BPR MCS | Bulletin of Pioneering Researches of Medical and Clinical Science

Bulletin of Pioneering Researches of Medical and Clinical Science

Available online: https://bprmcs.com
2023 | Volume 3 | Issue 1 | Page: 90-95

Treatment Outcomes of Early Corticosteroid Administration in Children with Macrolide-Resistant and Macrolide-Sensitive Mycoplasma pneumoniae Pneumonia

Da Yee Jeung[1*], Souvic Sarker[2], Il hyung Kim[3]

[1] Department of Pediatrics, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju 28644, Republic of Korea.
[2] Department of Pediatrics, CHA Bundang Medical Center, CHA University, Seongnam 13496, Republic of Korea.
[3] Department of Pediatrics, Samsung Medical Center, School of Medicine, Sungkyungwan University, Seoul 06351, Republic of Korea.

Abstract

Across five nationwide outbreaks in Korea, early use of corticosteroids was observed to markedly lessen disease severity. In this investigation, we examined clinical and laboratory outcomes in 56 pediatric patients who were given corticosteroids early for pneumonia caused by either macrolide-resistant (M. pneumoniae, MRMP) or macrolide-sensitive (M. pneumoniae, MSMP) strains between July 2019 and February 2020. Every patient tested positive on both PCR and serological assays and received corticosteroids within 24–36 hours after hospital admission. Mutations at nucleotides 2063, 2064, and 2067 within domain V of 23S rRNA were detected. The participants had an average age of 6.8 years, with a male-to-female ratio of 1.2:1 (31 males, 25 females). A majority (73%) were infected with MRMP strains, all showing the A2063G transition. When comparing MRMP and MSMP groups treated with early, dosage-adjusted corticosteroids, no major differences were found in clinical presentation or laboratory results. Nonetheless, children whose fever lasted beyond 48 hours or showed rising biomarkers such as elevated lactate dehydrogenase after standard steroid therapy might require increased corticosteroid dosage.

Keywords: Mycoplasma pneumoniae, Corticosteroid, Macrolide resistance, Pediatric pneumonia, Infection

Corresponding author: Da Yee Jeung
E-mail: Dr.daYeeJeung@yahoo.com

How to Cite This Article: Jeung DY, Sarker S, Kim I. Treatment Outcomes of Early Corticosteroid Administration in Children with Macrolide-Resistant and Macrolide-Sensitive Mycoplasma pneumoniae Pneumonia. Bull Pioneer Res Med Clin Sci. 2023;3(1):90-5. https://doi.org/10.51847/8CTZ72CXn6

Introduction

Mycoplasma pneumoniae (M. pneumoniae) is a leading cause of community-acquired pneumonia among children and adolescents [1]. In South Korea, epidemics tend to occur every three to four years, with the latest one reported in 2019 [2,3]. Although most infections are mild and resolve without complications, a proportion of cases develop into severe or treatment-resistant pneumonia, occasionally accompanied by extrapulmonary disorders such as encephalopathy, Stevens–Johnson syndrome, cutaneous vasculitis, myositis, and acute renal injury [4–6].

Since M. pneumoniae lacks a cell wall, it is intrinsically resistant to β-lactams, glycopeptides, and fosfomycin. However, it remains susceptible in vitro to macrolides, tetracyclines, and fluoroquinolones. Macrolides are

preferred in pediatric care due to their safety profile. Over the last decade, however, the frequency of macrolide-resistant M. pneumoniae (MRMP) has increased rapidly in East Asian regions such as Japan, China, and Korea [7–9]. In Korean isolates, resistance is predominantly associated with the A2063 mutation in the 23S rRNA domain V, and similar patterns are now emerging globally [9,10]. This rise has encouraged clinicians to seek new therapeutic options for managing MRMP infections both in Korea and abroad [11].

Some studies have shown that MRMP pneumonia tends to have a more severe course—with longer fever duration and hospitalization—compared to infections with macrolide-sensitive strains [7,10,12]. Others have reported minimal clinical differences, suggesting that resistance alone does not fully account for disease severity [13,14]. Consequently, adjunctive or alternative treatments are often considered for infections that do not respond to antibiotics. Despite ongoing debate about antibiotic efficacy in pediatric M. pneumoniae infection, physicians have increasingly turned to immune-modulating agents such as corticosteroids to manage persistent or resistant disease. Since the nationwide outbreak of 2003, our team has adopted corticosteroid therapy for serious M. pneumoniae pneumonia cases and documented reductions in disease burden during five successive epidemics [15–17]. The present study was therefore designed to assess both clinical and laboratory characteristics of children who received early corticosteroid intervention for pneumonia caused by macrolide-resistant or macrolide-sensitive M. pneumoniae.

Materials and Methods

Ethical approval

This investigation received clearance from the Institutional Review Board of Daejeon St. Mary's Hospital, Catholic University of Korea (approval code: DC20SASI0075).

Study population

The cohort comprised children previously in good health who were hospitalized with *Mycoplasma pneumoniae* pneumonia at Daejeon St. Mary's Hospital between July 2019 and February 2020. Inclusion required positive confirmation of *M. pneumoniae* by both polymerase chain reaction (PCR) and antibody testing. Individuals with negative PCR results or discordant findings (PCR positive but serology negative) were excluded from analysis.

Serologic evaluation used a commercial enzyme-linked immunosorbent assay (ELISA; Diesse Diagnostica, Senese, Italy). According to the manufacturer's interpretation chart, IgM values > 1.1 were defined as positive, < 0.9 as negative, and between 0.9–1.1 as indeterminate. Diagnosis was established when a child with radiographically verified pneumonia showed either an initial IgM > 1.1 or a conversion from non-reactive/equivocal to positive during admission.

Nasopharyngeal aspirates from all 56 participants were examined with a multiplex bacterial PCR kit including *M. pneumoniae* detection on a CFX96 Touch™ real-time system (Bio-Rad, Hercules, CA, USA). Remaining PCR products were preserved for subsequent sequencing work.

All participants began corticosteroid therapy within 24–36 hours after admission. Patients with less extensive parenchymal involvement received either oral prednisolone (1 mg/kg/day) or intravenous methylprednisolone (1–2 mg/kg/day). For cases showing severe segmental or lobar consolidation or clinical distress such as tachypnea or wheezing, higher doses (5–10 mg/kg/day) were administered. If after 48–72 hours fever or inflammatory activity persisted, the regimen was intensified (10–30 mg/kg/day) depending on laboratory indices and symptom burden.

Chest imaging was jointly interpreted by two physicians (E.-A. Y. and H. Y. H.) and categorized as either bronchopneumonia or segmental/lobar pneumonia. Demographic data, laboratory outcomes, and radiographic details were retrieved from hospital charts.

DNA preparation and mutation detection

All DNA-positive materials were kept frozen at –70 °C until tested. Nucleic acids were extracted using the Ribospin™ vRD Plus Kit (GeneAll Biotechnology, Seoul, Korea) following the supplied protocol. Amplification was carried out with Pfu Plus 5× Master Mix (Elpis Biotech, Daejeon, Korea). Primer pairs designed for domain V of 23S rRNA targeted bases 1998–2018 (forward, 5′-TCTCGGCTATAGACTCGGTGA-3′) and 2673–2692 (reverse, 5′-TAAGAGGTGTCCTCGCTTCG-3′).

PCR amplicons were resolved by 1% agarose gel electrophoresis using a Mupid-exU unit (Takara Bio Inc., Shiga, Japan). Bands of roughly 700 bp were visualized under UV illumination, captured with a Geldoc XR system (Bio-Rad, CA, USA), excised, and purified using the MGmed SV Gel Extraction Kit (Seoul, Korea).

Sequencing employed the BigDye® Terminator v3.1 Cycle Sequencing Kit on an ABI PRISM 3730XL Analyzer (Applied Biosystems, Thermo Fisher Scientific, Foster City, CA, USA). Nucleotide changes at positions 2063, 2064, and 2067 in domain V of 23S rRNA were identified by comparison with the GenBank reference sequence X68422.

Statistical procedures

All statistical computations were completed using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA). Continuous parameters were expressed as medians (interquartile range), and categorical variables as counts (percentages).

The Mann–Whitney U test compared continuous outcomes, while categorical distributions were assessed with either the chi-square or Fisher's exact test. Linear relationships between two quantitative variables were measured via Pearson's correlation. Two-tailed *p*-values < 0.05 were interpreted as statistically significant.

Results

Fifty-six children tested positive for *M. pneumoniae* by both PCR and serology. Their mean age was 6.8 years (range 1–15), and the male-to-female ratio was 1.2 : 1 (31 boys, 25 girls). Among them, 41 (73.2%) carried the A2063G substitution linked to macrolide resistance, while 15 showed no mutations at sites 2063, 2064, or 2067 and were classified as macrolide-sensitive.

No meaningful variations between resistant and sensitive groups were found with respect to age, sex, fever duration before or after hospitalization, total fever length, hospital stay, or chest-film pattern **(Table 1)**. Serological evaluation revealed that 36 children were IgM-positive on admission, whereas 20 converted from negative to positive upon follow-up, without significant intergroup differences **(Table 1)**.

Table 1. Comparison of clinical characteristics between macrolide-resistant and macrolide-sensitive *Mycoplasma pneumoniae* cases

Parameter	Total (n = 56)	MRMP (n = 41)	MSMP (n = 15)	p-value
Age, years (median, IQR)	6.8 (5.0 – 9.1)	6.3 (4.7 – 8.8)	7.0 (5.8 – 10.3)	0.264
Sex ratio (M : F)	31 : 25	25 : 16	6 : 9	0.162
Hospital stay, days (median, IQR)	5 (4 – 6)	5 (4 – 6)	5 (5 – 6)	0.774
Fever duration, days (median, IQR)				
Prior to admission	5.0 (3.3 – 7.0)	5.0 (3.5 – 7.0)	5.0 (2.0 – 7.0)	0.519
Overall course	5.0 (3.3 – 7.0)	6.0 (3.5 – 7.5)	5.0 (3.0 – 7.0)	0.864
Type of pulmonary infiltration, n (%)				
Bronchopneumonia	16 (28.6)	12 (29.3)	4 (26.7)	0.849
Segmental/lobar pneumonia	40 (71.4)	29 (70.7)	11 (73.3)	—
Serological findings, n (%)				
Initial IgM-positive by ELISA	36 (64)	27 (66)	9 (60)	0.686
IgM seroconversion during admission	20 (36)	14 (34)	6 (40)	—
Antibiotic treatment, n (%)				
Macrolide administered	51 (91)	38 (93)	13 (87)	0.484
Levofloxacin used	2 (4)	2 (5)	0 (0)	—
Corticosteroid regimen, n (%)				
Low dose (1–2 mg/kg/day)	46 (82)	34 (83)	12 (80)	1.000
High dose (5–10 mg/kg/day)	10 (18)	7 (17)	3 (20)	—
Escalated high dose (10–30 mg/kg/day)	2 (3.6)	2 (5)	0 (0)	—

MRMP = macrolide-resistant *M. pneumoniae*; MSMP = macrolide-sensitive *M. pneumoniae*. Continuous variables are shown as median (IQR); categorical data as count (percentage).

Corticosteroid therapy was administered to every patient within 24 to 36 hours following admission. Low-dose treatment was given to most patients (46 out of 56, 82%), either as oral prednisolone at 1 mg per kg per day or intravenous methylprednisolone at 1–2 mg per kg per day. Meanwhile, 10 patients exhibiting more severe symptoms received higher-dose corticosteroids ranging from 5 to 10 mg per kg per day. After starting treatment, fever subsided in 42 patients (75%) within the first 24 hours, in 53 patients (94.6%) by 48 hours, and in 54 patients (96.4%) within 72 hours. No meaningful difference in fever resolution was observed between low- and high-dose groups.

Two patients infected with macrolide-resistant *M. pneumoniae* continued to have high fevers and rapid worsening of their condition. Radiographic imaging revealed increased pleural effusion and progressive lung changes 48 hours after the initial therapy. These patients were treated with levofloxacin alongside escalated corticosteroid doses (20 and 30 mg per kg per day, respectively) and ultimately recovered completely without long-term complications. Apart from these two cases, no other patients received alternative antibiotics. Corticosteroid administration patterns were comparable between the resistant and sensitive groups **(Table 1)**.

Laboratory evaluation was performed for all patients at the time of admission. No significant differences were found between macrolide-resistant and macrolide-sensitive groups in any baseline laboratory measures. Follow-up testing was conducted for 33 patients on the third or fourth day of hospitalization. Both initial and follow-up results demonstrated statistically significant changes in markers including white blood cell counts and differentials (WBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) **(Table 2)**.

Table 2. Laboratory findings recorded at admission

Parameter	At Presentation			All Patients		
	MRMP (n = 41)	MSMP (n = 15)	p*	Initial (n = 56)	Follow-Up (n = 33)	p†
Hemoglobin (Hb)	12.3 (11.5–12.9)	12.4 (11.8–13.3)	0.774	12.4 (11.7–13.0)	12.5 (12.0–13.2)	0.068
White Blood Cell Count (WBC)	7.3 (5.7–8.8)	7.6 (6.1–8.7)	0.76	7.5 (5.7–8.7)	9.8 (7.9–14.1)	<0.001
Neutrophils (%)	65.9 (53.4–70.3)	62.0 (48.0–67.8)	0.379	64.8 (52.6–70.2)	74.6 (58.5–79.3)	0.026
Lymphocytes (%)	24.0 (19.1–37.0)	25.2 (20.5–38.3)	0.494	24.8 (20.0–37.3)	18.2 (11.3–30.3)	0.033
Monocytes (%)	8.1 (6.4–9.1)	8.4 (6.9–9.2)	0.465	8.1 (6.8–9.1)	7.7 (5.0–10.9)	0.823
Aspartate Aminotransferase (AST)	27 (23–33)	26 (21–30)	0.262	27 (23–32)	24 (20–29)	<0.001
Alanine Aminotransferase (ALT)	12 (10–16)	12 (8–14)	0.546	12 (10–15)	19 (13–26)	<0.001
Alkaline Phosphatase (ALP)	169 (153–207)	167 (141–180)	0.259	168 (150–202)	163 (126–186)	0.022
Lactate Dehydrogenase (LDH)	271 (247–330)	250 (220–273)	0.085	269 (243–317)	270 (231–308)	0.007
Erythrocyte Sedimentation Rate (ESR)	14 (8–24)	17 (9–29)	0.691	14 (9–24)	11 (4–17)	0.004
C-Reactive Protein (CRP)	1.7 (1.0–2.6)	2.2 (0.8–3.8)	0.505	1.8 (0.9–2.8)	0.4 (0.1–0.9)	<0.001

Reported values represent the median along with the interquartile range (IQR). The following abbreviations are used: Hb indicates hemoglobin concentration (g/dL); WBC refers to the white blood cell count ($\times 10^3/mm^3$); N stands for neutrophil proportion; L indicates lymphocyte proportion; M denotes monocyte proportion; AST and ALT are measured in U/L for aspartate and alanine aminotransferase, respectively; ALP represents alkaline phosphatase (U/L); LDH is lactate dehydrogenase (U/L); ESR corresponds to erythrocyte sedimentation rate (mm/h); CRP indicates C-reactive protein (mg/dL); MRMP signifies macrolide-resistant Mycoplasma pneumoniae; MSMP represents macrolide-sensitive Mycoplasma pneumoniae; p denotes the probability value for statistical testing.

Differences between MRMP and MSMP groups for continuous variables were examined using the Mann–Whitney U test, which is a nonparametric approach suitable for non-normally distributed data.

† For evaluating the laboratory values from admission to follow-up, paired comparisons were conducted using the Wilcoxon signed-rank test, which is a nonparametric test for matched data.

Discussion

During the 2019 *M. pneumoniae* outbreak in Korea, the A2063G mutation in domain V of 23S rRNA was detected in 73% of patients. Macrolides, including erythromycin, inhibit bacterial protein synthesis by binding to the peptidyl transferase loop of 23S rRNA. Resistance is associated with mutations at positions 2063, 2064, 2067, and 2617 [18]; nevertheless, A2063G appears to be the most frequent mutation, while changes at 2067 and 2617 are uncommon [19]. In Korean pediatric populations, this variant has been reported in 60–87% of children [10,13,20]. Japanese studies recorded an 87% prevalence in 2011 [21], although some more recent reports suggest a decline [22]. In contrast, Korea and China continue to report high rates of macrolide resistance [12, 23], while the United States (mean: 7.5%, range: 1.9–21.7%) [14] and several European nations [24, 25] show much lower frequencies. This suggests that resistance rates are influenced by geographical, temporal, and epidemiological factors.

Macrolide-resistant *M. pneumoniae* has been linked to prolonged fever, extended hospitalization, and increased use of alternative antibiotics in several reports [7,8,12,19,26]. However, other studies did not find notable differences in clinical presentation, imaging findings, or length of stay [13,14,20]. In our cohort, no significant distinctions were observed between macrolide-resistant and sensitive groups regarding clinical features or laboratory results at admission, including IgM status and corticosteroid response. The rapid resolution of fever within three days in both groups may reflect the early initiation of corticosteroid therapy.

The mechanisms underlying lung injury from *M. pneumoniae* and other infections such as COVID-19 are not fully understood. Exaggerated immune responses may contribute to tissue damage [1,27]. The immune system can react not only to microbial products, such as toxins or pathogen-associated molecular patterns, but also to host-derived molecules like pathogenic proteins and damage-associated molecular patterns. Substances released from injured lung cells can amplify inflammation locally and systemically. Controlling this early hyperinflammatory response is therefore critical to prevent severe complications. Corticosteroids have dose-dependent effects, and higher doses may be needed in patients with more severe pneumonia to mitigate the impact of pathogenic and immunological factors during the acute phase [28, 29]. Antibiotics alone may have limited efficacy against *M. pneumoniae* [17], supporting the rationale for corticosteroid therapy, although the timing and optimal dose remain debated [16,17,19].

There is no standardized definition of severe or refractory *M. pneumoniae* pneumonia. Some studies classify it as persistent fever and progressive pulmonary lesions despite at least seven days of adequate antibiotics. In both the 2015–2016 epidemic and the current study, a few patients did not respond to initial corticosteroids and required additional high-dose therapy [11,17]. Biomarkers such as AST, ALT, LDH, CRP, ferritin, and cytokines (IL-18, IL-6, TNF-α) have been investigated as predictors of refractory disease [4, 30–32]. Initial inflammatory insults can amplify tissue injury or predispose to secondary bacterial infections, suggesting that elevated LDH, CRP, and other markers reflect lung damage and risk of multi-organ involvement. Monitoring these biomarkers over time may assist in assessing disease progression. In this study, the two patients who required increased corticosteroid dosing initially had the highest LDH values, which further rose three days after starting standard therapy. They received 20 and 30 mg/kg/day corticosteroids, respectively. By contrast, most patients showed decreased LDH levels at follow-up. These findings support a strategy of adjusting corticosteroid therapy based on both laboratory trends and clinical severity, such as persistent fever beyond 48 hours.

This study has several limitations. First, the sample size was relatively small, and selection bias cannot be excluded. Nevertheless, all included patients had dual confirmation of *M. pneumoniae* infection by PCR and serology. Second, compared with previous studies at tertiary centers, our cohort included more patients with milder disease and earlier presentation. Third, the absence of a control group precluded direct evaluation of corticosteroid efficacy.

Conclusions

In the 2019 Korean epidemic, 73% of patients with *M. pneumoniae* pneumonia harbored the A2063G mutation in domain V of 23S rRNA. Early administration of appropriately dosed corticosteroids resulted in similar clinical and laboratory outcomes between macrolide-resistant and macrolide-sensitive infections. In the context of rising macrolide resistance, individualized treatment strategies may be necessary for patients with severe pneumonia who fail to respond to antibiotics.

Acknowledgments: None.

Conflict of interest: None.

Financial support: None.

Ethics statement: None.

References

1. Lee KY. Pediatric respiratory infections by Mycoplasma pneumoniae. Expert Rev Anti Infect Ther. 2008;6(4):509–21.
2. Korea Disease Control and Prevention Agency (KDCA). Infectious Disease Portal. Available from: http://www.kdca.go.kr/npt/biz/npp/iss/ariStatisticsMain.do. Accessed 28 Nov 2020.
3. Kim EK, Youn YS, Rhim JW, Shin MS, Kang JH, Lee KY. Epidemiological comparison of three Mycoplasma pneumoniae pneumonia epidemics in a single hospital over 10 years. Korean J Pediatr. 2015;58(5):172–7.
4. Zhang Y, Zhou Y, Li S, Yang D, Wu X, Chen Z. Clinical characteristics and predictors of refractory Mycoplasma pneumoniae pneumonia in children. PLoS ONE. 2016;11(6):e0156465.
5. Betti C, Camozzi P, Gennaro V, Bianchetti MG, Scoglio M, Simonetti GD, Milani GP, Lava SA, Ferrarini A. Atypical bacterial pathogens and small-vessel leukocytoclastic vasculitis of the skin in children: systematic literature review. Pathogens. 2021;10(1):31.
6. Simoni C, Camozzi P, Faré PB, Bianchetti MG, Kottanattu L, Lava SA, et al. Myositis and acute kidney injury in bacterial atypical pneumonia: systematic literature review. J Infect Public Health. 2020;13(12):2020–4.
7. Morozumi M, Takahashi T, Ubukata K. Macrolide-resistant Mycoplasma pneumoniae: characteristics of isolates and clinical aspects of community-acquired pneumonia. J Infect Chemother. 2010;16(2):78–86.
8. Cao B, Zhao CJ, Yin YD, Zhao F, Song SF, Bai L, et al. High prevalence of macrolide resistance in Mycoplasma pneumoniae isolates from adult and adolescent patients with respiratory tract infection in China. Clin Infect Dis. 2010;51(2):189–94.
9. Hong KB, Choi EH, Lee HJ, Lee SY, Cho EY, Choi JH, Kang HM, Lee J, Ahn YM, Kang YH, et al. Macrolide resistance of Mycoplasma pneumoniae, South Korea, 2000–2011. Emerg Infect Dis. 2013;19(8):1281–4.
10. Lee E, Cho HJ, Hong SJ, Lee J, Sung H, Yu JH. Prevalence and clinical manifestations of macrolide resistant Mycoplasma pneumoniae pneumonia in Korean children. Korean J Pediatr. 2017;60(5):151–7.
11. Yang EA, Lee KY. Additional corticosteroids or alternative antibiotics for the treatment of macrolide-resistant Mycoplasma pneumoniae pneumonia. Korean J Pediatr. 2017;60(6):245–7.
12. Lee H, Choi YY, Sohn YJ, Kim YK, Han MS, Yun KW, Kim K, Park JY, Choi JH, Cho EY. Clinical efficacy of doxycycline for treatment of macrolide-

resistant Mycoplasma pneumoniae pneumonia in children. Antibiotics. 2021;10(2):192.
13. Lee H, Yun KW, Lee HJ, Choi EH. Antimicrobial therapy of macrolide-resistant Mycoplasma pneumoniae pneumonia in children. Expert Rev Anti Infect Ther. 2018;16(1):23–34.
14. Waites KB, Ratliff A, Crabb D, Xiao L, Qin X, Selvarangan R, et al. Macrolide resistant Mycoplasma pneumoniae in the United States as determined from a national surveillance program. J Clin Microbiol. 2019;57(6):e00968-19.
15. Lee KY, Lee HS, Hong JH, Lee MH, Lee JS, Burgner D, et al. Role of prednisolone treatment in severe Mycoplasma pneumoniae pneumonia in children. Pediatr Pulmonol. 2006;41(3):263–8.
16. Youn YS, Lee SC, Rhim JW, Shin MS, Kang JH, Lee KY. Early additional immune-modulators for Mycoplasma pneumoniae pneumonia in children: an observation study. Infect Chemother. 2014;46(4):239–47.
17. Yang EA, Kang HM, Rhim JW, Kang JH, Lee KY. Early corticosteroid therapy for Mycoplasma pneumoniae pneumonia irrespective of used antibiotics in children. J Clin Med. 2019;8(5):726.
18. Bébéar C, Pereyre S, Peuchant O. Mycoplasma pneumoniae: susceptibility and resistance to antibiotics. Future Microbiol. 2011;6(4):423–31.
19. Chen YC, Hsu WY, Chang TH. Macrolide-resistant Mycoplasma pneumoniae infections in pediatric community-acquired pneumonia. Emerg Infect Dis. 2020;26(6):1382–91.
20. Yoon IA, Hong KB, Lee HJ, Yun KW, Park JY, Choi YH, et al. Radiologic findings as a determinant and no effect of macrolide resistance on clinical course of Mycoplasma pneumoniae pneumonia. BMC Infect Dis. 2017;17(1):402.
21. Okada T, Morozumi M, Tajima T, Hasegawa M, Sakata H, Ohnari S, et al. Rapid effectiveness of minocycline or doxycycline against macrolide-resistant Mycoplasma pneumoniae infection in a 2011 outbreak among Japanese children. Clin Infect Dis. 2012;55(11):1642–9.
22. Nakamura Y, Oishi T, Kaneko K, Kenri T, Tanaka T, Wakabayashi S, et al. Kondo E. Recent acute reduction in macrolide-resistant Mycoplasma pneumoniae infections among Japanese children. J Infect Chemother. 2021;27(2):271–6.
23. Zhao F, Li J, Liu J, Guan X, Gong J, Liu L, He L, Meng F, Zhang J. Antimicrobial susceptibility and molecular characteristics of Mycoplasma pneumoniae isolates across different regions of China. Antimicrob Resist Infect Control. 2019;8:143.
24. Dumke R, Ziegler T. Long-term low rate of macrolide resistant Mycoplasma pneumoniae strains in Germany. Antimicrob Agents Chemother. 2019;63(3):e00455-19.
25. Gullsby K, Olsen B, Bondeson KJ. Molecular typing of Mycoplasma pneumoniae strains in Sweden from 1996 to 2017 and the emergence of a new P1 cytadhesin gene, variant 2e. J Clin Microbiol. 2019;57(3):e00049-19.
26. Suzuki S, Yamazaki T, Narita M, Okazaki N, Suzuki I, Andoh T, Matsuoka M, Kenri T, Arakawa Y, Sasaki T. Clinical evaluation of macrolide-resistant Mycoplasma pneumoniae. Antimicrob Agents Chemother. 2006;50(2):709–12.
27. Youn YS, Lee KY. Mycoplasma pneumoniae pneumonia in children. Korean J Pediatr. 2012;55(2):42–7.
28. Lee KY. Pneumonia, acute respiratory distress syndrome, and early immune-modulator therapy. Int J Mol Sci. 2017;18(2):388.
29. Lee KY, Rhim JW, Kang JH. Immunopathogenesis of COVID-19 and early immunomodulators. Clin Exp Pediatr. 2020;63(6):239–50.
30. Oishi T, Uchiyama M, Matsui K, Shirai T, Matsuo M, Negishi J, Kaneko T, Tsukano S, Taguchi T, Narita M. Clinical implications of interleukin-18 levels in pediatric patients with Mycoplasma pneumoniae pneumonia. J Infect Chemother. 2011;17(6):803–6.
31. Miyashita N, Kawai Y, Inamura N, Tanaka T, Akaike H, Teranishi H, Wakabayashi T, Nakano T, Ouchi K, Okimoto N. Setting a standard for the initiation of steroid therapy in refractory or severe Mycoplasma pneumoniae pneumonia in adolescents and adults. J Infect Chemother. 2015;21(3):153–60.
32. Lu A, Wang C, Zhang X, Wang L, Qian L. Lactate dehydrogenase as a biomarker for prediction of refractory Mycoplasma pneumoniae pneumonia in children. Respir Care. 2015;60(10):1469–75.