**Distribution and Expression of IL-17 and Related Cytokines in Children with *Mycoplasma pneumoniae* Pneumonia**

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**SUMMARY:** The pathogenesis of *Mycoplasma pneumoniae* pneumonia (MPP), specifically the local immune responses in the lungs, is poorly understood. In this study, flow cytometry was used to analyze IL-17 and related cytokines in plasma and bronchoalveolar lavage fluid (BALF) samples from 18 and 30 pediatric patients with general MPP (GMPP) and refractory MPP (RMPP), respectively. The levels of IL-1Ra, IL-6, IL-8, IL-17, and TNF-α were significantly elevated in the BALF of MPP children compared to the plasma \((P < 0.01)\). Although the plasma IL-6 levels in the children with RMPP were higher than those in the children with GMPP \((P < 0.05)\), the IL-17 levels showed the opposite trend \((P < 0.05)\). The children with RMPP had significantly higher BALF levels of IL-8, IL-17, and TNF-α than the children with GMPP \((P < 0.05)\), and the elevated levels of IL-17 correlated with the increased focal size of the lung lesions \((P < 0.05)\). The elevated levels of IL-17 and related cytokines in the BALF samples could indicate that the local inflammatory response should be distinguished from the systemic inflammatory response in children with MPP. Moreover, RMPP might involve an aggravated inflammatory progression at the site of infection. The levels of IL-17 might correlate with the extent and severity of the lung lesions in MPP.

**INTRODUCTION**

*Mycoplasma pneumoniae* causes respiratory tract infections in all age groups, accounting for up to 40% of the community-acquired respiratory tract infections in children older than 5 years of age (1). Although *M. pneumoniae* pneumonia (MPP) is usually a benign and self-limiting process, *M. pneumoniae* infections can develop into severe life-threatening diseases such as refractory *M. pneumoniae* pneumonia (RMPP), acute respiratory distress syndrome, necrotizing pneumonitis, and fulminant pneumonia (2–4).

Although the detailed pathogenic mechanisms of RMPP are unclear, macrolide-resistant *M. pneumoniae* infections and excessive immunological inflammation are the most commonly proposed mechanisms. Previous studies have demonstrated that an excessive immune response against pathogens, including the vigorous expression of cytokines and highly activated cell-mediated immune responses, may play an important role in RMPP (5,6). However, the details of the local immune mechanisms of MPP are not known. Therefore, this study examined the cytokine levels in plasma and bronchoalveolar lavage fluid (BALF) samples in children suffering from acute-stage MPP. In addition, we analyzed the levels of cytokines in relation to the disease severity, extent of lung lesions, and antibiotic (macrolides) use in the patients at the time of sample collection.

**MATERIALS AND METHODS**

**Participants:** Five hundred and eleven patients with MPP were admitted to Guangzhou Women and Children’s Medical Center between April 2017 and April 2018. Pneumonia was defined as the presence of fever, acute respiratory symptoms (cough, tachypnoea, and difficult breathing), or both, along with the presence of new infiltrate detected by chest radiography and/or consolidation. All patients were positive for *M. pneumoniae*-specific immunoglobulin M (IgM) antibodies in the serum and/or for *M. pneumoniae* DNA in throat swabs by polymerase chain reaction (PCR) at the time of admission. In addition, they were compatible with the indication of flexible bronchoscopy. RMPP patients were classified on the following 2 criteria: i) prolonged fever for 7 days or more or ii) increasing cough and infiltrates seen by chest radiography despite the administration of appropriate antibiotics (7). The exclusion criteria were the presence of severe concomitant diseases (chronic pulmonary disease, cardiovascular disease, neoplasia, kidney or liver disease, and immunodepression), mixed infections with other microorganisms, and the use of hormones in the course of disease treatment before sample collection. In this study, the diagnostics were performed and the specimens were processed within 48 h after admission. Further, the 2 groups of MPP patients received the same dosage of antimycoplasma therapy: azithromycin (10 mg/kg/day) administrated orally. Twenty healthy
children were used as the control group, and their plasma was collected. The parents/guardians of all the participating children signed informed consents. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Guangzhou Women and Children’s Medical Center, Guangzhou Medical University. Written informed consent was obtained from all participants’ guardians.

Flexible bronchoscopy: Flexible bronchoscopy was performed on the children with MPP who exhibited consolidation, as determined by high-resolution computed tomography (HRCT). All bronchoscopies were clinically indicated and were performed under moderate sedation and local anesthesia with a flexible bronchoscope. Typically, bronchoalveolar lavage (BAL) was performed in the most affected areas (identified radiologically and/or endoscopically) and using normal sterile saline previously warmed to body temperature (37°C). The BAL samples were collected by instilling 3 or 5 fractions of the same volume (5–10 ml) according to the weight of child (BAL volume per unit body weight: approximately 3–5 ml/kg). The recovery volume of the BALF was more than 40% and was considered acceptable.

Cytokine assays: The cytokine levels in the plasma and BALF were measured using the Bio-Plex Pro™ Human Cytokine Standard 27-Plex, Group I kit (BioRad, Hercules, CA, USA) with a magnetic bead-based multiplex immunoassay for Luminex (LX1000), according to the manufacturer’s instructions. For samples under the limit of detection, the lowest value of the standard for the cytokine was used for statistical analysis.

Statistics: Data are expressed as the median and range. The non-parametric Mann-Whitney U test was used to compare continuous variables between the 2 groups, and the Wilcoxon matched-pairs signed-rank test was used for comparisons between the plasma and BALF in paired samples. Categorical variables were assessed using the χ² test. For all analyses, 2-tailed P values were calculated. A P value of ≤ 0.05 was considered as statistically significant. All data were analyzed using Prism 7.0 (GraphPad Software).

RESULTS

Details of the MPP patients: Forty-eight patients were enrolled in this study (Fig. 1) and comprised of 24 boys and girls each, aged between 13 to 125 months. There were a further 18 children with general M. pneumoniae pneumonia (GMPP) and 30 children with RMPP. The main clinical characteristics of the patients are presented in Table 1. The fever durations in these 2 groups were significantly different (P < 0.05), whereas the cough durations were not. The patients with RMPP had significantly elevated levels of high-sensitivity
Distribution of Cytokines in MPP

Table 1. Baseline characteristics of the patients with MPP in this study

| Variable                        | Control (n = 20) | GMPP (n = 18) | RMPP (n = 30) | P value (GMPP vs RMPP) |
|---------------------------------|-----------------|---------------|---------------|------------------------|
| Demographic                     |                 |               |               |                        |
| Age (months), median(range)     | 48(15-112)      | 78(72-113)    | 60(12-125)    | 0.7835                 |
| Male gender, n (%)              | 9(45.0)         | 10(55.6)      | 14(46.7)      | 0.7800                 |
| Symptoms                        |                 |               |               |                        |
| Total days with fever (d), median(range) | 8.5(1-11) | 10(6-14) | 0.0397 |
| Total days with cough (d), median(range) | 15 (0-30) | 27(2-27) | 0.5746 |
| Laboratory findings             |                 |               |               |                        |
| WBC(×10^9/l), median(range)    | 10.5(5-13.7)    | 8.7(5.3-15.6) | 0.6667 |
| HsCRP(mg/l) (<5), median(range) | 2.1(0-20.88)   | 34.14(25.58-190.52) | 0.0014 |
| LDH(U/l) (159-322), median(range) | 263(248-307) | 372(290-464) | 0.0159 |
| Radiology                       |                 |               |               |                        |
| Consolidation, n (%)            | 18 (100.0)      | 30(100.0)     | 1.0000        |
| Hydrothorax, n (%)              | 0 (0)           | 13(43.3)      | 0.0011        |

1: p values are two-sided and were adjusted by the Bonferroni method for multiple comparisons testing.
2: Laboratory data were collected for patients with an acute exacerbation of MPP.
3: Judged by chest radiograph or CT scan in the whole course of the patients.

C-reactive protein (Hs-CRP) and lactate dehydrogenase than the GMPP patients (P < 0.05). Abnormal chest HRCT, especially pulmonary consolidation, was also observed in all patients. Some of the GMPP patients also showed small-range consolidation (Fig. 2A). However, most RMPP patients presented unequivocal focal or segmental consolidation with pleural effusion (P < 0.05) (Fig. 2B).

Cytokine data: The levels of 5 inflammatory proteins, interleukin-1 receptor antagonist (IL-1Ra), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-17 (IL-17), and tumor necrosis factor-α (TNF-α), were

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**Fig. 2.** Imaging features of GMPP and RMPP patients. (A) High-resolution CT scan of the chest on the day of admission revealing diffuse infiltration and few areas of consolidation in the right upper lobes in a 6-year-old child with GMPP; (B) High-resolution CT scan of the chest on the day of admission revealing areas of airspace consolidation and pleural effusion in the right lobes in a 5-year-old child with RMPP.
compared (Table 2) between the MPP patients and healthy volunteers. The cytokines in the plasma from the acute-phase MPP patients indicated that the levels of IL-6, IL-8, IL-17, and TNF-α were increased significantly compared to the healthy children ($P < 0.05$). The levels of all the 5 cytokines were significantly elevated in the BALF samples compared to the plasma in the acute phase of MPP ($P < 0.01$).

Comparing the expressed cytokines in the plasma and BALF from the same patient with MPP: The plasma and BALF specimens were collected from 30 patients with MPP and analyzed for interleukin levels patient-wise (Fig. 3). The levels of IL-1Ra, IL-6, IL-8, and IL-17 were increased significantly in the BALF compared with the plasma ($P < 0.05$), but there was no significant difference in the TNF-α levels between the BALF and plasma ($P = 0.31$).

Correlation between cytokine concentration, and disease severity, lung involvement and macrolide use in MPP patients: For the 48 patients in the study, the effects of various parameters on the acute phase of MPP were analyzed, including the degree of disease severity, involvement of more than 1 lobe in the consolidated areas in the lungs, and treatment with macrolide antibiotics before sample collection. These comparisons were applied separately to the plasma and BALF samples of the patients and the data were tabulated (Table 3). Analysis of plasma samples revealed that the patients with RMPP expressed significantly higher levels of IL-6 than the patients with GMPP ($P = 0.0265$), as opposed to the IL-17 levels that showed the opposite trend ($P = 0.0264$). In contrast, the levels of IL-8, IL-17, and TNF-α in the BALF samples from the RMPP patients were significantly higher than those in the BALF from the GMPP patients ($P < 0.05$). In addition, the IL-17 levels showed a significant correlation with the

| Cytokine | Health control ($n=20$) Median cytokine concentration (pg/ml)(range) in samples from | Patients with MPP $n=48$ | $P$ value$^1$ | $P$ value$^2$ |
|----------|--------------------------------------------------------------------------------|--------------------------|--------------|---------------|
| IL-1Ra   | 12.55(6.06-249.97)                                                             | 45.87(1.83-658.86)       | 3,022.170(606.99-10,024.58) | 0.9872        | < 0.0001      |
| IL-6     | 0.37(0.37-1.70)                                                                | 2.01(0.13-17.54)         | 11.655(2.55-79.19)       | < 0.0001      | 0.0004        |
| IL-8     | 2.33(1.31-4.35)                                                                | 3.06(1.58-9.01)          | 642.495(72.34-9631.02)   | 0.0138        | < 0.0001      |
| IL-17    | 0.24(0.20-0.27)                                                                | 0.68(0.52-12.43)         | 19.935(2.71-43.54)       | < 0.0001      | < 0.0001      |
| TNF-α    | 1.51(0.18-7.73)                                                                | 1.703(0.06-92.9)         | 22.615(0.06-1320.03)     | 0.0402        | 0.0006        |

$^1$: Comparison between the plasma from patients with MPP and that from health children.

$^2$: Comparison between the plasma and BALF from patients with MPP.

Fig. 3. Comparison of the cytokine levels in paired plasma and BALF samples. (A) IL-1Ra; (B) IL-6; (C) IL-8; (D) IL-17; and (E) TNF-α.
Distribution of Cytokines in MPP

Table 3. Relation of the cytokine concentrations of patients with MPP with different parameters

| Result | Cytokine concentration (pg/ml) (range) and P value in plasma | IL-1Ra | IL-6 | IL-8 | IL-17 | TNF-α |
|--------|-------------------------------------------------------------|--------|------|------|-------|-------|
| Severity Degree | | | | | | |
| GMPP (n = 18) | | 19.825 (1.83-90.92) | 1.53 (0.13-6.61) | 3.59 (1.58-7.38) | 0.68 (0.68-12.43) | 4.11 (0.06-81.98) |
| RMPP (n = 30) | | 135.15 (1.83-658.86) | 7.79 (0.13-17.54) | 2.32 (1.58-9.01) | 0.52 (0.52-0.68) | 30.91 (0.06-92.9) |
| P value | | 0.1687 | 0.0265 | 0.3408 | 0.0264 | 0.1152 |
| Lung lesion<sup>1)</sup> | | | | | | |
| < 1 lobe (n = 14) | | 23.335 (1.83-658.86) | 1.53 (0.13-17.54) | 2.82 (1.58-7.38) | 0.68 (0.52-12.43) | 12.5 (0.06-92.9) |
| ≥ 1 lobe (n = 34) | | 22.77 (1.83-160.27) | 2.66 (0.13-10.21) | 3.59 (1.58-9.01) | 0.68 (0.52-9.14) | 10.07 (0.06-81.98) |
| P value | | 0.6781 | 0.5438 | 0.9565 | 0.2290 | 0.8442 |
| Macrolides antibiotics<sup>2)</sup> | | | | | | |
| Yes (n = 28) | | 16.83 (1.83-160.27) | 2.01 (0.13-9.52) | 2.32 (1.58-7.38) | 0.52 (0.52-0.68) | 7.97 (0.06-42.8) |
| No (n = 20) | | 51.265 (1.83-658.86) | 5.86 (0.43-17.54) | 3.59 (2.32-9.01) | 0.68 (0.52-12.43) | 20.49 (0.06-92.9) |
| P value | | 0.6405 | 0.1592 | 0.1048 | 0.1033 | 0.1985 |

| Result | Cytokine concentration (pg/ml) (range) and P value in BALF | IL-1Ra | IL-6 | IL-8 | IL-17 | TNF-α |
|--------|-------------------------------------------------------------|--------|------|------|-------|-------|
| Severity Degree | | | | | | |
| GMPP (n = 14) | | 2,324.725 (606.99-7,279.91) | 10.76 (0.66-69.73) | 290.185 (38.42-865.9) | 6.68 (2.71-18.38) | 11.525 (0.06-24.74) |
| RMPP (n = 30) | | 4,473.295 (943.8-10,024.58) | 14.26 (2.55-79.19) | 868.395 (124.95-9,631.02) | 28.63 (3.45-43.54) | 42.885 (0.33-1,320.03) |
| P value | | 0.1475 | 0.3384 | 0.0096 | 0.0035 | 0.0076 |
| Lung lesion<sup>1)</sup> | | | | | | |
| < 1 lobe (n = 12) | | 3,362.145 (606.99-7,279.91) | 9.145 (2.92-22.5) | 752.25 (72.34-2,902.16) | 17.22 (2.71-34.44) | 18.34 (0.06-1,320.03) |
| ≥ 1 lobe (n = 32) | | 2,780.03 (943.9-10,024.58) | 15.26 (2.55-79.19) | 489.14 (38.42-9,631.02) | 22.05 (3.45-43.54) | 32.545 (0.06-262.62) |
| P value | | 0.7647 | 0.2752 | 0.5404 | 0.0441 | 0.5399 |
| Macrolides antibiotics<sup>2)</sup> | | | | | | |
| Yes (n = 25) | | 2,795.68 (606.99-10,024.58) | 7.71 (2.55-79.19) | 720.06 (72.34-9,631.02) | 21.49 (2.71-43.54) | 40.35 (0.06-1,320.03) |
| No (n = 19) | | 4,293.76 (943.8-7,279.91) | 14.88 (0.66-69.73) | 413.35 (38.42-3,861.72) | 17.53 (3.45-39.14) | 24.74 (0.06-262.62) |
| P value | | 0.4902 | 0.6828 | 0.6827 | 0.8244 | 0.5506 |

<sup>1)</sup> Judged by chest radiograph or CT scan before specimen collection.
<sup>2)</sup> Patients were given macrolide antibiotic therapy before specimen collection.

areas of consolidation in the patient lungs (P = 0.0441). However, macrolide use in the patients before sample collection did not affect cytokine levels in the different subgroups (P > 0.05).

DISCUSSION

Respiratory infections due to *M. pneumoniae* are common in many areas of the world, resulting in atypical pneumonia and other respiratory tract diseases. Although MPP is thought to be a self-limiting process, the immunological pathogenesis remains unclear. In an effort to elucidate the underlying mechanisms, this study analyzed the expression of IL-17 and the related cytokines (IL-1Ra, IL-6, IL-8, and TNF-α) in plasma and BALF samples from pediatric MPP patients. Further, studying the levels of these cytokines in relation to disease severity, lung imaging, and macrolide use, allowed for a preliminary exploration of the immune response involved in MPP.

IL-17 is a key proinflammatory cytokine that is quickly released by innate IL-17-producing cells or Th helper 17 (Th17) cells after pathogen exposure (8). The differentiation of Th17 cells and innate IL-17-producing...
cells requires the presence of IL-1β, IL-6, IL-23, TGF-β, and others (8,9). In addition, IL-17 has the ability to induce the expression of IL-1β, IL-6, IL-8, and TNF-α (10). Therefore, the concerted induction of IL-6, IL-1β, and TNF-α expression by IL-17 constitutes a positive feedback loop during pulmonary infection (11,12). In our studies, the plasma levels of IL-6, IL-8, IL-17, and TNF-α were significantly higher in the children with MPP than the healthy children, suggesting that these cytokines could promote efficient anti-mycoplasma immunity during the acute stages of *M. pneumoniae* infection.

Previously published data identified IL-17 as a central player in the immune response at the sites most exposed to microorganisms (12). Our data indicated that the levels of IL-17 and other related cytokines (IL-6, IL-8, and TNF-α) in the BALF from the children with MPP were significantly higher than those in the plasma from the same children. This observation clearly indicated that a local inflammatory response occurred in the lungs during the *M. pneumoniae* infection. In addition, the results also identified that the levels of IL-1Ra, a naturally occurring anti-inflammatory antagonist of the IL-1 family, in the BALF, was significantly higher than that in the plasma. Importantly, IL-1Ra effectively ameliorates the detrimental effects of the proinflammatory cytokines (13). We hypothesize that the increased IL-1Ra expression in the lungs is an important mechanism to protect against inflammation around the damaged area in the context of pulmonary *M. pneumoniae* infection. Interestingly, in our paired samples from MPP patients, the levels of IL-1Ra, IL-6, IL-8, and IL-17 were elevated in the BALF samples, in contrast to TNF-α levels. In lung epithelial cells, the expression of TNF-α reaches its peak just hours after *M. pneumoniae* infection and then starts declining at approximately 12 h post-infection (14). This possibly explains why an increase in TNF-α level was not obvious in the BALF samples in the acute stages of infection, warranting dynamic observations of the TNF-α levels.

Given that IL-17 can induce strong inflammatory responses, its signaling must be kept under tight control in order to avoid detrimental inflammation. Aberrant IL-17 signaling resulting in excessive inflammation can have damaging consequences such as massive neutrophil recruitment (15), causing tissue injury and exacerbation of the disease. In our study, IL-17 analysis of the BALF samples revealed that the levels in RMPP patients were significantly higher than that in the GMPP patients. However, the opposite trend was observed in the plasma samples in the 2 patient groups with very low levels. This suggested that the overexpression of IL-17 in the lungs is important for driving the pathogenesis of RMPP, but the detailed mechanism is still not clear. However, given the pathogenic role of IL-17 in RMPP, the development of IL-17-neutralizing therapy as a potential treatment of RMPP warrants further investigation.

The differentiation of Th17 cells requires IL-6 during the early activation phase. Some studies have demonstrated that IL-6 has a very important role in regulating the balance between Th17 cells and regulatory T cells (Tregs) (16). An imbalance in the circulating Th17 cells and Tregs is associated with pulmonary injury and deterioration in patients with *M. pneumoniae* infections (17). In the current study, the levels of plasma IL-6 from RMPP patients were higher than in the GMPP patients, indicating the association of IL-6 with the severity of MPP. The data also suggested the potential role of IL-6 in immunity disorders during the initial stages of *M. pneumoniae* infections. However, there was a trend towards a higher level of IL-6 in the BALF samples compared to the plasma in the RMPP patients, but no significant difference was observed in the plasma IL-6 levels between the RMPP and GMPP patients. These observations warrant further studies with higher patient enrollment in order to elucidate the role of IL-6.

TNF-α is a strong inducer of inflammatory mediators. Specifically, the synergistic interactions occur between IL-17 and TNF-α, where IL-17 augments the effect of TNF-α, in part, by enhancing the expression of the TNF receptor (18). IL-17 cooperates with TNF-α to either stabilize the chemokine gene messenger RNA (mRNA) expression or to amplify antimicrobial peptide production (19). In our study, the higher levels of TNF-α and IL-17 in the BALF from the RMPP patients, compared to the GMPP patients, demonstrated that TNF-α plays a role in enhancing the local lung inflammatory response to *M. pneumoniae* by cooperating with IL-17. Therefore, the combination of TNF inhibitors and IL-17 inhibitors could represent a new approach to control the interactions between these 2 cytokines in RMPP. However, there was no significant difference in the TNF-α levels in the plasma between the GMPP and RMPP patients. One possible explanation is that the interactions between IL-17 and TNF-α mainly occur only at the site of the lesion.

Previous studies demonstrated that *M. pneumoniae* attaches to the bronchial epithelial cells and induces IL-8 release, which in turn drives the recruitment and activation of neutrophils to effectively eliminate the pathogen (20). However, excessive neutrophil infiltration mediates microvascular damage and contributes to lung tissue damage (21). In our study, a higher level of IL-8 was detected in the BALF samples from the RMPP compared with the GMPP patients in contrast to the plasma IL-8 levels, which were similar. Moreover, recent research has determined that IL-17 synergistically stimulates TNF-α-induced IL-8 production in human airway epithelial cells (22). Considering the higher levels of IL-17 and TNF-α in the BALF samples from the RMPP patients, this phenomenon appears to play a potential role in amplifying airway inflammation in RMPP.

Outside of host defense at mucosal surfaces, IL-17 stimulates the epithelium to release chemokines that augment neutrophil recruitment in the lungs (23). In addition, excessive alveolar neutrophil infiltration correlates with both increased hypoxemia and increased lung permeability (24), and is a potential cause of pulmonary consolidation. This study also determined that the IL-17 levels in the BALF samples were correlated to the extent of lung consolidation in the MPP children, and that increased IL-17 expression in the BALF (airway) might participate in the immunological mechanism of consolidation by disrupting homeostatic processes in alveolar epithelial cells.
of macrolides during the acute stage of MPP had no significant effect on the levels of these cytokines in either the plasma or BALF. These observations could be due to sampling from the MPP patients at early stages after macrolide use. Understanding the effects of drugs on immunity necessitate dynamic monitoring of the levels of cytokines after macrolide use.

Some limitations of the current study need to be discussed. First, the levels of cytokines during the recovery period were not dynamically monitored in our patients. In addition, the study had a small sample size. Although all the patients had typical cases of MPP, the plan is to carry out studies with a larger sample size in the near future. Despite these limitations, this study not only identified the changes in the levels of IL-17 and related cytokines in both the plasma and BALF samples of MPP children, but also performed preliminarily investigations into the immunological pathogenesis of MPP.

In conclusions, The levels of IL-17 and the related cytokines, IL-1Ra, IL-6, IL-8, and TNF-α, increased significantly in the BALF during the acute stages of MPP. Moreover, the children with RMPP had higher BALF levels of IL-8, IL-17, and TNF-α compared to the children with GMPP. These results highlight the importance of further exploration into the interplay of IL-17 with other cytokines that orchestrate the immune response to M. pneumoniae infections.

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Conflict of interest None to declare.

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