

Review

Current Challenges and Approaches to the Development of Novel Drug Products for Otic Administration: A Narrative Review

Elena O. Bakhrushina ^{1,*}, Natalia N. Mikhailova ¹, Anastasia N. Golub ¹, Ksenia V. Ereemeeva ², Anna-Daniela Koynova ^{1,*}, Anna A. Popova ³, Andrey B. Goryachev ⁴, Olga I. Stepanova ⁵, Ivan I. Krasnyuk, Jr. ⁶ and Ivan I. Krasnyuk ¹

¹ Department of Pharmaceutical Technology, A. P. Nelyubin Institute of Pharmacy, I. M. Sechenov First Moscow State Medical University (Sechenov University), 119571 Moscow, Russia; mikhaylova_n_n@staff.sechenov.ru (N.N.M.); nastia4a757@yandex.ru (A.N.G.); krasnyuk_i_i@staff.sechenov.ru (I.I.K.)

² Department of Ear, Nose and Throat Diseases, N.V. Sklifosovskiy Institute of Clinical Medicine, I. M. Sechenov First Moscow State Medical University (Sechenov University), 119021 Moscow, Russia; eremeeva_k_v@staff.sechenov.ru

³ Department of Biotechnology, A. P. Nelyubin Institute of Pharmacy, I. M. Sechenov First Moscow State Medical University (Sechenov University), 119571 Moscow, Russia; popova_a_a_1@staff.sechenov.ru

⁴ Department of Life Safety and Disaster Medicine, N.V. Sklifosovskiy Institute of Clinical Medicine, I. M. Sechenov First Moscow State Medical University (Sechenov University), 119021 Moscow, Russia; goryachev_a_b@staff.sechenov.ru

⁵ Department of Pharmacology, A. P. Nelyubin Institute of Pharmacy, I. M. Sechenov First Moscow State Medical University (Sechenov University), 119571 Moscow, Russia; Stepanova_o_i@staff.sechenov.ru

⁶ Department of Analytical, Physical and Colloidal Chemistry, A. P. Nelyubin Institute of Pharmacy, I. M. Sechenov First Moscow State Medical University (Sechenov University), 119571 Moscow, Russia; krasnyuk_i_i_1@staff.sechenov.ru

* Correspondence: bakhrushina_e_o@staff.sechenov.ru (E.O.B.); koynova2000@gmail.com (A.-D.K.)

Abstract

Acute otitis media is an inflammatory disease affecting all compartments of the middle ear, characterized by localized pain, fever, hearing impairment, and, occasionally, purulent exudate. It represents a significant clinical concern in both pediatric and adult populations, with approximately 709 million cases reported annually worldwide, 51% of which occur in children. However, currently available topical otic formulations are limited by their inability to achieve predictable therapeutic concentrations at the site of inflammation, resulting in reduced efficacy. In addition, the selection of appropriate active pharmaceutical ingredients (APIs) for drug products remains challenging; as a result, existing therapies do not comprehensively address all stages of pathogenesis. This study aimed to analyze existing locally acting formulations for middle ear drug delivery, evaluate their advantages and limitations, and assess modern approaches to the development of novel drug delivery systems and API combinations. A critical review of 69 publications (2010–2026) was conducted, supplemented by a strengths and limitations analysis of dosage forms and an evaluation of APIs based on clinical data. The findings highlight a lack of targeted drug delivery systems, limited efficacy of existing API combinations against bacterial biofilms, and their risk of ototoxicity. Emerging innovative drug delivery approaches, including microemulsions, vesicular systems, stimuli-responsive systems, and hydrogels, have demonstrated promising results in preclinical studies; however, their efficacy and safety remain to be confirmed in clinical settings before their full therapeutic potential in otitis media treatment can be realized.

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1. Introduction

1.1. Anatomy of the Ear

The middle ear is an air-filled cavity located within the temporal bone and comprises three interconnected anatomical compartments: the tympanic cavity, the mastoid air cell system, and the Eustachian tube. It is separated from the external auditory canal by the tympanic membrane. The cavity contains three auditory ossicles—the malleus, incus, and stapes—which transmit acoustic vibrations from the tympanic membrane to the inner ear. The Eustachian tube is responsible for pressure equalization.

Diseases of the middle and inner ear, including acute and chronic otitis, represent a major cause of hearing loss in adults and contribute to the widespread use of systemic antibiotics. Middle ear diseases are multifactorial; however, one of the most common underlying factors is inflammation involving all three compartments of the middle ear, which may result in persistent hearing impairment.

An illustration of the generalized anatomy of a human middle ear and adjacent structures is shown in Figure 1.

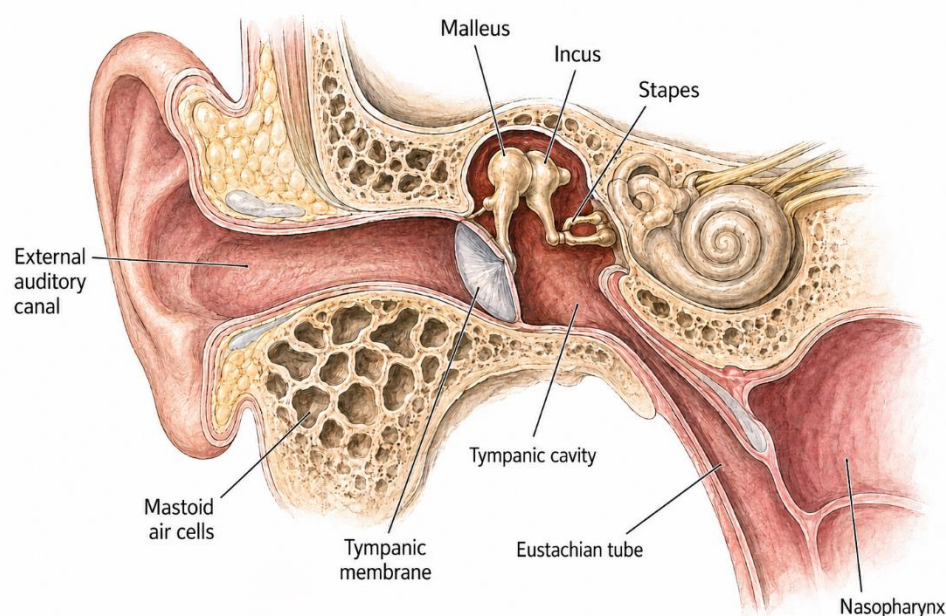


Figure 1. Anatomical overview of the human middle ear and adjacent structures.

1.2. Barriers to Middle Ear Drug Delivery

In acute otitis media, the inflammatory process primarily affects the tympanic cavity but may subsequently extend to the mastoid antrum and mastoid air cells, resulting in mastoiditis. In the case of chronic disease, the Eustachian tube is frequently involved, contributing to persistent impairment of middle ear ventilation and drainage.

In addition to the high prevalence of the disease, clinicians face significant challenges in delivering active molecules to the site of action due to the anatomy of the ear. Systemic administration of antibiotics and other pharmaceutical ingredients often fails to achieve

predictable therapeutic concentrations and is associated with the risk of antimicrobial resistance and systemic adverse effects. At the same time, when topical dosage forms are used, patients frequently encounter poor retention of ear drops within the external auditory canal, resulting in rapid leakage and only short-term drug exposure [1].

Intratympanic administration of antibiotics and anti-inflammatory agents into the middle ear cavity is an invasive procedure that is essentially parenteral in nature, with corresponding requirements for drug product quality. It is also associated with procedural discomfort and typically requires prior topical anesthesia with a 10% lidocaine solution in an outpatient setting. Currently, significant research efforts worldwide are focused on the development of targeted drug delivery systems with improved permeation across the tympanic membrane and optimized retention time [2].

Additional challenges arise from the anatomical characteristics of the ear. These include the presence of cerumen and hair within the external auditory canal, the tympanic membrane, which in its intact state exhibits limited permeability to large and hydrophilic molecules, and the Eustachian tube, through which administered formulations may rapidly drain into the nasopharynx. Consequently, the residence time of the drug product at the target site is substantially reduced.

Pathology-associated alterations represent further barriers to effective drug delivery. In acute otitis media with spontaneous tympanic membrane perforation, topical formulations may gain access to the middle ear cavity; however, the presence of accumulated exudate and pronounced edema often prevents uniform drug distribution. In chronic otitis media, long-term pathological changes, including granulation tissue formation and fibrosis, may result in preferential accumulation of the drug on damaged or necrotic tissue surfaces rather than penetration into deeper regions of the middle ear. Furthermore, the Eustachian tube frequently remains open in chronic disease, facilitating rapid drainage of the administered formulation into the nasopharynx.

As a result, peak drug concentrations within the middle ear may be achieved rapidly but decline shortly thereafter, necessitating frequent administration to maintain therapeutic levels. However, repeated dosing is associated with an increased risk of adverse effects, including ototoxicity, particularly in the case of aminoglycoside-containing formulations.

An illustration of anatomical and disease-induced barriers to middle ear drug delivery is shown in Figure 2.

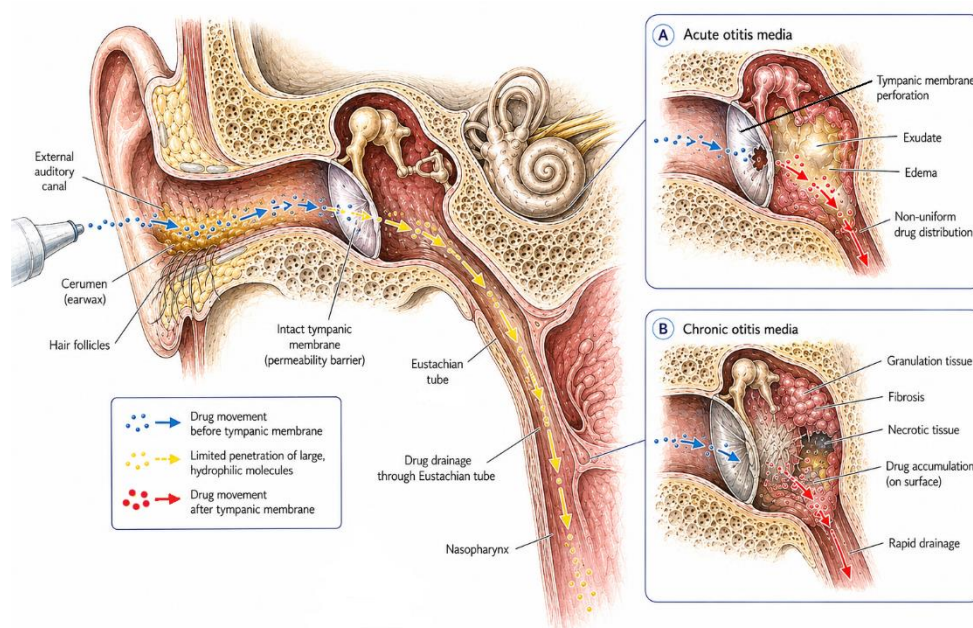


Figure 2. Anatomical and disease-induced barriers to middle ear drug delivery.

1.3. Epidemiology, Clinical Burden, and Current Therapeutic Challenges in Otitis Media

According to recent epidemiological data, the global incidence of acute otitis media averages 10.8 cases per 100 individuals per year, with geographical variation (3.6 in Europe and 34.4 in Africa). The total annual number of cases is estimated at 709 million worldwide, with 51% occurring in children under five years of age [3]. Clinical data indicate that 80–90% of children experience at least one episode of acute otitis media during early childhood, while the disease also remains prevalent in adults. The global burden of chronic otitis media is estimated at 297 million cases, with higher prevalence observed in low-income countries [4].

A major limitation of current systemic therapy is the increasing antimicrobial resistance among the principal causative pathogens. According to global surveillance data, the prevalence of penicillin-resistant *Streptococcus pneumoniae* reaches 25–40% in certain regions, while beta-lactamase production is detected in 15–30% of *Haemophilus influenzae* isolates. This trend reduces the effectiveness of amoxicillin, the first-line treatment for otitis media, and necessitates the use of alternative therapeutic regimens.

In countries with well-developed healthcare systems, the incidence of non-complicated acute otitis media has declined over the past two decades. However, the proportion of chronic and recurrent forms of the disease associated with bacterial biofilm formation has increased. Biofilms are detected in 60–80% of patients with chronic suppurative otitis media and represent one of the principal causes of failure of conventional antibiotic therapy.

Despite well-established indications for systemic antibacterial therapy, its excessive and often inappropriate use—without consideration of pathogen characteristics and in violation of prescribing guidelines—contributes to the development of antimicrobial resistance. Topical antibacterial and combination drug products may serve as an effective addition to systemic therapy in acute suppurative otitis media or as monotherapy, for example, in recrudescence of chronic suppurative otitis media with tympanic membrane perforation [5].

In international otorhinolaryngology practice, acute otitis media is recognized as one of the most common reasons for visits to healthcare professionals and one of the leading indications for systemic antibiotic prescription in pediatric patients [6].

Thus, the high prevalence of otitis media and the substantial limitations of currently available dosage forms highlight the need for the development of novel approaches to topical drug delivery to the middle ear.

The aim of this review is to examine specific features of topical drug delivery to the middle ear, analyze existing dosage forms, identify their advantages and limitations, and outline current trends in the development of innovative drug delivery systems, including microemulsions, vesicular systems, and stimuli-responsive systems.

2. Materials and Methods

This study represents a narrative review with a structured literature search conducted to evaluate existing approaches to drug delivery to the middle ear, as well as the use of active pharmaceutical ingredients (APIs) and their combinations in the treatment of otitis media. Unlike a systematic review, no formal meta-analysis was performed. However, the literature search and study selection were conducted according to a predefined protocol with specified inclusion and exclusion criteria.

A qualitative assessment of the “strengths” and “weaknesses” of existing dosage forms was performed using principles similar to SWOT (Strengths, Weaknesses, Opportunities, and Threats) analysis, although no formal SWOT framework was applied.

During the preparation of this manuscript, generative artificial intelligence (AI) was used (ChatGPT, OpenAI, GPT-5.3, accessed in 2026) to assist with the preparation of the illustrations. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

2.1. Literature Search Strategy

A literature search was conducted using the PubMed, Google Scholar, and eLIBRARY databases covering the period from 2010 to 2026. A total of 69 relevant scientific publications were identified.

The following search strategies were applied in PubMed:

1. For drug delivery systems:
 - (“middle ear” OR “otitis media”) AND (“drug delivery” OR “topical administration” OR “transtympanic”) (47,725 results);
 - (“middle ear” AND (“nanoparticles” OR “nanoemulsion” OR “microemulsion”)) (64);
 - (“tympanic membrane” AND (“permeation enhancer” OR “chemical enhancer”)) (3);
 - (“poloxamer 407” OR “thermosensitive gel” OR “in situ gel”) AND (“middle ear” OR “otitis media”) (21);
 - (“liposomes” OR “transfersomes” OR “niosomes” OR “hyalurosomes”) AND (“middle ear” OR “tympanic membrane”) (21);
 - (“ciprofloxacin” OR “antibiotic”) AND (“sustained release” OR “hydrogel”) AND (“middle ear”) (12);
 - (“biofilm” AND “otitis media” AND “drug delivery”) (9).
2. For active pharmaceutical ingredients:
 - (“acute otitis media” OR “chronic suppurative otitis media”) AND (“antibiotic” OR “topical antibiotic”) AND (“fluoroquinolone” OR “aminoglycoside”) (18);
 - (“ototoxicity” AND (“topical antibiotic” OR “ear drops”)) (75);
 - (“N-acetylcysteine” AND (“otitis media” OR “biofilm”)) (149);
 - (“corticosteroids” AND (“otitis media” OR “tympanic membrane”)) AND (“topical” OR “otic”) (47);
 - (“antiseptic” AND (“otitis media” OR “ear”)) AND (“povidone-iodine” OR “boric acid” OR “hydrogen peroxide”) (37).

After deduplication, articles were screened based on titles and abstracts for relevance to the objectives of the review. Eligible articles were subsequently subjected to full-text analysis. Additional relevant publications were retrieved using manual searches in Google Scholar and eLIBRARY. The selected literature was evaluated in terms of methodological rigor, scientific relevance, and applicability to the objectives of the review. A total of 69 original studies were included in the final analysis.

2.2. Selection Criteria

Inclusion criteria: original peer-reviewed publications published between 2010 and 2026 reporting data on topical drug delivery to the middle ear, drug delivery systems, and active pharmaceutical ingredients used in the treatment of acute and chronic otitis media.

Exclusion criteria: conference abstracts, studies published prior to 2010, and studies in the field of otology not specifically related to otitis media and case reports describing isolated clinical cases.

2.3. Assessment of Study Quality and Level of Evidence

Given the narrative nature of this review and the heterogeneity of the included studies, a formal quality assessment using standardized tools (e.g., Grading of Recommendations Assessment, Development, and Evaluation (GRADE) or the Cochrane Risk of Bias tool) was not performed systematically. Nevertheless, the methodological characteristics and level of evidence of key studies were taken into consideration during data synthesis.

2.4. Rationale for Market Selection

The pharmaceutical markets of Russian Federation, the United States (U.S.), and Japan were selected for analysis based on the following criteria: (1) their affiliation with three distinct regulatory systems: the Eurasian Economic Union (EAEU), the U.S. Food and Drug Administration (FDA), and Pharmaceuticals and Medical Devices Agency (PMDA); (2) differences in the degree of adoption of innovative dosage forms; (3) the availability of publicly accessible national drug registries; (4) the lack of comprehensive comparative studies of otic drug products across these markets; and (5) their practical relevance for developers pursuing global drug registration strategies.

3. Drug Delivery to the Middle Ear

3.1. Features of Topical Drug Delivery to the Middle Ear: Bioavailability Challenges

The absorption of APIs within the tympanic cavity is influenced by multiple factors related to ear anatomy, characteristics of the drug product, and the route of its administration. The main routes include topical administration (e.g., ear drops and semisolid formulations); intratympanic (transtympanic) administration via middle ear injection, which enables direct delivery into the tympanic cavity across the tympanic membrane; transtubal administration using a catheter inserted through the nasopharyngeal opening of the Eustachian tube (although this approach limits control over the delivered dose due to retrograde leakage into the nasopharynx); and oral and parenteral administration relying on systemic circulation for drug distribution to the inner ear.

Achieving a targeted influence on the site of inflammation is particularly important in otitis media, given its pathophysiology. Dysfunction of the Eustachian tube leads to fluid accumulation in the tympanic cavity behind an intact tympanic membrane. Although the cavity is initially sterile, impaired mucociliary clearance and involvement of the nasopharyngeal microbiota contribute to the initiation and persistence of inflammation. Tympanic membrane perforation may occur in cases of highly virulent infection due to enzymatic tissue degradation, whereas in less aggressive infections, persistent exudate and its physicochemical changes may lead to chronicity of the process and permanent hearing loss.

Systemic antibacterial therapy has well-defined indications according to clinical guidelines and is not effective at all disease stages, which necessitates broader use of locally acting formulations targeting the site of inflammation.

The limited variety of topical drug products can be attributed to several factors: challenges in drug delivery while achieving an effective drug concentration, the requirement to avoid oto- and vestibulotoxicity, and the need for the product to maintain pharmacological activity under inflammatory conditions [7].

The choice of administration route is further complicated by limited API absorption across the external auditory canal and the intact tympanic membrane, as well as limited distribution within the middle ear. The external auditory canal is lined with keratinized stratified squamous epithelium and contains ceruminous and sebaceous glands, which may hinder drug penetration and slow API absorption. Its slightly acidic pH (approximately 5–6) may also affect the ionization of active and excipient components.

The tympanic membrane acts as a semipermeable barrier, allowing pharmaceutical ingredients to penetrate primarily while being damaged or via specialized delivery methods such as intratympanic injection. For most compounds, however, it remains largely impermeable. An experimental study in rats [8] evaluating ofloxacin penetration across an intact tympanic membrane demonstrated that topical administration resulted in systemic distribution of the drug and could achieve concentrations comparable to those observed with systemic administration, although the concentration levels varied over time.

A 2023 review of clinical studies and case reports [9] indicates that topical drug products, including ciprofloxacin ear drops, ciprofloxacin and dexamethasone combinations, and the product Otiprio®, are effective in acute otitis media with a perforated tympanic membrane [10]. Notably, some preclinical studies and individual clinical cases have also reported permeability of an intact tympanic membrane to ciprofloxacin [11,12], although these findings require further investigation to elucidate underlying mechanisms and their applicability to other APIs.

Retention of topical formulations in the middle ear is further limited by the drainage and protective functions of the Eustachian tube, mediated by ciliated epithelium and mucociliary clearance directed toward the nasopharynx. While inflammation and increased viscosity of exudate may impair this process, these conditions may also prolong local drug exposure and enhance therapeutic effects.

In addition to anatomical and biomechanical barriers, API absorption is hindered by bacterial biofilm formation, creating an additional biological barrier [13]. Furthermore, API bioavailability is influenced by physicochemical properties, such as lipophilicity (which facilitates enhanced epithelial penetration), molecular weight (smaller molecules are absorbed more rapidly), solubility, and dosage form characteristics.

Considering the anatomical structure of the ear, two principal mechanisms of drug absorption can be identified:

1. Passive diffusion, which represents the primary route of absorption for lipophilic substances across epithelial cell membranes;
2. Transfollicular absorption—the transport of lipophilic and hydrophilic molecules through hair follicles and associated sebaceous glands of the external auditory canal, bypassing the stratum corneum.

Thus, API absorption in the middle ear is a complex process influenced by anatomical characteristics, the type and stage of the pathological condition, physicochemical properties of the drug product, route of administration, and the underlying absorption mechanisms.

3.2. Range of Drug Products for Topical Administration to the Middle Ear and Selection of Dosage Forms

The issue of pharmacotherapy for middle ear diseases remains particularly challenging compared to other otorhinolaryngological conditions, as there is a notable lack of targeted drug products and/or specialized dosage forms capable of addressing the underlying causes of ear diseases. The pharmaceutical markets of the countries analyzed in this review are saturated with similar drug products which share identical active ingredients and, in many cases, the same dosage forms.

Otic formulations are featured in several pharmacopoeias worldwide, including both national and international standards. The United States Pharmacopeia (USP) is one of the leading pharmacopoeias in the world, serving as a reference for the harmonization of national standards, including requirements for therapeutic dosage forms.

Based on an analysis of the USP, several main types of regulated dosage forms intended for administration into the external auditory canal can be identified (Table 1).

Table 1. Range of dosage forms for administration into the external auditory canal according to the USP.

Dosage Form Name	Characteristics
Ear drops (otic solutions/suspensions)	Aqueous or oily solutions or suspensions. Examples include antibiotics (ciprofloxacin), antifungal agents (clotrimazole), and corticosteroids (hydrocortisone).
Suspensions	Solid particles dispersed in a liquid medium (e.g., neomycin/polymyxin B). A key requirement is particle size being $\leq 50 \mu\text{m}$ to minimize irritation.
Semisolid dosage forms	Ointments and gels, typically based on petrolatum or polymers, used to provide prolonged topical effect.

The primary dosage form for the treatment of otitis remains ear drops, which may be either single-component or combination drug products. A major therapy limitation is the restricted range of combination drug products, as most ear drops contain fixed combinations of an antibiotic and a glucocorticosteroid. This limits therapeutic flexibility, particularly in antibacterial and antibiofilm therapy, and may contribute to the development of antimicrobial resistance.

Tables 2–4 present a qualitative analysis of topical otic drug products available on the pharmaceutical markets of the Russian Federation, the United States, and Japan.

Table 2. Analysis of the Russian pharmaceutical market for otic drugs (State Register of Medicines).

Trade Name	Dosage Form	Composition (International Nonproprietary Name, INN)	Pharmacological Effects
Otipax® Biocodex (France)	Ear drops	Lidocaine + Phenazone	Anti-inflammatory, analgesic, local anesthetic
Anauran® Zambon S.p.A (Italy)	Ear drops	Lidocaine, Neomycin, Polymyxin B	Local anesthetic, bactericidal
Otofa® Laboratoires Bouchara-Recordati (France)	Ear drops	Rifampicin	Bactericidal
Lorotox® (Russia)	Ear drops	Phenazone, Lidocaine	Anti-inflammatory, analgesic, local anesthetic
Kombinil® Sentiss Pharma, Pvt. Ltd. (India)	Eye/ear drops	Ciprofloxacin	Bactericidal, anti-inflammatory, antiallergic, antiproliferative
Candibiotic® Glenmark Pharmaceuticals, Ltd. (India)	Ear drops	Beclomethasone, Clotrimazole, Lidocaine, Chloramphenicol	Anti-inflammatory, antiallergic, antifungal, local anesthetic, bacteriostatic
Normax® Ipca Laboratories Ltd. (India)	Eye/ear drops	Norfloxacin	Bactericidal
Otinum® Viatris Healthcare GmbH (Germany)	Ear drops	Choline Salicylate	Anti-inflammatory; exhibits antimicrobial and antifungal activity in acidic and alkaline media
Polydexa® Laboratoires Bouchara-Recordati (France)	Ear drops	Dexamethasone, Neomycin, Polymyxin B	Anti-inflammatory, antiallergic, antiproliferative, antibacterial

Analysis of the Russian pharmaceutical market revealed a predominance of conventional fixed-dose combinations of antibiotics and glucocorticosteroids (Polydexa®, Anauran®), as well as analgesic–anti-inflammatory combinations (Otipax®). No formulations providing sustained drug release, exhibiting proven antibiofilm activity (e.g., acetylcysteine-containing products), or utilizing nanocarrier-based delivery systems (such as liposomes or emulsions) were identified. Several products (Kombinil®, Normax®) are ophthalmic formulations that are used off-label for otic administration, despite not being specifically optimized for drug delivery to the middle ear.

Table 3. Analysis of the U.S. pharmaceutical market for otic drugs.

Trade Name	Dosage Form	Composition (INN)	Pharmacological Effects
Ciprodex®	Ear drops	Ciprofloxacin, Dexamethasone	Anti-inflammatory, antiallergic, antiproliferative, bactericidal
Floxin Otic®	Ear drops	Ofloxacin	Bactericidal
Cortisporin®	Ear drops	Neomycin, Polymyxin B, Hydrocortisone	Anti-inflammatory, antibacterial, bactericidal
Aurodex®	Ear drops	Phenazone, Benzocaine	Anti-inflammatory, analgesic, local anesthetic
Lotrimin®	Ear drops	Clotrimazole	Antifungal
Otiprio®	Ear drops	Ciprofloxacin	Bactericidal

The U.S. pharmaceutical market is characterized by a broader selection of fluoroquinolone-containing products, including Otiprio®, the only approved single-dose formulation administered by a healthcare professional following myringotomy. Nevertheless, all marketed products can be defined as conventional otic drops or suspensions. Cortisporin®, which contains the aminoglycoside neomycin, has limited applicability in cases of tympanic membrane perforation due to the potential risk of ototoxicity.

Table 4. Analysis of the Japanese pharmaceutical market for otic drugs.

Trade Name	Dosage Form	Composition (INN)	Pharmacological Effects
Ciprox® Ear Drops	Ear drops	Ciprofloxacin	Bactericidal
TobraDex® Otic	Ear drops	Tobramycin, Dexamethasone	Bacteriostatic, anti-inflammatory, antiallergic, antiproliferative
Flumethasone Pivalate/Chloramphenicol	Ear drops	Chloramphenicol, Flumethasone	Bacteriostatic, anti-inflammatory
Pimaricin®	Ear drops	Natamycin	Antifungal polyene antibiotic, fungicidal
Gentacidin®	Ear drops	Gentamicin, Betamethasone	Bactericidal, anti-inflammatory

The Japanese pharmaceutical market shares similarities with the European and U.S. markets in terms of the range of antibacterial agents available; however, it is distinguished by the presence of several antifungal products (Pimaricin®) and formulations containing betamethasone.

Analysis of pharmaceutical markets in Russia, the United States, and Japan indicates a lack of topical antiviral drug products and a limited number of antifungal otic drugs. This may be attributed to diagnostic challenges, as viral and fungal otitis are often underdiagnosed or misidentified as bacterial infections, which leads to inappropriate treatment. These factors create significant challenges in clinical practice, especially in the treatment of resistant and chronic forms of ear diseases.

Based on the analysis of the current scientific literature, a key unmet need in otorhinolaryngology is the development of non-invasive drug delivery systems capable of targeting the middle ear via transtympanic delivery without tympanic membrane perforation (myringotomy) [9]. Achieving adequate bioavailability may be possible through the

application of advanced technologies, including stimuli-responsive delivery systems and nano- and microscale carriers for active pharmaceutical ingredients.

3.3. Current Approaches to the Development and Delivery of Drug Products for the Treatment of Middle Ear Diseases

The administration of active pharmaceutical ingredients in their conventional form is often ineffective in the treatment of otitis due to the lack of targeted action at the site of infection and the potential degradation or inactivation of the API prior to exerting its therapeutic effect. Therefore, polymer-based drug delivery systems, in which the API is encapsulated within a polymer matrix, represent a promising direction in formulation development. Such systems are capable of providing high local API concentrations at the site of infection, enabling modified drug release, and reducing API degradation under physiological or pathological conditions (e.g., pH variations). These characteristics contribute to improved therapeutic efficacy, reduced systemic adverse effects, and a lower risk of antimicrobial resistance.

Key directions in the development of novel therapeutic strategies for middle ear diseases include the design of nano- and microscale drug delivery systems (e.g., nanoemulsions, liposomes, glycosomes, and exosomes), the incorporation of permeation enhancers into conventional dosage forms to facilitate transport across the tympanic membrane, and the development of stimuli-responsive in situ systems capable of prolonging drug residence time and enhancing membrane permeability through polymer-mediated mechanisms.

3.3.1. Nano- and Microemulsions

The development of nanoemulsions represents a promising alternative to conventional drug formulations due to their ability to improve drug delivery efficacy. Nano- and microemulsions are systems composed of an oil phase, water, and surfactants. However, it is important to note that there is no universal consensus in the literature regarding the precise size ranges of nano- and microemulsions. In the present review, nanoemulsions are defined as systems with droplet sizes of 20–200 nm, whereas microemulsions are considered to have droplet sizes of 100–500 nm. Nevertheless, these size ranges may vary across different literature sources.

Microemulsions are thermodynamically stable systems, whereas nanoemulsions are generally considered kinetically stable, as their formation requires external energy input and they are inherently prone to gradual degradation over time. For the purposes of this review, the term “nano/microemulsions” is used collectively to refer to emulsion-based systems with droplet sizes below 500 nm that are capable of passive diffusion across epithelial barriers.

Their small droplet size provides a large surface area, thereby improving drug solubility and permeation. Such emulsions are versatile dosage forms applicable across multiple therapeutic areas, including otorhinolaryngology, as they can encapsulate both hydrophilic and hydrophobic compounds.

A schematic representation of the generalized structure of a nanoemulsion is shown in Figure 3.

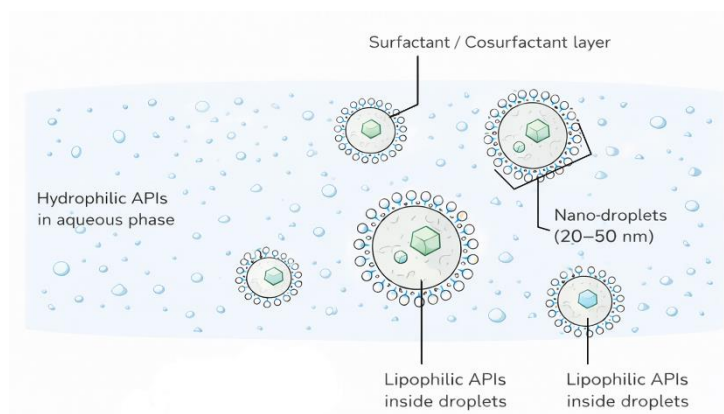


Figure 3. Schematic representation of the generalized structure of a nanoemulsion.

Nanoemulsions possess several advantages applicable to middle ear delivery, including enhanced penetration through physical barriers, such as cerumen in the external auditory canal and inflammatory exudate, allowing the drug to reach the site of infection. Additionally, their ability to provide modified drug release contributes to prolonged therapeutic effects and may reduce dosing frequency [14]. Nanoemulsions are considered an advanced technology for improving drug bioavailability due to their capacity to enhance solubility, stability, and enable targeted delivery.

Recent studies are focused on the development of nanoemulsion-based formulations with antifungal [15] and antibacterial activity [16]. In particular, polymer-based antibiotic drug products have been investigated, in which broad-spectrum antibiotics (e.g., josamycin, clarithromycin, levofloxacin) are incorporated into submicron spherical particles. These polymeric formulations demonstrate antibacterial activity against Gram-positive, Gram-negative, and atypical bacteria. In vivo studies using a murine model of staphylococcal sepsis have shown a 1.5-fold increase in efficacy of the polymeric drug product compared to the corresponding drug substances.

Nanotechnology-based drug delivery systems are also being explored to target bacterial biofilms and antimicrobial resistance. Current research is focused on identifying novel compounds capable of disrupting biofilms, thereby improving treatment outcomes in patients with otitis media. Considerable interest is attracted to nano- and microparticulate polymer carriers that facilitate the delivery of antimicrobial substances for biofilm eradication [17]. Polymers such as chitosan, polycaprolactone, and their combinations are widely investigated for this purpose.

A novel strategy for the treatment of middle ear infections involves the use of nanofibrous scaffolds composed of ethyl cellulose and polyhydroxybutyrate, which are loaded with ciprofloxacin and amoxicillin. As part of this approach, drug-loaded nanofibrous matrices were fabricated using electrospinning from biocompatible ethyl cellulose and biodegradable polyhydroxybutyrate. In in vivo studies conducted in Sprague–Dawley rats, the highest drug concentration demonstrated the most pronounced therapeutic effect [18].

3.3.2. Vesicular Systems for Middle Ear Drug Delivery

Topical delivery of antibiotics across an intact tympanic membrane for the treatment of middle ear infections remains challenging due to its low permeability, which restricts the passage of most molecules through the outer epidermal layer. Consequently, significant efforts are focused on the development of formulations in which APIs are incorporated into liposomes [19] or glycosomes (glycerol-modified vesicular systems designed to enhance mucoadhesion) [20]. These vesicular systems enhance therapeutic efficacy by stabilizing active ingredients, facilitating cellular and tissue uptake, and improving drug biodistribution at target sites in vivo, while minimizing systemic toxicity.

Recent studies indicate that antibiotic-loaded liposome usage might be a promising strategy for overcoming the intact tympanic membrane in acute otitis media, demonstrating high drug delivery efficiency. Optimization of liposome surface charge remains a key challenge: positively charged vesicles exhibit enhanced penetration ability through the intact stratum corneum, whereas negatively charged liposomes may be more effective under infectious conditions due to complement activation and subsequent neutrophil-mediated phagocytosis [19]. In addition, encapsulation of glucocorticosteroids into microcarriers is an important emerging area of research [20].

A schematic representation of the generalized structure of a vesicle (liposome) is shown in Figure 4.

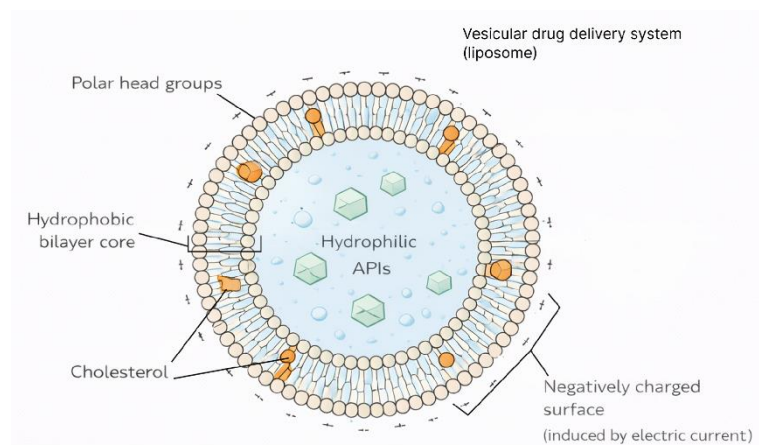


Figure 4. Schematic representation of the generalized structure of a vesicle (liposome).

Dexamethasone is one of the most widely used agents in topical otic therapy and is typically administered either intratympanically or systemically. In one of the studies [20], a biopolymer lipid hybrid microcarrier system was developed to improve local drug delivery and provide prolonged drug release at the site of the middle ear membrane. Encapsulation efficiency and in vitro drug release were assessed using UV–visible spectroscopy, demonstrating high encapsulation efficiency and prolonged release for up to six days.

For more than a decade, a research group from Cairo University (Egypt) has been investigating vesicular carriers for transtympanic drug delivery. Early studies reported the development of ciprofloxacin-loaded nanotransfersomes created using the thin-film hydration method with absorption enhancers characterized by different hydrophilic–lipophilic balance (HLB) values. Transfersomes are ultradeformable liposomes containing edge activators (e.g., sodium cholate), which are capable of traversing pores smaller than their own diameter. An optimized formulation consisting of phospholipids and sodium cholate (5:1 molar ratio) demonstrated superior drug permeation into the middle ear compared to Ciprocyn® ear drops [21].

Subsequent studies proposed the incorporation of ciprofloxacin into nanoelastic vesicles created using Span 60 as a base [22]. More recent work (2025) has focused on microvesicular drug delivery systems, such as novasomes (nonionic surfactant-based vesicles with enhanced physicochemical stability) and hyalurosomes (hyaluronic acid-containing hybrid vesicular systems characterized by high mucoadhesive properties). These systems demonstrated enhanced antibacterial activity, with lower minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values against *Staphylococcus aureus* and *Pseudomonas aeruginosa* compared to control formulations. Notably, biofilm inhibition was observed even at sub-MIC concentrations, highlighting the therapeutic potential of developed formulations [23,24].

These studies were conducted in accordance with modern pharmaceutical development standards, employing a Quality by Design (QbD) approach and factorial design implemented via Design-Expert® software, thereby supporting the robustness and potential clinical applicability of the investigated formulations.

3.3.3. Stimuli-Responsive Drug Delivery Systems

Stimuli-responsive (in situ) drug delivery systems have been investigated since the late 20th century [25]. For drug products for mucosal application, they enable an optimal balance between convenience of administration in liquid form and improved biopharmaceutical properties, including prolonged residence time and enhanced bioavailability, achieved through strong mucoadhesion and gel formation at the site of administration.

The generalized schematic structure of a stimuli-responsive drug delivery system is presented in Figure 5.

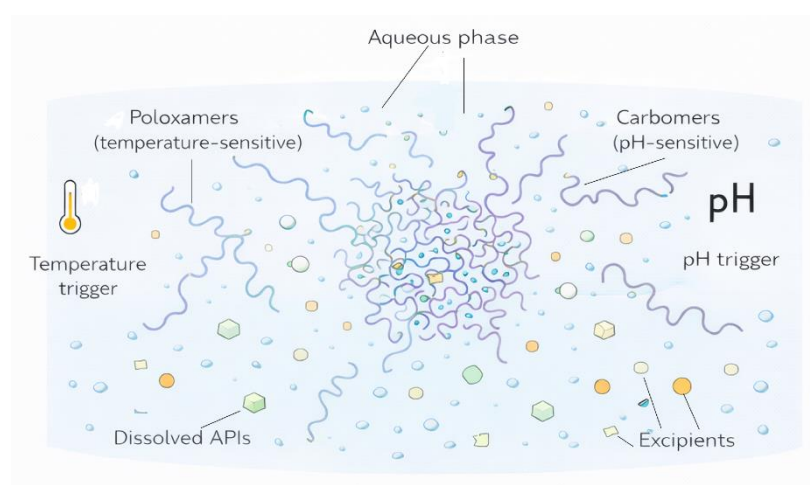


Figure 5. Generalized schematic structure of a stimuli-responsive drug delivery system.

Currently, thermosensitive systems based on poloxamer are investigated for their potential to prolong drug release and facilitate drug delivery across the tympanic membrane to the site of middle ear mucosa [26]. In 2016, a ciprofloxacin delivery system based on a poloxamer 407 and polybutylphosphoester matrix was developed for prolonged antimicrobial therapy. In a chinchilla model of otitis media, complete resolution was observed in 100% of treated animals, compared to 62.5% (by day 7) in the control group receiving conventional 1% ciprofloxacin ear drops. The hydrogel system demonstrated good biocompatibility and no detectable systemic drug levels, confirming localized drug delivery [27].

However, most studies indicate that poloxamer 407-based thermosensitive systems alone are insufficient to permeate the tympanic membrane barrier without additional actions such as permeation enhancer usage or mechanical intervention. This limitation may also be related to the physicochemical properties of the API [8].

The safety of poloxamer-based drug delivery systems for intratympanic injection was demonstrated as early as 2014 [28]. The formulation OTO-201 provided sustained ciprofloxacin release in the middle ear for a period starting from several days and up to two weeks, depending on the dose. No pathological changes were observed in the middle or inner ear of treated guinea pigs, whereas comparator formulations (Ciprodex® and Cetraxal®) showed signs of cochlear ototoxicity. Therefore, no side effects were observed for the poloxamer 407-based drug delivery system in the study.

In a study [29] a thermosensitive poloxamer 407 hydrogel containing 4.0% N-acetylcysteine (NAC) was evaluated following intratympanic injection in female guinea pigs. A

total of 49 animals were randomized into two treatment groups, receiving either a single intratympanic injection of a 4% NAC poloxamer 407 hydrogel or a 4% NAC solution. An additional eight animals served as untreated controls. NAC concentrations in perilymph, cerebrospinal fluid, and plasma were monitored over a 24 h period. Intratympanic administration of the 4% NAC poloxamer 407 hydrogel resulted in a fourfold increase in the area under the concentration–time curve (0–24 h) for perilymph compared to local administration of an equivalent concentration NAC solution, while plasma NAC levels remained comparable between the groups. NAC concentrations in cerebrospinal fluid were below the limit of detection (5 ng/mL) in both treatment groups. These findings demonstrate that intratympanic injection of thermosensitive poloxamer 407-based hydrogels enhances and prolongs NAC delivery to the inner ear. Given the observed low NAC concentration levels in plasma following local administration, along with the physiological pH and osmolality of the hydrogel, the risk of local adverse effects was considered minimal by the investigators [29].

The use of ultrasound has been proposed to enhance permeation across the tympanic membrane of thermosensitive gels administered into the external auditory canal. A thermosensitive formulation based on poloxamer 407 (10.0–12.5%) and dexamethasone, evaluated *in vivo* in a guinea pig model, demonstrated a 109.13% and 66.67% increase in dexamethasone delivery efficiency on days 1 and 7, respectively, following ultrasound exposure compared to a control group receiving the formulation without ultrasound exposure. Safety assessment conducted on day 28 post-administration revealed no significant changes in hearing thresholds and no structural damage to the cochlea or middle ear. Notably, this study was the first to demonstrate that the use of a thermosensitive system enables prolonged dexamethasone release in the middle ear for at least seven days [30].

In the study [31], a novel approach to antibiotic delivery to the middle ear was described, involving a topical thermosensitive hydrogel depot containing poly(lactic-co-glycolic acid) (PLGA) microspheres. The results from *in vitro* and *ex vivo* studies indicated that the developed formulation facilitated drug delivery to the middle ear at therapeutically relevant concentrations for up to 14 days. Animal studies further demonstrated that sufficient amounts of the antibiotic were released from the microsphere-based system to achieve therapeutic efficacy as early as 24 h after bacterial inoculation following topical administration [31]. This study is among the few reports of thermosensitive systems capable of facilitating drug transport across the tympanic membrane without mechanical intervention or permeation enhancers.

At the same time, the role of excipients that enhance transmembrane permeability of the tympanic membrane has been investigated in multiple studies. For instance, in the study [32], a poloxamer 407-based thermosensitive hydrogel for ciprofloxacin delivery across the tympanic membrane was tested using the incorporated bupivacaine, limonene, and sodium dodecyl sulfate as permeation enhancers. The results demonstrated that formulations containing enhancers had minimal impact on hearing thresholds and tissue response *in vivo* [32].

3.3.4. Permeation Enhancers

As previously described, many drug delivery systems for the middle ear effectively address the challenge of prolonged drug release; however, overcoming the barrier of the tympanic membrane remains a significant limitation [16].

The usage of chemical permeation enhancers remains a well-established and safe strategy for enabling non-invasive drug delivery across biological barriers, including both the skin and the tympanic membrane [33]. However, when selecting enhancers for topical formulations intended for middle ear application, several factors must be considered, including their potential irritant effects, the risk of ototoxicity, and their interactions with

the delivery system. It has been reported that certain enhancers may interfere with or even inhibit gel formation, negatively affect formulation stability, and alter API diffusion. Therefore, further investigation of interactions between permeation enhancers and hydrogel systems is required, particularly for compounds such as sodium dodecyl sulfate and methyl laurate [34].

Certain well-established active pharmaceutical ingredients may also serve as permeation enhancers to facilitate transport across the tympanic membrane. For example, in addition to its primary local anesthetic effect, bupivacaine has been investigated as a permeation enhancer for non-invasive transtympanic drug delivery. In studies [32,35], bupivacaine was used as part of chemical permeation enhancer combinations, together with sodium dodecyl sulfate and limonene, to increase ciprofloxacin flux across the intact tympanic membrane. The mechanism of action of enhancers such as bupivacaine is associated with their ability to disrupt the structural integrity of lipid bilayers in the stratum corneum, thereby facilitating the diffusion of therapeutic molecules [35]. A study [32] demonstrated that the incorporation of bupivacaine into a poloxamer 407-based hydrogel formulation not only increased tympanic membrane permeability but also provided prolonged action after a single application, while exerting minimal effects on hearing thresholds and tissue response *in vivo* [32].

Another study [35] demonstrated that combinations of permeation enhancers, including bupivacaine, exhibited a synergistic effect, with synergy being most pronounced at earlier time points (6 h) compared with later time points (48 h). These combinations also significantly increased the maximum achievable drug flux compared with individual enhancers [35].

The use of combinations of permeation enhancers to achieve synergistic effects and improve drug transport across the tympanic membrane has been widely discussed in the scientific community. The combination of sodium dodecyl sulfate, limonene, and bupivacaine hydrochloride has been studied using isobolographic analysis, where transtympanic flux of ciprofloxacin was measured for each enhancer individually, and isobolograms were plotted for enhancer pairs. The results demonstrated that synergistic effects were more pronounced at earlier time points (6 h) compared to later ones (48 h). Synergy was also observed in the combination of all three agents. Notably, combinations of enhancers significantly increased the maximum concentration of ciprofloxacin in the middle ear compared to individual enhancers [35].

In addition, a study [34] demonstrated that ciprofloxacin and methyl laurate form a pseudo-surfactant system that markedly enhances transtympanic drug transport. In a chinchilla model of acute otitis media, ciprofloxacin concentrations in the middle ear increased by approximately 70-fold, resulting in improved therapeutic efficacy and biocompatibility compared to previously developed drug delivery systems [34].

Overall, further evidence-based studies are required to fully assess the potential of enhancer combinations for overcoming the tympanic membrane barrier and enabling effective drug delivery to the middle ear. Nevertheless, the effectiveness of this approach is already strongly supported by existing data [36].

3.4. Safety Considerations of Excipients and Drug Delivery Systems

Most publications analyzed in this review focus primarily on the ototoxicity of active pharmaceutical ingredients, particularly aminoglycosides [37,38] as well as the potential ototoxicity of certain antiseptic agents [39,40]. However, the safety of excipients and drug delivery carriers represents an equally important consideration.

Potential safety concerns are associated with several categories of formulation components. Chemical permeation enhancers, including sodium dodecyl sulfate, limonene,

and bupivacaine, may induce reversible or irreversible damage to the tympanic membrane epithelium following prolonged exposure [32,35]. Additional risks may arise from residual monomers and solvents present in polymer-based drug delivery systems, such as unreacted ethylene oxide residues in poloxamer formulations. Furthermore, the *in vivo* degradation products of polymeric carriers may affect local tissue homeostasis; for example, acidic degradation products of PLGA can reduce local pH and potentially induce sterile inflammatory reactions.

Preclinical studies conducted in chinchillas and guinea pigs demonstrated no significant elevation of hearing thresholds following a single administration of poloxamer 407 hydrogels over observation periods of up to 14 days [28,29]. Nevertheless, long-term safety studies extending beyond one month, as well as investigations of chronic exposure, remain unavailable for the majority of innovative drug delivery systems. In particular, the effects of repeated administration on cochlear hair cells within the organ of Corti and on the vestibular neuroepithelium have not been adequately investigated.

These limitations should be carefully considered when extrapolating preclinical findings to clinical practice and when designing future studies. Until standardized protocols for assessing the ototoxicity of excipients and delivery system components become available, none of the vesicular or stimuli-responsive systems described in this review can be unequivocally recommended for clinical use, particularly in pediatric patients and in individuals with a perforated tympanic membrane.

4. Selection of Active Pharmaceutical Ingredients in the Treatment of Acute and Chronic Otitis Media

In addition to the development of effective drug delivery systems, a clear understanding of the properties of the delivered API is essential, as the choice of an appropriate carrier is directly determined by the physicochemical characteristics of the active ingredient. Currently, antibacterial and antifungal drug products, anti-inflammatory drugs (primarily glucocorticosteroids), analgesics, and keratolytics, as well as other ingredients, products, and their combinations, are used for the treatment of acute and chronic otitis media. The selection of the API depends on multiple factors, including disease etiology, its stage, and individual patient characteristics.

4.1. Antibacterial Drugs

4.1.1. Systemic Beta-Lactam Antibiotics

Penicillins

Systemic antibiotic therapy remains central to the treatment of acute otitis media, despite the increasing adoption of a watchful waiting strategy over the past two decades, involving the use of analgesics and delayed antibiotic prescribing to reduce the risk of adverse effects. Nevertheless, systemic antibiotics continue to be widely prescribed due to the significant risk of serious infectious complications in their absence [41].

According to the studies, most European clinical guidelines recommend systemic beta-lactam antibiotics as first-line therapy for acute otitis media in children. In approximately 82% of cases, oral amoxicillin is prescribed (with high-dose regimens used in about 50% of cases). In cases of treatment failure, oral or intravenous amoxicillin–clavulanic acid is frequently recommended [42,43].

Amoxicillin is underlined as the drug of first choice due to its high efficacy, favorable safety profile, and lower impact on the microbiome [43].

Cephalosporins

In cases of penicillin intolerance or suspected resistance of *Streptococcus pneumoniae*, second- and third-generation cephalosporins are recommended as second-line therapy agents. These include cefdinir, cefpodoxime, cefuroxime, or intramuscular ceftriaxone. However, these regimens are generally considered less effective than amoxicillin and may demonstrate reduced activity against *Haemophilus influenzae* or *S. pneumoniae* [44].

At the same time, evidence suggests that cephalosporins may demonstrate comparable clinical efficacy to amoxicillin/clavulanate in children with acute otitis media with effusion, while cefuroxime has been associated with improved tolerability [45].

4.1.2. Macrolides

Macrolides (e.g., azithromycin, clarithromycin) are currently considered an alternative in cases of true beta-lactam allergy. However, their therapeutic efficacy is generally lower than that of beta-lactams due to increasing resistance of *S. pneumoniae* and *H. influenzae* to macrolides. In addition, bacterial biofilms have been shown to exhibit greater resistance to azithromycin compared to amoxicillin. Therefore, the widespread use of macrolides is not considered rational [44].

Overall, systemic antibiotic therapy remains the most commonly used treatment approach for acute otitis media, particularly in pediatric practice. Amoxicillin is the most frequently prescribed agent due to its favorable balance of efficacy and safety. In cases of antimicrobial resistance risk, second- and third-generation cephalosporins are used, while macrolides are reserved for patients with beta-lactam allergy. Systemic antibiotics are also used for prophylaxis of otitis; however, the currently high rate of antibiotic prescribing is not justified from the standpoint of preventive use.

4.1.3. Antibiotics for Topical Administration

Given the high risk of adverse effects associated with systemic antibiotic therapy, topical formulations are also widely used, particularly fluoroquinolones and aminoglycosides. The use of topical agents is especially relevant in the treatment of chronic otitis media. Studies have not reported a high incidence of ototoxicity or other adverse events, such as otalgia, associated with these formulations [46].

Fluoroquinolones

Available evidence indicates that, when comparing topical and systemic quinolones, no significant advantage of systemic therapy has been demonstrated. Topical formulations have been shown to reduce otorrhea, with a modest acceleration of symptom resolution. Furthermore, the addition of oral therapy to topical treatment does not result in a significant increase in therapeutic efficacy [47].

Fluoroquinolones are primarily used as first-line therapy for chronic otitis media with a perforated tympanic membrane, particularly in pediatric patients. Recent reviews suggest that fluoroquinolones have a more favorable safety profile compared to aminoglycosides, while topical formulations demonstrate comparable efficacy to systemic therapy. However, fluoroquinolones are generally ineffective against bacterial biofilms, which may complicate treatment outcomes [48].

Topical fluoroquinolone formulations are often combined with glucocorticosteroids (e.g., in otic drops and suspensions), providing rapid relief of pain and pruritus, reduction of edema, and faster onset of clinical effect compared to monotherapy.

Aminoglycosides

Aminoglycosides are currently used as an alternative to fluoroquinolones in cases of allergy or lack of efficacy of the latter.

They exhibit high activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and a range of Gram-negative bacteria, with clinical efficacy comparable to that of fluoroquinolones. However, aminoglycosides are associated with a less favorable safety profile and a higher incidence of adverse reactions. Prolonged use increases the risk of vestibulotoxicity, particularly in patients with a perforated tympanic membrane [37,38].

Aminoglycoside-containing formulations are most commonly available as combination products (e.g., neomycin/polymyxin B/hydrocortisone, framycetin/gramicidin/dexamethasone). The inclusion of glucocorticosteroids allows for a more rapid clinical response compared to monotherapy.

In summary, fluoroquinolones and aminoglycosides are the most commonly used agents for the topical treatment of chronic otitis media. Fluoroquinolones offer a more favorable efficacy–safety balance and are, therefore, preferred, particularly in pediatric patients and in cases involving tympanic membrane perforation. Aminoglycosides may be used when fluoroquinolones are ineffective; however, their use is associated with risks of oto- and vestibulotoxicity. Notably, both classes of antibiotics demonstrate limited efficacy against bacterial biofilms when used as monotherapy.

Table 5 provides a comparative overview of antibacterial APIs with potential for incorporation into otic drug products.

Table 5. Comparison of antibacterial active pharmaceutical ingredients.

Group	Examples	Strengths	Threats
Systemic penicillins	Amoxicillin; amoxicillin/clavulanate	1. High efficacy 2. Good tolerability 3. Minimal impact on the ear microbiome	1. Increasing antimicrobial resistance of bacteria 2. Risk of systemic adverse effects
Systemic second- and third-generation cephalosporins	Cefdinir, cefpodoxime, cefuroxime, ceftriaxone	1. Good tolerability 2. Alternative for penicillin-allergic patients 3. Higher clinical efficacy than amoxicillin/clavulanate combination	1. Potentially reduced activity against <i>H. influenzae</i> and <i>S. pneumoniae</i> compared to amoxicillin
Systemic macrolides	Azithromycin, clarithromycin	1. Alternative for patients with beta-lactam allergy	1. Lower therapeutic efficacy compared to beta-lactams 2. Resistance of <i>S. pneumoniae</i> and <i>H. influenzae</i> 3. Limited activity against biofilms
Topical fluoroquinolones	Ciprofloxacin (otic drops/suspension)	1. Safe in cases of tympanic membrane perforation 2. Comparable efficacy to systemic therapy 3. Frequently combined with glucocorticosteroids (rapid symptom relief)	1. Limited activity against biofilms 2. Monitoring required during prolonged use
Topical aminoglycosides	Neomycin/polymyxin B/glucocorticosteroid; framycetin/gramicidin/dexamethasone	1. High activity against <i>P. aeruginosa</i> and <i>S. aureus</i> 2. Frequently combined with glucocorticosteroids (rapid symptom relief)	1. Less favorable safety profile compared to fluoroquinolones 2. Risk of oto- and vestibulotoxicity, especially with prolonged use or tympanic membrane perforation

4.2. Anti-Inflammatory and Analgesic Agents

In addition to etiological (causal) therapy, symptomatic treatment is often required, in which anti-inflammatory agents play a key role. Both nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroids are commonly used for this purpose.

4.2.1. NSAIDs

As pain is the primary symptom of acute otitis media, current clinical guidelines recommend the use of analgesics regardless of whether antibiotic therapy is prescribed. However, clinicians are advised to carefully balance the potential benefits of ibuprofen against its possible risks [49]. In clinical practice, paracetamol and ibuprofen are most frequently used and are considered essential components of the watchful waiting strategy prior to antibiotic prescription. Oral formulations are predominantly employed [50].

Although evidence regarding the efficacy of paracetamol and ibuprofen for pain relief in acute otitis media remains limited, both agents have demonstrated superiority over placebo, with no significant difference in efficacy between them. Their safety profiles are broadly comparable, and both are generally well tolerated at therapeutic doses. However, paracetamol may be associated with hepatotoxicity, whereas ibuprofen may cause gastrointestinal adverse effects and is contraindicated in patients with peptic ulcer disease or gastrointestinal bleeding [51].

Overall, NSAIDs remain first-line agents for pain management in acute otitis media. In pediatric practice, paracetamol is generally preferred due to its favorable safety profile; however, these drugs should be used with caution because of the potential risk of adverse effects.

4.2.2. Glucocorticosteroids

Glucocorticosteroids are used to reduce inflammation and edema in both acute and chronic otitis media and to alleviate pain. As a result, they are frequently included in combination topical formulations, particularly alongside antibiotics. Topical administration allows direct delivery to the site of inflammation while minimizing systemic adverse effects [52].

The most commonly used agents include hydrocortisone and dexamethasone (in ear drops), as well as mometasone, budesonide, beclomethasone, and, less frequently, flunisolide or fluticasone (in intranasal or intratympanic formulations) [53,54].

Among combination therapies, hydrocortisone-containing regimens with aminoglycosides (e.g., neomycin + polymyxin B + hydrocortisone; bacitracin + colistin + hydrocortisone) have been extensively studied. These combinations demonstrate a favorable safety profile and provide faster symptom relief and clinical improvement. However, the inclusion of aminoglycosides introduces a risk of ototoxicity, and hydrocortisone is generally considered less potent than dexamethasone [53,55].

Dexamethasone is commonly used in combination with fluoroquinolones (e.g., ciprofloxacin + dexamethasone) and exhibits a more pronounced anti-inflammatory effect, leading to faster reduction of edema, pain, and otorrhea. However, evidence suggests that dexamethasone may inhibit healing of a perforated tympanic membrane and increase the risk of steroid-associated adverse effects, necessitating caution in patients with a perforated tympanic membrane and careful control of treatment duration [56,57].

Intranasal glucocorticosteroids (e.g., mometasone furoate, budesonide, fluticasone propionate) are used in cases of Eustachian tube dysfunction, as well as in otitis associated with adenoiditis or allergic rhinitis [58,59].

In summary, glucocorticosteroids are most commonly used as components of combination topical formulations, primarily to reduce inflammation, relieve edema, and alleviate pain. While they contribute to improved clinical outcomes, their use requires careful

consideration of potential risks, including slowed tympanic membrane healing and ototoxicity (particularly in combination with aminoglycosides).

A summary of APIs' characteristics from the NSAID and analgesic groups is presented in Table 6.

Table 6. Comparison of NSAIDs and analgesics.

Group	Examples	Strengths	Threats
Oral NSAIDs/analgesics	Paracetamol, ibuprofen	1. Effective for pain relief in acute otitis media 2. Essential for watchful waiting strategy 3. Good tolerability at therapeutic doses	1. Risk of hepatotoxicity (paracetamol) 2. Gastrointestinal adverse effects and contraindications (ibuprofen) 3. Limited evidence supporting efficacy
Topical otic glucocorticosteroids	Hydrocortisone, dexamethasone	1. Rapid symptom relief 2. Absence of systemic adverse effects	1. Risk of ototoxicity when combined with aminoglycosides 2. Dexamethasone may delay healing of tympanic membrane perforation and increase steroid-related adverse effects 3. Duration of therapy has to be limited
Intranasal glucocorticosteroids	Mometasone furoate, budesonide, fluticasone propionate	1. Effective in otitis associated with adenoiditis or allergic rhinitis 2. Improve middle ear ventilation via effects on the nasopharynx and Eustachian tube	1. Requires prolonged use 2. Risk of steroid-associated adverse effects
Combination products (antibiotic + glucocorticosteroid)	Neomycin/polymyxin B/hydrocortisone; bacitracin/colistin/hydrocortisone; ciprofloxacin/dexamethasone	1. Faster clinical improvement compared to antibiotic monotherapy 2. Both symptomatic and pathogen-targeted effects are present 3. No systemic adverse effects	1. Risk of ototoxicity (especially with aminoglycosides) 2. All the risks of topical glucocorticosteroids

4.3. Antiseptics and Keratolytic Agents

Drugs with antiseptic effect also warrant attention, as they act as non-specific antimicrobial agents, do not cause the development of antimicrobial resistance, and contribute to ear hygiene, which plays an important role in the treatment of otitis.

Antiseptics

Antiseptics are used as adjuncts to standard therapy for both acute and chronic otitis media. Unlike antibiotics, they do not induce antimicrobial resistance and do exhibit activity against bacterial biofilms. The most commonly used agents include boric acid, miramistin (benzyl dimethyl [3-(myristoylamino) propyl] ammonium chloride), povidone-iodine, hydrogen peroxide, and acetic acid.

Boric acid exerts a bacteriostatic effect by altering the pH within the ear. One of its key strengths is its demonstrated in vitro activity against biofilms formed by methicillin-resistant *Staphylococcus aureus* (MRSA) and quinolone-resistant *Pseudomonas aeruginosa*. In addition, there is no conclusive evidence of ototoxicity associated with boric acid [60,61]. However, since boric acid is most commonly used in alcohol-based formulations, its administration may be associated with local discomfort, including burning, itching, and dryness.

Hydrogen peroxide is widely used for irrigation of the external auditory canal to remove purulent discharge. It acts as an effective cleansing agent, facilitating removal and softening of purulent material, thereby improving the permeation of other drug products. However, the release of gas bubbles associated with its usage may cause discomfort, and hydrogen peroxide itself may interfere with tissue healing [60,61].

Povidone-iodine is also commonly used for irrigation and instillation due to its effectiveness in reducing ear discharge. However, there is evidence suggesting potential ototoxicity, which necessitates its cautious usage [39,40].

Overall, antiseptic agents serve as adjunctive therapy in the treatment of acute and chronic otitis media. The choice of a specific agent should be guided by individual patient tolerability.

A summary of APIs from this pharmacological group is presented in Table 7.

Table 7. Comparison of antiseptic APIs.

Group	Examples	Strengths	Threats
Acidic solutions	Boric acid	1. Broad, non-specific antimicrobial activity 2. Does not promote antimicrobial resistance; active against MRSA and quinolone-resistant <i>P. aeruginosa</i> biofilms in vitro 3. No conclusive evidence of ototoxicity	1. Alcohol-based formulations may cause burning, itching, and dryness 2. Requires caution in cases of tympanic membrane perforation
Surfactant antiseptics	Miramistin (benzyl dimethyl [3-(myristoylamino) propyl] ammonium chloride)	1. Broad, non-specific antimicrobial activity 2. Does not promote antimicrobial resistance, exhibits activity against biofilms	Primarily used as an adjunctive therapy
Oxidizing agents	Hydrogen peroxide	1. Effective cleansing of the external auditory canal 2. Enhances permeation of other drug products	1. Associated gas formation may cause discomfort 2. Potential impairment of tissue healing 3. Not suitable for prolonged use
Iodine-containing agents	Povidone-iodine	1. Broad-spectrum antiseptic activity 2. Effective reduction of ear discharge	1. Potential ototoxicity 2. Requires caution in cases of tympanic membrane perforation

4.4. Other Pharmacological Groups of Active Pharmaceutical Ingredients

4.4.1. Mucolytics

Mucolytic agents such as carbocysteine, acetylcysteine (N-acetylcysteine, NAC), bromhexine, and ambroxol are used in the treatment of otitis media. These agents are primarily used to facilitate the drainage of purulent secretions and promote their breakdown. In addition, evidence suggests that certain mucolytics, particularly NAC, may exhibit activity against bacterial biofilms [62].

Acetylcysteine is one of the most extensively studied representatives of this group, particularly regarding its mechanism of action. By disrupting disulfide bonds, it alters the viscoelastic properties of mucus, enhancing the clearance of exudate. Furthermore, NAC has been shown to exhibit antibiofilm activity: it interferes with bacterial adhesion and biofilm formation and is capable of partially disrupting mature biofilms formed by *Pseudomonas aeruginosa*, MRSA, and other otitis-associated pathogens. In addition, NAC has

been reported to potentiate the activity of antibiotics, including ciprofloxacin and vancomycin [63].

4.4.2. Topical Anesthetics

Topical anesthetics are commonly used as components of combination formulations (e.g., Otipax® ear drops containing phenazone and lidocaine) to provide rapid symptom relief via local anesthetic and anti-inflammatory effects. It has been noted that these formulations do not cause systemic adverse effects typical of oral analgesics. Studies indicate that combination products containing topical anesthetics can relieve pain within the first minutes after administration.

However, these agents are contraindicated in the presence of tympanic membrane perforation due to the risk of entry into the middle ear, where they may exhibit ototoxic effects and cause local irritation [64].

A summary of the key characteristics of APIs from these pharmacological groups is presented in Table 8.

Table 8. Comparison of APIs from other pharmacological groups.

Group	Examples	Strengths	Threats
Mucolytics	Carbocisteine, bromhexine, ambroxol, acetylcysteine	1. Facilitate liquefaction of purulent secretions and improve drainage 2. Acetylcysteine exhibits antibiofilm activity (disrupts biofilm formation and structure) 3. Enhances antibiotic activity	1. Not recommended in cases of tympanic membrane perforation 2. Risk of cytotoxicity at high concentrations
Topical anesthetics	Phenazone, lidocaine	1. Rapid pain relief 2. Favorable tolerability profile 3. No systemic adverse effects observed	1. Not recommended for prolonged use 2. Contraindicated in cases of tympanic membrane perforation 3. Potential ototoxicity 4. Risk of local irritation

4.5. Prospects for the Development of Combination Drug Products for the Treatment of Middle Ear Diseases

At present, combination therapy represents one of the most promising strategies for middle ear disease treatment, as the usage of combination drug products enables simultaneous targeting of both etiological and pathogenetic mechanisms, while also allowing for rapid improvement in clinical outcomes. The most common combinations include “antibiotic + glucocorticosteroid”, “antibiotic + mucolytic/antibiofilm agent”, and “analgesic + NSAID/glucocorticosteroid”.

4.5.1. Combination of Antibiotics and Glucocorticosteroids

One of the most widely used combinations is applied in both acute and chronic suppurative otitis media. However, the clinical efficacy of antibiotic–glucocorticosteroid combinations in the treatment of chronic otitis media has not been conclusively demonstrated, particularly in regard to achieving a “dry ear” state. Evidence suggests that combinations of topical fluoroquinolone antibiotics with glucocorticosteroids may be comparable in efficacy to placebo or no treatment [65]. Furthermore, the review indicates that a steroid addition is unlikely to significantly influence the rate of cessation of otorrhea within 1–2 weeks. There is also evidence that fluoroquinolones alone may be more effective in achieving a “dry ear” state than aminoglycoside–steroid combinations [65]. The choice of antibiotic class appears to be a key determinant of therapeutic outcome, as fluoroquinolones

(even without steroids) may provide superior results compared to aminoglycoside-based combinations, while also presenting a lower risk of ototoxicity [65].

In contrast, in the treatment of acute otitis media in patients with tympanostomy tubes, antibiotic–glucocorticosteroid combinations demonstrate significantly higher efficacy. It has been shown that the ciprofloxacin/dexamethasone combination reduces the time to cessation of otorrhea by approximately 20%—an important clinical effect, particularly in pediatric patients. Notably, this combination has not demonstrated significant ototoxicity [65].

4.5.2. Combinations of Antibiotics with Mucolytics/Antibiofilm Agents

In light of the growing challenge of antimicrobial resistance, including the formation of bacterial biofilms, there is increasing interest in the development of combination therapies incorporating antibiofilm agents, particularly acetylcysteine. Several studies have demonstrated that acetylcysteine alone can disrupt bacterial adhesion and inhibit biofilm formation. Effective activity has been observed at concentrations above 0.5%, which are not associated with toxicity [66].

Moreover, the addition of acetylcysteine to a combination of ciprofloxacin and dexamethasone has been shown to completely suppress the growth of all 15 tested strains of *Pseudomonas aeruginosa* in both planktonic and biofilm forms. These findings suggest that acetylcysteine is a promising adjuvant in the treatment of chronic suppurative otitis media, particularly in cases associated with bacterial biofilms [63].

4.5.3. Combinations of Topical Anesthetics with Anti-Inflammatory Agents

The combination of topical anesthetics with anti-inflammatory agents enables rapid pain relief in otitis media and is considered a first-line option for analgesic therapy. A combination drug product containing lidocaine and phenazone is widely used in clinical practice, particularly in pediatric patients with acute otitis media. In accordance with clinical guidelines updated in 2021, it is recommended for local analgesic and anti-inflammatory therapy in patients with an intact tympanic membrane. However, its use is contraindicated in cases of tympanic membrane perforation because of the potential risk of lidocaine-induced ototoxicity.

The combination of antipyrine and benzocaine has also been investigated and has been shown to significantly reduce pain within 30 min of administration. However, despite its efficacy, this combination may cause local irritation and carries a risk of ototoxicity in cases of tympanic membrane perforation [67]. Therefore, the use of topical anesthetics is currently recommended only in patients with an intact tympanic membrane.

4.6. Prospects for the Development of Innovative Drug Products Containing the Proposed APIs

At present, several approaches are being investigated for the delivery of APIs in the treatment of otitis media, such as: the development of negatively charged liposomes encapsulating APIs, stimuli-responsive hydrogels, and nanoporous silicate coatings for otologic prostheses.

Negatively charged liposomal systems represent a promising strategy. A ciprofloxacin-containing hydrogel formulation incorporated in hydroxylated liposomes has been developed and evaluated in chinchillas with otitis media induced by nontypeable *Haemophilus influenzae*. In this model, ciprofloxacin concentrations in the middle ear were 36-fold higher than those achieved with non-liposomal hydrogels. Moreover, pathogens were no longer detectable within 24 h, which contrasts with the currently used 5–10-day course of antibiotic therapy. The authors emphasized that this system may potentially provide a low-cost, non-invasive treatment option for otitis media in pediatric patients [68].

Stimuli-responsive hydrogels are being actively explored to overcome the limitations of conventional otic drops. Although ear drops remain the most commonly used dosage form in otitis media therapy, their high fluidity often results in rapid leakage from the site of administration, leading to insufficient bactericidal activity and an increased risk of recurrence. To address this limitation, formulations are being developed that transition from a flowable injectable state in vitro to a non-flowable state in vivo, thereby ensuring prolonged residence at the mucosal surface and sustained exposure of bacterial colonies within the mucosal layer to the active ingredients. One such thermosensitive gel formulation based on Pluronic F127 and chitosan demonstrated antibacterial efficacy in vivo against antibiotic-resistant *Staphylococcus aureus* and other common pathogens associated with otitis media, including *Streptococcus pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa*, reaching 93.8% efficacy on day 7 [26].

Nanoporous silicate coatings for otologic prostheses have been proposed as an innovative local drug delivery strategy. In one study, a commercially available ear implant was immersed in a silica solution, chemically modified, and subsequently loaded with ciprofloxacin. The resulting coating almost completely eliminated *Pseudomonas aeruginosa* from the middle ear, prevented abscess formation, and limited the spread of infection. At present, this system is considered ready for preclinical and clinical evaluation, and nanoporous silica particles have received FDA approval for use in humans [69].

Thus, all of the approaches discussed above are aimed at developing safe, highly effective, and potentially non-invasive strategies for the treatment of otitis media. Of particular importance is their potential to reduce the duration of therapy and decrease the risk of recurrence, which is especially relevant in pediatric practice.

5. Discussion

The analysis of the available literature allowed several unresolved issues in the field of otic therapy and innovative middle ear drug delivery to be identified [9,48,66]. These include:

- The lack of effective topical agents targeting bacterial biofilms, which are detected in 60–80% of patients with chronic suppurative otitis media;
- The limited availability of formulations that can be safely used in the presence of tympanic membrane perforation and have a proven absence of ototoxicity;
- The need for prolonged-release, single-administration dosage forms, particularly in pediatric practice;
- The absence of marketed combination drug products with the “antibiotic + mucolytic/antibiofilm agent” formulation, despite in vitro evidence supporting the antibiofilm activity of acetylcysteine [63].

5.1. Limitations of Extrapolation and Barriers to Clinical Translation

Despite the encouraging results of the preclinical studies described in Sections 3.3.1–3.4, most innovative drug delivery systems remain at early stages of development and are not yet ready for transition into clinical trials. Several key limitations currently hinder their clinical translation.

First, standardized sterilization methods for such systems remain insufficiently established. Many polymers (poloxamers), as well as vesicular systems, such as transferosomes and novasomes, may be thermolabile or destabilized by irradiation, which complicates the use of conventional sterilization approaches and represents a technological challenge for the development of sterile otic products [23,24].

Second, storage stability remains a significant limitation. Aqueous nanoparticle dispersions may undergo aggregation and sedimentation during storage. Liposomes are particularly prone to phospholipid hydrolysis and oxidation of unsaturated lipid chains, which may compromise their structural integrity and drug delivery performance. Moreover, in most studies, formulation stability has been evaluated only over several weeks [21,22], which, according to regulatory legislation, is insufficient for a commercial medicinal product, as it requires long-term stability testing under defined storage conditions.

Third, industrial scale-up represents another important barrier. Laboratory methods such as thin-film hydration and ultrasonication may be effective for the preparation of small experimental batches. However, these methods are often difficult to reproduce when transferred to industrial-scale manufacturing, where process robustness, batch-to-batch consistency, and reproducible product quality are required.

Fourth, regulatory uncertainty remains substantial. None of the systems discussed in this review, including nanoemulsions, vesicular carriers, and poloxamer-based hydrogels containing permeation enhancers, are currently approved by the FDA, the European Medicines Agency, or other local regulatory authorities for transtympanic drug delivery. In addition, specific regulatory guidelines for the preclinical evaluation of such otic products are currently lacking, which further complicates their registration strategy.

Fifth, economic barriers may also limit further development. The relatively limited target patient population may reduce the commercial attractiveness of the mentioned products for large pharmaceutical companies, thereby restricting investment in advanced otic formulations and innovative middle ear drug delivery systems [2].

Thus, the transition from a laboratory prototype to a registered human medicinal product requires the resolution of a complex set of technological, regulatory, and economic challenges, many of which remain to be overcome.

5.2. Future Perspectives

The use of innovative drug delivery systems in pediatric patients deserves particular attention. Anatomical and physiological characteristics in children, including a shorter and wider Eustachian tube, immature mucociliary clearance, and frequent adenoid hypertrophy, may predispose this population to recurrent episodes and chronic forms of otitis media. These features should, therefore, be considered when designing novel otic formulations and evaluating their potential clinical applicability.

However, most currently developed drug delivery systems have been tested only in adult animal models, including chinchillas, guinea pigs, and rats, whereas pediatric models have rarely been used. Safety requirements for pediatric medicinal products are particularly stringent, which may further slow the translation of innovative delivery systems into clinical development, especially in pediatric populations.

A promising future direction of development in the area is personalized ototherapy based on the patient's microbiome profile and the biofilm-forming activity of the pathogen. Such an approach may be particularly relevant for biofilm-associated infections and recurrent or chronic otitis media. Nevertheless, this concept remains at the stage of fundamental research and requires substantial further investigation.

Overall, without careful consideration of age-related anatomical and physiological factors, as well as unresolved technological, manufacturing, stability-related, and regulatory challenges, innovative otic drug delivery systems may remain laboratory prototypes rather than progressing toward regulatory approval and clinical use.

6. Conclusions and Future Directions

Despite the wide range of drug products available for the treatment of otolaryngological diseases, the number of topical formulations specifically indicated for otitis media

remains limited worldwide, and most of these products are characterized by similar compositions and limited therapeutic efficacy.

The predominance of ear drops consisting of conventional antibiotics, corticosteroids, and their combinations highlights a lack of innovative solutions capable of enabling targeted antimicrobial effect, overcoming antimicrobial resistance, and minimizing adverse effects. In addition to the development of advanced drug delivery systems, there is a clear need for the rational design of API combinations capable of synergistically targeting multiple stages of otitis pathogenesis.

The analysis presented in this review has revealed a critical shortage of novel drug products, particularly in the treatment of fungal and viral otitis, as well as chronic forms associated with biofilms. Existing formulations often fail to adequately address key pathogenetic mechanisms, resulting in reduced clinical efficacy and an increased risk of recurrence.

Recent advances suggest promising directions that may significantly improve treatment outcomes, including nanostructured heterogeneous delivery systems, vesicular carriers, and polymer-based systems with stimuli-responsive properties (e.g., temperature- or pH-sensitive systems). Furthermore, the rational selection of drug delivery systems should be complemented by the appropriate choice and combination of APIs to overcome existing limitations.

Despite these advances, the translation of innovative approaches into clinical practice remains limited due to regulatory barriers, high development costs, and limited interest from pharmaceutical companies in specialized otic drug products. At the current stage, most innovative systems remain at the preclinical stage of development. Therefore, a comprehensive, multidisciplinary approach involving collaboration among researchers, clinicians, pharmaceutical developers, and regulatory authorities is essential to advance the treatment of ear diseases and provide patients with more effective and safer therapeutic options.

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Abbreviations

The following abbreviations are used in this manuscript:

API	Active Pharmaceutical Ingredient
SWOT	Strengths, Weaknesses, Opportunities, and Threats
AI	Artificial Intelligence
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
U.S.	United States

EAEU	Eurasian Economic Union
FDA	Food and Drug Administration
PMDA	Pharmaceuticals and Medical Devices Agency
USP	United States Pharmacopeia
INN	International Nonproprietary Name
HLB	Hydrophilic–Lipophilic Balance
PLGA	Poly(lactic-co-glycolic acid)
MBC	Minimum Bactericidal Concentration
MIC	Minimum Inhibitory Concentration
QbD	Quality by Design
NAC	N-acetylcysteine
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
MRSA	Methicillin-Resistant Staphylococcus Aureus

References

1. Zhang, Z.; Li, X.; Zhang, W.; Kohane, D.S. Drug Delivery across Barriers to the Middle and Inner Ear. *Adv. Funct. Mater.* **2021**, *31*, 2008701. <https://doi.org/10.1002/adfm.202008701>.
2. Magdy, M.; Elmowafy, E.; Elassal, M.; Ishak, R. Localized drug delivery to the middle ear: Recent advances and perspectives for the treatment of middle and inner ear diseases. *J. Drug Deliv. Sci. Technol.* **2022**, *69*, 103149. <https://doi.org/10.1016/j.jddst.2022.103149>.
3. Schilder, A.G.; Chonmaitree, T.; Cripps, A.W.; Rosenfeld, R.M.; Casselbrant, M.L.; Haggard, M.P.; Venekamp, R.P. Otitis media. *Nat. Rev. Dis. Primers* **2016**, *2*, 16063. <https://doi.org/10.1038/nrdp.2016.63>.
4. Onifade, A.; Katolo, H.W.; Mookerjee, S.; Bhutta, M.F. Epidemiology of Chronic Suppurative Otitis Media: Systematic Review To Estimate Global Prevalence. *J. Epidemiol. Glob. Health* **2025**, *15*, 55. <https://doi.org/10.1007/s44197-025-00396-9>.
5. Kosyakov, S.Y. *Izbrannyye Voprosy Prakticheskoi Otolirurgii*; MCFER: Moscow, Russia, **2012**; 224p. (In Russian)
6. Castelli Gattinara, G.; Bergamini, M.; Simeone, G.; Reggiani, L.; Doria, M.; Ghiglioni, D.G.; Terminiello, A.; Cosentino, F.; Corsi, L.; Donà, D.; et al. Antibiotic treatment of acute and recurrent otitis media in children: An Italian intersociety Consensus. *Ital. J. Pediatr.* **2025**, *51*, 50. <https://doi.org/10.1186/s13052-025-01894-z>.
7. Patel, J.; Szczupak, M.; Rajguru, S.; Balaban, C.; Hoffer, M.E. Inner Ear Therapeutics: An Overview of Middle Ear Delivery. *Front. Cell. Neurosci.* **2019**, *13*, 261. <https://doi.org/10.3389/fncel.2019.00261>.
8. Koulich, E.; Roland, P.S.; Pawlowski, K.S. Comparison of systemic and otic administration of ofloxacin. *Laryngoscope* **2010**, *120*, 2083–2088. <https://doi.org/10.1002/lary.21088>.
9. Delaney, D.S.; Liew, L.J.; Lye, J.; Atlas, M.D.; Wong, E.Y.M. Overcoming barriers: A review on innovations in drug delivery to the middle and inner ear. *Front. Pharmacol.* **2023**, *14*, 1207141. <https://doi.org/10.3389/fphar.2023.1207141>.
10. van Dongen, T.M.A.; van der Heijden, G.J.M.G.; Venekamp, R.P.; Rovers, M.M.; Schilder, A.G.M. A trial of treatment for acute otorrhea in children with tympanostomy tubes. *N. Engl. J. Med.* **2014**, *370*, 723–733. <https://doi.org/10.1056/NEJMoa1301630>.
11. Yang, R.; Sabharwal, V.; Shlykova, N.; Okonkwo, O.S.; Pelton, S.I.; Kohane, D.S. Treatment of Streptococcus pneumoniae otitis media in a chinchilla model by transtympanic delivery of antibiotics. *JCI Insight* **2018**, *3*, e123415. <https://doi.org/10.1172/jci.insight.123415>.
12. Early, S.; Yang, R.; Li, X.; Zhang, Z.; van der Valk, J.C.; Ma, X.; Kohane, D.S.; Stankovic, K.M. Initial method for characterization of tympanic membrane drug permeability in human temporal bones in situ. *Front. Neurol.* **2021**, *12*, 580392. <https://doi.org/10.3389/fneur.2021.580392>.
13. Silva, M.D.; Sillankorva, S. Otitis media pathogens—A life entrapped in biofilm communities. *Crit. Rev. Microbiol.* **2019**, *45*, 595–612. <https://doi.org/10.1080/1040841X.2019.1660616>.
14. Preeti; Sambhakar, S.; Malik, R.; Bhatia, S.; Al Harrasi, A.; Rani, C.; Saharan, R.; Kumar, S.; Geeta Sehrawat, R. Nanoemulsion: An Emerging Novel Technology for Improving the Bioavailability of Drugs. *Scientifica* **2023**, *2023*, 6640103. <https://doi.org/10.1155/2023/6640103>.
15. Bakhrushina, E.O.; Anurova, M.N.; Solov'eva, S.S.; Vorob'ev, A.M.; Shcherbina, Y.O.; Pasivkina, M.A.; Krekhtunova, L.O.; Demina, N.B.; Aleshkin, A.V. Development and study of ear drops with bacteriophages for the treatment of infectious otitis complicated by Pseudomonas aeruginosa. *Drug Dev. Regist.* **2022**, *11*, 74–78. <https://doi.org/10.33380/2305-2066-2022-11-2-74-78>. (In Russian)

16. Kono, M.; Umar, N.K.; Takeda, S.; Ohtani, M.; Murakami, D.; Sakatani, H.; Kaneko, F.; Nanushaj, D.; Hotomi, M. Novel Anti-microbial Treatment Strategy Based on Drug Delivery Systems for Acute Otitis Media. *Front Pharmacol.* **2021**, *12*, 640514. <https://doi.org/10.3389/fphar.2021.640514>.
17. Birk, S.E.; Boisen, A.; Nielsen, L.H. Polymeric nano- and microparticulate drug delivery systems for treatment of biofilms. *Adv. Drug Deliv. Rev.* **2021**, *174*, 30–52. <https://doi.org/10.1016/j.addr.2021.04.005>.
18. Karabulut, H.; Xu, D.; Ma, Y.; Tut, T.A.; Ulag, S.; Pinar, O.; Kazan, D.; Guncu, M.M.; Sahin, A.; Wei, H.; et al. A new strategy for the treatment of middle ear infection using ciprofloxacin/amoxicillin-loaded ethyl cellulose/polyhydroxybutyrate nanofibers. *Int. J. Biol. Macromol.* **2024**, *269*, 131794. <https://doi.org/10.1016/j.ijbiomac.2024.131794>.
19. Tang, W.; Ma, X.; Marlowe, C.; Liu, S.S.; Yang, R. Pathophysiology-Informed Design of Negatively Charged Liposomes for Enhanced Antibiotic Delivery across the Intact Tympanic Membrane in Acute Otitis Media Treatment. *ACS Nano* **2025**, *19*, 12787–12798. <https://doi.org/10.1021/acsnano.4c14097>.
20. Dindelegan, M.G.; Paşcalău, V.; Suci, M.; Neamţu, B.; Perde-Schrepler, M.; Blebea, C.M.; Maniu, A.A.; Necula, V.; Buzoianu, A.D.; Filip, M.; et al. Biopolymer Lipid Hybrid Microcarrier for Transmembrane Inner Ear Delivery of Dexamethasone. *Gels* **2022**, *8*, 483. <https://doi.org/10.3390/gels8080483>.
21. Al-Mahallawi, A.M.; Khowessah, O.M.; Shoukri, R.A. Nano-transfersomal ciprofloxacin loaded vesicles for non-invasive trans-tympanic ototopical delivery: In-vitro optimization, ex-vivo permeation studies, and in-vivo assessment. *Int. J. Pharm.* **2014**, *472*, 304–314. <https://doi.org/10.1016/j.ijpharm.2014.06.041>.
22. Al-Mahallawi, A.M.; Khowessah, O.M.; Shoukri, R.A. Enhanced non invasive trans-tympanic delivery of ciprofloxacin through encapsulation into nano-spanlastic vesicles: Fabrication, in-vitro characterization, and comparative ex-vivo permeation studies. *Int. J. Pharm.* **2017**, *522*, 157–164. <https://doi.org/10.1016/j.ijpharm.2017.03.005>.
23. Ahmed, S.; Fayed, A.; Attia, H.; El-Setouhy, D.A. Terpene-augmented novosomal carriers for trans-tympanic drug delivery: A comprehensive optimization and in vivo evaluation. *Naunyn Schmiedebergs Arch. Pharmacol.* **2025**, *Epub ahead of print*. <https://doi.org/10.1007/s00210-025-04659-x>.
24. Ahmed, S.; Attia, H.; Saher, O. Novel hybrid tri-polymer hyalurosomes: Unlocking next-generation trans-tympanic therapeutics through multi-scale evaluations. *Int. J. Pharm. X* **2025**, *10*, 100425. <https://doi.org/10.1016/j.ijpx.2025.100425>.
25. Bakhrushina, E.O.; Demina, N.B.; Shumkova, M.M.; Rodiuk, P.S.; Shulikina, D.S.; Krasniuk, I.I. Intranasal in situ delivery systems: Prospects of application and main pharmaceutical aspects of development (review). *Razrab. I Regist. Lek. Sredstv = Drug Dev. Regist.* **2021**, *10*, 54–63. <https://doi.org/10.33380/2305-2066-2021-10-4-54-63>. (In Russian)
26. Jin, Y.; Shang, Y.; Wu, C.; Chen, Z.; Shi, H.; Wang, H.; Li, L.; Yin, S. Conformal immunomodulatory hydrogels for the treatment of otitis media. *J. Nanobiotechnol.* **2024**, *22*, 619. <https://doi.org/10.1186/s12951-024-02908-4>. Erratum in: *J Nanobiotechnology*. 2024 Nov 11;22(1):695. doi: 10.1186/s12951-024-02959-7. PMID: 39395981; PMCID: PMC11475211.
27. Yang, R.; Sabharwal, V.; Okonkwo, O.S.; Shlykova, N.; Tong, R.; Lin, L.Y.; Wang, W.; Guo, S.; Rosowski, J.J.; Pelton, S.I.; et al. Treatment of otitis media by transtympanic delivery of antibiotics. *Sci. Transl. Med.* **2016**, *8*, 356ra120. <https://doi.org/10.1126/scitranslmed.aaf4363>. Erratum in: *Sci Transl Med.* 2025 May 7;17(797):eady2642. doi: 10.1126/scitranslmed.ady2642. PMID: 27629487; PMCID: PMC5615819.
28. Wang, X.; Fernandez, R.; Tsivkovskaia, N.; Harrop-Jones, A.; Hou, H.J.; Dellamary, L.; Dolan, D.F.; Altschuler, R.A.; LeBel, C.; Piu, F. OTO-201: Nonclinical assessment of a sustained-release ciprofloxacin hydrogel for the treatment of otitis media. *Otol. Neurotol.* **2014**, *35*, 459–469. <https://doi.org/10.1097/MAO.0000000000000261>.
29. Gausterer, J.C.; Saidov, N.; Ahmadi, N.; Zhu, C.; Wirth, M.; Reznicek, G.; Arnoldner, C.; Gabor, F.; Honeder, C. Intratympanic application of poloxamer 407 hydrogels results in sustained N-acetylcysteine delivery to the inner ear. *Eur. J. Pharm. Biopharm.* **2020**, *150*, 143–155. <https://doi.org/10.1016/j.ejpb.2020.03.005>.
30. Liao, A.H.; Shih, C.P.; Li, M.W.; Lin, Y.C.; Chuang, H.C.; Wang, C.H. Development of thermosensitive poloxamer 407-based microbubble gel with ultrasound mediation for inner ear drug delivery. *Drug Deliv.* **2021**, *28*, 1256–1271. <https://doi.org/10.1080/10717544.2021.1938758>.
31. Bruk, L.A.; Dunkelberger, K.E.; Khampang, P.; Hong, W.; Sadagopan, S.; Alper, C.M.; Fedorchak, M.V. Controlled release of ciprofloxacin and ceftriaxone from a single ototopical administration of antibiotic-loaded polymer microspheres and thermoresponsive gel. *PLoS ONE* **2020**, *15*, e0240535. <https://doi.org/10.1371/journal.pone.0240535>.
32. Khoo, X.; Simons, E.J.; Chiang, H.H.; Hickey, J.M.; Sabharwal, V.; Pelton, S.I.; Rosowski, J.J.; Langer, R.; Kohane, D.S. Formulations for trans-tympanic antibiotic delivery. *Biomaterials* **2013**, *34*, 1281–1288. <https://doi.org/10.1016/j.biomaterials.2012.10.025>.

33. Bakhrushina, E.O.; Shumkova, M.M.; Avdonina, Y.V.; Ananian, A.A.; Babazadeh, M.; Pouya, G.; Grikh, V.V.; Zubareva, I.M.; Kosenkova, S.I.; Krasnyuk, I.I., Jr.; et al. Transdermal drug delivery systems: Methods for enhancing skin permeability and their evaluation. *Pharmaceutics* **2025**, *17*, 936. <https://doi.org/10.3390/pharmaceutics17070936>.
34. Liu, S.S.; White, J.M.; Chao, Z.; Li, R.; Wen, S.; Garza, A.; Tang, W.; Ma, X.; Chen, P.; Daniel, S.; et al. A pseudo-surfactant chemical permeation enhancer to treat otitis media via sustained transtympanic delivery of antibiotics. *Adv. Healthc. Mater.* **2024**, *13*, e2400457. <https://doi.org/10.1002/adhm.202400457>.
35. Yang, R.; Okonkwo, O.S.; Zurakowski, D.; Kohane, D.S. Synergy between chemical permeation enhancers and drug permeation across the tympanic membrane. *J. Control. Release* **2018**, *289*, 94–101. <https://doi.org/10.1016/j.jconrel.2018.06.019>.
36. Yang, R.; Saarinen, R.; Okonkwo, O.S.; Hao, Y.; Mehta, M.; Kohane, D.S. Transtympanic delivery of local anesthetics for pain in acute otitis media. *Mol. Pharm.* **2019**, *16*, 1555–1562. <https://doi.org/10.1021/acs.molpharmaceut.8b01235>.
37. Macfadyen, C.A.; Acuin, J.M.; Gamble, C. Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations. *Cochrane Database Syst. Rev.* **2005**, *2005*, CD004618. <https://doi.org/10.1002/14651858.CD004618.pub2>.
38. Reed, M.D.; Wintermeyer, S.M.; Nahata, M.C. Chronic Suppurative Otitis Media. *Ann. Pharmacother.* **1994**, *28*, 1089–1091. <https://doi.org/10.1177/106002809402800915>.
39. Jatto, M.E.; Adeyemo, A.A.; Fasunla, A.J.; Ogunkeyede, S.A.; Makanjuola, O.; Nwaorgu, O.G.; Paul, A.A.; Chukwuma, E.O.; Enoch, V.O.; Oyedokun, C.O.; et al. Repurposing Povidone-Iodine for the Treatment of Chronic Suppurative Otitis Media in Nigerian Children. *Otol. Neurotol.* **2026**, *47*, 213–220. <https://doi.org/10.1097/MAO.0000000000004654>.
40. Özkiriş, M.; Kapusuz, Z.; Saydam, L. Ototoxicity of different concentrations povidone-iodine solution applied to the middle ear cavity of rats. *Indian J. Otolaryngol. Head Neck Surg.* **2013**, *65*, 168–172. <https://doi.org/10.1007/s12070-012-0615-5>.
41. Smolinski, N.E.; Djabali, E.J.; Al-Bahou, J.; Pomputius, A.; Antonelli, P.J.; Winterstein, A.G. Antibiotic treatment to prevent pediatric acute otitis media infectious complications: A meta-analysis. *PLoS ONE* **2024**, *19*, e0304742. <https://doi.org/10.1371/journal.pone.0304742>.
42. Rettig, E.; Tunkel, D.E. Contemporary concepts in management of acute otitis media in children. *Otolaryngol. Clin. N. Am.* **2014**, *47*, 651–672. <https://doi.org/10.1016/j.otc.2014.06.006>.
43. Suzuki, H.G.; Dewez, J.E.; Nijman, R.G.; Yeung, S. Clinical practice guidelines for acute otitis media in children: A systematic review and appraisal of European national guidelines. *BMJ Open* **2020**, *10*, e035343. <https://doi.org/10.1136/bmjopen-2019-035343>.
44. El Feghaly, R.E.; Nedved, A.; Katz, S.E.; Frost, H.M. New insights into the treatment of acute otitis media. *Expert Rev. Anti Infect. Ther.* **2023**, *21*, 523–534. <https://doi.org/10.1080/14787210.2023.2206565>.
45. McLinn, S.E.; Moskal, M.; Goldfarb, J.; Bodor, F.; Aronovitz, G.; Schwartz, R.; Self, P.; Ossi, M.J. Comparison of cefuroxime axetil and amoxicillin-clavulanate suspensions in treatment of acute otitis media with effusion in children. *Antimicrob. Agents Chemother.* **1994**, *38*, 315–318. <https://doi.org/10.1128/AAC.38.2.315>.
46. Chong, L.Y.; Head, K.; Webster, K.E.; Daw, J.; Richmond, P.; Snelling, T.; Bhutta, M.F.; Schilder, A.G.; Burton, M.J.; Brennan-Jones, C.G. Topical versus systemic antibiotics for chronic suppurative otitis media. *Cochrane Database Syst. Rev.* **2021**, *2*, CD013053. <https://doi.org/10.1002/14651858.CD013053.pub2>.
47. Renukananda, G.S.; UPS; George, N.M. Topical vs Combination Ciprofloxacin in the Management of Discharging Chronic Suppurative Otitis Media. *J. Clin. Diagn. Res.* **2014**, *8*, KC01–KC04. <https://doi.org/10.7860/JCDR/2014/8038.4421>.
48. Hura, N.; Xia, A.; Santa Maria, P.L. Management Strategies for Chronic Suppurative Otitis Media and Why They Fail. *J. Assoc. Res. Otolaryngol.* **2025**, *26*, 389–396. <https://doi.org/10.1007/s10162-025-00996-z>.
49. van Uum, R.T.; Venekamp, R.P.; Zuithoff, N.P.; Sjoukes, A.; van de Pol, A.C.; Schilder, A.G.; Damoiseaux, R.A. Improving pain management in childhood acute otitis media in general practice: A cluster randomised controlled trial of a GP-targeted educational intervention. *Br. J. Gen. Pract.* **2020**, *70*, e684–e695. <https://doi.org/10.3399/bjgp20X712589>.
50. Jamal, A.; Alsabea, A.; Tarakme, M.; Safar, A. Etiology, Diagnosis, Complications, and Management of Acute Otitis Media in Children. *Cureus* **2022**, *14*, e28019. <https://doi.org/10.7759/cureus.28019>.
51. de Sévaux, J.L.H.; Damoiseaux, R.A.; van de Pol, A.C.; Lutje, V.; Hay, A.D.; Little, P.; Schilder, A.G.; Venekamp, R.P. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. *Cochrane Database Syst. Rev.* **2023**, *8*, CD011534. <https://doi.org/10.1002/14651858.CD011534.pub3>.
52. Mulvaney, C.A.; Galbraith, K.; Webster, K.E.; Rana, M.; Connolly, R.; Tudor-Green, B.; Marom, T.; Daniel, M.; Venekamp, R.P.; Schilder, A.G.; et al. Topical and oral steroids for otitis media with effusion (OME) in children. *Cochrane Database Syst. Rev.* **2023**, *12*, CD015255. <https://doi.org/10.1002/14651858.CD015255.pub2>.

53. van Balen, F.A.; Smit, W.M.; Zuithoff, N.P.; Verheij, T.J. Clinical efficacy of three common treatments in acute otitis externa in primary care: Randomised controlled trial. *BMJ* **2003**, *327*, 1201–1205. <https://doi.org/10.1136/bmj.327.7425.1201>.
54. Venekamp, R.P.; Javed, F.; van Dongen, T.M.; Waddell, A.; Schilder, A.G. Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion. *Cochrane Database Syst. Rev.* **2016**, *11*, CD011684. <https://doi.org/10.1002/14651858.CD011684.pub2>.
55. Hajioff, D.; Mackeith, S. Otitis externa. *BMJ Clin. Evid.* **2010**, *2010*, 0510.
56. Roland, P.S.; Pien, F.D.; Schultz, C.C.; Henry, D.C.; Conroy, P.J.; Wall, G.M.; Garadi, R.; Dupre, S.J.; Potts, S.L.; Hogg, L.G.; et al. Efficacy and safety of topical ciprofloxacin/dexamethasone versus neomycin/polymyxin B/hydrocortisone for otitis externa. *Curr. Med. Res. Opin.* **2004**, *20*, 1175–1183. <https://doi.org/10.1185/030079902125004312>.
57. Wang X., Winterstein A.G., Alrwisan A., Antonelli P.J. Risk for Tympanic Membrane Perforation After Quinolone Ear Drops for Acute Otitis Externa. *Clin. Infect. Dis.* **2020**, *70*, 1103–1109. <https://doi.org/10.1093/cid/ciz345>.
58. Yu, X.; Xu, L.; Xie, Y.; Huang, M. Clinical study of the effect of mometasone furoate nasal spray treatment on hearing and in secretory otitis media in children. *Clinics* **2024**, *80*, 100551. <https://doi.org/10.1016/j.clinsp.2024.100551>.
59. Bilgili AM, Durmaz HÖ, Dilber M.. Eustachian Tube Dysfunction in Children with Adenoid Hypertrophy: The Effect of Intranasal Azelastine-Fluticasone Spray Treatment on Middle Ear Ventilation and Adenoid Tissue. *Ear Nose Throat J.* **2023**, *102*, 198–203. <https://doi.org/10.1177/01455613221140281>.
60. Aaron, K.; Cooper, T.E.; Warner, L.; Burton, M.J. Ear drops for the removal of ear wax. *Cochrane Database Syst Rev.* **2018**, *7*, CD012171. <https://doi.org/10.1002/14651858.CD012171.pub2>.
61. Singh, S.; Blakley, B. Systematic review of ototoxic pre-surgical antiseptic preparations—What is the evidence? *J. Otolaryngol. Head. Neck Surg.* **2018**, *47*, 18. <https://doi.org/10.1186/s40463-018-0265-z>.
62. Ersoy Çalloğlu, E.; Berçin, S.; Başdemir, G.; Kiriş, M.; Tatar, İ.; Tuzuner, A.; Oğuzhan, T.; Müderris, T.; Sargon, M.F.; Korkmaz, M.H. The effect of N-acetyl cysteine on biofilm layers in an experimental model of chronic otitis media. *Acta Otorhinolaryngol. Ital.* **2020**, *40*, 457–462. <https://doi.org/10.14639/0392-100X-N0996>.
63. Lea, J.; Conlin, A.E.; Sekirov, I.; Restelli, V.; Ayakar, K.G.; Turnbull, L.; Doyle, P.; Noble, M.; Rennie, R.; Schreiber, W.E.; et al. In vitro efficacy of N-acetylcysteine on bacteria associated with chronic suppurative otitis media. *J. Otolaryngol. Head Neck Surg.* **2014**, *43*, 20. <https://doi.org/10.1186/1916-0216-43-20>.
64. Foxlee, R.; Johansson, A.; Wejfalk, J.; Dawkins, J.; Dooley, L.; Del Mar, C. Topical analgesia for acute otitis media. *Cochrane Database Syst. Rev.* **2006**, *2006*, CD005657. <https://doi.org/10.1002/14651858.CD005657.pub2>.
65. Roland, P.S.; Anon, J.B.; Moe, R.D.; Conroy, P.J.; Wall, G.M.; Dupre, S.J.; Krueger, K.A.; Potts, S.; Hogg, G.; Stroman, D.W. Topical ciprofloxacin/dexamethasone is superior to ciprofloxacin alone in pediatric patients with acute otitis media and otorrhea through tympanostomy tubes. *Laryngoscope* **2003**, *113*, 2116–2122. <https://doi.org/10.1097/00005537-200312000-00011>.
66. Jotic, A.; Savic Vujovic, K.; Cirkovic, A.; Božić, D.D.; Brkic, S.; Subotic, N.; Bukurov, B.; Korugic, A.; Cirkovic, I. Antibiofilm Effects of Novel Compounds in Otitis Media Treatment: Systematic Review. *Int. J. Mol. Sci.* **2024**, *25*, 12841. <https://doi.org/10.3390/ijms252312841>.
67. Hoberman, A.; Paradise, J.L.; Reynolds, E.A.; Urkin, J. Efficacy of Auralgan for treating ear pain in children with acute otitis media. *Arch. Pediatr. Adolesc. Med.* **1997**, *151*, 675–678. <https://doi.org/10.1001/archpedi.1997.02170440037006>.
68. Tang, W.; Ma, X.; Marlowe, C.; Liu, S.S.; Park, K.W.; Chen, P.; Shu, H.; Yang, R. Neutrophil-mediated delivery of antibiotics across the tympanic membrane for otitis media treatment in a preclinical model. *Sci. Transl. Med.* **2026**, *18*, eadu9186. <https://doi.org/10.1126/scitranslmed.adu9186>.
69. Lensing, R.; Bleich, A.; Smoczek, A.; Glage, S.; Ehlert, N.; Luessenhop, T.; Behrens, P.; Müller, P.P.; Kietzmann, M.; Stieve, M. Efficacy of nanoporous silica coatings on middle ear prostheses as a delivery system for antibiotics: An animal study in rabbits. *Acta Biomater.* **2013**, *9*, 4815–4825. <https://doi.org/10.1016/j.actbio.2012.08.016>.

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