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Clinical practice guidelines for the diagnosis and management of acute sensorineural hearing loss

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ABSTRACT

Objective: Acute sensorineural hearing loss represents a spectrum of conditions characterized by sudden onset hearing loss. The "Clinical Practice Guidelines for the Diagnosis and Management of Acute Sensorineural Hearing Loss" were issued as the first clinical practice guidelines in Japan outlining the standard diagnosis and treatment. The purpose of this article is to strengthen the guidelines by adding the scientific evidence including a systematic review of the latest publications, and to widely introduce the current treatment options based on the scientific evidence.

Methods: The clinical practice guidelines were completed by 1) retrospective data analysis (using nationwide survey data), 2) systematic literature review, and 3) selected clinical questions (CQs). Additional systematic review of each disease was performed to strengthen the scientific evidence of the diagnosis and treatment in the guidelines.

Results: Based on the nationwide survey results and the systematic literature review summary, the standard diagnosis flowchart and treatment options, including the CQs and recommendations, were determined.

Conclusion: The guidelines present a summary of the standard approaches for the diagnosis and treatment of acute sensorineural hearing loss. We hope that these guidelines will be used in medical practice and that they will initiate further research.

1. Introduction

Acute sensorineural hearing loss represents a spectrum of conditions characterized by the sudden onset of hearing impairment. The etiologies encompass a range of diseases, from idiopathic conditions such as sudden deafness and low-tone sensorineural hearing loss to those caused by external factors such as acoustic trauma or viral infections like mumps-associated hearing loss. Despite extensive research, many of these conditions lack definitive treatments, emphasizing the need for ongoing research and development of diagnostic and therapeutic modalities.

The "*Clinical Practice Guidelines for the Diagnosis and Management of Acute Sensorineural Hearing Loss*" provide the first set of clinical practice guidelines in Japan to outline the standard practice with regard to the diagnosis and treatment of acute sensorineural hearing loss [1].

The clinical practice guidelines were developed by the members of the Research Group of the Ministry of Health, Labour and Welfare (MHLW) Japan for Intractable Hearing Disorders. Retrospective data analysis was performed using large-scale nationwide survey data, which included 3419 cases of idiopathic sudden sensorineural hearing loss (iSSNHL), 1305 cases of acute low-tone sensorineural hearing loss (ALHL), 497 cases of perilymphatic fistula (PLF), 67 cases of mumps-associated hearing loss, and 54 cases of acoustic trauma, collected between 2014 and 2016. The findings of the data analysis were published as a special issue of Acta Oto-Laryngologica "Acute sensorineural

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hearing loss" [2-11]. The systematic review was performed by a systematic literature search using the PubMed database in January 2017, with all English-language publications containing a description of treatment outcomes selected. After initial selection by abstract, a comprehensive assessment was performed for the selected papers and a summary was prepared. The article selection process for each disorder is shown in Supplemental Table 1.

Based on the nationwide survey results and the summary of the systematic literature review, the recommendation grades for the diagnosis and treatment of each disorder were determined. The guidelines were approved by the Japan Audiology Society and the Japanese Society of Otorhinolaryngology-Head and Neck Surgery. These guidelines, primarily developed for otolaryngologists, aim to consolidate the current knowledge on the diagnosis and treatment of acute sensorineural hearing loss. While tailored for specialists, the content has also been structured to be accessible to general physicians. The overarching goal is to foster a healthcare environment in which patients afflicted with these conditions can obtain optimal medical care.

In this article, an additional systematic review was performed using the PubMed database for articles from 2017 to December 2023 in the same manner as described above (Supplemental Table 2), and the latest diagnostic criteria and treatment recommendations for five representative disorders (iSSNHL, ALHL, PLF, mumps-associated hearing loss and acoustic trauma) related to acute sensorineural hearing loss were summarized. The Clinical Questions (CQs) within each respective disease were also described.

The guidelines were developed with the support of the Health and Labour Sciences Research Grant for Research on Rare and Intractable Diseases from the MHLW of Japan.

2. Criteria for determining evidence level and recommendation grades

The diagnostic and treatment guidelines used in this article employ evidence levels and recommendation grades based on the "Minds Clinical Guideline Creation Manual 2007." For iSSNHL, there is a significant number of publications, some of which are high-level evidence with double-blind trials or systematic reviews. However, for conditions such as ALHL, PLF, acoustic trauma, and mumps-associated hearing loss, there is a scarcity of reports based on high-level evidence. Despite the availability of reports with only low-level evidence, some treatments were recommended considering the current treatment status as clarified from the nationwide survey results. It is hoped that with the advancement of epidemiological studies, the availability of reports with higher levels of evidence will increase in the future.

Classification of evidence level is as follows:

- Level I is based on systematic reviews or meta-analyses of RCTs.
- Level II is derived from one or more randomized comparative trials.
- Level III comes from non-randomized comparative trials.
- Level IVa is from analytical epidemiological studies (cohort studies).
- Level IVb is from other analytical epidemiological studies (case-control studies, cross-sectional studies).
- Level V is descriptive research (case reports or case series).
- Level VI is based on opinions not derived from patient data, such as expert committees or individual experts.

Recommendation grades are as follows:

- Grade A has strong scientific evidence and is highly recommended.
- Grade B has scientific evidence and is recommended.
- Grade C1 lacks scientific evidence but is still recommended.
- Grade C2 lacks scientific evidence and is not recommended.
- Grade D has evidence of ineffectiveness or harm and is not recommended.

3. Diagnosis and management of each disease

One of the novel features of the *Japanese Guidelines for Acute Sensorineural Hearing Loss* is that they distinguish between iSSNHL, ALHL and PLF as distinct disorders (Fig. 1A, B). As described in each disease section, iSSNHL and ALHL have different epidemiological and clinical characteristics based on our nationwide survey results. iSSNHL is mainly observed in patients aged 50–60 years without gender bias (Fig. 2A), whereas ALHL is prevalent among female patients aged 30–40 years (Fig. 2B) [8]. The type of audiogram and prognosis for iSSNHL and ALHL also differ (Fig. 3, 4) [3,7-8]. Based on these data, the diagnostic flow chart (shown in Fig. 1) first divides acute sensorineural hearing loss patients into 2 groups by audiometric configuration (Fig. 1A and 1B).

With regard to PLF, it has been difficult to distinguish this condition from iSSNHL, particularly in cases without any antecedent event. Traditionally, a definitive diagnosis of PLF was based on the observation of perilymph or cerebrospinal fluid leakage or the identification of a fistula during endoscopic examination or surgery. However, this confirmation is invasive and difficult to perform in cases without any antecedent event [11]. Recently, a diagnostic method based on the detection the perilymph-specific Cochlin-tomoprotein (CTP) has been developed and applied in clinical settings [11]. This diagnostic method has been covered by social health insurance in Japan since July 2022, and has made it easier to distinguish PLF from iSSNHL.

3.1. Idiopathic sudden sensorineural hearing loss

Diagnostic criteria, epidemiology and clinical characteristics: Idiopathic sudden sensorineural hearing loss (iSSNHL) is one of the most common causes of acute sensorineural hearing loss, particularly unilateral severe-to-profound sensorineural hearing loss [2]. The diagnostic criteria for sudden hearing loss were first developed in 1973 by the Ministry of Health and Welfare's Research Group on Specific Diseases and revised in 2015 by the MHLW Research Group on Intractable Hearing Disorders to be consistent with diagnostic criteria used in other countries (Table 1). The new criteria were added to the criteria for hearing loss; i.e., hearing loss of 30 dB or more at each of three contiguous test frequencies in a pure-tone audiogram within 72 h. In addition, as these criteria at hearing levels and frequencies alone often overlap with acute low-frequency sensorineural hearing loss, an item was added to exclude cases that fulfill the diagnostic criteria for ALHL. The Research Group for Specific Diseases also proposed a classification of severity of iSSNHL and criteria for the recovery of hearing (Tables 2 and 3), which are commonly referred to when diagnosing and treating patients with iSSNHL.

A nationwide epidemiological survey of iSSNHL has been conducted almost every 10 years since the early 1970s by the Research and Study Group of the MHLW in Japan. A survey conducted in 2001 by the Ministry of Health and Welfare's "Research Group on Acute Severe Hearing Loss" estimated that there are 35,000 new cases per year in Japan (27.5 per 100,000 people annually) [12]. A 2012 survey conducted in Iwate, Aichi, and Ehime prefectures estimated 60.9 cases per 100,000 people annually [13]. In a nationwide survey performed from 2014 to 2016, we collected detailed clinical information for 3419 iSSNHL patients. In terms of age of onset, iSSNHL is mainly observed in patients aged 50–60 years without any clear gender bias (Fig. 2A) [8].

The main symptom is abrupt hearing loss, often noticed upon waking, with some patients experiencing tinnitus or ear fullness. The averaged pre- and post-treatment audiograms for the 3316 iSSNHL cases are shown in Fig. 3A [8].

In recent years, there have been several reports on the use of MRI findings in the diagnosis of sudden hearing loss, including the AAO-HNS guideline update 2019, which includes "MRI abnormality directly related to SSNHL" in the MRI findings section and mentions both "labyrinthine hemorrhage" and "cochlear inflammation" [14]. Labyrinthine hemorrhage is listed as a poor prognostic finding, although it is infrequent.

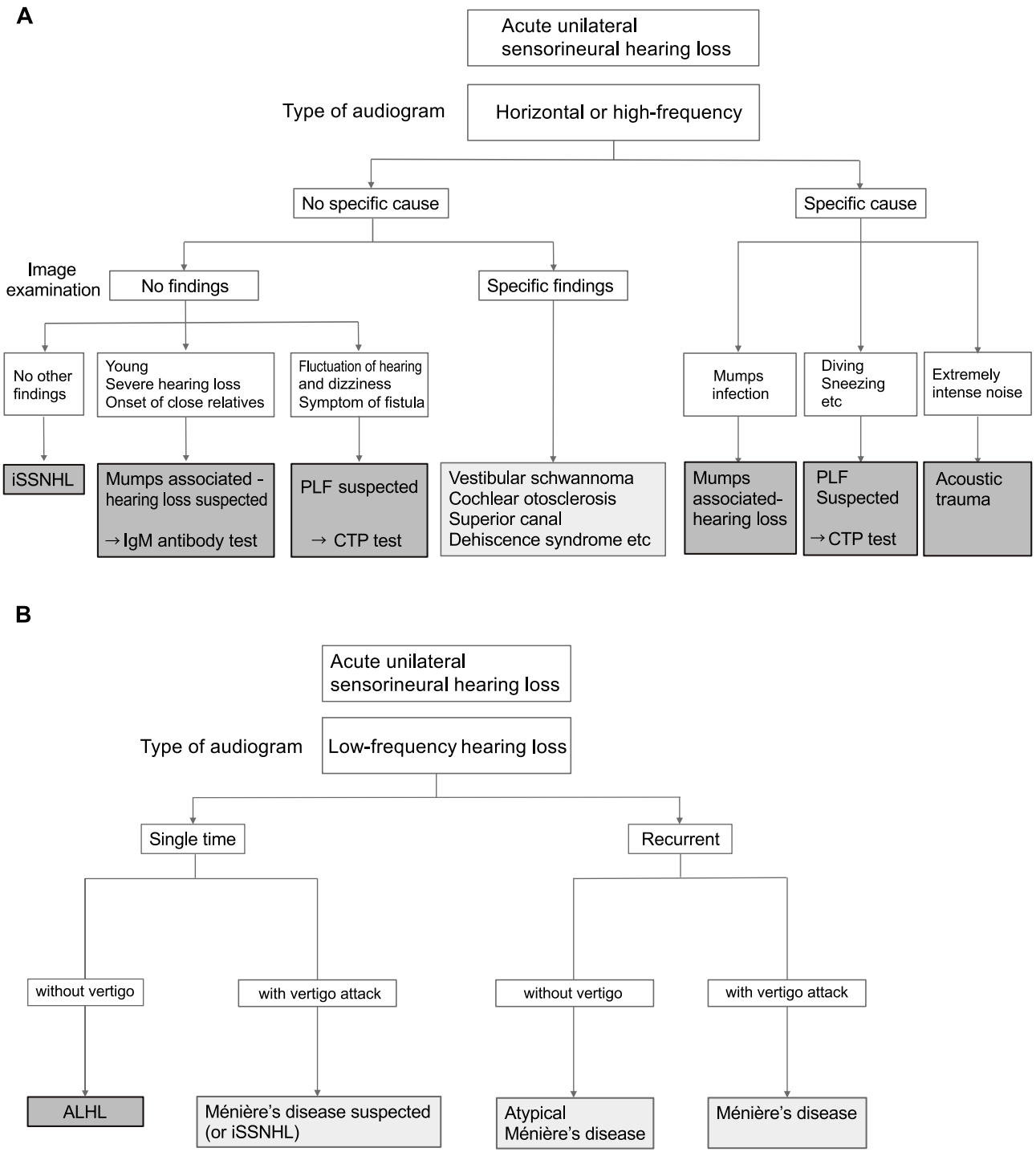

Fig. 1. A diagnostic flowchart for each disease covered in the guidelines. As the first step in the diagnosis, patients are divided according to their audiogram type. (A) Diagnostic flowchart for horizontal or high-frequency hearing loss. (B) Diagnostic flowchart for low-frequency hearing loss.

Treatment: iSSNHL is treated with corticosteroids and other medications during the acute phase of the disease. In an epidemiological survey conducted by the "Research Group on Intractable Hearing Disorders," corticosteroids were administered in more than 80 % of cases [3,15], Although scientific evidence remains limited, this is practically used as the standard treatment. The prognosis for SSHL is generally unfavorable. Despite standard treatments, only about one-third of patients fully recover, one-third achieve partial recovery, and one-third see no change (Fig. 4A) [3,15]. Once hearing stabilizes, further improvement is rare. Recurrence is uncommon, so reoccurring hearing loss may indicate other conditions such as Meniere's disease.

A treatment algorithm for sudden hearing loss has been reported based on the results of epidemiological studies in Japan [15]. The treatment algorithm is also published in the AAO-HNS guideline update [14].

CQ 1: Is the systemic administration of corticosteroids effective for iSSNHL?

Answer: While there is no clear evidence, systemic corticosteroids administration is suggested as one of the treatment options. (Evidence Level: I, Recommendation Grade: C1)

Comments: Systemic corticosteroids administration for sudden sensorineural hearing loss is widely used globally. In the above-

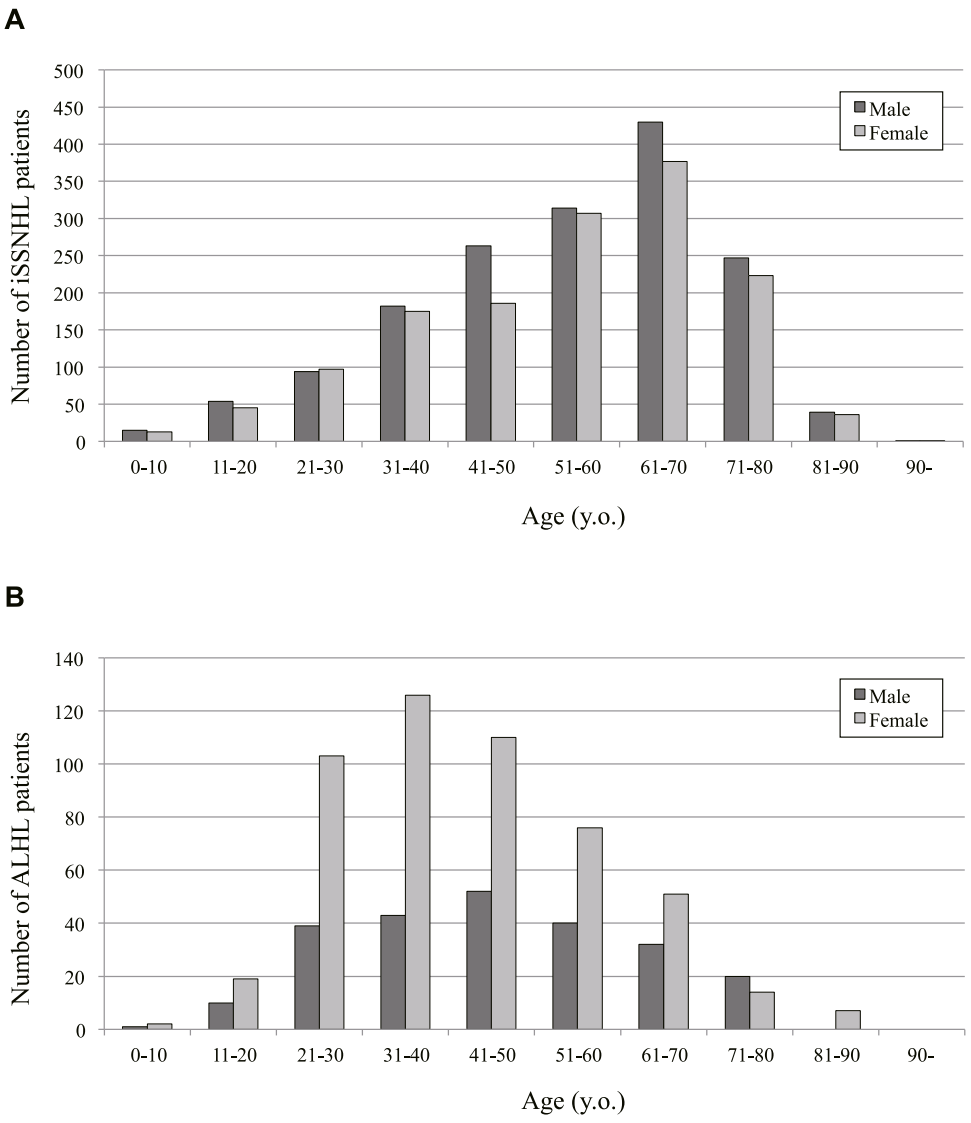

Fig. 2. Distribution of the incidence age of iSSNHL and ALHL in males and females from an epidemiological survey conducted from 2014 to 2016 by the "Research Group on Intractable Hearing Disorders." [8] (A) SSNHL patients. (B) ALHL patients.

mentioned epidemiological survey, systemic corticosteroids administration was performed in over 80 % of cases [3,15]. Numerous RCTs have been conducted on the efficacy of systemic corticosteroids administration, but evaluations vary. Moreover, in a meta-analysis, none of the RCTs could conclusively prove the efficacy of systemic corticosteroids due to significant biases and small sample sizes. Therefore, we concluded a recommendation of “Option” (Grade C1) in the Japanese guidelines. In the AAO-HNS guidelines, systemic corticosteroids administration is also positioned as an "Option" [14,16].

CQ 2: Is hyperbaric oxygen therapy (HBOT) effective for iSSNHL?

Answer:

1. If HBOT is administrated within 2 weeks of onset, it is believed to significantly improve hearing, but its clinical significance remains unclear. It is suggested as one of the treatment options. (Evidence Level: I, Recommendation Grade: C1)
2. There is no effect on hearing or tinnitus after symptom stabilization, so HBOT is not recommended after the acute phase. (Evidence Level: I, Recommendation Grade: C2)

Comments: In a meta-analysis, it was suggested that if administered within 2 weeks of onset, HBOT significantly improves hearing. However, due to the limited number of RCTs and the low quality of the study designs, caution is needed in interpreting these results. In the AAO-HNS guidelines, HBOT as an initial treatment is positioned as an "Option"[16]. There is no effect on hearing or tinnitus after symptom stabilization, so its use is preferable in the acute phase.

The AAO-HNS guideline update does not change the fact that HBOT is an “Option” for both initial and salvage treatment, but they both state "in combination with corticosteroids therapy" and recommend salvage treatment within 1 month of onset [14].

CQ 3: What is the timing and efficacy of intratympanic steroid injection (ITS) therapy?

Answer:

1. ITS as an initial treatment has an effect equivalent to or greater than systemic corticosteroids administration. Therefore, it is suggested as one of the treatment options. (Evidence Level: I, Recommendation Grade: C1)
2. While combining ITS with systemic corticosteroids administration as an initial treatment is believed to have no additive effect, no clear

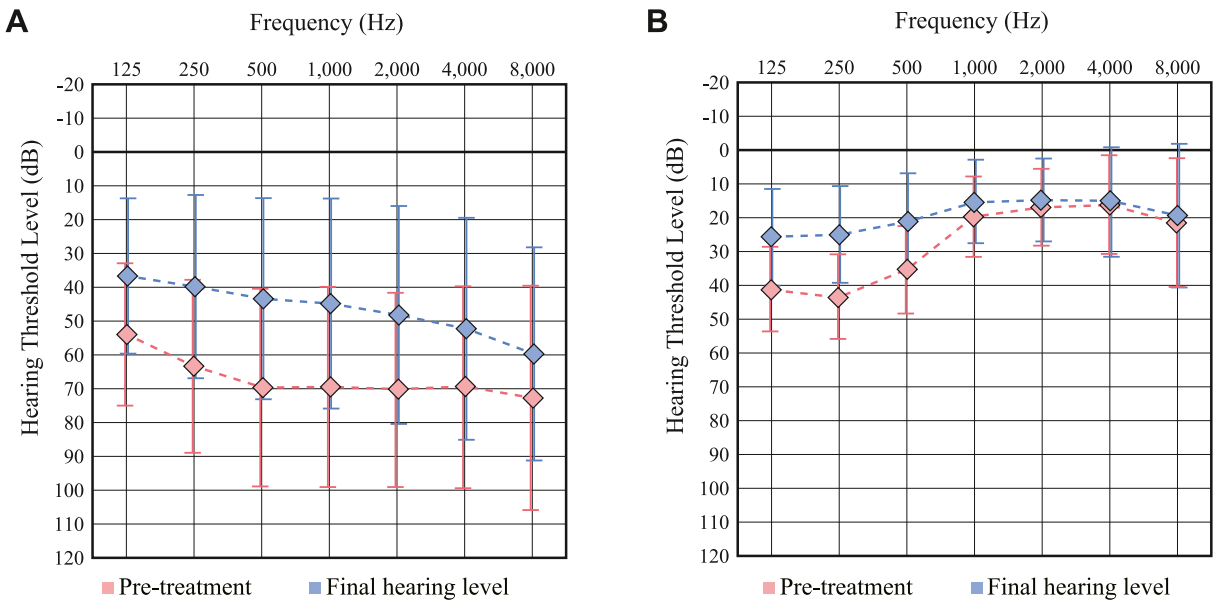

Fig. 3. The average initial and final pure-tone audiograms from an epidemiological survey conducted from 2014 to 2016 by the "Research Group on Intractable Hearing Disorders." [8] (A) SSNHL patients. (B) ALHL patients. Initial average pure-tone audiogram: pink; final average pure-tone audiogram: pale blue. The error bars in the figure represent the standard deviations for each frequency.

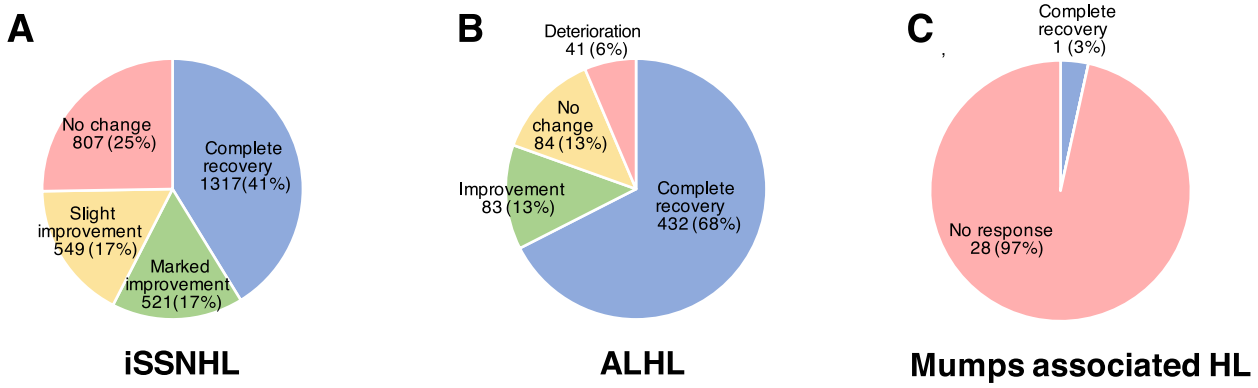

Fig. 4. The prognoses for standard treatment for (A) iSSNHL, (B) ALHL and (C) Mumps-associated hearing loss based on the hearing improvement criteria for each disease (shown in Table 3, Table 6 and Table 10, respectively). All data were obtained from our previous report on the epidemiological survey conducted from 2014 to 2016 by the "Research Group on Intractable Hearing Disorders" [3,8,9].

Table 1
Diagnostic criteria for iSSNHL in Japan (Intractable Hearing Loss Research Committee of the Ministry of Health and Welfare, revised 2015).

Main symptoms
• Sudden onset
• Sensorineural hearing loss, usually severe, of unknown etiology
For reference
• Hearing loss (i.e., hearing loss of 30 dB or more over three consecutive frequencies)
• Sudden onset of hearing loss, but may progressively deteriorate over 72 h. No history of recurrent episodes
• Unilateral hearing loss, but may be bilateral at the onset
• May be accompanied by tinnitus
• May be accompanied by vertigo, nausea, and/or vomiting, without recurrent episodes
• No cranial nerve symptoms other than from cranial nerve VIII

Definite diagnosis; all of the above main symptoms are present.

evidence has been obtained. It is suggested as one of the treatment options. (Evidence Level: I, Recommendation Grade: C1)

3. ITS as salvage therapy after systemic corticosteroids administration significantly improves hearing. Although its clinical significance is not definitively proven yet, its implementation is recommended. (Evidence Level: I, Recommendation Grade: B)

Comments: ITS is used as an initial or salvage treatment after the administration of systemic corticosteroids. When used initially, ITS can be used alone or in combination with systemic corticosteroids. As an initial treatment, many reports indicate that ITS alone and in combination with systemic corticosteroids administration are equally effective. Recent meta-analyses have shown the benefit of the combined use

Table 2
Criteria for the grading of hearing loss in iSSNHL (Intractable Hearing Loss Research Committee of the Ministry of Health and Welfare, revised 2015).

Grade	Criteria
1	PTA <40 dB
2	40 dB ≦ PTA <60dB
3	60 dB ≦ PTA <90dB
4	90 dB ≦ PTA

PTA: arithmetic mean of the hearing levels at five frequencies (250, 500, 1000, 2000, and 4000 Hz).

Table 3
Hearing improvement criteria for iSSHNL as defined by the Ministry of Health and Welfare in Japan (Intractable Hearing Loss Research Committee of the Ministry of Health and Welfare, revised 2015).

Hearing improvement status	Criteria
Complete recovery	All five frequencies in the final audiograms are 20 dB or less, or improvement to the same degree of hearing in the unaffected side
Marked improvement	PTA improvement ≧ 30 dB
Slight improvement	10 dB ≦ PTA improvement <30 dB
No change	PTA improvement <10 dB

PTA: arithmetic mean of the hearing levels at five frequencies (250, 500, 1000, 2000, and 4000 Hz).

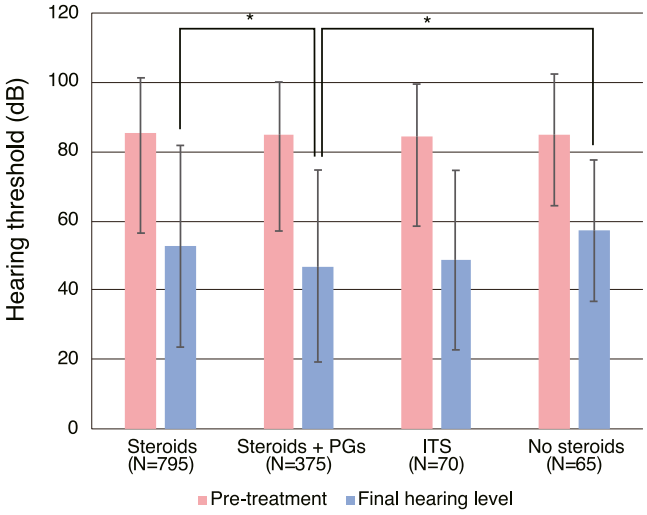

Fig. 5. Initial and final hearing thresholds after treatment for severe-to-profound iSSNHL including systemic corticosteroids administration, systemic corticosteroids with PGE1 administration and ITS compared with untreated patients. The error bars in the figure represent the relevant standard deviations. These data were obtained from our previous report on an epidemiological survey conducted from 2014 to 2016 by the "Research Group on Intractable Hearing Disorders" [6].

of ITS and systemic corticosteroids administration over systemic corticosteroids administration alone [17-19]. Tympanic membrane perforation occurs in 1–10 % of ITS cases. For patients concerned about the side effects of systemic corticosteroids, such as in those with diabetes or pregnant women, ITS is recommended as an initial option. As a salvage therapy, ITS is the most effective treatment and is recommended for initiation within 20 days of onset, although the average hearing improvement in such cases is limited.

CQ 4: Is prostaglandin E1 (PGE1) effective for iSSNHL?

Answer: While there is no clear evidence, the combined use of systemic corticosteroids and PGE1 may be effective as an initial treatment in severe-to-profound cases. It is suggested as one of the treatment options. (Evidence Level: I, Recommendation Grade: C1)

Comments: PGE1, an arachidonic acid metabolite with vasodilatory effects, has been used to improve inner ear blood circulation in iSSNHL, but its effectiveness remains controversial. A 2003 study by the MHLW research group found no significant difference in outcomes for PGE1 treatment alone compared to those for other drugs. A meta-analysis also failed to prove its efficacy. However, a study by Ogawa et al., found that adding PGE1 to corticosteroids administration improved high-frequency hearing and reduced tinnitus [20]. The results of a survey undertaken from 2014 to 2016 also supported the notion that combining corticosteroids with PGE1 in severe-to-profound cases led to better hearing outcomes (Fig. 5) [6]. If ischemia is a factor in iSSNHL, PGE1 might be beneficial, particularly for cases of severe-to-profound hearing loss.

3.2. Acute low-tone sensorineural hearing loss

Diagnostic criteria, epidemiology and clinical characteristics: Acute low-tone sensorineural hearing loss (ALHL) is a medical condition characterized by the sudden or abrupt onset of cochlear symptoms, such as ear fullness, tinnitus, and hearing loss. Hearing loss is often unilateral, but bilateral hearing loss is also present in 6.8 % of cases [7]. This impairment is specifically limited to low-frequency sensorineural hearing loss. A typical audiogram is shown in Fig. 3B [8]. In many cases, the exact cause of this hearing loss remains uncertain or unknown. However, recent studies have highlighted the involvement of endolymphatic hydrops as a potential underlying pathology [21,22]. It is difficult to distinguish the early stages of Meniere's disease from acute low-tone sensorineural hearing loss, and some cases of acute low-tone sensorineural hearing loss may progress to Meniere's disease, suggesting the involvement of similar etiology.

According to a 2005 epidemiological study by the MHLW Research Group on Acute Severe Hearing Loss, the incidence of ALHL is 40 to 60 cases per 100,000 people annually, which is the highest incidence among diseases known to cause acute sensorineural hearing loss. Compared to iSSNHL, the incidence of ALHL is higher among young people, with the highest incidence among those in their 30 s (Fig. 2B) [8]. The number of female patients is two to three times higher than that of males [8].

Following the draft of the diagnostic criteria developed in 2000, the current diagnostic criteria were revised in 2015. The current diagnostic criteria were again partially modified in 2017 (Table 4). As part of the 2015 revision of the diagnostic criteria for ALHL, a new severity classification was also established (Table 5). The criteria for hearing improvement are based on the 2000 draft criteria (Table 6).

Treatment: The primary treatment approach for ALHL focuses on addressing the presumed endolymphatic hydrops. Osmotic diuretics are commonly administered with this intent, although evidence for their efficacy has not been established (Grade C1). Additionally, corticosteroids are often prescribed, drawing parallels to the treatment regimen for sudden sensorineural hearing loss (Grade C1). Patients who respond positively to the acute-phase drug therapy and demonstrate early hearing improvement generally have a favorable prognosis (Fig. 3B). An epidemiological survey conducted from 2014 to 2016 by the "Research Group on Intractable Hearing Disorders" found that 67.5 % of cases resulted in complete recovery, with 12.9 % showing significant improvement in hearing (Fig. 4B) [7]. Overall, the prognosis for ALHL is considered to be good. However, due to the potential for recurrent symptoms and progressive deterioration of hearing, continuous monitoring and follow-up are essential. Several retrospective studies and meta-analyses on the efficacy of corticosteroids and diuretics were found in the review of literature from 2017 to 2023. As a result, corticosteroids and diuretics are regarded as equally effective as options, and combination therapy of corticosteroids and diuretics doesn't have any additional effectiveness. [23-25].

Table 4
Diagnostic criteria for acute low-tone sensorineural hearing loss in Japan (Intractable Hearing Loss Research Committee of the Ministry of Health and Welfare, revised 2017).

Main symptoms
1. Acute or sudden onset of cochlear symptoms including ear fullness, tinnitus, and hearing loss
2. Low-tone hearing loss
3. Without vertigo
4. Unknown cause
For reference
1. Audiometric criteria of low-tone hearing loss.
(1) The sum of hearing levels at low frequencies of 0.125, 0.25, and 0.5 kHz is 70 dB or more.
(2) The sum of hearing levels at high frequencies of 2, 4, and 8 kHz is 60 dB or less.
2. Cochlear symptoms may be recurrent.
3. May progress to Meniere's disease.
4. May be accompanied with light dizzy sensation.
5. May be bilateral.
Definite: All of the main symptoms. Audiometric criteria (1) and (2).
Probable: All of the main symptoms. Audiometric criteria (1) and the same hearing levels at high frequencies of 2, 4, and 8 kHz as the contralateral ear.

Table 5
Criteria for the severity of hearing loss in ALHL (Intractable Hearing Loss Research Committee of the Ministry of Health and Welfare, revised 2015).

Grade	Criteria
1	The sum of hearing levels at 3 low-tone frequencies <100 dB
2	100 dB ≦ The sum of hearing levels at 3 low-tone frequencies <130 dB
3	130 dB ≦ The sum of hearing levels at 3 low-tone frequencies <160 dB
4	The sum of hearing levels at 3 low-tone frequencies ≧160 dB

Table 6
Hearing improvement criteria for ALHL (Intractable Hearing Loss Research Comittee of the Ministry of Health and Welfare, revised 2015).

Evaluation	Criteria
Complete recovery	All 3 low-tone frequencies of final audiograms are 20 dB or less, or improvement to the same degree of hearing in the unaffected ear
Improvement	Mean hearing level of 3 low-tone frequencies improves more than or equal to 10 dB, but not completely recovered
No change	Mean hearing level of 3 low-tone frequencies improves less than 10 dB
Deterioration	Other than the above criteria

CQ 5: Is corticosteroid treatment effective for ALHL?

Answer: While there is no clear evidence, it is suggested as one of the treatment options. (Evidence Level: II, Recommendation Grade: C1)

Comments: Opinions on the efficacy of corticosteroids vary [26,27]. In other words, no firm conclusions have been reached regarding the efficacy or dosage of corticosteroids administration itself. Without randomized trials comparing corticosteroids to a placebo, their efficacy remains unproven. They are often used for sudden hearing loss treatment, so we concluded a recommendation of an "Option" for the treatment of ALHL patients.

CQ 6: Are osmotic diuretics effective for ALHL?

Answer: While there is no clear evidence, the potential to improve endolymphatic hydrops suggests it may be one of the treatment options. (Evidence Level: II, Recommendation Grade: C1)

Comments: Osmotic diuretics are often used with the hope of improving endolymphatic hydrops. Some find them effective, while some see benefits, particularly in terms of glycerol test results, and others think their effects are limited. There is no study with high-level evidence, such as the RCTs, on the use of diuretics.

3.3. Perilymphatic fistula

Diagnostic criteria, epidemiology and clinical characteristics: Perilymphatic fistula (PLF) is a condition in which a fistula or hole forms between the perilymphatic space in the inner ear and surrounding organs, leading to symptoms including vertigo, tinnitus, and hearing loss. This fistula can arise from various causes, including the oval and round windows, microfissures, bone fractures, inflammation-induced labyrinthine destruction, or congenital anomalies. Symptoms can worsen or fluctuate when perilymph leaks from the fistula. PLFs are classified into categories 1 to 4, depending on the cause or factors inducing onset (Table 7). In these guidelines, we mainly focus on patients in categories 2 to 4.

Traditionally, a definitive diagnosis of PLF was based on the observation of perilymph or cerebrospinal fluid leakage, or the identification of a fistula during endoscopic examination or surgery. However, this confirmation is invasive and difficult to perform in cases with mild–to-moderate hearing loss or idiopathic cases without any antecedent event. The revised diagnostic criteria include cases with a clearly identified fistula or the detection of perilymph specific protein. CTP has been reported as a marker for PLF and is used in clinical tests (Table 8) [11, 28-29]. This diagnostic method for PLF based on the detection of CTP has been covered by social health insurance in Japan since July 2022.

Treatment: If PLF symptoms arise acutely, patients are advised to rest for about a week to allow for potential spontaneous recovery of the fistula. If symptoms persist or worsen, surgical intervention to close the fistula is suggested as an option. In chronic cases, the decision for surgery should be made cautiously, considering the patient's symptoms and wishes. Various surgical techniques have been reported for sealing the fistula, including the round window reinforcement (RWR) method, which aims to provide a more robust closure of the inner ear windows (Grade C1). There's a lack of high-level clinical research on the prognosis and recurrence rates of PLF, mainly due to the difficulties associated with the traditional invasive diagnostic methods. Through use of the CTP test, the diagnosis of PLF has become objective.

In the recent prospective study of SSNHL cases, 22 % of the 74 enrolled patients had positive CTP results, suggesting PLF [30]. Age and pre-treatment hearing levels influenced CTP values, with higher values in patients aged 60 and above. Patients positive for CTP had worse outcomes with intratympanic dexamethasone (IT-DEX) treatment. This suggests that PLF may be a significant factor in SSNHL, particularly in older individuals, and IT-DEX may not be as effective for PLF-associated

Table 7
Categories of PLF.

Category	Criteria
1	Linked to trauma, middle and inner ear diseases, middle and/or inner ear surgeries
2	Linked to barotrauma caused by antecedent events of external origin (such as flying or diving)
3	Linked to barotrauma caused by antecedent events of internal origin (such as straining, sneezing or coughing)
4	Has no apparent antecedent event

Table 8
Diagnostic criteria for PLF (based on the criteria of the Intractable Hearing Loss Research Committee of the Ministry of Health and Welfare, revised 2016).

A. Symptoms
Hearing impairment, tinnitus, aural fullness, vestibular symptoms are observed in cases who had preceding events as listed below:
(1) Coexisting or pre-existing middle and/or inner ear diseases (trauma, cholesteatoma, tumor, anomaly, SCCD, etc.), middle and/or inner ear surgeries
(2) Barotrauma caused by antecedent events or external origin (e.g., blasting, diving or flying, etc.)
(3) Barotrauma caused by antecedent events of internal origin (e.g., nose-blowing, sneezing, straining or carrying heavy objects, etc.)
B. Laboratory findings
(1) Microscopic/endoscopic inspection
Visual identification of fistula(s) between middle and inner ear by microscope or endoscope. Fistulas can develop at the cochlear window, vestibular window, fracture site, microfissure, malformation, or destruction in bony labyrinth caused by inflammation, etc.
(2) Biochemical test
Perilymph-specific protein is detected from the middle ear
C. Reference
(1) A perilymph-specific protein; e.g., Cochlin-tomoprotein (CTP) detection test
After myringotomy, the middle ear is rinsed with 0.3 ml saline three times, the fluid is recovered (middle ear lavage (MEL)) and tested by poly-clonal antibody ELISA
The cutoff criteria: 0.4< CTP negative; 0.4< CTP< 0.8 intermediate;
0.8< CTP positive (ng/ml, polyclonal antibody ELISA)
(2) Idiopathic cases may exist
(3) Following symptoms and/or test results may be observed:
1. Streaming water-like tinnitus or feeling of running water in the middle ear
2. Popping sound can be heard at the onset
3. Nystagmus and/or vertigo induced by pressure application to the middle ear (Hennebert's phenomenon, fistula sign)
4. Imaging studies may show a fistula in the bony labyrinth or pneumolabyrinth
5. Progression of hearing impairment, tinnitus, aural fullness may be acute, progressive, fluctuating or recurrent
6. The main complaints can be vestibular symptoms without hearing impairment
D. Differential diagnosis
Inner ear diseases with known causes, such as viral infection, genetic, vestibular schwannoma, etc.
Definite: Symptoms and laboratory findings listed in B
Probable: Only symptoms listed in A

cases, raising the possibility of PLF repair surgery as a treatment strategy.

As for the vestibular symptoms, a retrospective study examined 22 cases of PLF treated with PLF repair surgery [31]. Following surgery, there was a rapid improvement in vestibular symptoms, with 82 % of cases showing significant progress within a week. The study suggested that surgical intervention was responsible for these improvements. CTP testing confirmed PLF involvement in symptoms.

These two studies provide insights into the diagnosis and management of PLF, even though they both originate from a single institute. Further insights into the condition, including the detailed epidemiology and appropriate treatment, are anticipated in the future.

CQ 7: How should perilymphatic fistula be treated?
Answer:

1. For PLFs caused by surgery, malformation, trauma, etc., surgical intervention is suggested as one of the treatment options. (Evidence Level: V, Recommendation Grade: C1)
2. In other cases, progression should be observed for about a week with rest. If symptoms persist or if progressive hearing loss is observed, surgery should be considered as one of the treatment options, referencing results from CTP testing. (Evidence Level: V, Recommendation Grade: C1)

Comments: For PLFs with a clear cause, treatment varies based on the cause. On the other hand, acute fistulas in Category 2 to 4 can naturally close, so rest and observation for a week is common, with specific care instructions (for example, head of bed elevated to 30°). If symptoms persist, surgery is an option. Chronic fistulas are harder to diagnose but are treated based on symptoms and CTP test results. Surgery for sealing the fistula is common and employs materials such as fascia, areolar tissue, and gelatin products. Post-surgery, vestibular symptoms often improve, and early intervention can benefit cochlear symptoms. Some cases see symptom recurrence after surgery. A modified surgical intervention; ie, round window reinforcement (RWR) involving additional techniques and materials, has been introduced. More research is needed on both conservative and surgical treatments.

3.4. Mumps-associated hearing loss

Diagnostic criteria, epidemiology and clinical characteristics: Mumps-associated hearing loss is caused by mumps virus infection in the inner ear. Two primary infection routes are hypothesized: hematogenous infection and cerebrospinal fluid infection. The virus can damage the inner ear either by entering from the blood vessels or directly affecting the nerve fibers and tissues forming the perilymphatic space [32-34].

Mumps typically affects children aged 3–6, with over 90 % of cases occurring in children under 10. Due to the majority of hearing loss cases being unilateral, it often goes unnoticed by the patients and their families.

Mumps-associated hearing loss is considered rare, occurring in 1 in 20,000 to 30,000 people affected by mumps. However, in recent years, reports have varied from 1 in 1000 to 1 in 10,000 people being affected by this form of hearing loss. The number of patients with mumps-associated hearing loss nationwide in Japan was estimated to be 300 in a 1987 survey, 400 in a 1993 survey, and 650 in a 2001 survey [35]. In the most recent insurance claims-based survey in Japan, the incidence of mumps-associated hearing loss per 10,000 patients aged 0–64 years was 15.0 (1 in 668 patients). Interestingly, it was shown that the risk of deafness following mumps was identified not only for children, but also for adolescents and adults [36]. A survey conducted by the Japanese Society of Otorhinolaryngology from 2015 to 2016 revealed at least 348 cases of mumps-associated hearing loss over the two-year period [9]. Of the 287 cases that ultimately experienced ongoing unilateral hearing loss, 261 (about 91 %) had severe or profound hearing loss. A further 16 (approximately 4 %) of the patients experienced bilateral hearing loss.

In Japan, diagnostic criteria for mumps-associated hearing loss were established in 1987 by the Ministry of Health and Welfare's Research Group on Acute Severe Hearing Loss and these have been used for many years. However, due to the time-consuming nature of diagnosis using paired sera in actual clinical practice and the widespread use of the mumps enzyme immunoassay (EIA)-IgM antibody test, the diagnostic criteria for mumps-associated hearing loss were revised in 2013 (Table 9). The criteria for hearing improvement are almost same as those for iSSNHL (Table 10).

Table 9
Criteria for the diagnosis of mumps-associated hearing loss (The Research Committee for Acute Profound Deafness of the Ministry of Health and Welfare, 2013).

Definite
1. Patients with evident clinical signs of mumps, such as swelling of the parotid gland and submandibular gland, and acute severe hearing loss during the period from 4 d before to 18 d after the appearance of such swelling
2. Patients without evident clinical signs of mumps, but IgM antibodies against mumps virus are detected within 3 months after the onset of acute severe hearing loss

Referent case
Patients in whom mumps deafness is suspected clinically
1. Patients whose family members or friends have mumps infection
2. Patients who have different periods to Definite Criterion 1

Table 10
Hearing improvement criteria for mumps-associated hearing loss (Intractable Hearing Loss Research Committee of the Ministry of Health and Welfare, revised 2015).

Hearing improvement status	Criteria
Complete recovery	All five frequencies in the final audiograms are 20 dB or less, or improvement to the same degree of hearing in the unaffected side
Marked recovery	30 dB ≦ PTA improvement
Slight recovery	10 dB ≦ PTA improvement <30 dB
No response	PTA improvement <10 dB

PTA: arithmetic mean of the hearing levels at five frequencies (250, 500, 1000, 2000, and 4000 Hz).

Treatment: There are no reports with a high level of evidence on the treatment of mumps-associated hearing loss, and drug therapy including corticosteroids, vitamin B12, adenosine triphosphate disodium (ATP), prostaglandin, circulatory improvement drugs, immunosuppressants and/or hyperbaric oxygen therapy, and ganglion block has been proposed as an option in accordance with the therapy for iSSNHL (Grade C1). There are a limited number of reports of improvement in mild cases, but the prognosis for mumps-associated hearing loss is generally poor. In a nationwide survey conducted between 2014 and 2016, the improvement rate was only 3.4 % (Fig. 4C) [9]. Cochlear implantation has been reported to improve hearing in cases of bilateral severe hearing loss. There were no additional reports on the diagnosis and/or treatment of mumps-associated hearing loss during the period from 2017 to 2023.

CQ 8: Is there an effective treatment for mumps-associated hearing loss?

Answer:

1. While there are no reports of drug treatment with a high level of evidence for improving hearing loss, some forms of drug treatment are suggested as one of the treatment options. (Evidence Level: IVb, Recommendation Grade: C1)
2. In bilateral severe-to-profound hearing loss cases, cochlear implants are effective. It is recommended to proceed based on the degree of hearing loss. (Evidence Level: V, Recommendation Grade: A)

There is no treatment for mumps-associated hearing loss supported by high-level evidence. Treatments similar to those for iSSNHL, primarily corticosteroids, are commonly performed. Some mild cases show improvement, but hearing is not improved in most cases [9]. Cochlear implantation has been reported to improve hearing in cases of bilateral severe hearing loss [37].

Prevention: Given the generally poor prognosis and lack of effective treatments, the World Health Organization (WHO) emphasizes the importance of vaccination as a preventive measure. In Japan, the MMR (measles, mumps, rubella) vaccine was introduced in 1989, but was later discontinued in 1993 due to concerns about post-vaccination aseptic meningitis. With the current voluntary vaccination policy, the vaccination rate remains at 30–40 %, leading to concerns about a potential increase in mumps and mumps-associated hearing loss cases. Side effects of the vaccine include mild salivary gland swelling and low fever in a small percentage of cases. Severe side effects, such as aseptic meningitis, are quite rare and occur less frequently than with natural infections. Other reported side effects include encephalitis, thrombocytopenic purpura, hearing loss, and orchitis, but these are also less frequent than with natural infections.

3.5. *Acoustic trauma and acute noise-induced hearing loss*

Diagnostic criteria, epidemiology and clinical characteristics: Loud sound is one of the major causes of hearing loss. This condition is broadly categorized into acute noise-induced hearing loss (caused by extremely loud sounds) and chronic noise-induced hearing loss. Acute noise-induced hearing loss can be further divided into two types: one caused by instantaneous exposure to sounds above 130 dB(A) and the other resulting from exposure to loud sounds between 100 and 120 dB (A) for several minutes to hours. The former is narrowly defined as acoustic trauma (AT) and the latter is considered as acute noise-induced hearing loss (ANIHL) (Table 11).

The primary cause of hearing loss from loud sounds is damage to the outer hair cells in the cochlea [38]. Factors, including fatigue, stress, lack of sleep, and alcohol consumption, can influence an individual's susceptibility to acoustic trauma. Symptoms include hearing loss, tinnitus, and a feeling of fullness in the ears.

Diagnostic criteria in Japan were developed in 2015, and studies are being conducted based on these criteria. There are no established criteria for the classification of severity or the determination of treatment efficacy (Table 12).

The diagnosis of AT involves a comprehensive evaluation of the patient's history, focusing on the details of their exposure to loud sounds. It is crucial to ascertain the type and circumstances of the noise exposure, as distinguishing between narrowly defined AT and ANIHL is vital because of their differing prognoses (Fig. 6).

Treatment: Once diagnosed, early treatment with corticosteroids, similar to other types of sudden sensorineural hearing loss, is generally recommended. However, the evidence supporting the efficacy of corticosteroids is not well-established (Grade C1). Other treatments, such as hyperbaric oxygen therapy, have been suggested, but their effectiveness is also not confirmed.

Hearing recovery for AT is very poor, whereas ANIHL is recoverable to some extent (Fig. 6) [10]. Therefore, it is essential to differentiate

Table 11
Classification of noise-induced hearing damage.

Classification	Typical causes of exposure	Duration of exposure
Acute noise-induced hearing loss		
Acoustic trauma (AT)	Gun-shot Firecracker	Instant
Acute noise-induced hearing loss (ANIHL)	Concert Other sources of sound	Usually, several minutes to hours
Chronic noise-induced hearing loss		
Occupational noise-induced hearing loss	Long-term noise exposure in occupational settings	5–15 years or more
Non-occupational noise-induced hearing loss	Long-term noise exposure in non-occupational settings	Depends on the case

Table 12
Diagnostic criteria for acoustic trauma and acute noise-induced hearing loss (Intractable Hearing Loss Research Committee of the Health and Welfare, 2015).

Definite
Hearing loss that develops promptly after exposure to extremely intense noise, such as from an explosion or concert. Any hearing type, degree of hearing loss, unilateral or bilateral.
Probable
Of the above, those with a sensorineural hearing loss plus a conductive component such as traumatic perforation of the tympanic membrane due to an explosion.
Referent case
The cases who are undeniable with perilymphatic fistula due to pressure.

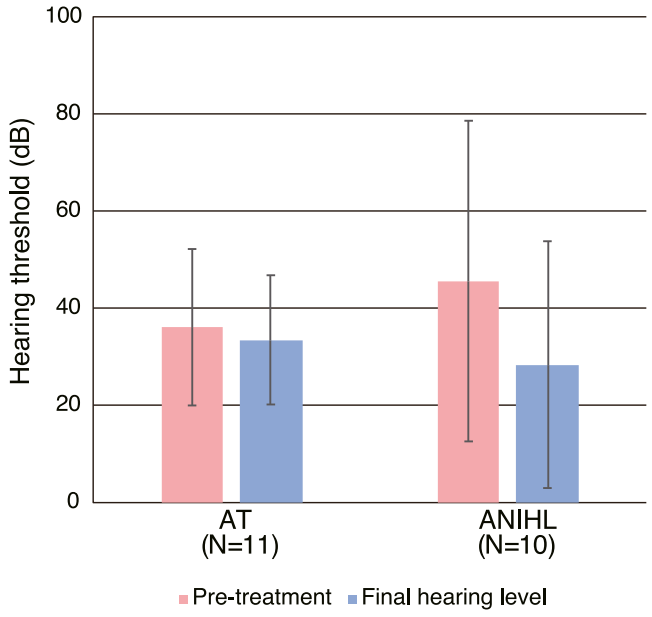

Fig. 6. Initial and final hearing thresholds after standard treatment for acoustic trauma and acute noise-induced hearing loss. The error bars in the figure represent the relevant standard deviations. These data were obtained from our previous report on an epidemiological survey conducted from 2014 to 2016 by the "Research Group on Intractable Hearing Disorders" [10].

between these two groups for accurate prediction of the hearing prognosis and evaluation of treatment effects. Prevention is emphasized due to the poor recovery rate once hearing loss occurs. It is advised to avoid loud sounds when possible and use ear protection such as earplugs or earmuffs when exposure is unavoidable.

A novel drug approach using ebselen, a GPx1 mimic, was reported in 2017. This study was randomized, double-blind, and placebo-controlled in design, and the results concluded that ebselen at a dose of 400 mg twice daily prevented a noise-induced temporary threshold shift [39]. Elsewhere, a few reports of intratympanic steroid injection for acoustic trauma have been published, but the clinical efficacy remains uncertain [40,41].

CQ 9: Is corticosteroid treatment useful for AT or ANIHL?

Answer: While there is no scientific evidence for corticosteroids use in AT or ANIHL, it is suggested as one of the treatment options. (Evidence Level: II, Recommendation Grade: C1)

Comments: There have not been any RCTs to date, so no proven scientific evidence supports the efficacy of corticosteroids treatment. Some reports suggest early treatment effectiveness, so early corticosteroids use is recommended with caution. In cases of narrowly defined AT, prognosis often remains poor even with corticosteroids treatment [10]. As there are no proven alternative treatments and no way to predict individual case severity or recovery potential, corticosteroids use is still advised.

4. Conclusions

In this article, we have enhanced the "Clinical Guidelines for the Diagnosis and Management of Acute Sensorineural Hearing Loss" with the latest literature review, and introduced the diagnostic criteria and treatments for each disease based on these guidelines. We hope that these guidelines will be used in medical practice and that they will initiate further research.

Author contributions

All authors meet the ICMJE authorship criteria.

Declaration of competing interest

All authors declare no conflicts of interest in this study.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.anl.2024.06.004.

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