Otitis media with effusion (OME), or “glue ear,” is characterized by an accumulation of fluid in the middle ear in the absence of acute inflammation. Otitis media with effusion is the most common cause of acquired hearing loss (HL) in childhood and may negatively affect language development. The reason why the condition develops is uncertain, but a low-grade infection, poor eustachian tube function, and adenoidal infection or hypertrophy have all been implicated. Otitis media with effusion has a prevalence of about 20% at around the age of 2 years, with another peak at the age of 6 years, and often resolves spontaneously. The prevalence of recurrent otitis media may be increasing. The total annual cost of treating children younger than 5 years for OME is more than $5 billion annually in the United States. The insertion of ventilation tubes is the second most common surgical procedure performed on children in the United States. In England and Wales, expenditure by the National Health Service on surgical treatment for OME is around $47.8 million. Otitis media with effusion is a common reason for prescribing antibiotics, which contributes to the growing problem of bacterial resistance. The optimal treatment strategy remains controversial, and there is wide international variability in clinical practice.

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There is in vitro and animal model evidence that steroids modulate effusions. It is hypothesized that steroids could clear effusions by (a) stabilizing...
membrane phospholipid breakdown and, thus, preventing the formation of arachidonic acid and associated inflammatory mediators; (b) shrinking peritubal lymphoid tissue; (c) enhancing secretion of eustachian tube surfactant; and (d) reducing middle ear fluid viscosity. Topical intranasal steroids may be safer than systemic preparations because the glucocorticoid is rapidly degraded in the nasal mucosa to less active metabolites and any unchanged drug that is absorbed is metabolized in the first pass through the liver. Systemic adverse effects are, therefore, less likely, while the desired anti-inflammatory effects may be similar. However, systemic steroids may be able to gain access to the middle ear, while topical nasal steroids would not be expected to reach the middle ear but may modulate eustachian tube function. Clinicians may be concerned about using systemic steroids for what may be a self-limiting condition.

This review determines the beneficial and harmful effects of treatment with steroids (systemic and intranasal) for children with OME. Our a priori hypothesis was that steroids (systemic or intranasal), either alone or in combination with another agent, are effective in treating the HL associated with OME and in resolving effusions in children. A more detailed review is published in the Cochrane Review on CD-ROM.

CRITERIA FOR CONSIDERING STUDIES

Types of Studies

Randomized controlled trials of oral and intranasal steroids were included. Randomized studies that used non-intervention controls were included, in which blinding of outcome assessment was adequate. Excluded were publications in abstract form, only because adequate appraisal was not possible; uncontrolled nonrandomized or retrospective studies; and studies reporting outcomes only with ears (rather than children) as the unit of analysis. Because observations made on the ears of a single child cannot be regarded as independent and carryover effects of treatments on patients in treatment periods of these studies cannot be considered independent and carryover effects of treatment periods are likely. Similarly, in multiarm studies on patients in treatment periods of these studies cannot be regarded as independent.

Types of Participants

The focus was on studies of children up to the age of 12 years diagnosed as having unilateral or bilateral OME and who had significant HL, however defined. We report when older subjects were included.

The studies were divided into subgroups according to the following ways of assessing exposure:

1. The diagnosis of OME was defined by (a) an airbone gap of 10 dB or more, (b) 2 or more of otomicroscopy readings with or without pneumatic otoscopy readings or tympanometry readings, (c) one of an otoscopy reading or a tympanometry reading alone, or (d) poorly or not defined.

2. Significant HL was (a) defined by pure tone audiometric HL of more than 20 dB at 2 or more times within 3 months; (b) defined, but less strict than a; or (c) uncertain or not defined.

Types of Interventions

The intervention was systemic or intranasal steroids compared with control (placebo or nonintervention control). Additional treatments, such as antibiotics, were included as long as they were identical in the treatment and the control groups.

Types of Outcome Measures

We examined studies for data on the effect of steroid treatment over time or at multiple points for (1) differences in hearing level, (2) degree of conductive HL, (3) presence or absence of fluid in the middle ear cavity (short- and longer-term), and (4) possible adverse effects.

We also examined studies for the effect of steroid treatment on secondary development outcomes, such as language development and behavior.

DATA SOURCES

We searched the Cochrane Controlled Trials Register in February 2000 using the following search strategies: (1) otitis media (MEDLINE Medical Subject Heading [MeSH] term, including all subheadings); (2) otitis media with effusion (MeSH term, including all subheadings); (3) glue ear (free-text term); (4) OME (free-text term); (5) (1), (2), (3), or (4); (6) steroids (MeSH term, including all subheadings); (7) glucocorticoids (MeSH term, including all subheadings); (8) glucocorticoids, synthetic (MeSH term, including all subheadings); (9) glucocorticoids, topical (MeSH term, including all subheadings); (10) anti-inflammatory agents, steroid (MeSH term, including all subheadings); (11) (6), (7), (8), (9), or (10); or (12) (5) and (11).

Additional information was identified by searching MEDLINE and EMBASE, using a similar search strategy. We also wrote to experts asking about knowledge of additional studies. Previous systematic reviews and references of trials identified by the search strategy were checked for additional relevant references. There was no language restriction. Searches were carried out by the 2 of us (C.C.B. and J.H.v.d.V.) independently. The full texts of all studies loosely meeting the inclusion criteria were independently assessed by us, and differences of opinion regarding inclusion were resolved by consensus.

DATA EXTRACTION

Data concerning methods, participants, interventions, and outcomes were extracted from the published reports by the 2 of us (C.C.B. and J.H.v.d.V.) independently, using standardized data extraction forms. Disagreement was resolved by consensus after returning to the original publication. In studies that provided data for various definitions of cure, data for the strictest definition were used. In trials with a crossover design, data from the postcrossover treatment period were not used because observations on patients in treatment periods of these studies cannot be regarded independent and carryover effects of treatment periods are likely. Similarly, in multiarm stud-
ies (eg, steroid vs antibiotic vs nonsteroidal anti-inflammatory vs control), only data for the steroid-treated and control groups were used.

The methodological quality of the included studies was independently assessed by the 2 of us (C.C.B. and J.H.v.d.V.) using the scheme described in the Cochrane Collaboration Handbook.²⁴ This involved assessing studies for (1) selection bias, (2) performance bias, (3) attrition bias, and (4) detection bias. A 3-point rating scale for overall validity was used, with the grading as follows: (a) low risk of bias—plausible bias is unlikely to alter the results seriously, (b) moderate risk of bias—plausible bias raises some doubt about the results, and (c) high risk of bias—plausible bias seriously weakens confidence in the results.

DATA SYNTHESIS

We used the statistical methods for dichotomous outcomes described by Yusuf and colleagues.²⁵ Results were expressed as an odds ratio for achieving the outcome at a given point together with the 95% confidence intervals for this estimate. Continuous data were analyzed using the weighted mean difference in a fixed-effects model. Tests for heterogeneity between studies were performed using a Mantel-Haenszel approach.

Description of Studies

Regarding ascertainment of the presence of OME, most studies documented effusions by a combination of pneumatic otoscopy and tympanometry (1b). No study documented HL from OME 2 or more times in the 3 months before study enrollment (2a). (Explanations of 1b and 2a are given in the “Types of Participants” subsection of the “Criteria for Considering Studies” section.) Only one study²⁶ required documented HL for all children before study enrollment. One trial²⁷ was open, comparing children treated with steroids with nonintervention controls.

Four included studies²⁶-²⁸ provided audiometric data at follow-up. However, only one²⁶ provided data that could be used in this review (numbers of children improving their HL by at least 10 dB). Audiometric data otherwise used ears as the unit of analysis or were unclear. No study reported effects on language or other aspects of development.

The adverse effects of steroid treatment were reported in 5 studies.¹³,²³,²⁷,³¹,³² In cases in which the same data are apparently published twice,²⁷,³³,³⁵ these data are used only once in this review.

Studies fell into 4 categories (oral steroid vs control, oral steroid plus antibiotic vs control plus antibiotic, intranasal steroid vs control, and intranasal steroid plus antibiotic vs control plus antibiotic or antibiotic alone) (Table 1). The study¹³ of intranasal steroid plus antibiotic vs control plus antibiotic also reported on symptoms in the form of a scale, which was considered as continuous data. This was the only study¹³ to report symptoms as an outcome, but validation of their symptom scale was not described.

Methodological Quality of Included Studies

Of the 10 included studies,¹³,²⁶-²⁸,³¹,³⁴,³⁶ there were 3¹³,²⁶,²⁸ that were rated A for quality. All other studies were rated B, apart from 2²⁷,³⁰ that were rated C for quality (Table 2).

Results

Overall, the number of studies for each comparison was small (Table 1). The number of participants available for each comparison ranged from 15 to 274. For the 4 groups of studies, a total of 10 comparisons were made. This reflects the use of various points and methods to measure outcomes. Three included studies²⁶,²⁷,³⁰ provided data for 108 patients randomized to treatment with oral steroid vs control. The odds ratio for OME persisting after short-term follow-up (≤2 weeks) was 0.22. Four included studies²⁸,²⁹,³¹,³⁴ provided data on a total of 274 patients randomized to treatment with oral steroid plus antibiotic vs control plus antibiotic.

Table 1. Comparison and Results*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>OR/WMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral steroid vs control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution at ≤2 wk²⁶,²⁷,³⁶</td>
<td>3</td>
<td>108</td>
<td>0.22 (0.08 to 0.63)</td>
</tr>
<tr>
<td>Resolution at 1 to 2 mo²⁴,²⁷,³⁶</td>
<td>3</td>
<td>106</td>
<td>0.55 (0.21 to 1.48)</td>
</tr>
<tr>
<td>Hearing gain by at least 10 dB²⁶</td>
<td>1</td>
<td>49</td>
<td>1.47 (0.39 to 5.57)</td>
</tr>
<tr>
<td>Oral steroid plus antibiotic vs control plus antibiotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution at 2 wk²²,²³,³⁴</td>
<td>4</td>
<td>274</td>
<td>0.32 (0.20 to 0.52)</td>
</tr>
<tr>
<td>Resolution at 2 mo²³</td>
<td>1</td>
<td>99</td>
<td>1.03 (0.47 to 2.30)</td>
</tr>
<tr>
<td>Resolution at 6 mo²³</td>
<td>1</td>
<td>15</td>
<td>0.15 (0.00 to 7.80)</td>
</tr>
<tr>
<td>Topical nasal steroid vs control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution at 3 wk²⁵</td>
<td>1</td>
<td>44</td>
<td>2.12 (0.65 to 6.90)</td>
</tr>
<tr>
<td>Resolution at 4 wk¹³</td>
<td>1</td>
<td>59</td>
<td>0.79 (0.20 to 3.19)</td>
</tr>
<tr>
<td>Resolution at 3 mo¹³</td>
<td>1</td>
<td>59</td>
<td>0.72 (0.21 to 2.44)</td>
</tr>
<tr>
<td>Symptom score at 3 mo¹³</td>
<td>1</td>
<td>39</td>
<td>−4.50 (−10.32 to 1.32)</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval; and WMD, weighted mean difference.
The odds ratio for OME persisting after short-term follow-up (≤2 weeks) was 0.32. There was significant heterogeneity between the studies involving steroids plus antibiotics (P<.01). Only one of these studies\textsuperscript{31} reported longer-term outcomes and provided data for only 15 patients. Seven comparisons across the study groups included only one study, so they offer no new information. Overall, 7 comparisons favored steroids, 2 favored controls, and 1 favored neither. However, the confidence intervals were generally wide and included

### Table 2. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Total No.</th>
<th>Age</th>
<th>Comment</th>
<th>Previous Treatment</th>
<th>Diagnosis†</th>
<th>Bilateral Effusions, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berman et al\textsuperscript{28}</td>
<td>Crossover</td>
<td>68</td>
<td>0.5-5.4 y</td>
<td>Those not returning to follow-up were excluded from analysis (9 in the prednisone group and 6 in the placebo group)</td>
<td>Antibiotic</td>
<td>1b and 2b</td>
<td>77</td>
</tr>
<tr>
<td>Giebink and Batalden\textsuperscript{29}</td>
<td>Four parallel groups, open</td>
<td>76</td>
<td>10-95 mo</td>
<td>Four children were excluded from analysis</td>
<td>Antibiotic</td>
<td>1b and 2c</td>
<td>60</td>
</tr>
<tr>
<td>Hemlin et al\textsuperscript{31}</td>
<td>Three parallel groups with random allocation in a ratio of 3:3:1</td>
<td>142</td>
<td>2-12 y</td>
<td>...</td>
<td>...</td>
<td>1b and 2c</td>
<td>84</td>
</tr>
<tr>
<td>Lambert\textsuperscript{29}</td>
<td>Crossover</td>
<td>60</td>
<td>2-15 y</td>
<td>...</td>
<td>...</td>
<td>1a and 2c</td>
<td>72</td>
</tr>
<tr>
<td>Macknin and Jones\textsuperscript{26}</td>
<td>Parallel, randomization to strata based on history (recent acute vs nonacute otitis media) and age</td>
<td>49</td>
<td>6 mo-14 y</td>
<td>...</td>
<td>...</td>
<td>1a and 2b</td>
<td>67</td>
</tr>
<tr>
<td>Niederman and Walter-Bucholtz\textsuperscript{36}</td>
<td>Parallel</td>
<td>26</td>
<td>2-14 y</td>
<td>...</td>
<td>...</td>
<td>1b and 2c</td>
<td>77</td>
</tr>
<tr>
<td>Podoshin et al\textsuperscript{30}</td>
<td>Three parallel groups</td>
<td>150</td>
<td>3-8 y</td>
<td>Children also underwent audiometry at enrollment</td>
<td>...</td>
<td>1b and 2b</td>
<td>...</td>
</tr>
<tr>
<td>Schwartz et al\textsuperscript{34}</td>
<td>Crossover</td>
<td>41</td>
<td>1.2-10 y</td>
<td>Effusions present despite previous treatment</td>
<td>Antimicrobial agents and/or decongestants</td>
<td>1b and 2c</td>
<td>48</td>
</tr>
<tr>
<td>Shapiro et al\textsuperscript{32}</td>
<td>Parallel</td>
<td>45</td>
<td>2-10 y</td>
<td>All had allergic rhinitis that failed to respond to 4 wk of treatment</td>
<td>Oral antihistamine and decongestants</td>
<td>1b and 2c</td>
<td>61</td>
</tr>
<tr>
<td>Tracy et al\textsuperscript{13}</td>
<td>Three parallel groups</td>
<td>61</td>
<td>3-11 y</td>
<td>...</td>
<td>...</td>
<td>1b and 2c</td>
<td>...</td>
</tr>
</tbody>
</table>

*Ellipses indicate data not available.
†See the “Types of Participants” subsection of the “Criteria for Considering Studies” section.
<table>
<thead>
<tr>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotic</strong> (trimethoprim-sulfamethoxazole) for 30 d plus prednisone, 0.5-1.0 mg/kg, per dose twice daily for the first 7 d (n = 26) vs antibiotic plus placebo (n = 27)</td>
<td>Pneumo-otoscopic and tympanometric resolution and/or speech threshold no greater than a 15-dB hearing loss on audiometry; follow-up at 2 wk</td>
<td>Not analyzed by intention-to-treat analysis; audiometric data use ear as unit of analysis</td>
<td>A</td>
</tr>
<tr>
<td>Prednisone, 1 mg/kg, in a tapering dose for 1 wk (n = 18) vs no treatment controls (n = 19)</td>
<td>For early follow-up, pneumo-otoscopic and tympanometric resolution; transient decrease in serum cortisol level in patients treated with prednisone; follow-up at 2 and 4 wk</td>
<td>Not placebo controlled; not analyzed by intention-to-treat analysis; audiometric data at 1 y on 35% of patients; follow-up given as a percentage, so actual numbers followed up not clear</td>
<td>C</td>
</tr>
<tr>
<td>Antibiotic (cefixime) for 10 d plus a single dose of betamethasone, 6 mg, on day 10 (n = 59) vs antibiotic plus placebo (n = 61)</td>
<td>Otomicroscopic and tympanometric resolution; cure defined as 1 of 2 affected ears clear or both clear after 1 was affected 2-11 d after completion of treatment; follow-up at 6 wk and 6 mo; no serious adverse effects (10 symptoms were reported in the antibiotic plus steroid group and 6 were reported in the antibiotic plus placebo group)</td>
<td>One patient from the cefixime plus placebo group (adverse event) and 1 from the cefixime plus betamethasone group (withdrawal before starting treatment) excluded from analysis</td>
<td>B</td>
</tr>
<tr>
<td><strong>Antibiotic</strong> (amoxicillin) plus prednisone, 1.5 mg/kg, daily in tapering doses (n = 32) vs antibiotic plus placebo (n = 28) for 2 wk</td>
<td>Resolution defined by otoscopy and tympanometry; improvement defined by better hearing on pure tone audiometry; measured 7-10 d after the completion of treatment</td>
<td>May not have been analyzed by intention-to-treat analysis; audiometric data use ear as unit of analysis and present outcomes as ears resolving with each treatment rather than for all subjects; not clear if resolution referred to clearing of both ears when bilateral otitis media with effusion is present at enrollment</td>
<td>B</td>
</tr>
<tr>
<td><strong>Prednisone</strong>, 1 mg/kg, daily tapering for 1 wk (n = 24) vs antibiotic plus placebo (n = 23)</td>
<td>Audiometric, tympanometric, and pneumo-otoscopic resolution; improved hearing by at least 10 dB in 1 or both ears; outcomes measured at 2 and 6 wk</td>
<td>Code broken early because remission rates less than expected spontaneously</td>
<td>A</td>
</tr>
<tr>
<td><strong>Prednisone</strong>, 1 mg/kg, tapering over 2 wk (n = 12) vs placebo (n = 10)</td>
<td>Pneumo-otoscopic and tympanometric resolution in both ears; outcomes measured at 2 and 5 wk; no significant adverse effects observed</td>
<td>Not analyzed by intention-to-treat analysis; of 26 randomized, 4 excluded from analysis at 2 wk and a further 2 excluded from follow-up at 5 wk due to lack of compliance</td>
<td>A</td>
</tr>
<tr>
<td><strong>Antibiotic</strong> (amoxicillin) plus prednisone, 1 mg/kg, daily in tapering doses (n = 50) for 2 wk vs antibiotic plus placebo (n = 49)</td>
<td>Audiometric and tympanometric improvement; follow-up at 2 mo</td>
<td>Confusion about outcomes; success defined as normal otoscopic and tympanometric readings and closure of the air-bone gap; no absolute values for audiometric data; yet, outcomes for “complete improvement” are given according to audiometric and tympanometric readings separately; not analyzed by intention-to-treat analysis; concealment probably inadequate</td>
<td>C</td>
</tr>
<tr>
<td><strong>Antibiotic</strong> (sulfisoxazole) plus prednisone, 1 mg/kg, daily tapering over 7 d (n = 24) vs antibiotic plus placebo (n = 17)</td>
<td>Tymanometric and pneumo-otoscopic clearing of effusions; follow-up after 1 wk</td>
<td>Not clear whether “cleared” refers to clearing in all affected ears; not clear why numbers in treatment groups unbalanced</td>
<td>B</td>
</tr>
<tr>
<td>Aerosolized dexamethasone phosphate, 1 spray in each nostril 3 times a day for 3 wk (n = 21) vs aerosolized placebo (n = 24)</td>
<td>Improvement in middle ear pressure and gradient; follow-up after 3 wk; transient decrease in serum cortisol levels in 2 dexamethasone-treated patients; no adverse reactions, and no pathological nasal mucosal changes</td>
<td>All children had allergic rhinitis</td>
<td>B</td>
</tr>
<tr>
<td><strong>Antibiotic</strong> (amoxicillin) plus aqueous intranasal beclomethasone dispropionate, 2 sprays twice daily in each nostril, both for 12 wk (n = 19) vs antibiotic plus placebo (n = 20) vs antibiotic alone (n = 20)</td>
<td>Tymanometric, otoscopic, and symptom scores; follow-up at 4, 8, and 12 wk; adverse effects were transient nasal stinging and epistaxis (number of patients not clear)</td>
<td>Antibiotic plus placebo and antibiotic alone groups pooled for some outcomes; no differences in outcome between atopic and nonatopic subjects; 2 subjects lost to follow-up and excluded from analysis</td>
<td>A</td>
</tr>
</tbody>
</table>

**CONCLUSIONS**

Steroids alone or together with an antibiotic appear to improve resolution of effusion in the short-term. However, there was significant heterogeneity between stud-

unity for all but 2 comparisons. Because of the small number of studies in many of the comparisons, we did not perform sensitivity analyses.

No serious or lasting adverse effects were reported in the 4 studies mentioning adverse effects.
ies involving steroids plus antibiotics. This could be explained by differences between studies in pharmacological interventions, including steroid formulation, steroid dose, duration of steroid treatment, and type and duration of concomitant antibiotic. Also, studies differed in terms of study population, including age, setting, proportion with bilateral OME, and duration of OME at study enrollment. The clinical significance of this finding is uncertain because we were not able to evaluate the effect of steroid treatment on hearing from these studies. Few data are available for longer-term outcomes, and no study assessed the effect of steroids on language in the longer-term. One study did assess hearing at 12 months, but this assessment was made on only 35% of the patients, so the results are difficult to interpret and were, therefore, not presented. Given concern about treating what is often a self-limiting condition with systemic steroids, we were particularly interested to examine evidence for the effect of topical nasal steroids. The one study included intranasal steroid vs placebo showed no benefit. The one study of intranasal steroid in combination with an antibiotic demonstrated an effect in clearing effusions in the short-term, but by 3 months, differences between study groups were no longer statistically significant. Adverse effects of steroid treatment were mentioned in a few studies. No study documented HL prospectively before study enrollment. Only one study attempted to measure the effect of steroids on subjective symptoms.

Previous reviews were published before the trial by Hemlin and colleagues. Some used different inclusion criteria (eg, Nuss and Berman included trials published in abstract form only and a nonrandomized open study). However, conclusions were similar to ours in that despite evidence for a short-term steroid effect, the general use of steroids for OME was not recommended. A cost-effectiveness review concluded that steroid plus antibiotic was the most cost-effective intervention for children found to have OME at a first follow-up visit 6 weeks after the diagnosis of acute otitis media. However, adverse effects were not considered.

Implications for Practice

There is imperfect evidence demonstrating short-term improvement in OME from oral steroids alone or combined with an antibiotic. However, we found no evidence for lasting benefit from oral or topical nasal steroid treatment of HL associated with OME. Based on the research we identified, these treatments are, therefore, not recommended.

Implications for Research

Otitis media with effusion may be present without significant HL. Positive predictive values range from 49% to 66.4% for an HL of 25 dB or greater after an abnormal tympanogram.

Given the high rate of spontaneous remission, future studies should document HL associated with OME for a period before beginning study treatment and at follow-up. In the absence of evidence that unilateral OME influences language development, the practice of enrolling children with unilateral OME into treatment studies is questionable. Follow-up should be longer and ideally include symptom, hearing, and language development outcome assessments. Audiometric data should be presented not as mean hearing levels for groups but as numbers of children with defined levels of HL in their best hearing ear. Data should not be presented only with ears as the unit of analysis because observations on the different ears of the same child cannot be regarded as independent. Assessors of outcomes should be blinded to the treatment condition. Improvement should be clearly defined (eg, researchers should present data for children with bilateral OME resolving in one but not both ears). Analysis should be based on the intention to treat. A short course of oral steroids followed by longer-term intranasal steroids has so far not been evaluated.

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REFERENCES


