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Review

Autoimmune Inner Ear Disease at the Otology–Rheumatology Interface: Mechanisms, Diagnosis and Treatment

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Received: 24 September 2026; **Revised:** 13 October 2026; **Accepted:** 29 October 2026; **Published:** 3 November 2026

Abstract: Autoimmune inner ear disease (AIED) encompasses immune-mediated sensorineural hearing loss occurring either in isolation or in association with systemic autoimmune, vasculitic or autoinflammatory disorders. Its diagnosis remains difficult because progressive or fluctuating hearing loss is not specific to immune-mediated cochlear injury, and no disease-specific biomarker has been validated. This review examines AIED from the combined perspectives of otology and rheumatology, focusing on systemic disease associations, pathogenic mechanisms, diagnostic limitations and therapeutic evidence. Experimental studies implicate blood–labyrinth barrier disruption, inflammatory cell recruitment, adaptive immune responses and microvascular injury, although direct confirmation of these mechanisms in primary human AIED remains limited. Clinically, serial audiometry, exclusion of alternative causes and targeted assessment for systemic inflammatory disease remain central to evaluation. Corticosteroids are commonly used as initial treatment, but therapeutic responsiveness does not establish the diagnosis. Evidence supporting conventional immunosuppressants and biologic agents remains insufficient for routine application in primary AIED. We distinguish findings obtained directly from patients with suspected AIED from evidence derived from related systemic disorders and experimental models, and identify the methodological priorities needed to improve diagnostic classification and treatment evaluation.

Keywords: Autoimmune Inner Ear Disease; Sensorineural Hearing Loss; Blood-Labyrinth Barrier; Cochlear Immunity; Biomarkers; Immunomodulatory Therapy

1. Introduction

Although historically considered immune privileged, the inner ear is now recognised as an immunologically active site in which resident immune cells and the blood–labyrinth barrier (BLB) regulate responses to systemic and local inflammatory signals [1,2]. Autoimmune inner ear disease (AIED) is a rare immune-mediated audiovestibular

disorder, with reported annual incidence estimates of fewer than 5 cases per 100,000 individuals [3,4]. Early observations by Cogan and Lehnhardt helped establish the concept of immune-mediated sensorineural hearing loss (SNHL) [5–7]. AIED most often presents with progressive or fluctuating SNHL, sometimes accompanied by vertigo, tinnitus or aural fullness [8], and may occur as an organ-confined disorder or in association with systemic autoimmune, vasculitic or autoinflammatory disease [9–11].

The central clinical difficulty is not recognising that immune mechanisms can injure the inner ear, but determining when an individual patient's hearing loss is genuinely immune mediated. No disease-specific biomarker has been validated, the phenotype overlaps with common inner-ear disorders, and corticosteroid responsiveness is neither universal nor specific [12,13]. These limitations make careful phenotyping, exclusion of relevant mimics and assessment for systemic inflammatory disease more informative than broad serological screening.

AIED lies at a practical intersection between otology and rheumatology: a similar audiovestibular phenotype may represent organ-confined immune disease, a manifestation of systemic autoimmunity, vasculitis or autoinflammation, or a non-immune mimic. In this Review, we therefore organise current evidence around three clinically linked questions: which systemic rheumatic contexts should raise suspicion for secondary AIED; which immune mechanisms are sufficiently supported to inform diagnostic or therapeutic reasoning; and how clinicians should interpret the limited evidence for biomarkers, corticosteroids, conventional immunosuppression and targeted agents. We then propose a pragmatic multidisciplinary framework and define research priorities for moving AIED from exclusion-based diagnosis towards validated, mechanism-informed stratification.

2. Literature Search and Evidence Selection

A structured, non-systematic literature search was conducted in PubMed on 1 March 2026, covering records from database inception to the search date. Medical Subject Headings (MeSH) and free-text terms related to autoimmune inner ear disease, immune-mediated hearing loss, systemic autoimmunity, blood–labyrinth barrier dysfunction, cochlear inflammation, biomarkers and immunomodulatory therapies were combined using Boolean operators. Relevant publications dated through 8 September 2026 were additionally considered during manuscript development and reference screening. Studies addressing the clinical manifestations, systemic associations, pathophysiology, diagnosis or treatment of autoimmune inner ear disease were eligible, whereas publications lacking direct clinical or mechanistic relevance were excluded. Human clinical studies, experimental investigations and pertinent reviews were evaluated according to methodological quality, relevance and clinical applicability. For evidence interpretation, controlled and prospective human studies were prioritised when assessing therapeutic outcomes, whereas retrospective cohorts and case reports were interpreted more cautiously. Findings from associated systemic autoimmune disorders, animal models and in vitro investigations were considered indirect evidence supporting mechanistic plausibility rather than proof of disease-specific mechanisms or treatment efficacy in primary human AIED.

3. Clinical and Pathogenic Complexity of Autoimmune Inner Ear Disease

AIED most often presents between 20 and 50 years of age [14], although paediatric cases have been described [15]. The characteristic phenotype is rapidly progressive or fluctuating SNHL, usually bilateral but sometimes beginning unilaterally [4,8,16]. Sudden-onset presentations also occur [17]. Audiometric configurations are heterogeneous. In a retrospective study of 53 patients classified as having autoimmune hearing loss, downsloping audiograms were the most frequent pattern (42.6% of ears), although flat, rising and other configurations were also observed [18]. Vestibular symptoms, tinnitus and aural fullness are common but non-specific [8,17]. Because individual symptoms and audiometric patterns overlap with other inner-ear disorders, serial audiometry and disease tempo are more informative than any single clinical feature.

The distinction between primary and secondary AIED is clinically useful but should not be interpreted as evidence for two biologically discrete disorders. Primary AIED refers to immune-mediated inner-ear disease in which no systemic autoimmune or inflammatory disorder can be identified, whereas secondary AIED describes a compatible audiovestibular syndrome occurring in the context of systemic autoimmune, vasculitic or autoinflammatory disease. For rheumatologists, the central question is therefore not whether an isolated autoantibody result establishes inner-ear autoimmunity, but whether the audiovestibular phenotype occurs within a coherent systemic in-

flammatory syndrome that changes diagnostic probability and management.

3.1. Primary AIED

Primary AIED denotes immune-mediated inner-ear disease without an identifiable systemic autoimmune or inflammatory disorder [11]. It is clinically important because the absence of systemic disease removes many of the peripheral immunological clues available in secondary AIED. Human mechanistic evidence is limited by the inaccessibility of inner-ear tissue, so current understanding derives largely from animal models and indirect human observations.

Proposed initiating events include local tissue injury or infection that exposes normally sequestered inner-ear antigens, followed by activation of resident cochlear immune cells and recruitment of circulating leukocytes [19,20]. Candidate effector pathways include T-cell-mediated inflammation, humoral responses, immune-complex deposition, oxidative stress and microvascular injury [20]. These mechanisms are not unique to primary AIED and should therefore be regarded as overlapping pathways capable of producing organ-confined cochleovestibular inflammation rather than as a single established disease cascade. Future studies comparing perilymph and blood [21,22], together with single-cell or spatial profiling, may help distinguish truly local immune programmes from nonspecific systemic activation [23–26].

3.2. Secondary AIED

Audiovestibular involvement in a patient with systemic autoimmune or inflammatory disease should not automatically be classified as secondary AIED, because vascular, neural, treatment-related and non-immune mechanisms can produce similar phenotypes. Secondary AIED is best regarded as a compatible audiovestibular syndrome plausibly linked to an established systemic autoimmune, vasculitic or autoinflammatory disease [11,27]. Such presentations have been estimated to account for approximately 15–30% of clinically diagnosed AIED cases [20,28], although the coexistence of systemic disease alone does not establish an immune-mediated cause of hearing loss. For practical rheumatological reasoning, reported associations can be grouped into connective-tissue diseases, vasculitides, systemic inflammatory/autoinflammatory disorders and other immune-mediated conditions [27]. This classification is useful because these groups differ in the mechanisms by which hearing loss arises and in whether treatment should be directed primarily at the inner ear or the systemic disease. **Table 1** summarises study-specific audiovestibular findings in selected systemic immune-mediated disorders and relevant neurological or vascular mimics. The reported figures refer to the defined outcomes and populations of individual studies and must not be interpreted as the prevalence of confirmed secondary AIED; causal attribution requires exclusion of alternative cochlear, neural, vascular, middle-ear and treatment-related mechanisms.

Table 1. Study-specific audiovestibular findings and relevance to suspected secondary autoimmune inner ear disease.

Disease	Defined Audiovestibular Outcome/Reported Result	Evidence Type, Population and Reference	Implications for Secondary AIED
Immune-related and neurological differentials			
Immune-mediated hypertrophic pachymeningitis	Progressive or asymmetric SNHL, sometimes accompanied by other cranial neuropathies; no defensible population prevalence estimate.	Individual cases involving hypertrophic pachymeningitis [29,30]	Dural or cranial nerve involvement is an important differential diagnosis; primary cochlear autoimmunity should not be assumed.
KLHL11-associated paraneoplastic encephalitis	Hearing loss in 15/39 (38.5%) and tinnitus in 14/39 (35.9%) in an antibody-defined clinical series.	Selected paraneoplastic encephalitis cohort [31,32]	Neural or paraneoplastic cochleovestibular dysfunction is a differential diagnosis; these findings do not establish AIED.
Autoimmune hepatitis type I	Rapidly progressive asymmetric bilateral SNHL documented in a reported concurrent presentation.	Single case report [33]	Co-occurrence has been reported, but causality and frequency remain unestablished.
Coeliac disease	SNHL in 13/32 (40.6%) paediatric patients versus 1/32 (3.1%) matched controls in one selected study.	Paediatric case–control study and narrative systematic review and findings vary across studies [34–36]	Supports an association with hearing impairment rather than confirmed secondary AIED.
Hashimoto's thyroiditis	Higher hearing thresholds at 250, 500 and 6000 Hz in a selected euthyroid cohort; no generalisable prevalence estimate.	Case–control audiometric study involving 30 euthyroid patients and 30 controls; additional observational study [37,38]	Thyroid autoimmunity may be associated with altered auditory thresholds, but immune-mediated inner-ear causality remains unproven.

Table 1. *Cont.*

Disease	Defined Audiovestibular Outcome/Reported Result	Evidence Type, Population and Reference	Implications for Secondary AIED
Multiple sclerosis	Pooled prevalence of hearing loss: 1.1% (95% CI 0.2–2.4%), with substantial heterogeneity.	Meta-analysis of eight studies including 5,187 patients; additional case literature [39,40]	Central or retrocochlear demyelinating mechanisms must be considered; hearing loss does not establish autoimmune labyrinthitis.
Vitiligo	Incident SNHL in 0.61% of 13,048 patients versus 0.29% of 52,192 controls; adjusted HR 2.18 (95% CI 1.66–2.86).	Nationwide population-based cohort; observational studies and meta-analysis [41–43]	These figures describe SNHL incidence and relative risk, not AIED prevalence; melanocyte-related cochlear mechanisms remain hypothetical.
Vogt–Koyanagi–Harada disease	Tinnitus, SNHL and vestibular symptoms have been described in patients with VKH.	Disease reviews [44,45]	Melanocyte-directed immune injury may affect the inner ear, but hearing abnormalities require individual clinical attribution.
Inflammatory bowel disease	High-frequency auditory abnormalities reported, particularly among patients with ulcerative colitis in selected investigations.	Prospective audiometric study involving 120 participants; selected ulcerative colitis cases and experimental investigation [46–48]	Clinical association and experimental gut–ear mechanisms do not establish secondary AIED; medication-related and alternative causes must be considered.
Myasthenia gravis	Reduced otoacoustic emissions reported in a selected physiological study involving 16 patients.	Prospective physiological study involving 16 patients [49]	Abnormal otoacoustic emissions do not necessarily indicate clinical SNHL or AIED; cholinergic efferent dysfunction may contribute.
Connective tissue diseases			
Rheumatoid arthritis	Association with SNHL: OR 3.42 (95% CI 2.50–4.69) compared with controls; not a prevalence estimate.	Systematic review and meta-analysis [50]; scoping review [51]	Hearing impairment may reflect inflammatory, vascular, conductive or treatment-related mechanisms; the systemic diagnosis alone does not establish AIED.
Sjögren's syndrome	Pooled prevalence of SNHL: 42.6%; prevalence of any hearing loss: 52.2%, with important study heterogeneity.	Meta-analysis of 11 observational studies and population-based studies and reviews [52–55]	Audiometric hearing loss is associated with Sjögren's syndrome but does not independently prove organ-specific inner-ear autoimmunity.
Systemic lupus erythematosus	Reported SNHL frequencies range from 6% to 70% across heterogeneous clinical studies; not a pooled AIED-specific estimate.	Review of clinical studies [56]; systemic-autoimmunity mouse model and clinical report [53,57,58]	Inflammatory, thrombotic, neural and treatment-related causes are possible; experimental BLB findings are not direct evidence in human AIED.
Systemic sclerosis	Audiometrically identified SNHL in 15/35 (42.9%) selected patients.	Case–control study involving 35 patients and 24 controls and clinical review and observational study [59,60]	Cochlear microvascular injury is plausible; the study-specific hearing-loss proportion is not an estimate of confirmed secondary AIED.
Spondyloarthritis and systemic cartilage inflammation			
Ankylosing spondylitis	Pooled prevalence of hearing loss: 42.4% (95% CI 29.2–56.2%); high-frequency abnormalities are frequently reported.	Meta-analysis of 14 studies involving 598 patients and 485 controls and additional audiological studies [61–63]	Increased hearing-loss burden does not establish cochlear autoimmunity; middle-ear pathology and confounding factors must be considered.
Relapsing polychondritis	SNHL and dizziness reported in selected symptomatic patients; no adequately supported general prevalence estimate.	Retrospective audiovestibular study of three symptomatic patients [64]	Inflammatory labyrinthine involvement is possible, but conductive impairment related to cartilage or middle-ear disease requires differentiation.
Autoinflammatory, granulomatous and thrombotic disorders			
Cryopyrin-associated periodic syndromes (CAPS)	Neurosensory hearing loss reported in 42% of 136 registry patients, with substantial differences between clinical subtypes.	Eurofever registry [65]; prospective audiological cohort [66]; mechanistic study [67]	Provides disease-linked evidence of NLRP3/IL-1-associated cochlear autoinflammation; genetically defined CAPS should not be conflated with primary AIED.
Sarcoidosis with cochleovestibular nerve involvement	Hearing loss in 36/39 (92%) patients specifically selected for cochleovestibular nerve involvement.	Selected retrospective case series and literature review [68]; diagnostic review [69]	This estimate cannot be generalised to unselected sarcoidosis patients; neural or meningeal involvement may explain hearing loss without primary cochlear autoimmunity.
Antiphospholipid syndrome	Sudden or fluctuating SNHL reported in selected patients; no reliable population prevalence estimate established.	Clinical reports and review [70,71]	Thrombotic or ischaemic cochlear injury differs from inflammatory autoimmune labyrinthitis.
Susac syndrome	SNHL often affects low or middle frequencies and may be accompanied by vestibular symptoms; findings from selected cohorts do not establish population prevalence.	Disease review [72]; observational cohorts [73,74].	Susac syndrome is an immune-mediated occlusive microangiopathy, distinct from conventional systemic necrotising vasculitis and primary AIED.

Table 1. *Cont.*

Disease	Defined Audiovestibular Outcome/Reported Result	Evidence Type, Population and Reference	Implications for Secondary AIED
Systemic vasculitis and inflammatory syndromes			
Cogan syndrome	Immune-associated SNHL and vestibular dysfunction are characteristic manifestations; percentages from selected clinical series should not be treated as population prevalence.	Clinical and histopathological evidence and comprehensive review [75–77]	Provides a coherent systemic inflammatory context for immune-mediated cochleovestibular injury, although individual clinical attribution remains necessary.
Behçet's disease	Abnormal hearing thresholds, SNHL and tinnitus reported in selected patients; no consistent pooled prevalence estimate.	Case–control audiological study involving 44 patients and 42 controls [78]	Vascular and inflammatory mechanisms are plausible, but an observed association does not independently establish AIED.
Eosinophilic granulomatosis with polyangiitis (EGPA)	Hearing loss reported in 76% of 219 published cases selected for otological manifestations; conductive and mixed mechanisms are common.	Systematic review of 15 reports or series focused on otological manifestations and additional clinical evidence [79,80]	This is not the prevalence of hearing loss among all EGPA patients; middle-ear effusion and potential cochlear or vascular injury must be distinguished.
Giant cell arteritis	Vestibular abnormalities in approximately 39/44 (89%) selected patients; hearing improvement after treatment in 12/44 (27.3%), not baseline hearing-loss prevalence.	Prospective clinical investigation of 44 patients with GCA and 10 patients with isolated polymyalgia rheumatica as comparators [81]	Vascular audiovestibular injury is possible; treatment-associated hearing improvement must not be presented as hearing-loss prevalence.
Granulomatosis with polyangiitis	Conductive, mixed and sensorineural hearing deficits reported in selected clinical series; no consistently established pooled prevalence.	Historical clinical series [82]	Eustachian-tube and middle-ear inflammation must be distinguished from potential vasculitic inner-ear injury.
Mixed cryoglobulinaemia	Bilateral SNHL in 7/32 (21.9%) patients; abnormal vestibular testing in a separate 7/32 (21.9%).	Clinical audiovestibular series involving 32 patients [83]	Immune-complex-associated microvascular injury is plausible, but the observed findings do not establish secondary AIED.
Polyarteritis nodosa	Bilateral sudden cochleovestibular dysfunction described in individual case reports; no reliable prevalence estimate.	Case report [84]	Vascular inner-ear injury is possible, but the available evidence is limited and not disease-specific.
Takayasu arteritis	Hearing loss in 16/53 (30.2%) selected patients versus 4/45 (8.9%) controls in one study; another study of 31 patients and 31 controls found no significant overall pure-tone average difference.	Two independent controlled observational studies published in 2024 [85,86]	Associations differ between cohorts and audiometric methods; hearing impairment should not automatically be attributed to vasculitic AIED.

Numerical estimates refer to the specific populations, audiovestibular outcomes and study designs reported in the cited literature. They should not be interpreted as the prevalence of confirmed secondary AIED. Differences in patient selection, diagnostic definitions, audiometric methods, age distributions and comorbid conditions limit direct comparisons across diseases. Hearing impairment in systemic immune-mediated disorders may result from inflammatory, vascular, thrombotic, neural, meningeal, middle-ear, treatment-related or unrelated mechanisms. The presence of systemic immune disease or an abnormal audiogram alone does not establish secondary AIED; clinical attribution requires a compatible phenotype, evaluation of alternative causes and a plausible relationship to the underlying systemic disorder. AIED, autoimmune inner ear disease; BLB, blood–labyrinth barrier; CAPS, cryopyrin-associated periodic syndromes; DPOAE, distortion-product otoacoustic emission; EGPA, eosinophilic granulomatosis with polyangiitis; GCA, giant cell arteritis; HR, hazard ratio; KLHL11, Kelch-like protein 11; OAE, otoacoustic emission; OR, odds ratio; PTA, pure-tone audiometry; SNHL, sensorineural hearing loss.

Among connective-tissue diseases, SLE, RA and Sjögren's syndrome are the most clinically relevant examples. Audiological studies have documented hearing abnormalities in SLE and primary Sjögren's syndrome, with vestibular abnormalities also reported in the latter [87,88]. In RA, a scoping review identified heterogeneous hearing findings and assessment methods, limiting conclusions about a uniform auditory phenotype or causal mechanism [51]. In SLE, both immune-mediated and vascular mechanisms are plausible. Experimental evidence from an induced SLE mouse model suggests that cytotoxic CD8+ T cells and NK cells can promote granzyme B-mediated endothelial injury and BLB disruption [58], while antiphospholipid antibodies may contribute to cochlear microvascular injury and ischaemia [70,89–91]. In RA, hearing abnormalities require assessment of both disease-associated and other potential causes [51]. In primary Sjögren's syndrome, extended high-frequency audiometry has identified predominantly high-frequency sensorineural hearing abnormalities [92]. These associations justify targeted rheumatological evaluation but do not mean that hearing loss in every patient with a connective-tissue disease represents

secondary AIED.

Systemic sclerosis provides another example of disease-associated auditory dysfunction. A controlled study involving 47 patients and 44 healthy controls reported reduced transient-evoked otoacoustic emission amplitudes in the patient group [93]. Such findings support an association with cochlear dysfunction but do not independently establish an autoimmune cause.

Vasculitis provides a more direct mechanistic link because inflammation of vessels supplying the labyrinth can compromise cochleovestibular perfusion. Cogan syndrome is the prototypic example, combining interstitial keratitis with fluctuating or sudden SNHL, vertigo and tinnitus [75, 76, 94, 95]. Histopathological studies demonstrate inflammatory injury within inner-ear vascular and sensory structures [76,95,96]. Similar cochleovestibular injury can occur in large- and medium-vessel vasculitides such as giant cell arteritis and polyarteritis nodosa [81,84,97]. Across these disorders, the clinically relevant common pathway is immune-mediated vascular injury with secondary labyrinthine ischaemia rather than a disease-specific audiometric pattern.

Systemic inflammatory and autoinflammatory disorders illustrate a different pattern. In neurosarcoidosis, hearing loss may reflect cochleovestibular nerve or meningeal involvement rather than organ-specific AIED [68,98]. Diagnosis requires integration of the clinical and imaging findings, pathological evidence where available, and exclusion of relevant mimics [69]. The high frequency of hearing loss reported in selected cohorts with cochleovestibular nerve involvement should not be extrapolated to systemic sarcoidosis as a whole [68]. By contrast, cryopyrin-associated periodic syndrome provides stronger evidence for inflammasome-driven cochlear autoinflammation. Pathogenic NLRP3 variants promote IL-1β signalling, experimental models demonstrate BLB disruption and macrophage-associated cochlear injury, and hearing manifestations may improve with IL-1 blockade [67,99–102]. Hearing loss may be the predominant presentation of NLRP3-associated autoinflammatory disease. A family study identified a gain-of-function NLRP3 variant associated with progressive hearing loss, increased caspase-1 activity and IL-1β secretion [103]. A predominantly auditory presentation therefore does not necessarily indicate organ-confined autoimmune disease. These examples emphasise why systemic context and mechanism should guide classification.

Other immune-mediated diseases may affect hearing without necessarily causing secondary AIED. In IBD, a prospective audiological study reported high-frequency hearing abnormalities, particularly in patients with ulcerative colitis [48], while experimental work linked intestinal inflammation and altered gut microbiota to cochlear dysfunction [47]. A Mendelian randomisation study also reported associations between genetic liability to IBD and hearing loss but did not detect mediation by its measure of autoimmunity [104]. These findings do not establish autoimmune injury within the inner ear. A systematic review of multiple sclerosis found more consistent evidence of brainstem and central auditory abnormalities than of peripheral auditory dysfunction, although methodological heterogeneity limited quantitative synthesis [105]. In multiple sclerosis, impaired speech perception and binaural processing have been associated with neurological disability and brain imaging abnormalities, supporting the need to consider auditory pathway involvement [106]. The coexistence of an immune-mediated disease and hearing dysfunction therefore requires clinical attribution rather than automatic classification as secondary AIED.

For practical classification, a stepwise clinical approach is recommended. First, a compatible audiovestibular phenotype should be documented through clinical history and serial pure-tone and speech audiometry, while relevant infectious, ototoxic, vascular, retrocochlear and other non-immune causes are evaluated. Second, targeted assessment for systemic autoimmune, vasculitic or autoinflammatory disease should be guided by clinical features rather than isolated serological findings. Presumed primary AIED may be considered when immune-mediated inner-ear dysfunction remains clinically plausible and no systemic immune disorder is identified that adequately explains the auditory presentation. Presumed secondary AIED requires an established systemic immune-mediated disorder and a clinically plausible relationship to the audiovestibular syndrome, supported, where available, by temporal association, systemic disease activity or corroborating organ involvement. Coexisting systemic disease alone is insufficient to establish secondary AIED, particularly when hearing loss may reflect unrelated vascular, neural or treatment-related mechanisms. Cases with uncertain attribution should remain provisionally unclassified and undergo longitudinal reassessment. Neither corticosteroid responsiveness nor an isolated autoantibody result reliably distinguishes primary from secondary AIED. This working classification is intended to guide multidisciplinary assessment rather than serve as a validated diagnostic standard.

4. Immunopathogenesis of Autoimmune Inner Ear Disease

The inner ear is an immune-responsive organ protected by specialised barrier systems and populated by resident immune cells [107–109]. The proposed immunopathogenesis of AIED encompasses several interacting processes, including blood–labyrinth barrier (BLB) dysfunction, innate immune activation, adaptive immune responses, cytokine signalling and microvascular injury (**Figure 1**). However, the supporting evidence differs substantially in source and clinical applicability. Direct observations in patients with suspected AIED remain limited, particularly for local cochlear mechanisms, whereas additional evidence derives from related systemic autoimmune disorders, experimental disease models and in vitro systems. Although these investigations provide valuable mechanistic insights, they do not necessarily establish that the same pathways operate in primary human AIED. The following sections therefore distinguish patient-derived observations from indirect clinical and experimental evidence, with mechanistic hypotheses interpreted according to their respective levels of support.

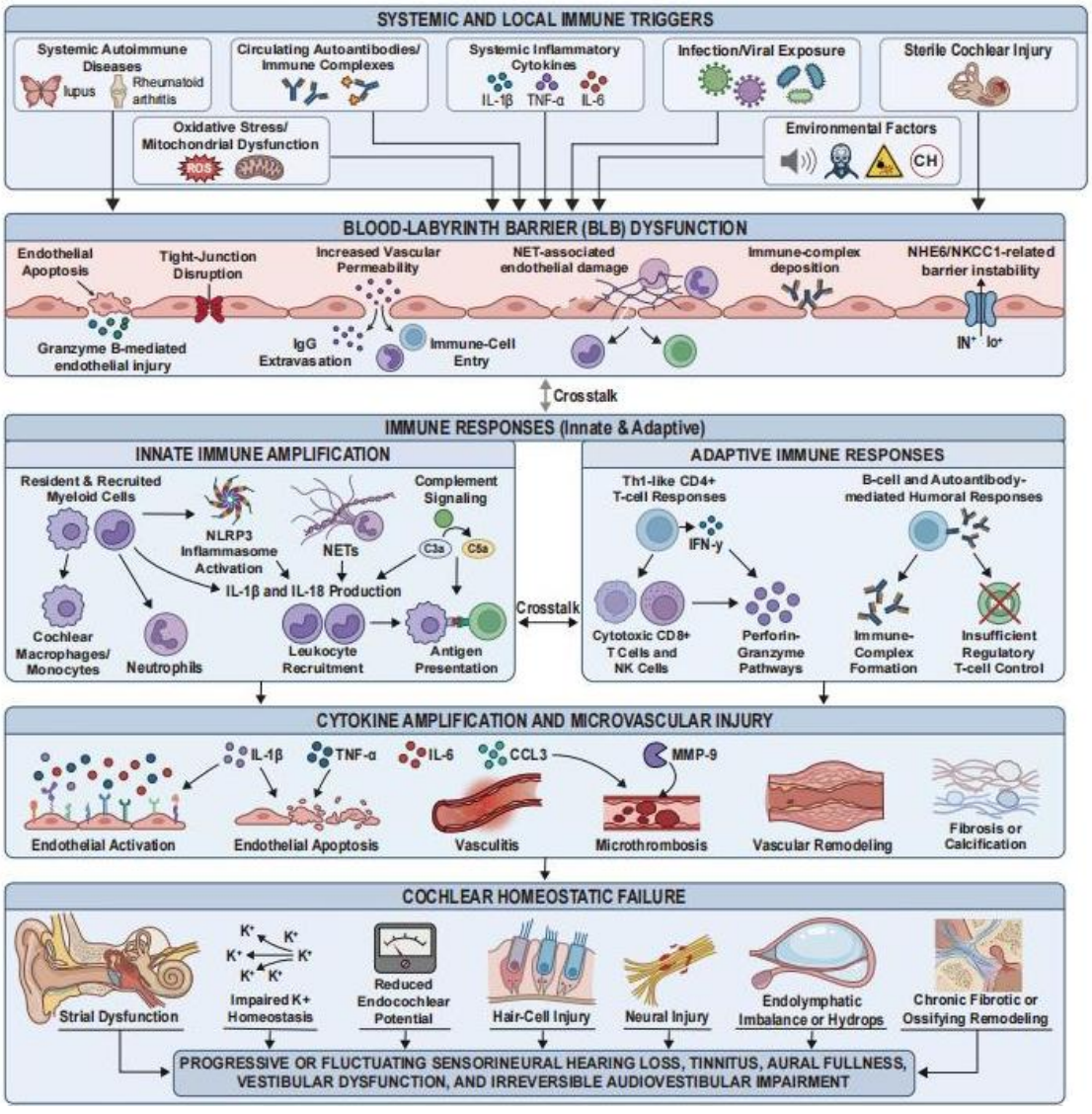


Figure 1. Proposed immune and inflammatory pathways potentially contributing to cochlear injury in autoimmune inner ear disease. The schematic integrates findings from experimental autoimmune and inflammatory models, systemic immune-mediated disorders, and in vitro investigations. Potentially interacting processes include BLB dysfunction, innate immune activation, adaptive immune responses, cytokine signalling and microvascular injury, which may contribute to disruption of cochlear homeostasis. The pathways represent a conceptual synthesis of heterogeneous evidence rather than a validated sequence of pathogenic events in primary human AIED.

4.1. Blood–Labyrinth Dysfunction

The blood–labyrinth barrier (BLB), best characterised in the strial microvasculature, maintains separation between the systemic circulation and inner-ear fluids through tight-junction-coupled endothelial cells supported by basement membrane, pericytes and perivascular macrophage-like melanocytes [2, 110–112]. This barrier is not only structural. By regulating molecular and cellular exchange, it helps preserve the ionic composition and endocochlear potential required for hair-cell mechanotransduction. Disruption of barrier integrity may therefore provide a pathway linking vascular inflammation to cochlear dysfunction.

Evidence implicating BLB dysfunction in immune-associated hearing impairment derives predominantly from experimental models of systemic autoimmune disease and cell-based investigations, rather than direct studies of primary human AIED. In an imiquimod-induced mouse model of systemic lupus erythematosus (SLE), cytotoxic CD8+ T cells and natural killer cells promoted granzyme B-mediated injury of cochlear microvascular endothelial cells, resulting in BLB disruption and hearing impairment [58]. In C3H/lpr mice exhibiting lupus-like systemic autoimmunity, increased extravascular IgG immunoreactivity around strial capillaries was observed during disease, consistent with increased vascular permeability [113]. Additionally, an experimental graft-versus-host disease model demonstrated the infiltration and local proliferation of circulating donor T cells in the perisaccular region of the endolymphatic sac [114]. Although these findings support the capacity of systemic immune processes to affect inner-ear barrier function and immune-cell trafficking, they do not establish that identical mechanisms operate in primary human AIED.

Complementary in vitro studies provide further mechanistic insights. Neutrophil extracellular traps increased endothelial permeability and altered intercellular junctional integrity in a human inner-ear-derived endothelial cell model [115]. Separately, NHE6 deficiency and pharmacological inhibition of NKCC1 were associated with altered junctional protein expression and increased permeability in mouse BLB-derived endothelial cell systems [116]. These findings demonstrate potential mechanisms of endothelial barrier destabilisation but do not constitute direct evidence of autoimmune injury in patients with AIED. In particular, transporter-associated changes reflect general BLB physiology rather than an established disease-specific mechanism.

Taken together, the available evidence supports BLB dysfunction as a biologically plausible pathway through which immune and inflammatory processes may contribute to cochlear injury. However, direct clinical evidence demonstrating these specific mechanisms in primary human AIED remains limited. BLB dysfunction should therefore be regarded as a potential convergent mechanism rather than a universal or disease-specific pathogenic feature. Further patient-based studies are needed to determine its relationship to disease phenotype, clinical activity and treatment responsiveness.

4.2. Innate Immunity

Innate immune activation is more plausibly an amplifier than a universal initiating event in AIED. Resident cochlear macrophage-lineage cells and recruited myeloid cells can respond to tissue stress, release pro-inflammatory mediators and recruit additional leukocytes [117–120]. Histopathological studies in Cogan syndrome demonstrate inflammatory-cell infiltration and vascular injury within inner-ear structures [76, 96]. However, resident and recruited myeloid populations are difficult to distinguish in human disease, and much of the functional evidence comes from other forms of cochlear injury. Evidence from presbyacusis also implicates dysregulated cochlear macrophage activity in auditory injury [121], supporting the view that macrophage-associated inflammation may occur across different inner-ear disorders rather than constituting an AIED-specific cellular signature [24].

NLRP3 inflammasome signalling has been implicated in inflammatory cochlear injury [100]. In a CAPS-associated mouse model, NLRP3 inhibition ameliorated hearing loss induced by systemic inflammation [101]. These findings provide evidence in a defined autoinflammatory model but do not establish the same mechanism in primary human AIED. More disease-specific observations have implicated dysregulated IL-1β signalling in corticosteroid nonresponsiveness. In a clinical cohort of patients with immune-mediated SNHL, predominantly comprising AIED cases, corticosteroid nonresponders exhibited elevated circulating IL-1β and impaired suppression of IL-1β release from peripheral blood mononuclear cells following dexamethasone exposure [122]. Subsequent experimental work identified a biologically active 28-kDa IL-1β fragment associated with AIED patient-derived immune cells and demonstrated its generation through caspase-7-mediated cleavage in vitro [123]. These findings provide a mechanistic

rationale for investigating IL-1-associated inflammation in corticosteroid-resistant AIED, but they do not establish a validated IL-1-defined clinical endotype or demonstrate that NLRP3 activation is responsible for corticosteroid resistance. Such an endotype remains investigational, without standardised diagnostic criteria, validated biomarker thresholds or large-scale prospective confirmation. IL-1β-related abnormalities should therefore be considered potential research markers rather than established tools for clinical classification or treatment selection.

4.3. Adaptive Immunity

Adaptive immunity may sustain inner-ear injury through antigen-specific T-cell responses and antibody-mediated immune mechanisms [124,125]. Loss of immune tolerance has been proposed to arise through molecular mimicry or bystander activation, although direct evidence for these initiating events in human AIED remains limited [124,126]. More convincing causal evidence comes from experimental autoimmune labyrinthitis. Following sensitisation with inner-ear antigens, Th1-like CD4+ T cells infiltrate the endolymphatic sac and subsequently extend into the cochlea and vestibular labyrinth [127]. In a complementary model, cochlin- and β-tectorin-specific CD4+ T cells induced autoimmune hearing loss, and adoptive transfer of activated cells reproduced disease in naïve mice [128]. These findings establish that antigen-specific T cells can cause immune-mediated cochlear injury, while leaving uncertain which antigens and T-cell programmes are most relevant in human AIED. Impaired regulatory T-cell control may further permit persistence of autoreactive responses [129,130].

Cytotoxic lymphocytes provide an additional adaptive effector pathway, particularly in systemic autoimmune disease. CD8+ T cells and NK cells can promote granzyme-mediated apoptosis of cochlear microvascular endothelial cells, thereby linking systemic immune activation to BLB disruption and local cochlear injury [58]. This mechanism is likely complementary to, rather than independent of, CD4+ T-cell-driven inflammation and illustrates how distinct adaptive effector populations may converge on vascular and sensory structures within the inner ear.

B-cell and antibody-mediated responses may also contribute to adaptive immune injury in selected patients. Anti-HSP70 antibodies are among the most extensively investigated serological markers in suspected autoimmune hearing loss; however, their diagnostic performance varies considerably across clinical populations and assay platforms [131,132]. Although antibody reactivity has been reported in selected patients, HSP70 is not an inner-ear-specific antigen, and a positive result does not establish autoimmune-mediated cochlear injury. Its clinical interpretation therefore requires consideration of the underlying audiovestibular phenotype and the limitations of the assay used. In systemic autoimmune or vasculitic phenotypes, antiphospholipid antibodies may contribute to cochlear microvascular injury and ischaemia [133], while antibodies directed against endothelial and inner-ear antigens have been reported in Cogan syndrome [134]. Collectively, these findings support a heterogeneous adaptive immune model in which T-cell-mediated inflammation, cytotoxic vascular injury and antibody-associated mechanisms may coexist to varying degrees. However, their diagnostic relevance remains substantially less established than their mechanistic plausibility.

4.4. Cytokine Networks and Microvascular Injury

Pro-inflammatory cytokines participate in immune signalling and inflammatory amplification in the inner ear [2,135]. IL-6, TNF-α and IL-1β may contribute to leukocyte recruitment, vascular permeability and inflammatory amplification [122,135–138]. Among these mediators, IL-1β has relatively direct clinical and translational evidence in corticosteroid-resistant AIED. Small human studies have associated abnormal IL-1β regulation in peripheral immune cells with corticosteroid nonresponsiveness, while experimental investigation of a caspase-7-generated 28-kDa IL-1β fragment has demonstrated its capacity to induce downstream inflammatory mediators, including IL-6, TNF-α and CCL3 [122,123]. However, these findings do not establish a direct causal relationship between circulating IL-1β abnormalities and local cochlear injury, nor do they demonstrate a clinically validated IL-1-driven AIED subtype. TNF-α and IL-6 may participate in additional inflammatory pathways, although direct evidence in human primary AIED remains limited.

Experimental studies identify distinct routes to cochlear endothelial injury. Neutrophil extracellular traps increase permeability in an inner-ear-derived endothelial cell model [115], whereas cytotoxic lymphocyte-derived granzymes damage cochlear microvascular endothelial cells in a mouse model of SLE [58]. These observations support endothelial injury as a plausible contributor to immune-associated hearing dysfunction, without establishing identical pathways in primary human AIED.

5. Diagnosis of Autoimmune Inner Ear Disease

5.1. Current Diagnostic Challenges

AIED remains a challenging clinical diagnosis because progressive or fluctuating SNHL is not specific to immune-mediated cochlear injury. Although classical descriptions emphasise progression over 3–90 days, presentations may also include sudden or initially unilateral hearing loss [8,12,135,139]. Ménière's disease is an important differential diagnosis, particularly when fluctuating hearing loss is accompanied by tinnitus, aural fullness and recurrent vertigo. Episodes of spontaneous vertigo lasting 20 min to 12 h, together with documented low- to mid-frequency SNHL and fluctuating aural symptoms, favour definite Ménière's disease, although clinical overlap remains possible [140]. Conversely, an isolated episode of sudden SNHL should prompt timely assessment and management according to established sudden-hearing-loss pathways rather than presumptive classification as AIED.

Several common non-immune conditions must also be considered. Age-related and noise-induced hearing loss typically follow a more gradual course, often with bilateral high-frequency involvement, while ototoxic injury should be suspected when auditory deterioration follows exposure to potentially ototoxic medications, including aminoglycosides or platinum-based chemotherapy. Chloroquine and hydroxychloroquine exposure also merits consideration: a systematic review and an observational SLE study raised concerns about possible ototoxicity [141,142], whereas another SLE cohort found no significant differences in conventional pure-tone or extended high-frequency hearing thresholds between hydroxychloroquine users and non-users [87]. Medication exposure should therefore be assessed alongside disease activity and alternative causes, rather than assumed to establish drug-induced hearing loss. Early-onset, familial or otherwise unexplained progressive hearing loss may warrant consideration of hereditary aetiologies and targeted genetic evaluation. Otosclerosis and chronic otitis media can produce conductive or mixed hearing loss and may occasionally involve a sensorineural component. Otoscopy, air- and bone-conduction audiometry, tympanometry and acoustic reflex testing help identify these conditions, with high-resolution temporal bone computed tomography reserved for selected cases in which structural pathology is suspected.

Cancer immunotherapy is a distinct treatment-related context. A small case series described audiovestibular immune-related adverse events following immune checkpoint inhibition or T-cell therapy [143]. In patients receiving these treatments, the temporal relationship to exposure should inform attribution rather than default classification as idiopathic primary AIED.

Retrocochlear, infectious and neurological disorders are particularly important to exclude when the clinical presentation is atypical. Vestibular schwannoma or other cerebellopontine-angle lesions should be considered in patients with unilateral or asymmetric SNHL, persistent unilateral tinnitus or associated neurological findings; magnetic resonance imaging (MRI) of the internal auditory canals and cerebellopontine angles provides an appropriate means of evaluation. Infectious labyrinthitis and related cochleovestibular complications should be considered in the setting of otitis media, meningitis, recent systemic infection or relevant infectious exposures, including those associated with otosclerosis or Lyme disease. Infectious investigations should be directed by clinical and epidemiological suspicion rather than performed universally.

Susac syndrome should be considered when SNHL accompanies visual or neurological abnormalities. The complete brain–eye–ear triad may be absent at presentation, contributing to diagnostic delay or misclassification; appropriate retinal and brain imaging assessment can help distinguish this microangiopathic disorder from presumed primary AIED [72,74]. Less common but clinically consequential mimics include paraneoplastic cochleovestibular syndromes and hypertrophic pachymeningitis. A paraneoplastic process should be considered when otherwise unexplained progressive audiovestibular dysfunction occurs with ataxia, additional neurological abnormalities or a relevant oncological history [31]. Hypertrophic pachymeningitis may present with SNHL accompanied by persistent headache or multiple cranial neuropathies and may be suggested by abnormal dural thickening or enhancement on contrast-enhanced MRI [29,30]. Recognition of these alternative diagnoses is essential because their investigation and management differ substantially from those of presumed primary AIED. No isolated symptom, audiometric pattern, serological result or corticosteroid response is sufficient to establish AIED; diagnostic confidence depends on serial audiological assessment, exclusion of relevant mimics and evaluation of the systemic immune context.

5.2. Current Diagnostic Approach

The diagnostic evaluation of suspected AIED should follow a stepwise, phenotype-directed approach. **Figure 2** provides an overview of the diagnostic framework, while the key differential diagnostic steps are outlined below. First, otoscopy, air- and bone-conduction pure-tone audiometry, speech audiometry and tympanometry should confirm sensorineural hearing loss and identify conductive or mixed components suggestive of middle-ear disease or otosclerosis. Second, the onset, progression and laterality of hearing loss should guide the differential diagnosis. Acute sudden SNHL requires prompt assessment and treatment according to established sudden-hearing-loss pathways, without delaying care for autoimmune investigations. Recurrent vertigo lasting 20 min to 12 h with fluctuating low- to mid-frequency SNHL favours Ménière's disease when established diagnostic criteria are met. Unilateral or asymmetric SNHL, disproportionate speech-recognition impairment or focal neurological findings should prompt MRI of the internal auditory canals and cerebellopontine angles to assess retrocochlear pathology. Third, medication exposure, noise history, familial hearing loss and relevant infectious risks should be assessed, with targeted investigations for ototoxic, hereditary or infectious causes when indicated. Acute neurological deficits or suspected vascular compromise warrant urgent evaluation for cerebrovascular disease, whereas systemic vasculitic or thrombotic features should prompt focused vascular and rheumatological assessment. Finally, after major alternative causes have been evaluated, rapidly progressive or fluctuating SNHL, particularly when bilateral and evolving over weeks to months, may raise suspicion for AIED. Serial audiometry and phenotype-directed evaluation for systemic autoimmune or inflammatory disease should then inform diagnostic confidence and provisional classification as primary or secondary AIED. This approach represents a pragmatic clinical framework rather than a validated diagnostic algorithm.

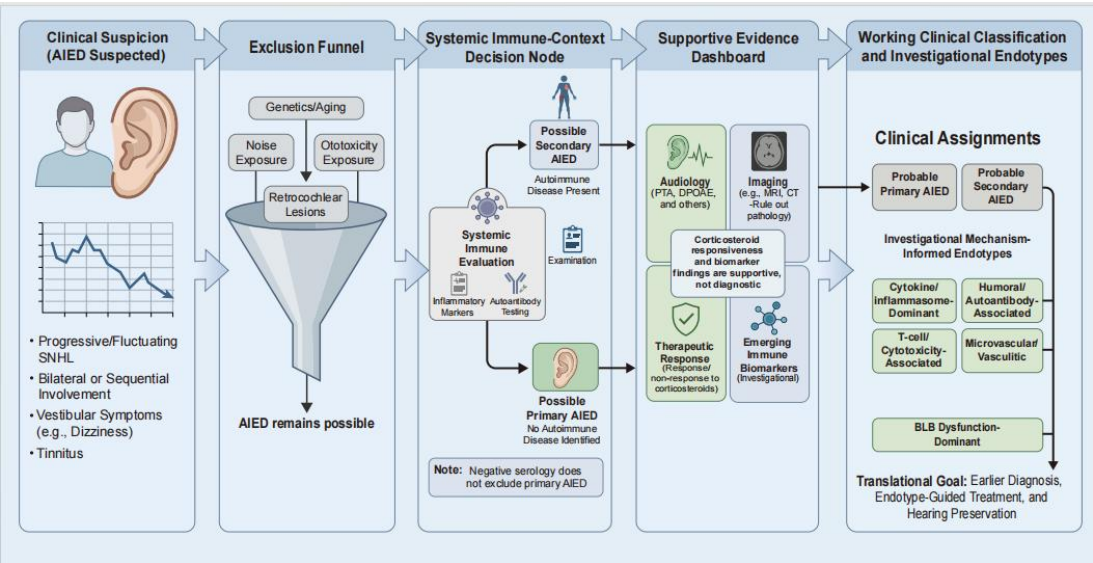


Figure 2. From exclusion-based diagnosis to mechanism-informed stratification in AIED. AIED remains primarily a diagnosis of exclusion because no validated disease-specific biomarker is currently available. Evaluation begins with recognition of a compatible audiovestibular phenotype, followed by systematic exclusion of common mimics. Assessment of systemic immune context then helps distinguish probable primary from secondary AIED, while supportive evidence from audiology, imaging, treatment response, and emerging biomarkers may increase diagnostic confidence but is not definitive in isolation. The figure also illustrates a future transition toward biomarker-guided and mechanism-based stratification of immune-mediated hearing loss. The exclusion funnel illustrates representative alternative diagnoses rather than an exhaustive diagnostic algorithm; a stepwise differential diagnostic approach is provided in Section 5.2. The presence of systemic autoimmune disease alone does not establish secondary AIED without a clinically plausible relationship to the audiovestibular presentation.

Standardised audiometric assessment is essential for characterising hearing loss and monitoring disease progression and treatment response in suspected AIED. Baseline and follow-up evaluations should include ear-specific

air- and bone-conduction thresholds, pure-tone averages calculated from consistent frequency sets, and speech-recognition scores. Serial assessments should use comparable testing protocols, speech materials and presentation levels whenever feasible, particularly before treatment, after the initial therapeutic course and when hearing changes or treatment is modified. Audiometric outcomes should be reported using predefined criteria, with hearing improvement, stabilisation and deterioration distinguished and potential test–retest variability considered. A recent retrospective cross-sectional study by Bulut Gökten et al. demonstrated elevated bone-conduction thresholds in patients with ankylosing spondylitis and psoriatic arthritis compared with healthy controls, highlighting the value of objective audiometry for identifying subclinical auditory abnormalities in systemic inflammatory diseases [144]. However, these findings do not establish autoimmune cochlear injury or validate audiometry as a disease-specific diagnostic test for AIED. In a cross-sectional study of 50 patients with rheumatoid arthritis, absent otoacoustic emissions were reported in 46%, whereas approximately 80% had normal hearing on conventional and extended high-frequency audiometry [145]. These findings illustrate that abnormalities detected by different auditory tests are not interchangeable and do not independently establish AIED. Serial audiometric findings should therefore be interpreted alongside the clinical phenotype and relevant systemic immune context.

Laboratory evaluation should be guided by the clinical probability of systemic immune disease rather than performed as a universal diagnostic panel for AIED. Full blood count and inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein may help identify systemic inflammation, whereas ANA and extractable nuclear antigens, ANCA, antiphospholipid antibodies, complement studies and other disease-specific tests should be selected according to the history, examination and suspected systemic phenotype [8,146]. Positive serological findings may support the diagnosis of an underlying rheumatic disease in the appropriate clinical context but do not establish AIED, while negative serology does not exclude organ-confined immune-mediated inner-ear disease.

A practical otology–rheumatology referral checklist should be incorporated into the evaluation of suspected immune-mediated hearing loss. Rheumatological assessment should be considered when a compatible audiovestibular presentation coexists with one or more clinically suggestive systemic features: (i) persistent sicca symptoms, including dry eyes or dry mouth, or recurrent salivary gland swelling; (ii) photosensitive rash, palpable purpura, or recurrent oral or genital ulcers; (iii) inflammatory arthritis or persistent joint swelling; (iv) ocular inflammation, particularly painful red eye, photophobia, uveitis or interstitial keratitis; (v) manifestations suggestive of systemic vasculitis, including recurrent sinonasal crusting or epistaxis, digital ischaemia, pulmonary involvement or unexplained peripheral neuropathy; (vi) renal or neurological abnormalities, such as haematuria, proteinuria, unexplained renal dysfunction or focal neurological deficits; and (vii) recurrent unexplained fever, constitutional symptoms or persistently elevated inflammatory markers, particularly when accompanied by other systemic findings. These features should be interpreted as clinical referral triggers rather than validated diagnostic criteria for secondary AIED. Isolated nonspecific symptoms, low-titre autoantibody positivity or mildly elevated inflammatory markers should not independently establish an immune-mediated aetiology. Suspected ocular inflammation, progressive vasculitic manifestations or renal or neurological involvement warrants prompt multidisciplinary assessment, including ophthalmological evaluation when indicated. Importantly, rheumatological investigation should proceed alongside, rather than delay, timely otological management of acute hearing deterioration. Further serological and organ-specific investigations should remain guided by the suspected systemic phenotype [8,10,11,27,94].

In patients with a compatible audiovestibular phenotype after evaluation of relevant alternative causes, corticosteroids may be prescribed for therapeutic purposes, with subsequent hearing changes providing supportive but non-specific diagnostic information. A commonly reported regimen involves oral prednisone at approximately 1 mg/kg/day (maximum 60 mg/day) for four weeks, followed by an individualised taper [139,147]. However, this treatment protocol does not constitute a validated diagnostic challenge for AIED. Objective assessment should include pure-tone thresholds and speech-recognition scores obtained before and after treatment. In a prospective AIED study, treatment response was defined as an improvement of ≥15 dB at one frequency, ≥10 dB at two consecutive frequencies, or ≥12 percentage points in word identification score [148]; these criteria assess hearing improvement rather than establish diagnostic specificity. Corticosteroid responsiveness may increase clinical suspicion but cannot confirm AIED, whereas nonresponse does not exclude immune-mediated disease, particularly when delayed treatment or irreversible hair-cell and neural injury limits hearing recovery. Treatment risks and individual tolerability should also be considered. Corticosteroid response must therefore be interpreted alongside serial audiometry, relevant differential diagnoses and systemic immune findings [9,139].

5.3. Candidate Biomarkers and Emerging Diagnostic Adjuncts

No circulating or imaging biomarker has yet demonstrated sufficient disease specificity and external validation to establish the diagnosis of AIED. Candidate immune markers should therefore be regarded primarily as investigational tools for biological stratification or treatment-response research rather than stand-alone diagnostic tests. IL-1β-related abnormalities have been reported in selected patients with corticosteroid-nonresponsive AIED. Peripheral blood mononuclear cells from these patients have shown dysregulated IL-1β production, while subsequent experimental work identified a biologically active 28-kDa IL-1β fragment generated through caspase-7-mediated cleavage [122,123]. Although these observations suggest a potential association between IL-1β signalling and corticosteroid responsiveness, no clinically validated threshold or prospective biomarker-guided treatment strategy has been established. Differences in IL-6 expression according to corticosteroid responsiveness further support the investigation of inflammatory profiles [136], but these findings remain exploratory and should not be used independently to classify AIED or determine treatment selection.

Among serological candidates, anti-HSP70 antibodies have been extensively investigated, although their diagnostic utility remains uncertain. A systematic review and meta-analysis including three case-control studies reported a pooled sensitivity of 70% (95% CI 59–80%) and specificity of 98% (95% CI 87–100%) for Western blot assays, with substantial between-study heterogeneity. The single ELISA-based study included in that review reported a sensitivity of 85% (95% CI 55–98%) and specificity of 98% (95% CI 86–100%) [132]. In contrast, a retrospective AIED cohort reported a sensitivity of 54.5% and specificity of 42.9% [13], while another study detected anti-HSP70 reactivity in 33% of patients with idiopathic sensorineural hearing loss and 7% of healthy controls [131]. These discrepancies may reflect differences in clinical case definitions, patient selection, antigen preparation, antibody detection methods and positivity thresholds. Western blot and ELISA results are not directly interchangeable, as assay comparisons have demonstrated poor agreement for antibody-positive samples [149]. Furthermore, positive predictive value depends strongly on disease prevalence and the pretest probability of AIED. For illustration, assuming a sensitivity of 70% and specificity of 98%, a hypothetical pretest probability of 5% would yield a positive predictive value of approximately 65%; this calculation does not represent validated test performance in routine practice. Given the methodological heterogeneity, potential selection bias and lack of independent validation, anti-HSP70 testing cannot currently establish or exclude AIED and should not be used as a stand-alone diagnostic criterion.

Imaging may provide complementary information but is not disease-specific. Contrast-enhanced inner-ear MRI can demonstrate labyrinthine enhancement or endolymphatic hydrops in selected immune-mediated disorders [150]. One retrospective MRI-based decision-tree study distinguished autoimmune inner-ear disease from chronic otitis media with SNHL with high specificity, but its small, selected cohort does not support use as a general diagnostic classifier for AIED [151]. MRI should therefore be used principally to identify structural abnormalities and alternative diagnoses, with inflammatory findings regarded as supportive rather than confirmatory. Proteomic and metabolomic profiling remains investigational [152], and high-frequency audiometry may identify subclinical auditory dysfunction in systemic autoimmune disease without establishing an immune aetiology [92]. Future biomarker studies require predefined phenotypes, clinically relevant comparator groups, reproducible thresholds and external validation.

5.4. The Complex Relationship between AIED and Ménière's Disease

AIED and Ménière's disease (MD) overlap clinically because both can present with fluctuating SNHL, tinnitus, aural fullness and vestibular symptoms [140, 153]. Immune activation may also contribute to selected MD phenotypes, with peripheral inflammatory signatures and labyrinthine microvascular or lymphatic abnormalities reported [154–157]. These findings support partial mechanistic overlap, not equivalence between the two disorders.

The distinction remains clinically important. AIED is approached as an immune-mediated syndrome requiring exclusion of mimics and assessment for systemic autoimmune or inflammatory disease, whereas endolymphatic hydrops is the characteristic pathological correlate of MD and its aetiology is heterogeneous [153,158]. Furthermore, several endolymphatic hydrops-associated variants and related conditions have overlapping audiovestibular presentations, making careful clinical differentiation important [159]. Current evidence is insufficient to classify MD as a uniformly autoimmune disorder [160,161]. Immune biomarkers or inflammatory MRI findings should therefore be interpreted as supportive features within the appropriate clinical phenotype rather than as evidence that AIED

and MD form a single disease spectrum.

6. Therapeutic Strategies and Translational Opportunities

Treatment selection in suspected AIED is complicated by substantial differences in the quality of evidence supporting individual interventions. Systemic corticosteroids have the most extensive clinical experience, with prospective and observational studies documenting short-term hearing improvement in selected patients. However, sustained benefit is less consistently demonstrated. Conventional steroid-sparing agents have not shown reproducible efficacy in controlled investigations, while evidence for biologic therapies is largely derived from small trials, uncontrolled cohorts and individual case reports. Outcomes observed in Cogan syndrome and genetically defined autoinflammatory disorders cannot be directly extrapolated to primary AIED. Accordingly, the following sections distinguish AIED-specific clinical findings from evidence obtained in related diseases and experimental systems, with particular attention to treatment response definitions, audiometric outcomes and the limitations of each study design.

6.1. Conventional Pharmacological Interventions

6.1.1. Glucocorticoids

Systemic glucocorticoids remain the principal first-line pharmacological treatment for suspected AIED, although treatment regimens and response definitions vary across studies. A commonly described approach involves oral prednisone at approximately 1 mg/kg/day, up to 60 mg/day, for four weeks, followed by an individualised taper according to audiometric response and treatment tolerability [139,147]. This regimen represents an established practice pattern rather than a universally validated treatment protocol.

In a prospective multicentre study involving 116 adults with clinically suspected AIED characterised by active, progressive bilateral sensorineural hearing loss, 67 patients (57.8%) demonstrated hearing improvement following a four-week course of prednisone at 60 mg/day [148]. Treatment response was assessed using predefined audiometric criteria: an improvement of at least 15 dB at one pure-tone frequency, at least 10 dB at two consecutive frequencies, or an increase of at least 12 percentage points in word identification score. Patients with Cogan syndrome were excluded, although coexisting autoimmune conditions were permitted; the reported response rate therefore should not be interpreted as a separately validated estimate for primary AIED.

Longer-term outcomes have been less favourable in selected observational cohorts. In a retrospective series of 42 patients with immune-mediated inner-ear disease, including seven patients with associated systemic autoimmune disorders, Broughton et al. reported initial clinical improvement in 23 of 33 patients (70%) who received corticosteroids [162]. However, some initial responses were based on subjective improvement or short treatment courses rather than uniformly documented audiometric recovery. Among 35 patients with follow-up audiometry, only five (14%) met the study's criteria for hearing improvement over a mean follow-up of 34.4 months, based on pure-tone average and/or speech discrimination outcomes [147,162]. Importantly, this long-term follow-up group was not explicitly restricted to initial corticosteroid responders, and some patients received additional immunosuppressive treatments. Consequently, the 14% figure should not be interpreted as the proportion of initial corticosteroid responders who maintained steroid responsiveness.

Together, these findings suggest that systemic glucocorticoids may provide short-term audiometric benefit in selected patients, but reported response rates depend on patient selection, treatment protocols, follow-up duration and the definition of hearing improvement. Available estimates should not be generalised indiscriminately across primary and secondary AIED. Serial pure-tone and speech audiometry are essential for assessing treatment response, guiding tapering decisions and distinguishing transient improvement from sustained hearing preservation.

Intratympanic corticosteroid administration has been explored as an adjunctive or alternative approach in patients with suspected AIED who experience an inadequate response to systemic corticosteroids or cannot tolerate prolonged systemic exposure. The direct clinical evidence, however, is limited to small and predominantly uncontrolled studies. In a retrospective series of patients with AIED, Matsuoka and Harris reported hearing improvement in 15 of 30 patients (50%) receiving intratympanic corticosteroid treatment, although concomitant or preceding therapies and the absence of a controlled comparison limit attribution of benefit to the local interven-

tion [13]. García-Berrocal et al. also described intratympanic methylprednisolone treatment in 11 selected patients with refractory immune-mediated inner-ear disease, with hearing improvement reported in a subset [163]. These observations suggest potential clinical benefit but do not establish a generalisable response rate, an optimal dosing regimen, or comparative efficacy in primary AIED.

The rationale for intratympanic delivery is supported by pharmacokinetic studies demonstrating higher perilymph concentrations and lower systemic exposure after local methylprednisolone administration than after intravenous dosing [164]. However, pharmacokinetic advantages do not establish superior clinical efficacy. The available AIED-specific evidence for intratympanic corticosteroid treatment remains limited and heterogeneous, as highlighted in a systematic review of AIED management [165]. In contrast, intratympanic corticosteroids have been evaluated more extensively in other inner-ear disorders. For example, clinical practice guidelines recommend intratympanic corticosteroids as salvage therapy for selected patients with idiopathic sudden sensorineural hearing loss, while sustained-exposure dexamethasone formulations have been investigated in randomised trials involving patients with Ménière's disease [166,167]. A Cochrane review of intratympanic corticosteroids for idiopathic sudden sensorineural hearing loss judged most available evidence to be of low or very low certainty [168]. These findings provide indirect clinical and drug-delivery evidence but do not establish treatment efficacy or justify extrapolating response rates to primary AIED. In the absence of adequately powered, controlled AIED-specific trials, intratympanic corticosteroids may be considered selectively as an adjunctive or alternative option, but their optimal indications, comparative effectiveness and long-term hearing outcomes remain uncertain. Treatment responses should be monitored using serial pure-tone thresholds and speech-recognition measures.

6.1.2. Biologicals

Evidence for biologic therapy in AIED remains limited, with substantial differences in study design and clinical population [169] (**Table 2**). Among TNF-α inhibitors, a small randomised placebo-controlled trial found no significant benefit of etanercept over placebo in patients with AIED [170]. Small uncontrolled studies of local infliximab and intratympanic golimumab have reported preliminary hearing outcomes, but their efficacy remains unconfirmed in controlled trials [171,172]. These findings do not support routine TNF inhibition for primary AIED.

Table 2. Biologic and Targeted Immunomodulatory Agents with Potential Relevance to AIED.

Target	Agent	Drug Class	Mechanism	Clinical Evidence and Applicability to AIED
TNF-α	Etanercept	TNF receptor–Fc fusion protein	Acts as a soluble decoy receptor that binds TNF and prevents TNF receptor activation	A randomised placebo-controlled pilot trial involving 20 AIED patients found no significant benefit over placebo. Controlled AIED evidence: negative [170]
TNF-α	Infliximab	Chimeric anti-TNF-α monoclonal antibody	Directly binds and neutralizes soluble and transmembrane TNF-α	Small uncontrolled studies of local administration suggested potential hearing benefit or corticosteroid-sparing effects. Controlled efficacy remains unestablished [171,173,174]
TNF-α	Adalimumab	Fully human anti-TNF-α monoclonal antibody	Directly binds and neutralizes TNF-α	Limited retrospective observations have not established reliable audiometric efficacy in primary AIED [13]
TNF-α	Golimumab	Fully human anti-TNF-α monoclonal antibody	Directly binds and neutralizes TNF-α	In a small open-label intratympanic study, 3 of 7 per-protocol patients achieved hearing stability with corticosteroid withdrawal. Evidence: uncontrolled AIED study [172]
CD20	Rituximab	Chimeric anti-CD20 monoclonal antibody	Depletes CD20-positive B cells and may reduce autoantibody-mediated humoral responses	An uncontrolled pilot study of immune-mediated inner-ear disease reported that 5 of 7 patients met a predefined audiometric endpoint. Evidence: preliminary, non-confirmatory [175–177]
IL-1	Anakinra	Recombinant human IL-1 receptor antagonist	Blocks IL-1α and IL-1β signaling by competitively inhibiting IL-1 receptor activation	An open-label trial reported improvement in 7/10 corticosteroid-resistant patients; a retrospective 49-patient study reported improvement or stabilisation using subgroup-specific endpoints. Evidence: preliminary AIED-specific clinical studies [178,179]
IL-1	Rilonacept	Dimeric IL-1 trap fusion protein	Directly binds and neutralizes IL-1α and IL-1β	AIED study registered (NCT02828033); the registration does not establish treatment efficacy.
IL-1β	Gevokizumab	Humanized anti-IL-1β monoclonal antibody	Selectively neutralizes IL-1β	AIED trial registered (NCT01950312); the registration does not establish treatment efficacy.
IL-1β	Canakinumab	Fully human anti-IL-1β monoclonal antibody	Provides long-acting neutralization of IL-1β	Hearing improvement reported in a patient with Muckle–Wells syndrome/CAPS. Indirect evidence for primary AIED [180,181]
IL-6R	Tocilizumab	Humanized anti-IL-6 receptor monoclonal antibody	Blocks IL-6 receptor signaling	Hearing benefit reported in refractory Cogan syndrome case literature. Case-level systemic-disease evidence; no controlled primary-AIED data [182–184]

Table 2. *Cont.*

Target	Agent	Drug Class	Mechanism	Clinical Evidence and Applicability to AIED
JNK	AM-111	Cell-penetrating synthetic peptide composed of 31 amino acids	Inhibits JNK signaling downstream of TNF-α and IL-1	Investigated in randomised trials for idiopathic sudden SNHL rather than AIED; the phase III trial did not meet its overall primary efficacy endpoint. No direct AIED evidence [185,186]
JAK	Tofacitinib	Small-molecule intracellular kinase inhibitor	Inhibits JAK–STAT signaling downstream of multiple cytokine receptors	A Cogan syndrome case reported improvement in joint symptoms and no further hearing deterioration, without demonstrated auditory recovery attributable to treatment. Case-level indirect evidence [187]

The clinical evidence column summarises study design, relevant patient populations and applicability to AIED. Findings from primary AIED, Cogan syndrome, CAPS and other inner-ear disorders are not directly interchangeable. Hearing stabilisation should not be equated with audiometric improvement, and trial registration alone does not establish treatment efficacy. No biologic or targeted agent listed has established efficacy for routine treatment of primary AIED.

IL-1 blockade has shown preliminary clinical activity in selected patients with corticosteroid-resistant AIED. An open-label phase I/II trial reported audiometric improvement in 7 of 10 patients receiving anakinra [178], while a subsequent retrospective study of 49 patients reported hearing improvement or stabilisation across clinically distinct subgroups, using different response definitions [179]. Evidence for B-cell depletion is similarly limited: in a small uncontrolled rituximab pilot study involving immune-mediated inner-ear disease, 5 of 7 patients met a predefined audiometric endpoint [175]. Although these findings suggest potential therapeutic benefit, they do not establish efficacy in primary AIED.

Evidence for IL-6 receptor blockade with tocilizumab is largely restricted to case reports involving Cogan syndrome [182,184], whereas hearing improvement with canakinumab has been reported in selected patients with Muckle–Wells syndrome, a genetically defined condition within the CAPS spectrum [181]. Such findings cannot be directly extrapolated to primary AIED. Biologic treatment should therefore be individualised according to the underlying systemic disease, prior treatment response and potential risks, with objective audiometric monitoring. No biologic agent currently has sufficiently established efficacy for routine treatment of primary AIED.

6.1.3. Traditional Immunosuppressive Drugs

Evidence supporting conventional steroid-sparing immunosuppression for primary AIED is limited. Methotrexate has historically been used for corticosteroid-responsive or corticosteroid-dependent disease; however, randomised placebo-controlled evidence did not demonstrate clear benefit in maintaining corticosteroid-induced hearing improvement, and the overall evidence for disease-modifying antirheumatic drugs remains heterogeneous. Evidence for azathioprine, mycophenolate mofetil and cyclophosphamide is derived predominantly from small observational studies or from their use in associated systemic autoimmune and vasculitic diseases [135,147,188]. Their use should therefore be individualised according to the underlying systemic diagnosis, previous corticosteroid response and expected toxicity rather than assumed to provide disease-specific efficacy for primary AIED.

6.2. Regenerative and Experimental Therapies

Experimental approaches should be clearly separated from therapies supported by direct AIED evidence. Human adipose-derived mesenchymal stem cells have shown immunomodulatory and hearing-preserving effects in experimental autoimmune hearing-loss models [130,189], but clinical evidence remains extremely limited. More broadly, inner-ear organoid, explant and animal models have been used to investigate hair-cell regeneration, although findings from these systems cannot establish regenerative efficacy in patients with AIED [190]. NLRP3 inhibitors such as piceatannol, oridonin and MCC950 have shown otoprotective effects mainly in age-, noise- or inflammation-related experimental models rather than clinical AIED [102,126]. Drug-delivery strategies involving nanocarriers and gene-based therapeutics are under development for sensorineural hearing loss, but their clinical efficacy in primary AIED remains unestablished [191]. These approaches provide useful directions for mechanistic and translational research but should not currently guide routine care.

6.3. Supportive Treatment and Rehabilitation

6.3.1. Plasmapheresis

Plasmapheresis has historically been explored as an adjunctive treatment for selected patients with presumed immune-mediated inner-ear disease, based on its capacity to remove circulating antibodies and immune complexes.

Small uncontrolled studies reported hearing stabilisation or improvement in some patients, including durable stability in a subset during long-term follow-up [192,193]. However, the available evidence is old, uncontrolled and insufficient to establish efficacy, identify appropriate candidates or define an optimal treatment regimen. Plasmapheresis should therefore be regarded as an exceptional, non-standard option rather than routine treatment for AIED.

6.3.2. Hearing Aids and Cochlear Implants

Hearing aids address mild-to-severe SNHL (25-70 dB) by amplifying residual function, though fluctuating thresholds in AIED complicate fitting and adaptation, with evidence from analogous conditions like MD suggesting better tolerance in stable phases despite recruitment phenomena and poor speech recognition, necessitating multidisciplinary audiological management to enhance communication and quality of life [28,194].

Cochlear implantation may provide substantial auditory rehabilitation in selected patients with severe-to-profound sensorineural hearing loss associated with primary or systemic immune-mediated disease [195]. However, cochlear fibrosis or ossification may complicate electrode insertion in some cases, particularly in inflammatory conditions such as Cogan syndrome [95]. Preoperative imaging and individualised perioperative planning are therefore important, although the available evidence is derived largely from small and heterogeneous clinical series [195]. A comparative study of cochlear implant recipients found greater electrode-impedance fluctuations associated with symptom reactivation in a subset of patients with immune-mediated inner-ear disease [196]. This observation supports attention to postoperative programming and longitudinal follow-up, but does not establish impedance changes as a validated biomarker of disease activity.

In summary, AIED treatment remains centred on corticosteroids and hearing rehabilitation, whereas evidence supporting conventional steroid-sparing immunosuppression, biologic therapies, targeted delivery and regenerative approaches remains limited or investigational. Future therapeutic development should prioritise prospective comparative studies using standardised audiometric, vestibular and patient-reported outcomes and clinically relevant patient stratification.

7. Research Priorities

Future AIED research should prioritise questions capable of improving disease definition and clinical decision-making. First, multicentre prospective cohorts and registries should adopt explicit entry criteria, standardised audiometric outcomes, documented disease tempo and treatment exposure, and prespecified definitions of primary and secondary AIED. Such harmonisation is necessary to determine whether currently heterogeneous clinical phenotypes represent reproducible biological subgroups.

Second, biomarker research should progress from discovery to independent clinical validation. Candidate autoantibodies, cytokines, cellular signatures and other circulating or inner-ear-derived biomarkers should be evaluated against clinically relevant comparators, including Ménière's disease, idiopathic sudden sensorineural hearing loss and non-immune causes of progressive sensorineural hearing loss [21,22,132,146,152]. Reproducible assay thresholds, independent replication and demonstration of incremental diagnostic value over clinical assessment are required before incorporation into routine practice.

Third, therapeutic studies should be organised around clinically and biologically defined strata, including the presence of systemic rheumatic disease, corticosteroid responsiveness and disease duration. Trials should use standardised pure-tone and speech-recognition outcomes together with vestibular and patient-reported measures and should distinguish short-term hearing improvement from durable preservation of function. Single-cell and spatial profiling and computational approaches may contribute to mechanistic discovery [197,198] and hypothesis generation in auditory research [199–202], but these technologies should currently be regarded as research tools rather than validated diagnostic, prognostic or treatment-selection components of routine AIED care.

8. Conclusion

The principal challenge in AIED is determining whether an evolving audiovestibular disorder reflects primary inner-ear autoimmunity, systemic immune-mediated injury or an unrelated condition with a similar clinical presentation. This distinction requires serial audiometric assessment, careful exclusion of alternative diagnoses and

selective rheumatological investigation. Although experimental and translational studies have identified several plausible mechanisms of cochlear inflammation and vascular injury, direct evidence from primary human AIED remains insufficient to support mechanism-based diagnosis. Corticosteroids continue to have a central role in initial management, whereas the long-term effectiveness of conventional immunosuppressants and biologic agents remains uncertain. Future progress will depend on prospective studies with clearly defined clinical phenotypes, appropriate comparator populations, validated biomarkers and standardised auditory outcomes. Such evidence is necessary to establish which patients benefit from specific immunomodulatory interventions.

Author Contributors

Conceptualization: W.L. and H.L. (Huawei Li); supervision: W.L. and H.L. (Huawei Li); writing—original draft: X.Y.; writing—review and editing: X.Y., F.L., X.W., Y.C., H.L. (Hongfei Lou), M.L., H.L. (Huawei Li), and W.L. All authors read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82425018) and the STI2030-Major Projects (No. 2022ZD0205400).

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

No datasets were generated or analyzed during the current study.

Conflicts of Interest

Xing Wang is an employee of Cochlear Limited. The other authors declare no competing interests.

AI Use Statement

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) solely for language refinement. No AI tools were used for data analysis, interpretation, or generation of scientific content. All outputs were critically reviewed and edited by the authors. The authors take full responsibility for the integrity and accuracy of the work.

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