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Review article

Biomedical application of materials for external auditory canal: History, challenges, and clinical prospects

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ABSTRACT

Biomaterials play an integral role in treatment of external auditory canal (EAC) diseases. Regarding the special anatomic structure and physiological characteristics of EAC, careful selection of applicable biomaterials was essential step towards effective management of EAC conditions. The bioactive materials can provide reasonable biocompatibility, reduce risk of host pro-inflammatory response and immune rejection, and promote the healing process. In therapeutic procedure, biomaterials were employed for covering or packing the wound, protection of the damaged tissue, and maintaining of normal structures and functions of the EAC. Therefore, understanding and application of biomaterials was key to obtaining great rehabilitation in therapy of EAC diseases. In clinical practice, biomaterials were recognized as an important part in the treatment of different EAC diseases. The choice of biomaterials was distinct according to the requirements of various diseases. As a result, awareness of property regarding different biomaterials was fundamental for appropriate selection of therapeutic substances in different EAC diseases. In this review, we firstly introduced the characteristics of EAC structures and physiology, and EAC pathologies were summarized secondarily. From the viewpoint of biomaterials, the different materials applied to individual diseases were outlined in categories. Besides, the underlying future of therapeutic EAC biomaterials was discussed.

1. Introduction

Biomaterials were defined as substances engineered to interact with biological systems for medical purposes with biocompatibility and biodegradability. Common biomaterials include biopolymers (such as collagen and gelatin), biological ceramics (such as hydroxyapatite), biological metal, and biological tissue (such as animal tissue and cells). Usually, biomaterials can interact with human tissue, favoring regeneration and healing.

The selection of appropriate biomaterials was important in treatment of external auditory canal (EAC) diseases. Relevant biomaterials can cover and pack the wound to assist regaining normal structure and function of the EAC. Regarding the specific anatomic structure and physiological environment of EAC, application of biomaterials may decrease inflammatory reaction, lower risk of infection, and accelerate healing. Therefore, understanding and applying biomaterials in proper ways have significance towards therapeutic procedures of EAC diseases. The reasonable exercise of biomaterials can improve management of EAC conditions with benefit for quality of life.

The EAC is important for both aesthetic and hearing function,

Abbreviations: EAC, External auditory canal; TM, Tympanic membrane; CAA, Congenital aural atresia; BAHA, Bone-anchored hearing aid; BIPP, Bismuth iodoform paraffin paste; RTSS, Silastic sheet; PVAc, Polyvinyl acetate; PRF, Platelet-rich fibrin; PRP, Platelet-rich plasma; COMEC, Cultured oral mucosal epithelial cells; CSOM, Chronic suppurative otitis media; CWD, Canal-wall-down; CWU, Canal-wall-up; MRSA, Methicillin-resistant *Staphylococcus* aureus; BAGs, Bioactive glasses; BMP-2, Bone morphogenetic protein-2; PCL, Polycaprolactone; PGA, Polyglycolic acid; hMSCs, Human multipotent mesenchymal stromal cells; ADM, Acellular dermal matrix; hTEOS, Hydrolyzed tetraethyl orthosilicate; HA, Hyaluronate; AOM, Acute otitis media; P407, Poloxamer 407; CPEs, Chemical permeation enhancers; IV, Intravenous.

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collecting sound waves and transmitting the sound energy into the middle and inner ear through the tympanic membrane (TM) to trigger auditory sensation [1]. The partial or complete obstruction of EAC can lead to conductive hearing loss, depending on the mass in the meatus [2]. Medical and surgical interventions were employed to treat the conditions blocking the EAC [3]. The restenosis rate was high in patients after treatment [4]. Multiple techniques were employed to reserve a patent EAC, including several EAC biomaterials applied under the certain conditions. The clinical requirements for EAC biomaterials vary, and characteristics of EAC materials differ greatly. The insertion of packing materials can support the stickiness between the skin graft and bony EAC surface after atresiaplasty. Materials moistened with antibiotics have been applied to patients with otitis externa to expand the receiving area for improved drug delivery. Obliteration of enlarged EAC cavity was performed through filler materials during canal-wall-down (CWD) mastoidectomy. Traditional non-biodegradable and biodegradable materials have been investigated in the field, along with the recent developments of biotechnology.

In this review, we firstly introduced anatomic structures and physiological characteristics of EAC. Pathological factors associated with EAC were described in the form of diseases, including congenital aural atresia (CAA), acquired aural atresia, chronic suppurative otitis media (CSOM), cholesteatoma, otitis externa, acute otitis media (AOM), and Ménière disease. Based on view of biomaterials, we summarized the applied biological materials for different EAC diseases, focusing on the recent advances of biomaterials explored for the treatment of various EAC conditions. In addition, the EAC biomaterials for other potential purposes were considered in the scope. Finally, we provided a brief of the most important challenges and attractive future orientation of the field.

2. Characteristics of EAC

The conservation of a healthy EAC is important for conductive hearing function. Several diseases cause obstruction of EAC, leading to conductive hearing impairment. The hearing loss has broad and profound impacts on life of patients especially for children and youth. The practice of otorhinolaryngologists takes advantage of a variety of medical techniques in curing the congestion of EAC. The surgical treatment plays an essential role in rehabilitating functional EAC. Multiple biomaterials were employed in therapeutic procedures of EAC diseases.

2.1. Relevant structures and functions of EAC

The EAC is a S-shaped osseo-cartilaginous structure that extends from the bottom of the concha to the TM in adult humans, containing cartilaginous portion continuous with the cartilage of the auricula (about 8 mm in length), while inward osseous portion (about 16 mm in length) ends blindly at TM [5]. The inner end of EAC is smaller than the outer with average 8 mm in diameter [6]. The skin lining the meatus is very thin, covering closely to the cartilaginous and osseous portions of the tube and outer surface of the TM (Fig. 1). In the subcutaneous tissue of the cartilaginous part of the meatus are numerous ceruminous glands. The structure of ceruminous glands resembles that of the sudoriferous glands. The ceruminous gland of the cartilaginous meatus plays a major role in formation of cerumen (Fig. 1) [7]. The main function of the EAC is to conduct sound waves in the form of vibrations to the TM (Table 1)

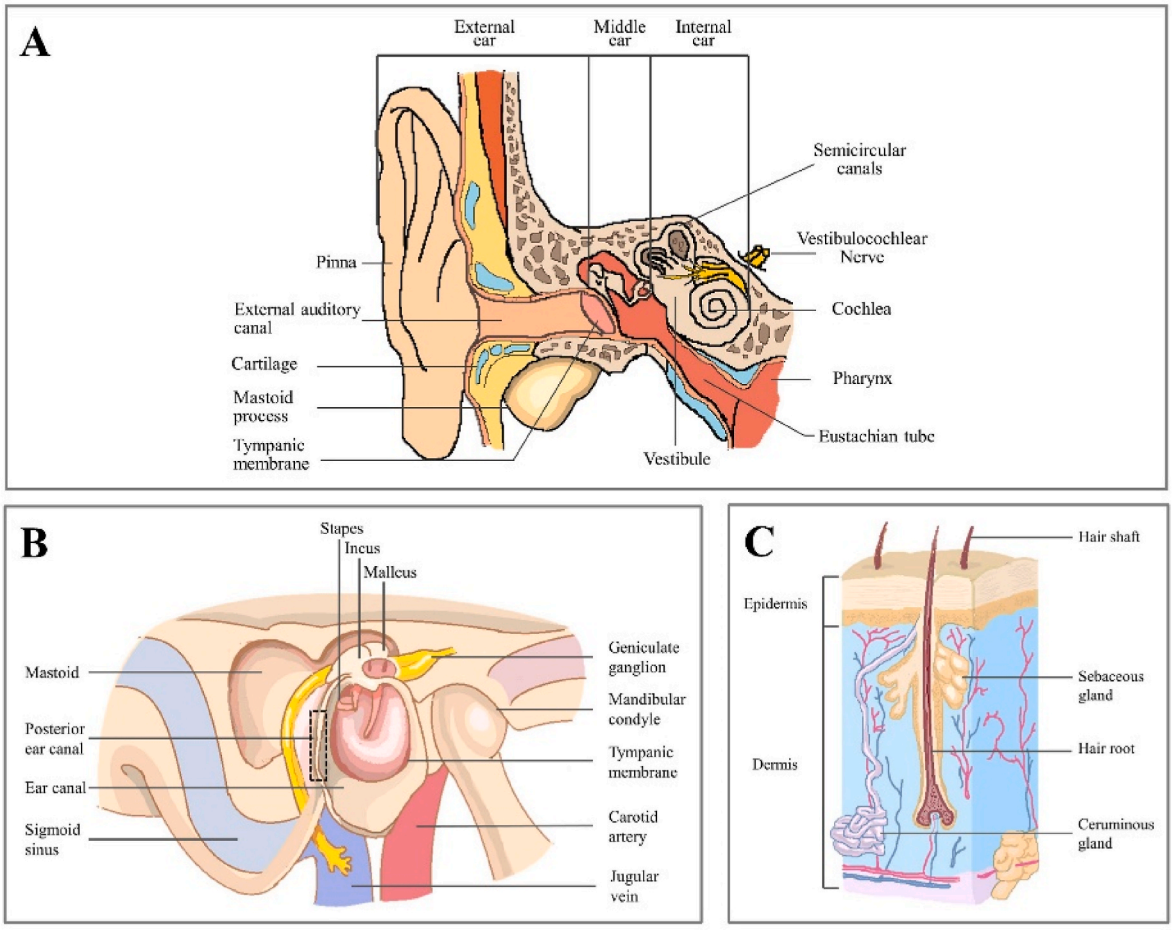

Fig. 1. Important anatomic structures of human ear. A) Anatomy of external ear, middle ear, and inner ear, B) Anatomy of mastoid and posterior ear canal wall, C) Ceruminous glands in the outer third of the external auditory canal.

Table 1
Important structures of external, middle, and inner ear.

Location	Anatomic structures	Functions
External ear	External auditory canal	Conduction of sound waves to the TM*
	Tympanic membrane	Separating the outer and middle ear
	Posterior bony wall of EAC[a]	Protection of EAC and separating the mastoid
	Ceruminous glands	Formation of cerumen to protect the ear from infection and foreign liquid
Middle ear	Mastoid	Regulation of pressure in the middle ear and protection of the inner ear
	Ossicles	Transmitting sounds from the EAC to the cochlea.
Inner ear	Cochlea	Auditory transduction to the brain
	Semicircular canals	Sensing the rotational position of the head

[a] Abbreviations: TM, Tympanic membrane, EAC, External auditory canal.

[1]. For healthy functional hearing, the structural integrity of EAC is essential [5]. The TM (eardrum) is a thin circular connective tissue membrane separating the outer ear from the middle ear. The TM is composed of three layers: outer epithelial layer, middle fibrous layer, and inner mucosal layer. The middle ear, known as tympanic cavity, is an air-filled membrane-lined space located between the EAC and the Eustachian tube. The middle ear contains ossicles (malleus, incus, and stapes) transmitting vibration from the TM to the inner ear [8]. The mastoid is located posterior to the middle ear cavity, contributing to the posterior bony wall of the EAC and tympanic cavity (Fig. 1). The function of mastoid includes regulation of pressure in the middle ear and protection of the inner ear [9]. Next to the middle ear is the compartment of inner ear with hearing and balance apparatus. The inner ear has two main parts: the cochlea for hearing function and semicircular canals for equilibrium, with vestibule located between the cochlea and semicircular canals in favor of maintaining equilibrium (Fig. 1) [10]. The semicircular canals are compositions of bony labyrinth.

2.2. Pathogenic factors of EAC

The EAC diseases are usually multifactorial. The most common EAC disease is otitis externa, with potential developing acquired aural atresia when left untreated. The inflammatory response provoked by bacterial or viral infections was the common pathological process of otitis externa [11]. Acquired aural atresia can be a result of ineffective treatment for advancing otitis externa.

Besides diseases of EAC, the health of external ear was associated with middle and inner ear conditions. The middle ear defects commonly coexist with malformations of the EAC. CAA was defined as a malformation of the EAC at birth. The EAC malformation may be associated with other congenital anomalies manifested in different syndromes. However, identifiable genetic mutations were absent for most cases. The EAC restenosis was common after treatment of acquired or congenital aural atresia [12].

The EAC is an important approach to the middle ear. The EAC structure can be impacted by surgical procedures in treatment for middle and inner ear diseases. An enlarged EAC cavity is curved in CWD mastoidectomy, leading to the requirement of preventing cavity problems [13].

Because the distinct pathogenic characteristics of different EAC diseases, features of EAC conditions were described separately in subsequent sections. In fact, biomaterials were required according to the characteristics of diseases in treatment of various EAC diseases (Table 2).

3. Diseases with EAC treatment

Local therapy is applicable for most EAC diseases including otitis externa, acquired or congenital aural atresia, CSOM and cholesteatoma. Furthermore, EAC can be potential approach for treatment of middle and inner ear diseases in consideration of crossing the barrier of TM. Different therapeutic strategies were employed in treating various EAC diseases (Table 2).

Table 2
Summary of EAC related diseases and therapeutic methods requiring application of biomaterials[a].

Diseases of EAC	Definition of the diseases	Therapeutic methods	Demands for biomaterials	Biomaterials applied
Congenital aural atresia	Malformation of the EAC at birth	Atresiaplasty for CAA with Jahrsdoerfer grading score above 6*	After atresiaplasty, biomaterials may support the skin graft placed on the bony surface of EAC, or materials for transplantation of dissected skin of EAC.	Non-biodegradable biomaterials: Ribbon gauze, Silastic sheet, Hydroxylated polyvinyl acetate, Aquasil Soft Putty. Biodegradable biomaterials: Gelatin, Platelet-rich fibrin, Oral mucosal epithelial cell sheet.
Acquired aural atresia	Absence of a patent EAC after birth	Atresiaplasty for acquired aural atresia in dry (later) phase	Same to atresiaplasty for CAA.	Same to atresiaplasty for CAA.
		Topical antibiotics for wet (primary) phase	Great swelling property when moistened with liquid and enlarging the absorption area of skin for medications in EAC.	Gelatin, Hydroxylated polyvinyl acetate, Polyurethane foam, Tetraethyl orthosilicate-based hydrogel,
Otitis externa	Inflammation of EAC	Topical antibiotics in similar with acquired aural atresia	Same to topical treatment for AAA.*	Same to topical treatment for AAA.
Chronic suppurative otitis media	Chronic inflammation of the middle ear and mastoid cavity	Canal-wall-down mastoidectomy for disease with damage of posterior EAC wall	Great rigidity and biocompatibility for obliteration of mastoid and EAC	Bioactive glass, Hydroxyapatite cement, Bioceramics, Polyglycolic acid sheet, Human multipotent mesenchymal stromal cells, Xenogeneic acellular dermal matrix, Cancellous bone dust.
Cholesteatoma	Diseased keratinized squamous epithelium in the middle ear	Same to CWD mastoidectomy for CSOM*	Same to CWD mastoidectomy for CSOM*	Same to CWD mastoidectomy for CSOM
Acute otitis media	Infection of the middle ear	Traditional treatment was oral antibiotics	Potential *trans*-TM delivery of medication to middle ear*	Poloxamer 407, Transferosomes, Chemical permeation enhancers.
Ménière disease	Fluid collects in the inner ear	Intratympanic corticosteroid injection or surgery.	Potential *trans*-TM delivery of medication to inner ear	Liposomal vesicles.

[a] Abbreviations: EAC, External auditory canal, CAA, Congenital aural atresia, AAA, Acquired aural atresia, CSOM: Chronic suppurative otitis media, TM, Tympanic membrane, CWD: Canal-wall-down.

3.1. Congenital and acquired aural atresia

Abnormal sound wave transmission of EAC leads to conductive hearing loss with impact on daily life in patients. The CAA is the congenital incomplete development of the EAC, the most common congenital lesion of EAC. The incidence rate of CAA was 1:10000–20000 in general population [14]. The presence of CAA was often associated with the malformation of middle and inner ear and can be a part of specific clinical syndromes [15]. Conversely, acquired aural atresia was defined as obstructed EAC blocked with fibrotic plug following recurrent otitis externa, trauma or otologic surgery. Patients may suffer conductive hearing loss and secondary infection when the aural atresia remains untreated [3].

3.1.1. Etiology and pathology of aural atresia

The CAA was a multifactorial condition. Several genetic syndromes were associated with CAA, including Treacher-Collins syndrome and Crouzon syndrome. A few spontaneous mutations were identified such as FOXI3 gene. For most cases of CAA, the identifiable genetic mutation was absent [16].

Acquired aural atresia is the absence of a patent EAC because of the chronic inflammation of EAC after birth [17]. The etiology of acquired aural atresia includes malignant otitis externa, bone tumors, EAC trauma, cholesteatoma, and cerumen. In the presence of ongoing inflammation, the production of immature granulation tissue occurs in the EAC, leading to the bluntness of epithelialization. The EAC skin progressively thickens if the inflammatory process repeats over a prolonged period. The medial aspect of the EAC is occupied by dense fibrotic tissue as a result [18].

Without adequate treatment, the inflammatory damage of aural atresia can be progressive processes, leading to irreversible hearing impairment. The treatment options were severely constrained in patients of advanced stage. The risk of post-treatment complication increased in the late-stage disease as well [19].

3.1.2. Treatment of aural atresia

There are two distinct phases in the development of acquired aural atresia: wet phase and dry phase [20]. The wet phase means recurrent otorrhea and serial inflammation, while the subsequent dry phase characterized by a non-discharging stenotic ear with dense fibrosis. The dry phase can be advanced phase of wet phase after inefficacious treatment. In the wet phase (primary phase), the granulations occurred repeatedly and subsequently grew over with progressive fibrosis and stenosis. A non-discharging and stenosed EAC was expected at dry phase (secondary phase). The treatment during the wet phase includes ototopical medications and regular suction toilet. Stenotic phase is often inevitable despite the efforts regarding relentless progression to the dry. The only effective intervention is surgery when the fibrous stenosis has occurred in dry phase [18,21–27].

3.1.2.1. Pharmacotherapy. The management principle of wet-phase acquired aural atresia was largely in similar with otitis externa. In conjunction with aural toilet, topical antibiotics and steroid ointments were regularly applied. Systemic drug delivery has not been proven beneficial, while there was evidence of effective topical antibiotic drops containing steroids decreasing inflammation and secretions [28–30]. In patients of wet phase, common topical antibiotics include ofloxacin, ciprofloxacin, polymyxin B and neomycin. The antibiotics application of acquired aural atresia and otitis externa was comparable. The combination of hydrocortisone with antibiotics was recommended [31]. Topical antifungal agents were considered when fungal etiology was suspected [30].

The drug delivery to EAC was usually hampered by noticeable edematous EAC itself. The placement of packing materials moistened with antibiotics drops into the EAC was required in facilitation of medication delivery [32]. The effect of topical treatment should be expected within 2-week administration, and the ear wick was removed when the swelling has been resolved [33]. Fluroquinolones were the exclusive recommendation for patients with TM perforation due to no ototoxicity for middle ear use [34]. However, the effectiveness of topical treatment was suspected with an inevitable progression to fibrosis by a number of studies, and early surgical treatment was advocated during the wet phase to alleviate repetitive and prolonged ear discharge [27].

3.1.2.2. Surgical techniques. For the CAA patients, the surgical strategy depends on the grading of evaluation. Atresiaplasty was the most common surgical technique for CAA patients, aiming to correct the underdeveloped or absent EAC (Fig. 2). Pattee reported surgical treatment of CAA in 1947, with the methodology changing over the decades [35,36]. The Jahrsdoerfer grading scale is the mostly used contemporary system for pre-operative assessment among CAA patients (Table 3) [37]. Compared to patients with a Jahrsdoerfer score of 6 or lower, patients with a score of 7 or higher can have significantly better hearing after atresiaplasty. Depending on Jahrsdoerfer grading results, the choice of therapeutic biomaterials was influenced by decision of treatment alternatives. For patients considered poor candidates for atresiaplasty surgery, bone-anchored hearing aid (BAHA) has become a reasonable alternative [38].

Regardless of the surgical procedures involved, the fundamental performance of atresiaplasty contains three important steps: i) excision of all fibrous tissue, ii) widening the bony canal, iii) grafting or skin flaps to cover bare bone and drum (Fig. 2) [18,20,21,39–42]. Atresiaplasty was referred as canalotympnolasty, implying both canaloplasty and tympanoplasty. Canaloplasty is the surgical procedure of widening EAC, while tympanoplasty is the surgical procedure of repairing the TM and ossicles. The individual surgical technique for particular patient was dependent on the degree of malformation, the Jahrsdoerfer grading results. The loss of some deep meatal skin and epithelial surface of TM was inevitable in atresiaplasty (Fig. 2). One of the commonest techniques was to use a split skin graft (Fig. 2) [43]. The split skin graft has the difficulty of adhesion to the bone surface because the lack of connective tissue. The incompatibility between the graft and bone surface resulted in incomplete post-operative healing characterized as delayed or absence of epithelialization and uncurable granulation tissue. The failure of re-epithelialization indicated unsuccess of surgery and long-term EAC problems [42]. The use of full thickness skin grafts has been reported by Moore et al. [44]. The full thickness skin grafts gave better cover of the bare bone. However, the space remaining for the EAC lumen became limited when the full thickness skin graft was applied.

The recurrence rate is high of both congenital acoustic canal atresia (25–31 %) and acquired atresia (11–33 %), even the denuded bone was grafted [27,42]. Restenosis has been reported in most series regardless of the surgical technique employed, indicating that the poor intervention was one of the essential factors of recurrence. The application of post-operative packing plays an important role in the healing process after surgery.

3.1.3. Demands for EAC biomaterials of atresiaplasty

After atresiaplasty, EAC packing materials were conventionally applied immediately following the surgery. The packing materials were remained in the EAC for about 1–2 weeks with replacement in consideration of the healing process. The main purpose of inserting packing materials into the created EAC was to support the skin graft placed on the undersurface of the bony atretic plate after atrsiaplasty (Fig. 2). Topical antibiotics were utilized to moisten the packing materials in favor of improved healing. Materials with strong adhesion and rigidity when soaked with liquid should be avoided due to the pain and mismatched skin during the removal operation [45]. There was a request for packing materials with regulatory effect during the healing process after atresiaplasty. However, the function of post-operative packing materials

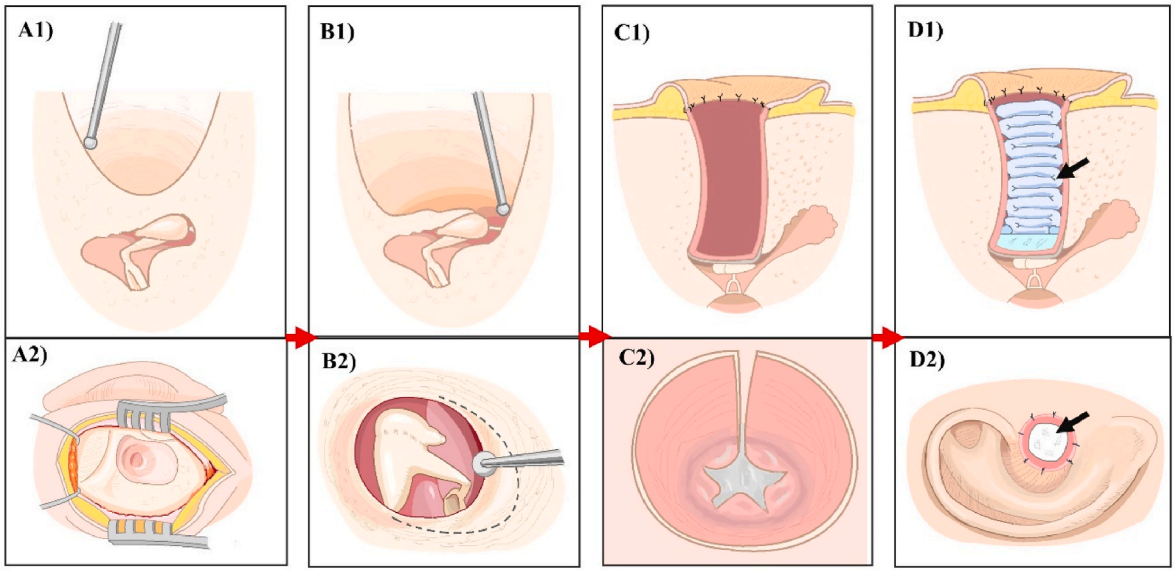

Fig. 2. Schematic diagrams of atreisaplasty surgical procedure. (A) Excision of all obstruction in EAC area: A1) Cross-section view, A2) Top view, **(B) Widening the bony EAC:** B1) Cross-section view, B2) Top view, **(C) Grafting or skin flaps to cover bare EAC bone and drum:** C1) Cross-section view, C2) Top view, **(D) Application of biomaterials to pack and support the skin flap stuck to the EAC,** the packing material was indicated by black arrow: D1) Cross-section view, D2) Top view.

Table 3
Jahrsdoerfer grading system for atresiaplasty.

Parameter	Points
Stapes present	2
Oval window open	1
Middle ear space	1
Facial nerve normal	1
Malleus-incus complex present	1
Mastoid well pneumatized	1
Incus-stapes connection	1
Round window normal	1
Appearance of external ear	1
Total points	10
Rating	**Type of candidate**
10	Excellent
9	Very Good
8	Good
7	Fair
6	Marginal
≤5	Poor

of EAC was limited once the restenosis began to develop after atresiaplasty.

Applied biomaterials can be classified into non-biodegradable and biodegradable materials. The advantage of biodegradable materials was great biocompatibility avoiding complications of removal. Non-biodegradable materials may bring discomfort during removal process and suffer the risk of skin graft displacement. Providing expansionary force in EAC lumen, employed biomaterials can help support the skin graft stuck to the bony EAC and expand the area receiving medication at the same time. The specific packing materials of wet phase will be discussed in the section of packing materials of otitis externa.

3.2. Chronic suppurative otitis media and cholesteatoma

CSOM and cholesteatoma were inflammatory diseases of mastoid with impact on EAC structure (Fig. 1). The diseases of mastoid can cause permanent hearing loss, debilitating vertigo, and irreversible nerve damage if left untreated. Surgery was standard treatment for CSOM and cholesteatoma. The surgical treatment of CSOM and cholesteatoma aims to eliminate the infected portion of ear, preserve the healthy anatomic structure, and protect hearing function. By removing the thin bony partitions of mastoid between postauricular air cells, mastoidectomy is widely accepted as standard surgical treatment of patients with CSOM or cholesteatoma.

3.2.1. Etiology and pathology of CSOM

CSOM is defined as chronic inflammation of the middle ear and mastoid cavity, leading to conductive hearing loss and risk for permanent sensorineural hearing loss. The prevalence of CSOM ranges from 1 % to 46 % worldwide [46]. The etiology of CSOM is usually polymicrobial. The most common microorganisms found in CSOM include Methicillin-resistant *Staphylococcus* aureus (MRSA), *Pseudomonas aeruginosa*, and *Proteus* spp [47]. Bacterial pathogens invade the mucosa of the middle ear through the EAC with an inflammatory reaction in the middle ear and mastoid. The most common complication of CSOM is hearing loss.

3.2.2. Etiology and pathology of cholesteatoma

The definition of cholesteatoma is a collection of keratinized squamous epithelium trapped in the middle ear space destroying vital locoregional structures within the temporal bone. Cholesteatoma is 6–9 per 100000 inhabitants in developed countries with higher prevalence in children [48]. The pathogenesis of acquired cholesteatoma is not fully understood. However, there are four main theories about pathogenesis of cholesteatoma including squamous metaplasia theory, squamous epithelium migration theory, basal hyperplasia theory, and retraction pocket theory, with the fourth most accepted theory by otorhinolaryngologists [49]. A secondary acquired cholesteatoma was formed by infection, trauma, or surgical manipulation. Regardless of the etiology, the cholesteatoma continues to proliferate and migrate causing damage to surrounding structures including the EAC, ossicles, facial nerve, and mastoid. Hearing loss was common due to the erosion of the ossicles. The cholesteatoma can extend to the face, brain, and the neck if left untreated [50]. When becoming infected, the cholesteatoma can grow faster.

3.2.3. Surgical treatment of CSOM and cholesteatoma

Mastoidectomy was surgical procedure treating CSOM and

cholesteatoma, removing the thin bony partitions of mastoid between postauricular air cells. There are two major types of mastoidectomy: canal wall up (CWU) and CWD. Both CWD and CWU procedures remove lateral part of the mastoid to create a communication with the middle ear cavity. The posterosuperior wall of the EAC should be removed in CWD, making CWD different with CWU (Fig. 3) [51]. As a result, an enlarged EAC was created in CWD mastoidectomy.

There are certain indications for CWD surgery influencing the EAC structure, including (i) extensive damage by disease to the posterior canal wall, (ii) severely contracted mastoid with low-lying tegmen and far forward sigmoid sinus preventing satisfactory viewing through CWU approach, (iii) cholesteatoma in an only hearing ear, (iv) labyrinthine fistula in an ear with extensive cholesteatoma [52,53]. The failure of previous CWU procedures with recurrent cholesteatoma from epitympanic retraction pockets was one of the indications for CWD mastoidectomy. The initial mastoidectomy strategy can be to perform a CWU mastoidectomy and can be changed over to a CWD procedure if any of the indications of CWD described above is encountered. A CWD mastoidectomy contains a complete mastoidectomy in addition to removal of the posterior osseous wall of EAC (Fig. 3) [51]. A large meatoplasty is created to allow adequate air circulation into the mastoid cavity [54]. The modified anatomy and physiology of the radical EAC need a filling biomaterial for obliteration in the field (Fig. 3).

3.2.4. Demands of mastoid obliteration materials in canal-wall-down mastoidectomy

The main goals of the CWD mastoidectomy are eradication of disease and prevention of recurrence. The healing after a CWD procedure takes longer than in a CWU procedure because a cavity of varying size created through CWD. A large cavity may cause chronic ear discharge without response to pharmaceutical agents. As a result, mastoid obliteration was applied to prevent cavity problems associated with CWD mastoidectomy (Fig. 3) [54]. Several techniques have been proposed to reconstruct the posterior canal wall and to obliterate the mastoid and epitympanic cavities involving a few materials. The permanent biomaterials used were supposed to help reconstruct the EAC attempting to replicate near-normal post-operative anatomy. Great rigidity and biocompatibility were major requirements of biomaterials for obliteration in CWD mastoidectomy with no need of further removal operation [55]. The materials involved can be classified into non-biogenic and biogenic materials. After mastoid obliteration, the post-operative disposable packing materials inside the EAC cavity were similar with the ones for atresiaplasty.

3.3. Otitis externa

Otitis externa is the inflammation of EAC. The symptoms of otitis externa include ear pain, feeling of fullness inside the ear, and itching in EAC. The symptoms of otitis externa can be treated and disappear within a few days. The mainstay of otitis externa treatment usually involves topical antibiotic drops and pain control. The safety and efficacy of antibiotic otic drops compared to placebo have been proven with excellent results in randomized trials [28]. However, 5 % patients with otitis externa were recalcitrant to treatment and can persist for several months or longer, with a potential of developing acquired aural atresia.

3.3.1. Etiology and pathology of otitis externa

Bacterial infection is the most common cause of acute otitis externa. Other risk factors include fungal infection, humidity, trauma, eczema, radiotherapy and narrow EAC itself [56]. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the frequent pathogens in otitis externa. Cerumen provides a protective barrier and an acidic environment inhibiting the fertility of pathogenic microorganisms [57]. The disruption of the protective factors leads to the inflammation in EAC. The edema of the EAC can be a major sign of otitis externa with suspected otitis media when there is evidence of middle ear effusion.

3.3.2. Medical management of otitis externa

Topical medications are preferred over oral medications as the topical medications target the infected tissue directly. The antibiotics, steroid and trichloroacetic acid have been used [58–60]. The topical medications typically require multiple operations daily for nearly two weeks, with one study finding that only 40 % of patients properly complied with the topical treatment over the course of the first 3 days [61]. Poor compliance with the antibiotic regime can lead to continued or worsening infection. Furthermore, unstable pharmacokinetics and difficulty sticking to inflammatory area limited the efficiency of topical medication to control the EAC inflammation.

3.3.3. Requirement for EAC biomaterials of otitis externa

In consideration of narrow EAC with edema, the insertion of packing material can enlarge the absorption area. The materials should have great swelling properties when moistened with topical medications [62]. Moderate rigidity is required to adapt the shape of narrow EAC

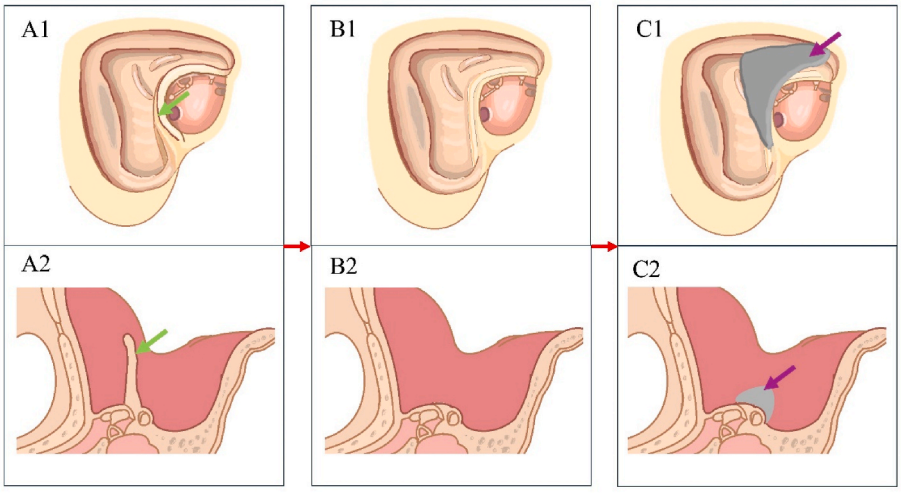

Fig. 3. Schematic diagrams of canal-wall-down mastoidectomy surgical procedure. (A) Mastoidectomy was performed with posterior EAC wall still existing, the posterior EAC wall was indicated with green arrow: A1) Top view, A2) Cross-section view, **(B) Canal-wall-down mastoidectomy with posterior EAC wall excised:** B1) Top view, B2) Cross-section view, **(C) Application of biomaterials for mastoid obliteration,** the area of biomaterials application was indicated by purple arrow: C1) Top-view, C2) Cross-section view.

with no bruise to the inflammatory EAC skin.

3.4. Acute otitis media

Acute otitis media (AOM) is defined as an infection of the middle ear space. The prevalence of AOM was reported varying from 2.3 % to 20 %. The condition can develop into CSOM when left untreated. AOM is a multifactorial disease. Allergic, infectious, and environmental factors contribute to AOM [63].

3.4.1. Etiology, pathology, and treatment of AOM

AOM can begin as an inflammatory process following an upper respiratory tract infection. The edema caused by inflammatory process obstructs the Eustachian tube. The ventilation of middle ear decreases, leading to a vicious circle for the microenvironment of middle ear [64]. The growth of pathogenic microorganisms causes inflammatory reaction including suppuration and frank purulence. Otitis media is one of the major causes of hearing loss and deafness, especially in children and population of developing countries [65]. The common treatment of uncomplicated AOM is oral antibiotics in adults. Amoxicillin is the most used antibiotics with a duration of therapy between 5 and 10 days for AOM patients.

3.4.2. Potential demands for EAC therapeutic materials of AOM

The current strategies of antibiotic delivery for treatment of AOM were unsatisfactory. Systemic antibiotic applications face higher risk of adverse reactions over local delivery [66]. The non-invasive *trans*-TM antibiotic delivery is a reasonable alternative but the intact TM a major barrier for delivery procedure. Well-designed packing biomaterials with ability of effective *trans*-TM delivery can provide great management of AOM.

3.5. Inner ear diseases

The inner ear plays a major role in function of hearing and equilibrium, mainly containing two parts: cochlea and semicircular canals (Fig. 1) [10]. The inner ear is beyond the middle ear, with cochlea supporting hearing function and semicircular canals supporting sense of equilibrium (Fig. 1). There are several types of inner ear balance disorders causing problems with vertigo and hearing loss, including Ménière disease, benign paroxysmal positional vertigo, and labyrinthitis and vestibular neuritis.

3.5.1. Characteristics of inner ear diseases

The most recognizable disease of inner ear is the Ménière disease, a disorder caused by build of fluid in the chambers in the inner ear. The exact etiology of Ménière disease is unclear, with accumulation of endolymphatic fluid in the cochlea and the vestibular organ as a main cause [67]. The specific pathophysiology of Ménière disease is unknown. The most consistent histologic abnormality is endolymphatic hydrops. Hearing loss, tinnitus, and vertigo are common symptoms of Ménière disease, like other inner ear diseases.

3.5.2. Potential treatment through EAC

Oral medications were employed to relieve dizziness including meclizine, diazepam, and glycopyrrolate. Intratympanic corticosteroid injection was recommended avoiding side effect of systemic therapy. However, the suffering of operation and difficulty of controlled release limited the use of intratympanic injection. Endolymphatic sac decompression is a choice for recalcitrant patients of Ménière disease. Non-invasive *trans*-TM delivery may help manage the inner ear disease as a method of local administration.

3.6. The importance of biomaterials for EAC treatment

Over the decades, the application of biomaterials has been regarded as established practice in patients with EAC diseases [68]. The materials applied in EAC vary depending on the requirements of different conditions (Fig. 4). The employed biomaterials can provide assistance for cure of external, middle and inner ear diseases.

For selection of EAC packing materials after atresiaplasty, there was similarity between CAA and acquired aural atresia. The theoretical benefit of EAC packing materials includes promoting healing and avoiding EAC stenosis. Although various studies reported benefits of no packing, most contemporary surgeons (96 %) were reluctant to provide no packing in prevention of stenosis of the EAC [45]. The purpose of the packing in this instance was to ensure adequate bedding down of the skin grafts onto the bone to promote good healing (Fig. 2). The packing was often removed 7–10 days after surgery [45,69]. Various kinds of non-biodegradable and biodegradable materials were evaluated in assistance of EAC re-epithelization.

The biomaterials for obliteration of CWD mastoidectomy were permanently implanted as part of the post-operative ear structure (Fig. 3). Excellent rigidity and biocompatibility were required for supporting the anatomic structure of created EAC. There should be no need of removal, and the filler materials function as part of skull [13].

For the otitis externa and wet phase of acquired aural atresia, the packing materials were supposed to insert into the edematous inflammatory EAC. When moistened with topical antibiotics, the packing can manage the long-term controlled release of the medication [70]. Removal or replacement of EAC packing should be performed according to the course of diseases. In attempt to provide better approach curing middle and inner ear diseases, various biomaterials were explored for non-invasive EAC delivery systems crossing the TM.

In brief, different kinds of biomaterials were employed in diseases with EAC treatment, fitting the specific requirements for therapy of various external, middle, and inner ear diseases (Fig. 4). A global view of various materials utilized for EAC with the relevant characteristics will be provided in the subsequent sections (Table 2).

4. Biomaterials applied in EAC treatment

According to the purpose of application, the EAC biomaterials can be classified into four parts: biomaterials for EAC treatment of atresiaplasty, biomaterials for mastoid obliteration in CWD surgery, EAC filler of otitis externa, and EAC biomaterials for other potential therapeutic purposes. Because the requirements for biomaterials of various therapeutic processes were different, the biomaterials applied were distinct accordingly (Table 2).

4.1. EAC biomaterials of patients receiving atresiaplasty

The choice of post-operative EAC biomaterials was similar for congenital and acquired aural atresia. Several different types of EAC packing materials were reported. The choice of biomaterials tends to lack consensus and be based more on tradition than evidence.

The primary aim of packing was to reinforce the contact between the graft and the bone promoting acceptance. The most common packing materials were gelatin sponge (Gelfoam) and silastic sheeting. The EAC packing materials after atresiaplasty can be classified into two main categories: non-biodegradable and biodegradable materials. Packing was usually removed 2–4 weeks after surgery. The early removal of packing materials prevented infection secondary to the mixture of inflammatory exudation and materials residue. However, the whole process of EAC epithelialization needs about 30 days after surgery [71]. The dilemma exists between the favor of healing process and the prevention of post-operative infection. Post-operative stenosis of EAC is the most prevalent complication after EAC surgery [72]. A variety of non-biodegradable and biodegradable materials were evaluated as post-operative EAC biomaterials in assist with the epithelialization process of EAC skin. The possibility of epithelium transplantation employing biodegradable materials was explored in favor of

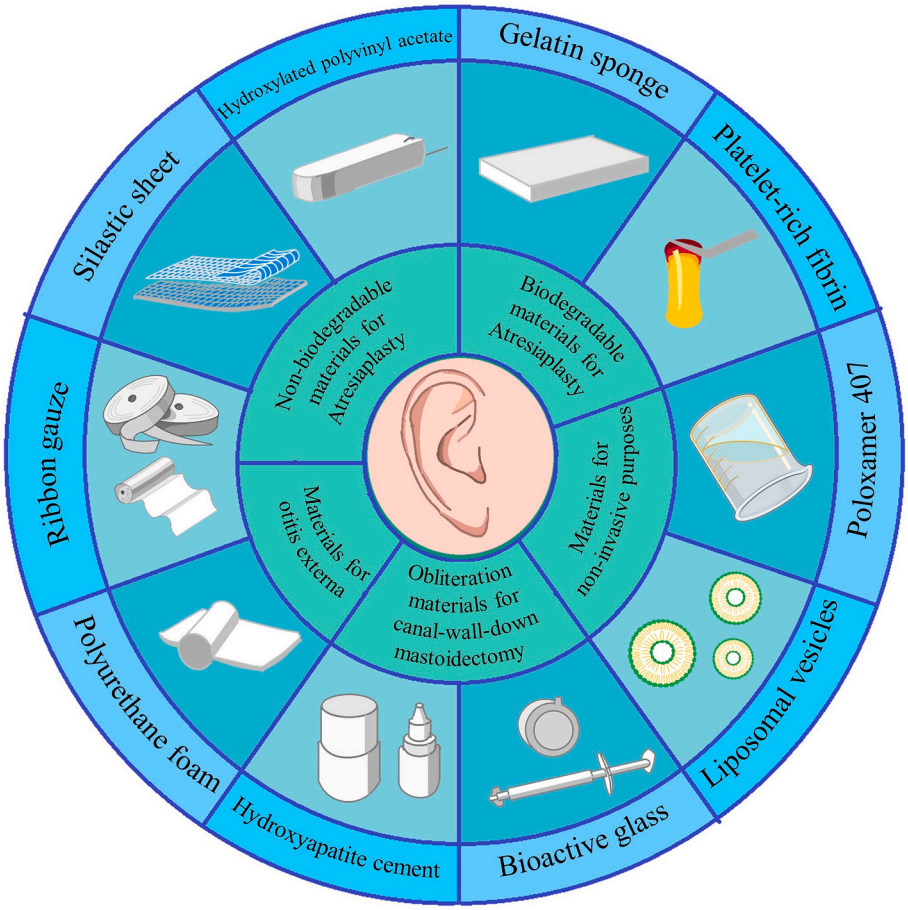

Fig. 4. Categories of biomaterials applied in external auditory canal for various purposes.

epithelization of EAC. However, there is a lack of effective biomaterials promoting re-epithelization process and preventing excessive scar hypertrophy at the same time.

4.1.1. Non-biodegradable biomaterials for EAC packing after atresiaplasty

Traditional EAC packing materials were usually non-absorbable, including silicone sheet, hydroxylated polyvinyl acetate, ribbon gauze and sterile foam rubber balls [24,27](Table 4). In 1970s, Beales and Marlowe both introduced stent mold made of acrylic prosthesis to fill into the EAC and left the materials for several weeks, avoiding fibrous tissue growth in EAC [73,74]. Non-absorbable packs were recommended to be removed 7–21 days after atresiaplasty in patients with CAA. Removal is usually conducted during post-operative visit without anesthesia. The discomfort and risk of skin flap displacement during packing removal were major problems faced with practitioners.

4.1.1.1. Ribbon gauze. Ribbon gauze was one kind of sterile wound dressing that binds bacteria and fungi. As one of the oldest wound dressing materials, the ribbon gauze has usually been used in combination with other materials including ear wick and bismuth iodoform paraffin paste (BIPP) [70]. In practice, ribbon gauze was usually dressed outside of the other packing materials of EAC cavity avoiding abscission of inner fillers. Gauze can absorb post-operative wound exudate and be added with antibiotics or steroids. Without gauze, the wound can trap fluid and possibly bacteria in the deeper areas, disturbing the healing process. However, the non-absorbable property made post-operative operation needed to remove the packing. In addition, adhesion of the gauze to the wound tissue may result new injuries, bleeding, infection in the process of removing gauze, and fibrosis, leading to granulomatous inflammation and scar formation in EAC [75].

For minimal inflammation and being antimicrobial, ribbon gauze impregnated with BIPP was widely applied following ear surgery. The addition of BIPP functions as antiseptic and astringent. However, BIPP can be associated with hypersensitivity reactions. Tight insertion causes difficulty of removal, and loose placement can lead to early extrusion [76]. The increased network porosity may be sufficient to require hemostasis while the porous surface should be chemically engineered to avoid post-operative adhesions.

4.1.1.2. Silastic sheet. Silastic sheet (RTSS) was selected to maintain the EAC skin graft in the proper position. The host material of the silastic sheet was a synthetic polymer with a silicone backbone based on dimethyl siloxane monomers [77]. As one kind of reusable material with non-slip surface, the silicone sheet stent has the potential to enable transcanal drainage and simultaneously allow for the inspection of the canal. The application of traditional gauze prevented inspection of the EAC after surgery. The drainage of accumulated fluid in the canal can be interfered by the packing gauze. The EAC was packed with a rolled, tapered RTSS after surgery to overcome the demerits of conventional post-operative gauze packing in study by Minoda et al. (Fig. 5) [78]. The application of silastic sheeting as EAC packing material was reported in several literatures [41,79]. The inserted RTSSs were post-operatively removed at 5–10 days. The morphological structure of RTSS made it convenient to check or treat the TM during post-operative period, allow transcanal drainage, and can easily be removed. Silastic sheeting has been shown safe and useful as post-operative packing material in otorhinolaryngology.

However, the additional procedure should be conducted at the removal of the non-absorbable material. The allergic reactions can be triggered in patients who were allergic to silicon. Several complications

Table 4
Non-biodegradable packing materials of external auditory canal after surgery.

Types of materials	Study	EAC packing[a]	Pack time (days)	Reference number
Ribbon gauze	Renard et al.	Paraffin gauze	7–10	45
	Jacobsen & Mills	"Swiss roll" of Silastic sheet + ribbon gauze + bismuth iodoform paste	14	79
	Ghani & Smith	Moistened Gelfoam pieces soaked in ciprofloxacin + ribbon gauze soaked with bismuth iodine paraffin paste	14	27
	Becker et al.	Gelfoam balls + antibiotic drugs + gauze + hydrocortisone and Terramycin ointment	21	17
	Tos & Bonding	Gelfoam + hydrocortisone terramycin gauze	21	18
Silastic sheet	Minoda et al.	Tapered silastic sheet with antibiotic ointment applied to one surface	5–10	78
	McDonald et al.	Two strips of medium-light silastic sheeting + Cortisporin-soaked iodoform packs	2	41
	Jacobsen & Mills	"Swiss roll" of Silastic sheet + ribbon gauze + bismuth iodoform paste	14	79
	Magliulo et al.	Gelfoam + silastic sheet	21	91
Hydroxylated polyvinyl acetate	Larson	Hydroxylated polyvinyl acetal wick + Cortisporin Otic drops	60	82
Aquasil Soft Putty	Bast et al.	Aquasil Soft Putty	permanently	83
Rubber ball	Cremers et al.	Foam rubber balls soaked in antibiotic ointment	7	24

[a] Abbreviations: EAC, External auditory canal.

of the silastic sheet have been reported including the formation of excessive collagen connective tissue, an increase of infection resulting from increased bacterial adhesion, displacement, and migration, limiting the duration of silastic sheet in post-operative service [80].

4.1.1.3. Hydroxylated polyvinyl acetate. Hydroxylated polyvinyl acetate (PVAc) was an artificial sponge tampon containing micro-oxidized cellulose, having great biocompatibility, softness, high water absorption capacity, good elasticity, and resistance to corrosion of body fluids [81]. The high tensile strength and flexibility makes PVAc appropriate for EAC packing material to prevent post-operative stenosis of EAC [82]. The great dilatability of PVAc provides mechanical support for post-operative EAC favoring the acceptance of graft and bone surface. The volume expansion of PVAc when added with steroids matched the materials with the irregular skin surface of EAC. Nevertheless, the swelling volume of PVAc was associated with absorbed dose of eardrops and exudation and difficult to control. In addition, PVAc was weakly absorbable and difficult to be completely degraded. Because the nonabsorbable property of PVAc, pain and bleeding upon removal were reported along with dermatitis. Additionally, the lack of antibacterial property makes it difficult to applied as inner packing.

4.1.1.4. Aquasil Soft Putty. Aquasil Soft Putty, one kind of dental impression material (made with silica crystalline, vinyldimethicone, and polydimethyl-hydrogen siloxane), was utilized as ear splint for the prevention of post-operative ear canal stenosis [83]. This type of silane-based material typically possesses good flexibility and can be employed as EAC packing material. After EAC surgery, Bast et al. fitted Aquasil Soft Putty immediately into the patients' ear canal, aiming to maintain ventilation and auditory function (Fig. 5) [83].

The application of Aquasil Soft Putty in the lesion area may be compromised in lack of stability. The poor stability and hydrophobicity lead to displacement or detachment of the filler. Furthermore, the relatively high cost of this material may impose more significant economic burden on post-operative patients.

4.1.2. Biodegradable materials of EAC in patients receiving atresiaplasty

The major disadvantages of non-absorbable packs were discomfort at removal and skin flap displacement following removal in CAA patients. Several studies introduced absorbable materials to avoid the drawbacks of non-absorbable materials. The biodegradable EAC materials can be biocompatible and prevent the complication related with packing removal. The current biodegradable EAC materials includes biodegradable polymers and autologous materials (Table 5).

4.1.2.1. Gelatin. Gelatin is a denatured collagen with great biodegradability and biocompatibility. The absorbable gelatin sponge, Gelfoam, is nonelastic, porous, pliable, and originally designed as a hemostatic. The arginine-glycine-aspartic acid (RGD) sequence of gelatin can promote the cellular behavior of adhesion and migration [84]. Additionally, the adhesion, spread, activation of cells can be invoked by the gelatin, making it candidate biomaterial of wound healing and tissue engineering [85,86]. The surface modified gelatin-based scaffolds have the potential to influence cellular behavior (adhesion, migration, and proliferation) [87]. Additionally, gelatin-based wound dressing can be loaded with various types of bioactive agents (e.g. nanoparticles, antibiotics, growth factors, and antioxidants, etc.) to improve biological activities and accelerate wound healing process [88]. As a result, gelatin-based polymeric hydrogel has been applied in wound healing due to biodegradation, biocompatibility, porosity, high swelling ratio, flexibility, and ability to encapsulate and deliver bioactive agents [88].

Gelfoam has been used for packing in otologic surgery for decades because of its absorbability and flexibility [89,90]. Besides, the application of Gelfoam was combined with several other materials including silastic sheets [17,18,91,92]. The EAC was packed of Gelfoam with Terramycin ointment by Becker et al. [17]. Hydrocortisone Terramycin gauze was add with Gelfoam in patients after atresiaplasty by Tos et al. [18]. Magliulo et al. placed Gelfoam in EAC with a thin sheet of silastic [91].

Nonetheless, there were disadvantages of applying gelatin sponges in treatment after atresiaplasty: i) the mechanical interposition between the gelatin sponge and skin edges may interfere with healing, ii) the use of gelatin sponge was associated with fever, failure of absorption, and hearing loss after surgery. Gelatin sponge was soft and can be easily misshaped or mismatched after packing, iii) the rapid biodegrading process of the material may influence the long-term mechanical stability. As a result, the precise surface modifications and synthesis with other bioactive materials may improve the mechanical strength and stability of gelatin-based biomaterials in application of EAC diseases [93].

4.1.2.2. Platelet-rich fibrin. Platelet-rich fibrin (PRF), a kind of

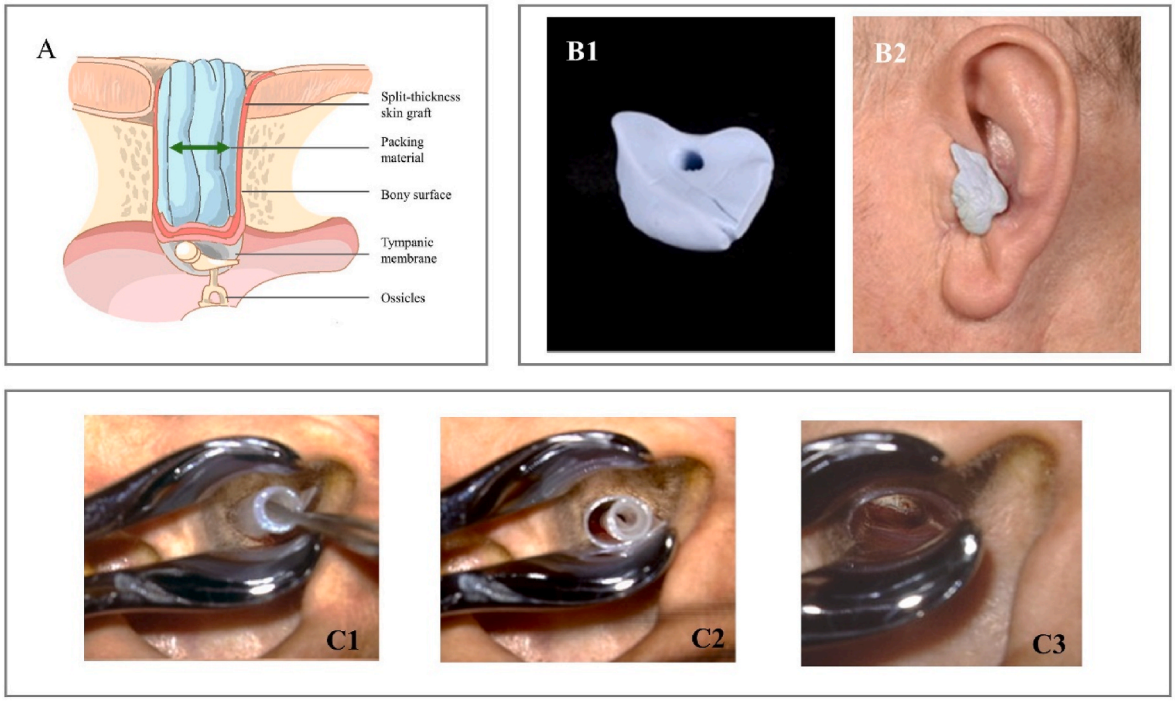

Fig. 5. The purpose and practice of biomaterials for external auditory canal after atresiaplasty. (A) The supporting strength of packing materials after atresiaplasty, the green two-way arrow indicates the supporting strength of the packing material. **(B) The EAC packed with Aquasil Soft Putty:** B1) An integrated ventilation hole in the center of packing. B2) EAC packing made of Aquasil Soft Putty [83]. Copyright 2017, Wiley. **(C) The procedure of inserting silastic sheet into EAC:** C1) A rolled silastic sheet was inserted into the EAC canal. C2) The inserted rolled silastic sheet automatically tapered, C3) The silastic sheet fitted the shape of EAC [78]. Copyright 2010, Elsevier. Abbreviations: EAC: external auditory canal.

Table 5
Biodegradable materials of external auditory canal in atresiaplasty.

Types of materials	Study	EAC biomaterials[a]	Pack time (days)	Reference number
Gelatin sponge	Ghani & Smith	Moistened Gelfoam pieces soaked in ciprofloxacin + ribbon gauze soaked with bismuth iodine paraffin paste	14	27
	Wiesenthal & Garber	Gelfoam + Thrombostat + acetic acid + Bacitracin ointment	14–21	89
	Lin et al.	Antibiotic-soaked Gelfoam	14	90
	Becker et al.	Gelfoam balls + antibiotic drugs + gauze + hydrocortisone and Terramycin ointment	21	17
	Tos & Bonding	Gelfoam + hydrocortisone terramycin gauze	21	18
	Magliulo et al.	Gelfoam + silastic sheet	21	91
	Birman & Fagan	Gelfoam + Celestone gentamicin ointment	NA[a]	92
	Turhal et al.	Gelatin sponge	7	96
Platelet-rich fibrin	Turhal et al.	Platelet-rich fibrin packing	7	96
Oral mucosal epithelial cell sheet	Inagaki et al.	Oral mucosal epithelial cell sheets	28 (rabbit)	97

[a] Abbreviations: NA, Not applicable. EAC, External auditory canal.

polymerized natural fibrin matrix, was introduced as autologous platelet concentrate that supported soft tissue regeneration and wound healing more than a decade ago [94]. Favoring healing of physiologic architecture of EAC, PRF contains a broad spectrum of bioactive molecules (e.g. TGF-beta, hepatoma-derived growth factor, and myeloid-derived growth factor, etc.). Cellular responses of fibroblasts were triggered by PRF lysates, including up-regulation of regeneration-related genes (e.g. NOX4, TSPAN13, and IL33, etc.) and anti-inflammatory genes (e.g. PRG4 and IL13RA2, etc.) [95]. PRF can activate TGF-beta signaling in human fibroblasts and improve proliferation of fibroblasts. The excellent hemostatic ability of PRF provides an alternative avoiding excessive exudation of post-operative EAC. Epithelial cell migration and micro vascularization can be initialed by PRF. Both PRF and platelet concentrate platelet-rich plasma (PRP) have been applied in otologic post-operative care, with positive effects on tissue healing. Turhal et al. reported that PRF was comparable to absorbable gelatin as EAC packing agent after tympanoplasty [96]. The sliced PRF pieces were used for packaging EAC and supporting graft. Healthy epithelization and successful graft intake were observed in patients receiving PRF (Fig. 6). The physical benefit was significantly higher in the PRF group than absorbable gelatine group. However, the protocol of producing PRF during operation was complex and time-consuming (Fig. 6) [94]. The therapeutic efficacy of PRF is limited by healthy condition of patients, the amount and quality of the collected blood, making PRF not applicable to all patients. The procedures of blood collection and transference for the centrifuge greatly affect the success of PRF. The alteration of structural integrity and shrinkage from dehydration requires immediate use of PRF after preparation. The PRF is difficult to preserve for repeat use.

4.1.2.3. Oral mucosal epithelial cell sheet. Minimalizing invasive procedure to harvest cells, cultured oral mucosal epithelial cells (COMEC) have an advantage over other autologous tissue in clinical treatment of

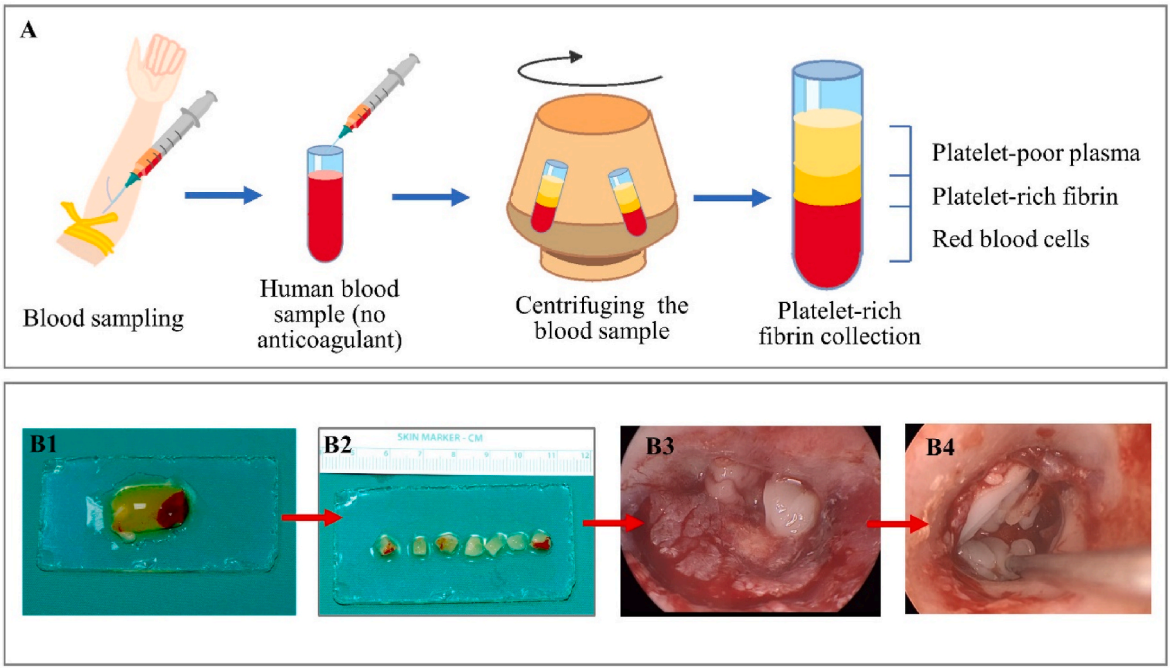

Fig. 6. Preparation and application of platelet-rich-fibrin for atresiaplasty (A) Preparation protocol of platelet-rich fibrin, (B) application of platelet-rich fibrin: B1). Collection of platelet-rich fibrin as fibrin clot, B2) Preparation of platelet-rich fibrin buffers, B3) Platelet-rich fibrin buffers were placed lateral to the cartilage graft in external auditory canal, B4) Platelet-rich fibrin buffers were used in middle ear to prevent cartilage graft medialization.

EAC diseases. The application of COMEC can reduce the risk of rejection and infection. The advanced biocompatibility of COMEC material improved post-operative recovery after atresiaplasty. In a rabbit EAC atresia model by Inagaki and colleagues, the buccal mucosal epithelium of the rabbits was cultured following collection to create cell sheets [97]. The epithelial cell sheets were cut into small sections for transplantation of dissected skin area of rabbit EAC, and the success of the transplantation procedure was evaluated. Transplantation of autologous COMEC sheets prevented the development of atresia in the acquired EAC atresia rabbit model [97]. Thickness of epithelial tissue was significantly thinner in COMEC sheet group when compared with control group. The use of COMEC sheets can be a promising method to reduce the recurrence of atresia. However, this method requires an equipped laboratory setting. The cost of COMEC materials was considerable.

4.2. Materials for mastoid obliteration of CWD mastoidectomy

The elimination of infection and creation of a dry ear while preserving hearing are the goals of CWD mastoidectomy in patients with CSOM or cholesteatoma [98]. However, the enlarged meatus has been identified a cosmetic problem. Regular care of the EAC with mastoid bowl was needed in prevention of water exposure and infection [99].

Mastoid obliteration employing different biomaterials aims to reconstruct EAC and reduce post-operative problems of CWD surgery, including otorrhea and granuloma of EAC. In performance of mastoid obliteration, the biomaterials were spread on the area of eliminated posterosuperior EAC wall and left permanently (Fig. 3). The essential requirements of obliteration materials include great rigidity and biocompatibility without need of further operation. Several autologous materials, including fascia grafts, deep temporal fascial–periosteal flap, conchal cartilage graft, were applied in mastoid obliteration [100–105]. However, autologous materials were limited to certain conditions of patients and were too small to cover the whole mastoid cavity. Considerable attempts using artificial materials have been conducted in CWD patients as well (Table 6).

Table 6
Materials of obliteration in canal-wall-down surgery.

Types of materials	Study	EAC biomaterials[a]	Reference number
Bioactive glass	Sorour et al.	Bioactive glass mixture with autologous blood	109
	Krol et al.	Bioactive glass (S53P4)	114
	Niparko et al.	Bioactive glass (Ceravital)	115
	Fassone et al.	Bioactive glass granules	55
	Yu et al.	Bioactive glass	106
	Clark & Bottrill	Glass ionmeric granules	112
Hydroxyapatite cement	Costantino et al.	Fast-setting hydroxyapatite cement	117
	Ridenour et al.	Hydroxyapatite bone cement	118
Bioceramics	Vidal et al.	Macroporous biphasic calcium phosphate ceramic	120
	Cho et al.	Silicone blocks	99
Polyglycolic acid sheet	Kobayashi et al.	Polyglycolic acid sheet + fibrin glue	123
Human multipotent mesenchymal stromal cells	Skoloudik et al.	Human multipotent mesenchymal stromal cells + hydroxyapatite	130
Xenogeneic acellular dermal matrix	Zang et al.	Xenogeneic acellular dermal matrix	133
Cancellous bone dust	Fieux et al.	Allograft bone	13

[a] Abbreviations: EAC, External auditory canal.

4.2.1. Non-biogenic materials for CWD mastoidectomy

The most common materials applied in CWD mastoidectomy is bioactive glass [106]. The other surface-active biomaterials have been used including hydroxyapatite cement and bioceramics. There are requirements of non-biogenic materials applied in CWD mastoidectomy: biocompatibility, high surface energy, high resistance to degradation and infection, lightweight, function-appropriate design, convenience of position, and no bone deposition.

4.2.1.1. Bioactive glass. Bioactive glasses (BAGs) are a group of silicate-based bioactive inorganic materials promoting new bone formation with activation and recruitment of osteoblast cells. Considerable biocompatibility and adhesiveness were observed in BAGs. In craniofacial surgery, proliferation of fibroblasts, synthesis of growth factors, and healing of granulation tissue can be improved by BAGs [107–109]. There were several types of BAGs applied in obliterating posterior meatal wall of EAC [109].

Glass-ionomer cements, one group of BAGs, have been used for medical purposes for over 30 years due to their excellent biocompatibility [110]. The properties that made ionomeric materials attractive as bone substitutes include a non-exothermic setting reaction with no thermal damage to tissue at the implant bed, minimal shrinkage on gelation, chemical adhesion to mineralized tissue and metals, the possibility of incorporating drugs, and growth factors within the cements, and improved bioactivity due to the release of potentially biologically active ions [111]. Clark et al. assessed the long-term effectiveness of SerenoCem™ granules as biomaterial for CWD obliteration [112]. Glass ionomeric granules provided significant reduced frequency of outpatient aural care visits, resultant dryer ears and improved hearing results for CWD patients. In similar to the results of Clark et al., BAGs were demonstrated as effective obliteration material in CWD patients by Fassone et al. [55]. Nonetheless, glass ionomeric granules were unsuitable for load-bearing applications in orthopedics. The potential risk of adverse reaction limited the applications of glass ionomeric granules.

BAGs S53P4 is another subclass of BAGs. The dissolution of BAG S53P4 increases the local pH and osmotic pressure, creating a bacteriostatic environment [113]. S53P4 BAGs have anti-inflammatory properties with a collection of studies reporting BAG S53P4 as a safe and efficient EAC filler material by Król et al. [114,115]. Obliteration of the mastoid cavity using BAG S53P4 in patients receiving CWD surgery significantly prevented post-operative infection [113]. Nevertheless, the disadvantages of BAG S53P4 were poor support of the EAC wall, low bioactivity, low biodegradability in vivo, and mismatch between the degradation and osteogenesis rates [114]. Those demerits limited the effect of BAG S53P4 as filler in patients receiving CWD surgery. To facilitate cell attachment to the surface of bioactive glass, surface modification by chemical treatment was one of the approaches to modify the surface morphologies and improve cell adhesion [116].

Some synthetic materials combining BAG S53P4 and other material were described to achieve better healing. Bone morphogenetic protein-2 (BMP-2) is a Food and Drug Administration-approved osteogenic protein applied in the treatment of bone defects. Polycaprolactone (PCL) was one kind of common material used as a scaffold-shaping material for bioactive factor load. Yu et al. reported one sort of BMP-2-loaded S53P4/PCL scaffolds for post-operative EAC reconstruction of CWD patients [106]. BAG S53P4 was modified and combined with PCL and BMP-2 to produce an individualized biological scaffold using 3D printing technique to expect a better method for EAC reconstruction. The S53P4/PCL scaffold demonstrated good biocompatibility, osteogenic activity, and capacity of reconstructing EAC in animal models. However, in consideration of the morphological appearance of the scaffold, the disordered fibers and irregular pore size on the surface of S53P4/PCL may affect the biological properties of the scaffold. The mismatch between the osteogenesis and scaffold degeneration resulted in poor volume morphology of the S53P4/PCL/BMP-2 intervened group.

4.2.1.2. Hydroxyapatite cement. Hydroxyapatite, a calcium phosphate compound, is the major structural component of the bone. Hydroxyapatite has been produced synthetically to be used in the form of cements, granules, and other bone implants [117]. Ridenour et al. described the negative effect of hydroxyapatite cement, stimulating granulation tissue formation in more than half of the patients [118]. Draining postauricular fistula, vertigo, and hearing loss were observed in post-operative patients receiving hydroxyapatite cement by Ridenour and colleagues. Revision surgery was required for all patients to remove the hydroxyapatite cement. The evidence provided by Ridenour et al. declared a great risk for failure when applying hydroxyapatite in CWD patients.

4.2.1.3. Bioceramics. The high biocompatibility and mechanical strength of ceramic-based biomaterials make them promising candidates for bone tissue engineering. Bioceramics can provide bioactive surface for hard tissue regeneration. The ion dissolution products (typically Si, Na, and phosphate ions) of bioceramics can promote angiogenesis and antibacterial effect. Additionally, bioceramics can be designed to mimic the mechanical properties of the surrounding tissue enhancing long-term stability of the implantation. The biocompatibility of bioceramics was related to the chemical stability of crystal lattice, giving bioceramics high anticorrosive performance and reliable in vivo behavior. Pore shape and size can be tailored to aid bone ingrowth and osteointegration [119]. Combining bioceramics with fibrin sealant can create moldable composite material, improving its handling and implantation on bony surface. Fibrin sealant can stimulate stem cell ingrowth, resulting in resorption and replacement by new tissue in EAC. Vidal and colleagues used a micro- and macro-porous biphasic synthetic bone substitute combined with a fibrin matrix, TricOs™/MBCP®, to fill the EAC in CWD patients [120]. TricOs™/MBCP® (Biomatlante, Vigneux de Bretagne, France) is an MBCP ceramic consisting of 60 % hydroxyapatite and 40 % β-tricalcium phosphate. The ceramic was hydrated with distilled water and combined with Tisseel/Tissucol® (Baxter Healthcare, Vienna, Austria), a biological fibrin sealant consisting of fibrinogen and thrombin. The mixture was applied to fill the EAC and covered with fascia temporalis and/or cartilage. The combination of TricOs™/MBCP® and fibrin sealant was reported an efficient, safe, and technically convenient way for mastoid obliteration in the CWD technique for cholesteatoma surgery. TricOs™/MBCP® can reduce recurrence and post-operative infections of CWD patients. The demerit of bioceramics was low brittleness. The porous characteristics have restricted ceramic implants to non-load-bearing applications [121]. Surface modification of bioceramics can promote cell proliferation, adhesion, and differentiation, inducing desired cellular response [122].

The silicone blocks, another kind of bioceramics, were flexible enough to handle and to fit into cavities of variable size, and rigid enough to prevent mastoid collapse. The usefulness of silicone blocks was evaluated as material for EAC obliteration in CWD patients by Cho et al. [99](Fig. 7). Most patients receiving silicone blocks obliteration maintained good healing of reconstructed EAC. However, there exists potential risk of ear drum perforation in CWD patients using silicone blocks.

4.2.1.4. Polyglycolic acid sheet. Polyglycolic acid (PGA) is multifilament suture material derived from a homopolymer of glycolic acid. The great biodegradability of PGA made it one of the common polymers for biomedical applications. Scaffolds containing PGA was commonly used in various tissue engineering applications such as bone, tendon, cartilage, tooth, and spinal regeneration. PGA sheet was tested to cover the mastoid bowl after CWD operation by Kobayashi et al. [123](Fig. 7). The PGA sheet with fibrin glue was placed on the bone surface of the enlarged EAC in completion of CWD tympanoplasty. Post-operative epithelialization of the EAC was effectively promoted by PGA sheet. No relevant side effects were reported in Kobayashi's observation. However, the effect of the PGA sheet disappeared within three months. The long-term impact of PGA sheets on skin tissue induced by this method needs further observation. PGA has limitations as its rapid degradation compromises its mechanical strength, and can potentially cause an undesirable inflammatory response due to the resulting increase of glycolic acid [124]. The modification can improve the hydrophilicity and cytocompatibility of PGA with the maintenance of tensile property [125]. Functional and bioactive scaffold can be

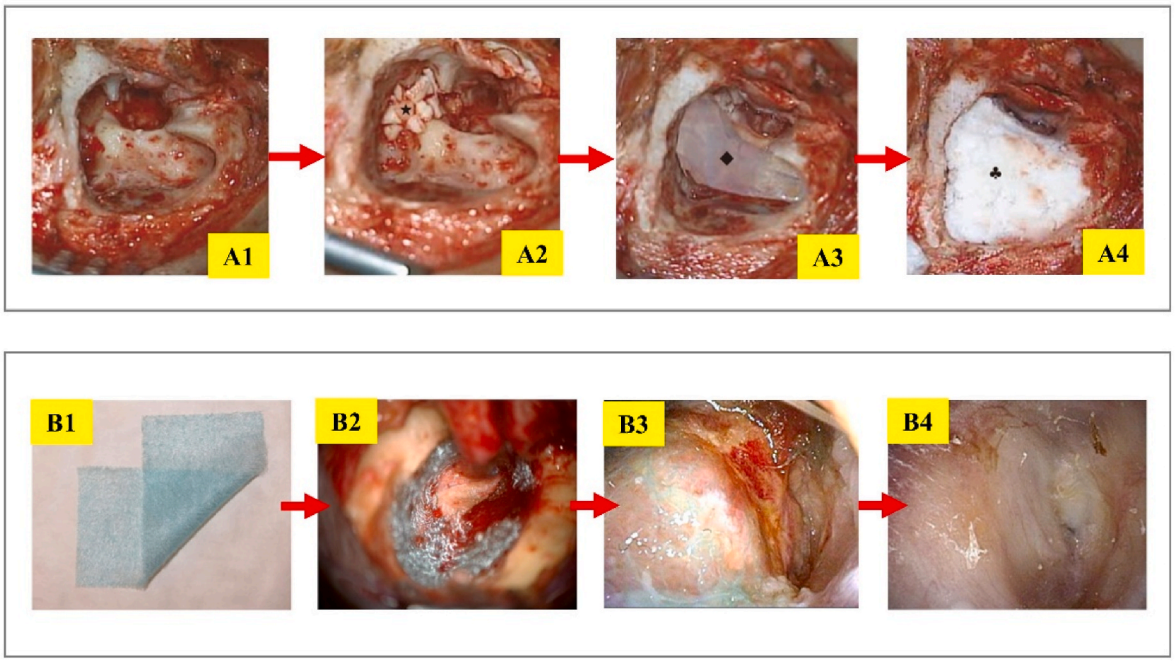

Fig. 7. Surgical procedures for mastoid obliteration with bioactive glass and PGA plus fibrin glue. (A) Mastoid obliteration with bioactive glass: A1) Canal wall down mastoidectomy as enlarged EAC. A2) Piecemeal cartilage obliterated epitympanic cavity. A3) Bioactive glass was used to fill the enlarged meatus. A4) Bioactive glass was fixed through fibrin glue with bone pate covering. ★, piecemeal conchal cartilage; ◆, silicone block; ♣, bone pate. Abbreviations: EAC: external auditory canal [99]. Copyright 2012, KOREAN SOC OTORHINOLARYNGOL. **(B) Mastoid cavity dressed with PGA sheet plus fibrin glue:** B1) PGA sheet, B2) Pieces of PGA sheet fixed to the bone surface using fibrin glue after canal-wall-down tympanoplasty, B3) Enlarged meatus was dry 25 days after surgery, B4) Epithelialization was obtained 81 days post-operatively. Abbreviations: PGA: polyglycolic acid [123]. Copyright 2017, Elsevier.

developed through the combination of the PGA and BAGs for bone repair [126].

4.2.2. *Biogenic materials for CWD mastoidectomy*

Numerous otologists have reported biogenic implants including fat, bone chips, cartilage, and acellular dermal matrix as fillers of CWD surgery [127,128]. The biogenic materials were considered mainly because of remarkable biocompatibility avoiding inflammatory reaction.

4.2.2.1. Human multipotent mesenchymal stromal cells. Human mesenchymal stromal cells (hMSCs) are the spindle formed plastic-adherent cell isolated from adipose, bone marrow, and other tissue sources, with multipotent differentiation capacity in vitro. In the field of regenerative medicine, hMSCs have tremendous potential as a therapeutic cell source for a wide range of diseases (e.g. autoimmune, cardiovascular, neurodegenerative, bone and cartilage diseases, etc.) [129]. In consideration of the disadvantages of hydroxyapatite along, human multipotent mesenchymal stromal cells (hMSCs) were introduced to use with hydroxyapatite as bony tissue engineering biomaterial. A method of preparing biomaterial composed of hMSCs, hydroxyapatite, and tissue glue was developed by Skoloudik et al. to repair the defected EAC in a guinea pig model [130]. The hydroxyapatite bone graft was powdered and combined with tissue glue and seeded with hMSCs as filler of the defected EAC. The guinea pig model implanted with hMSCs in EAC showed great bone formation of EAC when compared with the controls of hydroxyapatite implantation only. However, the application of the tissue engineering was subjected to the laboratory setting of the surgical treatment provider and conditions of the patients themselves.

4.2.2.2. Xenogeneic acellular dermal matrix. Acellular dermal matrix (ADM) was a dermal scaffold removing cellular components and retained the extracellular matrix components with great biocompatibility [131]. The xenogeneic ADM (xeno-ADM) has a wider source and avoids the possibility of ethical issues when compared with the allogeneic ADM (allo-ADM). The xeno-ADM was therefore more likely to meet clinical requirements. A variety of studies have reported xeno-ADM as a suitable dermal substitute repairing epidermal tissue defects [132]. Zang and colleagues retrospectively analyzed CWD patients using xeno-ADM to repair the skin defects of reconstructed EAC [133]. The therapeutic efficacy was observed in the study. The surgeons pruned xeno-ADM (bovine) graft according to the shape and size of the defect area with several holes punctured on the membrane. The xeno-ADM protected the wound surface, shortened the epithelialization time, reduced the times of dressing change, and avoided the trauma of the donor site. The xeno-ADM was proven an effective bioremediation material for EAC skin defects of patients receiving CWD surgery. The allograft acts as a bioactive scaffold for vascular endothelial cells and fibroblasts, with potential to improve post-operative EAC healing [134]. However, xeno-ADM can cause complications including infection, hematoma, seroma, and necrosis. The price of xeno-ADM is relatively high, making it inappropriate for all patients. The chemical modification of ADM usually includes the use of glutaraldehyde, carbodiimide, and epoxy compounds. Modified crosslinked structure can significantly improve the mechanical properties and degradation resistance of ADM [135].

4.2.2.3. Cancellous bone dust. Cancellous bone is characterized by spongy, porous, honeycomb-like structure and is typically located at the ends of long bones. Allograft of cancellous bone was usually collected from donors donating bone for living people, making it candidate for application of bone regeneration. From the viewpoint of regenerative medicine, cancellous bone dust can potentially release anabolic factors into the host environment and promote bone formation. Allograft cancellous bone dust reconstructions permit re-establishment of skeletal continuity and function, providing a treatment modality for management of difficult skeletal defects [136]. The comparison between BAGs and allograft cancellous bone dust was observed in rehabilitation

applications of CWD surgery by Fieux et al. [13]. In early follow-up (18 months), the effects of bone allografts were poor with significant resorption leading to 40.0 % revision surgery rate. The BAGs seem to be a better solution when compared to allograft bones.

4.3. Biomaterials as EAC filler of otitis externa

The conventional EAC packing materials applied in otitis externa patients were mostly those operated to patients receiving atresiaplasty, including ribbon gauze, gelatin and PVAc [28,59,137–140]. Biomaterials soaked with antibiotics and steroid were applied to attain improved persistent drug delivery in the narrow EAC. Several observations have been performed to investigate the effect of various biomaterials on otitis externa (Table 7). A few novel materials were observed to improve the effectiveness of EAC medication delivery [141].

4.3.1. Polyurethane foam

Polyurethanes are an immensely versatile class of polymers used in foams, characterized by the presence of a urethane linkage [142]. Facile synthesis and simple modification were merits of polyurethane, leading to various properties and a tunable biomaterial platform with potential use in a range of regenerative medical applications. The utilization of polyurethane foam to support the surrounding tissue when absorbing water was reported in nasal surgery studies [143]. Demir and colleagues evaluated biodegradable synthetic polyurethane foam in acute otitis externa, demonstrating the effect of polyurethane foam in treating severe acute otitis externa [70]. However, the biodegradable polyurethane lacked ability of relieving signs and symptoms during the healing process of acute otitis externa patients.

4.3.2. Tetraethyl orthosilicate-based hydrogel

The hydrogel made of hydrolyzed tetraethyl orthosilicate (hTEOS) and sodium hyaluronate (HA) carried intrinsic anti-inflammatory properties [144]. Catton and colleagues developed a cold-chain independent tetraethyl orthosilicate-based hydrogel with the potential of steady release a variety of model drugs regardless of changing physiological factors of the diseased EAC [145]. Additionally, the gel easily coated the entire EAC because of exceptional thixotropic nature. The assessment of releasing profile indicated that the tetraethyl orthosilicate-based hydrogel can be loaded with and release a wide variety of drugs with distinct release profiles and highlights the versatility of this drug delivery system. The materials may be used for incorporating two or more different drugs to obtain tailored release patterns. However, the complicated and unmanageable manufacturing process (longer gelation time, higher volume shrinkage, lower optimized transmission) limited application of tetraethyl orthosilicate-based hydrogel.

Table 7
External auditory canal packing materials of otitis externa.

Types of materials	Study	EAC packing[a]	Pack time (days)	Reference number
Ribbon gauze	Barr & al-Khabori	ribbon gauze + antibiotic steroid mixture	7	58
	Pond et al.	ribbon gauze	2–3	137
	Demir et al.	ribbon gauze	2	70
Ear wick	Bola et al.	Ear wick	5	139
	Pond et al.	Ear wick	2–3	137
	Demir et al.	Ear wick	2	70
Hypromellose gel	Hasselt & Gudde	Hypromellose gel + silver nitrate gel	7	140
Silver nitrate gel	Hasselt & Gudde	Silver nitrate gel	7	140
Polyurethane foam	Demir et al.	Polyurethane foam	2	70
Tetraethyl orthosilicate-based hydrogel	Catton et al.	Tetraethyl orthosilicate-based hydrogel	NA	145

[a] Abbreviations: NA, Not applicable. EAC, External auditory canal.

4.4. Noninvasive EAC materials for other purposes

The conditions of EAC can have an influence on the diseases of middle and inner ear. On the contrary, there are potential of intervening the middle and inner ear diseases through medication delivery of EAC crossing the TM [146]. Non-surgical management of middle and inner ear diseases have been unsatisfactory. Systemic medication delivery to the middle and inner ear is limited by the barriers between the blood and the fluid-filled spaces in the middle and inner ear. Non-invasive drug delivery through EAC was a promising approach for treatment of middle and inner ear diseases [147,148]. The TM separates the EAC from the middle ear, making the non-invasive medicine delivery to middle ear difficult. For better approach of solving middle and inner ear diseases, several studies have explored possibilities of local delivery crossing TM through materials of EAC to achieve controllable delivery efficiency and reduce systemic side effects. Furthermore, the possibility of designed biomaterials penetrating to the inner ear was evaluated.

4.4.1. Poloxamer 407

Poloxamer (known as Pluronic) is a series of linear di- and tri-block copolymers composed of hydrophilic polyethylene glycol and hydrophobic polypropylene oxide. Thermosensitive sol-gel transition was observed in Poloxamer in response to change in temperature. Poloxamer was ideal biomaterial for injectable adhesive due to the ability to form physical gel at body temperature [149]. Poloxamer 407 (P407) was one kind of thermosensitive hydrogel designed to delivery drugs with different characteristics [150]. The chemical structure of the poloxamer triblock copolymer leads to an amphiphilic aqueous solution and an active surface. Thermosensitive hydrogels remain fluid at room temperature and viscous gels at body temperature [151]. The excellent controlled-release effect of P407 has been utilized in *trans*-tympanic drug delivery. Khoo et al. developed a drug delivery system based on P407 for the treatment of AOM [152]. Yang et al. designed P407-polybutylphosphoester delivery systems to form hydrogel on the TM [153,154]. The liquid hydrogel was injected to the TM on chinchilla model before gelation. Chemical permeation enhancers (CPEs) were added to the system to attain increased permeation of medications. CPE-hydrogel formulations have potential for ototopical delivery of medications in EAC for the treatment of AOM and other middle ear diseases. The permeation of polyethylene glycols across the TM in P407 hydrogel was assessed by Zhang et al. [155]. However, the demerits of P407 include low gel strength, rapid dissolution of the gel, poor bioactivity, and weak adhesiveness to mucosa. The mix of poloxamer and hydrophilic polymers was conducted to improve the gel properties [156]. The modification of P407 can obtain specific biological properties of surface modified nanospheres.

4.4.2. Transferosomes

Transferosomes are vesicular carrier systems designed to have at least one inner aqueous compartment that is enclosed by a lipid bilayer [157]. Comparing conventional liposomes, the transferosomes generally have better permeation ability, leading to potential of encapsulating drugs and activating amphiphilic substances [158]. Several studies have demonstrated the employment of transferosomes as carriers for various compounds. Al-mahallawi and colleagues tested a transferosomal formulation enhancing the antibiotic flux across the intact TM into the infected middle ear [159]. The optimal formulation of transferosomes demonstrated a great extent of *in-vivo* drug deposition in the TM of laboratory animal model. Transferosomes can be promising for the

noninvasive *trans*-TM delivery of medication by Al-mahallawi et al. [159]. There were disadvantages of transferosomal systems including oxidative degradation and relatively high expense.

4.4.3. Peptides

The discovery of *trans*-TM mechanism of specific peptides provides a promising way for large-molecular weight drug delivery and gene therapy vectors. Kurabi et al. observed peptides able to cross the TM and the conditions influencing the *trans*-TM efficiency [160]. Structural analysis of peptides with different *trans*-TM efficiency indicated the importance of β-chain structure in high transport rate. However, the mechanism of action is obscure, and binding partners on the TM with peptides were unknown.

4.4.4. Liposomal vesicles

Liposome is an artificial vesicle composed of concentric phospholipid bilayers designed to deliver microscopic substances to body cells. Versatile structure and accommodation of various bioactive agents were advantages of liposome as drug delivery carrier. The current standard systemic drug administration methods for middle and inner ear diseases include oral intake and intravenous (IV) injection [161]. The systemic methods can cause nonspecific biodistribution with rising risk of side effects. The IV injection reduces side effects but painful experience for patients. As a result, topical drug delivery to the middle ear across the TM has gained increasing attention recently. Sadabad et al. investigated the capability of liposomal nanoparticle, particularly TLipo, used as drug delivery vesicles to penetrate the TM and round window membranes with high affinity, specificity, and retention time [162]. The TLipo was applied to the EAC and found to pass through the TM in 3 h after administration, with identification in the middle ear cavity in 6 h and in the inner ear 24 h after administration. Auditory brainstem response and immunohistochemistry results demonstrated no evidence of hearing loss or cytotoxicity in vivo animal study. The TLipo can be suggested as a vehicle for topical drug delivery to the middle ear and inner ear. A novel ear delivery system based on glycerosomes, a new generation of liposomes, was reported by Magdy et al. [163]. Several kinds of nanoliposomes were employed in EAC for treatment of middle ear diseases [164]. The application of liposomal vesicles may be tested in further research as a potential EAC packing material.

4.4.5. Chemical permeation enhancers

CPEs are a group of molecules interacting with the constituents of epithelium to increase the permeability of targeted medications, qualified to help drugs cross the skin. *Trans*-TM delivery requires drug diffusion out of the carriers and flux across the TM. CPEs have potential application for *trans*-TM delivery including sodium dodecyl sulfate, limonene, and bupivacaine. The extended work by Khoo et al. has proven the reversible increased fluidity created by CPEs providing a non-invasive way to deliver small molecular drug across the TM [152]. Nevertheless, CPEs have a tendency to destroy the outermost layer of epithelial tissue and lengthen the recovery time of damaged structure.

5. Future perspectives

A well epithelialized and complete EAC is the goal for all kinds of treatment regarding external ear. Post-operative EAC stenosis remains a challenging obstacle to acquire healthy hearing in patients with congenital and acquired aural atresia. Although EAC stenosis was expected to become the first leading cause of surgery failure, there has been progress in the development of biomaterials that prevent the post-operative stenosis to improve outcomes in the past decades. However, the clinical application of these strategies, hindered by the complication of the EAC anatomic structure with difficulty of matching the skin graft, performed less than satisfactory results. Therefore, the necessity to develop advanced strategies or improve the efficiency of current treatments is urgent. Biomaterials targeting EAC post-operative complications have attracted much attention.

Excessive fibrous connective tissue proliferation of EAC was a plaguing obstacle for the post-operative EAC healing. Failure of re-epithelization and activated fibroblasts have been considered the key roles of the development of EAC restenosis. Fibroblasts were assumed the primary responsibility behind the cicatrix initiation. The treatment of excessive inflammation of EAC skin was limited to topical corticosteroids conducted with ear packing materials. Several polymeric biomaterials (e.g. gelatin and PVAc, etc.) have been applied as the basic post-operative EAC packing materials exhibiting mechanical support for the adhesion between bone and skin grafts [3,19]. However, lack of improvise adaption to the healing process and need of removal limited the combined effect of steroids and ear packings. The mechanisms of re-epithelization in research treating cicatrix were convincing. Further research may focus on the development of biodegradable materials loaded with various therapeutic agents, such as TGF-beta, to regulate the performance of re-epithelization of post-operative EAC.

Another strategy to prevent post-operative EAC stenosis is to provide extra supportive pressure for post-operative EAC skin or graft. The anatomic structure of post-operative is complex and lacks mechanical support during the healing process. The PAVc ear packing was applied because of its swelling property and can produce extra pressure when infiltrated with topic steroids. However, with the re-operation of removal during the post-operative follow-up, this strategy is still bringing some complications such as displacement of post-operative EAC skin. The property of expansion and pressure-responsibility can be the directions of the development of further therapeutic agents for post-operative EAC stenosis.

Cellular microenvironment of EAC soft tissue was changing during the therapeutic procedure. The role of fibroblasts was diverse in the healing process, causing controlled re-epithelization or uncontrolled cicatrix formation. The cytokines associated with connective tissue proliferation functions differently under varied microenvironment, such as TGF-beta with promotion of fibrous connective tissue growth during the early healing phase and increase of cicatrix formation risk in the later post-operative period. Thermo- and chemo-responsive architected materials are triggered by temperature or chemical cues from the surrounding environment. The responsive materials can be further explored in the regulation of post-operative EAC skin microenvironment or achieve responsive release of the loaded regulators for healing process.

Different biomaterials, such as polymers and autologous materials, showed advantages and disadvantages for post-operative EAC anti-stenosis therapy. Lacking mechanical support of biodegradable materials, such as gelatin sponge, makes it difficult to prevent cicatrix formation in EAC. In contrast, non-biodegradable materials can lead to post-operative complication during the removal procedure. Polymers and hydrogel loaded with cargoes exhibited great biocompatibility and promising anti-fibrotic efficiency. With ingenious modifications, these smart biomaterials display promising potential for post-operative EAC packing. As for the multifunctional biomaterials, the unique concept still needs to be thoroughly evaluated in EAC treatment by further research.

The obliteration materials for CWD mastoidectomy remain unsatisfactory. The major complications were high recurrent rate requiring revision surgery. For mastoid obliteration, the autologous materials were the trend over the last decade. Further work should be performed searching materials with excellent availability, safety, biocompatibility, and user-friendliness. The modified surface based on current bioactive materials can be one of the potential directions for hard-tissue engineering.

As EAC can be a promising approach for drug delivery to the middle and inner ear, a growing number of studies have explored the materials with ability to achieve *trans*-TM delivery and relevant mechanisms. The well-designed biomaterials with controllable methodologies are expected for non-invasive *trans*-TM delivery in future.

Taken together, different EAC materials have been applied for various clinical practices with insufficient effect (Table 8). Further

Table 8
Summary of external auditory canal materials for different clinical situations.

Indications	Diseases	Methodology	advantages	disadvantages	Materials
Skin graft left on the osseous surface after atresiaplasty	Congenital aural atresia, Acquired aural atresia	Insert the materials into the cavity of EAC, and remove within 2 weeks	Support the tight stickiness between the skin graft and bony surface	Pain and risk of mismatching during removal	Ribbon gauze, Silastic sheet, Gelatin, etc.
Inflammatory or edematous EAC[a]	Otitis externa, Wet phase of acquired aural atresia	Moisten the materials with topical antibiotics and inserting the materials into the EAC, remove the materials after invalidation	Expand the area receiving drug, and extend the active time of drug	Hyper-inflation of the materials to pressure tissue, causing insufficient blood supply	Gelatin, ear wick, Polyurethane foam, etc.
Obliteration of enlarged mastoid cavity in canal-wall-down mastoidectomy.	Chronic otitis media, Cholesteatoma	Fill the cavity, leaving the materials permanently	Manage otorrhea and debris accumulation in the EAC	Infection, persistent granulation, retraction pocket formation	Bioactive glass, Hydroxyapatite cement, Acellular dermal matrix, etc.

[a] Abbreviations: EAC, External auditory canal.

fabrication of materials and modification of current materials are required for better prognosis in patients with EAC diseases. Novel techniques and methodologies can be provoked when the improved EAC biomaterials available.

6. Conclusion

The practice of EAC materials for various diseases was continuously explored in the last decades. We will be able to develop strategies for good EAC tissue healing in patients with relevant conditions. Yet few biomaterials have been translated into clinical application, and modification should be made to meet the demands of EAC healing for osseous tissue, connective tissue, and re-epithelialization. There is real hope that these biomaterials will provide enhanced efficiency for EAC healing in the foreseeable future.

Ethics approval and consent to participate

There are no human and animal subjects in this review and informed consent is not applicable.

Data availability

No data was used for the research described in the article.

CRediT authorship contribution statement

Yang Xu: Writing – original draft. **Zhongwu Bei:** Writing – original draft. **Mei Li:** Writing – review & editing. **Lin Ye:** Resources. **Bingyang Chu:** Supervision. **Yu Zhao:** Supervision. **Zhiyong Qian:** Writing – review & editing, Investigation.

Declaration of competing interest

Zhiyong Qian is an editorial board member for *Bioactive Materials* and was not involved in the editorial review or the decision to publish this article. All authors declare that there are no competing interests.

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