Commentary

Choosing the right combination therapy in severe community-acquired pneumonia

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Abstract

Recent studies have suggested that combination antibiotic therapy is preferable to monotherapy for severe community-acquired pneumonia (CAP). In this issue Mortensen and colleagues present retrospective data suggesting that combination therapy with a cephalosporin and a fluoroquinolone is inferior to combination therapy with a cephalosporin and a macrolide. Several mechanisms exist by which quinolones could be inferior to macrolides in combination therapy, so if these findings are confirmed by other groups they have significant implications for physicians treating patients with severe CAP.

In the past 5 years there has been a substantial shift in thinking regarding the optimal therapy of patients with severe community-acquired pneumonia (CAP), particularly with respect to pneumococcal disease. Observational studies by Mufson and Stanek [1], Waterer *et al.* [2], Martinez *et al.* [3], Baddour *et al.* [4] and Weiss *et al.* [5] have all identified significant mortality reductions in patients with bacteraemic pneumococcal pneumonia who received combination antibiotic therapy in comparison with patients who received monotherapy. Additional observational studies in more general CAP cohorts have also identified outcome benefits of combination therapy over monotherapy [6-9].

Despite the limitations of these primarily retrospective observational studies, the similar findings in different populations makes it very likely that the association is real. However, it remains unclear whether there is a true survival advantage of combination therapy or whether there are common confounding factors related to patient selection, to the process, to quality or to care.

In this issue, Mortensen *et al.* [10] demonstrate that, at least in their region, physicians have widely adopted combination therapy in patients with severe CAP. In contrast with previous studies, an important strength is that a large proportion of patients were intubated by severe respiratory failure. The findings of Mortensen *et al.* that fluoroquinolone/β-lactam combinations were associated with worse outcome than other combination regimens is both enlightening and disturbing.

The most consistent finding across the retrospective studies favouring combination therapy is that it is the addition of a macrolide to a third-generation cephalosporin that has the best outcome [1-3,6,7,9]. What is not clear is the mechanism by which the addition of a macrolide is beneficial. Possible explanations include coverage of unrecognized co-infection with atypical pathogens, non-ribosomal anti-pneumococcal activity such as impairment of epithelial adherence [11], and their increasingly used immunomodulatory actions [12]. The findings of Mortensen *et al.* [10], if proved correct, indicate that coverage of atypical pathogens is not the mechanism of benefit because there is no evidence that fluoroquinolones are inferior to macrolides for these pathogens and may even be superior [13].

Assuming that the findings of Mortensen *et al.* [10] are real and can be replicated by other groups, what possible explanations are there for the poor performance of fluoroquinolone/β-lactam combinations? First, it is important to remember that this was not a study of single compared with combination antibiotic therapy. No data were presented that suggested that the combination of a β-lactam and a fluoroquinolone is worse than either agent separately and there is no *in vitro* evidence of antagonism between these classes of antibiotics. However, one potential adverse impact of the much broader spectrum of coverage provided by a fluoroquinolone/β-lactam combination

CAP = community-acquired pneumonia; IL = interleukin.

is the selection of highly resistant nosocomial (hospital-acquired) pathogens, particularly *Pseudomonas aeruginosa*, which is the first cause of superinfection in intubated patients. Although no data on nosocomial infections were presented by Mortensen *et al.* [10], it is notable that the survival graph shows a continued disadvantage of initial fluoroquinolone/β-lactam combination therapy well beyond 7 days and into the time frame in which nosocomial sepsis would be expected to contribute to mortality.

A second possibility, put forward by Mortensen *et al.* [10], is that their findings favouring macrolides are due to the immunomodulatory properties of this class of antibiotics. In healthy subjects macrolides substantially reduce the *in vitro* pro-inflammatory response to infectious stimuli, including the key cytokines tumour necrosis factor, IL-1β, IL-6 and IL-8 [12]. However, the reduction in immune response is not global, with minimal to no change in response to interferon-γ [14], a key cytokine in the restoration of immune function after sepsis-induced immunoparalysis. Macrolides have also been reported to downregulate the production of reactive oxygen species, blocking the activation of nuclear transcription factors, inhibiting neutrophil activation and mobilization, accelerating neutrophil apoptosis, and improving the clearance of mucus [15,16]. In contrast to macrolides, quinolones seem to have a more global immunosuppressive effect [17], including significant impairment of interferon-γ production [14]. The combination of selection for multiresistant pathogens and potential prolongation of post-sepsis immunoparalysis certainly could explain the survival disadvantage observed with fluoroquinolones in comparison with macrolides.

All the potential explanations for the findings of Mortensen *et al.* [10] are worth exploring, but only if prospective, randomized, double-blind trials confirm the benefit of combination therapy in pneumococcal disease, including a clear benefit of having a macrolide as part of the combination. For a disease as common as CAP, with a mortality rate approaching or exceeding 20% in severe disease, it is unacceptable that the present level of uncertainty about optimal therapy exists. The large number of different combinations chosen by physicians in the study by Mortensen *et al.* [10] is a clear indication that the therapeutic uncertainty in severe CAP is perceived by physicians at the 'front line'. Indeed, other studies [18-20] have suggested that a substantial proportion of clinicians select the empirical antibiotic regimen by using a patient-based policy rather than by following general guidelines. Now that there is a strong suggestion that fluoroquinolones may be suboptimal compared with macrolides as one arm of combination therapy in severe CAP, conducting prospective, randomized clinical trials including a large proportion of Pneumonia Severity Index of V patients should be a priority.

Competing interests

The author(s) declare that they have no competing interests.

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