INVITED REVIEWS

Recent Advances in Medical Otology-Neurotology

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Recent advances in medical neurotology, basic science, and clinical investigations have greatly increased our understanding and ability to manage patients with disorders of the inner ear. The field is becoming more focused on the molecular biology of the inner ear to refine our understanding and the differential diagnoses of multilevel disorders. The time will come for us to utilize some novel diagnostic criteria that are very different from what is currently being used. For example, we may have to redefine Ménière's diseases and sudden hearing loss in terms of their molecular features. It is not unrealistic to predict that surgery for inner ear disorders will be replaced by direct perfusion of inner ear modulators to abort diseases in their earliest stage. The future of medical neurotology is evolving as a unique discipline of medicine with its own training and subspecialization dedicated to hearing and balance disorders.

Recent advances in basic science, technology and treatments have increased our abilities to manage hearing and balance diseases more effectively. The molecular dynamics of the stria vascularis and endolymph provided additional support for "old" and "new" treatments of Ménière's disease. The recent understanding of migraine and its association with episodic vertigo and hearing loss has improved our clinical ability to treat these patients. The videonystagmography (VNG) technology has made it easier to observe and record subtle eye movements to effectively examine and treat vestibular patients especially those with benign paroxysmal positional vertigo (BPPV) and dehiscence of the superior canal. Advanced audiometric and vestibular testing with rotating tuning fork test, stress electrocochleography (ECoG) and vestibular evoked myogenic potential (VEMP) have increased our diagnostic acumen. High-resolution computed tomography (CT) scans of the temporal bone allowed the visualization of several inner ear anomalies such as dehiscence of the superior canal and enlarged cochlear and vestibular

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aqueducts. Inner ear perfusion treatments with gentamicin and dexamethasone have effectively controlled Ménière's disease, by targeting the underlying pathology of disease, obviating the need for invasive surgery. Furthermore, and more importantly, dexamethasone perfusion leads to a 30% average recovery of speech discrimination. This paper is an overview of these recent advances and management of common vestibular disorders.

Molecular and ionic dynamics of the endolymph and stria vascularis

Recent studies of the inner ear molecular homeostasis have shown that the auditory and vestibular functions are dependent on active transport of ions (K^+, Na^+) and water between the different inner ear compartments, especially within the scala media.[1-4] The normal stria vascularis has several ion channels that move K^+ into the endolymph and Na^+ out of the endolymph. This is critical to maintain the auditory hair cell apex in the high K^+(endolymph) scala media and the body in the high Na^+ (perilymph) scala tympani to generate the endocochlear potential of hair cells. The cochlea also has active water channels, aquaporins, which play a major role in the maintenance of intracellular osmotic pressure.[5] Steroids have also been shown to exert positive effects on the inner ear function. In several animal studies, auditory-evoked brainstem response (ABR) thresholds and histopathology of the stria were improved, or stabilized, in treated animals by comparison to untreated controls. These effects appear to be due to increased Na^+ transport (out of the endolymph) and increased expressions of active water channels. Aldosterone has been shown to have positive effects on reversing stria pathology.[3] This finding explains, for the first time in our literature, why a low salt diet has been helpful to patients with Ménière's disease. A low salt diet increases systemic aldosterone via the renin-angiotensin cascade, which leads to increased aldosterone concentration; hence, its positive effects on the inner ear homeostasis. With added new knowledge in this area, our understanding of the mechanism of auditory and vestibular diseases will expand and new treatments will be developed. It will also allow us to redefine conditions like Ménière's disease and sudden hearing loss in terms of their underlying molecular dysfunction. Ultimately, intratympanic perfusion of different medicines and genetic vectors via the round window will be the optimal method to treat most inner ear disorders.

Office neurotologic exam

Traditional ENT, neuro exams and brain imaging are usually normal in patients with hearing and vestibular disorders. This is based on traditional teaching and practice probably worldwide. However, some institutions have changed their practices over the years, particularly in Europe. Recent knowledge of the anatomy and physiology of the inner ear and the development of clinical methods to observe and record vestibulo-ocular eye movements (VOR) and to evaluate vestibulo-spinal postural stability (VSR) have enhanced our ability to determine the side and site of dysfunction. The office-based video eye movement systems (VNG) have made it easier to observe and record normal and abnormal eye movements commonly associated with VOR abnormalities. For example, peripheral and central spontaneous eye movements, unilateral or bilateral vestibular hypofunction, and horizontal *vs* posterior canal BPPV nystagmus. Furthermore, subtle eye movements of incomplete vestibular compensation and those associated with the superior canal dehiscence syndrome have been easier to observe and record. Critical to the accurate interpretation of VNG is the familiarity with the semicircular canal innervations of the extraocular muscles that are shown in Fig. 1. There are several office VNG protocols, but the one that is most useful focuses on spontaneous nystagmus, vestibular head rotation nystagmus, post head-shaking and positional nystagmus exams. Several types of eye movements have been observed over the past eight years of using VNG in our institution.

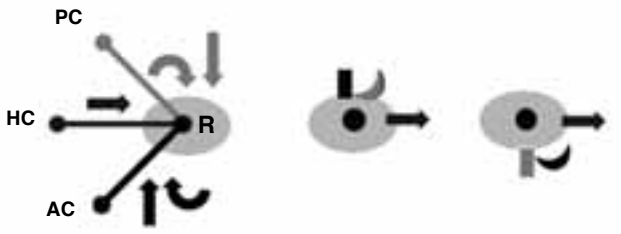

Fig. 1. Semicircular canal connections of the extraocular muscles. Note that stimulation of a given canal creates compensatory eye movements in the opposite direction of that canal. The horizontal canal (HC) innervates the ipsilateral medial rectus and the contralateral lateral rectus. The posterior canal (PC) innervates the ipsilateral superior oblique and the contralateral inferior rectus. The anterior canal (AC) innervates the ipsilateral superior rectus and the contralateral inferior oblique. Innervations of eye muscles differ for canal excitation and inhibition. This arrangement is for simultaneous excitation and inhibition of agonist and antagonist eye muscles.

Vestibular per-rotatory nystagmus intensity and symmetry can be observed or recorded to assess reduced unilateral and bilateral vestibular functions in the horizontal and vertical (which we have not traditionally examined) directions. The presence of post head-shaking nystagmus or ocular drift (without nystagmus) can help determine the side and the status of vestibular compensation. For example, post head-shake ocular drift to the right is a reflection of reduced right vestibular function with partial compensation, while a drift to the upward right oblique direction may be due to left anterior canal excitation or to right posterior canal inhibition. If post head-shake nystagmus is present, suppressed with optic fixation and associated with symptoms, it reflects uncompensated peripheral unilateral dysfunction. The office exam of VSR is less defined than that of VOR. Traditional stance, gait, and stepping tests can be used. The use of a high compliant foam pads to observe postural stability and reflexes with eyes open and eyes closed have been used to further "stress" and challenge the posture system. In my experience, active head-shake while standing on a high compliant foam pad is the most challenging part of the exam. Findings of increased postural sway, inappropriate sway strategy at the limits of stability and post stepping drift are very helpful for abnormal VSR. The neurotologic exam should also include examination of the cranial nerves and gross motor and sensory modalities. The cerebellar exam should include visual suppression of vestibular nystagmus during active head rotation.

Videonystagmography and benign paroxysmal positional vertigo

Videonystagmography is essential to determine the side, the involved canal, and the underlying mechanism in BPPV. Although not frequently stated in the literature, the Dix-Hallpike exam stimulates the posterior and horizontal canals on the down side and the anterior canal on the up side. Furthermore, as shown in Fig. 2, BPPV can be due to cupulolithiasis (otoconia adherent to the cupula) or canalithiasis (otoconia floating in the endolymph). With the aid of VNG, the canal, or canals, and the mechanism of BPPV can be determined. This is critical because the treatment is different for each canal and for each mechanism. In my experience, the Semont maneuver[6] is effective in treating posterior canal cupulolithiasis and the Epley maneuver[7] for posterior canal canalithiasis. With VNG, horizontal canal BPPV and its mechanism can be easily diagnosed. Nystagmus is horizontal, stronger, and with no rotational component. Excitatory nystagmus of the down ear is observed with canalithiasis and inhibitory nystagmus with cupulolithiasis. The Lempert maneuver is used for treating horizontal canal canalithiasis and the Hamid[8] maneuver is used for horizontal canal cupulolithiasis.

Traditional vestibular testing: what to order and when?

The time-honored electronystagmography (ENG) test remains the most frequently utilized vestibular test worldwide. Rotating chair and dynamic posturography have also been less frequently used. Several observations can be drawn from a database of 10,000 patients who underwent the three tests from 1985 to 1995 during my tenure at the Cleveland Clinic.[9] First, overinterpretation of the ENG results, especially the oculomotor test results, which frequently leads to unnecessary neurological investigations and magnetic resonance imaging (MRI) stud-

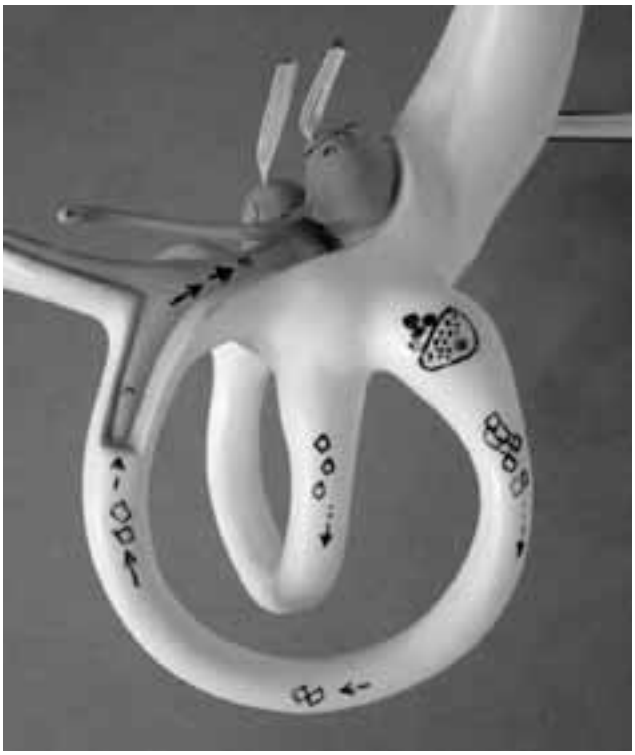

Fig. 2. Left Dix-Hallpike exam. Note that the left posterior and horizontal canals are being stimulated (i.e. vertical with respect to gravity). The right anterior canal, not shown, is also stimulated. Otoconia can be floating in either canal (canalithiasis) as shown in open diamonds. Otoconia can be adherent to the cupula (cupulolithiasis) as shown for the posterior canal (dark black dots).

ies. The yield of "central eye movement abnormalities" in the above database was less than 5%. Therefore, it is advisable for ENG readers, especially the new ones, to interpret eye movements cautiously. It is not inappropriate to read ENG oculomotor tests as normal for several years while "storing" their pattern for more accurate interpretation with increased experience. Most abnormal eye movements that are of clinical significance can be seen during a thorough neurotologic exam. Second, ENG raw tracings must be viewed and evaluated instead of solely relying on "computerized" printouts. Often, computer software will produce a result while the raw data is merely noise. Third, ENG is insensitive to record torsional nystagmus and, therefore, it cannot be used to record benign positional nystagmus. Fourth, care must be taken when interpreting the computerized results of the caloric test to accurately determine true *vs* relative unilateral vestibular hypofunction and to avoid missing true bilateral reduced caloric responses.[9,10] It is also important to recognize that ice-cold irrigation in the supine position is not a maximum stimulation of the vestibular nerve. The reason is that in the supine position, cold irrigation leads to canal inhibition and a reduction in the vestibular resting neural activities from 100 spikes/sec to zero. In the prone position, cold irrigation leads to canal stimulation and increases the vestibular nerve resting discharge from 100 to 400 spikes /sec, which is three times greater than that of the neural signal in the supine position.[9] Another important point is that the caloric response is a low-frequency response[10] of the VOR and absent caloric responses do not imply total vestibular function loss. Rotating chair test is useful in testing the high frequency VOR (up to 2 Hz), determining the degree of residual vestibular, slow-phase asymmetry and phase shift.[9] The degree of residual vestibular function can be obtained from the history, physical exam, and the shape of doll's eye movements if acquired during the standard ENG protocol. Increased phase has little clinical significance except for patients who undergo vestibular nerve section to determine if "true" loss is present. The active head rotation test is more practical in determining the VOR residual gain when ice caloric responses are absent and the history is positive for severe vestibular loss (i.e. evident oscillopsia). The phase and asymmetry from the active head rotation test are of limited clinical value. Dynamic posturography test has been used in several areas of the world since 1985.[11] The test is comprised of sensory and motor components. The sensory test gained wider acceptance and is useful in functional assessment of balance[11,12] and in tailoring vestibular rehabilitation programs.[13] The sensory test is also helpful in detecting "aphysiologic" sway patterns[13-15] especially in medical legal cases. The motor test is less utilized. The sensory test, including sway strategy, can be determined from the neurotologic exam as described above. The initial cost and maintenance of the chair and dynamic posturography systems are becoming unaffordable under current medical economic circumstances. The value of these tests in the research field and in special applications (e.g. space medicine) will naturally continue. Finally, it is critical to emphasize that vestibular tests are electrophysiologic functional tests that may not lead to a specific diagnosis of the underlying disease and that their results are part of the comprehensive medical evalaution needed to establish the diagnosis and treatment.

New auditory and vestibular tests: stacked ABR, VEMP, and rotating tuning fork tests

A new method of recording ABR, stacked ABR, has been introduced to increase the sensitivity of ABR to detect small acoustic tumors.[16] The protocol is based on stimulating "all cochlear nerve fibers" and "stacking" the amplitude of the response; however, it is time-consuming and requires new equipment. It has yet to be determined whether it is more cost-effective and reduces the number of MRIs often ordered for asymmetric sensorineural hearing loss to rule out acoustic tumors. Most patients and physicians, in my opinion, would eventually request an MRI to resolve the question as to whether an acoustic tumor exists. The protocol will naturally be of help in areas where MRI is not widely available.

A relatively novel evoked potential test, VEMP, will probably be more widely used in clinical settings.[17-20] Vestibular evoked myogenic potential response is acquired with acoustic stimulation of the inner ear saccule and the resulting myogenic inhibition response of the sternocleidomastoid muscle is recorded. The response is typically biphasic at 13 to 23 msec post stimulations at 95-100 dB HL tone burst intensity. Unlike the caloric ENG response, which is mediated via the superior division of the vestibular nerve and the vestibulo-ocular tracts, VEMP is medi-

ated via the inferior vestibular nerve and the vestibulospinal tracts. The test is used to measure the inferior vestibular nerve response (it may be absent in vestibular neuronitis and acoustic tumors) and the saccular function (often "hyperactive" in Ménière's disease and other "hydropic" inner ear diseases). It is particularly helpful in subclinical or atypical hydrops in cases of superior canal dehiscence, Tumarkin's crisis, or symptomatic large cochlear aqueducts.

New hearing tests to determine cochlear dead regions[21] and speech in noise[22] have not been widely utilized. It is also becoming more important to incorporate the frequencies of 125 Hz and 256 Hz into pure tone audiometry to allow for better identification of early low-frequency loss and abnormal audiometric configurations.

The rotating tuning fork test[23] has a high sensitivity and specificity for cochlear hydrops. This new test is administered by rotating the 256 Hz or the 512 Hz fork 360 degrees during the air conduction test. The resulting amplitude modulation, which is clearly heard by normal ears, is blunted in hydropic ears.

Superior semicircular canal dehiscence syndrome

Dehiscence of the superior canal is a congenital defect in the eminence of the temporal bone. The clinical picture is often subtle and most patients present with persistent motion intolerance and visual symptoms with loud sounds and pressure changes.[24] Neurotologic exam typically shows bone conduction hypersensitivity, down beat nystagmus or "jumping eye movements" to loud sounds or tragal compression. Audiometric findings show low-frequency conductive hearing loss, similar to that seen in Ménière's disease, and ipsilateral acoustic reflexes. Electrocochleography, with TM electrode, is usually positive with the SP/AP ratio greater than 0.5. Vestibular evoked myogenic potential shows elevated response thresholds and ENG is not usually helpful. It has been my experience that post head-shake ocular drift is also a sensitive clinical parameter. A high resolution CT scan of the temporal bone (<0.5 mm cuts), shown in Fig. 3, confirms the presence of the dehiscence. Coronal sections may not be sensitive enough especially with standard cuts. Although less common, dehiscence of the superior canal may be bilateral.[25] Treatment can be medical (acetazolamide, topiramate), PE tube (with pressure-induced symptoms), or surgical closure of the bony defect via a middle fossa or transmastoid approach.

Migraine and Ménière's vertigo

The differentiation between Ménière's disease and migraine is becoming more important in neurotology because the treatment approaches are different. Vestibular dysfunction in children or adults with vestibular Ménière's disease can be forms of migraine. The differentiation between migraine and Ménière may be challenging because migraine can mimic typical Ménière's disease, with fluctuating low-frequency hearing loss, tinnitus, and vertigo.[26,27] A careful history of past headaches, a family history of headaches, migraine trigger factors precipitating dizziness and non-headache migraine symptoms during dizziness (photophobia, phonophobia, and focal

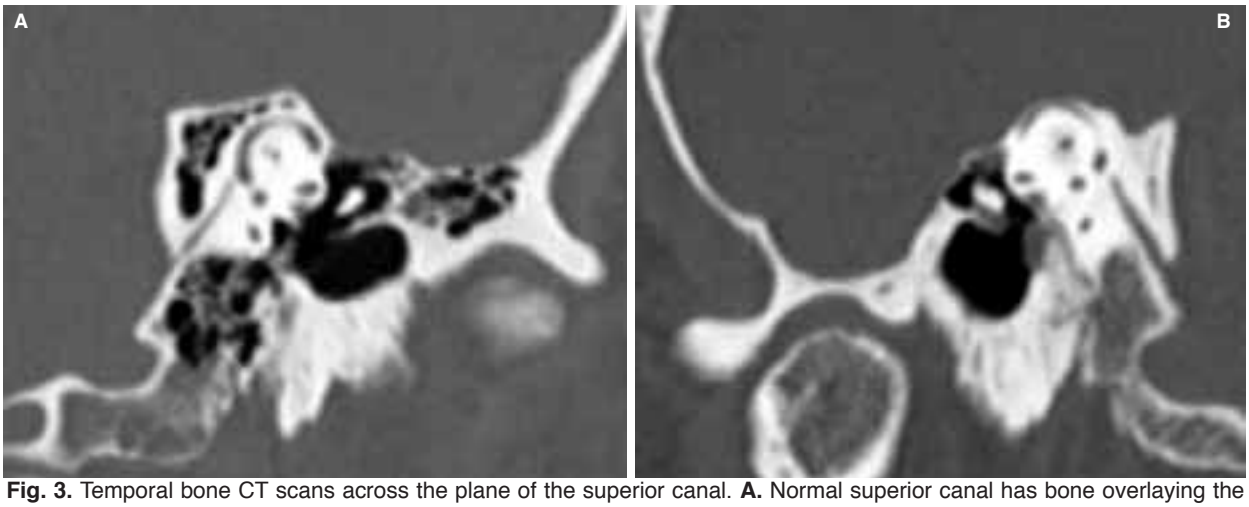

Fig. 3. Temporal bone CT scans across the plane of the superior canal. **A.** Normal superior canal has bone overlaying the superior aspect. **B.** A dehiscent canal has no bone.

neurologic symptoms) are very important to elicit. Most of these patients have had migraine or there is a strong family history of migraine. The history, neurotologic exam (as above), basic audiometry, and brain imaging (when indicated) are sufficient to make the diagnosis of migraine vertigo. The association of headaches with vertigo is typical of migraine, but is not present in all patients. In my experience, migraine dizziness is nonepisodic (as in Meniere's disease) and is not associated with severe fluctuating low-frequency hearing loss. The treatment of migraine is both abortive and prophylactic. A new seizure medication (topiramate) has been effective in treating migraine vertigo particularly in patients with Ménière and migraine. It is also important to optimize migraine treatment for better control of coexisting vestibular disease (e.g. compensated vestibular neuronitis and BPPV).

Intratympanic perfusion for Ménière's disease, immune inner ear disease and sudden hearing loss

The pathology of Ménière's disease is frequently "idiopathic" endolymphatic hydrops. Immune-mediated inner ear disease is similar to Ménière's, but has a more rapid course affecting both ears.[28-30] Recent data support an ionic imbalance of the endolymph as the final common pathway to endolymphatic hydrops and suggest that steroids improve and restore normal stria vascularis function by increasing Na^+ transport and expression of active water channels (aquaporins) in the endolymph surrounding tissues.[1-3,31,32] Several clinical studies have been published since the introduction of the use of intratympanic steroids to treat the inner ear.[33-35] A most recent review of published literature suggested "a weak recommendation" for the use of steroids in sudden hearing loss and indicated that the clinical studies did not adequately demonstrate the efficacy of intratympanic steroid treatment for Ménière's disease and tinnitus.[36] However, conclusions were drawn without much subjecting the relevant data to rigorous meta-statistical analysis; therefore, what the authors meant by "weak recommendation" was not clear. Another study found that intratympanic steroid perfusion did not result in relief of vertigo or improvement in hearing loss at least 12 months after the treatment, but the dose was not mentioned, nor were the inclusion criteria defined.[37] Long-term (3 years) results of dexamethasone (24 mg/ml) to treat early stages of Ménière's disease showed 90% vertigo control and significant increases in speech discrimination (30% to 60%) in 90% of patients.[28,38,39] In another study, where the stage of the disease was not stratified, the efficacy of dexamethasone (10 mg/ml) was evaluated with respect to the long-term control of vertigo in patients with Ménière's disease.[40] Only 24% of the patients had control of vertigo with a single course of injections. The rate of vertigo control increased only to 47% with subsequent courses of therapy.

There are several reasons, in my opinion, why the data on steroid perfusion are variable. First, the dose and the type of steroids used show a wide variation. Steroid doses ranged considerably from 4 mg/ml to 24 mg/ml (dexamethasone) or 40 mg/ml (methylprednisolone). While the advantage of intratympanic perfusion is to deliver a higher concentration to the inner ear, it appears for most studies that the dose was dependent on what was available in the market instead of the maximum dexamethasone dose of 24 mg/ml. In addition, some studies used a lower dose followed by multiple injections; however, from a pharmacokinetic point of view, this is not sufficient to deliver therapeutic concentrations.

The most common type of steroid used has been methylprednisolone, (based on) an animal study that favored methylprednisolone relative to dexamethasone because it yielded "higher concentrations" in the endolymph after intratympanic injections.[34] Although the above-mentioned study provided relevant information regarding the pharmacokinetics of different steroids, my re-evaluation of the results of these two medications has been in favor of dexamethasone, showing it more efficacious. The study clearly showed that absorption of dexamethasone into the stria and surrounding tissues was more rapid, in contrast to methylprednisolone, which remained in the endolymph longer than dexamethasone by a factor of 4 to 6 hours. It is known that steroids act intracellularly within the stria and surrounding tissues after being passively or actively endocytosed. Hence, the higher rate of endocytosis, the greater intracellular efficacy. Thus, the presence of high methylprednisolone concentrations in the endolymph reflects an inverse relationship with its intracellular incorporation and efficacy, making dexamethasone more efficacious for intratympanic perfusions. Unfortunately, dexamethasone 24 mg/ml was removed from the mar-

ket in the late 2000 and can now only be produced as a compound.

The second reason that lies in the variability of steroids is the disease stage. It appears that most studies perfused the ear at a late stage of the disease. Our experience has been that perfusion should be performed at an early stage of the disease before, supposedly, the stria has not undergone permanent damage. High concentration of dexamethasone has the best chance of controlling Ménière's disease at an early stage, at which point the cochlea is still amenable to the now well-established positive effects of steroids on the stria and its ionic homeostasis with surrounding structures.

Intratympanic gentamicin perfusion has long been used to treat Ménière's disease[41-48] on the basis that it reduces the production of endolymph by the vestibular dark cells and destroys the remaining "non-functioning" vestibular sensory epithelia. Gentamicin is effective in controlling vertigo in the late stage of the disease when hearing loss has already become severe. However, it is associated with significant hearing losses (10-30%) if used at early stages of the disease. The use of gentamicin and steroids has reduced the number of surgical operations for vertigo over the past decade.[49] Gentamicin was also found to be effective in treating drop attacks in Ménière's disease.[50]

Another important issue with intratympanic treatments is the need for controlled studies. Although we all would much appreciate seeing the results of long-term controlled studies in medicine, this may have significant drawbacks on economical and ethical grounds. These studies may indeed be justified for new, experimental, and expensive treatments that have significant morbidity, for example, cancer treatments. The natural history of Ménière's disease is well-documented and can actually serve as a benchmark against which treatments can be judged. The side effects of intratympanic steroids and gentamicin are minimal. A successful outcome is achieved in about 90%, with treatment at an early stage (steroids) or late (gentamicin), this far exceeds the placebo effect of about 30%.[51-53] Gentamicin perfusion has been used since 70's and clinical experience has validated its use even without the need for further "randomized" trails.

The basic science and clinical applications concerning gentamicin and steroids are so established that, in my opinion, it is difficult to justify reserving this treatment for two years (time required to elapse for the outcome of treatment for Ménière's disease), especially in situations in which steroid treatment for early Ménière's disease is associated with significant hearing gain and vertigo control.

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