Quality of Life Evaluation in Bone-Anchored Hearing Implant Users:

A Multi-Faceted Investigation

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Table of contents

Abstract

Background: Quality of life (QoL) is defined as the overall state of well-being regarding an individual's physical, mental, and emotional health. People living with hearing loss will generally report a lower quality of life compared to their normal-hearing peers due to the communication and listening challenges they face everyday, which may lead to lower occupational functioning and feelings of social isolation. One rehabilitative option is the placement of a bone-anchored hearing implant (BAHI). A thorough understanding and effective management of these disease-specific quality of life dimensions is essential for developing proper interventions to improve the overall wellness of these individuals.

Objectives: The overall objective of this thesis is to investigate various factors related to enhancing QoL outcomes in BAHI patients. Specifically, the objectives are (1) to identify differences in disease-specific QoL benefits in bone-anchored hearing implant users with either unilateral sensorineural hearing loss (U-SNHL) or conductive/mixed hearing loss (CHL) and (2) to assess the ototoxic safety of an antimicrobial powder for the treatment of chronic otitis media.

Methods: Firstly, a systematic review was conducted to identify articles that assessed disease-specific quality of life. Meta-analyses were then performed on the extracted data to detect significant differences between patients with different types of hearing loss. Secondly, a validated animal model was utilized to assess the ototoxicity potential of a powder composed of ciprofloxacin, trimethoprim/sulfamethoxazole, amphotericin B, and talcum. The safety of the powder was evaluated through auditory brainstem responses, scanning electron microscopy of the cochlea, and histopathological evaluation of the external auditory canal.

Results: (1) Differences in quality of life outcomes were found in patients with different types of hearing loss. Specifically, those with conductive/mixed hearing loss report greater benefits in environments with competing noise sources and perceive sounds with greater clarity. (2) The proposed antimicrobial powder exhibits signs of ototoxicity, as demonstrated by significant auditory threshold changes 4 weeks post-application and by outer hair cell damage.

Conclusion: By exploring the user experience and evaluating the safety of more efficacious otologic treatments, this thesis provides a better understanding of the quality of life implications

surrounding the fitting of a bone-anchored hearing implant as well as guiding future testing of antimicrobial treatments to address chronic otitis media.

Résumé

Avant-propos: La qualité de vie est définie par l'état global de santé physique, mentale et émotionnelle d'un individu. Les personnes vivant avec une déficience auditive présentent généralement une qualité de vie inférieure par rapport à leurs pairs normo-entendants en raison des défis de communication et d'écoute auxquelles elles font face chaque jour, ce qui peut entraîner une diminution de la performance professionnelle et susciter des sentiments d'isolement social. Une option de réhabilitation est la mise en place d'un implant auditif à ancrage osseux. Une compréhension approfondie et une gestion efficace des aspects liés à la qualité de vie spécifique à la maladie sont essentielles pour élaborer des interventions appropriées visant à améliorer le bien-être général de ces individus.

Objectifs: L'objectif global de cette thèse est d'étudier les différents facteurs liés à l'amélioration de la qualité de vie des patients avec un implant auditif à ancrage osseux. Plus précisément, les objectifs de cette thèse sont (1) d'identifier les différences des avantages sur la qualité de vie spécifiques à la maladie chez les patients ayant reçu un implant auditif à ancrage osseux et présentant soit une surdité neurosensorielle unilatérale, soit une surdité conductive/mixte et (2) d'évaluer l'ototoxicité d'une poudre antimicrobienne pour le traitement de l'otite moyenne chronique.

Méthodes: Tout d'abord, une revue systématique a été effectuée afin d'identifier les articles qui évaluent la qualité de vie spécifique à la maladie. Des méta-analyses ont ensuite été réalisées sur les données extraites afin d'identifier des différences significatives entre les patients ayant différents types de perte auditive. Deuxièmement, un modèle animal validé a été utilisé pour évaluer le risque d'ototoxicité d'une poudre composée de ciprofloxacine, triméthoprime/sulfaméthoxazole, amphotéricine B et talc. L'innocuité de la poudre a été évaluée par des potentiels évoqués auditifs du tronc cérébral, la microscopie électronique à balayage de la cochlée et l'évaluation histopathologique du conduit auditif externe.

Résultats: (1) Des différences de la qualité de vie ont été découvertes chez les patients atteints de différents types de perte auditive. Plus précisément, les personnes souffrant d'une surdité conductive/mixte rapportent de plus grands bénéfices dans les environnements avec des sources de bruit concurrentes et perçoivent les sons avec une plus grande clarté. (2) La poudre antimicrobienne proposée démontre des signes d'ototoxicité, comme en témoignent les

changements significatifs du seuil auditif quatre semaines après l'application et les dommages causés aux cellules ciliées externes.

Conclusion: En explorant l'expérience de l'utilisateur et en étudiant la sécurité des traitements otologiques plus efficaces, cette thèse permet de mieux comprendre les implications en termes de qualité de vie qui entourent la mise en place d'un implant auditif à ancrage osseux et de guider les futurs essais de traitements antimicrobiens pour traiter l’otorrhée chronique.

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Contributions of authors

Karina Théorêt performed the literature review and writing of the present thesis.

All co-authors of Manuscript 1 (Chapter 3), Karina Théorêt, Jiahao Deng, Dr. Sabrina Daniela da Silva, Elena Guadagno, and Dr. Sam J. Daniel, contributed to the writing and reviewing of the manuscript. Karina Théorêt established the protocol for the systematic review and Elena Guadagno designed the search strategy and performed the article searches. Karina Théorêt and Jiahao Deng performed the article screening and data collection. Karina Théorêt performed the data synthesis with support from Dr. Sabrina da Silva. Final review of the manuscript was done by Karina Théorêt and Dr. Sam J. Daniel.

Dr. Mohammed K. Alnoury and Dr. Sam Daniel contributed to the designing of the experiment in Manuscript 2 (Chapter 4) and applied for ethics approval. Karina Théorêt and Dr. Ostap Orishchak performed all data collection, with support from Don Nguyen for audiological brainstem response evaluation, Weawkamol Leelapornipist for scanning electron microscopy, Dr. Van-Hung Nguyen and Dr. Ajay Rajaram for histopathology, and the staff at the RI-MUHC histology platform for preparing slides. Animal care, anesthesia, and euthanasia were performed by the veterinary technician staff and the Animal Care Facility of the RI-MUHC. Karina Théorêt and Dr. Ostap Orishchak contributed to the writing of the manuscript. All co-authors, Dr. Mohammed K. Alnoury, Karina Théorêt, Dr. Ostap Orishchak, Don Luong Nguyen, Dr. Sabrina Daniela da Silva, Dr. Ajay Rajaram, Weawkamol Leelapornpisit, Dr. Van-Hung Nguyen, Dr. Tamara Mijovic, and Dr. Sam J. Daniel, provided guidance and reviewed the manuscript. This study was performed in animal models at the McGill Otolaryngology Sciences Laboratory located at the Animal Care Facility of the RI-MUHC and supported by the Canada Graduate Scholarships – Master's grant awarded to Karina Théorêt. Final approval of the manuscript was done by Karina Théorêt, Dr. Mohammed K. Alnoury, Dr. Ostap Orishchak, and Dr. Sam J. Daniel. Note that Dr. Mohammed K. Alnoury and Karina Théorêt are co-first authors of Manuscript 2.

List of figures and tables

List of abbreviations

μm, micrometer

ABR, auditory brainstem response

AmB, amphotericin B

APHAB, Abbreviated Profile of Hearing Aid Benefit

AV, aversiveness

B-CHL, bilateral conductive hearing loss

BA, boric acid

BAHI, bone-anchored hearing implant

BBSSD, Bern Benefit of Single-Sided Deafness

BM, basilar membrane

BN, background noise

CES, Chronic Ear Survey

CHL, conductive hearing loss

CMD, clinically meaningful difference

COM, chronic otitis media

COMOT-5, Chronic Otitis Media Outcome Test 15

dB, decibel

EAC, external auditory canal

EC, ease of communication

GBI, Glasgow Benefit Inventory

GCBI, Glasgow Children's Benefit Inventory

HUI-3, Health Utilities index – Mark 3

IHC, inner hair cell

IOI-HA, International Outcome Inventory for Hearing Aids

kHz, kilohertz

MD, mean difference

MHL, mixed hearing loss

MRSA, methicillin-resistant *S. aureus*

nm, nanometer

NR, not reported

OHC, outer hair cell

OM-6, Otitis Media-6

OMO-22, Otitis Media Outcome-22

OW, oval window

pBAHI, percutaneous bone-anchored hearing implant

QoL, quality of life

RV, reverberation

SD, standard deviation

SEM, scanning electron microscopy

SF-36, 36-item Short Form

SNHL, sensorineural hearing loss

SSQ, Speech, Spatial and Qualities of Hearing Scale

tBAHI, transcutaneous bone-anchored hearing implant

TM, tympanic membrane

TMP-SMX, trimethoprim/sulfamethoxazole

U-SNHL, unilateral sensorineural hearing loss

U-CHL, unilateral conductive hearing loss

Chapter 1: Introduction

1.1 Rationale

The increasing prevalence of hearing impairments presents substantial challenges at both the societal and individual levels. According to the World Health Organization, the number of individuals requiring hearing rehabilitation is projected to rise from 430 million to 700 million by the year 2050.[1] Among the factors that contribute to the increasing prevalence of hearing loss are global population growth and increased longevity, improved accessibility to healthcare services in lower-income nations, as well as the absence of adequate hearing protection against occupational and recreational noise sources.[2] Individuals with hearing loss face various challenges, including difficulties with communication, social isolation, and higher unemployment rates.[3,4] These challenges are particularly pronounced in children with hearing loss, who may experience difficulties with language acquisition, learning, and cognitive development.[5]

Treatment options for hearing loss typically include surgery, medication, or the use of hearing aids for amplification.[6] Surgical interventions may involve procedures such as myringotomy with the placement of ventilation tubes, tympanoplasty, stapedectomy, or aural atresia repair. Cochlear implants, either unilateral or bilateral, may be considered for patients with inner ear damage. Another potential treatment option is the fitting of a bone-anchored hearing implant (BAHI). BAHIs are recommended for patients diagnosed with unilateral sensorineural hearing loss (U-SNHL), conductive hearing loss (CHL), or mixed hearing loss (MHL). Typically, these patients are not suitable candidates for cochlear implants and/or are unable to use behind-the-ear or in-the-ear hearing aids due to external or middle ear deformities. Currently, over 250 000 individuals worldwide benefit from a BAHI.[7]

Since the inaugural surgery in 1977, there have been significant advancements in surgical techniques and processor technology for BAHIs, resulting in improved hearing performance for patients.[8] Numerous studies have reported on the audiological performance of these devices, demonstrating improvements in functional gain, speech intelligibility in both quiet and noisy environments, word recognition scores, and signal-to-noise ratio thresholds.[9-12] Surgical

techniques have also evolved, transitioning from a linear incision to a minimally invasive "punch" technique for percutaneous BAHIs, leading to reduced rates of post-operative skin complications and infections.[13] Moreover, the development of transcutaneous BAHIs has further improved outcomes by replacing the skin-penetrating abutment with a magnetically attached sound processor, resulting in fewer post-operative complications, skin reactions, and revision surgeries.[14,15] These advancements in sound processor performance and surgical innovations have significantly enhanced the quality of life (QoL) for both pediatric and adult populations,[9,16,17] and have contributed to overall improvements in patient well-being.[18]

Despite the general improvement in QoL after BAHI fitting, there are still gaps in the existing literature. First, there is uncertainty if QoL outcomes differ among different hearing loss populations. Patients with U-SNHL face unique challenges that patients with CHL/MHL may not encounter, such as the head shadow effect and difficulties with sound localization. Second, pre-existing ear conditions, such as chronic middle ear infections, can continue to negatively impact a patient's QoL. Patients with chronic otitis media (COM), a recurring middle ear infection characterized by fluid drainage from the ear, may require a BAHI as the occlusion caused by traditional hearing aids can lead to moisture accumulation and cause adverse skin reactions.[19] Patients with COM often report ear pain, discomfort, emotional distress, and poor mental health.[20,21] However, it is important to note that while the BAHI addresses the hearing loss experienced by COM patients, it does not cure the underlying cause of their decreased QoL, which is the ear infection itself.

Considering the above issues, there is a need for further investigation into the variation of QoL outcomes among BAHI patients with different types of hearing loss. This will help to gain a better understanding of their unique experiences with hearing impairment and rehabilitation. Additionally, there is a need to develop more effective treatments for COM in order to improve the overall well-being of BAHI patients affected by this middle ear infection. To address these needs, the objectives of this thesis follow.

1.2 Objectives

The overall aim of this thesis is to investigate factors related to enhancing QoL outcomes in BAHI patients by means of 2 objectives: First, to assess any differences in QoL outcomes

between BAHI patients with U-SNHL and CHL/MHL (Chapter 3). Second, to assess potential ototoxic effects of a powder that combines antibacterial and antifungal agents, for the treatment of COM by using an established guinea pig model (Chapter 4).

Chapter 2: Review of the literature

2.1 Auditory system

The topics discussed in this thesis require a basic understanding of the auditory system and the mechanisms pertaining to hearing impairment. Therefore, the following sections will provide an overview of the process of human auditory perception, including its anatomical structure, physiological functioning, and auditory mechanisms.

2.1.1 Anatomy

An overview of the anatomical structures of the human ear is provided in Figure 1. Sounds in the environment are captured by the outer ear (external ear) and delivered to the tympanic membrane (TM). The outer ear is composed of the pinna, also known as the auricle, and the external auditory canal (EAC). The pinna, which is the visible part of the ear, is composed of cartilage and covered by skin. It collects sounds and channels them into the EAC, a canal approximately 2.5 cm in length that terminates at the TM.[22] The skin of the EAC is hairy and secrets cerumen (ear wax) through sebaceous cells and ceruminous glands.[22] Cerumen acts as a protective barrier against foreign entities and contains antimicrobial peptides, acting as a defense against infections in the EAC.[23] An accumulation of cerumen in the EAC can obstruct the transmission of sound to the TM and may result in hearing impairment. The TM, a thin membrane covered by a layer of epidermal cells, connects the outer ear to the middle ear.

The middle ear is an air-filled cavity that contains the auditory ossicles, which are the 3 smallest bones within the human body: the malleus (hammer), incus (anvil), and stapes (stirrup). The function of the auditory ossicles is to transmit air vibrations to the inner ear by means of the oval window (OW).[24] The footplate of the stapes covers the OW, which is an opening to the

cochlea. The Eustachian tube, which links the middle ear to the pharynx located at the back of the nose, ensures that the air pressure within the middle ear remains at the ambient level.[22]

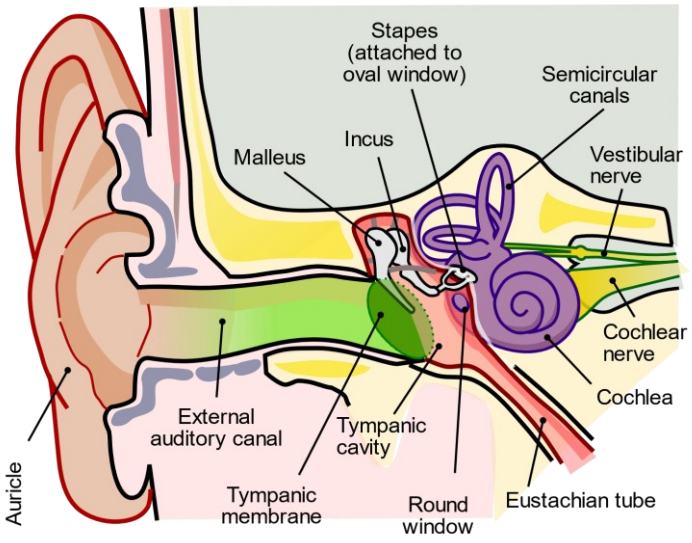

Figure 1. Anatomy of the human ear.

Anatomical depiction of the human ear demonstrating the outer ear (auricle and external auditory canal), the middle ear (malleus, incus, stapes, Eustachian tube, and tympanic cavity), and the inner ear (semicircular canals, cochlea, vestibular nerve, and cochlear nerve). The tympanic membrane separates the outer from the middle ear, and the round window separates the middle from the inner ear. Figure by Lars Chittka & Axel Brockmann, CC BY 2.5 <https://creativecommons.org/licenses/by/2.5>, via Wikimedia Commons.

The inner ear consists of two distinct systems: (1) the vestibular apparatus, which includes the utricle, the saccule, and the 3 semicircular canals, all aiding in balance, and (2) the cochlea, the organ responsible for the sense of hearing (Figure 2A). Both systems are enclosed together within the temporal bone of the skull. Since the vestibular system does not play a role in the auditory function, only the cochlea will be further discussed.

The cochlea is a spiral-shaped bony structure that completes just over 2.5 turns and contains 3 fluid-filled cavities: the scala vestibuli, scala media, and scala tympani.[22] The scala vestibuli and scala tympani are filled with perilymph while the scala media contains endolymph.[25] The ionic composition of the perilymph is similar to that of extracellular fluid, characterized by low concentrations of potassium and high concentrations of sodium.[25] Conversely, the endolymph's ionic composition resembles intracellular fluid, with high potassium and low sodium levels. The scala media and scala tympani cavities are separated by the basilar membrane (BM), where the organ of Corti is found (Figure 2B). The organ of Corti serves as the sensory organ of hearing and

is the site of sound transduction.[26] It consists of inner hair cells (IHCs), outer hair cells (OHCs), and the tectorial membrane. The IHCs have 60 stereocilia, which are finger-like protrusions located at the top of the hair cells, forming a single row on the BM.[22] On the other hand, the OHCs are made up of 50 to 150 stereocilia organized in 3 to 5 rows (Figure 3). The tallest stereocilia of each OHC are embedded in the tectorial membrane.

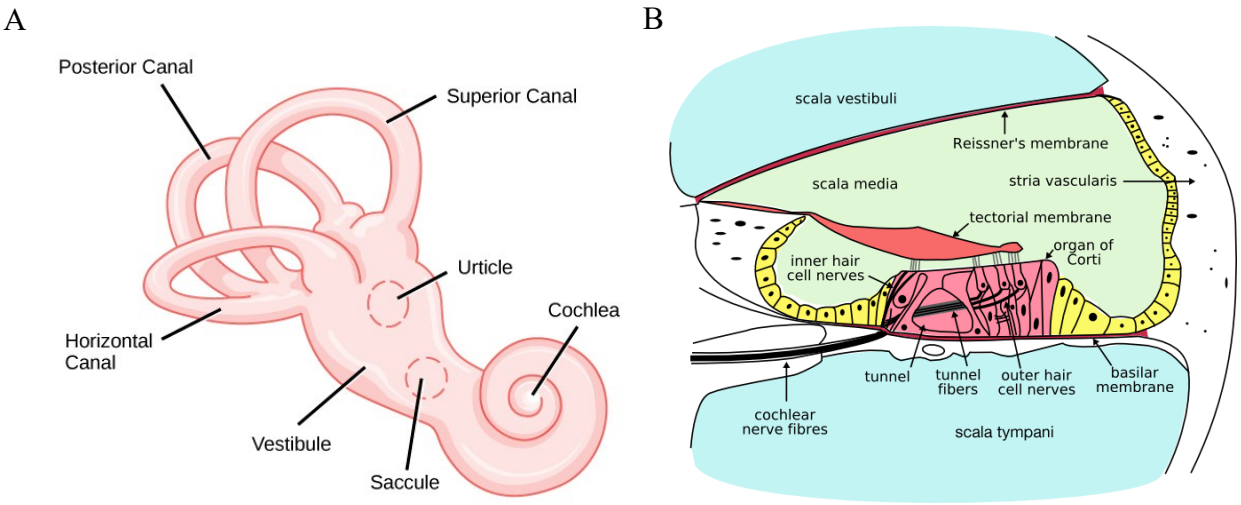

Figure 2. Vestibular and auditory organs of the inner ear.

A: Vestibular and hearing organs of the inner ear. Figure by CNX OpenStax, CC BY 4.0 <https://creativecommons.org/licenses/by/4.0>, via Wikimedia Commons; B: Cross-section of the cochlea. Figure by Oarih at English Wikipedia., CC BY-SA 3.0 <http://creativecommons.org/licenses/by-sa/3.0/>, via Wikimedia Commons.

2.1.2 Sound transduction

The process of sound transduction begins when sound vibrations are channeled by the pinna and transmitted through the TM. Subsequently, the vibrations are conveyed to the middle ear, enabling the footplate of the stapes to exert pressure on and pull the OW, thereby generating traveling waves within the fluid of the cochlea.[24,27] These traveling waves propagate to the BM, where the sound is analyzed into its constituent frequencies. This analysis occurs due to the distinctive property of the BM: the stiffness of the membrane decreases progressively as you move towards the apex of the cochlea. This varying stiffness means that the traveling wave of high frequencies is impeded near the base of the cochlea, while waves of lower frequencies continue traveling towards the apex, where the BM is more flexible.[27] Consequently, each frequency is associated with a specific

location on the BM where its traveling wave ceases and triggers the mechanoelectrical transduction of sound.

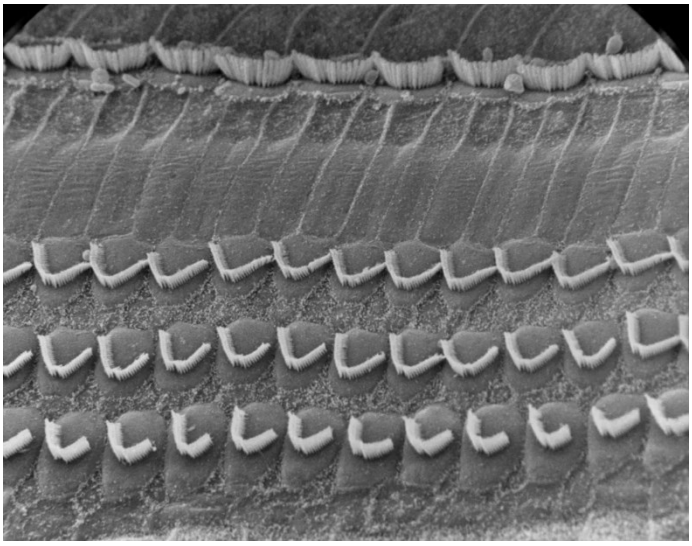

Figure 3. Scanning electron microscopy of a single row of inner hair cells (top) and 3 rows of outer hair cells (bottom).

Normal appearing inner and outer hair cells with characteristic linear configuration and V-shape, respectively. Figure from SickKids Hospital <https://lab.research.sickkids.ca/harrison/electron-microscopy/#>.

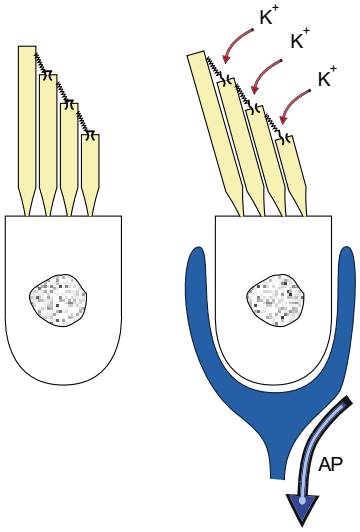

Figure 4. Demonstration of the mechanotransduction process at a singular hair cell.

The traveling wave deflects the outer hair cell, causing the tip links of the stereocilia to be pulled open. This action allows potassium ions to enter and rapidly depolarize the cell, leading to an action potential (AP). Figure by Thomas.haslwanter, CC BY-SA 3.0 <https://creativecommons.org/licenses/by-sa/3.0>, via Wikimedia Commons.

The hair cells located in the organ of Corti are specialized neurons responsible for transforming sound vibrations into neural information, which is subsequently processed by the central auditory system. The stereocilia within the hair cells are connected to each other through tip links, which are filaments that connect a stereocilium to its tallest neighbour.[28] When the traveling wave stops at a particular location on the BM, the tectorial membrane resonates, causing the tip links of the OHCs embedded within it to be pulled, consequently opening an ion channel (Figure 4). As a result of this channel opening, rapid depolarization of the hair cell occurs, activating the dendrites of auditory nerve fibers that innervate the base of the hair cell.[28] From there, the auditory signal is transmitted to the central auditory system.

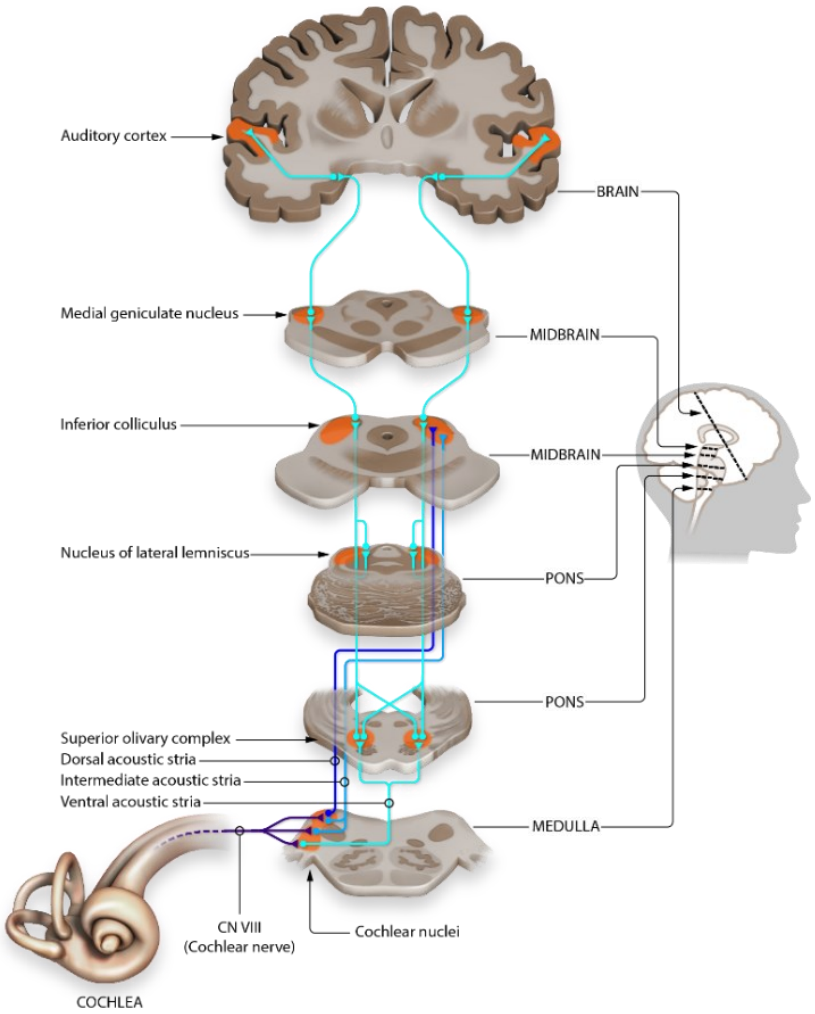

Figure 5. Overview of the central auditory pathways.

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Figure 5 offers a comprehensive diagram that illustrates the principal structures and pathways comprising the central auditory system. The auditory nerve fibers join to form the vestibulocochlear nerve, also known as cranial nerve VIII. These fibers project to the cochlear nucleus, and then to the superior olivary complex.[29] It is at this structure that bilateral representation of ipsilateral and contralateral acoustic input occurs. The bilateral representation of acoustic signals allows the brain to detect interaural time and intensity differences between inputs, enabling individuals to spatially locate sounds within their environment. From this point, the neural signals converge at the lateral lemniscus, which leads to the inferior colliculus in the midbrain.[29] The ascending pathways then progress to the medial geniculate body within the thalamus, ultimately culminating in the auditory cortex situated in the temporal lobe.

2.1.3 Hearing loss

As this thesis primarily focuses on hearing loss, it is imperative to provide a comprehensive review of the various types of hearing losses associated with patients who are fitted with BAHIs. These hearing losses can be categorized as either congenital (i.e., present from birth) or acquired.

SNHL is characterized by problems originating in the inner ear or the central auditory system.[30] It can be caused by factors such as infections (e.g., meningitis or Ménière's disease), malformations in the inner ear structures, exposure to excessive noise, or traumatic events.

CHL arises from abnormalities in the outer and/or middle ear.[30] Abnormalities in the outer ear, such as microtia (deformed or absent pinnae) and aural atresia (absence of external auditory canal), are factors that contribute to CHL. Moreover, the presence of otitis externa (infection in the EAC) can also result in hearing loss: the presence of inflammation and/or swell in the ear canal impedes the transmission of sound to the middle ear. In the case of CHL originating from the middle ear, it is often caused by the absence, malformation, or fixation of the ossicular chain. Cholesteatoma (an abnormal accumulation of skin cells) and otosclerosis (abnormal bone growth or fusion of the ossicles) may further contribute to the observed hearing impairment. Similarly to the outer ear, otitis media (infection in the middle ear) can also result in hearing loss. In this case, the accumulation of fluid in the middle ear hampers the proper vibration of the TM, thereby hindering the transmission of sound to the inner ear. Patients fitted with BAHIs may exhibit

unilateral or bilateral CHL. Finally, MHL involves a combination of both sensorineural and conductive hearing loss.

2.2 Bone conduction

This thesis investigates the QoL outcomes of patients fitted with BAHIs and explores ways to improve them. Therefore, a review of bone conduction hearing systems is necessary.

2.2.1 Bone conduction hearing

While conventional sound transmission typically occurs through the EAC and middle ear, it is also possible for sound vibrations to be transmitted directly through the temporal bone to either the ipsilateral or contralateral cochlea. This phenomenon is known as bone conduction hearing (Figure 6). By utilizing this method, the outer and middle ears are completely bypassed, as the sound vibrations directly stimulate the BM.[31] The earliest documentation of bone conduction devices can be traced back to the 16th century, where rods and spears were employed as conduits to transmit sound vibrations to individuals with hearing impairments.[31] Afterwards, audiphones (i.e., acoustic fans) and dental implants were developed to facilitate the transmission of sound vibrations to the listener.[32]

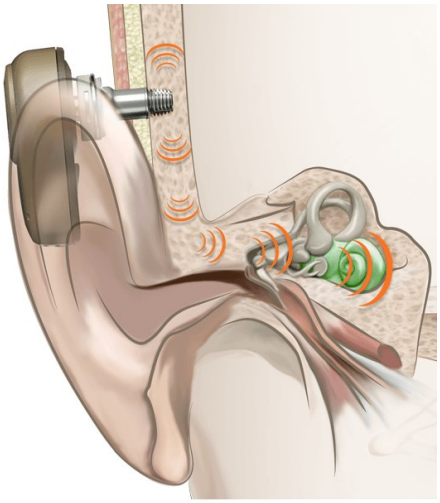

Figure 6. Percutaneous bone-anchored hearing implant.

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2.2.2 Bone-anchored hearing implants

It was not until 1977 that the first percutaneous BAHI (pBAHI) with an osseointegrated implant was implanted in a patient by Anders Tjellström in Sweden.[31] An incision was made behind the ear to install an abutment in the temporal bone, enabling direct transmission of sound vibrations without attenuation of the skin.[8] Nowadays, the linear incision surgical technique for pBAHI has evolved to a single punch incision, resulting in shorter surgical time and fewer post-operative skin complications and infections.[13] A modern pBAHI is illustrated in Figure 6.

A transcutaneous BAHI (tBAHI) is an alternative bone conduction device where the external sound processor is attached, either magnetically or with adhesive, to the internal implant. One advantage of tBAHIs is their cosmetically appealing feature of a completely concealed implant under the skin, while pBAHIs have a protruding abutment. Moreover, the absence of a skin-penetrating abutment in tBAHIs reduces the likelihood of post-operative skin complications.[14] tBAHIs can be either active, meaning that vibrations are directly transmitted to the bone without attenuation of the sound signal, or passive, where vibrations are transmitted through the skin.[33] Passive tBAHIs have an external sound processor that can be temporarily attached to the head with an adhesive, a headband, or an internal magnet. However, the layer of skin tissue can attenuate high frequencies of 6000 to 8000 hertz (Hz) up to 25 decibels (dB).[34] Active tBAHIs have an external sound processor that magnetically attaches to an internally implanted device, directly driving the sound vibrations to the bone. This direct drive enables active tBAHIs to overcome the skin attenuation effect.[31]

2.3 Quality of life outcomes

As noted previously, this thesis aims to investigate how hearing loss and the subsequent fitting of a BAHI affects patients' QoL. Therefore, it is essential to conduct a comprehensive review of the QoL domains that are relevant to both general health and hearing-related issues, as well as the clinical methods used to assess them.

2.3.1 Impact of hearing loss on quality of life

A cross-sectional survey conducted by the Canadian Health Measures Survey reported that 7.7% of Canadian children and adolescents are living with hearing loss in one or both ears, but

evidence suggests that this number may be an underestimate.[35] If left untreated, children with hearing loss may face various challenges such as difficulties in speech and language acquisition, cognitive functions, poor social skills, and a lower quality of life.[5] Mild or moderate hearing loss often goes unnoticed in children as they can still understand and produce intelligible speech.[35,36] However, they still encounter difficulties compared to their peers with normal hearing, often requiring a higher signal-to-noise ratio to understand their teachers and friends in noisy and reverberant environments.[37,38] Ear infections are common in children and may cause hearing loss if left untreated or hinder the utilization of hearing aids for those who already use them. It has been reported that 60 to 70% of children under the age of 3 will develop COM, a condition characterized by the constant discharge of fluid from the middle ear (i.e., chronic otorrhea).[39] This condition can often cause physical discomfort, emotional distress, and limit a child's activities.[21]

In Canadian adults, the prevalence of hearing loss rises to an estimated 19%, with approximately 65% of individuals between the ages of 70 and 79 being diagnosed with hearing loss across frequencies of 0.5, 1, 2, and 4 kHz.[40] Among these individuals, only 24% use hearing aids. Hearing loss in adulthood can lead to difficulties in communication both in the workplace and with friends and family.[4] These communication challenges can contribute to social isolation, which may directly or indirectly impact their psychosocial well-being, socioeconomic status, and overall health.[4,41] In fact, compared to adults with normal hearing, higher rates of unemployment and lower incomes are more common among those with hearing loss.[3] All the factors mentioned above contribute to a decreased QoL in individuals with hearing impairment.

As demonstrated in the preceding paragraphs, any degree of hearing loss can have a detrimental impact on an individual's general quality of life. However, it is also crucial to consider its impact on hearing-specific domains. It is widely recognized that individuals with hearing loss struggle to comprehend speech in acoustically challenging environments, such as when multiple speakers are present in a reverberant room. Engaging in extended conversations, particularly in the presence of background noise, can lead to mental fatigue due to the exertion of listening effort.[42] This can further result in disengagement from social situations and feelings of isolation. In fact, a study conducted by Bakkum et al[43] found that children with unilateral hearing loss experience greater listening-related fatigue compared to their peers with normal hearing.

The following section provides a brief overview of general and disease-specific questionnaires that have been developed to assess the impact of hearing loss on an individual's QoL.

2.3.2 Quality of life scales

Numerous scales are available nowadays to assess the QoL of patients with hearing loss before and after they receive their hearing aid. These scales can be categorized as either general health questionnaires or disease-specific questionnaires. General health questionnaires cover various health domains, including physical, mental, and emotional well-being. They are commonly used to inform public health changes and compare QoL changes across different diseases. Examples of generic questionnaires include the Health Utilities Index – Mark 3 (HUI-3) and the 36-item short-form (SF-36). The HUI-3 evaluates a patient's health status by examining 8 attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain.[44] The SF-36 also assesses 8 health concepts, focusing on limitations in physical and social activities, as well as mental health.[45] However, in the context of BAHI research, these scales have been found to be inadequate for capturing significant changes in patients' QoL. This may be due to the insufficient evaluation of auditory health or the lack of sensitivity of the questionnaires to capture the impact of hearing loss.[16]

In contrast, disease-specific QoL scales have been developed to specifically measure how hearing functions and qualities change after the fitting of a hearing aid, addressing the limitations of generic QoL scales. These scales are often designed as pre- and post-intervention questionnaires, allowing for the calculation of a benefit score attributed to the hearing device. Alternatively, some scales are administered only after the hearing aid has been fitted and worn for several months. The questions in these scales assess various aspects of the hearing aid's performance in everyday life, such as the naturalness, clarity, and aversiveness of sounds, the user's ability to understand speech in different settings with or without background noise, and the spatial characteristics of sound. Examples of disease-specific QoL measures used in hearing aid research include the Abbreviated Profile of Hearing Aid Benefit (APHAB), Glasgow Benefit Inventory (GBI), and the Speech, Spatial, and Qualities of Hearing Scale (SSQ). The characteristics and scoring methods of these scales, as well as others, will be discussed further in Chapter 3 of this thesis.

Chapter 3

Quality of Life Benefits in Bone-Anchored Hearing Implant Patients: A Systematic Review and Meta-analysis

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Keywords: Bone-anchored hearing implant, Bone conduction device, Quality of life, Sensorineural hearing loss, Conductive hearing loss, Mixed hearing loss

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3.1 Abstract

Objective: The purpose of this study was to systematically review the differences in disease-specific quality of life (QoL) benefits experienced by bone-anchored hearing implant (BAHI) users between those diagnosed with unilateral sensorineural hearing loss (U-SNHL) and those with conductive/mixed hearing loss (CHL).

Data Sources: Eligible studies were searched for in Medline (Ovid), Embase (Ovid), CINAHL (Ebsco), Cochrane (Wiley), Global Health (Ovid), Web of Science (Clarivate Analytics), Africa Wide Information (Ebsco) and Global Index Medicus (WHO) from inception to October 23, 2022. An updated search was performed on November 9, 2023.

Review methods: There were no restrictions on language. PRISMA standards were followed and screening was conducted by two independent reviewers in Rayyan, with a third reviewer resolving conflicts. Risk of bias was assessed using RoBANS. Articles were included if patients were implanted with a BAHI and administered a validated, disease-specific QoL measure.

Results: 1251 articles were identified after duplicate removal, with 61 articles meeting the inclusion criteria. Eight different disease-specific QoL measures were administered. In all, the APHAB's "Global" ($p < .0001$) and EC ($p < .0001$) scores, the GBI's "Global" ($p = .0004$), "General" ($p = .01$), and "Physical" ($p = .003$) scores, and the SSQ's "Qualities" ($p = .04$) scores were significantly different between U-SNHL and CHL populations.

Conclusion: These results demonstrated disease-specific QoL differences between BAHI users with U-SNHL and CHL. Specifically, patients with CHL reported greater benefits in domains pertaining to ease of communication, the clarity of sound, and their overall health and psychosocial status.

3.2 Introduction

Since the first bone-anchored hearing implant (BAHI) procedure in 1977, these implants have played a significant role in restoring hearing function for individuals with conductive hearing loss (CHL), mixed hearing loss (MHL), and unilateral sensorineural hearing loss (U-SNHL).[1] By capturing sound waves in the user's environment and transferring vibrations directly to the cochlea through the skull, the external sound processor bypasses the need for the outer and middle ear.[2] The sound processor is connected to an internal titanium implant that is osseointegrated into the temporal bone, enhancing sound transmission. Today, individuals can choose between a percutaneous BAHI (pBAHI), where the sound processor is connected to a protruding abutment, or a transcutaneous BAHI (tBAHI), where the sound processor is magnetically attached to an internal implant.

The audiological benefits of BAHIs have been extensively studied. Research has shown improvements in speech comprehension in both quiet and noisy environments, as well as in word discrimination tasks.[3,4] Other reviews have reported significant improvements in aided thresholds and functional gain.[5] However, Dornhoffer et al demonstrated that improvements in audiological performance do not necessarily correlate with an increased perception of quality of life (QoL) benefits.[6] In fact, no audiological tests were able to predict patient-reported QoL benefits, as measured using the Abbreviated Profile of Hearing Aid Benefits (APHAB). These findings suggest that disease-specific QoL measures may capture a dimension of benefit that audiological tests fail to assess. Therefore, understanding the daily hearing challenges faced by BAHI users and how their devices help them overcome these challenges is crucial for evaluating the overall effectiveness of the BAHI.

Previous systematic reviews have shown improvements in the QoL of BAHI users with U-SNHL, as measured by disease-specific QoL measures.[7,8] These findings have also been observed in pediatric populations and in patients with bilateral hearing loss fitted unilaterally or bilaterally with a BAHI.[3,9] However, no review has specifically examined the differences in QoL outcomes between patients with CHL, MHL, or U-SNHL.

The objective of our study was to systematically review disease-specific QoL benefits in BAHI patients with unilateral CHL/MHL, bilateral CHL/MHL, and U-SNHL. Identifying

variations in outcomes across these patient groups will help clinicians provide more informed counseling to prospective patients regarding the QoL benefits they may expect. This information will also facilitate better management of patient expectations concerning the device's performance, potentially resulting in greater long-term satisfaction and utilization of the BAHI.

3.3 Methods

The findings of this study are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol for this systematic review was registered in a publicly accessible database (PROSPERO ID: CRD42022367259) prior to searching the databases.

3.3.1 Information sources

A senior medical librarian searched the following databases Medline (Ovid), Embase (Ovid), CINAHL (Ebsco), Cochrane (Wiley), Global Health (Ovid), Web of Science (Clarivate Analytics), Africa Wide Information (Ebsco) and Global Index Medicus (WHO) from inception until November 9, 2023. The search strategy used variations in text words found in the title, abstract or keyword fields, and relevant subject headings to retrieve articles looking broadly at bone anchored hearing implants and patient reported quality of life, outcome, or experience measures, with no language restriction. The full search strategy for all databases, as well as the PRISMA literature search extension (PRISMA-S) and PRISMA checklists, can be found in "Supplementary materials" (eTables 1-3).

3.3.2 Inclusion criteria

The following inclusion criteria were considered: a) Population: studies involving patients of any age diagnosed with unilateral or bilateral CHL, unilateral or bilateral MHL, or U-SNHL, b) Intervention: participants implanted with either a percutaneous, passive transcutaneous, or active transcutaneous osseointegrated BAHI, c) Study design: randomized controlled trials, non-randomized comparative studies, cohort studies, case-control studies, cross-sectional studies, and retrospective questionnaire studies, d) Outcomes: studies that reported relevant outcomes related to type of hearing loss, treatment outcomes, disease-specific QoL, or adverse events were included.

Only QoL data collected by a valid disease-specific QoL measure was included in this review. The validation of a measure is characterized by its prior evaluation through preliminary pilot testing and psychometric analysis to determine the measure's reliability and validity.

3.3.3 Exclusion criteria

Studies where patients used any other type of hearing aids, such as air conduction hearing aids, cochlear implants, dental fixtures, or middle ear implants, were excluded. Studies that investigated QoL outcomes in patients using a non-implantable BAHI (BAHI on a headband or with adhesive) were also excluded. Additionally, studies that used a non-validated, disease-specific QoL measure or whose translation had not been validated were excluded from the review. Finally, studies that measured general health QoL were not included.

3.3.4 Study selection

The titles and abstracts of identified studies were screened on Rayyan by two independent reviewers (K.T. and J.D.) for relevance based on the inclusion criteria.[10] Articles that passed the first screening had their full texts retrieved and assessed for eligibility. Any disagreements were resolved through discussion or consultation with a third reviewer (S.J.D.). References of the included articles were manually searched to identify any other possible articles. The primary reasons for study exclusion were documented in an Excel spreadsheet.

3.3.5 Data extraction

The data from the included articles was extracted independently by two authors (K.T. and J.D.) using a standardized data extraction form in Excel (Microsoft Office 365, Windows). Extracted information included author, year of publication, country of study, study design, and number of participants that filled out a QoL measure. Patient demographics were also noted, such as participant's type of hearing loss, age, and sex (male or female). If available, the BAHI device and/or the nature of the device (percutaneous, passive transcutaneous or active transcutaneous) used by the participants was recorded. The QoL measure used by the authors was identified and the reported scores and follow-up periods were extracted. For simplicity, patients with CHL or MHL were combined into a single group named "CHL". The QoL scores were organized into one of four groups: U-SNHL, U-CHL, B-CHL, or "U-CHL + B-CHL". The "U-CHL + B-CHL" group

is for all participant data where the laterality of the hearing loss was not specified or reported. If necessary, a robust imputation strategy was employed in order to include the highest number of articles in the analysis. Articles that reported their results by means of graphs or bar plots rather than with numerical values did not have their data extracted. This system was implemented to enhance the reliability of the results.

3.3.6 Risk of bias assessment

The Risk of Bias (RoB) Assessment tool for Non-Randomized Studies (RoBANS) was utilized to assess the methodological quality of the included studies and evaluate their RoB.[11] Two authors (K.T. and J.D.) independently assessed the risk of bias, with any disagreements being resolved by a third reviewer (S.J.D.). RoBANS consists of six variants that determine whether there is a low, high, or unclear risk of bias: 1) selection of participants, 2) confounding variables, 3) measurement of exposure, 4) blinding of outcome assessments, 5) incomplete outcome data, and 6) selective outcome reporting. The fourth variant was deemed irrelevant for the risk of bias evaluation of the included articles and therefore was not utilized. An article is deemed to have a low RoB if the majority of the variants were scored as “Low risk” and a high RoB if the majority of the variants were scored as “High risk”. An article is considered to have an unclear RoB if two variants scored as “Low risk”, two as “High risk” and one as “Unclear risk”.

3.3.7 Statistical analysis

Statistical analysis was conducted to assess and synthesize the data collected by the QoL measures. Mean and standard deviation (SD) values for QoL scores were extracted from all included articles. The means and SDs of the benefit scores were calculated, with the latter following the formula provided in Chapter 6.5.2.8 of the Cochrane Handbook for Systematic Reviews of Interventions (2023). The correlation coefficient used to compute the benefit SD was 0.59, as determined by Balk et al.[8]

A random effect meta-analysis (Review Manager Version 5.4, The Cochrane Collaboration, 2020) was performed on the calculated benefit scores of QoL measures that had 4 or more studies for each type of hearing loss. Overall effect and subgroup differences were noted. High heterogeneity was defined as an $I^2 > 50\%$.[12] If a study had 2 or more follow-up periods, the

QoL scores from the longer follow-up period were included in the meta-analysis to control for patients' enthusiasm bias.[13] Additionally, Spearman correlations were performed in Rstudio (Rstudio 2023.9.1.494, Boston, MA) to determine the relationship between QoL scores and follow-up length (in months). The strength of the correlation was categorized as none (0 to 0.9), poor (0.1 to 0.29), fair (0.3 to 0.59), moderate (0.6 to 0.79), very strong (0.8 to 0.99), or perfect (1).[14]

Sensitivity analyses were performed for the QoL measures that underwent meta-analyses. Articles that administered QoL measures to children when they were only validated for adult use were excluded during the sensitivity analysis, as well as articles that required the utilization of imputation techniques to compute pre-operative QoL scores.

3.4 Results

3.4.1 Study selection

The results of the search are outlined in the PRISMA flowchart (Figure 1). Out of the 1551 articles identified, 300 duplicates were removed and 1251 assessed for eligibility. Among those assessed, 268 articles met the eligibility criteria and underwent full-text review, from which 60 articles were included in this systematic review. An additional article was identified by manually screening references and was included in the review, bringing the total to 61 articles. Out of the 61 articles included in this systematic review, 5 were added during an updated search on November 9, 2023.

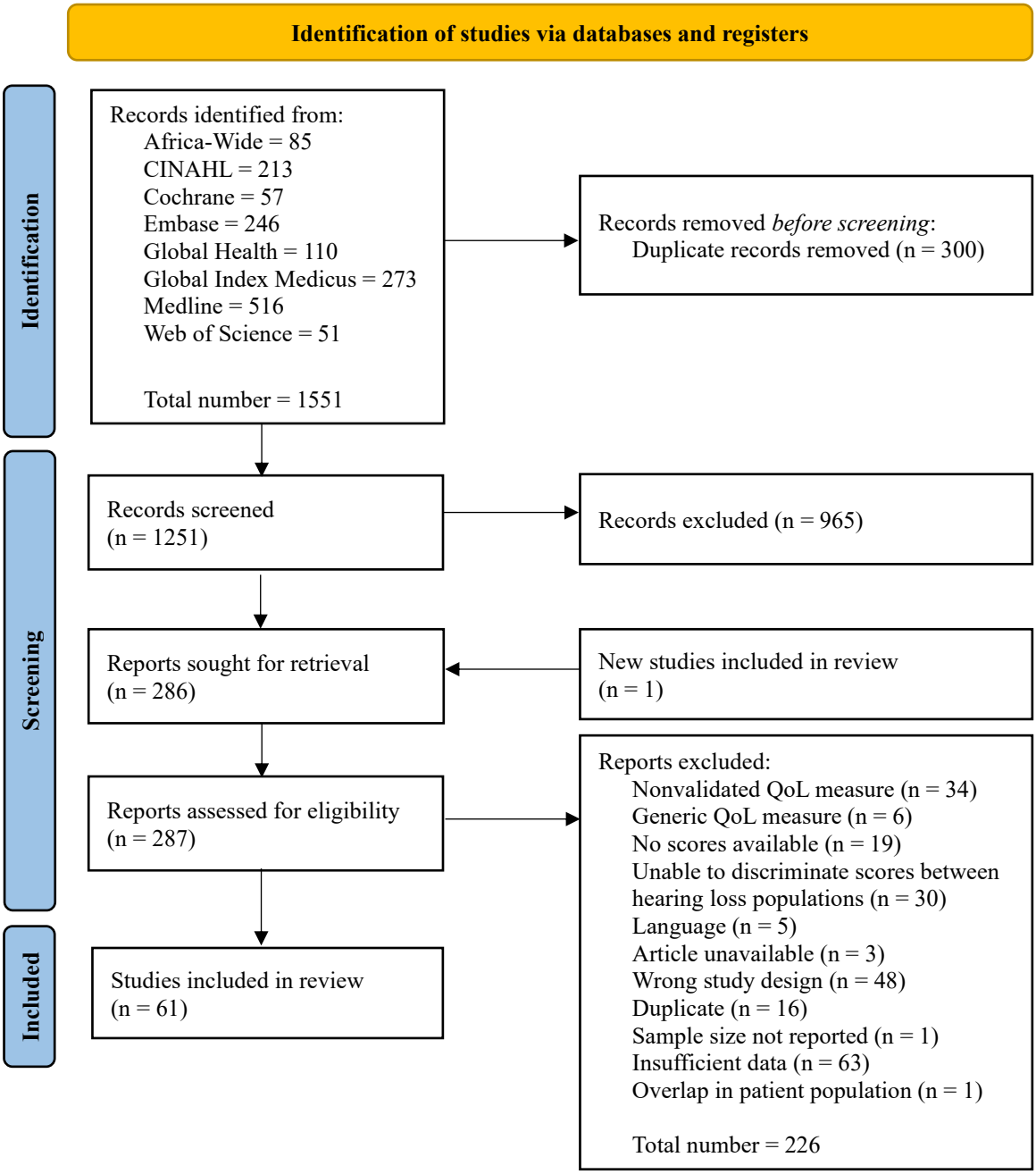

Figure 7. PRISMA 2020 flow diagram

3.4.2 Study characteristics

The study characteristics are presented in Table 1. A total of 45 studies were conducted in adult populations, while 13 studies included both adult and pediatric patients. Additionally, 3 studies exclusively focused on pediatric patients. These studies were conducted in 19 different countries, with 9 of them adopting an international multicenter design. The articles included in this analysis involved a total of 529 patients with U-SNHL and 1574 patients with CHL.

Table 1. Characteristics of included studies

First author (Year)	Country	Study design	Participants		Type of hearing loss	QoL measure	Follow-up
			No. of participants	Mean age (Range)			
Arunachalam (2001)[14]	UK	Retrospective	51	45 (4-79)	U-CHL + B-CHL	GBI	12 months
Wazen (2003)[15]	USA[a]	Prospective	13	50.61 (26-71)	U-SNHL	APHAB	1 month
Niparko (2003)[16]	USA	Prospective	10	45.4	U-SNHL	APHAB	1 month
McLarnon (2004)[17]	UK	Retrospective	69	49	U-CHL + B-CHL	GBI	NR
de Wolf (2009)[18]	Netherlands	Retrospective	135	52	U-CHL + B-CHL	IOI-HA	NR
Yuen (2009)[19]	Canada	Prospective	16	54.5 (33.1-72.1)	U-SNHL	APHAB	3 months
Ho (2009)[20]	UK	Retrospective	71	57[b] (20-83)	B-CHL	GBI	Unclear
de Wolf (2010)[21]	Netherlands	Retrospective	134	75 (62-93)	B-CHL	GBI APHAB	NR
Ricci (2010)[22]	Italy	NR	45	Adults: 61.6 (36-76) Children: 8.7 (5-14)	U-CHL + B-CHL	GBI GCBI	14 months (6-38 months)
Oeding (2010)[23]	USA	Repeated measures design	16	52.4	U-SNHL	APHAB	Unclear
House (2010)[24]	USA	Case series	68	54	U-SNHL	SSQ APHAB	NR
Dun (2010)[25]	Netherlands	Retrospective	20	15.33	B-CHL	GCBI	NR
Barbara (2010)[26]	Italy	NR	24	51.6 (12-74)	U-SNHL (n = 7) B-CHL (n = 17)	GBI	13.8 months (0-26 months)
Doshi (2010)[27]	UK	Retrospective	4	6 (5-8)	U-CHL + B-CHL	GCBI	6 months-4 years
de Wolf (2011)[28]	Netherlands	Retrospective	31	10 (6-17)	U-CHL (n = 15) B-CHL (n = 16)	GCBI APHAB	NR
Pai (2012)[29]	UK	Prospective	25	57.5 (24.5-76.8)	U-SNHL	SSQ-B	6 months
Doshi (2013)[30]	UK	Retrospective	8	9.8 (7.5-12.2)	U-SNHL	GCBI	34 months (16-56 months)
Desmet (2013)[31]	Belgium	Prospective	20	58 (25-80)	U-CHL + B-CHL	APHAB	3 weeks
Lekue (2013)[32]	Spain	NR	55	39.7 (8-76)	U-SNHL (n = 10) U-CHL + B-CHL (n = 45)	GBI	NR

McNeil (2014)[33]	Canada	Retrospective	58	N/A	U-CHL + B-CHL	SSQ	2.88 years ± 1.44 years
Marsella (2014)[34]	Italy	Prospective	6	10.7 (5-17)	B-CHL	GCBI	4 months
Desmet (2014)[35]	Belgium	Retrospective	44	55[b] (25-72)	U-SNHL	APHAB	50 months (14-103 months)
Faber (2015)[36]	Netherlands	Retrospective	102	Unclear	U-SNHL	APHAB	62 months (2-129 months)
Bianchin (2015)[37,c]	Italy	Retrospective	3	48.7 (31-49)	B-CHL	GBI	8.3 months (3-14 months)
Schwartz & Kobylk (2016)[38]	USA	Prospective	19	59 (36-79)	U-SNHL	GBI	NR
Polat (2016)[39]	Turkey[a]	Prospective	32	32.8 (6-67)	B-CHL	GBI GCBI	6 months
Ihler (2016)[40]	Germany	Prospective	38.8	8	U-CHL + B-CHL	GBI APHAB	3 months
Bernardeschi (2016)[41]	France	Prospective	9	50 (40-65)	U-SNHL	GBI	1 year
Gawecki (2016)[42]	Poland	Prospective	20	50 (24-67)	U-SNHL (n = 8) B-CHL (n = 12)	GBI APHAB	2 months
Eberhard (2016)[43]	Denmark	Prospective	12	45.1 (20-69)	U-SNHL (n = 4) B-CHL (n = 8)	IOI-HA SSQ12	4 months (5-9 months)
Schmerber (2017)[44]	France[a]	Prospective	25	44.1 (18-65)	U-SNHL (n = 12) U-CHL + B-CHL (n = 13)	APHAB GBI IOI-HA	12 months
Salcher (2017)[45]	Germany	Retrospective	10	45 (21-70)	U-SNHL	APHAB BBSSD	NR
McLean (2017)[46]	Australia	Prospective	4[f]	41.8 (22-64)	B-CHL	GBI	2 weeks
Hougaard (2017)[47]	Denmark[a]	Prospective	20	47.6 (8-72)	U-SNHL (n = 13) U-CHL + B-CHL (n = 7)	IOI-HA SSQ12	7 months
den Besten (2018)[48]	Netherlands[a]	Prospective	54	42.1 (18.3-70.3)	U-SNHL (n = 15) U-CHL + B-CHL (n = 39)	APHAB SSQ	6 months ± 4 weeks
Zanetti (2018)[49]	Italy	Retrospective	2	32 (29-35)	B-CHL	APHAB SSQ	36 months
Rahim (2018)[50]	Malaysia	Retrospective	35	13 (5-38)	U-CHL + B-CHL	GBI	3-6 months

Skarzynski (2019)[51]	Poland	Prospective	21	40.29 (18-58)	U-CHL + B-CHL	APHAB	3 months 6 months
Koro & Werner (2019)[52]	Sweden	Cohort study	16	49 (24-68)	U-SNHL (n = 10) U-CHL + B-CHL (n = 6)	GBI	NR
Yang (2020)[53]	China	Prospective	100	11.9 (6.1-46.3)	B-CHL	APHAB	25 weeks (12-36 weeks)
van Hoof (2020)[54]	Netherlands[a]	Prospective	103	Test group: 54.2 Control group: 51.5	U-SNHL (n = 22) U-CHL + B-CHL (n = 81)	APHAB	1 year 3 years
Mylanus (2020)[55,e]	Netherlands[a]	Prospective	51	47.4 (19-77.4)	U-SNHL (n = 14) U-CHL + B-CHL (n = 37)	APHAB SSQ12	3 months 12 months
Kruyt (2020)[56]	Netherlands[a]	Prospective	54	42.1 (18.3-70.3)	U-SNHL (n = 15) U-CHL + B-CHL (n = 39)	APHAB SSQ	4 months 24 months
Marszal (2021)[57]	Poland	Prospective	4	58 (38-76)	B-CHL	APHAB SSQ	4 months 9 months 12 months
Volgger (2022)[58]	Germany	Retrospective	18	23 (5-54)	U-CHL + B-CHL	SSQ-B	NR
Rauch (2022)[59,e]	Germany	Retrospective	22	44.3 (11-77)	U-SNHL (n = 3) U-CHL + B-CHL (n = 19)	SSQ APHAB	12 months 24 months 36 months
Lewis & Gergely (2022)[60]	Sweden	Retrospective	6	45	U-CHL + B-CHL	SSQ	12 months
Huber (2022)[61]	Switzerland[a]	Prospective	16	39.5 (18-62)	U-SNHL	SSQ-B BBSSD	4 months 12 months 24 months
Irmer (2022)[62]	Germany	Retrospective	12	57 (26-85)	U-CHL + B-CHL	SSQ12B	40 months (8-68 months)
Cywka (2022)[63]	Poland	Prospective	42	40.5 (19-74)	U-CHL + B-CHL	APHAB	4 months 12 months
Caspers (2022)[64]	Netherlands	Prospective	75	54	U-SNHL (n = 14) U-CHL (n = 22) B-CHL (n = 39)	GBI	3 months 12 months
Carnevale (2022)[65]	Spain	Retrospective	52	50.205 (19-74)	B-CHL	APHAB	6 months
Canale (2022)[66]	Italy	Prospective	7	30.3 (16-67)	B-CHL	APHAB	1 month
Auinger (2022)[67,d]	Austria	Retrospective	25	43	U-CHL + B-CHL	SSQ12	NR

Skarzynski (2022a)[68]	Poland	Retrospective	15	50.9 (21-74)	U-CHL + B-CHL	APHAB GBI	12 months
Skarzynski (2022b)[69]	Poland	Prospective	16	BCI 601: 56.7 (28-69) BCI 602: 48.7 (26-74)	U-CHL + B-CHL	APHAB	1 month 6 months
Kim (2023)[70]	South Korea	Prospective	30	50.9 (19-72)	U-SNHL	APHAB BBSSD	3 months
Luque (2023)[71]	Canada	Retrospective	9	10 (5-17)	U-CHL	GCBI	32.8 months (9-60 months)
Portelli (2023)[72]	Italy	Retrospective	11	pBAHA: 60.7 tBAHA: 40.6	U-CHL + B-CHL	APHAB GBI	6 months
Ye (2023)[73]	China	Prospective	12	28 (10-64)	B-CHL	SSQ	3 months 4 months 12 months
Canale (2023)[74]	Italy	Prospective	14	38.6 (9-67)	U-CHL (n = 7) B-CHL (n = 7)	APHAB	2 months

[a] Studies with a multicenter design
[b] Reported median value instead of mean
[c] Only extracted data from CHL patients (only had 1 SSD patient)
[d] Only extracted data from CHL/MHL population (no extractable scores for SSD population)
[e] There is an overlap of 10 patients between these two studies
[f] One patient was diagnosed with SSD and therefore excluded from analysis (n total = 5)

Abbreviations: U-SNHL, unilateral sensorineural hearing loss; U-CHL, unilateral conductive hearing loss; B-CHL, bilateral conductive hearing loss; APHAB, Abbreviated Profile of Hearing Aid Benefit; GBI, Glasgow Benefit Inventory; GCBI, Glasgow Children's Benefit Inventory; SSQ, Speech, Spatial, and Qualities of Hearing Scale; IOI-HA, International Outcome Inventory for Hearing Aids; BBSSD, Bern Benefit Single Sided Deafness; NR, not reported; pBAHA, percutaneous bone-anchored hearing aid; tBAHA, transcutaneous bone-anchored hearing aid

3.4.3 Risk of bias

There were no concerns for a high risk of bias in any of the included articles. However, 7 articles were assessed as having an "Unclear risk", but ultimately included in the analyses. A summary plot of the 5 RoBANS variants and the distribution of the judgements was created with the web application Robvis (Figure 2).[76] Individual ratings for each article can be found in "Supplementary materials" (eFigure 1).

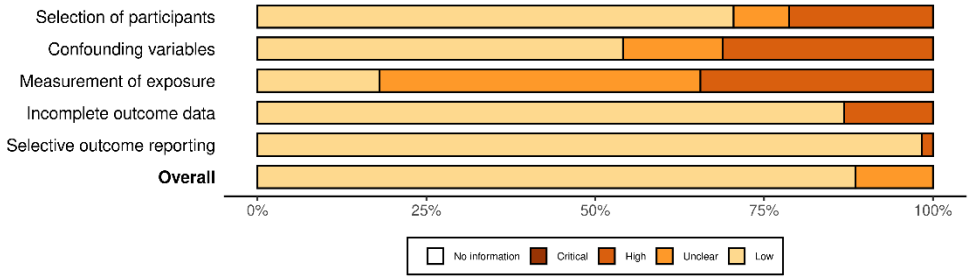

Figure 8. Summary plot of the risk of bias assessment for included studies

3.4.4 QoL measures

In this review, 8 QoL measures were utilized: Abbreviated Profile of Hearing Aid Benefit (APHAB), Glasgow Benefit Inventory (GBI), Glasgow Children's Benefit Inventory (GCBI), Speech, Spatial, and Qualities of Hearing Scale (SSQ), SSQ12, SSQ Benefit (SSQ-B), International Outcome Inventory for Hearing Aids (IOI-HA), and the Bern Benefit Single-Sided Deafness (BBSSD).

Table 2. Summary of quality of life measures included in the systematic review

Questionnaire	Description	Scoring
Abbreviated Profile of Hearing Aid Benefit (APHAB)	A 24-item questionnaire that evaluates the patient's speech understanding in everyday situations and the presence of unwanted noises in the environment.[76,77] It is composed of 4, 6-item subscales: ease of communication (EC), background noise (BN), reverberation (RV) and aversiveness (AV).	• Scale responses range from 1 (Never) to 99% (Always). • Global score = average of EC + BN + RV subscales. • Lower scores represent fewer problems in listening situations.
Glasgow Benefit Inventory (GBI)	A post-intervention questionnaire that aims to assess patient benefit following an otorhinolaryngology procedure.[78,79] It consists of 18 questions divided into 3 subscales: general (12 questions), social (3 questions) and physical (3 questions) benefits.	• Item scored on 5-point Likert scale, with the middle indicating "No change". • Scores converted to a -100 to +100 benefit scale.
Glasgow Children's Benefit	A parent-completed questionnaire which assesses their children's benefit following an otorhinolaryngology procedure.[80] It is composed of 24 questions and 4 subscales: emotion, physical health, learning, and vitality.	• Items scored like the GBI scale. • Items converted to a -100 to +100 score.

Inventory (GCBI)		
Speech, Spatial, and Qualities of Hearing Scale (SSQ)	A 49-item questionnaire examining the listener's ability to comprehend speech in scenarios with competing noises and various spatial characteristics, as well as assessing the clarity and naturalness of sounds.[81] Three subscales are evaluated pre- and post-hearing aid fitting: speech (14 questions), spatial characteristics (17 questions) and qualities of sound (18 questions).	• Items scored on a scale from 0 to 10. • Standard anchor terms of "Not at all" (0) to "Perfectly" (10).
Speech, Spatial, and Qualities of Hearing Scale 12 (SSQ12)	An abbreviated, 12-item questionnaire derived from the SSQ scale. 5 questions were associated with "Speech", 3 questions regarding "Spatial", and 4 questions for "Qualities".	• Same scoring and anchoring terms as the SSQ scale.
Speech, Spatial, and Qualities of Hearing Scale Benefit (SSQ-B)	A modified SSQ scale that tasks the patient with comparing their hearing experience now to how it was before being fitted with their hearing device.	• Items scored on a scale from -5 to +5, where the midpoint represents "Unchanged".
International Outcome Inventory for Hearing Aids (IOI-HA)	This questionnaire was developed to supplement existing health-related QoL outcome measures and to be accessible to international communities.[82] It measures the effectiveness of the patients' hearing aid by covering 7 domains: daily use, benefit, residual activity limitations, satisfaction, residual participation restrictions, impact on other, and QoL.[83]	• Items scored on a scale of 1 to 5.
Bern Benefit Single-Sided Deafness (BBSSD)	This 10-item questionnaire uses visual analogue scales, ranging from 0 to 10 points, to measure the patient's perceived benefit from their BAHI or contralateral routing of signal device in aiding them understand speech in various listening settings.[84]	

Abbreviations: QoL, quality of life; BAHI, bone-anchored hearing implant

3.4.5 Clinically meaningful differences

It is important to analyze QoL benefit scores in terms of their clinical relevance rather than relying solely on their statistical significance. A clinically meaningful difference (CMD) can be defined as the threshold at which the patient and/or clinician consider the intervention to have a meaningful impact.[86] In the context of this review, we will examine whether the patient perceives their BAHI as having a meaningful impact on their lifestyle. The CMD values for the APHAB, GBI, and SSQ scales are presented below:

- **APHAB**: 10-point change in the global benefit score was considered clinically meaningful.[78,87] Additionally, it was observed that patients experienced a true difference when a 10-point change was observed in all of the benefit scores of the EC, RV, and BN subscales, or if there was a 22-point increase in any of these scores.[78]

- **GBI**: Since the GBI is a post-intervention scale, it is already designed to capture the positive or negative impact of an otorhinolaryngology procedure on a patient's life. Therefore, its global and subscale scores would already reflect a clinically relevant change.
- **SSQ**: There is limited consensus on the CMD for the SSQ scale. A 2022 systematic review mentioned that it could range from a 0.7- to 1.3-unit decrease, indicating an improvement in the patient's QoL, while another article suggests that a 1.0-unit decrease would be clinically relevant.[8,82,88] For this systematic review, a 1.0-unit decrease in subscale score was established as the CMD. However, we acknowledge that further research is necessary to establish a validated value.

3.4.6 Meta-analysis results

Insufficient studies reported QoL scores specifically for U-CHL patients, making it impossible to conduct a subgroup analysis between U-SNHL, U-CHL, B-CHL, and "U-CHL + B-CHL" populations. Consequently, we combined all CHL patients into one group, regardless of the laterality of their hearing loss, to compare subgroup differences between U-SNHL and CHL patients.

An overview of all the meta-analyses results is provided in **Table 2**. Patients with U-SNHL reported significant benefits in most QoL measures, except in the APHAB's AV subscale ($p = .44$) and the GBI's "Physical" subscale ($p = .84$). In the CHL group, there were significant improvements in all QoL measures compared to baseline measurements. In most meta-analyses, heterogeneity was substantially high. Forest plots of all scales and individual subscales can be found in "Supplementary materials" (eFigures 2-4).

There were 6 subscale scores that were significantly different between the subgroups: the APHAB's "Global" ($I^2 = 94.7\%$, $p < .0001$) and EC ($I^2 = 94\%$, $p < .0001$), GBI's "Global" ($I^2 = 94.2\%$, $p < .0001$), "General" ($I^2 = 88.2\%$, $p = .004$), and "Physical" ($I^2 = 88.8\%$, $p = .003$), and SSQ's "Qualities" ($I^2 = 76.1\%$, $p = .04$).

Table 3. Summary of meta-analyses results of quality of life measures from patients with unilateral sensorineural hearing loss versus conductive hearing loss

	U-SNHL			CHL			Subgroup differences
	Mean (95% CI)	*p-value*	N	Mean (95% CI)	*p-value*	N	*p-value*
APHAB							
Global	13.54 (9.10-17.98)	$p < .00001$	154	28.99 (23.64-34.33)	$p < .00001$	390	$p < .0001$
EC	12.77 (9.13-16.41)	$p < .00001$	355	26.92 (21.19-32.65)	$p < .00001$	609	$p < .0001$
BN	20.30 (14.22-26.38)	$p < .00001$	358	27.42 (20.84-33.99)	$p < .00001$	627	$p = .12$
RV	16.29 (12.52-20.05)	$p < .00001$	355	22.88 (14.45-31.31)	$p < .00001$	609	$p = .16$
AV	-2.44 (-8.57-3.69)	$p = .44$	339	-7.38 (-12.40–2.37)	$p = .004$	609	$p = .22$
GBI							
Global	20.35 (14.56-26.14)	$p < .00001$	69	35.81 (31.34-40.27)	$p < .00001$	629	$p < .0001$
General	26.65 (15.05-38.26)	$p < .00001$	53	46.11 (40.04-52.18)	$p < .00001$	461	$p = .004$
Social	10 (1.73-18.28)	$p = .02$	39	19.71 (11.72-27.69)	$p < .00001$	400	$p = .10$
Physical	0.39 (-3.36-4.14)	$p = .84$	39	12.35 (5.45-19.25)	$p = .0005$	400	$p = .003$
SSQ							
Speech	1.85 (1.40-2.29)	$p < .00001$	96	3.22 (1.94-4.50)	$p < .00001$	155	$p = .05$
Spatial	1.21 (0.72-1.70)	$p < .00001$	95	2.67 (1.29-4.05)	$p = .0001$	155	$p = .05$
Qualities	1.22 (0.72-1.71)	$p < .00001$	96	2.66 (1.37-3.95)	$p < .0001$	155	$p = .04$

Abbreviations: U-SNHL, unilateral sensorineural hearing loss; CHL, conductive hearing loss; APHAB, Abbreviated Profile of Hearing Aid Benefit; EC, ease of communication; BN, background noise; RV, reverberation; AV, aversiveness; GBI, Glasgow Benefit Inventory; SSQ, Speech, Spatial, and Qualities of Hearing Scale

3.4.7 Summary statistics of GCBI, IOI-HA, BBSSD, SSQ12 & SSQ-B

Of the included studies, 7 studies reported results for the GCBI,[23,26,28,29,31,35,72] 3 articles described their results with the IOI-HA scale,[19,44,48] and 2 included articles used the BBSSD questionnaire.[71,89] Additionally, 5 included articles administered the SSQ12 scale[44,48,56,63,68] and 2 others reported results with the SSQ-B.[59,89] Descriptive statistics for these scales can be retrieved in “Supplementary materials” (eTables 4-8).

3.4.8 Correlation between QoL outcome measure scores over time

Spearman correlations were performed to investigate the relationship between global and subscale scores of the APHAB, GBI, and SSQ and the timepoint (in months) at which the patients completed the QoL measures. Only articles that report a follow-up time were included in this analysis. If a study collected QoL scores at multiple timepoints, they were all included in the correlation analysis.

In the U-SNHL population, only the AV subscale of the APHAB was significantly correlated with the time of administration (r = -0.577, p = .031). The "Social" subscale of the GBI questionnaire was near significance (r = -0.949, p = .051). In the CHL population, both the global score and AV subscale from the APHAB questionnaire were close to significance (r = 0.051, p = .467 and r = 0.443, p = .066, respectively). The complete results can be found in "Supplementary materials" (eTable 9).

3.4.12 Sensitivity analysis

The sensitivity analysis performed revealed that the statistical significance of the subgroup differences remained largely unchanged. However, the BN subscale became significant (p = .04), along with the "Speech" (p = .04) and the "Spatial" (p = .01) subscales. The "Qualities" subscale was the only one to lose significance (p = .05).

3.5 Discussion

3.5.1 Results from meta-analyses

The findings of this systematic review and meta-analyses show that QoL improvements for BAHI users vary based on their classification of hearing loss. Significant subgroup differences were found in the scores of 3 disease-specific QoL measures: the APHAB, GBI, and SSQ.

Several subscales showed statistically significant differences in QoL scores between patients with U-SNHL and CHL. These subscales include APHAB's "Global" and EC, GBI's "Global", "General", and "Physical", and SSQ's "Qualities". In fact, CHL patients scored higher in all these subscales, indicating that they reported greater benefits compared to those with U-SNHL. Therefore, CHL patients appear to have an easier time following conversations in

environments with varying numbers of speakers and background noise and perceive sound with more clarity and naturalness when using a BAHI. Additionally, being fitted with a BAHI seems to improve their overall health and psychosocial well-being. It is worth noting that all benefit scores for both populations were clinically meaningful, as demonstrated by their APHAB and SSQ scores.

The first reason that could explain the discrepancy in the experienced QoL benefits in these populations is the presence of the head shadow effect in patients with U-SNHL.[7] The head shadow effect causes an attenuation of the intensity of sound signals, particularly those above 1000 hertz (Hz), as the head reflects sound waves away from the ear with better hearing.[16] Although this effect can be alleviated with the help of a BAHI,[55,90] situations where unwanted noise is presented to the hearing device and a speaker is positioned in front of the patient can remain bothersome.[7,37]

Secondly, a predictive model has identified young age, a shorter period of follow-up after fitting the BAHI, and a higher pure-tone average in the better hearing ear as crucial factors in identifying who may experience greater benefit from their hearing aids.[91] An independent samples t-test comparing the mean ages of our different hearing loss populations revealed no significant differences in patients who responded to the APHAB ($p = .075$), GBI ($p = .320$), or SSQ ($p = .297$). However, it is important to note that the mean age for the CHL population was lower than U-SNHL in all cases, which may have contributed to the reporting of higher QoL benefit scores in this group.

As previously mentioned, the degree of hearing impairment in the ear with better hearing may also influence the perception of improvement attributed to the BAHI. Most patients in the combined CHL group had poorer hearing in their better ears, while patients with U-SNHL typically have normal or near-normal hearing in their better ear. Patients with bilateral hearing impairment may perceive greater sound amplification from the BAHI, as they may not have experienced normal binaural hearing. On the other hand, patients with low audiological thresholds in their better ear may not notice a significant difference in sound amplification and therefore may not use their hearing device. Nonetheless, patients with normal contralateral hearing may still benefit from the device in subtle ways, such as improved speech understanding in noisy situations. The same argument can be applied to patients with congenital and acquired hearing loss; those with acquired

hearing loss may be less satisfied with the BAHI if its performance does not match their previous experience of normal hearing.

3.5.2 Results in the context of other evidence

The MDs from the APHAB and SSQ questionnaires of our meta-analyses were similar to the ones calculated in the systematic review by Hampton et al, lending to the strength of our analyses and results.[8] As demonstrated in **Figure 3**, the global MD for APHAB in the U-SNHL population was 13.55, compared to Hampton's 15.5. The results for the subscales were also similar (EC: MD = 12.83 vs. 15.67, BN: MD = 20.11 vs. 22.7, RV: 16.00 vs. 18.10, AV: MD = -2.39 vs. 3.5). The MDs from the SSQ subscales were also comparable (Speech: MD = 1.85 vs. 2.0, Spatial: MD = 1.21 vs. 1.5, Qualities: MD = 1.21 vs. 1.2). Unfortunately, we could not find any other reviews that reported benefit scores from disease-specific QoL measures in CHL populations.

3.5.3 Limitations of the evidence

Our evidence is limited due to significant methodological and clinical heterogeneity in most meta-analyses.

The majority of the included articles did not specify the method of scale administration, making it impossible to determine if clinicians were present to clarify or answer any patient questions during questionnaire completion. This issue applied to both clinic and at-home completion of the questionnaire. Compared to at-home completion, face-to-face interviews were found to significantly improve the test-retest reliability of questionnaires among BAHI users, resulting in more accurate responses and less cognitive load.[92] Additionally, face-to-face interviews were deemed the optimal method for assessing the effectiveness of an intervention.[92] A systematic review in 2022 also highlighted the diverse ways in which QoL scales are administered in otolaryngology research, with some authors only collecting post-BAHI scores despite the scale having a before-and-after design.[8] Therefore, the validity of our results is limited due to a significant number of articles that may have administered QoL measures inappropriately, potentially leading to erroneous patient responses.

Regarding clinical heterogeneity, there was considerable variability in patient demographics both within and between the included studies. Firstly, there was a wide age range

among participants in many studies. Although the age differences were not significantly different between hearing loss populations in our review, it is still an important factor to consider. Different age groups have varying cognitive load capacities, which can influence their ability to focus on multiple questions for an extended period. Secondly, there were multiple factors that we could not control for, such as surgical techniques, post-operative complications, abutment type, cosmetic appearance, and sound processor technology. When completing their QoL measures, patients may express dissatisfaction with any of these outcomes rather than evaluating the device's hearing performance. Conversely, a positive post-operative experience may overshadow poor sound processor performance. There is also a risk that patients may answer positively to appear grateful to the clinicians, thereby not reflecting their true hearing performance. Thirdly, the nature of the BAHI (pBAHI or tBAHI) could potentially affect QoL outcomes. It has been demonstrated that patients with a tBAHI report greater QoL benefits compared to those who are fitted with a pBAHI.[93] Finally, due to the limited reporting of individual audiological thresholds, we grouped patients based on their type of hearing loss regardless of severity, symmetry, and whether they were fitted with BAHIs unilaterally or bilaterally. It is important to mention that Noble & Gatehouse identified correlations between audiological thresholds and SSQ scores.[94] Specifically, they observed that patients with an asymmetrical hearing loss greater than 10 dB rated their hearing abilities lower in all SSQ subscales. A subsequent study also noted significant differences in perceived benefits between patients who were unilaterally or bilaterally fitted with hearing aids.[95] In fact, in matched participants, those fitted with bilateral hearing aids reported greater benefits in situations with dynamic spatial characteristics, rapid attention changes, and listening effort.

3.5.4 Implications for practice & future directions

One of the strengths of this systematic review is the inclusion of a large number of articles and the computation of meta-analyses for multiple disease-specific QoL measures. This enabled a more comprehensive understanding and appreciation of the differences in QoL among BAHI patients with different types of hearing loss. Providing correct pre-operative counselling and setting realistic expectations regarding the performance of the sound processor are crucial steps in ensuring long-term benefits for BAHI patients.[96] It is now evident that QoL scales provide information on patient benefit that is independent of audiological tests and should be integrated into regular follow-up procedures.

Nevertheless, further research is necessary to fully comprehend the complex nature of hearing-related QoL and its association with hearing loss and BAHIs. More studies are needed to investigate underreported patient populations, such as pediatric and unilateral CHL/MHL patients. Furthermore, additional subgroup analyses are required to explore how patient demographics, sound processor technology, severity, and symmetry of hearing loss can impact QoL benefits in BAHI patients. Lastly, the disease-specific QoL measures used in this systematic review were originally developed and validated for traditional air conduction hearing aid users, not for BAHI users.[77,79,82] Therefore, it is important to develop updated score percentiles, norms, and CMDs specific to the BAHI population in order to enhance the confidence and reliability of our findings.

3.6 Conclusion

This systematic review and meta-analyses have uncovered noteworthy disease-specific differences in QoL among BAHI patients with U-SNHL and CHL. The findings indicate that CHL patients encounter fewer difficulties in noisy environments, perceive sounds with greater clarity, and experience better overall and psychosocial well-being after BAHI fitting. Conducting subgroup analyses would further elucidate the impact of specific characteristics on QoL benefits. Further research is warranted to gather data on underrepresented populations and validate the norms of disease-specific QoL measures for BAHI patients.

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3.8 Linking statement

Chapter 3 demonstrated the positive impact of bone conduction devices on the QoL of BAHI patients, taking into account their specific type of hearing loss. While QoL scales primarily focus on measuring hearing performance with the BAHI, it is important to consider that patients with unsatisfactory post-operative outcomes may provide negative ratings during their assessment to express their dissatisfaction, even if their hearing has improved. These outcomes can be attributed to factors such as skin infections at the abutment site, skin overgrowth, low aesthetic appeal, or the presence of comorbid ear infections.

As discussed in Chapter 1, chronic ear infections can have a significant impact on the QoL of individuals using BAHIs. For instance, COM, which is characterized by persistent fluid discharge from the ear, can result in various symptoms such as ear fullness, physical discomfort, pain, and hearing loss. The latter can potentially be resolved through the implantation of a BAHI. However, even with the restoration of hearing, BAHI users continue to experience a lower QoL due to the physical symptoms associated with the chronic ear infection itself.

A crucial aspect in addressing this issue is the swift resolution of the middle ear infection, which would allow BAHI users to resume their daily activities without hindrances or discomfort. Nonetheless, treating this condition poses challenges due to the diverse range of causative agents involved, including bacteria, fungi, or a combination of both. Consequently, there is a pressing need to discover a topical treatment that is both safe and effective for COM, in order to quickly resolve the adverse physical symptoms associated with this condition and enhance the QoL of these BAHI users.

The following chapter aims to evaluate the otologic safety of a potential antimicrobial treatment for COM.

Chapter 4

Otologic Safety of Ciprofloxacin, Trimethoprim/Sulfamethoxazole, and Amphotericin B Powder: An Animal Study

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This study was accepted as a podium presentation at the American Society of Pediatric Otolaryngology annual meeting in May 2024 and the Canadian Society of Otolaryngology – Head and Neck Surgery annual meeting in June 2024. This manuscript is in preparation for submission to Otolaryngology – Head & Neck Surgery.

4.1 Abstract

Importance: Chronic otorrhea in patients with a long-standing history of otitis media poses a significant challenge for otolaryngologists. The polymicrobial nature of chronic otitis media renders it difficult to effectively treat.

Objective: To determine the otologic safety of a novel powder composed of ciprofloxacin, trimethoprim/sulfamethoxazole, and amphotericin B.

Design, Setting, and Participants: The animal study was conducted at the animal facility of the Research Institute at McGill University Health Centre, Montreal, Quebec, and included 15 male Hartley guinea pigs with normal baseline hearing levels.

Intervention: The ears were randomly selected to receive either the study medication (ciprofloxacin, trimethoprim/sulfamethoxazole, amphotericin B, and talc) or the non-ototoxic control powder (boric acid) according to the animal's identifying tag number. A bilateral myringotomy was performed in order to deliver a single application of the powdered substances to the middle ear.

Main Outcome and Measures: Auditory brainstem responses were recorded at 8, 12, 16, 20, and 24 kHz at baseline, immediately post-myringotomy, and 2 and 4 weeks post-application. Ototoxicity was established through significant threshold changes compared to baseline measurements and damage to outer hair cells as determined by scanning electron microscopy of the cochlea.

Results: 13 of 15 animals showed significant changes to auditory brainstem response thresholds in the ears which received the study medication between baseline and 4 weeks post-application measurements at 8 kHz (mean difference [SD] dB, 18.077 [19.315]; 95% CI, 6.405-29.749; $p = .006$), 12 kHz (27.308 [16.281]; 95% CI, 17.469-37.146; $p < .001$), 16 kHz (13.462 [17.246]; 95% CI, 3.040-23.883; $p = .016$), and 20 kHz (20.000 [10.801]; 95% CI, 13.473-26.527; $p < .001$). Scanning electron microscopy of randomly selected cochleas demonstrated ototoxic damage to the outer hair cells exposed to the study medication.

Conclusions and Relevance: As evidenced by the study findings, the proposed powder demonstrates signs of ototoxicity. This combination of antimicrobials should not be used in clinical

settings to resolve cases of middle ear infections until further research is conducted to identify the component responsible for the observed ototoxicity.

4.2 Introduction

Persistent otorrhea in patients with chronic otitis media (COM) or those who have undergone canal wall down mastoidectomy poses a significant challenge for otolaryngologists. The consequences go beyond prolonged discomfort, exacerbating hearing loss and hindering the use of hearing aids. In fact, the World Health Organization estimates that COM contributes to over half of the global burden of hearing impairment.[1]

In patients with COM, the prevailing microorganisms include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*.[2,3] Notably, there has been a rise in methicillin-resistant *S. aureus* (MRSA) resistant to quinolones over the past decade.[4] Most COM cases demonstrate polymicrobial infections,[5] with fungal agents such as *Candida* and *Aspergillus* species often identified.[6]

Current treatments for COM include aural toileting, topical and/or systemic antibiotics, or surgical intervention.[7,8] However, some patients who have received previous procedures to resolve their COM still experience ongoing drainage from their ears. In such cases, the application of a powder may help resolve their chronic otorrhea.

Effective topical treatments could reduce the reliance on systemic antibiotics, mitigating off-target side effects and contributing to the general trend of battling antibacterial resistance.[9] Several powders exist and are used to treat granulation tissue, resistant bacterial and/or fungal infections, and excessive moisture in the ear cavity.[10,11] Nonetheless, exposed middle ear after radical mastoidectomy or tympanic membrane perforation narrows a physician's choice for topical treatment due to the potential risk of ototoxicity.

At our institution, we have implemented an antimicrobial, dry powder for treating COM with otorrhea. Our neurotology team has been prescribing a combination of ciprofloxacin, trimethoprim/sulfamethoxazole (TMP-SMX), and amphotericin B (AmB) in a talcum powder base with clinical success and symptom resolution. Notably, no signs of ototoxicity were observed with this powder. Despite its efficacy, the otologic safety of this treatment has not been comprehensively evaluated. Therefore, the objective of this study was to assess the safety of this antimicrobial powder when applied to an exposed middle ear by using a validated animal model.

4.3 Methods

4.3.1 Animal care & ethics

The study was approved by the Animal Care Committee of the McGill University Health Centre Research Institute and was conducted at the McGill Otolaryngology Sciences Laboratory following the guidelines of the Canadian Council for Animal Care (protocol #MUHC-5554).

This study comprised fifteen white male guinea pigs (*Hartley,* Charles River Laboratories), aged 6 to 8 weeks and weighing between 500 g and 600 g. A sample size of 12 animals was determined with power set to 80%, an alpha of 0.05, and a minimum absolute difference of 18 dB with a 15 dB standard deviation. Three additional animals were added to account for any adverse events, bringing the total to 15. Prior to starting the study, baseline auditory brainstem response (ABR) measurements confirmed normal hearing levels. Throughout the duration of the study, the animals were housed in temperature- and light-controlled rooms with free access to food and water and were monitored for any changes in behavior, activity levels, feeding, or significant weight changes by the veterinary technicians at the animal care facility.

4.3.2 Hearing assessment

Hearing evaluations were performed on the animals under general anesthesia. Each animal was sedated with a ketamine cocktail (Ketamine [100 mg/ml], Xylazine [20 mg/ml], Acepromazine [10 mg/ml]) injected subcutaneously prior to being anesthetized. Anesthesia was maintained with isoflurane gas ranging from 0.5% to 1.5%. The animal's vital signs were closely monitored throughout all hearing assessments.

ABR measurements were done using the Smart EP Device (Intelligent Hearing Systems, USA). Pure tone bursts of 24, 20, 16, 12, and 8 kHz were presented to a single ear at a rate of 39.1 bursts per second with 1600 sweeps through small foam ear tips, which were cut to fit the ear canal of the animal. Each ear was tested separately to minimize interference and increase result reliability. The pure tone bursts were presented starting at an intensity of 70 dB and decreased in steps of 5-10 dB until the threshold was identified. A normal hearing threshold on any tested frequency was established to be 20 dB. Since the ABR wave 3 is the most stable in guinea pigs, the threshold in our study was defined as a clear, duplicated response with an apparent wave 3

and/or wave 5.[12] ABR results were reviewed with an audiologist (D.N.). When no response was registered for a frequency, the threshold was noted as 70 dB.

The ABR measurements were taken at 4 occasions: baseline, immediately post-myringotomy (before the application of medication), 2 weeks post-myringotomy, and 4 weeks post-myringotomy. Before collecting post-intervention ABR measurements, all animals underwent otomicroscopy to ensure the external auditory canal (EAC) and middle ear space were free of medication, crusts, and/or inflammation.

4.3.3 Transtympanic application procedure

Approximately 10 days after the baseline ABR measurements were taken, a bilateral myringotomy was performed to introduce the experimental and the control into the middle ear cavity. A large perforation with folded edges was created in the posterior quadrants of the tympanic membrane under otomicroscopy. The middle ear cavity was visualized at the end of the surgery.

Each animal served as its own control, with one ear randomized to receive the study medication and the contralateral ear receiving a control powder. The study medication, provided by the McGill University Health Centre pharmacy, was in a 5 g vial containing ciprofloxacin (1000 mg), TMP-SMX (Sulfatrim DS 800/160 mg), AmB (120 mg), and Talc (2500 mg) as a powder base. Boric acid (BA) was utilized as the control powder since it has been shown as non-ototoxic in previous studies.[13] The animals' tag numbers, assigned by the veterinary technician staff, were utilized to randomize which ears received which powdered substance. Animals with an odd tag number received the study medication in their right ear and BA in the left, while animals with even numbers received the opposite.

Considering the volume of the ear canal and middle ear space, it was estimated that 30 mg of powder would be required to fill the middle ear space. The study medication and BA were applied once the post-intervention ABR measurements were completed. Medication was weighed and loaded into a modified insulin syringe and delivered through a 2.75 mm ear speculum (Welch Allyn, USA). The presence of the powder in the middle ear was visually confirmed during the procedure.

4.3.4 Ear examination, histopathology, and scanning electron microscopy

4 animals were randomly selected to be euthanized approximately 6 weeks after the end of the last measurements. The external and middle ears were examined for any skin, mucosal, and bony changes.

The EACs of 2 animals were dissected and placed in 10% formalin solution for 48 hours after the specimens were decalcified and embedded in paraffin. 5 μm sections were cut and stained with hematoxylin and eosin. Pathologists examined these sections under light microscopy for signs of inflammation and fibrotic changes. The cochleas were dissected and fixated in 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer for 36 hours. The samples were then gradually dehydrated in 30, 50, 70, 80, 90, 95, 100, and 100% ethanol, each step being performed for 30 minutes.[14] They were then critical-point dried (Leica CPD300, Germany) and sputter coated with 5 nm platinum (Leica ACE600, Germany) to enhance electrical conductivity. Scanning electron microscopy was performed using the FEI Quanta 450 Environmental Scanning Electron Microscope operating at an accelerating voltage of 5 kV in the secondary electron mode, located at the Facility for Electron Microscopy Research at McGill University.

4.3.5 Statistical analysis

ABR baseline thresholds were compared to the thresholds at 2 and 4 weeks post-intervention by using a paired t-test in both control and experimental ears for all tested frequencies (24, 20, 16, 12, 8 kHz). The threshold differences between the control and experimental ears at 4 weeks post-intervention were also evaluated at all frequencies. A *p-value* less than 0.05 was considered to be statistically significant. Analyses were performed using the statistical software package STATA-13 (STATA Corporation, College Station, TX, USA).

4.4 Results

4.4.1 Physical observations

Out of the 15 animals enrolled in the study, 13 were included in the final analysis. One animal died during surgery, and data collection was not performed for the remaining animal. ABR thresholds were lost for another animal at 2 weeks post-myringotomy due to technical issues during the data-saving process. Therefore, statistical analysis was only available for 12 animals at

that time point. All animals displayed normal behavior and weight gain throughout the experiment. One presented with large open abdominal wounds and had to be housed separately from its cage mates.

4.4.2 Evaluation of the ear

At 2 weeks post-intervention, significant inflammation was observed in all EACs that received the study medication but resolved without any external intervention at 4 weeks. Visualization of the inflamed ear canals with an ENT microscope confirmed the presence of remnant powdered medication both at 2 and 4 weeks post-intervention.

No inflammation was observed at 2 weeks in all EACs which received BA powder. In some animals, remnant BA powder and EAC debris were present at 2 weeks and was easily removed.

4.4.3 Auditory brainstem response thresholds

ABR thresholds taken at baseline and 4 weeks post-intervention demonstrated significant differences in both control and experimental ears (Table 1). In the control ears, there were significant threshold differences at 8 kHz (mean ± SD, *p-value*; 11.93 ± 15.8 dB, $p = .018$) and 12 kHz (13.07 ± 18.8 dB, $p = .027$) (Figure 1A). In the experimental ears, significant threshold shifts were observed at 8 kHz (18.07 ± 19.3 dB, $p = .006$), 12 kHz (27.3 ± 16.3 dB, $p < .001$), 16 kHz (13.46 ± 17.2 dB, $p = .016$), and 20 kHz (20 ± 10.8 dB, $p < .001$) (Figure 1B).

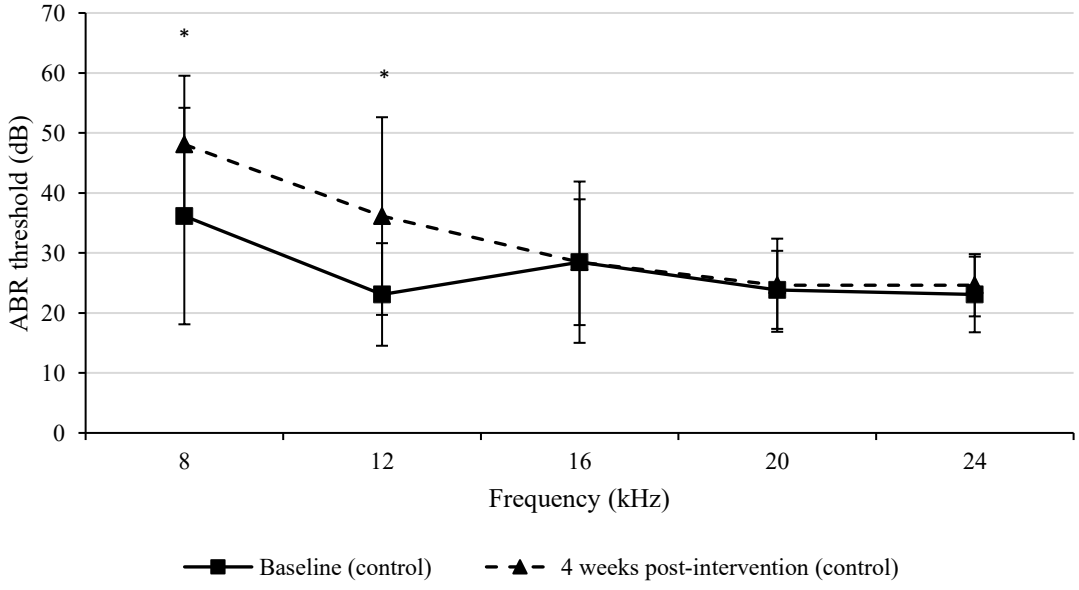
The difference in ABR thresholds between the control and experimental ears at 4 weeks post-intervention was also assessed (Figure 2). Results show significant differences in threshold at 12 kHz ($p = .002$), 16 kHz ($p = .013$), and 20 kHz ($p < .001$).

Table 4. Auditory brainstem response threshold differences from baseline to 4 weeks post-intervention in control and experimental ears

			95% CI		
Frequency	Mean	Standard deviation	Lower limit	Upper limit	*p-value*
Control ear					
8 kHz	11.923	15.750	2.405	21.441	.018*
12 kHz	13.077	18.768	1.735	24.418	.027*
16 kHz	0.000	16.457	-9.945	9.945	1.000
20 kHz	0.769	8.623	-4.442	5.980	.753
24 kHz	1.538	8.987	-3.892	6.969	.549
Experimental ear					
8 kHz	18.077	19.315	6.405	29.749	.006*
12 kHz	27.308	16.281	17.469	37.146	<.001**
16 kHz	13.462	17.246	3.040	23.883	.016*
20 kHz	20.000	10.801	13.473	26.527	<.001**
24 kHz	6.154	13.409	-1.949	14.257	.124

*$p < .05$. **$p < .001$.

A



B

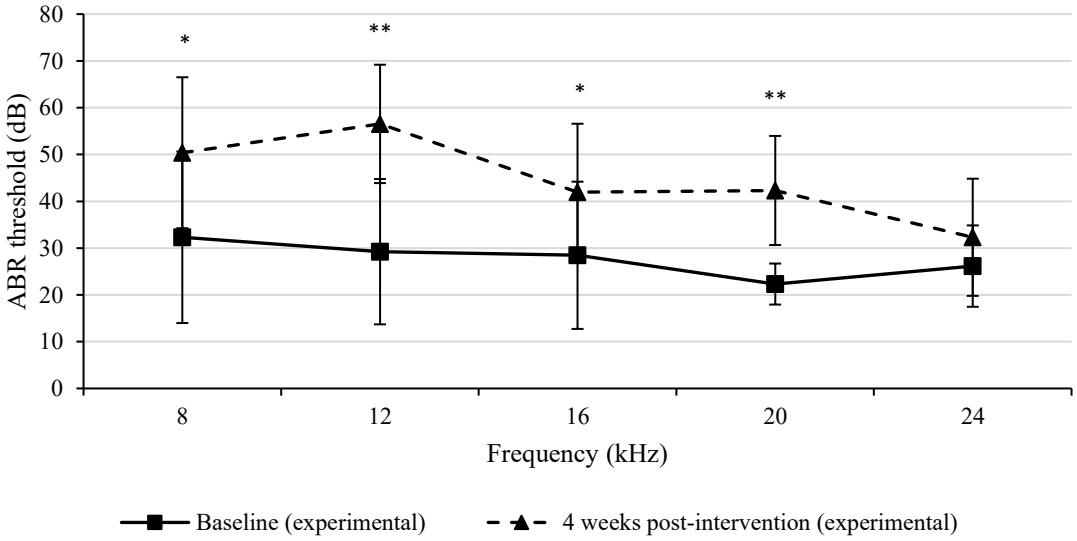


Figure 9. Auditory brainstem response thresholds in (A) control ears and (B) experimental ears at baseline and 4 weeks post-intervention.

*$p < .05$. **$p < .001$. Abbreviations: ABR, auditory brainstem response; dB, decibel; kHz, kilohertz.

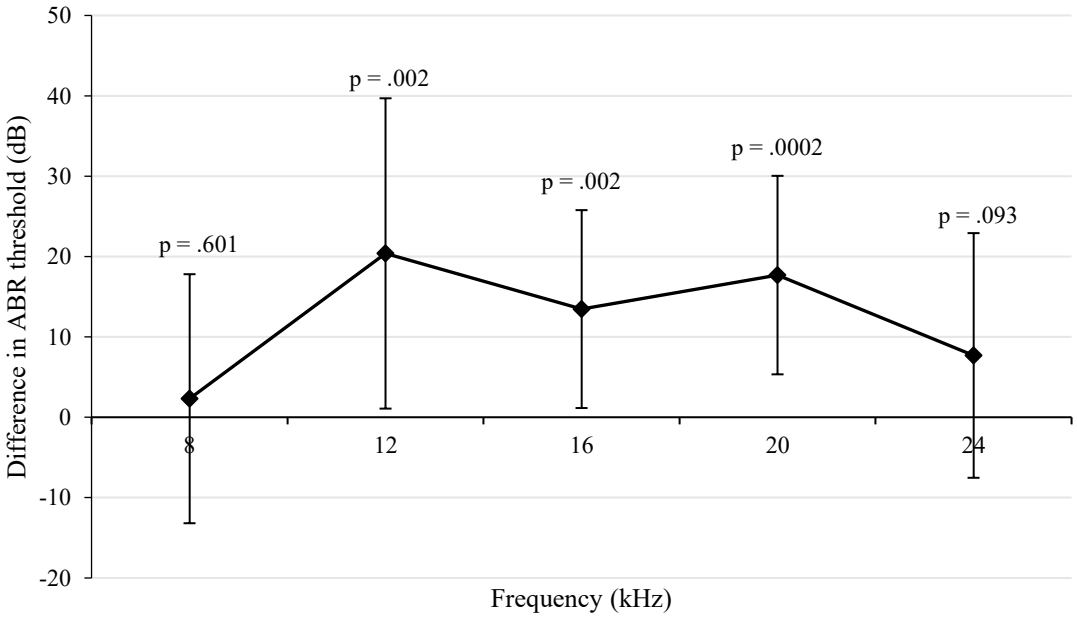


Figure 10. Differences in auditory brainstem response thresholds between control and experimental ears at 4 weeks post-intervention

Displayed above the entry points of each frequency is the corresponding *p-values*. Abbreviations: ABR, auditory brainstem response; dB, decibel; kHz, kilohertz.

4.4.4 Scanning electron microscopy

SEM analysis was performed on 8 cochleas, derived from 4 animals. Observations revealed signs of ototoxic damage specifically on the OHCs of the experimental ear (Figure 3). There was no evidence of ototoxic damage in the control cochleas.

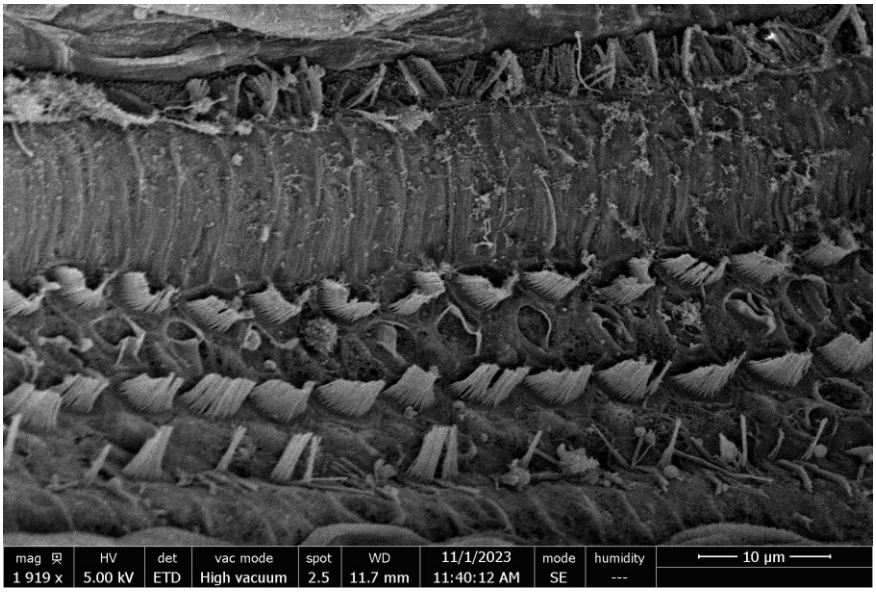


Figure 11. Scanning electron microscopy image of the cochlea which sustained damage to its outer hair cells due to the application of the study medication.

4.4.5 Histology

The ear canals of the randomly selected animals were dissected and analyzed for signs of inflammation. Sections were obtained from the inner osseous part of the EAC and one representative histological section was observed for each animal. The control EACs showed no signs of inflammation in the epithelium or subepithelial connective tissue and the underlying bone was normal. The experimental EACs showed an accumulation of talc crystals in the connective tissue. There was minimal to moderate chronic lymphocytic inflammation surrounding the talc crystals, along with calcification (Figure 4). However, no giant cell reaction, granuloma formation, or necrosis was observed.

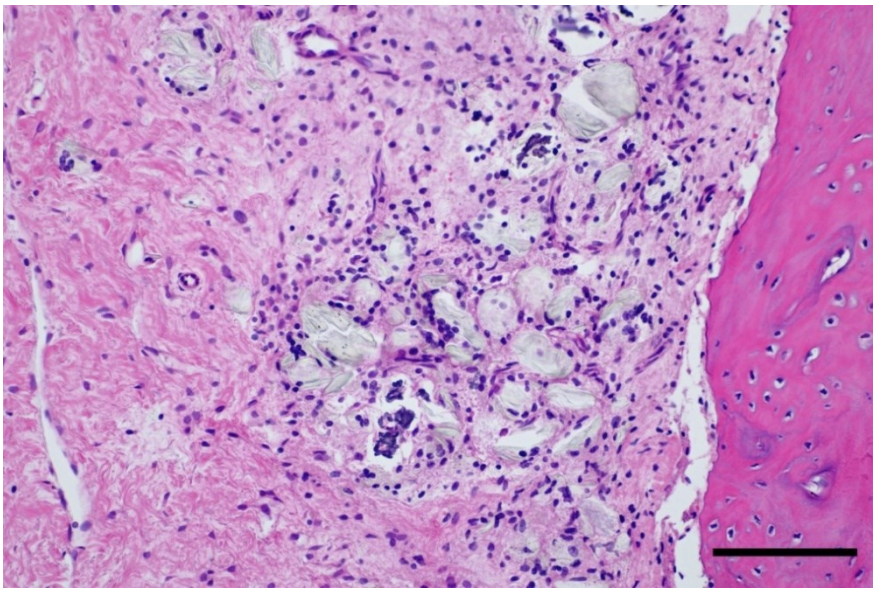


Figure 12. Histological slide of external auditory canal. Scale bar 100 µm (20x magnification)

4.5 Discussion

While ear drops are the most used topical medication to treat ear diseases, otolaryngologists have been using powders for many years to combat COM and manage postoperative chronically draining mastoid cavities.[10] The main advantages of powders over ear drops are their ability to coat and adhere to moist surfaces and granulation tissue, as well as their longer degradation time.

Powders are usually available as a combination of antibacterials, antifungals, and steroids, and are prepared in otic insufflators of various designs.[15] Many drug combinations have been developed at different institutions: a mixture of ciprofloxacin, clotrimazole, dexamethasone, and BA developed at the University of Texas, combination of chloromycetin, sulfanilamide, and fungizone used at the House Clinic, and two-component powder of BA and hydrocortisone used at Johns Hopkins.[5] Most powders are not readily available and need to be formulated by a pharmacist.

4.5.1 Ototoxicity

This study is the first to assess the ototoxicity potential of an antimicrobial powder composed of ciprofloxacin, TMP-SMX, and AmB for the treatment of COM in a validated animal

model. The ototoxic nature of the tested powder was demonstrated by significant threshold shifts in ABR evaluations 4 weeks post-application and OHC damage as shown on SEM imaging.

Ciprofloxacin has been well known for years as a gold standard in the treatment of COM, as it is non-ototoxic when applied either topically or systemically.[16-18] Based on our knowledge, other components of the tested powder have yet to be evaluated for topical ototoxicity. TMP-SMX is clinically used to treat a variety of bacterial infections, with over 90% of *S. aureus* strains, including methicillin-resistant pathogens, being susceptible to it.[19] Khanna et al[20] found that TMP-SMX was effective in treating 74.54% of COM cases. Additionally, it is FDA-approved for treating otitis media in the pediatric population.[21] However, we were unable to find studies that investigated the topical or systemic ototoxicity of Sulfatrim DS or its individual pharmacological components.

AmB is effective in treating severe, life-threatening fungal diseases,[22] with the *Candida* species remaining susceptible to this antifungal.[23] In one study, Sundar et al[24] investigated the intravenous application of AmB for the treatment of visceral leishmaniasis. Audiometric data from 147 patients demonstrated no threshold shifts due to ototoxicity. However, 3 cases of reversible ototoxicity due to AmB have been reported in the literature; 2 patients presented with visceral leishmaniasis and the other was diagnosed with disseminated histoplasmosis.[25-27] Both conventional and liposomal delivery of AmB caused unilateral or bilateral hearing loss to occur 5 to 10 days after the first infusion, but these all resolved with treatment discontinuation. The high affinity of AmB for cholesterol molecules found in mammalian cells puts patients who receive this antifungal at great risk of kidney, heart, and hematologic injuries, as well as nephrotoxicity.[28] The physiological, ultrastructural, and antigenic similarities between the kidney and inner ear are possible explanations for why both nephrotoxicity and ototoxicity can occur from a single agent.[29] Both systems rely on complex water and ionic processes to maintain homeostasis of ions and pH. One hypothesis states that transient hearing loss and subsequent kidney injury from the administration of AmB is due to a change in hemodynamics, although a clear explanation of the processes involved is lacking.[29]

The likelihood of developing ototoxicity in clinical settings is relatively low, and only a small percentage of otolaryngologists believe they witnessed irreversible inner ear damage from an ototopical medication.[30,31] Several anatomical structures also contribute to a decreased chance of developing ototoxicity; a considerably thicker round window membrane will make it less

permeable for the applied medication to reach the inner ear.[32,33] Additionally, the inflammatory process observed in COM cases causes the epithelium to thicken, therefore decreasing the medication's ability to infiltrate the round window membrane. However, clinicians should be wary of potential ototoxicity and if possible, avoid using ototoxic medication topically in patients with an exposed middle ear.

4.5.2 Ear canal inflammation

Extensive inflammation of the EAC was observed in the ears that received the medication 2 weeks post-application. The inflammation subdued at 4 weeks post-application and repeat ABR measurements were taken to ensure that the observed hearing loss had no conductive component.

The ear canal skin in guinea pigs is very thin and fragile, covered by a multilayered squamous epithelium rich in sebaceous glands and hair follicles.[34] In some animals, traumatic injuries, such as tearing and irritation, occurred during powder application due to the narrowness of the canal. This was supported by histological analysis of the EACs, where talcum crystals are vividly seen in soft tissue.

Talcum is used in the pharmaceutical industry to improve powder consistency and prevent clumping. It also absorbs moisture, which is desired in patients with chronically draining ears. The inflammatory properties of talcum are well-known.[35] Animal studies have demonstrated that the instillation of intrapleural talcum powder results in inflammation, edema, and fibrosis.[36,37] Additionally, talcum is used in pleurodesis procedures as an inflammatory agent to promote adhesions between visceral and costal pleura and prevent lung collapse.[38] Skin irritation has also been noted when AmB is topically applied,[39] although more research is needed to determine which medication component contributed to the irritation and inflammation observed in the animals' ear canals.

In our study, no inflammation was noted in the ears which received BA powder at any of the post-application checks performed. However, another animal study found mild inflammatory cells on histological slides 40 days after BA powder was put in the middle ear mucosa of rats, although this was in a non-significant number of animals.[13] A study by Dündar et al[40] reported three cases of external canal stenosis due to BA powder application, but 2 of the 3 patients had a

history of long-standing ear disease. Thus, it is unclear whether BA could potentially lead to local inflammation when applied topically.

4.5.3 Limitations

Due to our combined approach, we were unable to determine which pharmacological component contributed to the observed hearing loss. Future studies should be conducted to define the individual ototoxic potential of each tested powder component. Administering the medication was challenging due to the small size of the guinea pigs' ear canals. Using an animal model with a larger ear canal and middle ear could reduce inflammation from surgical delivery. Additionally, the powdered medication was only administered once, which does not reflect typical human treatment. Further studies with a longer follow-up time are necessary to accurately replicate standard care of COM in humans. Finally, an experimentally induced state of COM in an animal model could better duplicate the structural changes and inflammation that arises in the ear cavities.

4.6 Conclusion

The tested otic powder, a combination of ciprofloxacin, TMP-SMX, AmB, and talc, demonstrated signs of ototoxicity and transient inflammation when applied topically to the middle ear of guinea pigs. The topical application of talcum and traumatic insertion of the powder are hypothesized to have caused the inflammation observed in the ear canals and middle ears that received the medication. Further studies are needed to determine specifically which of the medical components are ototoxic and the concentrations at which they cause ototoxicity.

4.7 Acknowledgements

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Chapter 5: Conclusion

5.1 Overall discussion

Through a multi-faceted investigation, this present thesis assessed and enhanced the QoL of patients who have been fitted with a BAHI.

As stated in Chapter 1, individuals living with hearing loss face difficulties in communication, which can lead to obstacles in employment and social isolation from their friends and family.[4] In children, hearing loss has a detrimental effect on their language development and their learning abilities at school.[5] For some patients, one way to restore hearing is the placement of a BAHI, but there are disagreements regarding how to measure the success of this rehabilitative option. While some define a successful hearing aid fitting as improved audiological scores, others consider the usage of the device (i.e., the number of hours per day that the patient wears their BAHI) as a better parameter of success.[46,47] It has previously been observed that patients with CHL or MHL tend to wear their BAHI sound processor more frequently compared to patients with U-SNHL.[48] In fact, Hougaard et al[48] reported that CHL patients wore their BAHI on average for an additional 2 days per week compared to individuals with U-SNHL. Among the 13 U-SNHL patients included in that study, 7 used their hearing device for less than 4 hours per day. This finding is also evident in the pediatric population: Priwin et al[49] found that children with U-SNHL varied in their BAHI usage in the classroom, ranging from rarely to frequently, while their CHL peers always used it. However, the lower average usage time of their sound processor does not necessarily equate with U-SNHL patients' dissatisfaction towards their BAHI. While patients with U-SNHL tend to wear their bone conduction devices less compared to their peers with CHL, they still report and experience similar QoL benefits.[50] Therefore, an increased number of hours of BAHI usage may not necessarily be associated with better outcomes in hearing restoration.

Successful hearing rehabilitation is a complex process that cannot be attributed solely to one factor. While audiological scores are an important objective measure that can demonstrate improvements in hearing and speech perception, they are not reliable predictors of the success of a BAHI fitting, or of the patient's satisfaction with the device.[51] In fact, Dornhoffer et al[12] found

low to non-existent correlations between QoL measures and aided audiological tests, suggesting that simple audiologic tests cannot fully capture the complexity of the BAHI user's daily hearing experience. These findings suggest that disease-specific QoL measures provide a unique perspective in assessing the success of sound processor fittings. The results of Chapter 3, examining differences of QoL outcomes following BAHI fittings in patients with U-SNHL and CHL, revealed differences in disease-specific benefits between these 2 populations. This information should enable clinicians to provide better pre-operative counseling to potential BAHI users regarding the benefits they might expect from the sound processor in their daily lives. Specifically, the results revealed significant differences in QoL outcomes, with the CHL population reporting greater benefits in situations with competing noise sources, perceived clarity of sounds, and overall general and psychosocial health following BAHI fitting compared to the U-SNHL population. A sensitivity analysis showed that the BN subscale from the APHAB measure, as well as the "Speech" and "Spatial" subscales from the SSQ, became statistically significant, while the “Qualities” subscale was no longer significant. Additionally, a correlation analysis examining the relationship between post-BAHI fitting QoL scores and follow-up time revealed only one significant association: the AV subscale from the APHAB measure showed a fairly negative correlation with follow-up time in U-SNHL patients. Previous research has found that patient satisfaction towards the BAHI was dependent on appropriate counseling regarding the hearing benefits prior to abutment implantation.[52] With the new knowledge of hearing loss-specific differences identified in Chapter 3, clinicians will be better equipped to provide appropriate counseling and to establish realistic expectations regarding the sound processor's performance, thereby enhancing the patient's experience and satisfaction.

A subgroup of BAHI patients may also present with COM and persistent otorrhea. The placement of a BAHI not only addresses the hearing loss often associated with COM, but it also helps to resolve chronic otorrhea and reduce skin irritation.[53] There are two scenarios that indicate the need for a BAHI in patients with COM: (1) patients who are experiencing hearing loss as a result of COM and are unable to use conventional air conduction hearing aids due to the presence of fluid in the ear, or (2) patients who were previous hearing aid users who developed COM and require a new hearing device that will not be affected by the presence of fluid in the ear.[54] Patients with COM often report lower general and disease-specific QoL scores, in part due to physical

symptoms such as ear fullness, pain, headaches, and tinnitus.[20,55] Several QoL scales have been used to assess the outcomes of these patients, including the Chronic Otitis Media Outcome Test 15 (COMOT-5) and the Chronic Ear Survey (CES).[56,57] The Otitis Media-6 (OM-6) and its expanded version, the Otitis Media Outcome-22 (OMO-22), are validated disease-specific measures completed by the caregiver of the child to evaluate the post-intervention QoL in the pediatric population.[21,58] More effective treatments are necessary to relieve the physical symptoms of COM and to allow patients to promptly resume their normal day-to-day activities. Current options include aural toileting, topical and/or systemic antibiotics, and surgical intervention.[59,60] Given the increase in antibacterial resistance, the development of more effective treatments would avoid the prolonged use of medication.

The topical application of broad-spectrum antimicrobial treatments allows physicians to target various microbial organisms that may be responsible for COM. In addition to reducing the risk of off-target side effects, existing literature indicated that topical treatments are more effective than systemic application in resolving COM cases.[61,62] Topical treatments can be administered by means of ear drops or by a powdered substance, with the latter being capable of eliminating moisture from the ear canal and delivering a higher concentration of antimicrobials.[63] However, there are concerns regarding the otologic safety of topically applied medication, as certain antibacterial and antifungal medications can cause hearing loss.[54] When medication is delivered directly to the middle ear space, it can permeate the oval window and enter the inner ear, potentially leading to the destruction of OHCs and subsequent hearing loss. Therefore, it is crucial to test the ototoxicity of medications prior to administering them. In Chapter 4, the ototoxicity potential of a novel powder, composed of both antibacterial and antifungal components, was evaluated in a validated animal model. Its safety was assessed through ABR testing, SEM imaging of the OHCs, and histopathological evaluation of the EAC. The results demonstrated that the powder exhibited ototoxic properties, as indicated by significant threshold changes at 4 weeks post-application, as well as observable damage to the OHCs. Due to the combined nature of the approach used, it was not possible to identify the specific pharmacological component(s) responsible for the observed hearing loss in the animals.

5.2 Future directions

The first manuscript presented in this thesis provided a systematic review of how patients with BAHIs benefit from their hearing device in different listening environments, taking into account different types of hearing losses. It is important to translate the findings of this research into clinical practice and determine whether personalized pre-operative counseling can lead to greater patient satisfaction. Moreover, the development of a scale that not only assesses patient satisfaction with the BAHI and its performance in daily situations, but also evaluates the physical symptoms associated with the device and abutment, could provide a more complete QoL evaluation. The administration of this scale, combined with audiological test results and data on daily wear time, would allow for a more comprehensive assessment of the success of the BAHI fitting. Additionally, further subgroup analyses are needed to better understand (a) the complexities associated with the laterality and degree of hearing loss, and (b) how these factors may impact the QoL benefits of BAHI patients. This future research could allow clinicians to identify which patients may derive the most benefits and satisfaction from a BAHI. Lastly, additional studies are necessary to examine the QoL outcomes in pediatric populations.

The second manuscript of this thesis evaluated the safety of a novel powder for treating patients with COM and chronic otorrhea. However, this study only used a single application of the medication, which does not accurately reflect the typical treatment experience of COM patients. Usually, patients will undergo multiple applications of a prescribed antimicrobial substance over a period of several weeks. Furthermore, there is a need to improve the animal model used in this study to better mimic the conditions of human ear infections that are observed in clinical settings. Although a myringotomy was performed in the animal model to replicate the damaged tympanic membrane seen in COM patients, a more accurate representation of COM would involve creating a moist ear environment and introducing the most common bacteria and fungi that may cause the condition. By using this experimentally induced model of COM, the effectiveness of the powder could be better evaluated. Lastly, due to the combined approach taken in this project, it was not possible to identify which component of the medication caused ototoxicity. Therefore, future research should assess the safety of all the components of the proposed powder to determine each of their potentials for causing ototoxicity.

5.3 Overall conclusion

This thesis presents a comprehensive exploration that highlights the multi-faceted nature of hearing rehabilitation for patients fitted with BAHIs and its direct impact on their QoL. By systematically reviewing if patients derive varying QoL benefits from their BAHI depending on their type of hearing loss, Chapter 3 showed that CHL patients generally experienced greater benefits compared to patients with U-SNHL. Identifying these significant differences should allow clinicians to offer more effective counselling and expectation management to future BAHI patients, ultimately leading to greater satisfaction and success with their BAHI.

Chapter 4 described a safety evaluation of a novel powder in an animal model for the treatment of COM. Although the tested powder did demonstrate ototoxicity, this finding will inform future research investigating the otic safety of topically applied COM treatments.

Overall, this thesis underscores the importance of holistic assessments for BAHI patients and the provision of personalized care to optimize their QoL.

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