucous production [9]. The immunomodulatory effects of macrolides are illustrated by diffuse panbronchiolitis. A chronic progressive lung disease found largely in Japan, diffuse panbronchiolitis is characterised by mixed restrictive and obstructive pulmonary function, interstitial infiltrates and *Pseudomonas aeruginosa* infection. Long-term, low-dose macrolide treatment improves lung function and increases 10-year survival rates from around 15 to 90% [9].

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Macrolides are now being explored in new therapeutic strategies for a wide range of pulmonary and extra-pulmonary conditions, including asthma, cystic fibrosis, rhinosinusitis, inflammatory bowel disease, psoriasis and rosacea [9]. Clearly immunomodulatory effects could be important in altering mortality in CAP, but these drugs also have direct effects on bacteria through inhibiting quorum sensing.

Quorum sensing describes bacterial cell-to-cell communication that occurs as a function of changing cell density. These communication pathways are important in the pathogenesis of bacterial species causing human disease, including *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli* and *P. aeruginosa* [10,11]. Quorum-sensing bacteria produce and release signal molecules or autoinducers, which regulate gene expression within the bacterial population and are closely linked to both biofilm formation and expression of virulence factors. Biofilms are structured populations of bacteria within a polysaccharide matrix, and these growth forms are more resistant to antibiotics. The discovery of biofilms as an entity did not occur until the late 1970s, and they are often still only considered in the context of chronic or device-associated infections; however, pneumonia caused by *S. pneumoniae* exists as a biofilm in lung tissue [11]. Acute bacterial infections associated with biofilm formation might also be relatively common. One of the diagnostic criteria for biofilm infection is a culture-negative result despite a clinically documented infection [12], a situation encountered in 30 to 50% of severe sepsis and septic shock [6].

Macrolides at subminimum inhibitory concentrations have been demonstrated to antagonise quorum sensing in *P. aeruginosa*, resulting in diminished virulence, biofilm formation and oxidative stress response [13]. Significantly, inhibition of quorum sensing reduces pathogenicity of bacteria and impedes formation of antibiotic-resistant biofilms, and therefore offers an attractive mechanism whereby the addition of a macrolide could reduce mortality in CAP [6]. If macrolides do confer additional efficacy because of immunomodulatory effects or inhibition of quorum sensing, or both, one might expect them to be an effective therapeutic strategy applicable to many other infections encountered in critically ill patients. Indeed, the addition of clarithromycin to patients with ventilator-associated pneumonia accelerated resolution of pneumonia and weaning from mechanical ventilation [14].

It may be possible to approach the question of whether immunomodulation or inhibition of quorum sensing is more important in reducing mortality experimentally. Lesprit and colleagues described the important role of *P. aeruginosa* quorum sensing in rat pulmonary infection using the virulent wild-type strain *P. aeruginosa* PAO1 and the less virulent mutant strain *P. aeruginosa* PAOR with a deficient quorum-sensing pathway [15]. Using this model system it would be beneficial to examine whether macrolides act predominantly through disrupting quorum sensing, as one would then expect to see little reduction in mortality caused by a large inoculum of the mutant PAOR but a significant effect on pneumonia caused by a smaller dose of the wild-type PAO1.

At a time when few new antimicrobial agents are being commercially developed for clinical use and the burden of infection caused by multiresistant bacteria is increasing, the need for novel approaches to the management of infection is essential. Quorum sensing determines both bacterial virulence and biofilm formation; it is a common pathway for pathogens and represents an attractive new target for the development of drugs in the fight against infection [10].

Abbreviations

CAP, community-acquired pneumonia.

Competing interests

The authors declare that they have no competing interests.

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Questions remain regarding mandatory use of macrolides in community-acquired pneumonia

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Dear Editor,

We read with interest the article by Martin-Loeches and colleagues [1] regarding combination antimicrobial therapy for severe community-acquired pneumonia (CAP). After many years of hotly contested debate, definitive evidence that a specific component of therapy confers survival advantage would be welcome news indeed. However, several findings reported in their study highlight the limitations of observational design and reinforce the need for a randomized trial if this debate is truly to be resolved.

The authors define CAP as an infiltrate on chest radiograph with confirmatory clinical findings that was acquired outside a hospital. However, this does not necessarily exclude healthcare-associated pneumonias (HCAP). According to the 2005 IDSA/ATS guidelines, HCAP and associated multi-drug resistant (MDR) organisms should be considered in the following cases: antimicrobial therapy in the preceding 90 days; a high frequency of antibiotic resistance in the community; hospitalization for 2 days or more in the preceding 90 days; residence in a nursing home or extended care facility; receipt of home infusion therapy; chronic dialysis; home wound care; or a family member with an MDR pathogen [2]. A significant number of patients in this cohort (10.8%) were found to have *Pseudomonas pneumonia*, an atypical cause of CAP. Inclusion of patients with HCAP may have significant ramifications if these patients were more likely to receive a particular treatment regimen. Furthermore, background resistance patterns were not mentioned. High rates of quinolone resistance have been reported in some communities and may have further affected outcomes [3].

The 2005 ATS/IDSA guidelines suggest initial therapy for HCAP include an anti-pseudomonal cephalosporin, carbapenem, or beta-lactam/beta-lactamase inhibitor, plus either an anti-pseudomonal fluoroquinolone or aminoglycoside, plus either linezolid or vancomycin [2]. Macrolide use is suggested as an alternative to a quinolone if *Legionella* species are suspected. Compliance with IDSA/ATS guidelines was required for inclusion in the mortality analysis, and it would be valuable to know if patients with HCAP were over-represented in the quinolone group. A significant number of individuals had co-morbidities (18.3% with COPD, 15.1% with diabetes, 24.3% with cardiomyopathy) that likely placed them at increased risk of HCAP versus CAP.

The data suggest that patients receiving macrolide-containing regimens were quite different from those receiving quinolones. Only five patients receiving macrolides were given an anti-pseudomonal beta-lactam (representing 10.8% of the group); none received carbapenems. In contrast, in the quinolone group, 32 patients (representing 59.2% of the group) received either a fourth-generation cephalosporin (11.1%), carbapenem (22.2%), or co-formulated piperacillin/tazobactam (25.9%). By direct extrapolation from the 2007 IDSA/ATS CAP guidelines [4], *Pseudomonas* infection appears to have been suspected in a great deal more patients chosen to receive quinolone therapy. It should not be surprising that mortality would be higher in patients suspected of possible *Pseudomonas* or MDR infection.

Despite the authors' best attempts to apply adjustments for etiology and severity via Cox regression analysis, we remain unconvinced that these data mandate the use of macrolides in all cases of severe community-acquired pneumonia [5].

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