Comparison of high-dose and low-dose corticosteroid therapy for refractory *Mycoplasma pneumoniae* pneumonia in children

Toshihiko Okumura, MD[1], Jun-ichi Kawada, MD, PhD[1*], Masaharu Tanaka, MD[1], Kotaro Narita, MD[1], Tomonori Ishiguro, MD[1], Yuji Hirayama, MD[1], Sho Narahara, MD[1], Genki Tsuji, MD[1], Yuichiro Sugiyama, MD[2], Michio Suzuki, MD, PhD[3], Takeshi Tsuji, MD, PhD[4], Shin Hoshino, MD, PhD[5], Masahiro Nakatochi, PhD[6], Hideki Muramatsu, MD, PhD[1], Hiroyuki Kidokoro, MD, PhD[1], Yoshiyuki Takahashi, MD, PhD[1], and Yoshiaki Sato, MD, PhD[1,7], and Nagoya Collaborative Clinical Research Team[†]

[1]Department of Pediatrics, Nagoya University Graduate School of Medicine

[2]Department of Pediatrics, Anjo Kosei Hospital

[3]Department of Pediatrics, Nagoya Memorial Hospital

[4]Department of Pediatrics, Okazaki City Hospital

[5]Department of Pediatrics, Kasugai Municipal Hospital

[6]Statistical Analysis Section, Center for Advanced Medicine and Clinical Research, Nagoya University Hospital

[7]Division of Neonatology, Center for Maternal–Neonatal Care, Nagoya University Hospital

[†]A comprehensive list of collaborators appears at the end of the paper.

[*]**Corresponding author:** Jun-ichi Kawada, MD, PhD

1 Department of Pediatrics, Nagoya University Graduate School of Medicine,
2 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan,
3 Tel: +81-52-741-2111; Fax: +81-52-744-2974; E-mail: kawadaj@med.nagoya-u.ac.jp
4
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8

Abstract

Background

Mycoplasma pneumoniae pneumonia (MPP) is generally a self-limiting disease, but it may become refractory. It is thought that refractory MPP is linked to the excessive immunologic responses of the host. Consequently, the use of adjunctive systemic corticosteroids may have beneficial effects. In this study, we compared the effects of high- and low-dose corticosteroid therapy in a pediatric population with refractory MPP.

Methods

We retrospectively collected data from 91 pediatric MPP patients treated with adjunctive systemic corticosteroids between April 2014 and October 2016. The patients were divided into the following two groups: high-dose corticosteroid group (2 mg/kg/day or more of prednisolone equivalents; n = 38) and low-dose corticosteroid group (<2 mg/kg/day; n = 53). Additionally, we compared the number of febrile days post-corticosteroid administration. We used 25 paired patients in a propensity score matching analysis to correct for confounding factors both by age and by days (from onset till corticosteroid therapy initiation).

Results

We observed that in the high-dose corticosteroid group defervescence following corticosteroid therapy initiation was achieved significantly earlier and length of hospitalization was significantly shorter (0.8 ± 1.0 vs. 1.5 ± 1.4 days and 8.2 ± 2.4 vs. 10.7 ± 2.7 days, respectively). In the propensity score matching, we observed that significant differences in the length of fever following corticosteroid therapy initiation and hospitalization were still present. Further, neither of the groups developed corticosteroid-related adverse events.

Conclusion

Our results suggest that patients with refractory MPP treated with high-dose corticosteroid could achieve defervescence earlier and have a shorter hospitalization.

Key Words: *Mycoplasma pneumoniae* pneumonia, refractory pneumonia, corticosteroids

Abbreviations

M. pneumoniae: *Mycoplasma pneumoniae*

MPP: *M. pneumoniae* pneumonia

LDH: lactase dehydrogenase

PCR: polymerase chain reaction

LAMP: loop-mediated isothermal amplification

PSL: prednisolone

Introduction

Mycoplasma pneumoniae (*M. pneumoniae*) is among the most frequent causes of community-acquired pneumonia in children and young adults. Specifically, it has been shown that in Japan, *M. pneumoniae* accounts for 14%−27% of pediatric community-acquired pneumonia [1, 2]. The majority of *M. pneumoniae* pneumonia (MPP) cases are self-limiting. However, in spite of the appropriate antibiotic therapy, some patients may develop a severe and life-threatening pneumonia.

For the treatment of refractory MPP presenting clinical and radiological deterioration despite appropriate antibiotic therapy, adjunctive systemic corticosteroids are sometimes used. The Japan Pediatric Society and the Japanese Society of Mycoplasmology suggest that the systemic administration of corticosteroids represents a treatment option for refractory MPP patients [3]. Additionally, they propose the systemic administration of corticosteroids for refractory MPP patients with fever lasting for ≥7 days and elevated levels of serum lactase dehydrogenase (LDH) [3, 4]. Previous studies have suggested that refractory MPP is linked to the excessive immunologic responses of the host [5-7]. It is thought that adjunctive systemic corticosteroids may play a beneficial role in MPP refractory cases by downregulating aberrant immune responses [8, 9]. However, to date, the use of corticosteroid therapy in MPP is limited to small case series, and the corticosteroid dosage in pediatric MPP has not been established. In this study, we retrospectively collected refractory MPP pediatric cases, and compared the effects of high- vs. low-dose corticosteroids.

Materials and Methods

Patients

We retrospectively collected data from hospitalized MPP pediatric patients <15 years old. The evaluated patients were treated with adjunctive systemic corticosteroids in 12 general hospitals located in Japan's Aichi and Gifu prefectures between April 2014 and October 2016. The Institutional Review Board of Nagoya University Hospital (2016-03788935) approved the present study. All the evaluated patients had both symptoms and signs indicative of pneumoniae, including fever (>37.5 °C), cough, and abnormal chest X-rays. *M. pneumoniae* infection was confirmed by at least one of the following tests: 1) polymerase chain reaction (PCR); 2) loop-mediated isothermal amplification (LAMP); and 3) a four-fold or greater increase in antibody titer by either the particle agglutination test or complement fixation test. The aim of this study was to evaluate the effects of corticosteroid therapy on MPP patients who did not achieve defervescence despite the administration of an appropriate antibiotic therapy. Accordingly, we excluded the following cases: 1) corticosteroid use for wheezing or skin rash; 2) corticosteroid use for patient without fever; and 3) insufficient data.

Data collection

Clinical and laboratory findings data were collected. This included the medical records of treatment with corticosteroids and antimicrobial agents and the presence of comorbidities. The Guidelines for the Management of Respiratory Infection Disease in Children (Japan 2011) was used to determine the severity of the pneumonia. Specifically, their guidelines on blood oxygen saturation, respiratory rate, consolidation of chest X-ray, and pleural effusion were used to perform the assessment [10, 11]. To be able to

compare the dosage of corticosteroids, methylprednisolone and hydrocortisone dosages were calculated in prednisolone (PSL) equivalents. Specifically, 5 mg of PSL was considered equivalent to 4 mg and 20 mg of methylprednisolone and hydrocortisone, respectively. An initial corticosteroid dosage of 2 mg/kg/day or more in PSL equivalents was defined as high-dose corticosteroid. Further, low-dose corticosteroid was defined as an initial corticosteroid dosage lower than 2 mg/kg/day. In this study, defervescence and relapse of fever were defined as a decline in body temperature up to <37.5 °C for >24 h and an increase in body temperature up to >38.0 °C after defervescence, respectively. Upon extraction the patient's data were anonymized and analyzed within the protected environment of the Nagoya University Hospital.

Of the patients with suspected MPP, adjunctive systemic corticosteroids were administered to 131 patients. Among these, we excluded 21 patients for not meeting the diagnostic criteria and 19 patients following the exclusion criteria described in the previous section. Consequently, a total of 91 MPP patients were evaluated for further analysis. These patients were divided into the following corticosteroid groups: high-dose (n = 38) and low-dose (n = 53) (Figure 1).

Statistical analysis

Statistical analysis was performed expressing variables as mean ± SD or *n* (%) and then compared between the two groups using the Student's *t*-test and Fisher's exact test. Additionally, we used the propensity score matching method to correct for bias in corticosteroid's efficacy of dose. Specifically, we used the logistic regression model to calculate the propensity score by age and days from pneumonia onset to corticosteroid therapy initiation. We performed the Greedy matching (ratio 1:1 without replacement)

with a caliper of width of 0.25 standard deviations of the logit of the estimated propensity score. We considered as statistically significant a p-value < 0.05. SAS software version 9.4 (SAS Institute, Cary, NC, USA) was used to perform the statistical analyses.

Results

Table 1 describes patients' characteristics for each group. Prior to the initiation of systemic corticosteroid therapy, all patients were administered macrolide antibiotics and/or other antimicrobial agents effective for the treatment of *M. pneumoniae* infection. Corticosteroids' dosages (mean ± SD) calculated in PSL equivalents were 3.5 ± 1.1 mg/kg/day and 1.2 ± 0.3 mg/kg/day in the high- and low-dose corticosteroid groups, respectively. The number of patients treated with PSL, methylprednisolone, and hydrocortisone was 5, 18, and 15 in the high-dose corticosteroid group and 42, 9, and 2 in the low-dose corticosteroid group, respectively. Corticosteroids were administered in combination with antibiotics, except for in two cases. Initially, corticosteroids were administered orally and intravenously in 12 and 79 patients, respectively. After defervescence was achieved, corticosteroid dose was gradually reduced in 56 patients (62%). On an average, dose reduction was initiated on 3.93 days following the initiation of corticosteroid therapy.

Compared with the patients in the low-dose corticosteroid group, those enrolled in the high-dose corticosteroid group were younger (5.3 ± 3.1 vs. 7.1 ± 3.4 years, $p = 0.02$) and were treated with corticosteroids at an earlier time since high fever initiated (7.4 ± 2.1 vs. 9.0 ± 1.8 days, $p < 0.001$). We did not observe significant differences in antimicrobial agents, severity of pneumoniae, and other baseline data between the two groups. Minocycline, which can cause yellow dental discoloration in young children, was administered to 13 of 61 patients aged less than 8 years. In the high-dose corticosteroid group, defervescence after the initiation of corticosteroids was achieved at a significantly earlier time and length of hospitalization was significantly shorter than in the low-dose corticosteroid group (0.8 ± 1.0 vs. 1.5 ± 1.4 days, $p = 0.01$ and 8.2 ± 2.4

vs. 10.7 ± 2.7 days, $p < 0.001$, respectively). Furthermore, the duration of total corticosteroid therapy was significantly shorter in the high-dose corticosteroid group than in the low-dose corticosteroid group (4.2 ± 1.5 vs. 5.8 ± 2.6 days, $p < 0.001$). The mean number of days from defervescence to discharge was 5.2 and 5.0 days in the high- and low-dose corticosteroid groups, respectively ($p = 0.66$) (Table 2). In this study, 30 patients with MPP were considered as having severe pneumonia (Table 1). Among these, defervescence following the initiation of corticosteroid therapy was achieved significantly earlier in the high-dose corticosteroid group than in the low-dose corticosteroid group (0.5 ± 0.7 vs. 2.1 ± 1.4 days, $p < 0.001$).

In neither of the groups did we observe corticosteroid-related adverse events (e.g., hyperglycemia, hypertension, gastrointestinal bleeding, and nosocomial infections). We did not observe a difference in fever's incidence of relapse for both of the groups. Notably, there were no fatal cases in this study.

However, our analysis showed a significant difference in age and days from onset of fever to initiation of corticosteroids between the two groups. To reduce these biases, we generated matched groups by the propensity scores. Consequently, 25 paired patients were used for the analysis. These showed no differences in age and timing of corticosteroid initiation (Table 3). However, the significant differences in fever duration following corticosteroid therapy initiation were maintained after propensity score matching (0.9 ± 1.2 vs. 1.8 ± 1.5 days, $p = 0.02$). Additionally, the patients in the high-dose corticosteroid group were discharged significantly earlier following corticosteroid therapy initiation, and the total length of hospitalization was shorter than for the patients in the low-dose corticosteroid group (5.4 ± 2.0 vs. 7.1 ± 2.9 days, $p = 0.02$; 7.6 ± 2.4 vs. 10.8 ± 3.3 days, $p < 0.001$, respectively).

Discussion

Refractory MPP presents with clinical and radiological deterioration despite appropriate antibiotic therapy and can develop into severe life-threatening pneumonia. In the present study, we retrospectively analyzed pediatric refractory MPP cases treated with adjunctive systemic corticosteroids. Refractory MPP appears to be related to excessive immunologic responses of the host. Consequently, the administration of systemic corticosteroids may represent an effective treatment. Importantly, previous studies have shown the usefulness of adjunctive systemic corticosteroids in refractory MPP's treatment. Lee et al. reported that 14 out of 15 severe pediatric MPP patients treated with oral prednisolone became afebrile within 24 h [9]. Furthermore, two case series showed the positive effects of methylprednisolone pulse therapy (30 mg/kg once daily for 3 consecutive days) for refractory MPP [12, 13]. However, these reports evaluated a small number of patients and did they not compare different dosages of corticosteroids. Luo et al. prospectively demonstrated children with refractory MPP were treated more effectively with adjunctive oral prednisolone (2 mg/kg/day) than azithromycin alone [8]. Overall, all the above mentioned studies showed that systemic corticosteroids were an effective therapy for refractory MPP, while dosages were not constant. In the present study, we analyzed whether the effect of corticosteroids on refractory MPP depended on the dosage. Our results demonstrated that the treatment of refractory MPP patients with high-dose corticosteroids could lead to an earlier defervescence and shorten hospitalization. Earlier defervescence in the high-dose corticosteroid group may result in shorter duration of corticosteroid therapy than in the low-dose corticosteroid group. Furthermore, among the patients with severe MPP, defervescence was achieved significantly earlier in the high-dose corticosteroid group

than in the low-dose corticosteroid group.

In this study, corticosteroids were used earlier and in higher dose for younger patients. It might be possible that, compared with older ones, younger patients were likely to worsen. Of note, in this study, we retrospectively collected patient data. Therefore, each attending physician independently decided the initiation and dosage of corticosteroids. An earlier initiation of corticosteroids or an age difference might influence fever duration, post-corticosteroid treatment, or length of hospitalization. Therefore, to reduce the biases, we performed a re-analysis using propensity scores and confirmed that high-dose corticosteroid therapy could achieve defervescence significantly earlier and shorten hospitalization.

In none of the patients included in the study did we observe corticosteroid-related adverse events. Since the average length of corticosteroid administration was 5.1 days, it was suggested that adverse events were less likely to occur in pediatric patients due to the short period of administration. Conversely, it has been shown that adult patients with community-acquired pneumonia treated with oral prednisolone for a week had a higher incidence of hyperglycemia requiring insulin treatment compared with the placebo group [14]. Furthermore, Hirota et al. observed that adult patients treated with adjunctive corticosteroids are at higher risk of developing overall adverse events and hyperglycemia [15]. Although these studies were performed on adult patients, in pediatric patients, corticosteroids should be used with caution due to possible hyperglycemia.

In the present study, several limitations can be identified. First, corticosteroid therapy initiation and dosage were decided by each attending physician because an indication for the use of adjunctive corticosteroids for MPP’s treatment had not been

established. However, there are indications suggesting that most MPP patients included in this study were considered refractory cases. Specifically, in spite of the use of appropriate antimicrobial agents, 84% of the patients had a high fever for 7 days or more before the initiation of corticosteroids. Furthermore, 76% of the patients had elevated serum LDH levels, higher than 400 IU/L. Second, since the majority of refractory MPP patients were treated with adjunctive corticosteroids, we did not compare the usefulness of systemic corticosteroids with the use of antimicrobial agents alone. Third, macrolide-resistant *M. pneumoniae* was not evaluated here. In Japan, while the prevalence of macrolide-resistant *M. Pneumoniae* reached 81.6% in 2012, more recently, the prevalence is approximately 40% and is on a declining trend [16]. Refractory MPP may not be solely explained by macrolide resistance. Specifically, an earlier study has shown that defervescence occurred within 48 h in 41% of the patients with macrolide-resistant *M. Pneumoniae* infection treated with azithromycin [17]. Additionally, 64% of the MPP patients included in this study were treated with minocycline or tosufloxacin. Before the administration of corticosteroids, these agents are more efficient against macrolide-resistant *M. Pneumoniae*.

To the best of our knowledge, this study is the first to analyze the largest number of pediatric refractory MPP cases treated with adjunctive systemic corticosteroids. Our results suggest that high-dose corticosteroid therapy of patients with refractory MPP could achieve defervescence earlier and shorten hospitalization. Prospective randomized studies are needed to confirm the efficacy and safety of high-dose corticosteroids for patients with refractory MPP.

Collaborators: Nagoya Collaborative Clinical Research Team; Yuji Miyajima and Nozomi Uno (Department of Pediatrics, Anjo Kosei Hospital, Anjo, Japan), Noriko Nagai, Shotaro Ando, Yuji Sudo, Kazuhisa Naruse, Yuma Takahashi, Ryosuke Suzui, and Yoshihiro Nagata (Department of Pediatrics, Okazaki City Hospital, Okazaki, Japan), Takashi Kawabe (Department of Pediatrics, Kasugai City Hospital, Kasugai, Japan), Motohiro Shibata and Yusuke Shibata (Department of Pediatrics, Chukyo Hospital, Nagoya, Japan), Masashi Morishita (Department of Pediatrics, Tosei General Hospital, Seto, Aichi, Japan), Mitsuharu Kajita and Takuto Ito (Department of Pediatrics, Toyota Kosei Hospital, Toyota, Aichi, Japan), Shinji Kido (Department of Pediatrics, Nakatsugawa Municipal General Hospital, Nakatsugawa, Gifu, Japan), Shinji Hasegawa, Kei Ikeda, Noriko Tokumo, and Maki Kato (Department of Pediatrics, Nagoya Memorial Hospital, Nagoya, Japan), Koji Kato and Daichi Fukumi (Department of Pediatrics, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan) Satoru Doi and Marei Omori (Department of Pediatrics, Hekinan Municipal Hospital, Hekinan, Aichi, Japan), Nobuhiro Watanabe (Department of Pediatrics, Meitetsu Hospital, Nagoya, Japan), and Hiroyuki Takada (Department of Pediatrics, Tsushima City Hospital, Tsushima, Aichi, Japan).

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1 **Table 1. Patient characteristics**

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	High-dose corticosteroid therapy (n = 38)	**Low-dose corticosteroid therapy (n = 53)**	**P-value**
Sex (male/female)	21/17	28/25	0.84
Age (years)	5.3 ± 3.1	7.1 ± 3.4	**0.02**
Dosage of corticosteroids (in PSL equivalents, mg/kg/day)	3.5 ± 1.1	1.2 ± 0.3	**<0.001**
Days from onset to initiation of corticosteroid therapy	7.4 ± 2.1	9.0 ± 1.8	**<0.001**
Antimicrobial agents (including duplicated data)[2]			
Clarithromycin	23 (61)	36 (68)	0.51
Azithromycin	3 (8)	7 (13)	0.51
Erythromycin	3 (8)	3 (6)	0.69
Tosufloxacin	18 (47)	30 (57)	0.40
Minocycline	16 (42)	20 (38)	0.83
Others	7 (18)	11 (21)	1
SpO2 (%)	96.1 ± 2.7	96.2 ± 3.0	0.87
Tachypnea	11 (32) (n = 34)	12 (25) (n = 48)	0.62
Oxygen administration	12 (34) (n = 35)	13 (25) (n = 52)	0.47
Pleural effusion	3 (8)	6 (11)	0.73
Consolidation of chest X-ray			
Area of consolidation in worse lung			
<1/3	25 (66)	33 (62)	0.69
1/3–2/3	13 (34)	18 (34)	
>2/3	0 (0)	2 (4)	
Severe pneumonia*	13 (34)	17 (32)	0.83
Laboratory data			
WBC ($\times 10^3/\mu l$)	6.2 ± 2.3	5.1 ± 2.2	0.06
PLT ($\times 10^4/\mu l$)	23.6 ± 6.0	22.6 ± 7.0	0.55
CRP (mg/dL)	2.2 ± 1.9	2.4 ± 2.6	0.72

AST (IU/L)	54.8 ± 29.0	84.6 ± 144.5	0.29
ALT (IU/L)	33.5 ± 40.3	59.8 ± 157.1	0.39
LDH (IU/L)	504.5 ± 178.1	574.6 ± 249.7	0.20

Data are presented as mean ± SD or *n* (%).

*Severe of pneumonia was defined based on the Guidelines for the Management of Respiratory Infection Disease in Children in Japan 2011 [10].

PSL, prednisolone; WBC, white blood cell; PLT, platelet; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase. P-values were calculated by Student's *t*-test or Fisher's exact test. Bold values represent $p < 0.05$

Table 2. Comparisons of clinical courses between the patients treated with high-dose and low-dose corticosteroid therapy

	High-dose corticosteroid therapy (n = 38)	Low-dose corticosteroid therapy (n = 53)	P-value
Days from initiation of corticosteroids to defevrescence	0.8 ± 1.0	1.5 ± 1.4	**0.01**
Duration of corticosteroids therapy (days)	4.2 ± 1.5	5.8 ± 2.6	**<0.001**
Days from initiation of corticosteroids to discharge	6.0 ± 2.2	6.5 ± 2.5	0.28
Days from defevrescence to discharge	5.2 ± 2.1	5.0 ± 2.5	0.66
Length of hospitalization (days)	8.2 ± 2.4	10.7 ± 2.7	**<0.001**
Corticosteroid-related adverse events	0 (0)	0 (0)	
Relapse of fever	3 (8)	6 (11)	0.73

Data are presented as mean ± SD or *n* (%). P-values were calculated by Student's *t*-test or Fisher's exact test. Bold values represent $p < 0.05$

Table 3. Patient characteristics and comparisons of clinical courses between groups matched by propensity scores

	High-dose corticosteroid therapy (n = 25)	**Low-dose corticosteroid therapy (n = 25)**	**P-value**
Age (years)	6.1 ± 3.3	6.5 ± 3.6	0.69
Days from onset to initiation of corticosteroids	8.4 ± 1.7	8.3 ± 1.8	0.75
Days from initiation of corticosteroids to defervescence	0.9 ± 1.2	1.8 ± 1.5	**0.02**
Days from initiation of corticosteroids to discharge	5.4 ± 2.0	7.1 ± 2.9	**0.02**
Length of hospitalization (days)	7.6 ± 2.4	10.8 ± 3.3	**<0.001**

Data are presented as mean ± SD. P-values were calculated by Student's *t*-test or Fisher's exact test.

Bold values represent $p < 0.05$

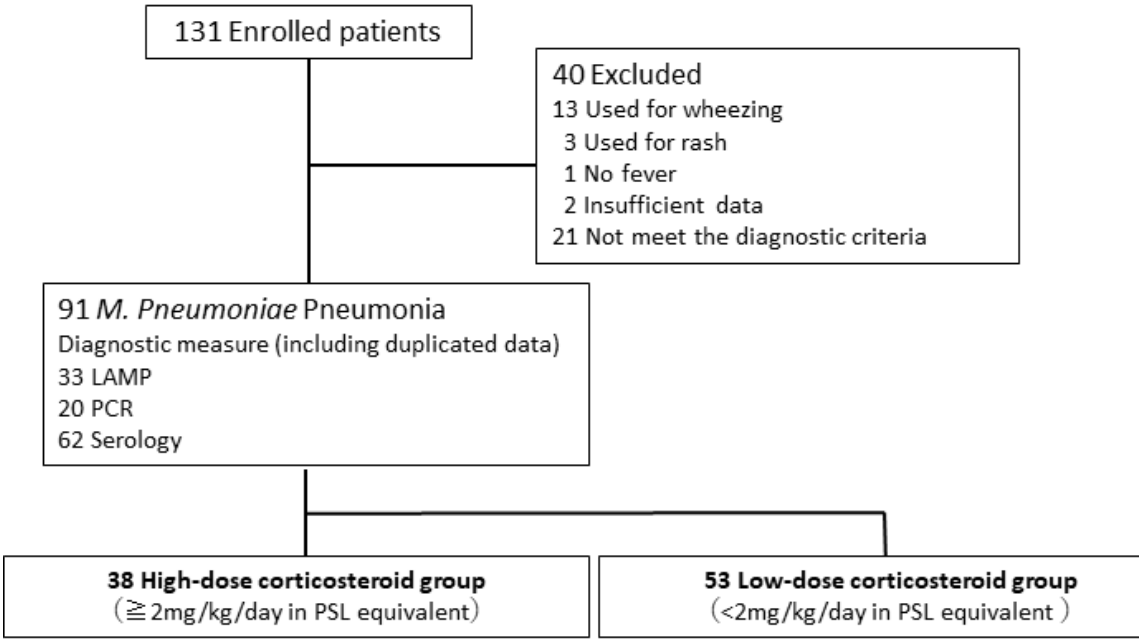

Figure 1.

Flowchart showing the various steps of the present study

LAMP, loop-mediated isothermal amplification; PCR, polymerase chain reaction; PSL, prednisolone