AARD
Allergy Asthma Respir Dis 14(1):14-19, January 2026 https://doi.org/10.4168/aard.2026.14.1.14
pISSN: 2288-0402
eISSN: 2288-0410
ORIGINAL ARTICLE

Th17-related cytokines are involved in the response to step-wise treatment of *Mycoplasma pneumoniae* pneumonia in children

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Purpose: Treatment responses to *Mycoplasma pneumoniae* (MP) pneumonia in children exhibit considerable variability. It is essential to identify predictive indicators and elucidate mechanisms associated with treatment responses. This study aimed to characterize the clinical, radiological, laboratory, and cytokine profiles associated with treatment responses in pediatric MP pneumonia.
Methods: A retrospective analysis was performed in 85 children hospitalized with MP pneumonia between May 2019 and March 2020. Patients were categorized into the good response group (n=74) or the poor response group (n=11) based on clinical responses to step-wise treatment. Clinical characteristics, radiological findings, laboratory parameters, and serum levels of 27 cytokines obtained at admission were compared between the groups.
Results: Compared to the good response group, the poor response group exhibited significantly longer fever duration (11.36±5.33 days vs. 5.77±3.95 days, $P=0.006$), more frequent lobar consolidation (63.6% vs. 20.3%, $P=0.043$), and higher lactate dehydrogenase levels (1,146±505 IU/L vs. 731±231 IU/L, $P=0.008$) and MP-specific immunoglobulin M index (6.49±3.01 vs. 3.85±3.28, $P=0.014$). Among the cytokines assessed, IL-21, IL-22, and IL-31 levels were significantly elevated in the good response group. IL-17A levels were also higher in this group, albeit not statistically significant.
Conclusion: Early identification of clinical, laboratory, and radiologic markers may facilitate early prediction of treatment response in pediatric MP pneumonia. Elevated IL-21, IL-22, and IL-31 levels in the good response group suggest a potential role for Th17-related cytokine activity in favorable treatment outcomes, warranting further investigation in larger cohorts. (*Allergy Asthma Respir Dis 2026; 14:14-19*)

Keywords: *Mycoplasma pneumoniae*, Pneumonia, Child, Th17, Response

INTRODUCTION

Mycoplasma pneumoniae (MP) is a major cause of community-acquired pneumonia (CAP) in children, accounting for approximately 10%–40% of pediatric CAP cases.[1] Although MP infection is typically mild and self-limiting in children,[2] a subset of patients develop severe or refractory disease necessitating step-wise and intensive therapeutic interventions.[3] The global rise in macrolide resistance has contributed to an increasing prevalence of severe or refractory MP pneumonia, which is strongly linked to the development of complications such as postinfectious bronchiolitis obliterans (PIBO).[4,5] These trends underscore the need for effective strategies to predict and manage severe or refractory MP pneumonia.

Clinical responses to antibiotic therapy in MP pneumonia vary markedly, ranging from rapid resolution to persistent or worsening disease courses. Patients who fail to respond to step-wise treatment often experience prolonged fever and progressive pulmonary involvement, potentially resulting in long-term lung injury. Several clinical and laboratory indicators, such as prolonged fever duration and elevated C-reactive protein, have been associated with refractory MP pneumonia.[6,7] However, these markers primarily reflect nonspecific inflammation and do not fully explain the mechanisms underlying treatment response heterogeneity. Emerging evidence suggests that variability in host immune responses, including differences in cytokine production and immune cell activation, may contribute to these divergent clinical outcomes.[8,9] However,

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• This study was financially supported by Chonnam National University (Grant number: 2025-0920).

Received: July 13, 2025 **Revised:** August 27, 2025 **Accepted:** August 27, 2025

most prior studies are limited by small sample sizes, measurement of only a subset of cytokines, and lack external validation, leaving the immunopathologic mechanisms incompletely defined.

The present study was designed to test the hypothesis that children with differing treatment responses to MP pneumonia display distinct clinical, laboratory, and radiologic characteristics, along with divergent immune profiles. To investigate this, demographic and clinical features, laboratory values, and imaging findings were compared between response groups, with a specific focus on comprehensive serum cytokine profiling to elucidate potential immunologic mechanisms.

MATERIALS AND METHODS

This retrospective observational study included pediatric patients aged 18 years or younger who were diagnosed with MP pneumonia and admitted to a tertiary children's hospital between May 2019 and March 2020. Only previously healthy children were eligible for inclusion; patients with chronic comorbidities, except for allergic conditions (atopic dermatitis, food allergy, allergic rhinitis, or asthma), were excluded. Clinical characteristics, laboratory data, and radiologic findings were retrieved from electronic medical records. The study protocol was approved by the Institutional Review Board of Chonnam National University Hospital, which waived the requirement for informed consent (IRB No. CNUH-2019-261).

The diagnosis of MP pneumonia was based on the following criteria: (1) recent onset of respiratory symptoms (e.g., cough, sputum) in a child without underlying chronic illness; (2) radiographic evidence of pneumonia and/or abnormal chest auscultation findings; and (3) laboratory confirmation of MP infection by either MP-specific immunoglobulin M (IgM) serologic testing (positive result defined as an index value $\geq$1.1, measured by enzyme-linked immunosorbent assay (ELISA) using the CHORUS *Mycoplasma pneumoniae* kit, DIESSE, Italy) or polymerase chain reaction of respiratory specimens.

Step-wise treatment strategies were determined at the time of hospital admission, taking into account prior treatment received at local clinics. Initial therapy consisted of macrolide antibiotics. For patients with severe MP pneumonia, intravenous methylprednisolone was administered at a dose of 1–2 mg/kg/day (maximum 30 mg/dose) for 3–5 days. If clinical improvement was not observed within 3–5 days, second-line antibiotics were initiated—ciprofloxacin for children younger than 8 years and doxycycline for those aged 8 years or older. The same treatment protocol was applied to all patients, and there were no differences in treatment strategies between the good and poor response groups. The poor response group was defined as patients who showed a lack of clinical or radiologic improvement, or worsening of these features, after $\geq$7 days of step-wise treatment.[3]

The extent of pulmonary involvement was assessed using initial chest radiographs and classified as mild (infiltrative lesions affecting $<$1/3 of total lung volume), moderate (1/3 to 1/2), or severe ($>$1/2). The diagnosis of PIBO was established based on persistent respiratory symptoms indicative of fixed airway obstruction, supported by pulmonary function tests where available and characteristic findings on high-resolution chest computed tomography, including mosaic attenuation, air trapping, and bronchial wall thickening. Macrolide resistance of MP was identified by detecting point mutations at positions 2063 or 2064 within domain V of the 23S rRNA gene, using the GENECUBE system with the GENECUBE Mycoplasma detection kit (Sin Corp., Japan).

Serum cytokine levels at the time of admission were quantified using multiplex bead-based immunoassays. Concentrations of CCL-11 (eotaxin), interferon-gamma (IFN-γ), interleukin (IL)-1α, IL-1β, IL-1 receptor antagonist (IL-1RA), IL-2, IL-4, IL-5, IL-10, IL-13, IL-17, tumor necrosis factor (TNF)-α, TNF-β, monocyte chemoattractant protein-1, and granulocyte-macrophage colony-stimulating factor were measured using the Human Cytokine/Chemokine Magnetic Bead Panel (#HCYTOMAG-60K, Merck, USA). Additionally, IL-21, IL-22, and IL-31 were measured using the Human Th17 Magnetic Bead Panel (#HTH17MAG-14K, Merck, USA). For these assays, serum samples were incubated with precoated magnetic beads, followed by the sequential addition of biotinylated detection antibodies and streptavidin-phycoerythrin. Median fluorescent intensity was detected using the Magpix system (Luminex, USA), and cytokine concentrations were calculated from standard curves. For CCL5 (RANTES), a quantitative sandwich ELISA was performed using the Human CCL5/RANTES Immunoassay (#DRN00B, R&D Systems, USA), in accordance with the manufacturer's instructions. Optical density was measured using a SpectraMax190 microplate reader (Molecular Devices, China). All cytokine assays were conducted at Seoul Clinical Laboratories (SCL, Korea).

Comparisons of continuous variables between the good and poor treatment response groups were conducted using the Wilcoxon rank-sum test. Categorical variables were compared using Fisher

exact test. Serum cytokine concentrations were summarized as mean ± standard deviation, and nondetectable values were handled according to each cytokine's predefined reporting limit.[10] A 2-sided *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed using R ver. 4.2.1 (R Foundation for Statistical Computing, Austria).

RESULTS

1. Characteristics of the study population

A total of 85 children diagnosed with MP pneumonia were included in the analysis. Based on clinical response to step-wise treatment, 74 children were classified into the good response group and 11 into the poor response group. There were no significant differences in age (5.68 ± 3.77 years vs. 5.45 ± 2.54 years) or sex distribution (52.7% vs. 54.5% male) between the groups (Table 1). The prevalence of allergic diseases and the proportion of referred cases were also comparable between groups.

2. Comparisons of clinical features and radiologic findings

The poor response group exhibited a significantly longer duration of fever during the illness (11.36 ± 5.33 days vs. 5.77 ± 3.95 days, $P = 0.006$) and more frequently demonstrated severe pneumonia on chest radiographs (81.8% vs. 17.6%, $P = 0.001$) (Table 2). Lobar consolidation was more common in the poor response group (63.6%) than in the good response group (20.3%). The incidence of PIBO was also higher in the poor response group (36.4% vs. 8.1%, $P = 0.027$). No significant differences were observed between groups in the rates of pleural effusion, pulmonary thromboembolism, or oxygen requirement.

3. Comparisons of laboratory findings

The white blood cell count was significantly elevated in the poor response group compared with the good response group (11.47 ± 5.51 × 10^3/μL vs. 8.70 ± 4.18 × 10^3/μL, $P = 0.034$) (Table 3). The neutrophil count was higher in the poor response group (8.21 ± 4.11 vs. 5.26 ± 2.87, $P = 0.020$), while the lymphocyte count was lower (2.19 ± 1.43 vs. 2.41 ± 1.63, $P = 0.027$). Serum lactate dehydrogenase (LDH) levels were significantly increased in the poor response group

Table 1. Demographic characteristics according to treatment response

Variable	Good response (n = 74)	Poor response (n = 11)	*P*-value
Age at diagnosis of MP pneumonia (yr)	5.68 ± 3.77	5.45 ± 2.54	0.7972
Male sex	39 (52.7)	6 (54.5)	1.000
Presence of allergic diseases	42 (56.8)	5 (45.5)	0.7051
Referred cases	70 (94.6)	11 (100.0)	1.000
Time from symptom onset to presentation (day)	6.21 ± 3.58	8.73 ± 4.05	0.074

Values are presented as mean ± standard deviation or number (%).
MP, *Mycoplasma pneumoniae*.

Table 2. Comparison of clinical and radiologic characteristics between good and poor treatment response groups

Variable	Good response (n = 74)	Poor response (n = 11)	*P*-value
Total duration of fever (day)	5.77 ± 3.95	11.36 ± 5.33	0.006
Oxygen requirement	2 (2.7)	2 (18.2)	0.080
Macrolide-resistant MP	68 (91.9)	11 (100)	0.727
Virus coinfection	18 (24.3)	2 (18.2)	1.000
No. of coinfected respiratory viruses	0.58 ± 0.77	0.70 ± 0.67	0.440
Main radiographic features at admission			0.043
Lobar consolidation	15 (20.3)	7 (63.6)	
Patchy consolidation	35 (47.3)	2 (18.2)	
Peribronchial infiltration	18 (24.3)	2 (18.2)	
Diffuse nodular opacity	2 (2.7)	0 (0.0)	
Diffuse infiltration	4 (5.4)	0 (0.0)	
Severity of pneumonia on chest radiograph at admission			< 0.001
Mild	7 (9.5)	0 (0)	
Moderate	54 (73.0)	2 (18.2)	
Severe	13 (17.6)	9 (81.8)	
Pleural effusion	8 (10.8)	3 (27.3)	0.300
Pulmonary thromboembolism	2 (2.7)	1 (9.1)	0.340
Postinfectious bronchiolitis obliterans	6 (8.1)	4 (36.4)	0.027

Values are presented as mean ± standard deviation or number (%).
MP, *Mycoplasma pneumoniae*.

Table 3. Comparison of laboratory findings at the time of admission between good and poor treatment response groups

Variable	Good response	Poor response	*P*-value
WBC (× 10^3/μL)	8.70 ± 4.18	11.47 ± 5.51	0.034
Neutrophil (%)	60.42 ± 15.72	71.54 ± 10.15	0.020
Lymphocyte (%)	27.73 ± 13.12	19.05 ± 8.49	0.027
Eosinophil (%)	1.92 ± 2.50	1.06 ± 1.93	0.168
Monocyte (%)	8.98 ± 4.09	7.85 ± 2.31	0.380
AST (IU/L)	39.89 ± 19.06	56.55 ± 62.77	0.927
ALT (IU/L)	27.28 ± 28.49	44.64 ± 64.39	0.181
Albumin (g/dL)	5.40 ± 1.46	5.59 ± 1.58	0.922
LDH (IU/L)	730.62 ± 231.24	1,146.36 ± 504.99	0.008
C-reactive protein (mg/dL)	2.26 ± 3.06	6.57 ± 8.12	0.075
MP-specific IgM (index)	3.85 ± 3.28	6.49 ± 3.01	0.014

Values are presented as mean ± standard deviation.
WBC, white blood cell count; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; LDH, lactate dehydrogenase; MP, *Mycoplasma pneumoniae*; IgM, immunoglobulin M.

(1,146 ± 505 IU/L vs. 731 ± 231 IU/L, $P = 0.008$), and MP-specific IgM index at admission were also elevated in this group (6.49 ± 3.01 index vs. 3.85 ± 3.28 index, $P = 0.014$). No significant differences were found in C-reactive protein levels, liver enzyme activity, or serum albumin concentrations.

Table 4. Comparison of serum cytokine levels at the time of admission between good and poor treatment response groups

Variable	Good response (n = 74)	Poor response (n = 11)	*P*-value
IL-1α (pg/mL)	203.80 ± 314.24	50.52 ± 98.19	0.069
IL-10 (pg/mL)	37.92 ± 81.37	232.34 ± 624.12	0.670
Eotaxin (pg/mL)	87.95 ± 43.54	112.75 ± 75.57	0.448
IL-13 (pg/mL)	41.37 ± 65.27	12.31 ± 22.42	0.357
IL-5 (pg/mL)	11.30 ± 14.72	6.60 ± 7.07	0.714
IL-17A (pg/mL)	15.12 ± 41.79	11.06 ± 18.39	0.974
TNF-α (pg/mL)	22.57 ± 15.74	25.11 ± 13.71	0.313
MCP-1/CCL2 (pg/mL)	320.97 ± 243.53	390.37 ± 516.08	0.642
IL-1β (pg/mL)	12.10 ± 55.30	3.95 ± 3.28	0.436
IL-1ra (pg/mL)	233.57 ± 871.20	158.41 ± 169.27	0.979
TNF-β (pg/mL)	95.84 ± 170.34	15.14 ± 32.71	0.086
GM-CSF (pg/mL)	17.17 ± 22.21	34.35 ± 77.78	0.817
IL-2 (pg/mL)	2.90 ± 4.35	3.08 ± 4.24	0.865
IL-4 (pg/mL)	483.16 ± 717.06	125.32 ± 142.88	0.126
IFN-γ (pg/mL)	59.36 ± 148.86	54.01 ± 60.62	0.339
RANTES (pg/mL)	23,423.36 ± 26,168.45	32,424.24 ± 37,718.19	0.569
IL-21 (pg/mL)	52.99 ± 42.51	36.46 ± 50.36	0.021
IL-22 (pg/mL)	1.82 ± 2.11	0.84 ± 1.91	0.007
IL-31 (pg/mL)	0.25 ± 0.26	0.13 ± 0.23	0.014

Values are presented as mean ± standard deviation.
Group differences were assessed using the Wilcoxon rank-sum test. Nondetectable cytokine values were handled based on predetermined criteria according to the proportion of nondetectable values and cytokine-specific reporting limits.
IL, interleukin; TNF, tumor necrosis factor; MCP-1/CCL2, monocyte chemoattractant protein-1/C-C motif chemokine ligand 2; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; RANTES, regulated upon activation, normal T-cell expressed and secreted.

4. Comparisons of serum cytokine profiles

Among the 27 cytokines analyzed, serum concentrations of IL-21 (52.99 ± 42.51 pg/mL vs. 36.46 ± 50.36 pg/mL, $P = 0.021$), IL-22 (1.82 ± 2.11 pg/mL vs. 0.84 ± 1.91 pg/mL, $P = 0.007$), and IL-31 (0.25 ± 0.26 pg/mL vs. 0.13 ± 0.23 pg/mL, $P = 0.014$) were significantly higher in the good response group compared with the poor response group (Table 4, Fig. 1). Although IL-17A levels were not significantly different between groups (15.12 ± 41.79 pg/mL vs. 11.06 ± 18.39 pg/mL, $P = 0.974$), mean concentrations were higher in the good response group. No significant differences were observed in the levels of other cytokines, including Th1-associated (e.g., IFN-γ), Th2-associated (e.g., IL-4, IL-5, IL-13), and proinflammatory cytokines such as TNF-α and IL-1β.

DISCUSSION

This study characterized the clinical, laboratory, radiologic, and immunologic features associated with treatment response to stepwise therapy in pediatric MP pneumonia. Children in the poor response group exhibited prolonged fever duration, more severe radiographic abnormalities, particularly lobar consolidation, and elevated inflammatory markers, including LDH. In contrast, children in the good response group demonstrated significantly higher serum levels of Th17-related cytokines, including IL-21, IL-22, and IL-31. Although IL-17A concentrations were also elevated in the good response group, the difference did not reach statistical significance. These findings suggest that the Th17-associated cytokine

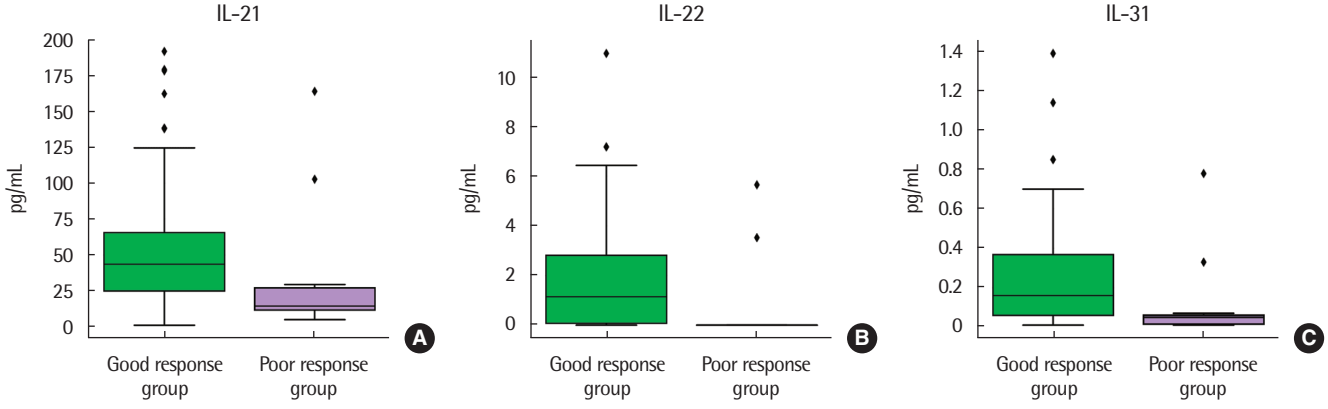

Fig. 1. Box plot distributions of IL-21 (A), IL-22 (B), and IL-31 (C) levels according to treatment response group. Box plots illustrate the median, interquartile range, and full range of cytokine concentrations. Outliers are indicated as individual dots. Group comparisons were performed using the Wilcoxon rank-sum test. Good response group: n = 74; poor response group: n = 11.

axis may contribute to the immunopathologic mechanisms underlying differential treatment responses in MP pneumonia.

While disease severity, poor prognosis, and treatment response in MP pneumonia are often interrelated, they represent distinct aspects of the clinical course. Previous studies have identified prolonged fever, elevated inflammatory markers, and multilobar involvement as indicators of severe or adverse outcomes in MP pneumonia.[11,12] Similarly, our findings showed that prolonged fever, lobar consolidation on chest imaging, and elevated LDH and MP-specific IgM index at admission were associated with poor treatment response. These findings highlight the potential utility of early clinical, laboratory, and radiographic features in predicting therapeutic outcomes and informing management strategies in pediatric MP pneumonia.

Previous studies of cytokine profiles in MP pneumonia have shown that elevated proinflammatory mediators, such as IL-6, IL-8, and TNF-α, are associated with severe disease, reflecting an exaggerated immune response.[8,13] IL-17A has also been linked to refractory MP pneumonia, with higher serum levels reported in patients unresponsive to macrolide therapy, although data remain limited.[8] In contrast, little is known about the roles of IL-21, IL-22, and IL-31 in MP pneumonia, and their contributions to disease pathophysiology are poorly defined. Evidence from other respiratory infections, including *Streptococcus pneumoniae* and influenza, suggests that IL-22 may support epithelial barrier integrity and repair, while IL-21 modulates humoral immune responses.[14,15] However, these cytokines have not been extensively investigated in the context of MP pneumonia.

IL-21, IL-22, and IL-31 are key cytokines within the Th17-related immune pathway, which coordinates host defense against pathogens and maintains mucosal barrier integrity.[16,17] IL-21 promotes B cell activation and sustains Th17 responses to enhance pathogen clearance during infection.[16,18] IL-22 contributes to epithelial barrier maintenance and facilitates tissue repair in the lungs, thereby limiting structural damage during pulmonary infections.[14,15,19] IL-31 has been implicated in chronic airway diseases and pulmonary fibrosis through its involvement in airway remodeling, collagen deposition, and neuroimmune signaling pathways that may amplify chronic inflammation.[20] Although these cytokines have not been directly investigated in relation to treatment response in MP pneumonia, our study demonstrated consistently higher serum levels of IL-21, IL-22, and IL-31 in the good response group. Despite their limited predictive performance, as reflected by low AUC values, these findings suggest that they may contribute to the immunopathogenesis underlying differential clinical outcomes.

Prior reports have linked elevated IL-17A levels with refractory MP pneumonia.[21] In contrast, our findings demonstrate that three Th17-related cytokines, including IL-21, IL-22, and IL-31, were significantly and consistently elevated in children with favorable treatment responses. While IL-17A levels were not significantly different between groups, their higher mean concentrations in the good response group paralleled the pattern observed for the other Th17-associated cytokines. Taken together, these results strengthen the evidence that favorable clinical outcomes may be driven not by excessive IL-17A-mediated inflammation, but rather by a regulated Th17-related cytokine profile that supports effective pathogen clearance and epithelial repair in MP pneumonia.

This study has several limitations. First, the relatively small sample size in the poor response group may limited detection of subtle differences and reduce generalizability. Second, cytokine concentrations were measured at a single time point, which precluded assessment of temporal dynamics throughout the disease course. Third, cellular immune responses such as T-cell subsets and innate lymphoid cells were not analyzed, which could have provided additional mechanistic insights. Nonetheless, a key strength of this study is its integrative evaluation of clinical, radiologic, and immunologic parameters in a well-characterized pediatric cohort.

In conclusion, early indicators such as lobar consolidation, elevated LDH, and MP-specific IgM levels at admission may facilitate timely identification of children at risk for poor treatment response, thereby supporting individualized therapeutic decision-making in MP pneumonia. The consistent elevation of IL-21, IL-22, and IL-31 in the good response group further suggests that a regulated Th17-related cytokine profile contributes to favorable outcomes. Incorporating immune profiling with clinical assessment may improve prognostication in pediatric MP pneumonia. Future studies with larger cohorts and serial immune measurements are needed to validate these findings and clarify underlying mechanisms.

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