

TITLE: Controversies in Treatment of Meniere's Disease

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Meniere's Disease was first described by Prosper Meniere in 1861 as a disease complex associated with vertigo, deafness, nausea, vomiting and aural fullness. Meniere postulated a labyrinthine origin of these symptoms. In 1871, Knappin theorized that a dilatation of the membranous labyrinth was responsible for these symptoms. In 1938, Hallpike and Portman confirm endolymphatic engorgement, or hydrops causing dilatation of the membranous labyrinth when they histologically examined temporal bones. Since that time, despite a great deal of research into the topic, we have yet to have a much deep understanding of the disorder than did Meniere. A great deal of controversy exists surrounding the pathophysiology of Meniere's disease and treatments for the disorder.

The American Academy of Otolaryngology and Head and Neck Surgery has refined the definition of Meniere's several times. In examining the literature on Meniere's disease, it is important to have an understanding of these definitions. It is useful for researchers to use the definitions to standardize reporting of results. The most recent revision was set forth by the AAO-HNS Committee on Hearing and Equilibrium in 1995. The definitions are listed below:

- Possible Meniere's disease
 - Episodic vertigo of the Meniere's type (>20 minutes, associated with horizontal rotatory nystagmus) without documented hearing loss, or
 - Sensorineural hearing loss, fluctuating or fixed, with dysequilibrium but without definitive episodes
 - Other causes excluded
- *Probable Meniere's disease*
 - One definitive episode of vertigo
 - Audiometrically documented hearing loss on at least one occasion
 - Tinnitus or aural fullness in the treated ear
 - Other causes excluded
- *Definite Meniere's disease*
 - Two or more definitive spontaneous episodes of vertigo 20 minutes or longer
 - Audiometrically documented hearing loss on at least one occasion
 - Tinnitus or aural fullness in the treated ear

- Other cases excluded
- *Certain Meniere's disease*
 - Definite Meniere's disease, plus histopathologic confirmation

Staging of hearing loss in definite or certain Meniere's is as follows:

Stage:	Four Tone Average dB
1	≤25
2	26-40
3	41-70
4	>70

The AAO-HNS also developed a functional level scale for use in surveys:

- Regarding my current state of overall function, not just during attacks (check the ONE that best applies):
- My dizziness has no effect on my activities at all.
- When I am dizzy I have to stop what I am doing for a while, but it soon passes and I can resume activities. I continue to work, drive, and engage in any activity I choose without restriction. I have not changed any plans or activities to accommodate my dizziness.
- When I am dizzy, I have to stop what I am doing for a while, but it does pass and I can resume activities. I continue to work, drive, and engage in most activities I choose, but I have had to change some plans and make some allowance for my dizziness.
- I am able to work, drive, travel, take care of a family, or engage in most essential activities, but I must exert a great deal of effort to do so. I must constantly make adjustments in my activities and budge my energies. I am barely making it.
- I am unable to work, drive, or take care of a family. I am unable to do most of the active things that I used to. Even essential activities must be limited. I am disabled.
- I have been disabled for 1 year or longer and/or I receive compensation (money) because of my dizziness or balance problem.

For reporting the results of treatment, the post-treatment meniere's spells as a percentage of pre-treatment spells is used:

- 0 is Class A
- 1-40 is Class B
- 41-80 is Class C
- 81-120 is Class D
- >120 is Class E

Need to initiate secondary treatment is Class F.

The physiology of the inner ear is intricately designed to allow hearing and balance. The perilymph, which exists outside of the membranous labyrinth, is similar in composition to CSF. It contains high sodium and low potassium content. The endolymph is similar in composition to intracellular fluid. It is low in sodium and high in potassium. Endolymph is believed to be produced by the stria vascularis or the membranous labyrinth. The membranous labyrinth separates endolymph from perilymph. While there is no difference in pressure between the two regions, there is a difference in charge of 80 mV.

There are several theories about the production and flow of endolymph, as put forward in a review article by James in 2004:

- Longitudinal – endolymph is produced in membranous labyrinth, flows to endolymphatic sac, then to dural venous sinuses
- Diffuse – endolymph is produced and absorbed along the membranous labyrinth
- Periodic Flow – endolymph flows only with changes in volume or pressure

Endolymphatic hydrops leads to distortion of the membranous labyrinth. A build up in pressure may lead to micro-ruptures of the membranous labyrinth. Minor *et al* posit in their 2004 review article that this build-up in pressure may lead to micro-ruptures of the membranous labyrinth. The intermittent ruptures may be responsible for the intermittent nature of the attacks. Healing of the ruptures may account for return of hearing.

The etiologic agent for hydrops is not clear. Endolymphatic sac or duct obstruction has been proposed as an etiology. Though animal models in which hydrops is induced by endolymphatic sac obstruction, not all animals exhibit this effect and vertigo/nystagmus is present in few of those animals with hydrops. Clear a poorly understood alteration of production or absorption of endolymph is the cause of hydrops. Although immunologic insult to the inner ear has been proposed as an inciting event, this theory is controversial. Additionally, the role of hydrops itself in causation of Meniere's is not clear. Rauche *et al* in 1998 performed a study of 19 temporal bones with hydrops and did chart reviews. Upon chart reviews, 13 patients had Meniere's and 6 did not, suggesting that a subgroup of individuals have hydrops, but no Meniere's.

The natural course of Meniere's disease is often relenting. Silverstein *et al* in 1989 retrospectively reviewed patients with severe Meniere's disease who refused surgery and found that 57-60% of patients had few or no Meniere's-type complaints at 2 years, and 71% had few or no complaints at 8 years. The long term pure tone average in the group was about 50dB, with a 53% speech discrimination score. Caloric response was reduced 50%.

Medical management of Meniere's disease can be grouped into two categories: acute treatment and maintenance therapy. There is little controversy over medications to use for acute vertiginous symptoms. Medications with anticholinergic, antihistaminergic, and antiemetic properties are useful. See Slide #16 in the PowerPoint presentation for a table comparing some available acute remedies.

Maintenance, or preventive medical therapy is much more controversial. Diuretics and salt restriction are often cited as the first-line treatment for Meniere's disease. The putative mechanism of action is to alter fluid balance in the inner ear leading to a depletion of endolymph. Shinkawa and Kimura, in 1986 animal studies, were unable to demonstrate any beneficial effect on hydrops. Ruckenstein *et al* (1991) evaluated data from two double-blind studies by Klockhoff and Linblom and found that there was no statistical difference in measures of hearing, tinnitus, vertigo, or general condition between placebo groups and groups receiving diuretics.

Osmotic Diuretics such as urea or glycerol have been consistently shown to reduce symptoms in patients with Meniere's, but the effect lasts only for a few hours. Objective data about the efficacy of osmotic diuretics includes the normalization of the SP:AP ratio on electrocochleography.

Acetazolamide is a diuretic that has been shown to increase symptoms and hearing loss when given IV. It showed no benefit when given by mouth.

Vasodilators are purported to work by decreasing ischemia in the inner ear and allowing better metabolism of endolymph. Betahistine, a histamine agonist, has been a popular choice, albeit, not an intuitive one because antihistamines are used to combat acute symptoms. While several studies have claimed to show decreased vertigo with use of betahistine, a comprehensive review of the literature in Cochrane Database (2004) by James, *et al* found only one grade B study and four grade C studies, none of which produced convincing evidence for use of betahistine.

Immunologic therapy has been attempted for management of Meniere's. Systemic and intratympanic steroids have been of questionable efficacy. A double-blinded prospective crossover study by Silverstein *et al* showed no difference from placebo with intratympanic dexamethasone injections in patients with severe disease. He posited that steroids may have some efficacy in milder disease.

The Meniett Device, by Xomed, is an FDA approved class II device used for treatment of vertigo. The advocates of the device do not present a strong case for why it should work. It is a portable, low intensity, alternating pressure generator that is applied to the external auditory canal. It transmits pressure to the round window via a tympanostomy tube. Gates *et al* in 2004 published a prospective, randomized, placebo controlled trial of the Meniett device. Gates is also a paid consultant of Xomed. The study showed a statistically significant difference in "vertigo scores" between 1 and 3 months, with the users of the device reporting better control of symptoms. The difference vanishes at four months. The study was a short-term one (2 year data is pending) and did not use standardized measures of vertigo. Also good data on objective testing was not provided.

Intratympanic therapies aim to maximize the local effects of medication in the inner ear while minimizing systemic effects. The round window is the point of diffusion to the inner ear, and so some authors recommend visualizing the round window and removing mucosal bands that are often present over it. Aminoglycoside antibiotics, particularly gentamicin, are the most commonly applied intratympanic therapies. They damage hair cells of the crista, ampulla and cochlea.

Fowler in 1948 and later Schuknecht established the role of systemic streptomycin for bilateral disease, given 2g intravenously every day until bedside findings such as nystagmus, unsteadiness, or hearing loss were noted. Hearing loss and oscillopsia were a problem with this therapy, though reduction of the dosage of medications seemed to help. Systemic aminoglycoside administration is rarely indicated.

Many methods of intratympanic delivery of gentamicin exist. Side effects for all of the delivery methods include temporary imbalance or nystagmus, and hearing loss. Titration therapy is a well-established and popular regimen that was studied again recently by Martin and Perez in 2003. The prospective study of 71 subjects with severe vertigo is summarized below:

- Serial daily injections of buffered (pH 6.4) 26.7mg/cc gentamicin solution via 27 gauge needle into middle ear

- Injections repeated until vestibular symptoms developed (spontaneous or evoked nystagmus)
- At 2 years, 69% had Class A vertigo control, 14.1% had Class B
- 32.4% had hearing loss

The study overall shows a high rate of good responders, at 83.1%. But hearing loss was high, as is a problem with many gentamicin therapies.

Another method of gentamicin therapy is ablation using multiple daily treatments. A study by Jackson and Silverstein of 92 patients treated over an eight month period explores this method:

- Jackson and Silverstein – Study on 92 patients who underwent myringotomy and wick placement through to round window niche.
 - Pts. self-administered gentamicin drops TID until 100% reduction on ENG of vestibular response
 - 85% relief of vertigo, 67% improvement in aural pressure
 - 36% hearing loss

Harner *et al* in 2001 advocated low dose therapy:

- Harner *et al* 2001 – retrospective study of 51 patients who received 1 dose of 40mg/mL injection and were re-evaluated in 1 month and given another if needed
- At 2 years, 86% had vertigo class A or B
- He reported minimal change in PTA but drop in SRT's
- Claimed better hearing preservation with this regimen

Another method of gentamicin delivery is weekly administration of a single dose of gentamicin treatment for four treatments, or a continuous administration via microcatheter delivery. The microcatheter method results in extremely variable total dosage of gentamicin.

Chia *et al* performed a meta-analysis of different modalities of therapy in 2004. They found that low-dose therapy was the least effective in controlling symptoms, which is not surprising because of the lower amount of gentamicin used. However, hearing preservation was no better in this group than any other. The titration method exhibited the best results, and had the best hearing outcomes. Hearing loss was greatest for multiple daily dosing, but vertigo symptoms were not more improved in this group. Chia recommended titration therapy as a very useful method.

Endolymphatic sac surgery is purported to address the site of obstruction causing hydrops. There are 4 basic types of endolymphatic sac surgery:

- Decompression – removal of bone around the sac
- Shunting – placement of synthetic shunt to drain endolymph into mastoid
- Drainage – incision of the sac to allow drainage
- Removal of sac – to address the possibility that the sac may actually play a role in endolymph production

Jens Thomsen *et al* (1981) performed a double-blinded placebo-controlled study

comparing a sham surgery (cortical mastoidectomy) to endolymphatic shunt placement in 30 patients. Though all patients (placebo and control) statistically improved after surgery, there was no difference between placebo and control groups. A previously mentioned study by Silverstein in patients who refused surgery showed that non-operated patients did as well as operated patients. Endolymphatic sac surgery remains an extremely controversial operation. Potential complications include CSF leak, damage to the posterior semicircular canal, and meningitis.

Vestibular nerve section has been advocated because it can achieve vestibular suppression with minimal effect on hearing. It is a single step procedure, but often requires a neurosurgical approach (middle fossa, retrolabyrinthine/retrosigmoid) with the attendant potential complications of damage to the facial nerve, cochlear nerve, CSF leak, and meningitis. Hillman *et al* in 2004 retrospectively compared vestibular nerve sectioning to weekly intratympanic gentamicin. They showed significantly better vertigo control rates (25/27 Vertigo class A or B, 2.9 point improvement in functional level scale) compared to IT gent (10/15 class A or B, 2.3 point improvement in functional level). Hearing preservation was dramatically better in the vestibular nerve sectioning group (see slide 40 of powerpoint presentation). In spite of these seemingly superior results, many patients either cannot, or will not want to undergo an intracranial procedure when a minimally invasive one with good results exists. Hillman *et al* reported a 12.6% incidence of CSF leak requiring lumbar puncture and extended hospital stay.

Another surgery for Meniere's disease is the labyrinthectomy, which can be done through the mastoid or transcanal. This procedure is useful in patients with no serviceable hearing or who cannot tolerate an intracranial procedure. It is similar in efficacy to vestibular nerve section.

A bewildering array of medical and surgical therapies exist for treatment of Meniere's disease. The therapies that are well-accepted and likely beneficial include vestibular suppressant medications, intratympanic gentamicin, vestibular nerve section and labyrinthectomy. Though the other treatments have some strong advocates, they are clouded in controversy.

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