TAKE-HOME MESSAGE

For adult patients with severe community-acquired pneumonia, corticosteroids reduce morbidity and mortality. For pediatric patients and adults with nonsevere community-acquired pneumonia, corticosteroids appear to reduce morbidity, but not mortality.

Are Corticosteroids Beneficial in the Treatment of Community-Acquired Pneumonia?

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METHODS

DATA SOURCES

The authors searched the Cochrane Acute Infections Group's Specialized Register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and Latin American and Caribbean Health Sciences Literature from inception through March 2017 for eligible studies, without language or publication restrictions. The reference lists of all included studies and previous systematic reviews were searched manually. In addition, the authors searched conference proceedings of major infectious disease and intensive care meetings, as well as multiple ongoing trial registries.

STUDY SELECTION

Eligible studies included adults or children with radiographically-confirmed community-acquired pneumonia, health care–associated pneumonia, hospital-acquired pneumonia, and ventilator-associated pneumonia who were randomly assigned to corticosteroids versus either placebo or no treatment. Studies of neonates, *Pneumocystis jiroveci* pneumonia, and patients with HIV were excluded. There were no limitations on the dose, route, or duration of corticosteroid use. Eligible studies reported on at least one of the following outcomes: all-cause mortality, early clinical failure

Results

Comparison of corticosteroids with control for community-acquired pneumonia.

Outcome	No. of Studies (No. of Participants)	Relative Risk (95% CI)	I^2, %
Mortality (adults with severe CAP)	9 (995)	0.58 (0.40–0.84)	12
Mortality (adults with nonsevere CAP)	4 (868)	0.95 (0.45–2.00)	0
Early clinical failure (adults with severe CAP)	5 (419)	0.32 (0.15–0.70)	74
Early clinical failure (adults with nonsevere CAP)	2 (905)	0.68 (0.56–0.83)	0
Early clinical failure (children)	2 (88)	0.41 (0.24–0.70)	25
Hyperglycemia	7 (1,578)	1.72 (1.38–2.14)	21

CI, Confidence interval; *CAP*, community-acquired pneumonia.

The search strategy initially yielded 4,273 potential studies. After review, 17 randomized controlled trials containing 2,264 patients were included in the meta-analysis. Thirteen randomized controlled trials (1,954 participants) studied adult participants and 4 (310 participants) investigated pediatric populations. Of the 4 pediatric studies, 2 trials investigated children with solely *Mycoplasma pneumoniae*, 1 trial included any cause of pneumonia, and 1 trial included children with respiratory syncytial virus. The 17 included studies had variable routes of administration, classes of corticosteroid, and durations of treatment. Thirteen trials used intravenous dexamethasone, hydrocortisone, or methylprednisolone, whereas 3 trials used oral prednisone, and 1 trial did not put limits on oral versus intravenous routes. The average duration of treatment was 7 days. Seven trials used a duration of 7 days, 2 used 7 to 10 days, 3 used 5 days, and 4 used 2 to 4 days. Most adult studies used a corticosteroid dose equivalent to 40 to 50 mg of prednisone per day.

Corticosteroids were found to decrease mortality in adults with severe community-acquired pneumonia (defined as a Pneumonia Severity Index score $\geq$4), but not in patients with nonsevere

(defined as death from any cause, radiographic progression, or clinical instability within 5 to 7 days), time to clinical cure, development of respiratory failure (defined as the need for invasive or noninvasive mechanical ventilation), development of shock, transfer to the ICU, duration of hospital stay, duration of ICU stay, pneumonia complications (defined by the individual study), secondary infections greater than or equal to 72 hours postrandomization, and adverse events. Two authors independently reviewed studies for inclusion, with disagreements resolved by consensus with the addition of a third reviewer if needed.

DATA EXTRACTION AND SYNTHESIS

Two authors independently abstracted data from the individual studies, with disagreements resolved by discussion and, as necessary, in consultation with a third reviewer. Risk ratios were calculated for dichotomous data and mean differences for continuous data. Bias was assessed with the Cochrane Risk of Bias tool and overall quality of evidence was assessed with the Grading of Recommendations Assessment, Development and Evaluation tool. All differences were resolved through discussion between the 2 reviewers. Heterogeneity was assessed with the I^2 statistic.

community-acquired pneumonia (Table). The use of corticosteroids was also found to cause a reduction in early clinical failures, time to clinical cure, length of overall hospital stay, total ICU days, development of respiratory failure or shock, and rates of pneumonia complications in adults. Among children, corticosteroids were shown to reduce clinical failure and time to clinical cure in bacterial pneumonia, with no difference in mortality rates. However, this was based on limited data from 2 small studies. Corticosteroids were not associated with an overall difference in adverse events or secondary infection. However, hyperglycemia was more common in adults given corticosteroids. Overall, selection bias and attrition bias were assessed to be low or unclear, whereas performance bias was judged to be low for 9 trials, high for 7 trials, and unclear for 1 trial. Reporting bias was assessed as high for 14 trials and low for 3 trials.

Commentary

Lower respiratory tract infections remain the third most common cause of death worldwide.[1] In 2013, pneumonia was the sixth leading cause of death among persons aged 65 years or older in the United States, and the most common cause of death from an infectious disease.[2] Additionally, the treatment of pneumonia in the United States costs in excess of $10 billion per year.[3] Therefore, there is great interest in providing improved treatments for the reduction of morbidity, mortality, and costs in the management of pneumonia. Corticosteroids have been suggested as one adjunct based on previous beneficial outcomes in other infectious processes, including meningitis, pneumocystis pneumonia, and tuberculosis.[4] Cytokine release and the resulting immune response are needed in a host's defense against an infection. However, an excess release of cytokines can be harmful, leading to increased lung inflammation, sepsis, and acute respiratory distress syndrome.[5] One proposed mechanism for the beneficial role of corticosteroids is reduction in cytokine release, thereby decreasing local inflammation at the site of infection.[6] Another possible role of corticosteroids is in mitigating a Jarisch-Herxheimer–like reaction (described as a heightened immune response to high cytokine burden shortly after initiation of antibiotics), which is thought to be similar to its role in meningococcal meningitis.[7]

This is an update to a previous review from 2016 that found a decrease in the need for mechanical ventilation, progression to acute respiratory distress syndrome, and total length of hospital stay for patients treated with corticosteroids.[8] The previous review, however, did not demonstrate a significant difference in mortality rates or admission to the ICU, which was likely a result of a low adverse event rate. The current meta-analysis included 12 new randomized controlled trials (4 of which were studies examining corticosteroid use in children) and excluded 1 previously included study (excluded because of use of inhaled corticosteroids). This meta-analysis showed reductions in mortality, clinical failure, complication rates, length of hospitalization, total ICU stay, and time to clinical cure, which was most pronounced in patients with severe community-acquired pneumonia. It also showed reduced rates of early clinical failure among patients with nonsevere community-acquired pneumonia; however, it did not demonstrate a

difference in mortality in this subgroup.

The current systemic review has several limitations that must be considered in light of the above findings. First, the studies included in the meta-analysis varied in the doses, days of total treatment, and type of corticosteroid administered. Future studies should compare the effect between different types, doses, and treatment durations of corticosteroids. Although statistical heterogeneity was relatively low, there was a moderate amount of clinical heterogeneity between the populations. Additionally, this review included patients with a variety of medical conditions (eg, chronic obstructive pulmonary disease, diabetes), who may respond differently than patients without these comorbidities. Moreover, many of the outcomes were limited by small sample sizes, with one study comprising nearly half of all of the included patients.[9] Finally, the sample sizes in the pediatric studies were very small, limiting the conclusions that can be drawn from those data.

In summary, the current data suggest that corticosteroids reduce morbidity and mortality in severe community-acquired pneumonia. Corticosteroids were also shown to be beneficial in patients with nonsevere community-acquired pneumonia who were admitted to the hospital. The administration of corticosteroids was associated with an increased rate of hyperglycemia, without a difference in other adverse events.

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Stern A, Skalsky K, Avni T, et al. Corticosteroids for pneumonia. *Cochrane Database Syst Rev.* 2017;12:CD007720.**

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