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Efficacy of Methylprednisolone in Children With Severe Community Acquired Pneumonia

Bela Nagy, MD, PhD,[1]* Imre Gaspar, MD,[1] Agnes Papp, MD,[1] Zsolt Bene, MD,[1] Bela Nagy Jr, MD, PhD,[2] Zoltan Voko, MD, PhD,[3] and Gyorgy Balla, MD, PhD[1]

Summary. Background: The clinical value of adjuvant corticosteroid treatment in community-acquired pneumonia (CAP) seemed to be controversial in adults, and even less data are available on the use of corticosteroids in children with CAP. Materials and Methods: In this study, we investigated the efficacy of a 5-day adjuvant methylprednisolone therapy to imipenem in 29 children with severe CAP. In parallel, 30 subjects with the same disease were treated with imipenem and placebo, and the two study groups were compared based on the different parameters of the primary and secondary end points. The primary end points were the duration of fever, the levels of white blood cells (WBC) and high sensitive C-reactive protein (hsCRP). Secondary end points were the length of hospital stay, and the number of severe complications with or without surgical interventions. Results: The additive methylprednisolone treatment significantly reduced the duration of fever with 2.5 days, the WBC counts ($P = 0.014$), the hsCRP levels showing a 48.7% decrease, and the length of hospital stay with 5.2 days versus the placebo group. Moreover, patients treated on imipenem alone had twice more complications and four times more invasive interventions compared to those on the combined therapy. Conclusions: The 5-day methylprednisolone therapy with imipenem was found effective in children having severe CAP. However, trials with larger cohorts are needed to study further beneficial effects of corticosteroids in children with CAP. **Pediatr Pulmonol. 2013; 48:168–175.**

Key words: imipenem; childhood; community acquired pneumonia; corticosteroid.

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INTRODUCTION

Streptococcus vaccination has markedly reduced the incidence of pneumococcal diseases such as meningitis or pneumonia in children worldwide.[1,2] However, the case number of severe bacterial pneumonia with abscess formation, empyema, or pleural effusions is still considerably high in childhood,[3] and Streptococcus pneumoniae (S. pneumoniae) remained the main pathogen of community-acquired pneumonia (CAP).[1,2] This tendency was primarily described in children aged 2–4 years and individuals with co-morbidities or impaired immune responses.[4] The major causes of severe CAP in children are non-vaccine serotypes, e.g., serotype 1, preceding respiratory viral infections, delay in medication with antibiotics, therapeutic resistance of bacteria to second-generation macrolides, and the development of penicillin-resistant Pneumococcus species.[3–7] In addition, severe pneumococcal pneumonia is still often associated with sepsis causing increased mortality, and substantial cost of the intensive care.[8]

Antibiotics are considered as the first-line treatment in CAP with or without septic phase.[9–11] The utility of corticosteroids in infectious disease such as CAP is still a matter of debate. There is some clinical evidence that adjuvant therapy such as corticosteroids shortened the length of hospitalization and significantly improved the

[1]Department of Pediatrics, Medical and Health Science Center, University of Debrecen, Debrecen, Hungary.

[2]Department of Laboratory Medicine, Medical and Health Science Center, University of Debrecen, Debrecen, Hungary.

[3]Department of Health Politics and Health Economy, Eötvös Lóránd University, Budapest, Hungary.

*Correspondence to: Bela Nagy, MD, PhD, Department of Pediatrics, Medical and Health Science Center, University of Debrecen, Nagyerdei körút 98. H-4032 Debrecen, Hungary. E-mail: bnagy@dote.hu

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outcomes of sepsis, septic shock, and bacterial meningitis in both adults and children[12–14] or in an animal model.[15] However, others claimed that corticosteroids did not work effectively in patients with severe CAP.[16] Current guidelines recommend corticosteroid therapy in a combination with antibiotic(s) or in a single administration prior to the first dose of antibiotic(s) in bacterial meningitis in order to prevent further complications such as neurological injury, loss of hearing, and to decrease the rate of mortality in patients of any age.[12]

Previous clinical studies have demonstrated somewhat controversial results regarding the benefits of adjunctive corticosteroid treatment to antibiotics in adult patients with CAP. Systemic steroids produced a marked improvement in P_aO_2/FiO_2 with better survival rate of adults suffered from severe CAP by reducing pulmonary inflammation.[17–19] Seven-day prednisolone treatment generated a shorter time to defervescence and a faster decline in C-reactive protein (CRP) serum levels in patients with CAP compared with those treated with placebo.[20] However, the length of hospital stay, the time to clinical stability, and the number of adverse events did not differ between the two adult groups.[20] Due to the small number of evidence about the efficacy of corticosteroids, this regimen was not recommended for routine adjunctive treatment in adults with severe CAP.[16,18,21,22] Only one case report showed that hydrocortisone along with antibiotics elucidated severe CAP and sepsis in children.[23] Very recently, Weiss et al.[22] used various types of corticosteroid with or without beta-receptor agonist in a multicenter studies in children aged 1–18 years with CAP. Overall, corticosteroid had a positive effect in the outcomes, but only in those subjects who took beta-agonist as well.

Here, an open-label, unblinded, randomized, and placebo-controlled study was conducted to determine the efficacy and the safety of methylprednisolone therapy combined with imipenem in children with severe CAP. Our hypothesis was that the 5-day administration of methylprednisolone with imipenem would improve the clinical outcomes by the day 7 (primary end points), and decrease the duration of hospital stay and the number of complications and invasive interventions (secondary end points) in children in such severe clinical status.

MATERIALS AND METHODS

Patients were enrolled from June 2007 through September 2009 at the Division of Pediatric Pulmonology, Department of Pediatrics, Medical and Health Science Center, University of Debrecen, Debrecen, Hungary. The National Ethics Committee for Clinical Pharmacology, Medical Research Council, Budapest, Hungary approved the trial (EudraCT registration number: 2007-006602-24.). Written informed consent was obtained from the parent or legal guardian of each child before the study entry.

Study Design

We performed an open-label, unblinded, and placebo-controlled study where the randomization was based on one to one allocation ratio. The sequence of random numbers for the parallel groups was computer generated. We did not use block randomization because we thought that the learning effect would not influence the distribution of per group random allocation in our patient cohort. We performed a sample size calculation in order to recruit 30-30 patients into both groups. Because of the rapid clinical progression in severe pulmonary disorders and the increasing therapeutic resistance of Pneumococcus to amoxicillin and cephalosporins,[6,11,24,25] all study participants were treated with imipenem (60 mg/body weight kg) divided into four doses, i.v. in 100 ml saline solution for at least 7 days. The antibiotic infusion was started immediately after the clinical diagnosis on admission. Children were randomly assigned to receive simultaneously either i.v. methylprednisolone 20 mg (0.5–2.0 mg/kg body weight in different ages), or 5% dextrose as placebo. Blood samples were obtained on days 1 and 7 to analyze renal and liver functions, electrolytes, hsCRP, glucose, hematology, and blood gas parameters. Oxygen, fluid supply, and non-steroid drugs (acetaminophen or diclofenac) were used as needed. However, the use of vasopressores or inotropes was not necessary in either patient. Chest radiography was taken on the day of the study entry and day 7 in each patient. Depending on the delayed improvement or sudden complications, further control X-ray examinations were done on days 3, 14, 21, or 28. The antibiotic treatment was maintained after day 7 based on the disease course. Microbiological analyses in blood and throat samples were done prior to the imipenem therapy. Pleural fluid if present was examined by culture and Gram's stain.

Clinical Assessment

During the study period 356 children with different severity of CAP were admitted to our Department. Of them 254 (71.3%) suffered from mild and moderate pneumonia with viral, bacterial (mostly S. pneumoniae), or atypical bacterial (Mycoplasma pneumoniae) origin. Patients with severe CAP ($n = 102$; 28.7%) were prospectively enrolled into the study. The length of case history and pre-hospital fever was defined based on the medical report obtained from the G.P. They were previously treated with empiric antibiotics (amoxicillin/clavulanic acid, macrolides, or cephalosporins) according to the current guidelines for 4.3 days of average.

Hospital admissions were indicated because of rapid worsening of clinical symptoms due to treatment failure. Of them 39 children met one of the following exclusion criteria such as chronic respiratory disease, asthma, other severe systemic disease, malignancy, previous adverse reaction to corticosteroids, or known immunodeficiency. Although we had several children with asthma treated with continuous inhalative corticosteroid, they were not recruited eventually into this study, because we could not evaluate effectively the beneficial impact of i.v. adjuvant corticosteroid therapy to imipenem. Four patients were also excluded because of refused consent by their guardians.

Finally, 59 patients with severe CAP were eligible and randomized: 29 children received methylprednisolone along with imipenem, while placebo with imipenem was administered to 30 patients as seen in the study flow chart (Fig. 1). These patients in the two study groups met all of the following inclusion criteria: <18 years of age, pallor or cyanosis, irritability or lethargy, cough, axillary body temperature ($>38.5^{\circ}$C), symptoms of respiratory distress (dyspnoe, respiratory rate: >2SD above normal value for age), new consolidation on chest X-ray, and positive laboratory tests for systemic inflammatory response syndrome (SIRS) such as elevated white blood cell (WBC) counts with $>10\%$ immature neutrophils, $P_aO_2 \leq 92$ Hgmm, tachycardia (>2SD above normal value for age), increased blood pressure (systolic value >90 Hgmm and diastolic value >60 Hgmm, i.e., no sepsis-induced hypotension). These parameters were defined according to the current guidelines and the international consensus.[26,27]

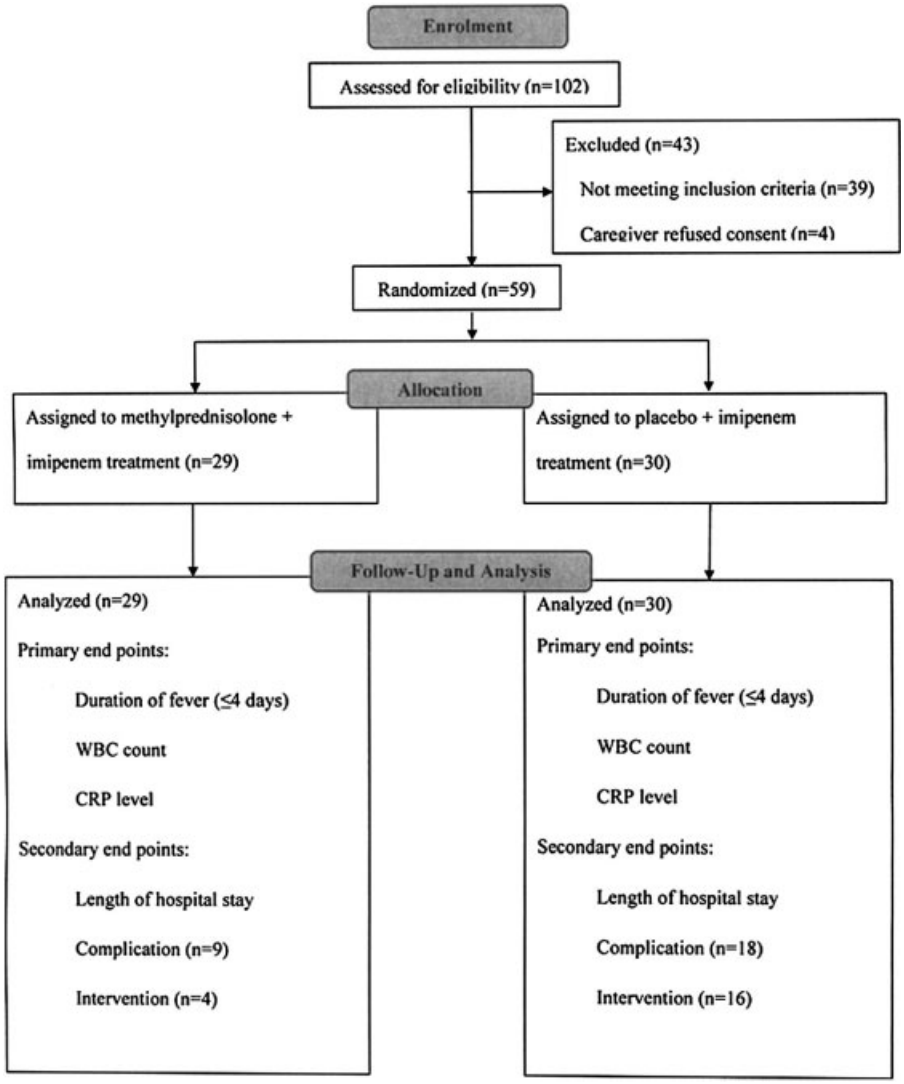

Fig. 1. Study flow chart with enrolment, randomization, follow-up, and data analysis. Fifty-nine out of 102 children met all the criteria for inclusion as suffering from severe CAP, and were then treated with imipenem with (n = 29) or without methylprednisolone (n = 30).

No patient from either study group had been formerly vaccinated with the heptavalent pneumococcal conjugate vaccine.

Outcomes

Clinical outcomes at day 7 were defined as (1) improvement of symptoms and clinical parameters with no need for additional treatment and interventions, or (2) the worsening in the clinical status and/or deterioration of chest X-ray. The primary end points were set as the characteristics of clinical and radiological status on day 7. Children were found clinically improved if the following criteria were present: Decrease in coughing and respiratory distress, $\leq$4 days to defervescence, improving level of WBCs and hsCRP values. Defervescence was defined as temperature $<37.5^{\circ}$C. Secondary end points were the length of hospital stay and the number of severe complications with surgical interventions if necessary. Complications were defined as progressively worsening radiological findings such as pleural effusion, abscess formation, empyema, and pneumothorax. The findings from patients on combined therapy were compared to data obtained from those who received imipenem alone. To avoid observer bias, results were determined and double-checked by an independent clinician and radiologist. Suction drain replacement, video assisted thoracoscopy, or thoracotomy for decortication were performed in patients with complications. The consequence of longer case history and pre-hospital treatment was also evaluated. All randomized patients were followed up after 2 weeks of discharge.

Statistical Analysis

Kolmogorov–Smirnov test was used for the evaluation of the normality of the data distribution. According to this analysis, results were expressed as mean $\pm$ standard deviation (SD), or median (inter-quartile range). Normally distributed variables were analyzed by using two-tailed Student's independent *t*-test. Nonparametric parameters between the two distinct treatment groups were compared by using Mann–Whitney U-test or chi-square test as appropriate. The significance of differences in mean hsCRP, the duration of fever, the WBC count, the length of hospital stay, the length of pre-history values, and gender were tested by analysis of variance (ANOVA) using the Bonferroni correction for multiple comparisons. *P*-values <0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

Fifty-nine randomized patients were at the age of 1–12 years, and there was no significant difference in mean years of age ($P = 0.987$). The gender ratio was also similar in the two groups: Methylprednisolone + imipenem group (15 males, 14 females) and placebo + imipenem cohort (19 males, 11 females) ($P = 0.197$). Other baseline clinical characteristics and laboratory results did not vary either between the two groups. There were no significant differences in terms of the length of case history ($P = 0.981$), and the duration of pre-hospital fever ($P = 0.715$). In addition, no significant differences were shown in the initial WBC counts and hsCRP levels ($P = 0.237$ and $P = 0.559$, respectively) (Table 1). Furthermore, day-time and midnight cortisol levels were measured in all study participants prior to the corticosteroid administration. We found highly increased levels of cortisol in both groups (median level of 666.3 vs. 738.3 nmol/L and 475.1 vs. 364.7 nmol/L) showing a severe inflammatory response in these CAP patients. Radiological examinations on admission revealed extensive consolidation in the lung associated with pleural thickness and/or effusion in 72.4% vs. 76.6% of patients in methylprednisolone and placebo groups (Table 1).

TABLE 1— Baseline Characteristics of All Study Subjects With Severe CAP

Characteristics	Methylprednisolone + imipenem n = 29	Placebo + imipenem n = 30	*P*-value
Age (year)	4.6 $\pm$ 2.7	5.2 $\pm$ 4.0	0.987
Gender (M/F)	16/13	19/11	0.197
Length of case history (day)	5.6 $\pm$ 2.8	5.7 $\pm$ 2.7	0.981
Duration of pre-hospital fever (day)	4.4 $\pm$ 2.0	4.3 $\pm$ 1.9	0.715
White blood cell count (G/L)	19.6 (15.9–23.8)	15.7 (12.8–21.8)	0.237
hsCRP (mg/L)	307.8 (272.8–339.1)	281.5 (181.9–377.6)	0.559
Serum cortisol (day-time) (nmol/l)	666.3 (464.3–1036.9)	738.3 (497.5–1012.6)	0.647
Serum cortisol (midnight) (nmol/l)	475.1 (245.8–734.9)	364.7 (240.6–471.4)	0.621
Pleural thickness w/o effusion on admission	21	23	0.897

The number of patients is presented as n, mean $\pm$ SD (95% CI of the mean), median (inter-quartile range); CAP: community acquired pneumonia.

According to blood culture analyses, samples were positive for S. pneumoniae in steroid group (51.7%) and in the placebo group (43.3%) except for one patient (Staphylococcus aureus). S. pneumoniae isolates from the throat were detected in 37.2% of children within the entire cohort. Cultures of pleural fluid were also analyzed in 20 children with different complications, and only two samples were positive for S. pneumoniae.

Clinical Outcomes

On day 7 we analyzed the parameters of the primary end points. In the methylprednisolone + imipenem group the duration of fever was shorter with 50% ($P = 0.006$), WBC counts were significantly lower ($P = 0.023$) and hsCRP serum levels decreased to 20.5 vs. 35.1 mg/L compared to subjects in the placebo group indicating the substantial suppression of acute inflammatory processes (Table 2). During statistical analyses we also studied the influence of different cofounders on other parameters. Accordingly, the duration of fever and hospital stay was adjusted for hsCRP levels. WBC counts were affected by gender, while hsCRP levels were influenced by the length of hospital stay, duration of case history, and fever. Thus, these variables were adjusted for these confounders. Although hsCRP levels markedly varied between the study groups, there was no statistically significant difference after the adjustment.

Twenty out of 29 patients (68.9%) in the corticosteroid group considerably improved based on their clinical and radiological status, but four children (13.7%) had longer period (>4 days) to defervescence. Among placebo and imipenem-treated patients, 14 (46.7%) patients had longer duration of fever, and 12 from 30 (40%) subjects recovered by the day 7. The secondary outcomes included the length of hospital stay ($P = 0.006$), which was significantly longer with 5.5 days in children on imipenem monotherapy. In the placebo group, there was a significantly ($P = 0.026$) higher number of patients (18; 60.0%) who had complications versus the corticosteroid-treated group with nine patients (31.0%) having pleural effusion (5 vs. 3), empyema (12 vs. 5), and abscess formation (1 vs. 1).

According to additional subgroup analysis, within the placebo group in case of 7 out of 18 (38.8%) children with complications the duration of hospital stay was longer with 11 days than the mean group value. Interestingly, this ratio was not smaller in the corticosteroid group [five from nine patients (55.5%)]. In both groups, children with complications had significantly longer length of case history before the study entry compared to those without any: In the methylprednisolone group (7.7 days vs. 4.9 days; $P = 0.009$), while in the placebo group (6.7 vs. 4.2; $P = 0.011$) (data not shown). Overall, late referral to hospital was considered as a risk factor in severe CAP itself regardless having complications or not. Among placebo-treated patients suffered from complications, significantly more surgical interventions were necessary versus in individuals on the combined therapy ($P = 0.001$) because of the higher rate of empyema development (12 vs. 5 patients, respectively). However, no patient suffered from long-term sequelae in either group, but the overall outcome was more favorable in patients treated with the combined therapy. No treatment-related adverse events were found in any of the patients, as the parameters of liver and renal function were measured within the normal ranges (data not shown).

DISCUSSION

In this single center, open-label, unblinded, placebo-controlled clinical trial, 59 children were randomized

TABLE 2— Primary and Secondary Outcomes

Characteristics	Methylprednisolone + imipenem n = 29	Placebo + imipenem n = 30	*P*-value
Duration of fever (days)[1]	2.0 (1.0–4.0)	4.0 (3.0–6.0)	0.006*
White blood cell count (G/l)[1]	8.4 (7.2–10.2)	11.1 (8.5–14.5)	0.023**
hsCRP (mg/l)[1]	20.5 (15.6–30.4)	35.1 (17.1–82.3)	0.532***
Length of hospital stay (days)	11.0 (9.0–15.0)	16.5 (12.3–20.3)	0.006*
Complications	9	18	0.026
Pleural effusion	3	5	
Empyema	5	12	
Abscess formation	1	1	
Interventions[2]	4	16	0.001

The number of patients is presented as n, median (inter-quartile range); CAP: community acquired pneumonia.
[1]On the 7th day of the treatment.
[2]Video assisted thoracoscopy or thoracotomy for decortication and/or use of suction drain.
*Adjusted for CRP.
**Adjusted for gender.
***Adjusted for length of case history, length of hospital stay and duration of fever.

who suffered from severe CAP. We found that the 5-day adjuvant methylprednisolone therapy to imipenem treatment showed clinical utility in decreasing the duration of fever and the levels of hsCRP with 50%, and the length of the hospital stay with 5.5 days of average. Furthermore, this regimen seemed to be more protective against the development of empyema compared to the imipenem monotherapy. This study suggests that corticosteroid treatment along with this broad-spectrum antibiotic may be effective in the treatment of children with severe CAP to improve the efficacy of antimicrobial medication and prevent further complications especially in those who were formerly treated empiric antibiotic(s).

To choose an appropriate, initial antibiotic regimen in critically ill patients, the national resistance data have to be considered. In the last two decades, in Hungary the prevalence of penicillin resistance of S. pneumoniae strains was found to be extremely high (58% non-susceptible).[28] Moreover, resistance to amoxicillin, ceftriaxone, and erythromycin was 2.62, 1.12, and 42.06%, respectively.[28] Others found 40% macrolides resistance in a large national epidemiological survey.[29] In Spain, the rates of penicillin resistance or semi-responsiveness were also high (52.3%) in S. pneumoniae isolates especially in children with age of $\leq$4 years.[30] Different international guidelines recommend amoxicillin, cefuroxime, cefotaxime, or amoxicillin-clavulanic acid with or without macrolides routinely in CAP. However, the 4th generation cephalosporin cefepime or the beta-lactam carbapenem/imipenem antibiotics are suggested for the treatment of severe CAP in either monotherapy or combination therapy in adults.[14] Considering these suggestions and due to the increased antibiotic resistance to Streptococcus pneumoniae,[25–30] as well as the high ratio of non-responsiveness to empiric antibiotic pre-treatment in this study patients, we used imipenem in those with severe CAP. Our aim was to investigate whether the additive administration of methylprednisolone might improve the beneficial effect of imipenem in a combined medication in children.

The effects of corticosteroid on the immune system are complex. It is difficult to estimate how corticosteroids alter immune responses in infectious diseases.[31] The activity of released cytokines and other inflammatory mediators from immune cells has a key role in the elimination of pathogens. On the other hand, excessive expression and constant high levels of cytokines may cause severe damage especially in the lung resulted in pneumonia with many complications.[32,33] Systemic corticosteroids were effective in the inhibition of the recruitment of leukocytes and macrophages into the inflamed tissues, and blocking of increased cytokine production including interleukin (IL)-1ß, IL-6, and tumor necrosis factor-α.[34] Moreover, the combined administration of methylprednisolone with antibiotics attenuated the local inflammatory responses by decreasing the concentration of IL-6 even in the bronchoalveolar lavage, and thus significantly reduced tissue damage in the lung of an animal model with severe pneumonia.[15]

The dosage and timing of corticosteroid medication with or without antibiotic pre-treatment and the etiology of pneumonia are important factors when predicting the impact of systemic corticosteroids on clinical outcome. Methylprednisolone is the most widely used corticosteroid in the clinical practice, because it accumulates in even higher concentration in the lungs compared to other corticosteroids due to its larger volume of distribution, longer mean residence, time and greater retention in the epithelial lining fluid of the alveoli.[35] The use of early, short-term, and low-dose methylprednisolone was found as effective as in prolonged therapy in animal model of acute lung injury.[36] This regimen resulted in a complete resolution in the mechanical and histological alterations of the lung in vivo, and avoided fibroelastogenesis in vitro.[36]

There is a large body of controversial evidence on the efficacy of corticosteroids in mono or combined therapy with antibiotics in adults with severe conditions such as sepsis and meningitis, but only a few studied its effect in CAP.[12] A 7-day course of hydrocortisone infusion resulted in significant reduction in the duration of mechanical ventilation, length of hospital stay, and mortality in adults with CAP.[18] As a result of adjuvant corticosteroid treatment, a markedly decrease in the levels of pro-inflammatory cytokines and a lower mortality rate were observed in patients with severe pneumonia requiring mechanical ventilation.[17] Agusti et al. examined the relationship between the intensity of the inflammatory response, the corticosteroid dosage, and the disease prognosis in patients with severe pneumonia who received corticosteroid treatment for a short (9 ± 7 days) and a long (>30 days) time period.[37] They found that a short-term corticosteroid treatment demonstrated a major attenuation of the inflammatory responses with a beneficial modulation of the prognosis of pneumonia. However, prolonged corticosteroid medication was associated with several side effects inducing further complications.[37] Similarly to our results, concomitant administration of corticosteroids with antibiotics has been proved to be a protective approach in adult patients with ICU-acquired pneumonia that required mechanical ventilation.[38] Dexamethasone (5 mg/day for 4 days) reduced the length of hospital stay when added to antibiotic treatment in adults with CAP in a randomized, double-blinded, placebo-controlled trial.[39] Mortality data showed a decrease in patients with severe CAP who received simultaneous administration of systemic corticosteroids

along with antibiotic treatment.[19] A recent randomized study on the efficacy of adjunctive prednisolone treatment (40 mg/day for 1 week) in adult patients with CAP showed earlier defervescence and faster decline in hsCRP serum levels compared to placebo.[20] However, there was an increase in the development of late complications, which was seen more common in the corticosteroid group, so authors did not recommend prednisolone as a routine adjunctive treatment in adults with CAP.

In summary, several previous studies pointed out that treatment with low dose of corticosteroids was able to reduce the inflammatory responses, and improve the prognosis in critically ill adult patients with CAP. The clinical results were, however, conflicting, which may be derived from the different study populations, (pre)-hospital distinct antibiotic treatment, the diverse severity of the disease process, and delay in diagnosis and treatment.[40]

In this study, we applied modified SIRS criteria for pediatric clinical trials with age-specific normal vital signs and laboratory parameters. The major novelty in this definition was an obligatory requirement for abnormality of temperature or leukocyte count for a diagnosis of SIRS in a pediatric patient.[27] In our randomized cohort, the age-specific vital signs and laboratory variables were analyzed and evaluated regarding the two different regimens. Elevated day-time and midnight cortisol levels were detected in our both groups that indicated the presence of severe infection and stress condition on admission. Others formerly also found that high cortisol levels were frequent in patients with severe infections.[36,41] Although increased cortisol levels were present, adjunctive methylprednisolone as an anti-inflammatory agent was given to patients in the combined therapy group, and we found that this medication was more effective compared to the imipenem alone in severe CAP. However, a relative adrenal insufficiency may also occur in patients with severe CAP and septic shock.[42] This finding also highlights the importance of corticosteroid administration as an additional indication in severe CAP.

There are some limitations of our study. This open-label and unblinded trial comprised a relatively small number of patients. However, this study had an 80% statistical power to demonstrate significant difference between the two groups with distinct therapies. This 5-day methylprednisolone therapy was considered as a short-term medication, so there was no need to assess number needed to harm analysis, which was approved by our present data. Thus, we conclude that the use of methylprednisolone along with imipenem treatment had a superior effect than that of antibiotic alone in children with severe CAP. The number of complications and the ratio of interventions were significantly lower in patients on combined therapy compared to placebo group even in this relatively small cohort.

In conclusion, our study revealed that methylprednisolone as an adjunctive therapy to imipenem produced a positive impact on severe CAP in children. In contrast to the former findings in adults, an early, low-dose, and short-term systemic corticosteroid regimen may improve the outcomes in children. However, further randomized pediatric trials with larger number of participants need to be performed for comprehensive analyses on the effects of corticosteroid.

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