Adjunctive Systemic Corticosteroids for Hospitalized Community-Acquired Pneumonia: Systematic Review and Meta-Analysis 2015 Update

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Previous randomized controlled trials (RCTs) and meta-analyses evaluated the efficacy and safety of adjunctive corticosteroids for community-acquired pneumonia (CAP). However, the results from them had large discrepancies. The eligibility criteria for the current meta-analysis were original RCTs written in English as a full article that evaluated adjunctive systemic corticosteroids adding on antibiotic therapy targeting typical and/or atypical pathogen for treating hospitalized human CAP cases. Four investigators independently searched for eligible articles through PubMed, Embase, and Cochrane databases. Random model was used. The heterogeneity among original studies and subgroups was evaluated with the I² statistics. Of 54 articles that met the preliminary criteria, we found 10 eligible RCTs comprising 1780 cases. Our analyses revealed following pooled values by corticosteroids. OR for all-cause death: 0.80 (95% confidence interval (95% CI) 0.53–1.21) from all studies; 0.41 (95% CI 0.19–0.90) from severe-case subgroup; 0.21 (95% CI 0.0–0.74) from intensive care unit (ICU) subgroup. Length of ICU stay: −1.30 days (95% CI (−3.04)–(−0.44)). Length of hospital stay: −0.98 days (95% CI (−1.26)–(−0.71)). Length to clinical stability: −1.16 days (95% CI (−1.73)–(−0.58)). Serious complications do not seem to largely increase by steroids. In conclusion, adjunctive systemic corticosteroids for hospitalized patients with CAP seems preferred strategies.

Respiratory infection including pneumonia is the third-leading cause of death worldwide¹–³. A majority of patients with pneumonia presents with community-acquired pneumonia (CAP). Despite recent advances in diagnostic methods and antibiotic treatment, the overall mortality rate of CAP remains approximately

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Although it had been considered that corticosteroids may exacerbate the control of infectious disease, the recent consensus is that adjunctive corticosteroids added to antibiotic treatment is a reasonable strategy when treating patients with critical infectious diseases namely bacterial meningitis, sepsis and septic shock. The therapeutic efficacy of corticosteroids may be based on down regulation of excessive inflammation via controlling cytokines. Similarly, corticosteroids attenuate the action of many cytokines involved in the inflammatory response associated with CAP. Thus, the use of adjunctive corticosteroids is an appealing option for CAP treatment and has been evaluated in many randomized controlled trials (RCTs) for decades. However, the results from previously reported RCTs that evaluated the impact of systemic corticosteroids for CAP had large discrepancies with each other. In addition, meta-analyses of these RCTs did not reach complete agreement. Furthermore, a middle-scale and a large scale RCTs published in 2015 were not included in these published meta-analysis. Moreover, some recent studies were focused on the time to clinical stability, however, none of the previous meta-analyses evaluated the time to clinical stability. Therefore, we believe an updated meta-analysis is required. The aim of this study was to evaluate the efficacy and safety of adjunctive corticosteroids for patients with CAP.

Methods
Study search. Institutional review board approval and patient consent were not required because of the review nature of this study.

Four investigators independently searched for eligible articles as of March 2015 through PubMed, Embase, and Cochrane databases. One reviewer used the following search formula for PubMed: “(community acquired pneumonia) AND (RCT OR randomized) AND (steroid OR corticosteroid OR cortisol OR methylprednisolone OR prednisolone OR dexamethasone OR hydrocortisone)”.

The eligibility criteria for the current meta-analysis were original RCTs written in English as a full article that evaluated adjunctive systemic corticosteroids adding on antibiotic therapy targeting typical and/or atypical pathogen for treating hospitalized human CAP cases. Any types, any doses, and any durations of systemic corticosteroids were allowed. Articles focusing on an immunocompromised host, inhaled corticosteroid, nosocomial pneumonia, child cases, or specified pathogens were excluded. Included articles had to evaluate at least one of the outcomes mentioned below.

Outcomes. Mortality that can be expressed as an odds ratio (OR) was evaluated. If two or more types of mortality were described, the mortality of longer duration was selected. For example, 90-day mortality was preferred followed by 30-day, in-hospital, intensive care unit (ICU) mortality, in that order.
Length of ICU stay, length of hospital stay, and length to clinical stability in the form of a hazard ratio (HR) or mean difference were also meta-analyzed.

**Statistics.** If both an intention-to-treat analysis and per-protocol analysis were conducted, we adopted the result from the intention-to-treat analysis. Throughout the meta-analyses random model, not fixed model, was used. If necessary, mean and standard deviation (SD) of length of ICU stay, length of hospital stay, and length to clinical stability were estimated from median, range, or interquartile range of them. The heterogeneity among original studies and subgroups was evaluated with the I^2 statistics whereby I^2 = 0% indicates no heterogeneity, 0% < I^2 < 25% indicates the least heterogeneity, 25% ≤ I^2 < 50% indicates mild heterogeneity, 50% ≤ I^2 < 75% indicates moderate heterogeneity, and 75% ≤ I^2 indicates strong heterogeneity.

**Results**

**Study search.** Of 54 articles that met the preliminary criteria, we found 10 eligible RCTs (Fig. 1). These 10 RCTs include four single-facility trials and six multiple-facility trials. Concerning blinding, seven were blinded for both physicians and patients, one was blinded for only patients, and two were not blinded. Prednisolone (PSL), hydrocortisone (HC), methylprednisolone (mPSL), and dexamethasone (DEX) were administered for four, three, two, and one trial, respectively. One study used HC bolus only, while the others administered corticosteroids for three to nine days. The numbers of cases included in each study ranged from 30 to 785 with a median of 100. The average ages of patients in each study were early 60s for seven studies. In each study, 48–73% of cases were men (Table 2). Each study had a low or unclear risk of bias (Table 3).

**Mortality.** All included studies, except for one reported mortality. A report from Mikami did not report data concerning mortality. Moreover, no response to our e-mail inquiry was obtained from the author. Thus, data concerning mortality in this report was derived from a systematic review by Salluh et al.

<table>
<thead>
<tr>
<th>Study</th>
<th>Origin of report</th>
<th>Blinding</th>
<th>Facility</th>
<th>Age criteria</th>
<th>Severity criteria</th>
<th>Steroid regimen</th>
<th>Antibiotics</th>
<th>Number of patients</th>
<th>Average age</th>
<th>Men%</th>
</tr>
</thead>
<tbody>
<tr>
<td>McHardy 1972</td>
<td>Australia</td>
<td>Not-blinded</td>
<td>Single</td>
<td>12-</td>
<td>not at risk of dying within 24 hour</td>
<td>PSL 20 mg/day for 7 d</td>
<td>Ampicillin 1 or 2 g/day</td>
<td>40 + 86 = 126</td>
<td>61</td>
<td>48%</td>
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<tr>
<td>Marik 1993</td>
<td>USA South Africa</td>
<td>Single-blinded</td>
<td>Multi</td>
<td>18–70</td>
<td>ICU, BTS criteria severe</td>
<td>HC 10 mg/kg bolus</td>
<td>Cefotaxime based regimen</td>
<td>14 + 16 = 30</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
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<td>Italy</td>
<td>Double-blinded</td>
<td>Multi</td>
<td>not specified</td>
<td>ICU, ATS criteria severe</td>
<td>HC 200 mg bolus + 240 mg/day for 7 d</td>
<td>Based on guidelines</td>
<td>23 + 23 = 46</td>
<td>64</td>
<td>70%</td>
</tr>
<tr>
<td>Mikami 2007</td>
<td>Japan</td>
<td>Not-blinded</td>
<td>Single</td>
<td>adult</td>
<td>Moderate to severe. Not ventilated at admission</td>
<td>PSL 40 mg/day for 3 d</td>
<td>Amoxicillin and Moxifloxacin were preferred</td>
<td>15 + 16 = 31</td>
<td>72</td>
<td>74%</td>
</tr>
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<td>Netherlands</td>
<td>Double-blinded</td>
<td>Single</td>
<td>18-</td>
<td>NS</td>
<td>PSL 40 mg/day for 7 d</td>
<td>Amoxicillin and Moxifloxacin were preferred</td>
<td>104 + 109 = 213</td>
<td>64</td>
<td>58%</td>
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<td>Fernandez-Serrano 2011</td>
<td>Spain</td>
<td>Double-blinded</td>
<td>Single</td>
<td>18–75</td>
<td>P/F ratio &lt; 300, Not ventilated at admission</td>
<td>mPSL 200 mg bolus + 80 mg/day for 3 days + 40 mg/day for 3 days + 20 mg/ady for 3 days.</td>
<td>Ceftriaxone + Levofloxacin</td>
<td>22 + 23 = 45</td>
<td>64</td>
<td>67%</td>
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<td>Multi</td>
<td>18-</td>
<td>Non-ICU</td>
<td>DEX 5 mg/day for 4 d</td>
<td>Amoxicillin/Clavulanate and Cephalosporin were preferred</td>
<td>151 + 153 = 304</td>
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<td>56%</td>
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<td>Sabry 2011</td>
<td>Egypt</td>
<td>Double-blinded</td>
<td>Multi</td>
<td>adult</td>
<td>ICU Ventilated</td>
<td>HC 200 mg bolus + 300 mg/day for 7 d</td>
<td>NS</td>
<td>40 + 40 = 80</td>
<td>62</td>
<td>73%</td>
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<tr>
<td>Blum 2015</td>
<td>Switzerland</td>
<td>Double-blinded</td>
<td>Multi</td>
<td>18-</td>
<td>NS</td>
<td>PSL 50 mg/day for 7 d</td>
<td>Based on guidelines</td>
<td>392 + 393 = 785</td>
<td>73</td>
<td>62%</td>
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<tr>
<td>Torres 2015</td>
<td>Spain</td>
<td>Double-blinded</td>
<td>Multi</td>
<td>18-</td>
<td>“ATS criteria severe” or “Pneumonia severity index = V and CRP &gt; 150 mg/L”</td>
<td>mPSL 1 mg/kg/ day for 5 d</td>
<td>Ceftriaxone + Levofloxacin or + Azithromycin were preferred</td>
<td>61 + 59 = 120</td>
<td>65</td>
<td>62%</td>
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Pooled OR for all-cause death by adjunctive corticosteroids estimated from the results of 10 RCTs was 0.80 (95% confidence interval (95% CI) 0.53–1.21, P = 0.29. I² = 0%, P for heterogeneity = 0.46) (Fig. 2A).

Because previous meta-analyses suggested that systemic corticosteroids improve the mortality only for severe CAP17,20,21, we performed a subgroup sensitive analysis dividing studies into those with severe case only and those not limited to severe cases. Previous meta-analyses used different criteria of “severe pneumonia”17,20,21. Here, we selected studies that clearly indicated “severe CAP” in the title and/or abstract and studies limited to ICU cases. We observed a strong subgroup difference between the results from five trials not limited to severe cases and those from five trials limited to severe cases (I² = 73.5%, P for subgroup heterogeneity = 0.05) (Fig. 2A). Five RCTs limited to severe cases yielded a pooled OR of 0.41 (95% CI 0.19–0.90, P = 0.03. I² = 0%, P for heterogeneity = 0.45) (Fig. 2A). In addition, we conducted another subgroup analysis dividing studies into those limited to ICU cases and those not limited to ICU cases. Again, we observed a strong subgroup difference (I² = 79.7%, P for subgroup heterogeneity = 0.03). Three RCTs limited to ICU cases yielded a pooled OR of 0.21 (95% CI 0.06–0.74, P = 0.01. I² = 0%, P for heterogeneity = 0.43) (Fig. 2B).

Since Nie et al. reported that CS > 6 d was more beneficial than CS ≤ 5 d20, we performed a sensitivity analysis. However, we could not find a significant subgroup OR difference between prolonged and short corticosteroids treatment for all-cause mortality. (I² = 0%, P for subgroup heterogeneity = 0.99) (Fig. 2C).

Using data from the five trials limited to severe cases, the pooled risk difference for mortality was -0.10 (95% CI -0.21–(-0.00), P = 0.04). This pooled difference of -0.10 was equivalent to a number needed to treat of 10 (Fig. 2D).

Length of ICU stay. A random-model meta-analysis using data from five RCTs indicated that length of ICU stay slightly favored the steroid arm but was not significantly different between the two arms with...
<table>
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<th>Study Author, year</th>
<th>Randomization Method</th>
<th>Allocation Concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
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<td>Low</td>
<td>High(g)</td>
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Table 3. Risk of bias. (a) Not centralized randomization. (b) Open-label study. (c) Open-label or single-blinded study. (d) 20% of cases were excluded after randomization and per-protocol analysis was conducted. (e) Mortality was not reported. (f) Considering relatively small sample size ($n < 50$), possible publication bias could not be denied. (g) Insufficient description of methods and results.

Figure 2. Forrest plots. OR: odds ratio. HR: hazard ratio. 95% CI: 95% confidence interval. M-H: Mantel-Haenszel. ICU: intensive care unit.
a mean difference of $-1.30$ days ($95\% CI (-3.04) -0.44$, $P = 0.14$. $I^2 = 25\%$, $P$ for heterogeneity = 0.26) (Fig. 2E).

No study reported HR for length of ICU stay.

Length of hospital stay. Seven studies reported difference of length of hospital stay in days. Based on these data, the length of hospital stay was shorter in the steroid arm with a pooled mean difference of $-0.98$ ($95\% CI (-1.26) -(-0.71)$, $P < 0.001$. $I^2 = 4\%$, $P$ for heterogeneity = 0.39). We performed a sensitivity analysis comparing the result from a study by Blum et al. and those from the others because the study by Blum et al. had very large weight of 86.8%. However, there was no significant subgroup heterogeneity between them ($I^2 = 0\%$, $P$ for subgroup heterogeneity = 0.85) (Fig. 2F).

When evaluated using HR for hospital discharge, the length in hospital stay was also shorter in the steroid arm with a pooled HR of 1.23 ($95\% CI 1.07 -1.41$, $P = 0.003$. $I^2 = 14\%$, $P$ for heterogeneity = 0.32) (Fig. 2G).

Length to clinical stability. Length to clinical stability was evaluated in three recent studies. They yielded pooled difference of $-1.16$ days ($95\% CI (-1.73) -(-0.58)$, $P < 0.001$. $I^2 = 43\%$, $P$ for heterogeneity = 0.17) (Fig. 2H).

The same three studies yielded a pooled HR of 1.29 ($95\% CI 1.14 -1.45$, $P < 0.001$. $I^2 = 0\%$, $P$ for heterogeneity = 0.55) (Fig. 2I).

Adverse effects. In this systematic review, we noticed that some reports described adverse effects. However, these data were not suitable for qualitative meta-analysis due to discrepancy of descriptive method. Confalonieri et al. reported that major complication (steroid: 6/23 vs. placebo 18/23, $P < 0.001$) and delayed septic shock (steroid: 0/23 vs. placebo: 10/23, $P < 0.001$) were less frequently observed in the steroid arm. Mikami et al. reported no significant difference in deterioration of glucose intolerance, electrolyte abnormalities, nor other adverse effects was observed. Snijders et al. revealed that the overall adverse effect was not different in two arms (steroid: 63/104 vs. placebo: 72/109, $P = 0.41$). Meijvis et al. reported that hyperglycemia was more common in the steroid arm (steroid: 67/151 vs. placebo: 35/153, $P < 0.001$) but that the requirement for glucose-lowering treatment and superinfection were not significantly different between arms. Blum et al. wrote that overall adverse events were frequently observed in the steroid arm (steroid: 96/392 vs. placebo: 61/393, $P < 0.001$), and the difference was mainly attributed to the increase of hyperglycemia requiring new insulin (steroid: 76/392 vs. placebo: 43/393, $P = 0.001$). Torres et al. compared the incidence of six adverse effects including hyperglycemia but none differed significantly.

In general, although patients in the steroid arm might have a higher risk for overall adverse events and hyperglycemia, serious complications do not seem to largely increase due to use of systemic steroids.

Discussion
This updated systematic review and meta-analysis had the largest sample size ever (Table 1). The key findings from this analysis are as follows: (i) corticosteroids shortens length of hospital stay for CAP; (ii) corticosteroids shortens length to clinical stability for CAP; and (iii) corticosteroids lowers mortality for severe CAP. Additionally, we revealed that the incidence of major complications was not greatly increased by systemic steroids, though quantitative synthesis was not feasible.

Inflammation is part of the complex biological response to harmful stimuli such as pathogens and damaged cells. This response is essential to control CAP. However, fulminant inflammation often results in organ failure. The rationale of using adjunctive systemic corticosteroids for CAP is to down-regulate excessive inflammation. Corticosteroids are very potent and by far the most frequently used type of immunosuppressant. The mechanism of corticosteroids is not fully clear; however, it is believed that corticosteroids switch off genes that encode pro-inflammatory cytokines and switch on genes that encode anti-inflammatory cytokines. Based on our analysis, corticosteroids decreased mortality for severe/ICU CAP only. In this subgroup, merit of controlling systemic inflammation may overweight demerit of deteriorating innate body antibacterial action due to immunosuppressant.

Except for the OR for death, frequently used outcomes that we also evaluated in this study need be interpreted carefully. The length of hospital stay and ICU stay are often affected by non-pharmacological reasons, such as availability of ICU and non-ICU beds in a hospital. In this view, the time to clinical stability can evaluate more physiological aspects of a patient. However, some items included in the definition of clinical stability are known to be relieved by the administration of the systemic corticosteroids. The rationale of using corticosteroids for CAP only. We performed a sensitivity analysis comparing the result from a study by Blum et al. and those from the others because the study by Blum et al. had very large weight of 86.8%. However, there was no significant subgroup heterogeneity between them ($I^2 = 0\%$, $P$ for subgroup heterogeneity = 0.85) (Fig. 2F).

When evaluated using HR for hospital discharge, the length in hospital stay was also shorter in the steroid arm with a pooled HR of 1.23 ($95\% CI 1.07 -1.41$, $P = 0.003$. $I^2 = 14\%$, $P$ for heterogeneity = 0.32) (Fig. 2G).

Length to clinical stability. Length to clinical stability was evaluated in three recent studies. They yielded pooled difference of $-1.16$ days ($95\% CI (-1.73) -(-0.58)$, $P < 0.001$. $I^2 = 43\%$, $P$ for heterogeneity = 0.17) (Fig. 2H).

The same three studies yielded a pooled HR of 1.29 ($95\% CI 1.14 -1.45$, $P < 0.001$. $I^2 = 0\%$, $P$ for heterogeneity = 0.55) (Fig. 2I).

Adverse effects. In this systematic review, we noticed that some reports described adverse effects. However, these data were not suitable for qualitative meta-analysis due to discrepancy of descriptive method. Confalonieri et al. reported that major complication (steroid: 6/23 vs. placebo 18/23, $P < 0.001$) and delayed septic shock (steroid: 0/23 vs. placebo: 10/23, $P < 0.001$) were less frequently observed in the steroid arm. Mikami et al. reported no significant difference in deterioration of glucose intolerance, electrolyte abnormalities, nor other adverse effects was observed. Snijders et al. revealed that the overall adverse effect was not different in two arms (steroid: 63/104 vs. placebo: 72/109, $P = 0.41$). Meijvis et al. reported that hyperglycemia was more common in the steroid arm (steroid: 67/151 vs. placebo: 35/153, $P < 0.001$) but that the requirement for glucose-lowering treatment and superinfection were not significantly different between arms. Blum et al. wrote that overall adverse events were frequently observed in the steroid arm (steroid: 96/392 vs. placebo: 61/393, $P < 0.001$), and the difference was mainly attributed to the increase of hyperglycemia requiring new insulin (steroid: 76/392 vs. placebo: 43/393, $P = 0.001$). Torres et al. compared the incidence of six adverse effects including hyperglycemia but none differed significantly.

In general, although patients in the steroid arm might have a higher risk for overall adverse events and hyperglycemia, serious complications do not seem to largely increase due to use of systemic steroids.
a 5–7 days treatment course seems reasonable for now. The best dosage of corticosteroids is also unclear. Most studies used HC 200–300 mg/day, PSL/mPSL 20–50 mg/day, or mPSL 1mg/kg/day (Table 2). Thus, a so-called low- or middle-dose of corticosteroids seems an acceptable choice in practice. Corticosteroids in these doses are also chosen for treatment of other common form of critical systemic inflammatory disease such as acute exacerbation of chronic obstructive pulmonary disease27, acute respiratory distress syndrome28, and septic shock29.

Some studies that were not included in this study have also revealed the efficacy of systematic corticosteroids for CAP. García-Vidal et al. conducted a retrospective study with 308 severe CAP patients, which concluded that risk of death was reduced with adjusted OR of 0.28730. A cohort study in 2013 by Nagy et al. reported that the 5-day methylprednisolone therapy with imipenem was found to be effective in children with severe CAP31. Adjunctive systemic corticosteroids may be effective for CAP patients of any age.

Limitations of this study should be mentioned. First, we could not meta-analyze the data for adverse effects. Second, although four studies that evaluated the length of ICU stay constantly indicated the tendency of a steroid-favored outcome, these results did not reach statistical significance probably due to lack of power. Third, we could not infer the impact of corticosteroids for outpatients with CAP. Forth, the best corticosteroids regimen could not be clarified. Lastly, our analysis could not directly explain why the adjunctive corticosteroids have different impact for mild and severe CAP.

In conclusion, although further RCTs focusing on severe CAP are anticipated, adjunctive systemic corticosteroids for hospitalized patients with CAP seem preferred strategies because this treatment shortens the length of hospital stay and the length to clinical stability without increasing severe adverse effect. In addition, adjunctive systemic corticosteroids lowers the mortality of severe CAP cases. Prolonged use of corticosteroids (>5 days) was more effective than a short course of corticosteroids (<5 days). The best corticosteroids regimen is not clear, however, a middle dose of corticosteroids, for example PSL/mPSL 40 mg/day to 1 mg/kg/day for 5–7 days seems a reasonable choice.

References

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Author Contributions
H.N. served for analysis and drafting. H.N., O.T., S.H. and H.N. worked for study search. M.M., N.M., F.H., H.T. and T.K. served for analysis and interpretation of data. Y.M. is a statistical advisor. K.S. managed this study as the Chair of Japanese Respiratory Society Practical Guideline for Pneumonia. All authors critically revised the manuscript and finally approved the manuscript.

Additional Information
Competing financial interests: The authors declare no competing financial interests.


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