MACROLIDE VERSUS NON-MACROLIDE IN COMBINATION WITH STEROIDS FOR THE TREATMENT OF LOBAR OR SEGMENTAL *MYCOPLASMA PNEUMONIAE* PNEUMONIA UNRESPONSIVE TO INITIAL MACROLIDE MONOTHERAPY

Eunha Bae, Ye Ji Kim, Hyun Mi Kang*, Dae Chul Jeong, Jin Han Kang
Department of Pediatrics, College of Medicine, The Catholic University of Korea, Seoul, Korea

BACKGROUD

- *Mycoplasma pneumoniae* (MP) is one of the most common causes of bacterial pneumonia in children. In the recent decade, macrolide-resistant MP (MRMP) has been increasing in proportion, leading to children unresponsive to initial macrolide therapy. In patients that are unresponsive to initial macrolide therapy, for children that have severe pneumonia, the 2019 guideline from the Korean Society of Pediatric Infectious Disease (KSPID) and Korean Academy of Pediatric Allergy and Respiratory Disease (KAPARD) recommends one of the following: 1) a switch to non-macrolides such as quinolones or tetracylines; 2) addition of steroids in combination with a macrolide; or 3) addition of steroids in combination with a non-macrolide.
- The purpose of this study was to evaluated the outcomes of children with lobar or segmental MP pneumonia unresponsive to initial macrolide therapy, who received non-macrolide (NM), macrolide plus steroids (M+S), and non-macrolide plus steroids (NM+S) according to the 2019 guideline during the 2019-2020 Mycoplasma epidemic in South Korea.

METHODS

- This was a retrospective cohort study of children below 18 years old, admitted during the 2019-2020 MP outbreak for lobar or segmental MP pneumonia at a tertiary referral university hospital located in Seoul, Korea.
- The inclusion criteria were as follows : 1) diagnosed with lobar or segmental *Mycoplasma pneumoniae* pneumonia, 2) initially treated with macrolide monotherapy, and 3) unresponsive to macrolide after ≥ 72 hours of administration. These patients were considered 'macrolide-refractory severe mycoplasma pneumonia' and were included in the study for further analyses.
- The exclusion criteria were as follows : 1) underlying immunocompromising disease, 2) administration of immunosuppressing agents, 3) initial use of steroids, tetracyclines, or quinolones, 4) co-infection with another virus or bacteria, 5) history of pneumonia within one month, and 6) other cause of pneumonia other than *Mycoplasma pneumoniae*.
- Children that were unresponsive to the initial 3-5 day macrolide treatment were divided into three groups depending on the next step treatment : Non-macrolide group (NM), macrolide plus steroid group (M+S), and non-macrolide plus steroid (NM+S) group. Their outcomes were assessed.

RESULTS

Table 1. Demographic data according to treatment groups in patients refractory to initial macrolide monotherapy

	Total N = 158	Non-Macrolide *n* = 13	Macrolide + Steroid *n* = 120	Non-Macrolide + Steroid *n* = 25	*p*
Age, years, median (IQR)	7 (5–9)	7 (6–11)	7 (5–9)	6 (4–9)	*0.610*
Male, no. (%)	73 (46.2)	3 (23.1)	58 (48.3)	12 (48.0)	*0.218*
Fever duration before admission, days, median (IQR)	5 (4–6)	5 (5–6)	5 (3–6)	5 (4–7)	*0.374*
Fever duration after regimen change, days, median (IQR)	2 (1–3)	2 (1–4)	2 (1–3.3)	1 (0–3)	*0.004*
Admission duration, days, median (IQR)	5 (4–6)	4 (3–5.5)	5 (4–6)	5 (3–5.5)	*0.010*
Bilateral lung involvement, no. (%)	29 (18.4)	3 (23.1)	20 (16.7)	6 (24.0)	*0.621*
Lobar pneumonia, no. (%)	62 (39.2)	6 (46.1)	47 (39.2)	9 (36.0)	*0.831*
Pleural effusion, no. (%)	15 (9.5)	0	15 (12.5)	0	–
Atelectasis, no. (%)	1 (0.6)	0	1 (0.8)	0	–

IQR, interquartile range. Macrolide—roxithromycin or clarithromycin; non-macrolide—doxycycline or levofloxacin.

- During the May 2019 to March 2020 MP epidemic, a total 190 patients were admitted for *Mycoplasma pneumoniae* lobar or segmental pneumonia and were initiated with macrolide therapy. Of these, 158 patients were considered refractory to initial macrolide monotherapy, and were therefore included as study participants.
- The median age of the patients was 7 (Interquartile range [IQR], 5-9) years old and 46.2% (n=73/158) were male. The median fever duration prior to admission was 5 (IQR, 4-6) days, and the median duration of admission was 5 (IQR, 4-6) days.
- A total of 18.4% (n=29/158) of the study participants had bilateral lung involvement in the chest x-rays. Lobar involvement was observed in 39.2% (n=62/158) while 60.8% (n=96/158) had segmental pneumonia, and pleural effusion was observed in 12.5% (n=15/158) of the patient's chest x-ray.

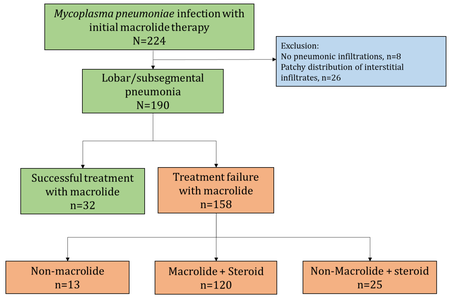

Figure 1. Flow chart of patients included as study participants

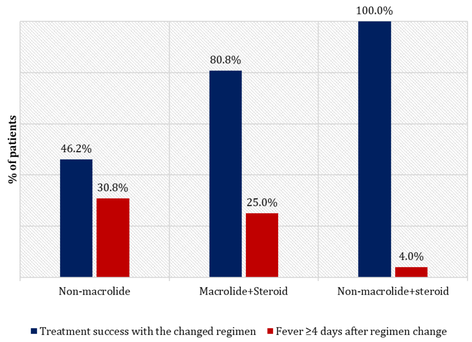

Figure 2. Comparison of the percentage of patients with treatment success versus fever duration of 4 days or more after regimen change. The treatment success rates of the regimens were as follows: non-macrolide, 46.2%; macrolide + steroid, 80.8%; non-macrolide + steroid, 100.0%. The percentage of patients with a fever duration of ≥ 4 days was highest in the non-macrolide group (30.8%) and lowest in the non-macrolide + steroid group (4.0%).

Table 2. Changes in laboratory parameters according to treatment groups in patients refractory to initial macrolide monotherapy

	Non-Macrolide *n* = 13		*p*	Macrolide + Steroid *n* = 120		*p*	Non-Macrolide + Steroid *n* = 25		*p*
	Initial	Follow Up		Initial	Follow Up		Initial	Follow Up	
WBC, 10^3/uL	7120 (5960–8350)	8455 (5493–9850)	*0.580*	6730 (5745–9118)	7685 (5745–9640)	*0.281*	6720 (5960–10,050)	7515 (6360–8335)	*0.420*
ESR, mm/h	21.0 (17.0–26.0)	18.0 (14.0–24.0)	*0.263*	23.0 (17.0–31.0)	28.0 (18.5–33.5)	*0.581*	25.0 (18.8–31.0)	18.0 (11.0–22.0)	*0.128*
CRP, mg/dL	2.0 (1.6–5.2)	1.6 (1.2–2.9)	*0.015*	3.2 (1.3–4.8)	1.9 (0.7–3.8)	*<0.001*	2.5 (1.8–6.4)	1.5 (1.1–2.7)	*0.023*
LDH, mg/dL	590.0 (535.0–663.5)	781 (591.0–819.0)	*0.073*	658.5 (550.0–810.0)	714.0 (599.0–844.0)	*0.130*	649.0 (559.0–1031.5)	626.5 (610.5–862.3)	*0.238*
AST, mg/dL	35.0 (27.0–39.0)	33.0 (33.0–42.0)	*0.742*	34.0 (28.0–42.0)	33.0 (27.3–39.8)	*0.401*	29.0 (27.0–44.0)	35.5 (23.8–44.0)	*0.414*
ALT, mg/dL	15.0 (13.0–28.0)	28.5 (15.3–41.8)	*0.591*	15.0 (13.0–20.3)	19.0 (15.0–29.8)	*0.012*	16.0 (11.0–23.0)	45.5 (17.5–50.5)	*0.357*

Values are median (interquartile range). Abbreviations: ALT—alanine transaminase; AST—aspartate aminotransferase; CRP—C-reactive protein; LDH—lactate dehydrogenase. Macrolide—roxithromycin or clarithromycin; non-macrolide—doxycycline or levofloxacin.

Table 3. Factors associated with fever duration after admission

	Univariable					Multivariable				
	ß	HR (95% CI) Lower	HR (95% CI) *Upper*	*SE*	*p*	ß	HR (95% CI) Lower	HR (95% CI) *Upper*	*SE*	*p*
Age	−0.080	−0.171	0.010	0.046	*0.080*					
Chest X-ray image findings										
Bilateral lung involvement	0.059	−0.66	0.778	0.364	*0.871*					
Lobar pneumonia	−0.389	−0.955	0.178	0.287	*0.177*					
Pleural effusion	0.647	−0.223	1.517	0.440	*0.144*					
Atelectasis	2.478	−1.010	5.965	1.765	*0.162*					
Initial laboratory findings										
CRP	0.059	−0.018	0.137	0.039	*0.134*					
AST	0.018	0	0.036	0.009	*0.053*					
ALT	0.006	−0.008	0.020	0.007	*0.398*					
Ferritin	0.001	−0.008	0.01	0.003	*0.805*					
Follow-up laboratory findings										
CRP	0.246	0.110	0.382	0.068	*0.001*	0.169	0.050	0.287	0.060	*0.006*
AST	0.014	0.006	0.021	0.004	*<0.001*	0.008	−0.003	0.018	0.005	*0.151*
ALT	0.007	0	0.014	0.003	*0.037*	0.002	−0.009	0.012	0.005	*0.741*
Treatment regimen										
Non-macrolide			R							
Macrolide + steroid	−1.704	−2.310	−1.099	0.306	*<0.001*	−1.694	−2.463	−0.925	0.386	*<0.001*
Non-macrolide + steroid	−2.452	−3.260	−1.645	0.409	*<0.001*	−2.224	−3.321	−1.127	0.551	*<0.001*

Abbreviations: ALT—alanine transaminase; AST—aspartate aminotransferase; CI—confidence interval; CRP—C-reactive protein; HR—hazard ratio; linear regression model, dependent variable: duration of fever after admission. Macrolide—roxithromycin or clarithromycin; mon-macrolide—doxycycline or levofloxacin.

- Of the 190 patients with lobar or segmental pneumonia, only 16.8% (n=32/190) were responsive to initial macrolide monotherapy. Of the 83.2% (n=158/190) patients refractory to initial macrolide therapy, 8.2% (n=13/158) were switched to a non-macrolide (doxycycline, n=13), 75.9% (n=120/158) were maintained on the macrolide and added steroids, and 15.8% (n=25/158) were switched to a non-macrolide (doxycycline, n=21; levofloxacin, n=4) plus steroids (Figure 1).
- The overall treatment success rates of the regimens were 46.2%, 80.8%, and 100.0% in the non-macrolide, macrolide plus steroid, and non-macrolide plus steroid groups, respectively. Moreover, 53.8% of the patients in the non-macrolide group eventually needed an addition of steroids and 19.2% of the patients in the macrolide plus steroid group needed a change to non-macrolide plus steroid before fever termination (Figure 2).
- Patients that initially switched to a non-macrolide had an odds ratio (OR) of 10.7 (CI, 1.5-108.7; *P=0.046*) times more likely to have fever ≥ 4 days after the switch compared to patients that switched to non-macrolide plus steroid. Patients that switched to macrolide plus steroid were 8.0 (CI, 1.3-61.7; *P=0.046*) times more likely to have fever ≥ 4 days after the switch compared to patients that switched to non-macrolide plus steroid.
- The changes in initial and follow up laboratory markers according to treatment groups are shown on Table 2.
- A univariable analyses was carried out to assess factors associated with fever duration after admission. In a linear regression model, elevated follow up CRP (β, 0.246; CI, 0.110-0.382; *P=0.001*), AST (β, 0.014; CI, 0.006-0.021; *P<0.001*), and ALT (β, 0.007; CI, 0-0.014; *P=0.037*) levels were shown to be associated with an increase in fever duration.
- Both macrolide plus steroid therapy (β, -1.704; CI, -2.310- (-1.099); *P<0.001*) and non-macrolide plus steroid therapy (β, -2.452; CI, -3.260- (-1.645); *P<0.001*) were associated with a decrease in the duration of fever after admission.
- A multivariable analysis was undertaken to find factors significantly associated with the fever duration after admission after adjusting for potentially confounding variables. Follow up CRP (β, 0.169; CI, 0.050-0.287; *P=0.006*), macrolide plus steroid therapy (β, -1.694; CI, -2.463- (-0.925); *P<0.001*), and non-macrolide plus steroid therapy (β, -2.224; CI, -3.321- (-1.127); *P<0.001*) were shown to be significantly associated with fever duration after admission (Table 3).

CONCLUSION

- Delayed effective antimicrobial treatment can lead to progression of disease, therefore, in children refractory to initial macrolide therapy, the addition of steroids, or a switch to a non-macrolide have been treatment options.
- In patients with lobar or segmental MP pneumonia and failure of response to initial macrolide therapy, a non-macrolide antibiotic plus steroid combination had the highest treatment success rate and shorter duration of fever.

References >
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* Hyun Mi Kang, MD, PhD
Professor of Pediatrics
The Catholic University of Korea College of Medicine
E-mail: pedhmk@catholic.ac.kr