SUDDEN SENSORINEURAL HEARING LOSS

by

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Sudden Sensorineural Hearing Loss

submitted by Temitope Grace Joshua in partial fulfillment of the requirements for the degree of Master of Science in Surgery

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Abstract

Objective

The purpose of this study is to evaluate the effectiveness of oral, intratympanic steroid (IT) and Hyperbaric Oxygen therapy (HBOT) based treatments on hearing outcomes in patients with Sudden sensorineural hearing loss (SSNHL).

Methods

A systematic review of primary studies published in the English language between January 2000 to June 2018 identified by searching Medline, PubMed, Web of Science, and Embase databases was performed. Inclusion criteria were Primary articles on the treatment with (oral, IT steroid and HBOT) of patients diagnosed as having SSNHL. Patients with all other types of hearing loss were excluded. A retrospective chart review of patients presenting with SSNHL at Vancouver general hospital from 2015 to 2017 was also performed. The outcomes studied include; Averaged PTA threshold change between pre/posttreatment.

Results

223 articles were identified of which 24 articles meet the study inclusion criteria. The quality of evidence was good in 20 articles, and poor in the remaining 4 articles. Overall, 90% of 687 patients in the 8 studies who received oral and IT steroids (combination therapy) and 86% of 494 patients in the 5 studies who received triple therapy with HBOT demonstrated hearing recovery compared to a 75% recovery rate in 548 patients who received oral steroids alone. Combination therapy had statistically significant hearing improvement compared with oral steroids alone (Chi squared, p < 0.05).
The retrospective chart review of 37 SSNHL patients charts which fulfilled inclusion criteria were reviewed. Patients who received combination steroid therapy showed a significant hearing improvement based on their initial and final PTA readings. There is a significant difference in PTA average of the diseased ear between pre and post treatment (p<0.001) and a significant clinical hearing improvement (>15db) noticed in patient groups of prednisone alone and prednisone + IT and IT alone (p <0.05).

**Conclusions**

The systematic review and the retrospective charts review conclude that there is weak evidence of a beneficial effect of combination therapy (oral and IT steroids; or oral, IT steroids and HBOT) for patients with SSNHL over and above that achieved with mono-therapy with oral steroids (Chi squared, p < 0.05).
**Lay summary**

Sudden hearing loss is caused by damage to the sensitive hair cells inside the inner ear or damage to the auditory nerve. The causes are unknown. A careful examination is needed to exclude life threatening or treatable causes such as vascular events and malignant diseases, and patients should be referred urgently for further assessment. About half of patients completely recover, usually in about 2 weeks. Many treatments are used, including corticosteroids and oxygen-based treatments. Steroids are a mainstay of therapy.
Preface

**Systematic review study**: The idea of this study was established by myself and my thesis supervisor. Key word searches and study selection criteria were established by me under supervision of Dr. Desmond Nunez. Searching the databases and obtaining initial titles and abstracts was performed by myself with the help of Dr. Printha Wijesinghe (Dr Nunez’s Research Assistant). The initial phase of selecting the title-relevant articles was performed by Printha and myself. The second phase of full text review and further exclusion of articles was performed by me. Data extraction, and data entry was performed by me. Statistical analysis was undertaken by Printha. The interpretation of the findings and writing the manuscript was done by myself with guidance from Dr. Desmond Nunez.

**Retrospective cohort study** was conducted under the supervision of Dr. Desmond Nunez. Dr Nunez’s research group members and I were responsible for formulating the research objectives, the study design, and obtaining ethical approval. The UBC ethics certificate number is H18-00736 and the study title is Audiological Patterns and Outcomes in Sudden Sensorineural Hearing Loss Patients (APOST Study). I was responsible for the data collection (chart review), interpreting the data analysis and writing the manuscript.
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List of Abbreviations

dB-decibel

HBOT- Hyperbaric oxygen therapy

IT- intratympanic

No-number

PTA – pure tone average

SSNHL- sudden sensorineural hearing loss

S.D. -standard deviation

VGH- Vancouver General Hospital
Acknowledgements

The completion of this work is owed to the collective input of many people who must be thanked for their time and efforts.

First and foremost, I am deeply grateful to Dr. Desmond Nunez for his kind support and tireless reviewing of my work. He has cultivated enormously to both my personal and professional Potential with his constant support.

I am also very grateful to the faculty of UBC department of surgery for this incredible opportunity. I have been humbled and deeply privileged to be a part of this program.

Thank you, Printha for your contribution and earnest support.

My family and friends thank you for the encouragement, sage advice and love and sacrifice.
Dedication

This study is dedicated to my parents and siblings, for without them and their blessings, I would not have achieved my goals.
Chapter 1: Introduction

Sudden sensorineural hearing loss (SSNHL) is defined as sensorineural hearing loss of 30dB or greater over at least three contiguous audiometric frequencies occurring over 72 hours. It was first described by De Kleyn in 1944 (1). A double-blind study conducted by (Wilson et al., 1980), for the treatment of idiopathic sudden hearing loss with oral steroids defined the condition as not less than a 30-dB loss over three contiguous frequencies in three days or less (2).

A specific cause has been identified in 7% to 45% of patients (2-4), and a precise therapeutic regimen used for treatment in those cases. Different theories attempt to explain this problem including disturbance of cochlear blood flow, viral infections, autoimmune disease and Reissner's membrane rupture (2–4). Theories presently favored for idiopathic cases include viral etiology or a vascular event within the cochlea giving rise to a sudden elevation in hearing thresholds and a degradation in speech discrimination (4).

The term “idiopathic” is used to qualify patients with no identifiable cause for their hearing loss (5–9). Controversy remains in the area of etiology, and management of patients with idiopathic SSNHL irrespective of the etiology. Recovery of hearing thresholds may not occur, may be partial or even complete after SSNHL. Some of the factors that affect hearing recovery include delay in starting treatment, age at onset of hearing loss, the severity of hearing loss and pure tone audiometric frequencies affected, as well as the presence of vertigo.(5).
Cochlear activity is known to require a high oxygen supply. Especially as the stria vascularis and the organ of Corti have a high energy demand. Perilymphatic oxygen tension decreases significantly in patients with SSNHL. Oxygen administration may improve cochlear metabolism.

1.1 Epidemiology

The exact incidence of SSNHL is uncertain. Estimates of incidence based on studies in the previous century typically ranges from 5-20 per 100,000 persons per year (5,7,10). The true incidence of SSNHL may be more than these estimates because affected individuals who recover quickly do not present for medical care (5,11). Most cases are unilateral; less than 2% of patients have reported bilateral involvement, and bilateral involvement usually occurs sequentially. Accompanying symptoms include tinnitus (41% to 90%) and dizziness (29% to 56%) (5,7,12,13). Many patients report first noting their hearing loss on awakening (6).

The first large study population-based examination of the incidence of SSNHL in the United States estimated annual incidence of 27 per 100,000 corresponds to more than 66,000 new cases per year in the United States (14).

The search revealed 3 other studies examining the incidence of SSNHL since Byl’s oft-cited 1984 review (14). Teranishi et al., 2007 reported results from a series of surveys sent to inpatient hospitals throughout Japan in 1972, 1987, 1993, and 2001 enquiring about the number of patients treated for SSNHL. The population served by the hospitals was used to estimate the nationwide incidence of the disorder. They reported an increase in incidence during the 30 years examined,
with a final incidence of 27.5 per 100,000 in 2001, a number in close agreement with the incidence observed in Alexander et al’s study (14).

Klemm et al. (2009) report on the number of SSNHL cases treated by specialty physicians in Dresden, Germany in 2004 arrived at an annual incidence of 160 per 100,000 based on the population of Dresden at the time of their study. The authors speculated that the much higher incidence relative to previous reports was related in part to a higher awareness of SSNHL better record-keeping, and greater health-care access in Germany relative to that observed in other studies (15).

Wu et al. 2006 studied the incidence of SSNHL in Taiwan from 1998 to 2002 (13) using a methodology similar to (Alexander et al 2013) (14). Data from the country’s National Health Insurance program database capturing inpatient medical claims for the more than 20 million population was used. They found an annual incidence of 10.21 per 100,000 in 2002, a number that is lower than the incidence in the (Alexander et al., 2013). This could represent a real difference in incidence between the United States and Taiwanese populations or could be due to differences in methodology. One potential reason for the difference could relate to the use of inpatient claims only in the study from Taiwan compared with both inpatient and outpatient claims in the United States study. All SSNHL patients in Taiwan are recommended to undergo inpatient treatment, whereas in the United States, most cases are treated as outpatients. It is possible that patients with milder hearing loss may be less willing to undergo inpatient admission for treatment, and presumably, they would have been excluded in the study from Taiwan.
Byl’s 1977 (16) estimate of the incidence of SSNHL in the United States was based on a series of 52 patients treated through the Kaiser Foundation Health Plan in Northern California. The number of patients enrolled in the plan was the denominator, used to arrive at an annual incidence of 10.7 per 100,000. It is unclear if the higher incidence seen in Alexander et al.’s (2013) study reflects an actual change in the epidemiology of SSNHL in the U.S. population or is due to methodologic differences between the studies. The studies from Taiwan and Japan did show an increasing incidence of SSNHL over time (17) (18).

Alexander et al., 2013, found that the incidence of SSNHL increased with age, with 70 cases per 100,000 per year in those age 65 and older compared to 11 per 100,000 for patients younger than 18 years. Byl (1977) also found an increasing incidence of SSNHL with increasing age, with a peak incidence of 47 per 100,000 in patients 65 years and older. Teranishi et al., 2007 reported a peak annual incidence of 58 per 100,000 in patients aged 60 to 64 in Japan, with a steep decline in incidence with increasing age above 65 years. Klemm et al. reported bimodal peaks at 40 to 49 years and 60 to 69 years in Germany. In the study from Taiwan, incidence steadily increased with age, with a peak of 23.15 per 100,000 in patients older than 70 years (18). Some of the differences between the studies are likely related to the different cutoffs chosen for age groups.

Byl performed a limited ‘‘meta-analysis’’ of studies published before 1984 and identified 200 male and 191 female patients, giving a male-to-female ratio of 1.05:1, similar to that in Alexander et al.’s (2013) study. The male-to-female ratio in Taiwan was reported as 1.14:1 (18). Interestingly, the German study by Klemm et al. found an overall female preponderance with a female-to-male ratio of 1.22:1. The reason for this difference is unclear, but differences across cultures and sexes
may affect the likelihood of an individual self-reporting an otologic condition (19). Idiopathic SSNHL may be the result of multiple etiologies. The leading proposed causes include vascular events, viral infection, and autoimmune disorders (6). The increase in incidence of SSNHL with increasing age may point to differences in etiology in younger and older patients (18). Vascular events causing SSNHL may be more common in the elderly and in men because of their increased rates of underlying cardiovascular disease (20). Risk factors for cardiovascular thromboembolic disease have been shown to increase the risk of developing SSNHL although temporal bone histopathology studies have not found evidence to support a vascular etiology (21). A variation in the population-specific incidence of underlying causal factors could also explain the differences in incidence reported in different countries (21).

The use of medical claims data to examine the epidemiology of SSNHL offers the benefit of a large sample size, but also reduces risk of selection bias since all health care events are captured. Almost 25% of the insured U.S. population were included in Alexander et al., 2013 study. However, there is susceptibility to bias that must be recognized when using medical claims data for epidemiologic studies. First and foremost, there is no guarantee that patients coded as having SSNHL actually meet accepted guidelines for clinical diagnosis. Furthermore, patients with the disorder who do not seek medical care will be missed. Another possible explanation for the differences in the results of the Alexander et al study and that of the studies previously discussed may be related to geographic location of the different patient populations. Additionally, in comparing Alexander et al., 2013 study with that of Wu et al., 2006 and other previous studies, it is important to note that the number of patients studied by Alexander et al., 2013 was significantly
larger than that in all the previous studies, and it is possible that the larger study detected small variations that would be missed in the previous analysis.

In conclusion, the current estimate of the incidence of SSNHL in the United States is 27 per 100,000. It is slightly more likely to occur in men, and the incidence increases dramatically with increasing age.

![Figure 1-1: Incidence rates of patients with SSNHL (22)](image)

1.1.1 Identifiable Causes of SSNHL

In 7% to 45% of patients presenting with SSNHL an identifiable cause can be found (5–9,12,22). Several potential etiologies for SSNHL have been identified. The broad categories under which cases with a potentially discoverable etiology fall include infectious, autoimmune, traumatic, vascular, neoplastic, metabolic, and neurologic. (Table 1-1). A meta-analysis of 23 studies of SSNHL conducted by Chau and colleagues in 2010, shows that the most common identified causes
were infectious (13%) followed by otologic (5%), traumatic (4%), vascular or hematologic (3%), neoplastic (2%), and other (2%) (6). Other causes such as malingering, conversion disorder, and ototoxic drug administration, were not examined in this study, and should be added to the list of identifiable etiologies of SSNHL as depicted in Table 1-1. In many of these etiologies hearing loss usually results from damage to hair cells or cochlear structures that is irreversible. Occasionally, further damage can be prevented when the etiology is identified early and treated promptly. In rare cases, SSNHL because of identifiable causes can be reversed. Many of these known causes of SSNHL have wider health implications for the patient therefore, the identification of conditions underlying SSNHL can be justified in terms of the patients’ overall health rather than in terms of hearing outcomes (6).

Table 1-1: Identifiable Causes of SSNHL

<table>
<thead>
<tr>
<th>Infection</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Viral infection, for example, mumps, measles, herpes zoster</td>
<td></td>
</tr>
<tr>
<td>• Bacterial labyrinthitis secondary to chronic middle ear disease</td>
<td></td>
</tr>
<tr>
<td>• Lyme disease, Syphilis, Toxoplasmosis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ear disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fluctuating hearing loss, Enlarged vestibular aqueduct</td>
<td></td>
</tr>
<tr>
<td>• Ear surgery</td>
<td></td>
</tr>
<tr>
<td>• Ototoxicity, for example, aminoglycosides</td>
<td></td>
</tr>
<tr>
<td>• Autoimmune disease, for example, autoimmune inner ear disease (AIED)</td>
<td></td>
</tr>
<tr>
<td>• Otosclerosis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trauma</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Head injury (temporal bone fracture or cerebral trauma)</td>
<td></td>
</tr>
<tr>
<td>• Inner ear concussion, iatrogenic trauma/surgery, Peri lymphatic fistula</td>
<td></td>
</tr>
<tr>
<td>• Sudden loud noise exposure</td>
<td></td>
</tr>
</tbody>
</table>
- Barotrauma resulting in round window rupture, for example, from diving or flying

### Neurological and vascular disease
- Pontine ischemia
- Transient ischemic attack
- Multiple sclerosis

### Neoplastic
- Vestibular schwannoma
- Meningioma

### Autoimmune
- Autoimmune inner ear disease
- Bechet’s disease
- Cogan’s syndrome
- Systemic lupus erythematosus

### Infectious Causes

#### Bacteria

In the (USA), the two most common bacterial infections known to cause SSNHL are Lyme disease and syphilis. Lyme disease has been reported as an epidemic in North America with the highest incidence in Maine (23). The disease is currently concentrated in northeastern part of the US and is caused by the spirochete Borrelia burgdorferi. The carrier is deer ticks. The bacteria are transferred when the tick attaches to a human host for 2-3 days. One of the early symptoms include an erythematous rash (erythema migrans), and this can persist for 2-3 weeks without treatment. Other manifestations of Lyme disease which are more chronic usually occur within the first year of infections and include systemic neurologic involvement such as facial paralysis and asymmetric sensorineural hearing loss. The long-term sequela of the infection includes arthritis, cardiac
conditions such as atrioventricular block, neurologic disorders including chronic meningoencephalitis, and fibromyalgia (23). Some studies examining rates of Lyme disease in SSNHL find up to a 20% rate of positive Lyme titers (24,25); however, some authors report a 0% incidence or very low incidence of Lyme titer positivity in their series (25,26).

One of the higher incidence studies (24) found that elevated Lyme titers were not typically associated with a history of erythema migrans (only 1 of 10 Lyme-positive patients had that history) and many (40%) were not associated with risk factors for Lyme disease (living in an endemic area, history of tick bite, history of pet with ticks). Hearing recovery was similar for Lyme-positive and Lyme-negative SSNHL patients, although there was a trend for worse hearing in the Lyme-positive group thus providing a limited rationale for routine testing (24).

Syphilis, which is caused by bacterium Treponema pallidum is a sexually transmitted disease. Syphilis has a broad clinical manifestation, and it is termed a great “imitator” (27). Ab initio, the patients usually show a painless skin lesion, called a chancre after infection on the genitalia (primary infection). The infected patients are at risk of neurosyphilis, and one of the manifestations can be otosyphilis even at the early stage (27). Otosyphilis has numerous presentations which include SSNHL, progressive hearing loss, fluctuating hearing loss, or a Meniere’s-like syndrome with episodic attacks of vertigo, increased tinnitus, and hearing loss (6,13,28–31). Immunosuppressed patients, especially those living with HIV, are at greatest risk of developing neurosyphilis even after proper administration of treatment at primary, secondary and latent disease stages, in the presence of decreased serum Rapid plasma reagin RPR and high CD4 counts (27,32).
Protozoa and virus  Toxoplasma gondii is a protozoal infectious agent that has also been linked with SSNHL. Toxoplasmosis is a treatable condition mostly contracted through contact with cats’ feces or ingestion of undercooked meat (33). Herpes simplex, varicella zoster, enteroviruses, and influenza are viruses that have been implicated occasionally in the etiology of SSNHL (6). The only virus that is commonly known to be a cause of SSNHL is mumps (34)(35).

Up to 4.7% of patients who initially present with SSNHL will ultimately be diagnosed with another otologic disorder as their disease fully manifests over time (6). The leading final otologic diagnosis is Meniere’s disease. A typical case presentation is illustrated in (Figure 1-2). Other common otologic diseases that can be present at initial stage with SSNHL include otosclerosis, trauma which can cause SSNHL; often the history in these cases is obvious (6). However, patients with enlarged vestibular aqueduct syndrome, can present with SSNHL after a minor trauma (36).
Figure 1-2: Audiograms of a patient initially presenting with SSNHL ultimately found to have Meniere’s disease (37)

Note near resolution of initial hearing loss following high-dose corticosteroid therapy. Initial audiogram at presentation with SSNHL (A) audiogram following 10-day course of 1mg/kg prednisone; (B) and audiogram following onset of episodes of spinning vertigo lasting 30-60 min accompanied by left aural fullness and tinnitus (C).

Hematologic and vascular pathologies have been linked with SSNHL. They include emboli, transient ischemic attacks, sickle cell anemia, macroglobulinemia, and hematoma, to mention a few (6,38–40). They all decrease the blood supply to the cochlea, which invariably reduces intracochlear oxygen levels and this can result in either a transient or permanent hearing loss in experimental models (41,42).
The main neoplasms that can cause SSNHL are vestibular schwannomas (acoustic neuromas). The incidence of vestibular schwannoma in series of patients with SSNHL varies from none to about 4%. The presenting symptoms of Vestibular schwannomas are variable and include hearing loss, dizziness, and tinnitus. Progressive hearing loss is the most common presenting symptom of Vestibular schwannomas, and ~1% of patients with SSNHL are found to have Vestibular schwannomas. The higher rate (4%) seems to be attributed to widespread use of MRI. (43). Gadolinium-enhanced MRI is recognized widely as the gold standard in the diagnosis of vestibular schwannomas. However, most studies only find at most one or two percent within their patient groups (5,6,8,13,26,28,33,44).

A review evaluated the incidence of all neoplastic causes of SSNHL at 2.3%. This included rare Internal auditory canal (IAC) metastasis from primary tumors such as a primary gastric cancer (6). It also included benign tumor such as, meningiomas, epidermoids, lipomas as well as vestibular schwannomas (6). Hearing recovery does not signify the absence of neoplasms as SSNHL due to these causes can show spontaneous recovery or recover after treatment with systemic steroids(45,46). The pathophysiology of neoplasm induced SSNHL is uncertain however evaluating patients with SSNHL for neoplasms cannot be omitted in patients with hearing recovery (Figure 1-3)
This patient’s moderate flat SSNHL interestingly resolved completely following treatment with 1mg/kg prednisone and oral antiviral medications for 10 days followed by a short prednisone taper despite the finding of a small left intracanalicular enhancing mass consistent with a vestibular schwannoma (arrowhead). MRI, magnetic resonance image.

1.2 Theories of the Etiology of Idiopathic SSNHL

The incidence is approximately 5 to 20 per 100,000 population in patients who presents with SSNHL of an unknown etiology, and their hearing loss is referred to as idiopathic (5–9). There are various hypotheses of the pathophysiology of idiopathic SSNHL that have been proposed. They include vascular compromise which is the most widely accepted theory (39,47–49). Cochlear membrane rupture(50) as well as unidentified viral infection (5,22,51).
The American Academy of Otolaryngology–Head and Neck Surgery Foundation published the Clinical Practice Guideline: Sudden Hearing Loss (Update) August 1, 2019 (52). It focuses on sudden sensorineural hearing loss in adult patients aged 18 and over and primarily on those with idiopathic sudden sensorineural hearing loss. Other causes of SNHL such as infectious, autoimmune are not considered SSNHL according to these guidelines as these are known causes with available treatments. The guideline update group made strong recommendations for the following: clinicians should distinguish sensorineural hearing loss from conductive hearing loss when a patient first presents with sudden hearing loss Key action statements (KAS 1); clinicians should educate patients with sudden sensorineural hearing loss about the natural history of the condition, the benefits and risks of medical interventions, and the limitations of existing evidence regarding efficacy (KAS 7); and clinicians should counsel patients with sudden sensorineural hearing loss who have residual hearing loss and/or tinnitus about the possible benefits of audiological rehabilitation and other supportive measures (KAS 13). These strong recommendations were modified from the initial clinical practice guideline for clarity and timing of intervention.

The guideline update group made strong recommendation against the following: clinicians should not order routine computed tomography of the head in the initial evaluation of a patient with presumptive sudden sensorineural hearing loss (KAS 3); clinicians should not obtain routine laboratory tests in patients with sudden sensorineural hearing loss (KAS 5); and clinicians should not routinely prescribe antivirals, thrombolytics, vasodilators, or vasoactive substances to patients with sudden sensorineural hearing loss (KAS 11).
The guideline update group made recommendations for the following: clinicians should assess patients with presumptive sudden sensorineural hearing loss through history and physical examination for bilateral sudden hearing loss, recurrent episodes of sudden hearing loss, and/or focal neurologic findings (KAS 2); to help identify patients with potentially serious alternative conditions as the cause for their sudden hearing loss, clinicians should obtain, or refer to a clinician who can obtain, audiometry as soon as possible (within 14 days of symptom onset) to confirm the diagnosis of sudden sensorineural hearing loss (KAS 4); clinicians should evaluate patients with sudden sensorineural hearing loss for retrocochlear pathology by obtaining a magnetic resonance imaging or auditory brainstem response (KAS 6); clinicians should offer, or refer to a clinician who can offer, intratympanic steroid therapy when patients have incomplete recovery from sudden sensorineural hearing loss 2 to 6 weeks after onset of symptoms (KAS 10), this statement appears to reflect a view of IT steroids as a rescue treatment for patients failing initial po steroids and clinicians should obtain follow-up audiometric evaluation for patients with sudden sensorineural hearing loss at the conclusion of treatment and within 6 months of completion of treatment (KAS 12). These recommendations were clarified in terms of timing of intervention and audiometry, as well as method of retro cochlear workup.

The guideline update group offered the following KASs as options: clinicians may offer corticosteroids as initial therapy to patients with sudden sensorineural hearing loss within 2 weeks of symptom onset (KAS 8); clinicians may offer, or refer to a clinician who can offer, hyperbaric oxygen therapy combined with steroid therapy within 2 weeks of onset of sudden sensorineural hearing loss (KAS 9a); and clinicians may offer, or refer to a clinician who can offer, hyperbaric
oxygen therapy combined with steroid therapy as salvage therapy within 1 month of onset of sudden sensorineural hearing loss (KAS 9b) (52).

Two small terminal arteries are responsible for the blood supply to the cochlea. The arterial circulation of the inner ear is completely supplied by the labyrinthine artery. The labyrinthine artery has a variable origin. Most often, it is a branch of the anterior inferior cerebellar artery (AICA), but occasionally it is a direct branch of the basilar artery. As it enters the inner ear, it divides into the anterior vestibular artery and the common cochlear artery. The anterior vestibular artery supplies the vestibular nerve, most of the utricle, and the ampullae of the lateral and anterior semicircular canals. The common cochlear artery divides into a main branch, the main cochlear artery, and the vestibulocochlear artery. The anterior vestibular artery supplies part of the cochlea, ampulla of the posterior semicircular canal, and inferior part of the saccule. The labyrinth has no collateral anastomotic network and is highly susceptible to ischemia (53).

Some authors have shown that the risk factors for ischemic vascular disease including cigarette smoking, hypertension, and hyperlipidemia, are the risk factors for the development of idiopathic SSNHL (6), but other authors have not been able to link idiopathic SSNHL with any of the aforementioned risk factors (33,53). In vascular etiology theories, the sudden loss of hearing could be as a result of acute vascular hemorrhage (54), occlusion by emboli, vascular disease(55), vasospasm (22), or change in blood viscosity (39).
A study conducted by Schweinfurth and colleagues many years ago employed magnetically guided iron particles to embolize the cochlear vasculature of six New Zealand white rabbits, which resulted into 12-37 dB drop in distortion product otoacoustic emissions (DPOAEs; (42). It was noted that 33% of animals had spontaneous recovery of hearing in their study. These changes correspond to those found in clinical studies of patients with idiopathic SSNHL (56).

Patients with sudden sensorineural hearing loss of known etiology from intravascular insult usually develop a permanent loss, while the majority of idiopathic SSNHL cases are reversible (5,22) As a result of the amount of damage, and permanence of the hearing loss following occlusion of the cochlear vasculature, cochlear fibrosis occurs over the subsequent weeks, with low frequency hearing loss. (57), and this is visible in radiologic studies of patients with hearing loss of known vascular occlusion (38). In idiopathic SSNHL, typical cochlear fibrosis is not observed (58,59). Overall, a vascular etiology may explain most cases of idiopathic SSNHL, however, it may not be the only cause of this disorder.

Another pathophysiologic factor that has been proposed in the development of idiopathic SSNHL is cochlear trauma with tearing or rupture of the delicate inner ear membrane. A study conducted by Simmons has it that several patients who presented with complaints of sudden onset of hearing loss accompanied by a “pop”, often occurring at a time of strenuous activity or elevated intracranial pressure, and proposed Reissner’s membrane was identified as the site of injury (60). Postmortem histopathologic temporal bone evaluation of patients with idiopathic SSNHL who later died due to other causes revealed rupture of Reissner’s membrane which supported the membrane rupture theory as proposed potential pathophysiology of idiopathic SSNHL (48,60). A challenge is that
most patients do not remember a significant Valsalva, trauma, or a “pop” immediately before the onset of hearing loss; and many studies could not identify inner membrane ruptures in temporal bone studies in patients with idiopathic SSNHL (21,59).

A series of cases of patients with SSNHL after a popping sensation presented by Goodhill proposed that their hearing loss was due to perilymphatic fistulae (50). This lead to the practice of middle ear exploration and fistula repair in most cases of idiopathic SSNHL (61). The concept of perilymphatic fistula as the underlying cause of idiopathic SSNHL has lost acceptance, because, there is little evidence of a PLF in most cases of sudden hearing loss (62) though fistulae clearly underlie some cases of SSNHL in patients with a clear history of barotrauma, temporal bone fractures, or trauma after otologic surgery (62).

1.2.1 Sudden Deafness: Is It Viral?

Viral Hypothesis of SSNHL

There are two potential mechanisms that have been proposed to explain how a viral infection can lead to SSNHL. One mechanism is viral invasion of the fluid spaces and/or soft tissues of the cochlea (cochleitis) or invasion of the cochlear nerve (neuritis). The virus is presumed to reach the inner ear via the hematogenous route, although other routes of spread are also possible such as from the cerebrospinal fluid (CSF) space or via the middle ear. The second mechanism is reactivation of a virus that is latent within tissues of the inner ear. It has been hypothesized that neurotropic viruses could infect the cochlear neurons, remain dormant for varying lengths of time, and then become reactivated later in life to result in a viral neuritis and/or cochleitis, leading to SSNHL.
1.2.1.1 Bradford Hill Criteria

Bradford Hill criteria, otherwise known as Hill's criteria for causation, are a group of nine principles, established in 1965 by the English epidemiologist Sir Austin Bradford Hill. They can be useful in establishing epidemiologic evidence of a causal relationship between a presumed cause and an observed effect and have been widely used in public health research.

Henle-Koch's postulates were selected for this research because of its’ criteria showing a causal relationship between a causative microbe and a disease.

1.2.1.2 Proof of Causation: The Henle-Koch Postulates

The classic concepts of causation in infectious diseases as elaborated by Henle and Koch in the 1800s for bacterial and parasitic diseases have been adapted and modified for viral infections. These postulates state that (1) a specific virus must be regularly present with the disease; (2) the virus must occur in an affected individual as the cause of the disease, rather than an incidental or accidental finding; and (3) one must show that the infection is transmissible by inoculation of material from a patient with the disease into a suitable experimental host.

In addition, a set of immunologic criteria have been developed for putative viral infections. According to these criteria, immunologic proof of causation requires that virus-specific antibody is absent prior to the illness; antibody appears during the illness accompanied by the presence of the virus in appropriate tissues; absence of antibody indicates susceptibility to disease; presence of antibody indicates immunity to the disease; production of the antibody by immunization prevents the disease. There are exceptions to these postulates.
1.2.1.3 Analysis of Evidence for and Against the Viral Hypothesis

1.2.1.3.1 Epidemiologic and Serologic Studies

Mumps virus has been reported to cause sudden deafness, based on clinical and serologic studies, the latter demonstrating seroconversion or the appearance of mumps IgM antibodies. However, many of these same studies found that mumps which presents as unilateral profound hearing loss accounted only for a small fraction (less than 10%) of cases with ISSHL. Measles and rubella have also been temporally or serologically associated with a few cases of sudden deafness. Measles can lead to deafness. However, unlike rubella, which is another virus infection, measles does not cause congenital deafness. With widespread immunization against mumps, measles and rubella, the incidence of these diseases has fallen drastically, along with the near eradication of these agents as an etiological agent for SNHL. However, there has not been a concomitant decline in the incidence of ISSHL, further supporting the argument that these particular viruses are not the cause of most cases of SSNHL (63).

Members of the Herpesviridae family of viruses have been proposed as causes of ISSHL (64). The herpesvirus family includes herpes simplex types 1 and 2, varicella zoster virus (VZV), CMV, Epstein-Barr virus, human herpesvirus 6, 7 and 8 (HHV-6, HHV-7, HHV-8). All of these viruses, once acquired, persist in latent form lifelong. Most adults are seropositive for many of these viruses, having acquired them during childhood. For example, approximately 90% of adults are seropositive for HSV-1, 90% for VZV, 70% for CMV, 90% for EBV, 95% for HHV-6. They are, therefore, not susceptible to new (acute) infection from these viruses, and the hypothesis that ISSHL is caused by one of these viruses in a seropositive patient can only be explained by reactivation of latent virus. Unfortunately, there are no good serologic tests to diagnose reactivation. Once an individual is seropositive for a latent herpes virus, an increase in titer does
not diagnose reactivation. An example of this is shingles, which represents a reactivation of latent infection due to VZV, a virus often acquired decades earlier. Shingles is not diagnosed by a rise in an already positive VZV antibody titer. Serologic studies of ISSNHL that use increases in IgG titers for HSV or VZV, for example, in already seropositive patients as evidence of a causal relationship, do not conclude that serology can be used for diagnosis of viral reactivation.

Other types of viruses such as respiratory viruses, adenoviruses and arenaviruses have also been implicated in ISSHL, based on anamnestic or serological data. On the other hand, some studies have reported lack of increases in antibodies against multiple tested viruses(63). In patients with ISSHL, Pitkäranta et al. 1998 could not detect production of interferon or interferon-induced gene expression in peripheral blood samples, both of which are useful diagnostic markers for systemic viral infections. Pitkäranta et al., 1998 study is unique and significant, because it did not target specific viruses, but rather, it assayed for sensitive markers of any systemic viral infection. Their study supports the argument that ISSHL is not commonly associated with a systemic viral infection.

1.2.1.4 Clinical Studies Involving Antiviral Therapy

Clinicians have used anti-herpes virus medications prescribed at the time of the hearing loss, either alone or in combination with corticosteroids, on an empirical basis. The two antiviral drugs used most commonly, acyclovir and valacyclovir, are essentially the same drug. Acyclovir is an antiviral drug that acts as a specific inhibitor of herpesvirus DNA polymerase. It shows good activity against herpes simplex and varicella-zoster viruses. Valacyclovir is a prodrug of acyclovir that produces serum acyclovir levels that are 3–5 times as high as those achieved with oral acyclovir therapy, and similar to levels achieved by intravenous acyclovir. The problem with such
therapy is the lack of adequate controls in most cases. Controls are especially important, because of the significant rate of spontaneous recovery of hearing in SSNHL.

There have been at least four published, randomized, placebo-controlled, prospective clinical trials using acyclovir or valacyclovir (65). However, none showed any benefit in using these drugs to treat ISSHL. For example, in a prospective study of 166 cases over 5 years, (22) reported that 65% of patients recovered their hearing, independent of any treatment. Acyclovir or valacyclovir are active only against HSV or VZV. Therefore, the lack of efficacy supports the contention that HSV and VZV do not play a role in SSNHL, although it does not exclude the potential causative role of other viruses.

**Why Are the Henle-Koch Postulates Not Fulfilled for the Viral Hypothesis of SSNHL?**

The preceding review demonstrates that the majority of the Henle-Koch postulates remain unfulfilled with respect to a viral etiology of SSNHL. There are four possible explanations:

1) Inaccessibility of the Cochlear during Life: It is very difficult to gain access to cochlear tissue during life in order to test for the morphologic presence of viruses.

2) Paucity of Cochlear Tissue after Death: Examination of cochlear tissue obtained at postmortem can provide material for investigation of a viral etiology for SSNHL. However, such material remains extremely sparse for a variety of reasons. Sudden deafness is not a fatal disorder. Therefore, autopsy studies often occur many years after the acute event that led to SSNHL. Another problem is that temporal bones are not routinely removed at the time of autopsy or routinely studied by general pathologists. Otopathology studies are
performed in specialized laboratories typically in departments of otolaryngology, and only a handful of such laboratories remain active worldwide.

3) Technical and Scientific Limitations: Some studies looking for evidence of a viral etiology for SSNHL have suffered from flaws in their design.

4) Viruses Do Not Cause SSNHL: If the postulates of causation cannot be proven, then one has to entertain the explanation that SSNHL is not commonly the result of a viral infection.

1.2.1.5 Conclusions Regarding the Viral Hypothesis and Future Studies

The evidence to support the hypothesis that viral infections are a common cause of SSNHL is indirect and circumstantial. There is also evidence against viral causation, but again, this is not conclusive. It is evident, in light of the above discussion, that there are some very significant challenges to attempts to investigate whether SSNHL is of viral etiology. Nevertheless, the potential exists that carefully designed investigations may shed more definitive light on the subject in the future.

1.3 Natural History

Most of the discoverable causes of SSNHL cause permanent hearing loss due to damage to hair cells or other inner ear structures. In contrast, many patients with idiopathic SSNHL regain some of degree of hearing (Figure 1-4). A recovery rate of 32% to 65% (averaging 46.7%) without treatment typically within 2 weeks of onset has been shown by natural history and placebo-controlled studies (1,5,8,22). One of the studies demonstrated that 45% of patients with idiopathic SSNHL regain their hearing spontaneously in the affected ear to within 10 dB of the contralateral ear (5). The probability of hearing recovery decreases as the hearing loss duration increases, with
Deficits lasting for more than 2-3 months, being more likely to become permanent. Other factors that can affect the rate of hearing recovery for idiopathic hearing loss are hearing loss severity, duration, and age at presentation (1, 5, 8, 9).

Figure 1-4: Audiograms of two patients presenting with idiopathic SSNHL (47)

Both patients were women in their mid-40s who presented with complaints of SSNHL within less than 1 week of onset. Both patients were treated with 1mg/kg prednisone and oral antiviral medications for 10 days. Initial audiogram following onset of SSNHL for Patient 1 (A); follow-up audiogram at 2 weeks (B); initial audiogram following onset of SSNHL for
Patient 2 (C); follow-up audiogram at 3 weeks for Patient 2 (D). SSNHL, sudden sensorineural hearing loss.

1.4 Evaluation

Patients presenting with SSNHL should undergo investigations to establish their diagnosis, and most importantly, to rule a known underlying causes of hearing loss. Standard pure tone audiometry will not only provide the criteria for diagnosis of SSNHL; the characteristics of the initial audiogram have prognostic value has been discussed below. Patients do undergo a series of audiograms to document recovery, monitor treatment, guide aural rehabilitation, screen for relapse, as well as to rule out hearing loss in the contralateral ear. The Stenger test can be carried out if malingering is suspected (66). Auditory brainstem response (ABR) threshold testing is an alternative method to investigate malingering and inter-aural wave latency can be employed to rule out a cerebellopontine angle (CPA) lesion as an etiology of unilateral hearing loss. ABR is important when MRI is unavailable or is contraindicated. However, the sensitivity of traditional ABR in diagnosing tumors is much lower than MRI (88% vs. 99%), and it is substantially lower for tumors smaller than 1 cm in diameter (79%; (67,68)). Stacked ABR has been shown to improve the sensitivity to 95% and specificity to 88% for tumors less than 1 cm in size, making it a more practical replacement for MRI (69). From a practical point of view, ABR cannot be used to rule out vestibular schwannomas from all patients with SSNHL, because enough residual hearing must be present for the ABR response to be observed (thresholds of at least 75-80 dB or less; (68).

Some authors recommend electronystagmography (ENG) for patients with idiopathic SSNHL to obtain further prognostic information (13,70). On the other hand, some studies showed that ENG
was either not predictive or not independently predictive of prognosis and thus, the costs of the studies were not justified for this purpose (1,7,22).

The diagnostic evaluation of SSNHL, can potentially include a number of serologic tests and radiographic studies. These tests can be extremely low yield; hence several authors have questioned the cost of effectiveness of using a standard testing battery for patients with SSNHL (26). However, as it has been noted above, there are health consequences for patients with known causes of SSNHL. Therefore, certain tests should be performed especially for patients with risk factors for an underlying condition.

The laboratory tests that are commonly ordered for patients with SSNHL include nonspecific markers of inflammation as well as tests for specific infections. Abnormal serum cholesterol or coagulation panels can suggest a vascular etiology. Also, autoimmune studies are carried out to identify potential collagen-vascular, granulomatous, or rheumatologic causes of SSNHL. Furthermore, alterations in the patient’s metabolism can be evaluated with serum studies. Tests typically include rheumatoid factor (RF), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

The U.S. Centers for Disease Control (CDC) recommends, enzyme-linked immunosorbent assay (ELISA) for Lyme antibodies, either by a total titer or separate IgG and IgM levels as the first step in testing for Lyme disease. Lyme disease is then confirmed by Western blot. Although, patients still present with characteristics erythema migrans, antibody testing may be falsely negative due
to the lack of enough time for the antibody titers to rise (73). Patients with characteristics of Lyme
disease but no positive ELISA results, should be treated presumptively followed by retesting for
anti-Lyme antibodies 3-4 weeks later (73). However, in cases with neurologic involvement but an
unclear diagnosis, there is need to test their cerebrospinal fluid (CSF) for cell counts and Lyme
antibody titers and tests for other infectious agents(23).

The Syphilis serum screening tests rapid plasma reagin (RPR) and venereal disease research
laboratory (VDRL) which are screening test may not be positive in cases of otosyphilis. In
addition, serum fluorescent treponemal antibody absorption (FTA-ABS) which is a definitive test
may not be positive in this disease (74). In cases of SSNHL in which otosyphilis is high on the
differential, particularly in patients with HIV disease, cerebrospinal fluid VDRL testing (CSF-
VDRL) reactivity may be required to determine whether otosyphilis is the causative agent (74).

Serological testing for markers of cardiovascular risks such as lipid analysis and serum glucose
are often ordered by medical practitioners in the evaluation of idiopathic SSNHL. 35 to 40% of
patients presenting with idiopathic SSNHL will likely have hypercholesterolemia (33). In a similar
way, it has been reported that 37% of patients presenting with idiopathic SSNHL have elevated
blood glucose (26,33). In some cases, these tests might have been performed previously by the
primary care physician that is looking after the patient’s well-being and may not necessarily need
to be reordered for the purpose of identification of hypercholesterolemia or diabetes unless the test
has not been done for over 6 months or 1 year. From a practical perspective, however, it is
important to order complete blood chemistries within four weeks prior to an MRI in many U.S.
centers, Cr/eGFR is the standard, but in the U.S, complete blood chemistries are also often ordered so most times these will need to be reordered (26,33).

Thyroid dysfunction can be found in patients presenting with SSNHL, with one report of a 15% rate of hypothyroidism (26). Ideally, modern evaluation of thyroid function starts with total TSH level as a screening test, because it has a high negative predictive value (75). In case of abnormal TSH level, the patient is typically referred back to their primary care providers or to an endocrinologist for further analysis and treatment. Evaluation of low TSH levels (suspected hyperthyroidism) include a total triiodothyronine (T3) and free thyroxine (T4 level); whereas evaluation of high TSH levels (suspected hypothyroidism) will typically involve a free T4 level (75). Hearing function is believed by some to be affected by both hyperthyroidism and hypothyroidism. Oiticica et al., 2010 did a cross sectional study where they studied the metabolic disorders of 166 patients diagnosed with sudden hearing loss. They reported that thyroid hormone levels were normal in 116 (78.4%) patients and abnormal in 32 (21.6%) patients. Arcgil M and Abitter Yucel (2016), studied the effects of thyroid hormone levels on hearing and its prognosis in patients without any known risk factors including hyper or hypothyroidism and found that free T4 levels were lower in the group that did not respond to treatment than in the group that did. However free T4 levels were within the normally accepted reference range in Arcgil M et al’s study. In conclusion more work is required to determine if thyroid function affects SSNHL.

The major component of the evaluation of SSNHL is radiographic evaluation of the internal auditory canal and cerebellopontine angle for tumors, and it include vestibular schwannomas and meningiomas. The specificity and sensitivity of MRI scanning of the tumor through an impaired
vasculature barrier resulted from the active angiogenesis of the tumor with gadolinium in the diagnosis of vestibular schwannomas greater than 3 mm in diameter is nearly 100% (67,68). Gadolinium-contrast MRI detects VS by demonstrating the uptake of the contrast agent in the tumor through an impaired vasculature barrier resulted from the active angiogenesis of the tumor. There would be a positive finding on MRI in about 1% to 6% of patients presenting SSNHL on average (6–8). Contraindications to the use of gadolinium include glomerular filtration at a rate of <30 mL/min and nephrogenic systemic fibrosis (76). In cases where gadolinium is contraindicated, a high-resolution MRI of the brain and brainstem, including a constructive interference in the steady state (CISS) sequence can be carried out instead, with an estimated sensitivity of nearly 100% for tumors over 5 mm in diameter (68).

The type and number of tests required for the evaluation of SSNHL differs significantly between geographical locations and individual physicians. One recently conducted study on practice patterns in Sweden showed that all of the 400 patients with SSNHL in study had standard audiological test, however, only 65% and 40% underwent laboratory testing or MRI imaging respectively, even when managed by otolaryngologists (8). In contrast, a recent study of the diagnostic evaluation of 128 patients with SSNHL presenting to a major U.S. medical center revealed that six diagnostic tests on average were ordered. Eighty-five percent of these patients had an MRI with gadolinium (26). For many of the tests, the likelihood of a positive result is very low, which leads to a higher cost per positive test finding (26). In spite of these results, identifying the etiology of SSNHL still remains an integral part of the clinician’s evaluation. An algorithm for the evaluation of SSNHL has since been replaced by the 2019 American Academy of
Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) clinical practice guideline (52).

At the least, evaluation of patients with SSNHL should include a study to rule out vestibular schwannoma or other retro cochlear pathology as well as a laboratory evaluation for a known etiology of SSNHL according to the patient’s history and risk factors.

<table>
<thead>
<tr>
<th>Historical factors</th>
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<tbody>
<tr>
<td>Noise exposure</td>
</tr>
<tr>
<td>Tobacco use</td>
</tr>
<tr>
<td>Sudden, fluctuating unilateral hearing loss, tinnitus,</td>
</tr>
<tr>
<td>and episodic vertigo</td>
</tr>
<tr>
<td>Head trauma</td>
</tr>
<tr>
<td>Rapidly progressive hearing loss, fluctuating</td>
</tr>
<tr>
<td>Bilateral loss</td>
</tr>
</tbody>
</table>

Figure 1-5: Historical factors that should prompt further evaluation in patients

1.5 Treatment

Treatment of SSNHL remains somewhat controversial. Corticosteroids have been the mainstay of treatment for SSNHL since Wilson et al., 2005 reported their potential benefit. High-dose oral corticosteroids are considered the mainstay of treatment for SSNHL with intra-tympanic steroid injections also in wide use. Numerous treatments have been studied for the treatment of idiopathic SSNHL, including anti-inflammatory agents, vasodilators, calcium channel blockers, diuretics and HBOT. Despite extensive research, a clear superior therapy in terms of effectiveness has not been identified.
The fact that idiopathic SSNHL spontaneously resolves adds to the controversy surrounding the necessity for treating idiopathic SSNHL. The various treatment methods available reflect the ongoing debate over the etiology of idiopathic SSNHL, the relative rarity of the condition, and the lack of a clearly superior therapy (22). Often promising results were found in case series and small trials, that in further larger studies were either inconclusive or failed to demonstrate a clinically important improvement in hearing outcomes from that therapy (22,77).

A surveyed conducted in the U.S. shows that, 98% of otolaryngologists reported treating idiopathic SSNHL with oral steroids; additionally, 8% of otolaryngologists reported the use of intratympanic steroids (78). Corticosteroids are thought to improve idiopathic SSNHL by reducing inflammation and edema in the inner ear (79). An early study combined the data from two separately administered double-blinded randomized controlled trials of a total of 67 patients using different corticosteroid regimens, finding improved hearing recovery in patients receiving steroids (78%) compared to placebo (38%).

Subsequently, attempts to replicate this study shows inconsistent findings with respect to the benefit of corticosteroids in idiopathic SSNHL (77).

Intratympanic (IT) corticosteroids are being used increasingly in the management of idiopathic SSNHL. IT-steroids utilization results to increase in perilymph levels of steroids than systemic administration, however, IT steroids are not absorbed into the systemic circulation (80). Earlier, they were used in the context of patients with contraindications to systemic steroid therapy and
patients who have failed systemic steroid administration (81,82). A study conducted by Rauch and colleagues reveals that IT application of corticosteroids is not inferior to systemic steroids for idiopathic SSNHL with thresholds less than 70 dB HL (83). However, combined systemic steroids with IT dexamethasone did not result in significant improvements in the study of (84).

In a survey of 104 otolaryngologists practicing in the USA, 50% of respondents reported using antiherpetic therapy (acyclovir, famciclovir, etc.) in combination with corticosteroids for the treatment of idiopathic SSNHL despite a lack of evidence of efficacy (77,78). Other therapeutic modalities, including “shotgun” approaches which incorporate multiple modalities of treatment, are also performed without good clinical evidence of their utility.

1.6 Prognosis

The prognosis of SSNHL owing to a discernable etiology relies mostly on the disease process, its duration, specific impact on cochlear structures, and available method of treatments (5,35,45).

There are several risk factors that determine the prognosis of idiopathic SSNHL patients including, their demographics, duration of hearing loss, associated symptoms, and audiogram characteristics (Table 1-2).
Table 1-2: Prognosis Factors for Hearing Recovery Following Idiopathic SSNHL

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age &lt; 60</td>
<td>Age &gt; 60</td>
</tr>
<tr>
<td>Duration of hearing loss</td>
<td>&lt; 1-2 weeks</td>
<td>&gt; 3 months</td>
</tr>
<tr>
<td>Pattern of hearing loss</td>
<td>Low frequency</td>
<td>Flat</td>
</tr>
<tr>
<td></td>
<td>Mid-frequency</td>
<td>Down sloping</td>
</tr>
<tr>
<td>Related symptoms</td>
<td></td>
<td>Vertigo</td>
</tr>
</tbody>
</table>

Patients presenting with severe SSNHL are known to have a decreased rate of hearing recovery in contrast to patients with mild hearing losses (5,13). The shape of the pure tone audiogram has been shown in many studies to determine hearing recovery, with higher rates of recovery usually found for low-frequency (63% to 88%) or mid frequency (36% to 71%) hearing losses compared with flat (40% to 56%) or down sloping hearing loss (19% to 38%) (8,9,22).

Early presentation less than a week to a physician after the onset of SSNHL aligns with improved odds of hearing recovery, with diminishing odds of complete hearing recovery after that time. The rates of hearing recovery after treatment within one week of onset is 87%, 2 weeks 52%, and 10% or less after 3 months (5,7,11,13). Some authors have suggested that the relationship between SSNHL onset and presentation to a physician implies that earlier treatment leads to enhanced
hearing outcomes; however, this effect is noted for different types of treatment and in natural history studies. Therefore, the poorer prognosis linked with a longer time between onset of SSNHL and presentation may be a reflection of the natural history of SSNHL. Sensorineural hearing loss of shorter duration is most likely to recover regardless of modality of treatment (22).

Signs and symptoms of comorbidity have been investigated as prognostic indicators for SSNHL recovery. Studies have shown that patients who complain of imbalance or vertigo have a poorer prognosis for hearing recovery following SSNHL (5,70,71), whereas in other studies, dizziness was not found to affect prognosis (7,8,13). In a similar vein, abnormalities on electronystagmography (ENG) have been linked with poorer hearing recovery in many patients (1,13,70), unfortunately, not all studies are supportive (7). In some studies, ENG affected prognosis only in patients with unfavorable audiograms (22); while in another study, ENG abnormalities were found not to be independently associated with hearing prognosis when other factors (age, degree of hearing loss) were incorporated in the analysis (1). Tinnitus on presentation with SSNHL has been noted to be a negative prognostic indicator (Ben-David et al., 2002), a positive prognostic indicator (70), or not to influence outcome (71). In all, vertigo, tinnitus and ENG abnormalities are less predictive of hearing outcomes than the other previously discussed prognostic factors.

Some researchers have made an attempt to come up with an algorithm which combines multiple prognostic factors to yield a percentage likelihood of hearing recovery or an odds ratio for recovery for patients with multiple risk factors (5)(22). Although the discernment of these numbers can assist in counseling patients about hearing recovery, care must be taken to ensure that every patient
has a clear understanding of the number of factors peculiar to their hearing prognosis. Thus, a 90% chance of hearing recovery does not necessarily mean that an individual patient will recover 90% of their hearing.

For patients with idiopathic SSNHL, one concern has been the development of bilateral SSNHL. In more than one study, the prevalence of bilateral SSNHL is about 2%, and this includes patients with simultaneous bilateral onset (5,7,12,13). Thus, patients can be reassured that the risk of sequential involvement of the contralateral ear is very low.
Chapter 2: Methodology

2.1 Literature review: A Systematic Review

Objective: The purpose of this study is to evaluate the current literature on the effectiveness of oral steroids, IT steroids and HBOT based treatments on hearing outcomes in patients with SSNHL.

Hypothesis: We hypothesize that there is no statistically significant difference in the treatment outcomes of SSNHL patients who receive oral steroids, compared to combination therapy including in addition to oral steroids IT steroids plus or minus HBOT.

2.1.1 Identification and Inclusion of Studies

Search methods for identification of studies
Electronic searches
Medline, PubMed, Web of Science, and Embase databases were searched for the period January 2000 to June 2018 with the aim of identifying recent literature. Articles were searched using medical subject headings MeSH terms “Sudden sensorineural hearing loss” combined with “steroids”, “oral” “Intratympanic” and hyperbaric oxygen therapy. Exploded terms, and spelling variants were not used due to the time constraints of the MSc program. The reference lists in the reviewed articles were also searched for additional references.

The results of the search were presented in the PRISMA guidelines recommended format, which depicts the flow of data through the different phases of a systematic review (72). The quality of evidence of individual studies was graded as poor, fair or good using the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) Study Quality Assessment Tools (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).
Inclusion criteria

Primary articles types include;

• Retrospective study
• Prospective randomized controlled trial
• Cross sectional study
• Case controlled study

Patients with SSNHL treated with;

• oral steroids
• IT steroids
• HBOT

Exclusion criteria

• Case reports
• Articles without an abstract
• Review articles
• Conference abstracts
• Letters
• Editorial
• Survey
• Articles in non-English language
• Anonymous authorship
2.1.2 Evaluation of Methodological Quality

The methodological quality was evaluated independently by one reviewer to determine the validity of each study. The reviewer was not blinded to the authors, institutions, journals of publication, or results of the studies, consistent with the Berlin method. The following validity criteria for assessing the study results were adapted from National Heart, Lung, and Blood in Institute of the National Institutes of Health (NIH) Study Quality Assessment Tools.

The ’Risk of bias’ tool (Higgins et al., 2011) was adopted for the assessment of study quality.

• sequence generation;

• allocation concealment

• blinding;

• incomplete outcome data;

• selective outcome reporting; and

• other sources of bias

The ’Risk of bias’s involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: ’low’, ’high’ or ’unclear’ risk of bias.

2.1.3 Types of Interventions

Oral versus IT steroids

• Oral versus Oral + IT steroids
• Oral versus IT steroids versus Oral + IT steroids
• Oral + IT steroids versus Oral + IT steroids + HBOT

2.1.4 Data Collection and Analysis

Selection of studies

Two investigators scanned the initial search results to identify trials that loosely met the inclusion criteria. The full-text articles of the identified trials were then re-viewed, and the inclusion criteria applied by one investigator. The reviewer was not blind to the study authors, journals of publication and the study results whilst applying the criteria for determining which studies to include in the review.

2.1.5 Data Extraction and Management

Data were extracted from included trials by one reviewer (GJ). Information on the patients, investigations, methods, interventions, and outcomes were recorded on a standardized data collection table. The primary outcome measure was the change in averaged air conduction pure-tone audiometric (PTA) threshold over 500,1000,2000,4000 Hz in response to treatment.

Outcomes

Study outcomes were measured using a variety of methods and presented in the most clinically relevant manner. For each trial the following aspects was documented:

• participants (inclusion/exclusion criteria, method of diagnosis)
• Interventions (including dosage of steroids and duration, category of non-steroid treatment modalities used in combination with steroids)
• Comparator- oral steroids.
• outcomes primary - the proportion of patients showing a hearing gain >15 dB in averaged PTA thresholds in response to treatment, secondary outcome - treatment side effect

2.1.6 Data Synthesis

Characteristics and results of all included studies were reviewed systematically. Study characteristics, including Objectives, Study design, intervention, major findings, evidence quality (NIH) were tabulated and compared across all included articles. Outcome measures and results of each study were summarized and tabulated. Data were analyzed by grouping the studies into intervention (e.g. steroid method of delivery); study design; setting; and by outcome (primary, and secondary). Heterogeneity was not assessed statistically. Two forest plots were used to analyze and summarize the data, which was grouped into (combination oral and intra-tympanic steroids vs oral steroids and combination steroids + HBOT vs oral steroids) using a random-effects model. Subgroup analyses based on the severity of the presenting hearing loss; presence of vertigo; delay in the onset of treatment; or other factors were not undertaken.
2.2 Retrospective Chart Review

Objective: The purpose of this study is to evaluate the effectiveness of oral steroid, IT steroid and HBOT based treatments on hearing outcomes in patients with SSNHL presenting to Vancouver General Hospital (VGH).

Hypothesis: We hypothesize that there is no statistically significant difference in the treatment outcomes of SSNHL patients who receive oral steroids, compared to combination therapy including in addition to oral steroids IT steroids +/- HBOT.

Study Design: Retrospective cohort study

Setting: Vancouver General Hospital (VGH)

2.2.1 Study Design and Participants

A retrospective case review of patients who presented with SSNHL to VGH over a period from January 1st, 2015 to December 31st, 2017 was performed. International Classification of Disease Diagnostic, treatment, and Medical Service Plan billing codes was used to identify patients with SSNHL from both VGH emergency Otology-Neurotology clinic, and the Resident clinic. The clinical records of these patients were retrieved and reviewed by the study investigators to identify those with SSNHL.

Parameters recorded included patient demographics (age, gender, postal code), medical comorbidities (Hypertension, Diabetes, Dyslipidemia), medications, associated vertigo,
audiometric findings, treatment details, smoking and alcohol status. Experienced staff otolaryngologists and residents and fellows under their supervision made all SSNHL diagnoses and treatment modalities administered included a combination of oral prednisone, IT dexamethasone and Hyperbaric Oxygen Therapy (HBOT) three hours per session for an average of twenty dives. A shared decision-making model was utilized in which patients were given a choice of available treatments by describing each including their risks, and benefits. Patients’ use of any other therapies for their hearing loss not prescribed by VGH clinicians were not specifically monitored for study purposes. The recording of treatments taken were subject to patients’ recall at the time the history was taken and the clinicians accurate recording of any treatments therefore, introducing potential unexplored biases.

Patients: The target population in this study is adult patients (>19 years of age) presenting with SSNHL to VGH.

Inclusion criteria for the study population:

- Age 19 or older
- Hearing loss of greater than 30 dB over 3 contiguous frequencies

Exclusion criteria for the study population:

Patients identified with acoustic neuromas or other structural etiologies on imaging, trauma, exposure to ototoxic medications, familial hearing loss, Meniere’s disease, infectious and
inflammatory middle/inner ear disease, and autoimmune sensorineural hearing loss was excluded. Patients without radiological and follow-up audiological evaluations was likewise excluded.

2.2.2 Outcomes

Primary Outcome

- To determine if there is an inter-group difference in the number of SSNHL patients showing an improvement of >15 dB in mean PTA threshold averaged across 4 frequencies 500,1000,2000,4000 Hz in patients who received oral steroids compared to those who received combination treatment.

2.2.3 Data Collection

Patient data collected include:

- Patient Demographics (age, sex)

Clinical data:

case record derived data include:

- Prescribed medications
- Smoking/drinking history,
- Vertigo
- Tinnitus
- Other diseases/systems (vestibular diseases in particular)
- illnesses (e.g. diabetes, hypertension, dyslipidemia, etc.)
- clinical examination findings (micro otoscopy, tuning fork examination),
• Audiometric findings (frequency specific thresholds at 500, 1000, 2000, 3000, 4000 Hz and Pure Tone Audiogram average at 500/1000/2000/4000 Hz),
• Treatment type (oral steroid, hyperbaric oxygen, or intratympanic steroid).

2.2.4 Description of Research Workflow

The case records of consecutive patients referred to VGH for hearing loss between January 1st, 2015 to December 31st, 2017 is obtained using MSP billing code, designated for SSNHL patients from VGH emergency Otology-Neurotology clinic. Cases meeting the study inclusion criteria were assigned an anonymous study identification number and then further evaluated to extract the relevant study data. This data was collected and stored in an encrypted excel sheet on a password protected computer for further analysis.

2.2.5 Evaluation of Hearing Outcomes

Audiogram PTA thresholds were recorded for bone conduction at 500, 1000, 2000, and 4000 Hz and air conduction at 500, 1000, 2000, and 4000 Hz. Serial four frequency PTA threshold averaged over 500, 1000, 2000 and 4000 Hz prior to and post treatment was recorded. Averaged pre-treatment PTAs were used to classify patients according to severity of hearing loss at time of presentation (Mild 25-40dB, Moderate 41-55dB, Moderately Severe 56-70dB, Severe 71-90dB, Profound 91-120dB) (107) Hearing outcomes were evaluated using average PTA change over the course of treatment. Patients were characterized to either have a clinically relevant improvement in hearing levels (a decrease of >15dB from the pre-treatment PTA threshold to the most recent post-treatment PTA threshold), to have no change, or worsened hearing loss (increase of >15dB
PTA threshold). Patients with improvement in hearing were further classified to have full recovery of hearing (PTA < 25dB on most recent post treatment audiogram) or have sub-optimal hearing recovery (PTA = or > 25dB on most recent post treatment audiogram).

2.2.6 Statistical Analysis
Statistical analyses were performed using the Statistical Package for the Social Sciences software (SPSS V.25, IBM).

The Chi-Square test (Fisher’s exact test, 2x2 table) was used to measure the degree of association between hearing improvements [no (<15dB) or yes (>15dB)] and other nominal variables include gender (male or female), vertigo (yes or no), alcohol drinker (yes or no), smoker (yes or no), history of diabetes (yes or no), history of hypertension (yes or no) and history of dyslipidemia (yes or no) were tested.

Independent samples t-test were used to measure the continuous variables [mean age, pure tone average (PTA), days of treatment, number of injection, number of dives] with respect to nominal/categorical data [pre and post treatment, hearing improvement, treatment types (prednisone alone, oral prednisone + intratympanic steroid, oral prednisone + HBOT, and oral prednisone+ intratympanic+ HBOT treatment)] with a significance value set at $p < 0.05$. No sample size calculation was performed a priori.
Chapter 3: Results

3.1 Systematic Review

The literature search resulted in 649 articles, 426 of which were duplicates, 129 were review articles, conference abstracts, letters, editorial, survey, report, articles in non-English language, and anonymous authorship. A total of 94 full-text articles were than assessed for eligibility out of which 70 articles were excluded based on inclusion/exclusion criteria, leaving a final collection of 24 primary articles for review.

The results of the meta analyses which include (84,87,92,94,98,99,100,102) for Steroids combination therapy analysis and (86,90,103,105,106) for HBOT treatment analysis. These articles were selected out of the 24 because they reported the numbers of patients that recovered both in the treatment and control group and others (83,85,88,89,91,93,95-97,101,104) were rejected because they did not report the exact number of patients that recovered either in treatment or control groups. Studies were similar in terms of patients, intervention, comparison and outcome. Our findings are presented as Forest plots. Figures 3.2 demonstrates the results of the analysis which shows the following; authors name and year of publication, graphical representation of result findings and statistical findings. In our meta-analysis odds ratios were converted to log odds ratios which results in symmetry around zero, which is easier for the non-expert statistician to understand. Thus, when we compared combination steroids vs oral steroids alone the probability of hearing recovery in the combination steroids group is greater than that in the oral steroids alone group, the odds ratio is greater than 1, and the log odds ratio is greater than 0 (0.94, 95% confidence interval 0.28 – 1.59) and also when we compared HBOT combination therapy vs non-HBOT combination therapy the probability of hearing recovery occurring in the HBOT group is greater
than that in the non-HBOT group, the odds ratio is greater than 1, and the log odds ratio is greater than 0 (0.83, 95% confidence interval 0.24 – 1.41). The differences found both inter-group comparisons were statistically significant. (Forest plots p-value 0.005) as illustrated in figures 3-2 and 3-3.

Overall, 90% of 687 patients in the 8 studies who received oral and IT steroids (combination therapy) and 86% of 494 patients in the 5 studies who received triple therapy with HBOT demonstrated hearing recovery compared to a 75% recovery rate in 548 patients who received...
oral steroids alone. Combination therapy had statistically significant hearing improvement compared with oral steroids alone (Chi squared, p < 0.05). Some authors demonstrated that combination therapy not only improved PTA average but resulted in statistically significant higher post treatment speech discrimination scores than those treated with oral steroids alone. However, combined HBOT and steroid treatment did not always result in significant improvements (84).

The articles that fulfilled the inclusion criteria are summarized in table 3-1
<table>
<thead>
<tr>
<th>Publication</th>
<th>Objectives</th>
<th>Study design/Intervention</th>
<th>Major findings/Results</th>
<th>Evidence quality (NIH)</th>
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</thead>
<tbody>
<tr>
<td>Cho et al., 2018 (86)</td>
<td>To investigate the efficacy of simultaneous steroid and hyperbaric oxygen therapy (HBOT) in patients with severe to profound idiopathic SSNHL, which has a poor prognosis</td>
<td>Prospective randomized controlled trial 60 patients were randomly divided into 2 groups 1. Control group - oral steroid + IT steroid injection (ITSI) 2. Study group - oral steroid + ITSI + HBOT</td>
<td>1. Significantly better hearing levels were achieved in the study group compared to the control group at 500 Hz (p &lt;0.05). 2. Complete and partial hearing recovery for the study group was significantly higher than that for the control group</td>
<td>Good</td>
</tr>
<tr>
<td>Tsounis et al., 2018 (87)</td>
<td>To compare the therapeutic efficacy of systemic versus IT versus combined administration of steroids in the treatment of SSNHL.</td>
<td>Prospective randomized multicenter clinical trial 102 patients with 14 days history of SSNHL were randomized to 1 of 3 arms and followed prospectively. Group A: Systemic steroid (35 patients) Intravenous prednisolone for 7 days followed by methylprednisolone orally Group B: IT steroid (34 patients) IT injections - 0.4–0.6 ml Group C: Combined treatment (33 patients) Combination of above treatments</td>
<td>1. No statistically significant differences among 3 treatment groups. 2. Patients &lt;60 years showed significantly better hearing outcomes than those &gt;60 years.</td>
<td>Good</td>
</tr>
<tr>
<td>Almosnino et al., 2018 (90)</td>
<td>To evaluate hearing outcomes after salvage therapy with HBOT for the treatment of SSNHL.</td>
<td>Retrospective case series 36 patients were divided into 2 groups. Patients received initial therapy with oral and/or IT steroids with an incomplete response. Group 1 - 18 patients underwent salvage therapy with IT steroids and HBO Group 2 - 18 matched controls underwent salvage therapy with IT steroids alone.</td>
<td>1. No significant difference in mean post-treatment PTA between groups 1 and 2 2. No significant difference in mean post-treatment WRS between groups 1 and 2</td>
<td>Poor</td>
</tr>
<tr>
<td>Publication</td>
<td>Objectives</td>
<td>Study design/Intervention</td>
<td>Major findings/ Results</td>
<td>Evidence quality (NIH)</td>
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<tr>
<td>Kim et al., 2015 (92)</td>
<td>To compare the recovery rates of patients with idiopathic SSNHL treated with oral systemic steroids (PO) or IT steroid injection or both.</td>
<td>Retrospective observational study 844 patients were divided into different treatment modality. 1. Oral steroid used in the PO group was methylprednisolone 80 mg for 7 days and IT steroid injection 0.3–0.4 cc dexamethasone 2. Combined method group combination of oral steroids and IT steroid injection</td>
<td>1. The recovery rates in the oral and combined groups were significantly higher than in the IT steroid injection group</td>
<td>Good</td>
</tr>
<tr>
<td>Gundogan et al., 2013 (94)</td>
<td>The purpose of this study was to compare the efficacy of systemic steroid alone and combined with intratympanic methylprednisolone (ITMP) in the treatment of patients with SSNHL</td>
<td>Prospective randomized controlled trial There are 79 patients divided into 2 treatment group: 1. 37 patients - ITMP + oral steroid (combination therapy) 2. 36 patients - oral steroid alone treated with a 14-day course of oral steroid (1 mg/kg of oral methylprednisolone and 10 mg taper every 3 days).</td>
<td>1. Combination therapy had a statistically greater significant hearing improvement compared with oral steroid alone. (p &lt; 0.05) 2. In hearing outcomes in patients with severe hearing loss, combination therapy had statistically significant hearing improvement compared with oral steroid alone (P &lt; .05).</td>
<td>Good</td>
</tr>
<tr>
<td>Lim et al., 2013 (84)</td>
<td>The study compared the efficacy of 3 different steroid treatments for ISSNHL.</td>
<td>Prospective randomized controlled study 60 patients were randomly and equally divided into 3 groups based on therapy: 1. 20 patient- oral steroid for 10 days 2. 20 patient- intratympanic dexamethasone injection (ITDI) 4 times 3. 20 patient- combination of both</td>
<td>1. There was no significant difference in hearing gain and recovery rates for the 3 groups.</td>
<td>Poor</td>
</tr>
<tr>
<td>Publication</td>
<td>Objectives</td>
<td>Study design/Intervention</td>
<td>Major findings/ Results</td>
<td>Evidence quality (NIH)</td>
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<tr>
<td>Jung da et al., 2016 (98)</td>
<td>The aim of this study was to compare the hearing results of patients with sudden sensorineural hearing loss (ISSNHL) who initially were treated with either a combination therapy of systemic steroids (SS) and intratympanic steroid injection (IT-S) or SS only.</td>
<td>Retrospective case-control 105 patients were enrolled in this study. 1. control group (n = 52) was treated with SS 2. study group (n = 53) received SS as well as IT-S.</td>
<td>1. No significantly different in the hearing outcomes between the study and control groups.</td>
<td>Good</td>
</tr>
<tr>
<td>Battaglia et al., 2008 (99)</td>
<td>To compare hearing results in ISSNHL patients who have received high-dose prednisone taper (HDPT) alone, IT-Dex alone, or IT-Dex and HDPT (combination therapy)</td>
<td>Multicenter, double-blinded, placebo-controlled, randomized study 51 patients with a less than 6-week history of ISSNHL were randomized into 3 groups 1. Group A (17 patients) received IT-Dex therapy with placebo taper 2. Group B (18 patients) were administered HDPT and placebo intratympanic injections. 3. Group C (16 patients) combination therapy.</td>
<td>1. Patients receiving combination therapy (IT-Dex + HDPT) in Group C had an average improvement in speech discrimination score of 44 percentage points and a 40-dB improvement PTA. 2. Patients in Group C had statistically significant improvements in speech discrimination score compared with Group B patients (HDPT alone; p &lt; 0.05). proportion of patients achieving a significant PTA improvement in Group C was statistically greater than patients in Group B (p &lt; 0.02).</td>
<td>Good</td>
</tr>
<tr>
<td>Koltsidopoulos et al., 2013 (100)</td>
<td>To investigate the therapeutic efficacy of intratympanic dexamethasone combined with systemic prednisolone in patients with sudden sensorineural hearing loss (SSNHL)</td>
<td>Prospective, randomized, multicenter clinical trial 92 patients were allocated into 2 groups. 1. control group patients were treated with systemic prednisolone alone. 2. combined treatment group patients received additionally 3 intratympanic dexamethasone injections within 5 days.</td>
<td>1. No statistically significant difference between the 2 groups 2. No serious complications or adverse reactions were reported.</td>
<td>Good</td>
</tr>
<tr>
<td>Publication</td>
<td>Objectives</td>
<td>Study design/Intervention</td>
<td>Major findings/Results</td>
<td>Evidence quality (NIH)</td>
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<tr>
<td>Ahn et al., 2008 (102)</td>
<td>To evaluate the therapeutic efficacy of intratympanic dexamethasone (ITD) injections added to systemic steroids in patients with idiopathic sudden sensorineural hearing loss.</td>
<td>Prospective, randomized, controlled clinical trial 120 patients were divided into 2 groups 1. Combined treatment group ITD injections + 48 mg methylprednisolone 2. oral steroid group -methylprednisolone alone</td>
<td>The combined treatment group showed significantly better hearing improvement compared to the oral steroid group.</td>
<td>Good</td>
</tr>
<tr>
<td>Alimoglu et al., 2011 (103)</td>
<td>To compare the efficacy of hyperbaric oxygen, oral steroid, intratympanic steroid therapy and their combinations in idiopathic sudden sensorineural hearing loss patients.</td>
<td>Retrospective Cohort study 217 patients were divided into 4 groups 1. oral steroid + hyperbaric oxygen group 2. oral steroid group 3. intratympanic steroid group 4. hyperbaric oxygen group</td>
<td>1. Oral steroid + hyperbaric oxygen group has the highest mean hearing gain among all groups (p &lt; 0.05) followed by oral steroid group.</td>
<td>Good</td>
</tr>
<tr>
<td>Topuz et al., 2003 (105)</td>
<td>To investigate the therapeutic effects of HBO therapy in the 1st 2 weeks of the onset of ISSHL</td>
<td>Prospective randomized study 51 hospitalized patients with confirmed ISSHL were randomly divided into two groups. 1. oral steroid group - 21 patients received oral steroids 2. Combination group - 30 patients received the same oral steroid treatment with the addition of HBO therapy</td>
<td>1. Significantly high mean hearing gains were found in combination treatment group (Oral steroid +HBOT) patients in comparison to patients in Oral steroid alone group (p&lt;0.005)</td>
<td>Good</td>
</tr>
<tr>
<td>Fujimura et al., 2007 (106)</td>
<td>To investigate the therapeutic effects of HBO therapy combined with steroid administration for idiopathic SSNHL in comparison with that of steroid administration alone.</td>
<td>Retrospective controlled study 130 inpatients with SSNHL 1. HBO group - 67 patients underwent HBO plus intravenous drip infusion steroid therapy 2. steroid group - 63 were given intravenous drip infusion steroids alone. They were given 8 mg/day of dexamethasone followed by tapered doses for 12 days</td>
<td>1. Significantly higher hearing improvement rate was observed in the HBO group than in the steroid group (P &lt; 0.05) 2. Hearing outcomes were not statistically different between the two groups. In both the HBO and steroid groups</td>
<td>Good</td>
</tr>
</tbody>
</table>
The studies excluded from the data synthesis due to lack of adequate data

<table>
<thead>
<tr>
<th>Publication</th>
<th>Objectives</th>
<th>Study design/Intervention</th>
<th>Major findings/ Results</th>
<th>Evidence quality (NIH)</th>
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</thead>
<tbody>
<tr>
<td>Witsell et al., 2018 (85)</td>
<td>To describe patterns of corticosteroid treatment for SSNHL and evaluate the effectiveness based on delivery mode [oral vs intratympanic (IT)].</td>
<td>Cross-sectional study 117 patients were divided into 2 groups 1. oral steroids 2. simultaneous oral + IT steroids</td>
<td>1. No statically significant differences between treatment groups. 2. Both groups showed improvement in both pure tone and speech audiometry scores.</td>
<td>Good</td>
</tr>
<tr>
<td>Ermutlu et al., 2017 (88)</td>
<td>To evaluate the effectiveness of the different application routes of steroids in the treatment of SSNHL.</td>
<td>Prospective randomized case-controlled clinical trial 41 patients were randomized into 2 groups (age and gender matched) 1. Oral steroids - 21 patients 2. IT injection - 20 patients</td>
<td>1. No statistically significant differences between 2 groups 2. No side effects associated with IT injection</td>
<td>Poor</td>
</tr>
<tr>
<td>Swachia et al., 2016 (89)</td>
<td>To evaluate the efficacy of steroids given orally and by the IT route.</td>
<td>Prospective randomized open-labeled study 42 Patients were randomized into 2 groups; 1. 25 patients - Oral prednisone tapered over 14 days 2. 21 patients - IT methylprednisolone (40 mg/mL)</td>
<td>1. Statistically significant improvement in hearing was observed in both groups, but it was not significant when group I and group II were compared. 2. Improvement of 18.24±8.72 dB was recorded in group I patients treated with oral prednisone in comparison to 14.68±12.88 dB improvement in group II</td>
<td>Poor</td>
</tr>
<tr>
<td>Chen et al., 2015 (91)</td>
<td>To describe the efficacy of long-term oral steroids in idiopathic SSNHL.</td>
<td>Retrospective study 215 patients received oral steroid therapy 3 months follow up with oral administration of high-dose steroids</td>
<td>1. All patients showed a statistically significant difference with better hearing recovery in their final PTA</td>
<td>Good</td>
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<tr>
<td>Publication</td>
<td>Objectives</td>
<td>Study design/Intervention</td>
<td>Major findings/ Results</td>
<td>Evidence quality (NIH)</td>
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<tr>
<td>Filipo et al., 2014 (93)</td>
<td>To assess the therapeutic effectiveness of an IT steroid protocol compared to a systemic steroid protocol.</td>
<td>Retrospective study 265 patients were divided into 2 groups. 1. Oral steroid of prednisone tablets (25 mg) at tapering doses: 62.5 mg per day for 4 days, 37.5 mg for 2 days and 25 mg for 2 days 2. IT steroid administration of prednisolone at a dose of 62.5 mg/ml once a day for 3 days</td>
<td>1. The strong efficacy of steroid therapy was evident in both groups, with PTA and hearing improvement 2. The evaluation of the hearing outcomes shows a significantly better result for the short-term IT steroid; this result is ascribable to two types of audiometric curves: down- and upsloping</td>
<td>Good</td>
</tr>
<tr>
<td>Baysal et al., 2013 (95)</td>
<td>The aim of this study was to evaluate the effectiveness of oral steroid treatment versus combined oral and IT injection for idiopathic sudden sensorineural hearing loss.</td>
<td>Retrospective case review 1. 30 patients in the oral steroid group 2. 39 patients in the combined oral and intratympanic steroid injection group were compared.</td>
<td>1. The comparison of the initial pure tone audiometry (PTA) threshold results revealed a significant difference between the systemic steroid (SS) group and the systemic and intratympanic steroid group (P &lt; 0.05, P = 0.032) 2. No significant difference in pure tone gain in the SS group was 20.97 ± 27.47 dB (mean ± SD), and that of the group treated with both systemic and intratympanic steroids was 19.36 ± 22.16 dB (mean ± SD) (P = 0.49).</td>
<td>Good</td>
</tr>
<tr>
<td>Rauch et al., 2011 (83)</td>
<td>To compare the effectiveness of oral vs intratympanic steroid to treat sudden sensorineural hearing loss.</td>
<td>Prospective, randomized trial 250 patients were divided into 2 groups. 1. 121 patients received either 60 mg/d of oral prednisone for 14 days with a 5-day taper. 2. 129 patients received 4 doses over 14 days of 40 mg/mL of methylprednisolone injected into the middle ear</td>
<td>In the oral prednisone group, PTA improved significantly compared to the intratympanic treatment group.</td>
<td>Good</td>
</tr>
<tr>
<td>Publication</td>
<td>Objectives</td>
<td>Study design/Intervention</td>
<td>Major findings/Results</td>
<td>Evidence quality (NIH)</td>
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<tr>
<td>Lee et al., 2011 (96)</td>
<td>To analyze the efficiency of intratympanic dexamethasone injection (ITDI) as a sequential treatment in the patients who failed initial systemic steroid treatments for SSNHL.</td>
<td>Case-controlled study 46 patients were classified into 2 groups; 1. ITDI group (21 patients) 2. control group (25 patients) Initial standard treatments consisted of administration of oral steroids (60 mg/day for 5 days, followed by tapering for 5 days).</td>
<td>1. The ITDI group showed a statistically significant greater hearing improvement than the control group.</td>
<td>Good</td>
</tr>
<tr>
<td>Arslan et al., 2011 (97)</td>
<td>To compare hearing results in idiopathic sudden hearing loss patients treated with systemic steroids alone or combined intratympanic and steroids.</td>
<td>Prospective cohort study 175 patients were divided into 2 groups 1. systemic therapy received consecutive administration of 100 mg intravenous methylprednisolone in the 1st day, 80 mg/day oral prednisolone in 3 divided doses for the next 2 days and continued with oral administration of steroids by tapering the dose 20 mg in every 2 days. 2. combined treatment group received both systemic therapy and intratympanic injection of methylprednisolone (an approximate dose of 0.5 ml of 125 mg/ml).</td>
<td>1. The mean PTA gains were statistically significantly different between Systemic and Combined groups. 2. The mean PTA gains of systemic steroid therapy group were 7.5 and 5 dB at 5th day, 12.1 and 7.5 dB at 10th day, and 13.0 and 8.8 dB at 15th day. The mean PTA gains for combined treatment group were 12.5 and 7.5, 17.8 and 13.8, 21.8 and 20.0 dB, respectively</td>
<td>Good</td>
</tr>
<tr>
<td>Bae et al., 2013 (101)</td>
<td>To compare the efficacy of Intratympanic steroid (IT-S), systemic steroid therapy (SST), and combined therapy (CT) for treating SSNHL</td>
<td>Retrospective, multicenter study 735 Patients were divided into three groups 1. 94 IT-S group were Dexamethasone disodium phosphate (0.5–0.6 ml of 5 mg/ml) was instilled into the antero-superior portion of the tympanic membrane using a 25-gauge needle. 2. 444 SST group were administered 60 mg/day prednisone for 6 days 3. 197 CT group were administered prednisone using the same method as the SST group, and IT-S.</td>
<td>No difference in the level of hearing gain or ratio of hearing improvement was observed among the three groups</td>
<td>Good</td>
</tr>
</tbody>
</table>
Inci et al., 2002 (104)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Objectives</th>
<th>Study design/Intervention</th>
<th>Major findings/ Results</th>
<th>Evidence quality (NIH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inci et al., 2002 (104)</td>
<td>To determine the efficacy of HBO treatment in patients with SSNHL unresponsive to medical treatment.</td>
<td>Retrospective Cohort study 51 patients with SSNHL were treated with HBO following unsuccessful medical treatment. 1. 2 sessions daily for the first 3 days, followed by a single daily session, to make 20 sessions of 90 minute</td>
<td>1. No significant differences were found between the patient groups in terms of improvement and hearing gain (p&gt;0.05)</td>
<td>Good</td>
</tr>
</tbody>
</table>

The study design method is varied from Prospective RCT in 12, Retrospective series in 10 study, Case-controlled study 1, to Cross-sectional study in 1. The sample size ranged from 35 – 844 patients, with a mean of 164. Three types of interventions were studied namely oral steroids alone, combination therapy with oral and intratympanic steroids and triple therapy consisting of oral and intratympanic steroids and HBOT.
Figure 3-2: Forrest plot showing comparison of Combination therapy (Oral +IT) Vs Oral steroids
Figure 3-3: Forrest plot showing comparison of HBOT versus non-HBOT (oral steroids, IT dex)
Figure 3-4: Forrest plot showing comparison of IT versus Oral Steroids
3.2 Retrospective Cohort Study

A total of 49 patients treated for SSNHL were identified of these, 12 were excluded following application of inclusion/exclusion criteria resulting in a final cohort of 37 patients (Figure 3-5).

Figure 3-5: Cohort Selection

- Total number of patients’ charts reviewed 2014-2017 (n = 49)
- Incomplete Data (n = 7)
- Patients with complete data (n = 42)
- Exclusions (n = 5)
  - Acoustic neuromas (1)
  - Trauma (1)
  - Ototoxic medications (1)
  - Familial hearing loss
  - Meniere’s disease
  - Infectious and inflammatory middle/inner ear disease (2)
  - Autoimmune sensorineural hearing loss
- SSNHL Patients Cohort (n = 37)
Demographics of the 37 patients identified with idiopathic SSNHL at VGH over a period of 2 years is described in Table 3-2.

**Table 3-2: Characteristics of Study Cohort**

<table>
<thead>
<tr>
<th></th>
<th>Prednisone alone (n=14)</th>
<th>Prednisone + IT (n=5)</th>
<th>All treatment (n=15)</th>
<th>IT steroid alone (n=1)</th>
<th>Prednisone + HBOT alone (n=2)</th>
<th>SSNHL patients (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ±S.D. years</td>
<td>56.5 ± 16.4</td>
<td>57.2 ± 20.3</td>
<td>52.0 ± 8.2</td>
<td>60 years</td>
<td>71 years</td>
<td>55.22 ± 13.7</td>
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<tr>
<td>Age range, years</td>
<td>31-89</td>
<td>34-80</td>
<td>41-67</td>
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<td>-</td>
<td>31-89</td>
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<td>Gender, No.</td>
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<tr>
<td>male</td>
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<td>3</td>
<td>7</td>
<td>-</td>
<td>2</td>
<td>20</td>
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<tr>
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<td>2</td>
<td>8</td>
<td>1</td>
<td>-</td>
<td>17</td>
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<td>3</td>
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<td>0</td>
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<td>1</td>
<td>0</td>
<td>0</td>
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<td>Comorbidities No.</td>
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<tr>
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<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
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<tr>
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<tr>
<td>Dyslipidemia</td>
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<td>0</td>
<td>8</td>
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<tr>
<td>Vertigo</td>
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<td>3</td>
<td>1</td>
<td>2</td>
<td>11</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
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<td>Temporal bone trauma (optic capsule)</td>
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<td>0</td>
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</table>

Abbreviation: SSNHL- sudden sensorineural hearing loss; S.D. -standard deviation; No-number
3.2.1 Severity of the Hearing Loss

The initial averaged PTA threshold pre and post treatment was 62.7 dB (30 – 113 range, SD 24.4) and 32.6 dB (8 -76 range, SD 22.2). There is a significant difference in PTA average of the diseased ear between pre and post treatment with two sample independent t-test (p<0.001).

The severity of hearing loss among the various groups showing both the initial and final PTA of the diseased ear, respectively (Table 3-4). The mean initial PTA change in the severe group (71-90 dB hearing loss) was 79 dB versus 34.1, 46, 65 and 103 dB for the mild (25-40 dB), moderate (41-55 dB), moderately severe (56-70 dB) and profound (91-120 dB) hearing loss groups, respectively. The mean final PTA change in the severe group (71-90 dB hearing loss) was 75 dB versus 33, 42, and 63.2 dB for the mild (25-40 dB), moderate (41-55 dB), and moderately severe (56-70 dB) hearing loss groups, respectively.
The final PTA average showing the number of patients with respect to severity of the hearing loss after the treatment (Table 3-3).

Table 3-3: Change in distribution of cases by severity of hearing loss based on initial and final 4 frequency averaged air-conduction PTA thresholds

<table>
<thead>
<tr>
<th>Severity of the hearing loss</th>
<th>Initial PTA</th>
<th>Final PTA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>normal</td>
<td>mild (25-40dB)</td>
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<tr>
<td>mild (25-40dB)</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>moderate (41-55dB)</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>moderately severe (56-70dB)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>severe (71-90dB)</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>profound (91-120dB)</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>
3.2.2 Association Between the Average PTA Thresholds and Treatment Types

The average number of days for prednisone treatment was 7 (3-14 range, SD 2.43), the average number of IT dexamethasone injections was 4 (3-7 range, SD 1.22), and the average number of hyperbaric oxygen dives was 21 (11-40 range, SD 7.89) in the treatment groups, respectively. Patients who received prednisone alone or a combination of prednisone and IT dexamethasone or prednisone + HBOT or triple therapy, demonstrated no significant difference in averaged PTA threshold change with treatment. However, there was a significant clinical hearing improvement (>15db) noticed in patient groups of prednisone alone and prednisone + IT and IT alone (p=0.043) Chi-Square tests. Change in distribution of treatment identified between initial and final 4 frequency averaged air-conduction PTA thresholds across the treatment groups prednisone alone, IT steroid alone, prednisone and IT steroid only and triple therapy were as follows 57db-27db, 45db-18db, 73-38db and 65db-36db.

![Figure 3-6: Average initial and final PTA among different treatment groups](image_url)
There was a significant clinical hearing improvement (>15db) noticed in patient groups of prednisone alone and prednisone + IT and IT alone (non- HBOT group) (p=0.043) Chi-Square tests. (Figure 3-74). The number of patients that showed hearing improvement (>15db) recovery rate was 59.3% in above groups compared to 40.7% in patient groups who received HBOT additionally.

The patients who received Prednisone alone was 14 out of 37, and among them within 2 weeks were 11. The initial PTA of patients who received within 2 weeks was 57.4db compared to the initial PTA of patients who received after 2 weeks was 56db. Similarly, the final PTA of patients who received within 2 weeks was 33.7db compared to the final PTA of patients who received after 2 weeks was 8.7db. However, all the patients showed hearing improvement (>15db) either within 2 weeks or after 2 weeks.

Figure 3-7: Hearing improvement between non- HBOT and HBOT treatment groups
Chapter 4: Discussion

A literature review and a retrospective review of charts obtained from Vancouver General Hospital was undertaken to compare the effectiveness of oral steroids, IT steroids and HBOT for the treatment of SSNHL.

4.1 Systematic Literature Review

The systematic review identified a total of 24 original research articles that fulfilled the inclusion criteria and it a combination of all studies with outcomes observed in the treatment group. The overall studies show a significant difference in the recovery rates and improvement in hearing outcome of patients who received combination therapy and triple therapy with HBOT compared to monotherapy. Steroids have both local effects (by directly influencing the inner ear) and systemic effects (by indirectly influencing the inner ear by systemic immunosuppression). A total of 5 (86,90,103-106) studies included HBOT of which 4 studies found a statistically significant difference, while the other 2 studies did not show a significant difference.

Over the past decade, there have been numerous reports that HBOT may have a role in the treatment of SSNHL, as either primary therapy or salvage therapy. Six articles (86,90,103-106) included HBOT out of the 24 articles that meet the study inclusion criteria. The quality of evidence was good in all six articles. Cochlear activity is known to require a high oxygen supply. Especially as the stria vascularis and the organ of Corti have a high energy demand. Perilymphatic oxygen tension decreases significantly in patients with SSNHL. Oxygen administration may improve cochlear metabolism. Two of these studies (86,105 ) are both prospective trials and four (90,103 104,106) of these studies were retrospective reports which evaluated the effectiveness of salvage HBOT for SSNHL (primarily in conjunction with steroid
therapy) compared to a control group of patients who did not get HBOT and (90,104) found no significant difference in hearing improvement using both WRS and PTA as primary endpoints, though HBOT proved safe and was well tolerated by all patients. Inci et al. (2002) (104) included 51 patients in the study and reported that late cases 15 to 45th day of idiopathic SSNHL who had not responded to medical therapy were given HBOT and no significant differences were found between the patient groups in terms of improvement and hearing gain (p>0.05). Alimoglu et al., 2011(103), involved 217 patients and reported that the addition of HBOT to oral steroid therapy provided greater treatment response as measured by cure rate and mean hearing gains. Treatment success was assessed by Siegel’s criteria for degree of recovery and classified into four groups complete recovery, partial recovery, slight recovery, and non-recovery. The complete recovery group included patients with final hearing abilities <25 dB HL. The partial recovery group included patients with hearing recovery >15 dB HL with final hearing abilities between 25-45 dB HL. The slight recovery group included patients with hearing recovery of >15 dB HL with final hearing abilities >45 dB HL. The non-recovery group included patients with hearing recovery <15 dB HL with final hearing abilities >75 dB HL (107). Fujimara et al (2007) (106) and Topuz et al. (2004) (105) who studied 130 patients and 51 patients respectively found similar results. The lack of benefit of the addition of HBOT to oral steroids in other studies may be attributed to small patient groups. Cho et al., (2018) (86) studied 60 patients and found a significant difference in hearing improvement in patients who received HBOT. HBOT may be a management option for late cases.

Koltsidopoulos and colleagues (2013) (100) 92 patients study demonstrated that the addition of IT steroids to conventional systemic steroid therapy may provide a safe and more effective
therapeutic option in patients with mild-to-severe idiopathic SSNHL. On the other hand, in a much larger study of 735 patients, Bae et al (2013) (101) concluded that combined treatment did not have additional benefits compared with either systemic or IT steroids alone. The diversity in the results of these studies can be partially due to the relatively number of patients that they enroll as well as to the different criteria that they use. The study treatments with the administration procedure were all well tolerated, and no major side effect was noted.

**Conclusion**

Treatment of SSNHL remains somewhat controversial. Corticosteroids have been the mainstay of treatment for SSNHL. High-dose oral corticosteroids are considered the mainstay of treatment for SSNHL with intra-tympanic steroid injections also in wide use. The study treatments with the administration procedure were all well tolerated, and no major side effect was noted. Our investigation indicates that combination steroid therapy with HBOT may be of benefit in cases SSNHL. This evidence is weak for several reasons described under limitations below.
Limitations

The systematic review has limitations that should be considered when interpreting the results. Firstly, SSNHL has mild to severe cases, and therapeutic regimens may have varied according to disease severity. The method of steroid administration and therapy duration differed among the studies. These differences influence the comparability of various study cases and cause confounding bias. These factors will likely have affected reported hearing outcomes.

The systematic review is also inherently limited as it included only recent articles published between 2000 to 2018. Additionally, we did not check for missing terms, synonyms, spelling variations of MeSH terms. Finally, only articles published in English Language were included in the review, introducing notable Language bias. Therefore, the literature review conducted for this thesis is not comprehensive.

A substantial proportion of patients with SSNHL experience spontaneous recovery, therefore the benefit of HBOT or medical treatment may not have been accurately evaluated. There may be a bias effect caused by spontaneous recovery during HBOT as a salvage treatment or prolonged HBOT. For prolonged HBOT, spontaneous recovery during therapy cannot be distinguished from treatment benefits. However, given a sufficient pooled sample size, it is reasonable to assume that the likelihood of such benefit would be evenly distributed in both groups. The limitations mentioned in this systematic review should be considered when evaluating its outcomes.
4.2 Retrospective Chart Review
The retrospective charts review identified the clinical characteristics and hearing outcomes in SSNHL patients treated at Vancouver General Hospital within a 2-year period. The multiple treatment modalities utilized in our center reflect the lack of clear evidence of a superior treatment for SSNHL. Evaluation of therapy for SSNHL is complicated by the wide range of spontaneous recovery. In our study, we found significant differences in hearing outcomes among patients treated with combination steroid treatment modality which demonstrated greater PTA change post treatment and higher rate of clinically relevant hearing improvement compared to patients receiving triple therapy with HBOT.

There was a significant clinical hearing improvement (>15db) noticed when patients receiving steroids alone or in combination either oral prednisone, IT dexamethasone or oral prednisone + IT dexamethasone compared to those who received triple therapy. The number of patients that showed hearing improvement (>15db) was 59.3% in the steroid group compared to 40.7% in the HBOT (p=0.043, Fisher’s exact test).

Currently, steroid therapy is the primary treatment for SSNHL. The retrospective chart review and systematic literature review shows a significant greater hearing improvement in patients who received combination therapy compared to monotherapy (Chi squared, p < 0.05).
4.3 Limitation

Limitations of this study include its retrospective nature, small sample size, lack of control group, and lack of long-term follow up. Our results are confounded by the possible contribution of spontaneous recovery to hearing improvement.
Chapter 5: Conclusion

Our investigation highlights the multi-modal approach in the treatment of idiopathic SSNHL. Systematic review and the retrospective charts review conclude that there is weak evidence of a beneficial effect of combination therapy (oral and IT steroids; or oral, IT steroids and hyperbaric oxygen therapy) for patients with SSNHL over and above that achieved with mono-therapy with oral steroids (Chi squared, p < 0.05). This does not provide grounds for doctors altering their current treatments for SSNHL. In light of ongoing uncertainty and debate over standard therapy for SSNHL, future well-powered prospective randomized control studies comparing various treatment protocols are warranted.
Bibliography


39. Scheibe F, Haupt H, Baumgärtl H. Effects of experimental cochlear thrombosis on


52. Wilson WR. The relationship of the herpesvirus family to sudden hearing loss: A
82. Plontke SK, Löwenheim H, Mertens J, Engel C, Meisner C, Weidner A, et al. Randomized, double blind, placebo controlled trial on the safety and efficacy of continuous intratympanic dexamethasone delivered via a round window catheter for severe To profound sudden idiopathic sensorineural hearing loss after failure of systemic
98. Jung DJ, Park JH, Jang JH, Lee KY. The efficacy of combination therapy for idiopathic


