**Objective:** To pool and meta-analyze the results of all randomized controlled trials (RCTs) on treatment of sudden sensorineural hearing loss (SSHL).

**Data Sources:** A MEDLINE search and hand search were conducted to identify RCTs published between January 1966 and February 2006 in the English language on the treatment of SSHL. Search terms included *hearing loss*, *sensorineural* (MeSH term), *sensorineural hearing loss* (text words), and *sudden deafness* (text words).

**Study Selection:** Prospective RCTs on the treatment of patients diagnosed as having sudden sensorineural hearing loss.

**Data Extraction:** A meta-analysis using the random effects model was conducted when data existed for 2 or more studies. Odds ratios (ORs), 95% confidence intervals (CIs), and tests for heterogeneity were reported.

**Data Synthesis:** Twenty RCTs were identified, of which 5 met inclusion criteria for meta-analysis. Pooling of data from 2 RCTs that compared steroids with placebo showed no difference between treatment groups (OR, 2.47; 95% CI, 0.89-6.84; *P* = .08). No difference existed between patients treated with antiviral plus steroid therapy vs placebo plus steroid therapy (OR, 0.92; 95% CI, 0.29-2.92; *P* = .88). Finally, there was no difference between subjects treated with steroids vs subjects treated with any other active treatment (OR, 1.27; 95% CI, 0.64-2.55; *P* = .50).

**Conclusions:** Despite the traditional practice in North America of treating of SSHL with systemic steroids, a meta-analysis revealed no evidence of benefit of steroids over placebo. There was also no difference in the addition of antiviral therapy to systemic steroids, nor was there difference between systemic steroids and other active treatment.

_Arch Otolaryngol Head Neck Surg. 2007;133:582-586_

**SUDDEN SENSORINEURAL HEARING LOSS (SSHL)** is an idiopathic condition of acute hearing impairment with an incidence of 5 to 20 per 100,000 persons per year, for which a variety of treatments exist. Many causes have been proposed for SSHL. Among these, the 2 most common theories are (1) circulatory disturbance and (2) viral infection. It is plausible that both these mechanisms play a role. Evidence supporting the circulatory disturbance theory is circumstantial, based on case reports of sudden deafness in patients with known systemic vascular disease and animal models showing histopathological cochlear changes due to vascular occlusion. Both direct and indirect evidence exist for the inflammatory reaction theory: SSHL has been associated temporally with active viral upper respiratory illnesses; patients with SSHL have antibody titers to several viruses; temporal bones examined at postmortem exhibit histopathologic evidence consistent with viral deafness in patients with SSHL; and finally, animal experiments have demonstrated viral penetration of the inner ear.

An array of treatments have been tried for SSHL, including vasoactive hemodilutional substances, systemic antiviral agents, carbogen, vitamins, and more commonly, oral or intratympanic steroids. However, an evidence-based approach to treatment of this condition remains unclear. Due to the relatively low incidence of SSHL, researchers are often faced with considerable challenges in conducting a randomized controlled trial (RCT) with a sufficiently large sample size to permit a highly statistically powered study. Meta-analysis presents a powerful tool to pool data across several RCTs and thus increase the chance of detecting a real, statistically significant effect. We therefore...
undertook this review to (1) identify, evaluate, and review all RCTs on the treatment of SSHL (see Treatment of Sudden Sensorineural Hearing Loss: I. A Systematic Review13 [part I]) and (2) to pool and meta-analyze the results of individual RCTs, when possible, to increase the statistical power and produce reliable estimates of the efficacy of a given treatment. Implications for clinical practice and future research are discussed herein.

A MEDLINE literature search was conducted to identify RCTs on the treatment of SSHL, published between January 1996 and February 2006. Details of this literature search are described elsewhere (see part I13). Data were extracted by one reviewer (A.E.C.) as per the Berlin method,14 whereby there was no blinding to authors, journals of publication, or results of the studies. Characteristics and results of all included studies were reviewed systematically. Studies were then categorized by treatment protocol and evaluated for suitability for meta-analysis.

Meta-analyses were performed using RevMan 4.2 (The Cochrane Collaboration, Oxford, England). For continuous data, the means and standard deviations were recorded for each study arm. If continuous data were reported as a mean change or if standard deviations were not reported, the data were excluded from pooled analysis. For dichotomous data (eg, subjective report of tinnitus), absolute numbers were expressed as fractions. If the dichotomous data were expressed as a proportion, the data were converted to the original fraction. In studies in which continuous outcomes were translated into dichotomous variables (eg, pure-tone average scores reported categorically as “improvement” or “no improvement”), data were analyzed as dichotomous data. Studies in which only graphical representations of data were used, and thereby raw data were not reported, were excluded from pooled analysis.

Statistical tools for the meta-analysis were chosen in recognition of the broad inclusion criteria within the studies and the expectation of between-study variability. Data from individual studies were combined by means of a random effects model of meta-analysis,15 which assumes a population, or distribution, of true effect size with each source study representing one member of the population. Using this model, we weighted studies by the inverse of variance, and a random effects estimate of the combined effect and 95% confidence interval (CI) were calculated. The random effects model of meta-analysis generates a wider 95% CI of the pooled result, which therefore generates a more conservative estimate of the treatment effect.

A test of heterogeneity was performed using the χ² statistic to evaluate whether the pooled studies represented a homoge-

neous distribution of effect sizes. Significant heterogeneity beyond random fluctuation is known to exist if P < .05. A statistic for quantifying inconsistency, I², also was reported. The inconsistency statistic describes the percentage of the variability in effect estimate that is due to heterogeneity rather than to sampling error or chance. A value greater than 50% may be considered substantial heterogeneity, while a value lower than 30% may represent inconsequential heterogeneity.16

Graphic displays of the results, termed forest plots, were provided for all meta-analyses to aid in interpretation. The forest plot is a widely used form of presentation that depicts point estimates (black squares) and error bars (horizontal lines) for each study.15 Each black square is proportional to the sample size of the study it represents. The combined result of the pooled data are depicted by a black diamond spanning the 95% CI. When most or all of the 95% CIs in the individual studies contain the combined rate difference, the studies are considered to be relatively homogeneous.16

CHARACTERISTICS OF INCLUDED STUDIES

Twenty RCTs,17-36 reporting 21 treatment comparisons, met the inclusion criteria of this review. The characteristics, interventions, outcome measures, and results of these studies are described elsewhere (see part I13).

STEROID THERAPY VS PLACEBO THERAPY

Two studies investigated oral steroids vs oral placebo for the treatment of SSHL.17,38 Figure 1 displays the data on hearing recovery rates reported by Wilson et al17 and Cinamon et al.18 Data from a total of 88 patients were pooled for meta-analysis. The test for heterogeneity was not significant (P = .29) and inconsistency was marginal (I² = 9.5%), which indicated that pooling the data was valid. Pooled analysis of the data revealed no statistically significant difference between systemic steroids and placebo (odds ratio [OR], 2.47; 95% CI, 0.89-6.84; P = .08).

ANTIVIRAL PLUS STEROID THERAPY VS PLACEBO PLUS STEROID THERAPY

Four studies evaluated treatment of SSHL with antiviral therapy and steroid therapy vs placebo and steroid therapy. Among the 4 RCTs comparing antiviral agents plus steroids vs steroids alone, 2 were excluded from the meta-

### Figure 1. Meta-analysis of steroids vs placebo. CI indicates confidence interval; OR, odds ratio.
analysis on the basis of incomplete data reporting. Consequently, pooled analysis of the data was possible for 2 studies that evaluated the utility of antiviral therapy combined with steroid therapy. Figure 2 displays the pooled analysis of rates of improvement reported in these 2 studies across 138 patients. The most similar outcome data reported in each study, defined as at least 50% improvement over baseline, was pooled, as was the actual percentage of improvement. There was no significant heterogeneity ($P = .16$) and there was an acceptable degree of inconsistency ($I^2 = 48.4\%$) between the 2 studies, suggesting validity of the pooled analysis. The forest plot indicated no significant difference between steroid plus antiviral therapy vs steroid therapy alone (OR, 0.92; 95% CI, 0.29-2.92; $P = .88$).

**STEROIDS VS OTHER THERAPY**

To determine whether steroid treatment might constitute the gold standard in treatment of SSHL, pooled analysis was completed across all studies that compared steroid therapy with any other active treatment. Two studies were included in this category. Active treatments of carbogen inhalation and fibrinolysis were compared with steroid treatment alone. Figure 3 demonstrates a pooled analysis of the objective outcome measure data across 183 patients in 2 studies. There was no significant heterogeneity ($P = .30$) or inconsistency ($I^2 = 5.9\%$). The data did not reveal any overall effect in favor of steroid therapy over other treatment (OR, 1.27; 95% CI, 0.64-2.55; $P = .50$).

**VASOACTIVE AND HEMODILUTION THERAPY**

Five RCTs assessed the utility of vasoactive and hemodilution treatments, including pentoxifylline, dextran, Ginkgo biloba, nifedipine, and combinations thereof. The treatment methods described in the studies varied widely, and no 2 studies used treatment regimens that were sufficiently homogeneous to permit valid between-study comparisons. Therefore, pooled analysis of outcome measures of studies regarding vasoactive and hemodilution therapies was not applicable.

**MAGNESIUM VS OTHER THERAPY**

Two RCTs compared the addition of magnesium with other active treatment for patients with SSHL. Gordin and colleagues reported a greater rate of recovery among patients treated with carbogen than without and provided percentages of patients demonstrating categorical improvement defined as fair, good, recovery, or no improvement. Nageris et al also reported a greater rate of recovery among patients treated with magnesium vs without but provided only a graphical representation of recovery and not the actual number of patients demonstrating recovery. Therefore, owing to the incomplete reporting of data in the study by Nageris et al, pooled analysis of studies evaluating magnesium was not possible.

### OTHER THERAPIES

Five RCTs assessed the utility of other treatment protocols. Because of the inherent heterogeneity of the treatment regimens in these studies (see part I), pooled analysis of these studies was not applicable.

**COMMENT**

There is a remarkable array of therapeutic approaches to the treatment of SSHL. While the idiopathic nature of this condition inherently presents a therapeutic dilemma, it nonetheless is important to identify the treatment that is most beneficial to the patient.

Steroids have been used widely in the treatment of SSHL because of their proposed benefit in infectious, inflammatory, and other immune-mediated conditions and despite the fact that their specific mechanism of action is unknown. Independently, the study by Wilson et al indicated that treatment with systemic steroids resulted in a statistically significant greater rate of recovery than placebo. When the data in this study were pooled with the data of the RCT by Cinamon et al in a comparison of systemic steroid therapy vs placebo, there was no longer a statistically significant treatment effect. To this extent, systemic steroids do not appear to represent an effective treatment of SSHL.

Viral infection has been proposed as a possible cause of SSHL, and a unifying theory implicates both viral infection resulting in an inflammatory response and circulatory disturbance as components of a causative cascade. Viral injury can cause direct vascular and erythrocyte injury, resulting in secondary vascular insufficiency. Viruses also can cause direct inflammation, which similarly causes secondary vascular insufficiency.
meta-analysis, among the 4 RCTs that compared antiviral plus steroid therapy with placebo plus antiviral therapy for the treatment of SSHL, none identified any statistically significant difference between the 2 treatment groups. Moreover, in a pooled analysis of 2 of these trials, there was no significant evidence that combining antiviral and steroid therapy is better than steroids alone.

While systemic steroids have been labeled the gold standard for treatment of SSHL, this conclusion was based on a comparison of systemic steroids with placebo. To our knowledge, a review of systemic steroids vs another active treatment protocol that targets 1 or more of the possible causes of SSHL never has been done. Therefore, pooled analysis was completed across all studies that compared steroid treatment with another treatment. Only 2 RCTs evaluated steroids alone vs a single active treatment modality. Meta-analysis of the data reported in these studies failed to support a statistically significant treatment effect favoring systemic steroids. This meta-analysis was unable to definitively support systemic steroids as the gold standard for treatment of SSHL.

Limitations of the literature search and the studies on which this meta-analysis are based are discussed elsewhere (part I). Another limitation is that pooled analysis was only possible for a small number of RCTs. Of the studies identified, only 5 were sufficiently similar in treatment protocol and reported sufficiently complete results to permit pooled analysis. Also, this meta-analysis is inherently limited by the outcome measures reported in the studies. There appears to be no universally accepted best outcome measure for defining success of treatment in SSHL. Many of the outcome measures reported in the RCTs were subjective outcome measures, such as perceived improvement in hearing and presence of tinnitus, as well as indirect objective data, such as categorical improvement by pure-tone average. Moreover, among categorical outcome measures of improvement, the definition of improvement that was used varied across studies, from 50% reduction in a symptom in some studies to 75% in others. Not only does conversion of continuous outcome measures to dichotomous measures introduce the potential for bias, it necessitates using a weaker statistical measure (ORs) instead of weighted mean differences. For future research, hearing levels should be reported as decibels with means and standard deviations to permit more meaningful statistical analyses.

This meta-analysis and systematic review does, however, have several important strengths. First, there was no significant heterogeneity or inconsistency across any of the meta-analyses. Despite the diversity of the included studies, use of the random effects model of meta-analysis permitted valid pooling of the data. This is very beneficial for the clinician because the diversity of the studies in this meta-analysis helps to support the validity of the findings and increases the likelihood that the results could be applied in a given clinical encounter.

Despite the traditional view in North America that systemic steroids are the standard of treatment for SSHL, this meta-analysis showed no benefit of systemic steroids vs placebo when data were pooled across 2 studies. Also, when compared with other forms of active treatment, steroids offered no greater treatment effect. These quantitative findings regarding the data, in conjunction with the qualitative findings regarding the methods (see part I), considerably challenge the conventional view that systemic steroids constitute the gold standard for treatment of SSHL.

At present, SSHL remains a medical emergency without a scientific understanding of its cause or a rational approach to its treatment. The low incidence of SSHL presents a considerable challenge in designing any single RCT with sufficient power to detect a real, statistically significant treatment effect. To review any condition with a controversial or unclear treatment protocol, such as SSHL, systematic review and meta-analysis are powerful tools to integrate prior research, identify research gaps, define priorities for future research, and guide clinical management. Therefore, it is imperative that future reports describing research on the treatment of SSHL include all pertinent data. Continuity in reporting outcome measures across studies will permit powerful calculations of treatment effect, by means of meta-analyses, and will aid the clinician in identifying the best treatment protocol for the patient.

Submitted for Publication: August 8, 2006; final revision received December 1, 2006; accepted January 3, 2007. Correspondence: Lorne S. Parnes, MD, FRCSC, Department of Otolaryngology, University of Western On-


©2007 American Medical Association. All rights reserved.