



The Efficacy of Glucocorticoid on Macrolide Resistant Mycoplasma Pneumonia in Children

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Mycoplasma pneumoniae (MP) is a common etiology of pediatric and adult community-acquired pneumonia that represents 10%-40% of cases;¹⁻³ however, the immunopathogenesis of MP in humans is poorly understood. The role of cell-mediated immunity in MP infections is controversial. Both human infection tissue and animal model lung tissue are consistent in demonstrating mononuclear periluminal infiltrates. Animal model studies have found hyperaccentuated reactions after repeated infection that is also mimicked by repeated exposure to non-viable microbe.⁴

Macrolides are first-line antimicrobials against MP pneumonia.⁵ Treatment of MP pneumonia with appropriate antibiotics (such as macrolides) is found to significantly improve the course of the disease. Observations have demonstrated that MP in a clinical sample obtained from patients successfully treated with macrolides was detectable by culture.⁶ However, in some cases, the suppression of microorganisms by a macrolide may be inadequate for the treatment of MP pneumonia. The worldwide prevalence of macrolide-resistant MP has increased to 10%-30% since macrolide resistance (such as erythromycin resistance) was first reported in Japan in 1970. Macrolide-resistant strains are known to cause severe refractory MP. The M144V mutation of the L4 protein and mutation at position 2064 of domain V in the 23S rRNA gene of *M. pneumoniae* was reported in Korea in 2010; consequently, the appearance of macrolide-resistant strains has increased.

The immune status is T-helper 2 dominant after infection by MP.⁷ This is confirmed by an MP infection that exacerbates inflammation in asthma patients^{8,9} associated with the activation of nuclear factor κB.^{10,11} Serum levels of VEGF and IL-5 increased more in atopic children with MP pneumonia. These cytokines may act through their respective pro-inflammatory pathways to aggravate the allergic status and induce airway hypersensitivity during MP pneumonia in atopic children.¹² These observations suggest that MP pneumonia is a combination of infection and

over-reaction of host-defense reactions versus a simple infectious disease.

Macrolide functions as an antimicrobial as well as a control for mucus secretion¹³ and cytokine production.^{14,15} It affects the growth of microorganisms by inhibiting their adherence and virulence factors,¹⁶ biofilm formation.¹⁷ However, only a few macrolides possess anti-inflammatory properties that may contribute to clinical benefits observed in patients with airway inflammation. They can modulate the function of several inflammatory cells (such as polymorphonuclear leukocytes, lymphocytes, and macrophages); however, they seem to affect neutrophil migration, the oxidative burst in phagocytes, the production of proinflammatory mediators and eosinophilic inflammation.^{18,19}

Evidence of acute MP infection is found in up to 20% of acute asthma exacerbations in adolescents and adults.^{20,21} The relationship between MP infection and asthma development has been debated for the past 20 years. Previous studies have demonstrated that the incidence of MP infection is higher in patients with chronic stable asthma or acute exacerbation than in control subjects.²² Systematic steroids are preferred over the routine administration of antibiotics for more severe asthma exacerbations because the microbiologic etiology of asthma exacerbations is not frequently determined in routine practice. However, observational data from both children and adults have indicated that the addition of systemic steroids to antimicrobial therapy may improve the outcome of severe MP pneumonia. As a result of these clinical observations, systemic steroids have been advocated in addition to antibiotic therapy for severe MP

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pneumonia.^{23,24}

Extrapulmonary manifestations are common in patients with MP infections, with encephalitis being the most common extrapulmonary manifestation. Aggressive management (including intravenous corticosteroids) of seizures in patients diagnosed with MP encephalitis can potentially support the improvement of functional recovery and future seizure control. The antibiotic of choice to treat pulmonary infection in children is a macrolide; however, there is no consensus on central nervous system treatment. This class of antibiotic does not properly penetrate the blood membrane barrier; however, it is a treatment option due to its bacteriostatic and immunomodulatory effect as well as the possible immunologic pathological mechanism of the disease. The use of corticosteroids (adopted in CNS involved cases) is considered as immunosuppression depending on the degree of neurologic involvement. Steroid therapy is of possible benefit to treat inflammation related to infectious diseases such as certain types of bacterial meningitis.^{25,26} The pathogenesis of a macrolide-nonresponsive and progressive condition is suggested to be related to cellular immunological responses.^{27,28} Corticosteroids have been used for severe or refractory MP in adulthood with promising efficacy based on the proposed mechanism.²⁹ In contrast, little is known about the effect of corticosteroid therapy on patients in a pediatric population. A recent study showed that oral prednisolone of 1 mg/kg/day for more than 1 week for severe MP in children may be helpful to reduce morbidity.³⁰ However, appropriate steroid use methods (in particular, dosage, administration route, or duration of treatment) have not been fully clarified.

In the present issue, You et al.³¹ presented the effect of methylprednisolone pulse therapy on refractory MP pneumonia in 12 Korean children who appeared to be efficacious and well-tolerated. Tamura et al.³² reported 5 years ago on the effectiveness of methylprednisolone pulse therapy for refractory MP pneumonia in 6 children. They suggested that a 3 consecutive day methylprednisolone pulse therapy is an efficacious and well-tolerated treatment for refractory MP in children.

The effects of optimal dose and timing of pulse corticosteroid treatment remain unclear for MP infection; therefore, there remains a need to evaluate further mechanisms and the efficacy of methylprednisolone pulse therapy for MP pneumonia in childhood.

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