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Intratympanic Gentamicin for Menière's Disease: a Meta-Analysis

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Objectives: **To systematically review the published experience on intratympanic gentamicin treatment for intractable Menière's disease.** ***Study Design:*** **Meta-analysis using a random effect model.** ***Methods:*** **A comprehensive literature search was performed for articles using intratympanic gentamicin as a sole treatment modality with reporting of results according to the American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) guidelines for Menière's disease. Two reviewers independently assessed trial quality and extracted data.** ***Results:*** **Fifteen trials with 627 patients met the inclusion criteria. All trials reported "before-after" outcome measures, using patients as their own controls. No double-blind or blinded prospective control trials were identified. Complete (class A) vertigo control was achieved in 74.7% (confidence interval [CI]$_{95\%}$ 67.8–81.5%) of patients, and complete or substantial (class B) control was achieved in 92.7% (CI$_{95\%}$ 89.5–96.0%). The success rate was not affected by gentamicin treatment regimen (fixed vs. titration). Hearing level and word recognition were not adversely affected, regardless of gentamicin treatment regimen. Analysis of functional level was not performed because of lack of data in the selected articles.** ***Conclusions:*** **Intratympanic gentamicin treatment for intractable Menière's disease appears to be effective in the relief of vertigo. Cochleotoxicity and ototoxicity is unlikely to be a major side effect. However, the level of evidence reflected from the eligible articles is insufficient, especially because of relatively poor study design. Therefore, it is prudent that patients eligible for this type of treatment should be selected carefully and titrated with low-dose gentamicin. Further investigation with this treatment modality with control subjects is warranted.** ***Key Words:*** **Menière's disease, gentamicin, meta-analysis, intratympanic.**

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INTRODUCTION

Over the past decade, intratympanic gentamicin has become a major treatment modality for intractable Menière's disease. A large number of reports have been published examining the outcome and complications in patients with Menière's disease who have been treated with this modality. Those reports encouraged increasing numbers of practicing otologists/neurotologists to change their approach and to recommend intratympanic gentamicin treatment for vestibular deafferentation.[1]

Since 1972, the American Academy of Otolaryngology Head and Neck Surgery (AAO- HNS) have recommended guidelines for reporting the results of treatment for Menière's disease.[2] These recommendations have been revised and refined twice, in 1985 and 1995.[3,4] In the context of Menière's disease, few patients overall would ultimately require or be considered candidates for intratympanic gentamicin treatment. Presently, no attempt has been made to review systematically the evidence on effectiveness and toxicity of gentamicin application for Menière's disease. The objective of this study was to systematically review the world literature on intratympanic treatment for Menière's disease and aggregate their outcomes data in a quantitative synthesis.

METHODS

Study Criteria

The criteria for inclusion of studies in this analysis were articles reporting a clinical trial of patients who had been diagnosed according to the Committee on Hearing and Equilibrium (CHE) of the AAO-HNS 1985 or 1995 as having definitive Menière's disease.

Acceptable designs were those designed as randomized control trials, case control studies, and prospective cohorts or retrospective cohorts reporting on 10 or more patients. In studies reporting on the same patients, only the most updated version was considered. The Methods and Results sections were translated from non-English articles that were considered for analysis.

Administration of gentamicin into the middle ear, either by transtympanic injection or by using a specially designed catheter as the only intervention, was considered. Studies reporting on

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concomitant administration (by local, oral, or parenteral route) of other drugs, such as dexamethasone, were excluded.

There was no age limitation for inclusion of studies. Studies reporting on patients with a Menière's-like condition (posttraumatic, postinfectious, syphilis, Cogan syndrome, etc.) were excluded. Studies reporting on animal trials, comments, letters, editorials, and reviews were excluded as well.

Article Retrieval and Data Extraction

A medical literature search was performed using MEDLINE and EMBASE databases for studies that were published in the years 1985 to 2003. All clinical trials dealing with intratympanic gentamicin treatment for Menière's disease were considered. A combination of words (intratympanic, transtympanic) and Medical Subject Headings (MeSH) terms (Endolymphatic Hydrops, Menière's disease, Injection, Aminoglycosides), under clinical trial category, were used as search strategy. All titles and abstracts were evaluated, regardless their language. References from reviews, the retrieved articles and from those that were rejected, were scanned as well to identify further articles.

Each article was evaluated by two independent, certified otolaryngologists who decided on inclusion or exclusion in mutual agreement. In cases where reviewers were in disagreement, a decision was made by a third reviewer who is a certified otolaryngologist as well. Both reviewers extracted the data from each article. The retrieved data were compared and revised in mutual agreement.

Outcome measures collected from the considered studies were in accord with AAO-HNS guidelines for reporting on Menière's disease and included vertigo control, hearing, and word recognition.[3,4] Assessment of functionality and disability was introduced in the 1995 CHE AAO-HNS guidelines for reporting results in Menière's disease, which made it impossible to compare with data based on 1985 guidelines.

Information regarding the treatment regimen was retrieved as well. Caloric tests results, although not part of the AAO-HNS guidelines, were reported on as well. In studies that failed to report according to guidelines (e.g., <2 years of follow-up) and had raw data delineated for each patient, only those that were appropriate were considered.

Data Analysis

To combine data across groups, we used a random effects meta-analytic model. This approach weights outcome by the size of each study, with larger studies receiving greater weights. As well, this approach weights according to between-study variance, incorporating any minor differences in outcomes into the overall calculations. Two variants of the technique were used. The first was the classic form, as presented by Cochran,[5] to examine differences in outcomes. The second was used to combine rates across studies, as presented by Einarson.[6]

Success rates were calculated across studies using two different definitions of success. The first included only those with complete remission of vertigo (class A), and all others were considered to be failures. The second counted both class A and B as successes and all others as failures. Subsequently, data were compared between baseline and follow-up (i.e., after 18–24 months) to identify potential changes in either vertigo control or hearing (outcomes of interest were hearing [measured in dB] and word recognition [expressed as a percentage]). A change in hearing of 10 dB or more and a change of 15% in word recognition score were considered clinically relevant.

A priori, we identified subgroups that warranted examination. According to the data collection method, studies were separated into prospective and retrospective designs. As well, we grouped studies according to methods of drug administration, separating those that used fixed regimens and those that titrated doses. Stratifying studies according to dose was not performed because of the high variability and range among patients, especially those who were treated according to a titration based protocol.

RESULTS

Of 226 publications retrieved from the literature search, 61 were considered, from which only 15 were suitable for analysis (Table I). The rejected studies have been referenced and listed online. The study by Abou-Halawa and Poe[7] was considered as two trials because they reported on two groups treated by two different regimens. Accordingly, 16 groups of patients were analyzed. Two studies, by Corsten et al.[8] and by Harner et al.,[9] did not report standard deviations for hearing scores or for word recognition scores. In these two studies, rather than omitting the data, we used the average of the reported standard deviations from all other studies in each analysis or subanalysis. We calculated the SD for the data from the study by Perez et al.,[10] using the 95% confidence interval (CI) that was reported.

The first reported study matching the inclusion criteria was published in 1997. Eight studies were designed as prospective and eight as retrospective cohorts. Twelve studies followed the AAO-HNS guidelines of 1995, whereas four followed the AAO-HNS 1985 guidelines. All studies except one,[11] in Italian, were published in English. The overall number of patients that were included in those studies and were eligible for meta-analysis according to the AAO-HNS guidelines was 627.

None of the analyses of differences displayed evidence of heterogeneity of treatment effects (i.e., all $P > .05$). Therefore, combining these studies was considered justified.

Effectiveness: Frequency of Vertigo

Frequency of vertigo was reported in 15 articles with 580 patients. The success rates reported in these articles are presented in Table II. The overall success rate was 74.7% ($CI_{95\%}$ 67.8–81.5%) for class A and 92.7% ($CI_{95\%}$ 89.5–96.0%) for classes A and B. When examining the seven studies in which data were collected prospectively (n = 351), the overall success rate was 81.5% ($CI_{95\%}$ 76.3–86.8%) for class A and 91.5% ($CI_{95\%}$ 86.7–96.3%) for classes A and B. For the eight retrospective studies (n = 229), the overall success rate was 65.2% ($CI_{95\%}$ 51.4–78.9%) for class A and 94.1% ($CI_{95\%}$ 89.8–98.5%) for classes A and B.

In articles describing patients who were treated with a fixed gentamicin dose protocol (n = 121), the overall success rate was 68.7% ($CI_{95\%}$ 43.0–94.5%) for class A and 94.8% ($CI_{95\%}$ 91.0–98.7%) for classes A and B. In articles based on titration according to patients' symptoms (n = 459), the meta-analytic success rate was 75.2% ($CI_{95\%}$ 68.0–82.5%) for class A and 91.9% ($CI_{95\%}$ 87.9–95.9%) for classes A and B. For both sets of outcomes, the CIs overlapped substantially.

There was heterogeneity among the individual success rates. Two outliers were identified, namely, those reported by Longridge and Mallinson[12] and by McFeely et

TABLE I.
Characteristics of Studies Included in the Meta-Analysis.

Reference	Country/Language	Type of Study	AAO-HNS Definition	Sample Size	Protocol Type	Administration Profile	
						Delivery Method	Dose
Abou-Halawa* 2002[7]	US/English	Retrospective Cohort	1995	44	Titration	Transtympanic injection, supine for 45 minutes	1–8 injections of 30 mg/mL
Abou-Halawa* 2002[7]	US/English	Retrospective Cohort	1995	43	Titration	Transtympanic injection, supine for 45 minutes	1–8 injections of 40 mg/mL
Atlas 1999[18]	Canada/English	Retrospective Cohort	1995	68	Titration	Endoscopy of the round window niche, injection and further administration through a tube, supine for 10 min	1–8 injections of 0.3–0.5 mL of 26 mg/mL
Corsten 1997[8]	Canada/English	Retrospective Cohort	1995	21	Fixed	Intravenous tubing attached to a ventilating tube	12 injections of 18 mg (~218 mg)
Harner 2001[9]	US/English	Prospective Cohort	1995	56	Titration	Transtympanic injection, supine for 45 minutes	1–4 injections of 0.5–0.75 mL of 40 mg/mL
Hirsch 1997[25]	US/English	Retrospective Cohort	1985	15	Titration	Transtympanic injection, supine for 20 minutes	1–6 injections 0.3–0.5 mL of 30 mg/mL
Kaasinen 1998[14]	Finland/English	Prospective Cohort	1985	93	Titration	Transtympanic injection, supine for 15 minutes	1–4 injections of 0.3–0.5 mL 30 mg/mL
Kaplan 2000[19]	Canada/English	Prospective Cohort	1985	90	Fixed	Catheter connected to a "T" type ventilation tube, supine for 30 min	12 injections of 0.7–0.8 mL of 26.7 mg/mL (~208 mg in total)
Leone 2000[11]	Italy/Italian	Prospective Cohort	1995	20	Fixed	Transtympanic injection	2 injections of 18 mg (2 patients received 3 injections)
Longridge 2000[12]	Canada/English	Retrospective Cohort	1995	23	Titration	Several were injected through a tube and the majority Transtympanic, supine for 20 minutes	1–4 courses of 0.5 mL of 27 mg/mL
McFeely 1998[13]	US/English	Retrospective Cohort	1985	11	Fixed	Through catheter attached to a "T" tube or polyethylene tubing, supine for 30 minutes	12 injections of ~1.0 mL of 26.7 mg/mL
Perez 2003[10]	Spain/English	Prospective Cohort	1995	71	Titration	Injection through myringotomy, after endoscopic evaluation supine for 30 minutes	1–2 courses of 1–6 injections of 26.7 mg/mL (~0.4 mL)
Quaranta 1999[16]	Italy/English	Prospective Cohort	1995	11	Titration	Injection following tympano-meatal flap elevation and round window niche obliteration, supine for 20 minutes	2 doses of 0.5 mL 80 mg/mL (~80 mg in total)
Quaranta 2001[17]	Italy/English	Prospective controlled Cohort	1995	15	Titration	Transtympanic injection, supine for 20 minutes	2–4 courses of 2 doses of 0.3–0.5 mL 20 mg/mL (~20 mg in total)
Rauch 1997[15]	US/English	Retrospective Cohort	1995	12	Titration	Transtympanic injection, supine for 60 minutes	2–24 injections of 0.3–0.7 mL of 40 mg/mL
Wu 2003[26]	US/English	Prospective Cohort	1995	34	Titration	Injection through myringotomy, supine for 30 min followed by aspiration	1–3 courses of 1–7 injections of 26.7 mg/mL (~0.4 mL)

*Both groups were reported in the same article.

TABLE II.
Meta-Analysis of All the Studies that Met the Inclusion Criteria with Respect to Success Rate of Intratympanic Gentamicin Treatment.

Author and Year	Sample Size (useable data)	Success Rate	
		Complete (Class A)	Complete to substantial (Classes A + B)
Abou-Halawa* 2002[7]	44 (36)	0.750	0.986
Abou-Halawa* 2002[7]	43 (31)	0.742	0.984
Atlas 1999[18]	68 (68)	0.838	0.897
Corsten 1997[8]	21 (20)	0.850	0.976
Harner 2001[9]	56 (55)	0.673	0.836
Hirsch 1997[25]	15 (28)	0.714	0.929
Kaasinen 1998[14]	93 (84)	0.786	0.786
Kaplan 2000[19]	90 (90)	0.844	0.933
Longridge 2000[12]	23 (23)	0.304	0.826
McFeely 1998[13]	11 (11)	0.273	0.909
Perez 2003[10]	71 (62)	0.790	0.952
Quaranta 1999[16]	11 (11)	0.909	0.958
Quaranta 2001[17]	15 (15)	0.867	0.933
Rauch 1997[15]	12 (12)	0.583	0.583
Wu 2003[26]	34 (34)	0.882	0.971
Meta-analytic average rate (95% confidence limits)		0.747 (0.678–0.815) (n = 580)	0.927 (0.895–0.960) (n = 580)

*Both groups were reported in the same article.

al.[13] Removal of those two studies actually raised the rate of success (class A) from 74.6% to 80.3% (no significant heterogeneity present). Similarly, studies by Kaasinen et al.[14] and Rauch and Oas[15] were classified as outliers because both were below the expected average effect size. Therefore, their removal would also lead to a higher success rate. Overall, the success rates from this analysis may be considered conservative.

Hearing

Hearing outcome after intratympanic gentamicin was reported in 15 articles on 549 patients (Table III). The overall reduction in hearing was 1.5 dB, which was neither clinically nor statistically significant ($CI_{95\%}$ −12.0–9.1dB). In the eight studies reporting a prospective follow-up (n = 373), the hearing reduction after gentamicin treatment was 2.3 dB ($CI_{95\%}$ −16.5–12.0dB), whereas in the seven retrospective reports (n = 176), hearing reduction was 0.5 dB ($CI_{95\%}$ −15.2–16.2dB). Hearing of patients (n = 132) who were treated with fixed gentamicin dose protocol was reduced by 5.4 dB ($CI_{95\%}$ −14.6–25.5dB). Hearing for those who were treated with gentamicin titration (n = 417) was reduced by 0.02 dB ($CI_{95\%}$ −12.3–12.4dB). Thus, no outcomes were clinically important or statistically significant.

Word Recognition

Twelve studies met the inclusion criteria with respect to word recognition. The overall number of patients reported with sufficient follow-up was 395 (Table IV). According to our analysis, word recognition was worsened by 2.0% after intratympanic treatment with gentamicin ($CI_{95\%}$ −16.5–20.4%). Subanalysis of the six studies (244 patients) with prospective designs showed mean reduction of 0.6% ($CI_{95\%}$ −24.9–23.7%) after gentamicin treatment. In the six studies (151 patients) with retrospective data collection, word recognition was reduced by a nonsignificant mean of 4.9% ($CI_{95\%}$ −33.1–23.4%). Patients (n = 93) who were administered a fixed protocol had reduced their word recognition by 6.5% ($CI_{95\%}$ −42.9–29.9%), whereas patients who were titrated (n = 302) had reduced word recognition by 0.4% ($CI_{95\%}$ −21.5–20.7%). As with hearing, no outcomes were identified that were clinically important or statistically significant.

Functional Level

Functional level at baseline and during follow-up was reported in five studies only (n = 172); four had prospective design,[9,10,16,17] and one was retrospective.[8] All adhered to the 1995 committee. It appears that the majority of patients moved from functional levels "five" and "four" to levels "two" and "one" ($P < .001$), rendering a positive effect of the treatment on quality of life as it is reflected from success rate analysis.

Caloric Tests

Seven studies[9,12,13,15–18] reported caloric test results before and after intratympanic gentamicin treatment, whereas one study[7] reported only follow-up results without a baseline measurement. Caloric tests were not part of the AAO-HNS guidelines; therefore, they were collected at different points in the follow-up period and reported in various nonstandardized fashion (e.g., percents, degrees/second). Thus, because of noncomparable reporting of results, we were not able to synthesize these data.

TABLE III.
Meta-Analysis of All the Studies that Met the Inclusion Criteria with Respect to Hearing Outcome after Intratympanic Gentamicin Treatment.

	Baseline			Follow-Up		
Author	PTA* (dB)	SD	n	PTA (dB)	SD	n
Abou-Halawa† 2002[7]	57	21.6	44	64.3	26.1	44
Abou-Halawa† 2002[7]	58.6	19.1	43	60	23.2	43
Corsten 1997[8]	52.8	17.1	16	64.1	22.1	16
Harner 2001[9]	56	17.1	55	57	22.1	44
Hirsch 1997[25]	52.6	21.5	28	53.04	25.4	28
Kaasinen 1998[14]	59.1	24.7	93	67.9	29.4	93
Kaplan 2000[19]	58.3	18	90	64.5	26.47	85
Leone 2000[11]	58.5	15.98	20	69.37	21.07	20
Longridge 2000[12]	49	15.8	23	47.3	19.6	22
McFeely 1998[13]	57.5	18.6	11	50	22.2	11
Perez 2003[10]	67.25	19.45	71	68.37	25.64	71
Quaranta 1999[16]	57	15.3	11	56.1	19.6	11
Quaranta 2001[17]	59.1	19.6	15	55.4	16.8	15
Rauch 1997[15]	52	13.6	12	47	27.7	12
Wu 2003[26]	60	15	34	59	24	34
Meta-analytic average		56.6 (47.6–65.6)			58.2 (46.6–69.8)	
(95% confidence limits)		(n = 566)			(n = 549)	

*PTA = four-tone average of 0.5, 1, 2, and 3 kHz (pure tone average).
†Both groups were reported in the same article.

Dosing

Of the 16 groups of patients, four[8,11,13,19] were treated with a fixed dose of gentamicin. Three[8,13,19] had approximately 210 mg over a short period of time (3 days), and one had a low dose of 36 mg (divided in 2 doses). The majority of patients were treated by titrating gentamicin according to the clinical effect on the vestibular system (e.g., appearance of nystagmus). Most of those patients, except the study by Leone et al.,[11] received lower doses than the doses administered in the fixed regimen. However, the difference in regimens and the variability within patients in each group made it impossible to quantify the dose response relationship or to identify a threshold dose that would minimize gentamicin toxicity. Overall, pa-

TABLE IV.
Meta-Analysis of All the Studies that Met the Inclusion Criteria with Respect to Word-Recognition Outcome after Intratympanic Gentamicin Treatment.

	Baseline			Follow-Up		
Author	WR (%)	SD	n	WR (%)	SD	n
Abou-Halawa* 2002[7]	54.3	33.4	44	42.1	37.8	44
Abou-Halawa* 2002[7]	44.2	33.8	43	46.1	37.4	43
Corsten 1997[8]	78.9	29.3	13	46	32.0	13
Harner 2001[9]	45	29.3	55	36	32.0	44
Hirsch 1997[25]	64.7	37.6	28	60.2	37.6	28
Kaplan 2000[19]	50.9	29.1	88	56.4	32.6	69
McFeely[13]	60.7	38.3	11	68.9	35.8	11
Perez 2003[10]	68.57	29.0	71	71.73	27.4	71
Quaranta 1999[16]	63.6	26.9	11	54.5	31.4	11
Quaranta 2001[17]	47.3	30.6	15	58.7	29	15
Rauch 1997[15]	56.8	26.9	12	64.7	35.4	12
Wu 2003[26]	44	31	34	46	37	34
Meta-analytic average		56.7 (39.1–74.3)			55.4 (36.3–74.4)	
(95% confidence limits)		(n = 425)			(n = 395)	

*Both groups were reported in the same article.
WR = word recognition.

tients who adhered to a titration regimen and received cumulative high dose received it over a longer period of time (i.e., weeks to months) compared with the high-dose fixed regimen (3 days).

DISCUSSION

This is the first systematic review on the effectiveness and safety of intratympanic gentamicin for Menière's disease. Excluding the article by Quaranta et al.,[17] which compared patient outcome with a group of patients who refused any surgical treatment, none of the reports used a control group; all patients served as their own control in a "before and after" design. This holds true also to other aspects of treatment for Menière's,[20] where most reports were categorized as level II-3 according to the U.S. Preventive Service Task Force. One can speculate that the absence of randomized controlled trials that incorporate a higher level of evidence may reflect the lack of sufficient numbers of patients, multiple treatment strategies for Menière's, and the variability of experience and beliefs incorporated in terms of the treating physician's preference for their patients.

The adherence of authors to the criteria established by the CHE of the AAO-HNS was inconsistent. Only 15 of 226 articles met our inclusion criteria on the basis of those measures. Moreover, within several of the selected articles, data were used partially because not all patients were reported according to the suggested criteria, especially with respect to well-defined follow-up guidelines posttreatment. Most of the articles that did not meet our inclusion criteria claimed to have followed the AAO-HNS recommendations regarding disease definition but failed to do so with respect to follow-up period and outcome reporting, thus failing to contribute to knowledge accumulation on this matter. The adherence of researchers to the AAO-HNS criteria was partial and was found to be adequate in only 50% of the publications reviewed by Thorp et al.[21]

Overall, our systematic review reveals a high success rate, especially when considering both classes A and B together, regardless of whether gentamicin was administered in a fixed or titration regimen or whether data were collected in a prospective or a retrospective manner. Achieving a success rate of over 90% would be considered excellent in any respect and may suggest that other modes of treatment are questionable. However, lack of control groups interferes with the objective assessment of confounders such as the natural course of the disease, diet modifications, selection choice, etc. Therefore, these encouraging results should be considered with caution.

Toxic effects of intratympanic administration of gentamicin on hearing and word recognition were found to be neither statistically significant nor clinically important. Subanalyses based on study design and treatment regimen did not change the overall conclusion. However, it appears that patients who were administered the drug on a titration regimen experienced a worsening of their hearing and word recognition (0.02 dB and 0.4%, respectively) to a lesser extent than those who had the drug administered on a fixed dose regimen (5.4 dB and 6.5%, respectively). The interpretation of these results is even more complicated because it is known that hearing in Menière's disease tends to fluctuate.

As was shown in animal studies, the elimination half-lives of gentamicin in the blood and inner ear fluids was found to be in the magnitude of hours, whereas in the inner ear tissue, it was found to be approximately 30 days.[22] It is therefore pharmacologically plausible that administration of repeated doses of gentamicin over a short period of time will enhance tissue saturation and increase the likelihood of both vestibular ablation and cochleotoxicity. On the other hand, repeated doses over a prolonged time frame may enable gentamicin levels to wear off from the inner ear tissues and its accumulation to a lesser extent, therefore lowering the risk of toxicity. Therefore, a titration regimen with monitoring patient's symptoms appears to be a safer approach. However, genetic susceptibility to aminoglycosides may also play a role as well in facilitating ototoxicity,[23] which cannot be answered from the data reviewed.

The power of meta-analysis is in its ability to synthesize data from small studies and to clarify debates. This advantage is diminished when the quality of evidence in the selected studies is relatively low. This shortcoming can be addressed by an appropriately powered, double-blind, placebo-controlled, randomized trial. A call, coming from an editorial footnote in the *Laryngoscope*,[24] for a multi-institution, prospective, randomized study has yet to be addressed.

CONCLUSIONS

Administration of gentamicin for intractable Menière's disease appears to be effective as reflected from this meta-analysis. However, the safety of this route of administration with respect to the patient's hearing has not yet been sufficiently established. One can quite definitely state that administering a high dose over a short period of time is not more beneficial than either a low dose or a high dose over a prolonged period of time. The analysis suggests that it is safer to avoid the short, high-dose regimen. The longer-term control of vertigo (>2 years) and its effects on hearing preservation cannot be analyzed from the data available.

Administration of gentamicin to patients resistant to conservative dietary and medical management is appealing when comparing its mildly invasive nature to surgical interventions. However, each patient must be evaluated individually and should be informed of all possible therapeutic options and consequences.

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