**Editorial**
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# Additional corticosteroids or alternative antibiotics for the treatment of macrolide-resistant *Mycoplasma pneumoniae* pneumonia

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*Mycoplasma pneumoniae* (MP) pneumonia has occurred in periodic epidemics of 3–4 years in Korea. The peak prevalent age group has become younger in recent epidemics (2–4 years) compared to that in past epidemics in Korea. The infection rates in each age group have decreased with increasing age, with corresponding positive rates of anti-MP IgG detected in the populations. We have observed that there is no serologically confirmed reinfected MP pneumonia case during the 3 most recent epidemics, by using a repeated serologic test performed at presentation and again at discharge[1]. Thus, adolescent and young adult patients are rarer in Korea, but older children and young adults are prone to developing severe pneumonia. The epidemiological characteristics of MP infection suggest that it may act like a viral infection, such as measles in the prevaccination era[2]. During an epidemic, the majority of MP infected patients may present as asymptomatic or with mild symptoms such as fever and myalgia. Among infected patients, a small proportion of patients manifest pneumonia, and a small part in pneumonia patients affect severe pneumonia or extrapulmonary manifestations such as encephalopathy and other organ involvement. These clinical characteristics are similar to those observed in viral infections such as influenza. Although MP is believed to be an extracellular small bacterium, it may invade host cells *in vivo*. Recently, Hegde et al.[3] demonstrated that a MP species, *Mycoplasma agalactiae*, is capable of entering host cells and systemically disseminates to distant organ cells, using *in vitro* and *in vivo* studies in the sheep infection model. Therefore, it is possible that lung or other organ cell injury in MP infection may be caused by pathogen-derived substances and/or the host cell-derived substances produced during MP replication in the host cells, like that in other respiratory viral infections[4].

The prevalent MP strains during each epidemic may be different, and the main MP strain causing the 2015–2016 epidemic in Korea might be a macrolide-resistant MP (MRMP) strain, similar to that in Japan and China[5]. Considering the epidemiological and clinical similarity of MP infection with viral infections, it is natural that the effect of antibiotics on MP pneumonia in children and adults has been controversial for some time. The majority of MP pneumonia patients present a self-limited clinical course without antibiotics, although macrolides are still recommended as the first-line antibiotic for MP infection. There are no differences in the outcomes of MP pneumonia patients between those treated with a beta-lactam only and those treated with additional macrolides[6,7], and some patients present progressive pneumonia despite early treatment with adequate antibiotics for macrolide-sensitive MP (MSMP) or MRMP strains[8,9].

The recent appearance of MRMP strains in Korea has presented an opportunity to discuss this issue once again. Yang et al.[10] reviewed the mechanism of resistance acquisition by MP, and discussed the issue of alternative antibiotics or additional immune-modulators for treating MRMP pneumonia. For patients with severe progressive MRMP pneumonia, Yang et al.[10] recommend the use of alternative antibiotics, and/or the addition of systemic immune-mo-

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dulators (corticosteroids and/or intravenous immunoglobulin). We suspect that many pediatricians treating protracted MRMP pneumonia in Korea, and possibly in other MRMP endemic countries, would choose the latter method, based on experience with immune-modulators during previous MP pneumonia epidemics, as cited by Yang et al.[10]. Quinolones and tetracycline are not recommended in pediatric patients because of potential side effects such as arthropathy or tooth discoloration, and the use of these alternative antibiotics is not approved by the Korean Food and Drug Administration at present time[10]. During advanced MP pneumonia, host cell-derived substances from injured lung tissue may induce more inflammation, affecting the corresponding immune cells and prolonging morbidity; thus, early control of disease progression is important[11].

In the present article, we aim to review and discuss the available information regarding early immune-modulator therapy for treatment of MRMP pneumonia. Pneumonia, including MP pneumonia and even other bacterial pneumonia, is a self-limiting disease. Although antibiotics for bacterial pathogens and antivirals for viral pathogens can contribute to early recovery from the disease, some pneumonia patients experience a severe clinical outcome and even death, despite extensive antimicrobial treatment. This finding suggests that the immune status of a patient is an important factor in deciding the prognosis of the disease[11]. The precise mechanisms of lung cell injury in pneumonia resulting from various pathogens, including MP pneumonia, remain unknown. Whole MP (or respiratory viruses) induce direct injury to target cells is unlikely because MP is probably an extracellular mucosal pathogen, and few intact MPs are found in pulmonary and extrapulmonary lesions, such as Stevens-Jonson syndrome or meningoencephalitis[11,12]. Structural components of MP, such as lipoproteins from the cell membrane or secretary toxins such as community-acquired respiratory distress syndrome (CARDS) toxin, can induce inflammation and cytokine production[13,14]. Thus, it is reasonable to assume that there are etiological substances that induce lung cell injury and an immune reaction during MP infection. It has been proposed that immune cells and immune proteins control these etiologic substances, based on their size and biochemical properties. The substances that induce lung inflammation either originate from the pathogens or from injured host cells and activated immune cells[15]. The hyper-immune reaction of the corresponding immune cells may be involved in target cell injury in the early stages of the disease, and early control of this type of immune disturbance may be crucial for prevention of pneumonia progression[11]. We have reported that systemic immune-modulators halt the progression of pneumonia, and induce rapid clinical and radiological improvement in patients with severe MP pneumonia or severe influenza pneumonia[4,8,16-19]. Recent studies have reported that additional corticosteroids, administered within 24–36 hours after admission, are effective in reducing treatment failure and morbidity in adult patients with severe community acquired pneumonia[20,21]. In the 2015–2016 MP pneumonia epidemic in Korea, we tried to administer early corticosteroids (1 mg/kg/day of oral prednisolone or 1–2 mg/kg of intravenous methylprednisolone for 3 days, tapered and stopped within a week) to all MP pneumonia patients within 24–36 hours after admission. The patients with respiratory distress, with or without extensive lung lesions at presentation, or those who had persistent fever for 48 hours after initial steroid therapy, or disease progression, were treated with a high-dose of methylprednisolone (5–10 mg/kg/ day for 1–3 days, tapered over a week). All patients responded well to the treatment, and no patient had fever for over 72 hours or disease progression after high-dose steroid treatment. In addition, we observed no differences in clinical outcomes, such as the total fever duration and the number of cases of disease progression, between 2 patient groups: the patients treated only with a beta-lactam (cefuroxime or amoxicillin/clavulanate) and those treated with a beta-lactam and additional clarithromycin (unpublished observation). Our results suggest that patients infected with MRMP strains present varied clinical phenotypes, as well as MSMP strains, and that genotype variation *in vitro* may not be correlated with clinical outcomes *in vivo*. Further, the rapid response of MRMP strains to corticosteroids indicates that immunopathogenesis of MRMP infection is also associated with the host hyper-immune reaction. Some MP pneumonia patients may require a higher dose of corticosteroids in the early stages of the disease. Although some studies have reported that patients with MRMP pneumonia had more complications than those with MSMP pneumonia, in our experience of over a decade, the occurrence rates of antibiotic-susceptible, but nonresponse cases among all MP patients may be similar in past MSMP epidemics and in recent MRMP epidemics. In addition, it is also likely that early control of the initial pneumonia is more effective for prevention of disease progression and reduction of morbidity, comparing our previous findings where corticosteroids were administered >48–72 hours after admission[8,16-18].

In conclusion, the immunopathogenesis of pneumonia and recovery from the disease are associated with the immune status of the host. Patients with advanced pneumonia or acquired respiratory distress syndrome, including cases caused by MP, are associated with prolonged morbidity, possibly permanent lung sequelaes and poor prognosis. Because the immunopathogenesis of mild and severe pneumonia may be the same, early control of the initial hyper-immune disturbance is crucial. It is reasonable to recommend that the early use of immune-modulators, without waiting for the antibiotic's effect, contributes to the effective reduction of immune-mediated lung injury in MP infection.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

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