

***Mycoplasma pneumoniae* pneumonia, bacterial pneumonia and viral pneumonia**

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Pneumonia is one of the most frequent diseases treated by pediatricians. The majority of pneumonia patients recover uneventfully as a self-limited disease, but some patients experience a severe clinical course and even death. The difference of clinical course is associated with the virulence of etiologic agents and/or the host immune status. Antibiotics for bacterial pathogens and antivirals, if possible, for viral pathogens may help induce early recovery from pneumonia by reducing the number of pathogens and the host immune response to etiologic agents. The circulating immune cells including neutrophils, lymphocytes, and monocytes may be involved in the pathogenesis of pneumonia. Thus, change of these parameters may reflect the severity of pulmonary lesions. The pathogenesis of pneumonia in each etiologic agent may be different; in general, patients with typical bacterial pneumonia manifest more toxic clinical symptoms with leukocytosis, neutrophilia with band form neutrophils, and bacteremia. In initial pneumonia lesions, mainly activated neutrophils and mononuclear phagocytes are predominantly observed, and mediators such as proteolytic enzymes, oxygen radicals, and cytokines from these cells may be associated with host lung injury.¹ In *Mycoplasma pneumoniae* (MP) pneumonia and viral pneumonias appearing in measles, severe acute respiratory syndrome (SARS), and influenza, the patients show leukopenia with lymphopenia. The infiltration of immune cells, especially numerous T cells, is prominent in initial lung lesions, and mediators such as proinflammatory cytokines from these cells may be associated with lung injury of the host. To be aware of

these differences among pneumonias, it may be helpful to understand the pathogenesis of MP pneumonia, although MP has been regarded as a small bacterium.²

MP is one of the most common agents of community-acquired pneumonia in children and young adults worldwide. MP pneumonia has been reported in 10-40% of cases of community acquired pneumonia and shows an even higher incidence during epidemics. Although there are some geographical and timing variations, MP infection is endemic in the larger communities of the world with 3-7 year cyclic epidemics that last from several months to years.^{2,3} In a study by Vervloet et al.,⁴ more than half of the subjects were serologically MP positive, indicating that MP is also one of most common pathogens of pneumonia in Brazil. The pathogenesis of lung injury (pneumonia) in MP infection is unknown, but experimental and clinical evidence have supported the notion that the pathogenesis of MP pneumonia is associated with excessive host immune reaction including cell-mediated immune response.²

As for the diagnosis of pneumonia, there are some difficulties in the detection of etiologic agents for lower respiratory tract infections in children (especially younger children) due to the inconsistency of adequate sampling of respiratory materials for pathogen culture and polymerase chain reaction (PCR) and the need for paired blood sampling for serologic tests. In addition, the higher rates of nasopharyngeal carriage of bacterial pathogens, including *S. pneumoniae* in healthy children (10-50%), make it more difficult.⁵ Vervloet et al. used an enzyme-linked immunosorbent assay (ELISA, IgM and IgG) for diagnosis

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of MP pneumonia in their study.⁴ Although we can consider an IgM positive as a MP infection, this examination may be incomplete for final diagnosis of MP infection, especially during epidemics. Since in some patients the diagnostic IgM antibodies are not detected in the early stage of MP pneumonia (30-45% in our series),^{2,3,6} and MP IgM antibody could remain for a long-term period after primary infection, paired serologic study (IgM and IgG) is more desirable for a definitive diagnosis. In addition, MP can also remain in the respiratory tract for a long time in children, especially younger children (< 5 years of age) after primary infection, and a PCR study alone may also be incomplete for a definitive diagnosis of MP infection.^{2,3}

For pneumonia patients, early detection of an etiologic agent is important for treatment including selection of proper antibiotics. However, since early diagnosis of etiologic pathogens has been unsatisfactory and some pneumonias can progress to a fatal outcome, clinicians have used empirical antibiotics for pneumonia patients, especially those who have severe respiratory distress and/or segmental/lobar infiltration. There has been controversy on whether we can distinguish the pneumonias as being of viral-origin or bacterial-origin by means of laboratory findings and chest radiographic findings on admission. Some studies, including the one by Vervloet et al., indicated that the score system using white blood cell (WBC) and neutrophil counts, chest radiographic findings, and other factors could be a useful tool for the differentiation of pneumonia etiology.⁷ Vervloet et al. found that MP pneumonia is more likely to have characteristics of bacterial pneumonia in the score system.⁴ However, recent studies have reported that the clinical, laboratory, and radiological findings between atypical pneumonias, including MP pneumonia, and bacterial pneumonias are similar in children and adults.⁸ The score system based on clinical, laboratory, and radiological findings may have some confounding factors. We cannot detect the etiologic agents for all pneumonia subjects using the current diagnostic tools, and some pneumonia patients have mixed infections. Total and differential WBC count in pneumonia patients may be affected by the stage of illness, the age of patients, and possibly the host immune status. For example, younger children have a higher WBC and lymphocyte differential compared to older children. In previous studies, we found that more severe MP pneumonia patients had prolonged fever, higher C-reactive protein (CRP), and lower WBC count with lower lymphocyte counts.⁶ In addition, the most severely affected pneumonia patients during the 2009 pandemic influenza showed the highest WBC count with the lowest lymphocyte differential (mean 11,800/mm³ and 8.8%) compared to those of patients without pneumonia (6,500/mm³ and 30%) or with mild pneumonia (8,800/mm³ and 21%, respectively) in the acute stage of this viral infection (unpublished observation). As previously described, since neutrophils may be the major

effectors for typical bacterial insult and lymphocytes may be the major effectors for MP and viral insults, the changes of WBC count with differentials need periodic reevaluation if the pneumonia is progressive. In general, the majority of bacterial pneumonia in healthy children responded to antibiotic treatment within 48-72 hrs after initiation of antibiotic treatment. The pediatrician may be confused when the patients have a progressive pneumonia despite antibiotic treatment. At this time, follow-up and differential WBC may helpful in the differentiation of the causative agent. If the pneumonia patient shows a decreased WBC count with lower lymphocyte count, the patient may have a higher possibility of having MP or viral pneumonia. The pneumonia patient who shows increased or unchanged WBC and neutrophil counts with more band forms may have a bacterial infection which is resistant to antibiotics. However, in clinical practice antibiotic-resistant bacterial pneumonia in healthy children is very rare, and the majority of antibiotic-non-responsive patients may have an atypical pneumonia (MP, viral or other atypical pathogens) or a hyperimmune state against bacterial insults. Since MP pneumonia and some viral pneumonias appear during an epidemic, awareness of the infectious epidemiology in a society is very important for assumption of pneumonia pathogens.

It is well-known that chest radiologic findings of MP pneumonia are varied as shown in the Vervloet et al. study.⁴ Interstitial and/or bronchopneumonic patterns similar to viral pneumonia are more common, but segmental and/or lobar pneumonia patterns with pleural effusion similar to typical bacterial pneumonia (*S. pneumoniae*) are also evident. In our experience with 191 MP pneumonia patients, half of the patients (96 cases) showed a mild pattern (interstitial/bronchopneumonia), and the other half showed a segmental/lobar pneumonia pattern (alveolar consolidation) at presentation, with 14 patients progressing to severe pneumonia despite antibiotic therapy.⁶ Recently, during the 2009 pandemic influenza we also found that 61% of patients (49/80) showed a mild pattern (interstitial/bronchopneumonia), and 39% of patients (31/80) showed a severe pattern (segmental/lobar pneumonia) at presentation, with five patients progressing to a more severe form despite early antiviral treatment (unpublished observation). Since the pneumonia pattern may reflect the degree of host immune response in these infections, initial chest findings may be determined by the stage of illness (the intensity of immune reaction of the host), and, in some patients, mild pneumonic infiltrations (interstitial/bronchial) can progress rapidly to more severe pneumonia (segmental/lobar pattern) despite antibiotic or antiviral treatment.⁹

Clinical manifestations of pneumonia may also be different according to the age of the patient (the state of immune maturation). We found that, in the epidemics of MP and 2009 pandemic influenza virus, younger children

(< 5 years of age) had a relatively mild clinical course with less severe-type pneumonia pattern (i.e., rare alveolar consolidation), compared to older children (> 6 years of age). In contrast, younger patients with bacterial pneumonia, such as pneumococcal pneumonia or staphylococcal pneumonia, are more prevalent and may experience a more severe clinical course compared to older children.

Recently, macrolide-resistant MP strains have been detected in Far East countries including Japan, China, and possibly in Korea.^{2,3} These strains can spread worldwide and may affect macrolide therapy. Although the patients affected with macrolide-resistant MP had a prolonged duration of fever and cough, fortunately there are few reports of apparent treatment failure, such as a progression of pneumonia to acute respiratory distress syndrome (ARDS), despite macrolide treatment.¹⁰ Although the effect of antibiotics on MP pneumonia in children is still a controversy,¹¹ the candidate antibiotics for children with macrolide-resistant MP infection are quinolones and tetracyclines, which are no longer in use in children, emphasizing the need for further controlled-clinical studies.

Previously, we reported that the use of immune-modulators (prednisolone) for antibiotic non-responsive MP pneumonia patients was very effective in improving clinical and radiographic findings.¹² Other studies have revealed that corticosteroid treatment is beneficial in intractable MP pneumonia.² Interestingly, during the recent pandemic 2009 influenza, we found that pneumonia severity was associated with lymphocyte differential at presentation and early corticosteroid treatment had a dramatic effect in severe pneumonia patients with pandemic 2009 influenza virus infection.⁹ In addition, the patterns of pneumonia in both influenza virus and MP infections were similar although pneumonic infiltrations appear faster in the former after fever onset (unpublished observation). Lung tissue injury itself by MP or viral insults (possibly bacterial insults) may be responsible for aggravation of lung injury by immune cells, predisposing to other bacterial infections. Therefore, for pneumonia patients with hyperimmune reaction of the host, early immune-modulators may be helpful to alleviate the host immune responses that could induce further lung injury.⁹ For viral pneumonia, prophylactic antibiotic treatment against secondary bacterial infections would also be necessary when the patient's pneumonia progresses to a severe form and ARDS. Empirical use of early, short-term (within a week), and properly dosed immune-modulators

(corticosteroids) after diagnostic work-up may be helpful to reduce the morbidity and the mortality in antibiotic non-responsive MP pneumonia and some viral pneumonias.

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