# Recent Advances in the Diagnosis and Treatment of Meniere's Disease

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Anna Scala: Welcome everybody and thank you very much for being with us today. I'm Anna, Education Manager in Inventis. Welcome to this second appointment with our webinar campaign on balance, campaign, which is part of the Inventis project, Academia. Academia educational program is an initiative aimed to promote the scientific divulgation on topics related to the equipment we supply among professionals in hearing and balance care. The webinar is today led by an excellent guest, Professor Augusto Casani of the University of Pisa, whom I would like to thank for his precious collaboration. The main subject of the webinar is the recent advances in the diagnosis and treatment of Meniere's disease. The moderator is, as usual, Dr. Enrico Armato, ENT doctor at ULSS 3 Regione Veneto and Inventis brand ambassador. I warmly invite all of you as usual to write down any questions in the space provided that you should see on the screen. All the questions will be display on the spot by Dr. Armato, who will collect them and then ask them to Professor Casani at the end of the webinar. One more thing. I take this occasion to remind you all the appointment with the third webinar that Inventis Academia schedule for this new year. Next March the 3rd, Dr. Andrea Castellucci will talk about the feasibility of using the wage IT to detect the Dane Vul canal in BPPV, presenting with positional downbeat in stackables. If you haven't done it yet, I warmly invite all of you to subscribe from the Inventis social media pages. You can even e-mail me at webinar@inventis.it. I will be more than glad to provide the registration link to you. Now, I leave the ward to my guests. Enjoy the webinar.

Enrico Armato: Hello, the attendees. The topic today is Meniere's disease is a challenge for the auto mineralogist that is always ongoing. There are many pathogenetic hypotheses, a variable spectrum of symptoms. Different therapy has been proposed, each one with own timing. Managing a patient with endolymphatic hydrops is never easy. The repetition of crisis over time very often also put a strain on the patient's emotional balance. Today, we will have the opportunity to hear from a friend and colleague, who, for decades, has focused his attention on this clinical entity.

With great competence, he will guide us through the diagnostic and therapeutic manners with the hope of making our daily activity similar, but above all, more effective. Thanks. I will stop for all z's. The world is yours.

Augusto Pietro Casani: Thank you, Enrico. First of all, I would like to thank you, Inventis, for this possibility to talk about a topic that is very interesting and is very challenging. Thanks for the introduction to Dr. Armato, to my friend, Enrico. Well, Meniere's disease was described in the 18th century, but now, Meniere's disease remains a puzzle in etiology, prognosis and treatment. For my clinical point of view, Meniere's disease is a syndrome that is caused by uncommon disorders affecting the inner ear and is characterized by episodes of acute rotatory vertigo, tinnitus, sensorineural hearing loss and also fullness. This disease is chronic, is debilitating, and the course absolutely is unpredictable. It usually afflicts one here. In the majority of the cases, we have a unilateral Meniere's disease, but sometimes we can have also an involvement of the other ear. This is a very big problem because the bilateral Meniere's disease cause some problem from therapeutic point of view. Normally, this condition is associated with endolymphatic hydrops, but endolymphatic hydrops itself doesn't explain the attacks of vertigo because sometimes we can find endolymphatic hydrops also in individuals without any symptoms compatible with Meniere's disease or with something of vertigo and hearing loss. We can consider that endolymphatic hydrops is a hallmark of Meniere's disease, and this may be necessary but is not sufficient for the development of the disease. This is very important. Well, regarding the epidemiology, these are some data about the incidence. If you know that the incidence is the number of new cases for years, but the very important thing is the point prevalence. The prevalence is the number of cases that is relative to a number of subjects. Normally, in Italy and also in USA, the data are similar. We can evaluate that we have a prevalence of 190 cases over 1,000 of people. This is very important. For example, a city like my city, that is, Pisa is a university town. We have almost 1,000 inhabitants. We think that in Pisa, we have almost 200 persons suffering from Meniere's disease. Regarding the

epidemiology, we have to consider that the age of onset is normally during the mean age from 30 to 50 years, with a mild prevalence in females, but we have to consider that this Meniere's disease, this syndrome, is uncommon in childhood. But we have to consider that almost in 10 percent of cases, Meniere's disease is diagnosed after 65 years of age. This is very important because Meniere's disease that appears in the old age can create some problems. For example, the Tumarkin's otolithic crisis is more common in patients suffering from old Meniere's disease, but also in patient in which Meniere's disease appear after the 60 years old age. Also, we have to consider that when the Meniere's disease is associated, and this is very common, with migraine, the age of the patient is younger, so there is some difference also in the comorbidity of these diseases. Regarding the bilateral of Meniere's disease, this is a very important topic because when I had bilateral Meniere's disease, this create a lot of problems regarding the therapy. I cannot perform an ablative, a surgical treatment of Meniere's disease, for example, vestibular neurectomy or also panic gentamicin in a patient with a suspected bilateral Meniere's disease. Regarding the incidence of Meniere's disease, there is a very spread of present age because for example, in some cases, this older Arenberg talk about 50, 60 percent of bilateral Meniere's disease. In other type of casistic, we can add only 10 percent in our experience, no more than five, seven percent of Meniere patients suffering from bilateral Meniere's disease. Normally, in our experience, the onset of the hydropic symptoms in the other ear appears after many years from the initial diagnosis. Usually also, the clinical picture is different because normally, the second ear that are involved with this involvement from the hydropic problem show a less intense crisis. The vertigo is less than tracks, is less frequent. Normally, we have a more prominent audiological involvement, this fissure are typically in our casistic. Well, regarding the etiopathogenesis of Meniere's disease, this is another very difficult topic to explain because we have a lot of trigger factors. For example, allergens, infectious agents, vascular events, genetic variants. These create some problems of the inner ear homeostasis and, in particular, the production and the absorption of endolymph. Probably after the influence of the endocrine response and

also after the influence of the innate immune response, we can have the possibility of an alteration of the inner ear homeostasis, and this creates the phenotype of Meniere's disease. The aural fullness, the tinnitus, the hearing loss, the vertigo syndrome, characterized by recurrent crisis and also the EH. We have to consider that Meniere's disease is a final type relative to alterated inner ear homeostasis that create this endolymphatic hydrops. There is a lot of experience support in various hypotheses of the Meniere's disease, for example. Some doctors talk about the high prevalence of autoimmune disorders. Other, they talk about the presence of both respiratory and food allergy. This has been a staffer that in Meniere's disease patients and in some patient, treatment of the allergy can reduce the symptoms typical of Meniere's disease. Also the migraine is very important and it's possible that Meniere's disease and migraine have a common it's ideology, this communist ideology has been suggested. We can talk about genetic factor, inflammatory factors immunologic in this function, infection, trauma, and also vascular events that create this alteration of the homeostasis of the inner ear, that create the conditions for the endolymphatic hydrops and also for the manifestation of the Meniere's disease. We have to remember, we have the two Always in mind that endolymphatic hydrops itself, does it mean absolutely Meniere's disease. Probably we need the other conditions that create the conditions for transform and endolymphatic hydrops in clinical symptoms typical of many this is, and this is another slide that try to explain that the characteristic of the isopod genesis of Meniere's disease. Well, what's the problem in Meniere's disease? First of all, the diagnosis and the recently a joint committee between the American Academy of Otolaryngology and Surgery the baton in society, the Japan and the Korean society for balance and equilibrium. Also, the European Academy of new ontology defined some issue about the guidelines for diagnosis of Meniere's disease and this is very important because, with this type of resolution, we have the possibility to define the Meniere's disease, so we can evaluate Meniere's disease as definite. When we have two or more spontaneous episodes of vertigo lasting from 20 minutes to 12 hours. This is very important. We have to know it automatically documented either

sensory neural, low to medium frequency in the affected here, at least in one occasion, before, during, or after one of the episodes of vertigo and the symptoms eps to be fluctuating. We have the possibility that in the initial phase of disease, during the intercritical phase, we have no absolutely possibility to evaluate a damage to the hearing and also a damage to the vestibular symptoms using the vestibular instrumental assessment. Well, but we have to consider something. For example, in the late phases of the Meniere's disease, brief episodes of acute dizziness and unsteadiness can be preserved also without rotational vertigo. Rotational vertigo are more common in the early phases of Meniere's disease. Also, sometime some brief episode, especially in the late phase of Meniere's disease, can be triggered by positional change. A differential diagnosis with benign positional vertigo can be made. Duration of the episode. Not even is possible to evaluate correctly because our patients say, Dr, I have a long period. My vertical asked the two days, three days. But you have to ask the patient to talk about the acute phase where the patient refer the spinning sensation. This is very important for the diagnosis. Also, we have to consider that the vertical episode of vertigo are to be spontaneous. But sometimes we have the possibility that the patient that reports the episode of acute vertigo after, for example, excessive consumption of sodium or pathway. This is very important because sometimes the same triggers, death rate triggers formula disease are the same for the vestibular migraine and sometimes some patients can have some episode triggered by low-frequency sound of high intensities, the so-called Tullio phenomenon, and also by changes in pressure. These episodes normally are present in the late phase of the disease, where there is the possibility that they are dropped off the saccule can create a life few bruises with the stapes, footplate and so. The saccule became sensitive to the pressure and also to high sound out in density and low-frequency sounds. Well, but also we have to consider the Meniere's disease can have also a familiar origin. This is a slide from my friend Anthony Lopez. His gametes who study a lot about the subtitle of Meniere's disease and also of the familiar possibility of the genetic origin of Meniere's disease. But we have only to consider that familiar Meniere's disease, be observed in

no more than 10 percent of the cases, and normally show a feature of autosomal dominant inheritance. This is very important for the clinically history-taking because we have to ask the patient if there is any other subject in the family that suffer from vertigo or a clinical type of Meniere's disease? Well, this is the typical Meniere's disease, but we have some clinical variants of this problem because, for example, sound spaceships can have a delight endolymphatic hydrops. What is this problem? The problem is that these patients have seen those in the new ear that occur many years after the onset of profound deafness on the other ear. We can impotise that the damage induced by a viral infection, trauma, or other causes produce in a ear in unilateral sensorineural hearing loss and probably some alteration of the hidden ear. For example, in the endolymphatic sac on the vestibular aqueduct that after a period that can be very long, could produce an endolymphatic hydrops in the same ear. This is the so-called ipsilateral. The life and the lymphatic hydrops are also in the contralateral ear. The so-called contralateral delight and the lymphatic atoms. In this last cases, we are typically linear in a patient in which the other ear is deaf. The ipsilateral delayed endolymphatic hydrops is characterized by recurrent vertigo attacks caused by endolymphatic hydrops in the ear without hearing. We have no hearing symptoms, we have only some recurrent vertigo. I'm sorry for the low quality of my picture. This is a case of patient, male, 45 years with the right profound hearing loss from childhood. From 2010, recurrent attacks lasting 2-4 hours. The patient suffered from migraine with aura, but the patient had no improvement with antimigrainous treatment. We can see that the video that he posted is normal even with the shift paradigm, but we can evaluate with the caloric test a reduction of the activity on the right labyrinth . This is very important because as we've seen in the next slide, the dissociation between VHIT test and caloric test is a typical owner of Meniere's disease. On the basis of this result, we have treated this patient in March 2020 with intratympanic gentamicin. After eight months, the patients have no more vertigo attacks. This is a typical case of ipsilateral delayed endolymphatic hydrops, but another important variant of Meniere's disease is the tumarkin's otolithic crisis. This is a clipper with the patients that's talking without

any problem. Quite sudden delayed, there is a loss of equilibrium, and the affected collapsed on the ground. This is the so-called tumarkin's otolithic crisis. This is the original description. One day he was standing at his desk talking to a client when suddenly he slumped to the floor. He had no vertigo, no loss of consciousness, and no malaise. This condition can be due to apoplexy, the so-called otolithic crisis, otolithic catastrophe in which there is the possibility that the otolithic is destroyed completely. This is another interesting clip, taken from a camera. This man suddenly is incredible, but this is the typical tumarkin's otolithic crisis. Well, normally as we have seen in the previous slides, tumarkin's crisis occur typically in Meniere's disease patients in the late stage of the disease, or in Meniere's disease, patients whose onset is over the six decades of life. This is very important because tumarkin's otolithic crisis can have dramatic consequences from a traumatic point of view, probably in the younger patient, the saccular structure could be more resistant to the sudden hydropic enlargement. The occurrence is very variable, but we must pay attention to the description of the patients because this photo reports up to 72 percent of dropout, absolutely is not true. They real tumarkin's otolithic crisis is that we have seen in the previous slides. In the advanced phase of Meniere's disease, sometime the patient can have a brief conditional unsteadiness of loss of balance, but the sudden loss of equilibrium, typical tumarkin's otolithic crisis is absolutely different to which describe them from this photo. This is a very disabling symptoms because it occurs without any warning, can result in severe injury, but differently from the syncope of drop attacks coming from neural central nervous system disease. The preservation of sensorium is absolutely normal and there is no precipitating factor, no aura, and the falls normally are abrupt and violent. Regarding the prognosis the majority of the patients remit spontaneously, although other Meniere's symptoms continue to progress, the prognosis is relatively benign, but it's not benign the risk of severe injury. A conservative approach is recommended. Sometimes it's possible to make ineffective treatment with intratympanic gentamicin as reported in this paper, but recently also from this paper, from the jobs in Med School of Medicine, intratympanic steroid we use

it as first-line therapy conservative treatment for Meniere's disease and also for drop attacks related from hydropic condition. But in our experience the best results are obtained with intratympanic gentamicin. Well, the other variance of Meniere's disease is the so-called vestibular Meniere's disease or Cochlear Meniere's disease. What means vestibular Meniere's disease? Well, sometimes in the initial phases of the hearing loss could not be clearly interpreted by the patients, but in this case, it is very important to have a different diagnosis with vestibular migraine because probably a lot of vestibular Meniere's disease are only and simply patients suffering from vestibular migraine. More important is the concept of cochlea Meniere's disease. We know that a lot of patients with a sudden sensory neural hearing loss with the involvement of the low tones can evolve towards a definite Meniere's disease and this evolution is more frequent when the sudden hearing loss is recovered. Another possible indicator of evolution towards Meniere's disease is the presence of tinnitus during the first episode of low-tone sudden hearing loss. This is the incidence of Meniere's disease during the presentation with the low-frequency hearing loss more than one episode that the gent age of evolution Meniere's disease is very high. Well, vertigo attacks is the most frequent symptom in the initial phase. Also as we can report that in these two tables, there is the possibility that hearing loss is present in all the symptoms as initial symptom of Meniere's disease in 13 percent of the patients. In these other tables, we can evaluate as hearing loss alone is present that all in six percent of the patients, but when the hearing loss is associated with the tinnitus we have white 20 percent of the patient that had this type of symptoms as the initial symptoms. Less than 30 percent of Meniere's disease patient has the two symptoms in the initial phase. This is very important because not even these patients fulfill the typical condition of the definition of Meniere's disease. The guidelines say that the diagnosis of Meniere's disease is primarily a clinical diagnosis, but not all the Meniere's disease are definitely there. If we don't get a diagnosis, you will not get therapy. For example, in this case these patients has multiple acute attack of vertigo with fullness but no hearing loss and no migraine. Other patients multiple attacks with sudden and stable hearing loss, other patients

were left severe hearing loss with a lot of crisis of vertigo attacks and which here is responsible of the Meniere's disease. This is very important also because if I have to treat the patient with an ablative therapy, I am absolutely to know which ear is involved from the hydropic condition. Also I have to exclude the presence of the disease and the hydropic condition in the other ear. This is very important because we have to approach the role for instrumental assessment. In the early Meniere's disease, the instrumental assessment for us is very important and would be of great interest for the clinicians because sometimes the diagnosis is doubtful. Because sometimes the patients have symptoms that don't meet the international criteria. Also if we suspected a bilateral involvement too the hearing test is very important. These are the stage typically, first with the involvement that's prevalent on the low frequencies, sometimes there is the possibility of an evolution with the acute of the high frequency. Sometimes we have a flat involvement type of hearing loss and normally is not so common that the patient has a complete deafness, sometime something in the ear remain. On the basis on the level of hearing loss, this is the stage of Meniere's disease as being proposed from the guidelines of 1995. Interesting methods, I don't use this method, but I think it's very important to mention in that comprehensive review is the electrocochleography. This measure the electrical potential arising in the cochlea and the VII nerve in responsive to stimuli within the first five milliseconds. When we add the condition of endolymphatic hydrops, we're in amplitude rational summating potential, amplicon potential, action potential that is more consistent with the presence of Meniere's disease. On average, this ratio of more than 0.45 is considered abnormal. We have abnormalities of the amplitude ratio with a more summation potential inside the action potential. The most important thing that reduce the application of the electrocochleography in the clinical practice was that the registration has to be made with an electrode, the best to place it in the promontorium. Now there is also some type of electrode that can be applied only to the membrane today to the eardrum without any eardrums perforation by this electrode. Well, the vestibular tests of the bedside examination is very important and I report cases of patients that arrived to our

observation. Because this patient has to be treated with intratympanic gentamicin. We can see it right beat in the second degree of nystagmus that increase the NAs after head-shaking test. While I was preparing the solution for intratympanic gentamicin after half an hour, this is the condition. First, we have right beat nystagmus, and now we have a life B nystagmus. The patient develop a vertigo attacks during our observation. This is one of the less of the few demonstration of the so-called irritative nystagmus. But as we have seen in the previous slides, a condition very important to evaluate is the instrumental assessment with caloric tests and video head impulse test. This is an hour experience in 2015 in which we used the video impulse test and the caloric test in two patients. One group of patients were treated with intratympanic gentamicin. Another group of patients were treated with the conservative therapy. Well, the results are that. The next slide. In the group where the patients were treated only with the conservative therapy, we have a normal response of the video impulse test. But on the contrary, we have a reduction of the activity of delivery using the caloric test. In the patients treated with intratympanic gentamicin, we have a reduction of the activity of delivery with the caloric test. Also, the video impulse test showed a reduction of the activity. The high-frequency vestibulo-ocular reflex is preserved even in the late stage of Meniere's disease. The dissociation between the Caloric test and the video head impulse test is an instrumental hallmark of Meniere's disease. While the video impulse test can be considered as at the endpoint of the treatment when they use the intratympanic gentamicin These are, an example of a patient is very interesting because this patient is very old,86 years. The patient was diagnosed as affected by right Meniere's disease 30 years ago, was treated with betahistine and benzodiazepine with good results for almost 25 years. But, recently in October 2019, a reappearance of vertigo attacks with the last episode in December 2020. This is the hearing test with a bilateral hearing loss more evident in the right ear. These are the results. That absolutely no melody of the video impulse test also with the shift paradigm, but a reduction or the caloric test. This can be considered a late Meniere's disease because the patient is suffering from a disease from 30 years. So this is very important for an

assessment, vestibular instrumental assessment of this pathology because there is two possibilities. For example, we know that the eye drop create the damage, particularly on the peripheral part of the crista ampullaris where there is the Type II hair cells. While normally intratympanic gentamicin affect more. He believed the eye cells on the central part of the cupula receptor. In this part of the crista ampullaris, where we have the Type I, the basic, the hair cells that respond to high-frequency stimulation. Another explanation is that the hydropic expansion of the semicircular canal reduce the possibility of the hydrostatic pressure that create the displacement of the cupula so the pressure is dissipated, so we have less movement of the cupula. This creates the condition of the reduction of the activity on video head impulse test. But using the video head impulse test, we have also another possibility. This is very important because when you register the caloric test with a video histamographic system, you have two parameters: the frequency and also the slow phase velocity. In this paper, we have shown that the slow phase velocity of the caloric test nystagmus is reducing the Meniere's disease. We have found a dissociation from caloric tests and the video head impulse. Video head impulse is normal, caloric test is abnormal, and this is an hallmark of the Meniere's disease. But also there is another dissociation. Because, especially during the early stages of the disease, we are evaluating a dissociation between the frequency and the slow phase velocity. The slow phase velocity is barely affected from the hydropic dilatation in the early Meniere's disease and so this is very important to consider. Other vestibular assessment with the VEMPs. This is the practice guideline published recently in the neurology. This acclaim that there is no demonstrable role of VEMPs in diagnosis of Meniere's disease. A lot of paper analyze the role of VEMPs for the diagnosis of Meniere's disease with result that they are absolutely heterogeneous. Sometimes we can have a particular type of results. This is a cervical VEMPs using 500 frequency tone burst and we have no response of the left side. But we can use also the 1,000 hertz tone burst and we have the possibility to evaluate the reappearance of the potential on the left side. When there is an hydropic dilatation of the circuit, we can have a shift of the frequency tuning from 500 to 1,000 hertz. This is very important. But

not even in our experience is very few cases in which we can evaluate this condition with the cervical VEMPs. The instrumental assessment is very important to provide the information that are very useful for management of the specific individual. When we have a Meniere's disease that doesn't meet the typical condition of the guidelines, the instrumental assessment is very useful, and also it's very useful before using any ablative procedures from Meniere's disease treatment because we have to consider the possibility of a bilateral involvement. For an early diagnosis, we can use that early treatment so we can have better management and a better prognosis Meniere's disease with these three type of evaluation: dissociation between parameters of the caloric test, dissociation with the caloric test and video head impulse test, and also the alteration of a frequency tuning in the cervical VEMPs. Before approaching the treatment of Meniere's disease, there is a potential benefit of the confirmation of endolymphatic hydrops with MRI. These are clearly reported in these slides. I have not experienced because this type of evaluation is a off-label in Italy. So we can use the intratympanic gadolinium in order to evaluate the presence of the eye drop directly in the labyrinth. These are some types, you can have these slides so I go very fast. The radiological features of endolymphatic hydrops may be approached in different way. Also, there is different type of using the MRI because normally the best MRI techniques to evaluate the lymphatic hydrops is the 24 hours delayed three-dimensional fluid-attenuated inversion of the so-called 3D-Flaire following intratympanic contrast. In this slide, we can see a normal labyrinth and also in dilated enlarged endolymphatic space of this is in black, because normally the gadolinium arrive in the perilymph not indirectly. If I have an endolymphatic hydrop, there is a reduction of the enhancement of the perilymphatic space, and this can be done, but I have not experience in this topic about Meniere disease. We now approach the therapeutic option. The therapy in Meniere disease aims to prevent the attacks. The spectrum of therapy varies and ranges from a salt-free diet, diuretics, endolymphatic sac surgery, intratympanic steroid or gentamicin, and also surgery. We have only two aims; reduce the number and the severity of the vertigo attacks, relieve the chronic symptoms, in particular the tinnitus.

But besides more than 3,500 papers published on this topic, the Meniere disease treatment now, there is no effective medical therapy, and there is no therapy for long-term preservation of hearing, and also no therapy for tinnitus. But we have to consider that Meniere disease is a phenotype. This is a clinical presentation of a condition of instability of the hearing of the balance that may arise from different insults to the inner ear. A normal ear has a normal activity of the homeostatic system of reabsorption of the endolymph. This system can be damaged from a lot of conditions. As a consequence of this impaired homeostasis, hearing and balance functions become vulnerable to a lot of internal and external factors; stress, sleep deprivation, dietary changes, hormonal changes, allergies, barometric pressure change. I love this type of concept. The fragile ear, the ear of Meniere patient is fragile, so can be vulnerable to a lot of internal and external factors. The first thing to do, we have to consider lifestyle, dietary adjustment, and the correction of any comorbidities. This is very important because we have also to consider that the fluctuating nature of symptoms is very challenging, because when I treat a patient for one year and the patient has no symptoms, my question is, the improvement is due to the therapy or only simply a condition in which the Meniere is quiescent, is not active. This is very important. In order to have some results valid from a scientific point of view, the period of treatment has to be no less than two years. Hence, this reduce the possibility to make some studies with valid therapeutic results. Also, we have to consider that every type of treatment created in a short or intermediate period has shown positive results. We have to start from the dietary and lifestyle change, then the medical, and also when this type of approach is not working, we have to go towards surgical treatments. Firstly, the treatment must be customized according with the different factors like age, duration of the disease. This is very important to correct every comorbidities, and also we have to correct any psycho-pathological disturbances that can create an attack of vertigo. During the acute phase, we can use any vestibular suppressant that you know. Normally this is the Italian experience. A lot of doctors in Italy use diuretics in the acute phase like the so-called osmotic diuretics, and also sometimes can prescribe some

vestibular suppressant like the anticholinergic. Sometimes we can use, in Italy, we have a combination of [inaudible] that is anticholinergic agent. This is very important to reduce also the narrow vegetative symptom of the acute phase. But the important thing is to have the possibility to reduce the vertigo attacks, and so we have to make a prophylactic treatment. The lifestyle stage is very important. You have to restrict the sodium intakes, but probably it's better to have a constant sodium level. This is the critical factor, because a fragile ear may be intolerant to variations in sodium levels. This is very important. This paper evaluates how the compliance of Meniere disease patients to dietary modifications could impact the clinical course. This study say that nutrition can play a role in the management of Meniere disease, because strict adherence to the recommendation in dietary and lifestyle change can reduce the vertigo symptoms. For the moment, we have considered the reduction of caffeine, of alcohol, or coffee, and also a constant reduced sodium level in the diet. But another very important thing is the increase of water intake, and this has a scientific clear condition. The possibility that the aquaporins, some type of molecule that transports water through the membranes, and also these are under the control of anti-diuretic hormones. You note that the anti-diuretic hormones are sensible to stress. The stress increase the anti-diuretic hormones, the vasopressin. If I have an increase of vasopressin, I have an increase of the representation of the aquaporins and this creates the possibility of an increase of the endolymph, and this can create the attack of vertigo. Using more water, you increasing your water intake and reduce these hormones, stress-related, this can reduce the possibility of inactivation of the aquaporins, reduces the risk of the endolymphatic hydrops. The increase of water intakes is a very important topic in Meniere disease. We can use also the diuretics. Diuretics represent the most commonly used first-line therapy in Meniere disease. But the Cochrane review says diuretics have a low level of evidence in treating Meniere disease. Normally I use the hydrochlorothiazide, but some doctors use the acetazolamide, and also chlorthalidone. We have to consider we also the side effect. For example, for hydrochlorothiazide, there is some problem in patients with renal

disease, with diabetes. Also, this type of drug, acetazolamide can create some problem of paresthesia and also increased risk for kidney stones, but can be used with good results also in patients with association between migraine and Meniere disease. Although there is no scientific proof of affectivity in Meniere disease, can be used as a safe, inexpensive opportunity for patients to exert control over the disease with the nonspecific treatment effect. Now the betahistine. This is the most widely used drugs for Meniere disease in Europe. This is strange molecule because a contemporary histamine like activity, and antihistamine activity. It's agonist and antagonists. Agonists for H1 receptor, antagonists for H3 receptor. There is a lots of reports that betahistine have a good therapeutic benefit of vertiginous symptoms both in Meniere disease and also in other vestibular vertigo patients. There are a lot of paper that remark that the use of high dose betahistine can reduce the attack of vertigo in Meniere disease. These are experimental study in which we can have a strong increase in the blood flow in the stria vascularis when we have an increase of dosage Meniere disease. This was used also in therapy. But independence study 2016 in Germany, using betahistine in 221 patients with high dose betahistine or low dose betahistine respect to vary 124 or only 48 milligram betahistine. There is no difference after two years of treatment in between low dose, high dose and placebo. These experiences before the contract to that betahistine is a placebo. But my friend Michael Strupp, recently reported his managed experience because he said betahistine has to be used in Meniere disease in the same way as the therapeutic approach in epilepsy using Tegretol Carbamazepine. You have to increase progressively the dosage of the betahistine until the patients have a reduction or decreases is a strange opinion. But this is the experience of my friend Michael Strupp from Munich. in order to evaluate from a group of doctors expert in Meniere disease, we recently ever Delphi methods and Delphi consensus using the opinion of 88 European experts and 78 Italian expert on vestibular disorder. First, we evaluated the literature about Meniere disease, and then we make a logical answer and all the experts has to express a negative consensus, no consensus or positive consensual. These are the result. The result was that all these experts use the

betahistine in the intercritical face therapy in the presentation of positive consensus was 87 percent. This is the expert panel considered betahistine the first choice drug, this 71 percent. Also, betahistine was used with a high dosage, at least 48 milligrams a day. The majority of the experts. The majority of experts use this drug for more than six months without adverse effects they are very, very low. These consensus concluded that betahistine is the first choice drug in the intercritical phase therapy for Meniere disease and betahistine has a positive effect in the prophylaxis without absolutely any type of important side effect. The expert clinical practice said the best health experience with the patients supported use of betahistine for Meniere disease to reduce the number of the severity of the vertiginous crisis and particularly during the intercritical phase of the disease. However, betahistine do not show positive effect on auditory symptoms for Meniere disease. But it's use seems to be at low risk of major side effect. However, we have to support that. We need clinical study based on rigorous methodologies and outcome measure and these are absolutely necessary to clearly evaluate the role of betahistine in treatment of Meniere disease. Well, regarding the association with migraine, we had good results associating betahistine with these calcium antagonists, with antihistaminic activity that generates it. This is a paper from my friend Roberto Taiji from Milan, that induce to think that the association of this new drug reduce significantly the vertigo spell impression with migraine and Meniere disease. There is other treatment, the ventilation tube, the so-called Meniett absolutely in Europe is now not considered and also the hyperbaric oxygen therapy that increase the oxygen in inner ear, and also stimulate the longitudinal flow of endolymph. But these are treatments that are absolutely not universally indicated, a non universally attracted. Why is universally accepted? This is the last part, I'm sorry, for the length of my lecture. This is the last part of my presentation. The intratympanic therapy. First, the amino glycosides and gentamicin was used for the intratympanic therapy. The issue are; the amount of the substance introduced in the middle ear that arrive in the inner ear. Absolutely,  there is no possibility to know how much of this drug arrived in this inner ear, and this is the most important topic. We don't know. When I put gentamicin

or thrive in the middle here, I don't know absolutely how much of this substance arrive in the inner ear. But normally, from the first experience, we have a tendency to reduce the dose and the number of injection. This meta-analysis clearly state that despite the type of administration iteration, low-dose, multiple day, weekly, the possibility to have a complete vertic control is almost in 80 percent of the cases. Regarding the intratympanic steroid, there is a lot of different experience, positive or negative. The activity of intratympanic steroid in the inner ear can depends from the anti-inflammatory effect, can depends of the control of the aquaporin channel, can depends also to a control of the inner area and fluid homeostasis. Also some experiences say that for experimental point of view, there is an improvement of the autoregulation of the cochlea blood flow. This is our experience using intratympanic gentamicin with a low dose, low dose means one dose of gentamicin, and eventually a second dose after 10 days. We have a control of vertigo attacks in more than 90 percent of the patients. Also, the hearing outcome is not so bad because in our experience, we have not more than 11.5 percent of patients with a hearing loss, but we have to consider that increase of the interval between the two dose. We have the possibility to reduce significantly the risk of hearing loss. Intratympanic dexamethasone, in our experience, we have not so good results. We have an improvement all in the 70 percent of the patient, and this is the natural history of Meniere's disease. The hearing outcome is very good because we have the preservation of the hearing, but normally, the vertigo attacks are more controlled with the gentamicin than the dexamethasone. We use the dexamethasone and the steroid only in patient with refuse ablative treatment in bilateral medicines when we have some ideas of autoimmune meniere disease the complication are very low. Recently, this paper published in the last demonstrated that there was no significant difference between the intratympanic steroid and intratympanic gentamicin for the control vertigo. This is absolutely not comparable with my experience. In my experience, intratympanic steroid works very low presentation of reduction over the reduction of vertigo attack in respect with gentamicin. Also, this meta-analysis say that intratympanic gentamicin is

superior to intratympanic steroid in reducing the number of the vertigo attacks. This is very interesting, because this meta-analysis that the superiority of intratympanic gentamicin is published in Otolaryngology journal. This is [inaudible] publishing in a neurology journal and this meta-analysis say that intratympanic gentamicin that add intratympanic steroid are very similar in the management of Meniere's disease. I repeat, in my experience, intratympanic gentamicin work very well and absolutely more favorable result than intratympanic steroid. Sometimes, we use an exploratory tympanotomy. Because sometimes there is the possibility the gentamicin doesn't arrive the round window, and so we put with the direct exposure of the region. Some form with gentamicin aside, and this is a second level treatment with the possibility of a good result. Finally, this guideline action statements say that for the gamete, there is a recommendation for Meniere's disease on dietary and lifestyle modifications that may reduce and prevent symptoms, the clinician may offer diuretics and betahistine is an option for me is my recommendation. The positive pressure, Meniere's is not recommended for Meniere's diseases. We can have an option to recommend the intratympanic steroid when we have no possibility to reduce the symptom with a conservative therapy, we can't recommend intratympanic gentamicin. This is very important because now we are approaching the three slides about the surgical management of Meniere's disease. This is a slide that treat the endolymphatic sac surgery. This type of surgery was introduced at early 1927 in the surgical treatment of Meniere's disease. Now, it's considered a placebo surgery. This is a very important paper. We have to check. These paper came from Los Angeles House Ear Institute, that is the kingdom of the endolymphatic sac surgery. In five cases, the sac was not exposed relief from vertigo in four patients. In these other cases, the sac was entered, the lumen was entered, and the sac was exposed, and there was no relief from vertigo. We think that endolymphatic sac surgery does not relieve hydrops in patients with Meniere's syndrome. These are a condition in which this author use the endolymphatic sac surgery in addition with injection of dexamethasone directly into the sac with the gelatin sponges. This auto report good results and among the surgical technique, really

effective for Meniere's disease, the only two methods that gained evidence in case of intractable vertigo attacks are labyrinthectomy, that is the oldest surgical method of treating Meniere's disease that is indicated in patient from poor hearing. Again, associated with cochlear implant to restore hearing at the same time, or the vestibular neurectomy that tends to be more favorable regarding hearing outcomes can be used where the hearing is present. This is the most efficient technique for the Tumarkin authoritative crisis. These are the two last slides, this is patient perception of effectiveness of treatment in Italy is a national survive and defined this in the present studies support the prominent placebo effect for the conservative treatment of Meniere's disease. But compared with other treatments, the chemical labyrinthectomy with intratympanic gentamicin was associated with the greatest treatment effect, and we are very prone to this type of document. A lot of algorithms are presented for Meniere's disease. This is from the European annals of otorhinolaryngology. This is from John Kerry, John Hopkins, I think. This is the recommendation and the therapeutic option coming from the American Academy Otolaryngology and surgery, and this is the algorithm of the conclusion of the clinical practice guideline from Meniere's disease from American Academy Otolaryngology, and these are my honest and very little therapeutic option when we have a Meniere's disease, we are first to treat the co factors; migraine, allergy, autoimmune disease, or any other comorbidities. First, low-salt diet and increase of water intakes. Then we can even understand diuretics and betahistine. When we have no results with this type of treatment, we can use the intratympanic dexamethasone. If we have persistent vertigo, we can have impatience of no good hearing intratympanic gentamicin. Impatience can be considered as optional. The endolymphatic sac surgery, and in cases in which also with intratympanic gentamicin, we have no results labyrinthectomy with no hearing and vestibular nerve section with good hearing. This is our approach. In Italy, the treatment of Meniere's diseases stand on the gradual approach, the start from the dietary-behavioral change and the basic pharmacological therapy based on betahistine and diuretics in cases with no response to this approach intratympanic treatment

initially with steroid. Then if we have no results with gentamicin allow the control of vertigo in the majority of the case in this. In our experience, only a percentage no more than 3-4 percent of all the Meniere's patients needs a surgical approach. The vestibular nerve section is the surgery of choice, when there is a service able hearing. I have finished and I'm sorry for the length of my presentation. From Pisa, from the Leaning Tower, I have to thank you very much for your attention.

Enrico Armato: Okay. Augusto, you gave us so many clear useful precise info about the Meniere's disease, so my warm congrats and many congrats from our attendees too. Then I proceed very much your slide about the early diagnosis of Meniere's disease with the three types of these associations; the DHT, the calorics, and the VEMP's, very, very useful and interesting. I believe that from our attendees, there are some question. One of our attendees want to know more about the dose of diuretic in the acute stage of Meniere's disease.

Augusto Pietro Casani: Yes. Thank you for this question. In the acute phase of Meniere's disease, normally, we use the osmotic diuretics because sometimes, the patients have some problem of nausea and vomiting, so to use some oral drugs is not so easy. Normally, we use Glycerol 10 percent and we use it for intravenous administration very slowly, because sometimes fast administration of Glycerol can create an increase of the volume of the blood circulation that this can create some problem of compensation and a failure in patients with some problem or some severe problem and also can create the sub problem of hemolysis and hematuria, so the administration as to be very slowly. Glycerol, 10 percent, 250 centigram. This can be used for some days and also this type of therapy can be done also for prophylactic proposes. Some authors use, for example, one week every 40 days of glycerol in order to reduce the amount of fluid in the hidden area. We have to consider all these treatment are empiric. We have no absolutely any scientific demonstration of the

effectiveness of this treatment, but normally, with the clinical practice, we have good results.

Enrico Armato: Okay, thank you very much. A second question. Would you give intratympanic of dexamethasone in a only hearing error with Meniere's disease in that hearing error?

Augusto Pietro Casani: Yes. The intratympanic steroids can be used. Normally, I use the dexamethasone. I prefer dexamethasone instead of methylprednisolone because sometimes the methylprednisolone create problem of burning sensation when it's inserted in the middle ear. I use without any problem also in all the severable ear because the risk of complication are very low. I have only one quick question with the residual membranic perforation, but very little, and sometimes this is very useful with the presence of the perforation because normally, the therapy, the intratympanic treatment with steroid Has to be repeated like on-demand treatment. Sometimes the presence of a little perforation is not like obligation, but these can help because you can't put directly without any anesthesia the steroid inside the middle ear. I use the dexamethasone in the, for example, ipsilateral endolymphatic eye drops, and I use the endolymphatic steroid without any problem, also in the all-hearing ear. This is very useful because the percentage of side effects are very, very low.

Enrico Armato: Than you, Augusto. Another one, which approach do you chose for vestibular nerve section?

Augusto Pietro Casani: Depends for the hearing because the translabyrinthine approach is the simplest, absolutely, and also can be performed without low risk of complication, low rate of complications. This is my preferred approach. Normally, the majority of the cases, the patients that arrived with the surgical treatment are patient with a very low hearing. In these cases when it's possible, I prefer labyrinthectomy and

contemporary, we can use the cochlear implant in order to restore the hearing. Now, I think that the labyrinthectomy and the insertion of the cochlear implant, that is the probably the new deal of the surgical treatment of Meniere's diseases.

Enrico Armato: Okay. Pietro Augusto, in your experience, what is the risk of contralateral Meniere's disease after intratympanic gentamicin?

Augusto Pietro Casani: Well, my experience is different from many other author because I have not more than seven percent of patients with bilateral Meniere's disease. When I was young, because now I am not so young, when I was young, some of my teachers say, remember, probably you don't see a lot of cases or bilateral Meniere's disease because I was so young, but if you waited, you have to consider that in the future, you will have a lot of cases because you have to attend the involvement of the other ear. This statement was done when I was 30. Now, I am 62 and the percentage danger of bilateral Meniere's disease is not more than seven percent of our patients. The presence of bilateral involvement is very important because when I approach a treatment with interdependent gentamicin, I need to have the certainty of no involvement of the other ear, so the vestibular assessment is absolutely fundamental. Important in this case is also the vamps because sometimes the vamps are useful to evaluate the pressure of clavicle vamps of the saccular involvement. Do you know that the saccule probably is the first structure of the inner ear that involve in the hydrophobic disease? But in my experience, also the bilateral involvement is not so traumatic like the first ear. Normally, I have very, very few cases of synchronous bilateral Meniere's disease. The majority of bilateral case are metachronic. First, we have the one ear and second, after a long or short period of time, the second ear, and probably the second ear is affected because of autoimmune condition. Probably during the first ear involvement, we have some liberation of some antigens, there is an immune response. When I have a bilateral involvement, the condition clinically are characterized from few, less frequent, and not so important vertigo attacks, and is

prevalent, the hearing involvement, and in this cases, I use the steroid both from systemic and intratympanic.

Enrico Armato: Okay. What is your experience with the SPC flex?

Augusto Pietro Casani: Okay. If the attendees have the possibility to check my slides, I have a slide about it. Well, this special presented SPC Flex are based on the fact that there is the secretory factor that can reduce the risk of eye drops because reduce the absorption at the lymph. There is an experience from Italy recently from the group of Salerno that my friend, [inaudible] Consider if you want, I have to.

Enrico Armato: Augusto we are not able to hear you. We lost for one minute.

Augusto Pietro Casani: No problem. But this study is because this is a study very, very recent, publish it on the European archivists otolaryngology that show a reduced number of vertigo attacks and a positive effect on the discomfort generated by tinnitus in patients with unilateral Meniere's disease. In my experience, it is not so easy because of first, the cost of this therapy, this is a very costly therapy, and secondly, the taste of this special processes sera is very bad, so a lot of patients that refuse to use this therapy.

Enrico Armato: Very good. Another question. Could the COVID 19 virus be a co-factor to Meniere's disease?

Augusto Pietro Casani: Absolutely, I don't know. In my experience during the COVID in Italy, we had the period of a lot of cases of COVID. The number of the great digital specialists arriving to our unit was very low. I don't think that this virus have an impact on Meniere's disease. I don't know, but probably in the future, we can consider that some patients with COVID that overcome the infection probably has to be studied and

probably, we can have more information. But in my experience for the moment, I have not seen any impact of COVID, not only eliminate disease, but also in, for example, vestibular neuritis. I don't think that there is a strict association between this condition.

Enrico Armato: Another question. How much dexamethasone do you use and the does hearing improve after this injection, intratympanic injection?

Augusto Pietro Casani: This is a very interesting question because in Italy we have only the solution with four milligrams of dexamethasone for one milliliter. In USA, they have the 24 milligrams, four milliliter. Probably these can be the cause of the difference in terms of result of control of vertigo attacks. They have more results than us and probabilities. On the other side, we have to consider that the recent experience with the so-called auto 104 is like a polymer that can be transform the interdict panic injection of steroids, dexamethasone in like a rhetor, the composition has failed to demonstrate a positive impact on Meniere's disease. This has erased results from the Autonomy. Autonomy is the company that produced this drug. Regarding the hearing. Yes, this is true in our experience, the steroid has reduced the risk of we will lose and in 30 percent of the cases, we have noticed an improvement of the reading, but the improvement is only present in the first three months after the treatment because they will then progress independently from the treatment with steroids.

Enrico Armato: What is your idea about the central concentration in chronic Meniere's disease?

Augusto Pietro Casani: Well, in the chronic, I think that modern chronic, we have to consider the delayed phase of Meniere's disease. The center composition is very important. In the patient with chronic Meniere's disease or better late Meniere's disease, we have no crisis or less crisis also because the labyrinth doesn't work well, because there is a damage of the labyrinth. In this case is the patient have instability,

dizziness, some loss of balance and in these cases, vestibular rehabilitation is a very good therapeutic option to reduce the imbalance, the chronic imbalance of these patients.

Enrico Armato: Should patient with Meniere's disease had an attack within three days of taking the COVID vaccine and have you some input about some correlation in your opinion absolutely?

Augusto Pietro Casani: I would like to have some information about it, because normally Meniere's patients are not a group of patients that in Italy are considered as priority for oxygenation. In the future, probably we could have more information, but for the moment I have no absolute idea about it.

Enrico Armato: Another important question, in my opinion. Do you use or have some experience about the Epsilon?

Augusto Pietro Casani: Yes. The Epsilon is a new drug. This is a secret tropic drag that was used and also against depression. This drug has overcome the third phase of experimentation and probably can be used in the clinical practice in the next year. Absolutely, I have no experience. I had only checked the results on their website of a clinical clinicalgov.trial, but for the moment I have no experience. I hope that this is worth because it will be a very good drug and I hope that it will be a surprise for a positive treatment of Meniere's disease.

Enrico Armato: Thank you very much Augusto. I believe our attendees will be satisfied for your answers and I would remember in all the suggestion of my friend or equal matter before they using of the PhET when the side of the disease is not so clear. Using the epidermal caloric test, please notice that the healthy side get always the same amount of reflectivity because the affected side can vary plus or minus his total

reflectivity. I believe this is an important observation about this. Thank you very much and please Anna, we have arrived to the end.

Anna Scala: Yes, definitely, we are. Thank you very much, Professor Casani for these outstanding learning opportunity. Of course, it is always a pleasure for inventors and I to have. Here with us a professional, as you are in the balance feed them. Thank you one more time to Professor Casani and of course, to Dr. Enrico Armato. See you next March 3rd with Dr. Andrea  Castellucci the feasibility of using the wage IT to detect that the ear canal in BPPV presenting with positional downbeat nystagmus. So have a nice evening or have a nice morning and thank you once again to everybody. Arrivederci. Thank you .