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Eosinophilic otitis media; state-of-the-art diagnosis and treatment

Yukiko Iino [a,b,*]

[a] Department of Otolaryngology / Deafness and Middle Ear Surgicenter, Tokyo Kita Medical Center, 4-17-56 Akabanedai, Kita-ku, Tokyo 115-0053, Japan
[b] Department of Otolaryngology-Head and Neck Surgery, Jichi Medical University Saitama Medical Center, 1-847 Amanuma-cho, Omiya-ku, Saitama 330-0834, Japan

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ABSTRACT

Eosinophilic otitis media (EOM) is an intractable otitis media with highly viscous middle ear effusion and is usually associated with bronchial asthma. Since the diagnostic criteria of EOM were established in 2011, the concept of EOM has been known worldwide. EOM is caused by Type 2 inflammation in the respiratory tract, similar to bronchial asthma and eosinophilic rhinosinusitis. With the appreciation of Type 2 inflammatory diseases, EOM is no longer considered to be a rare disease and should be specifically treated to improve quality of life. The diagnosis of EOM needs to be reconsidered because many reports have described varying pathogenesis and mechanisms of rare middle ear conditions. Systemic and topical administration of corticosteroids is presently the most effective treatment to control EOM. However, EOM treatments are developing because various biologics have been used to treat patients with bronchial asthma with and without eosinophilic rhinosinusitis and EOM. Surgical intervention is also no longer contraindicated with the use of biologics. These advances represent the beginning of a new stage of basic and clinical research for EOM. This review focuses on the diagnosis and treatment of EOM based on the most recent advances regarding EOM.

1. Introduction

Eosinophilic otitis media (EOM) is a newly recognized form of otitis media, which was first reported in Japan. It is an intractable otitis media with highly viscous middle ear effusion and is usually associated with bronchial asthma and chronic rhinosinusitis. The middle ear effusion (MEE) of EOM contains many eosinophils; therefore, Tomioka et al. [1] named this condition EOM in 1997. In 2011, the diagnostic criteria of EOM were proposed by an EOM study group, and were published in *Auris Nasus Larynx* [2]. Since then, many EOM studies have been published in English language academic journals.

EOM is caused by Type 2 inflammation in the respiratory tract, similar to bronchial asthma and chronic rhinosinusitis with nasal polyposis/eosinophilic chronic rhinosinusitis (ECRS). Recently, there have been many reports concerning the pathogenesis of Type 2 inflammation and the mechanisms responsible. Based on this new knowledge, various molecular targeted drugs or biological drugs (biologics) have been used to treat patients with bronchial asthma and ECRS. We are now entering a new stage of basic and clinical EOM research. This review focuses on the diagnosis and treatment

* Corresponding author at: Department of Otolaryngology / Deafness and Middle Ear Surgicenter, Tokyo Kita Medical Center, 4-17-56 Akabanedai, Kita-ku, Tokyo 115-0053, Japan
E-mail address: yiino@jichi.ac.jp

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Table 1. Demographic information

	Suzuki et al. (2003) [3]	Iino et al. (2011) [2]	Esu et al. (2020) [4]	Chen et al. (2021) [5]
No. patients	190	138	68	393
Gender (F:M) (F %)	116:74 (61.0%)	86:52 (62.3%)	38:30 (55.9%)	250:143 (64%)
Age (years)				
Mean (SD)	most age: 50s	50.5 (13.1)	55.7 (11.8)	N/A
Bilaterality	81%	114 (82.6%)	68 (100%)	298 (88%)
Highly viscous MEE	100%	128 (92.8%)	N/A	216 (85%)
Granulation tissue formation	N/A	45 (32.1%)	18/136 ears (13.2%)	N/A
Resistant to treatment	100%	128 (92.8%)	N/A	147 (58%)
Deterioration of BCHL	47%	81 (59.1%)	14 (20.6%)	N/A
(deafness)	6%	8 (5.8%)	N/A	N/A
Associated diseases				
Bronchial asthma	100%	124 (89.9%)	63 (92.6)	241 (95%)
NERD	N/A	N/A	6 (8.8%)	N/A
Chronic rhinosinusitis	74%	102 (75.6%)	54 (79.4%)	N/A
Nasal polyposis	N/A	85 (62.0%)	N/A	181 (71%)
Allergic rhinitis	N/A	52 (42.6%)	N/A	N/A

F, female, M, male; MEE, middle ear effusion; BCHL, bone conduction hearing level; NERD, NSAIDs exacerbated respiratory disease; N/A, not applicable.

of EOM based on the pathogenesis of EOM, in particular on studies undertaken after the diagnostic criteria of EOM were published in 2011.

2. Clinical features and types of EOM

In 2003, a large survey of EOM patients was performed in Japanese hospitals by the completion of questionnaires. A resulting 190 definite cases were collected and analyzed [3]. An EOM study group consisting of five otologists analyzed a further 138 EOM cases to develop diagnostic criteria [2]. Esu et al. [4] assess the effectiveness of myringoplasty in 55 EOM patients. Recently Chen et al. [5] collected 393 patients with EOM of 26 studies, and performed systematic review. The clinical characteristics of the EOM patients in four reports [2–5] are shown in Table 1.

Summary characteristics of EOM:

- Female predominance
- Age >50 at first visit
- Mostly bilaterally affected
- High incidence of deterioration of bone conduction hearing level
- High prevalence of bronchial asthma and chronic rhinosinusitis

Before the first referred visit to a hospital, most patients had been treated by other clinics or hospitals for several years. Therefore, the average age of EOM onset might be 40-plus years of age. Kanazawa et al. [6] reported that EOM onset was approximately ten years after the onset of bronchial asthma and chronic rhinosinusitis. Concerning bilateral affection, EOM appears to be a “one airway one disease” Type 2 inflammatory disease of the upper airway, similar to ECRS [7].

There are two types of EOM; otitis media with effusion (OME) and chronic otitis media (COM). The latter type is further divided into two subtypes: COM with simple perforation and COM with granulation [8]. In OME type, the eardrum is not perforated and contains yellowish highly viscous MEE (Fig 1a). In COM type, the eardrum is persistently perforated because of myringotomy, insertion of a tympanostomy tube or spontaneous rupture. COM with simple perforation shows highly viscous MEE without bacterial infection (Fig. 1b). When the ear is infected, the effusion loses viscosity. COM with granulation shows extensive granulation tissue formation in the ear. The granulation tissue frequently extends to the external auditory canal beyond the eardrum level (Fig. 1c). EOM is frequently associated with bacterial infection, with *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus (MRSA)* and *Pseudomonal aeruginosa* [9]. This type of EOM is the most intractable and resistant to treatment including topical/systemic administration of corticosteroids and antibiotics.

A striking characteristic of EOM is the high risk of developing severe mixed hearing loss or deafness. Reported risk factors associated with deterioration of bone conduction hearing level include a long duration of EOM [10], male sex, older age, infection by pathogenic bacteria, severe mucosal change [11], *Pseudomonas* infection, and eardrum perforation [9]. However, the cause of inner ear damage remains controversial. Eosinophilic inflammation may induce a change in the permeability of the round window membrane allowing the entry of inflammatory substances such as bacterial toxins and cytokines into the inner ear, resulting in inner ear damage. Indeed, infiltration of eosinophils into the inner ear was found to damage the organ of Corti in an animal model of EOM [12].

3. Diagnosis and evaluation of EOM

3.1. Diagnostic criteria of EOM

Although several clinical characteristics of EOM have been reported [2,3,13], nothing is known about the incidence of each EOM characteristic in common types of otitis media to enable definitive diagnoses of EOM to be made. The members of an EOM study group collected 138 patients who had COM or OME with the presence of eosinophils in the MEE

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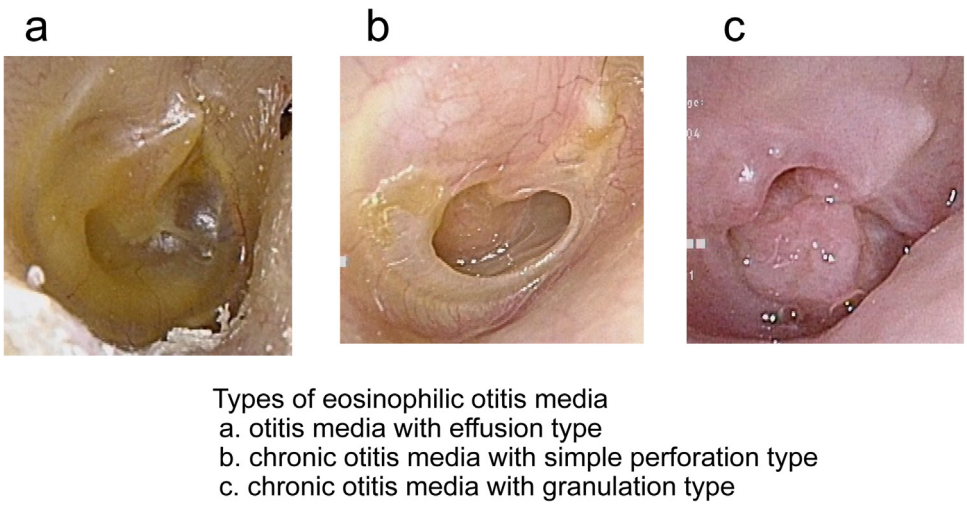

Figure 1. Types of eosinophilic otitis media. a. otitis media with effusion type. b. chronic otitis media with simple perforation type. c. chronic otitis media with granulation type

Table 2. Diagnostic criteria of eosinophilic otitis media (EOM)[2]

Major: Otitis media with effusion or chronic otitis media with eosinophil- dominant effusion
Minor
1. Highly viscous middle ear effusion
2. Resistance to conventional treatment
3. Association with bronchial asthma
4. Association with nasal polyposis
Definitive case: positive for major + two or more minor criteria
Exclusion criteria: Churg-Straus syndrome*, hypereosinophilic syndrome

*eosinophilic granulomatosis with polyangiitis (EGPA)

or middle ear mucosa. They compared the characteristics of EOM patients with those of non-EOM control COM patients and, using logistic regression analysis, diagnostic criteria were proposed and published in 2011 as shown in Table 2 [2]. A positive diagnosis is defined by meeting the major criterion and two or more minor criteria.

3.1.1. Major criterion

The major criterion is the predominance of eosinophils in cytological or histological MEE specimens (Fig. 2). When there is an association with bacterial infection, the infiltration of neutrophils is frequently seen. Further examination should be performed after the bacterial infection is controlled using antibiotics and the effusion becomes viscous. Recently, an anti-IL5 antibody drug (mepolizumab) and an anti-IL5 receptor α (IL5Rα) antibody drug (benralizumab) have been used to treat moderate to severe bronchial asthma. These biologics reduced the number of eosinophils in MEE [14]. Thus, it is difficult to meet the major criterion if such biologics are used.

To detect eosinophils in MEE and otorrhea, Saliba et al. [15] reported cytometric immunophenotyping using flow cytometry. They concluded that it may be helpful as an additional diagnostic tool and for monitoring the response to treatment, in particular for patients without bronchial asthma.

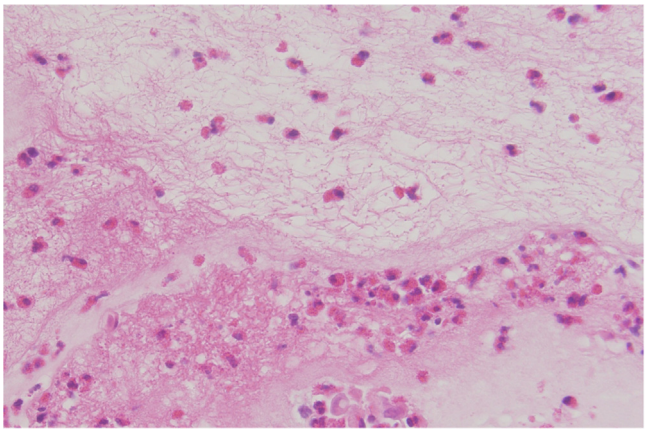

Figure 2. A histological feature of middle ear effusion of eosinophilic otitis media Many eosinophils are observed in the eosinophilic mucin. (Hematoxylin and eosin staining, X400)

3.1.2. Minor criteria

The first minor criterion is the presence of highly viscous effusion. The main component of MEE is mucin produced from goblet cells in the epithelial mucosa of the Eustachian tube and around the tympanic orifice of the Eustachian tube. It is also produced from gland tissues under the tubal mucosa. Mucus hypersecretion and goblet cell upregulation are common features of Type 2 inflammation in the respiratory tract, such as in bronchial asthma, ECRS and EOM. Mucin is a major mucoprotein produced by MUC gene expression in goblet cells. MUC5AC is the major macro-molecular constituent of airway mucus, and it is specifically expressed in goblet cells. Expression of MUC5AC is induced by IL13 or epidermal growth factor receptor at mRNA and protein levels [16].

Another contributing factor to increase airway mucus viscosity is aggregated eosinophilic extracellular DNA trap cell death (EETosis). EETosis is an innate immune mechanism

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for trapping pathogens during programmed cell death of eosinophils. Active cytolytic eosinophils release total cell contents, extracellular granules, DNA fibers and histones. EETosis has been reported in allergic bronchopulmonary aspergillosis, ECRS and EOM [17,18]. The pathological contribution of EETosis was made more cogent by the recent finding that the classical pathology of eosinophilic inflammation, Charcot-Leyden crystal formation, is closely associated with EETosis. In EOM, both mucus hypersecretion and EETosis are common features in the creation of highly viscous effusion. However, in the presence of bacterial infection, lysate or elastase produced by neutrophils destroy the fiber net of EETosis, leading to reduced viscosity [17].

The second minor criterion is resistance to conventional treatment for otitis media; myringotomy and tympanostomy tube insertion for OME, and administration of antibiotics and tympanoplasty for COM. There are several chronic intractable middle ear diseases showing clinical characteristics that are extremely different from the common type of OME and COM. Each disease requires a specific treatment to cure or control the disease; otherwise, patients suffer persistent otorrhea and progressive hearing loss, resulting in a worsening quality of life. The following were nominated as chronic intractable middle ear diseases: otitis media tuberculosis, cholesterol granuloma, otitis media with anti-neutrophil cytoplasmic antibody (ANCA)-related vasculitis (OMAAV), skull base osteomylits (malignant external otitis) and EOM.

The third minor criterion is association with bronchial asthma. Patients with EOM usually also present moderate to severe bronchial asthma. Table 1 shows high prevalence of bronchial asthma in EOM patients of previous studies. However, when bronchial asthma patients are considered, the prevalence of EOM is only approximately 2%–4%. This is because approximately 10% of patients with ECRS have an association with EOM [19], while the prevalence of ECRS is 22%–42% in patients with bronchial asthma [20]. Recent studies indicate that the association of ECRS with EOM is a risk factor for severe and refractory bronchial asthma, together with obesity, sensitization to *Staphylococcus aureus* enterotoxin and fungi such as *Aspergillus* and *Penicillium* [21]. Therefore, it is important to treat ECRS and EOM to control bronchial asthma.

The fourth minor criterion is an association with nasal polyposis. Chronic rhinosinusitis was associated with 75.6% of EOM patients, and among them nasal polyposis was observed in approximately 80% of patients [2]. The condition can be called chronic rhinosinusitis with nasal polyposis or ECRS. ECRS is more resistant to treatments for sinusitis, such as macrolide therapy and endoscopic sinus surgery, compared with the common type of chronic sinusitis. The recent Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) study established diagnostic criteria of ECRS [7]. Since 2015, moderate to severe ECRS has been designated as an intractable disease in Japan (No. 306). In addition, a patient with EOM is also certified to have an intractable disease independent of the severity of ECRS.

3.1.3. Exclusion criteria

The exclusion criteria are two diseases, eosinophilic granulomatous polyangiitis (EGPA) formally called Churg-Strauss Syndrome, and hypereosinophilic syndrome. EGPA is a rare multi-system autoimmune disease characterized by diffuse eosinophilic infiltration and necrotizing vasculitis. Patients with EGPA usually show refractory rhinosinusitis, nasal polyposis and bronchial asthma. There have been several reports of patients with EGPA who manifested intractable otitis media, whose characteristics are quite similar to those seen in patients with EOM. Fukuda et al. [22] compared the clinical signs and symptoms between EOM and EGPA. The incidence and age of onset for asthma and CRS were almost the same. In addition, otological findings and hearing outcome, CT findings of the paranasal sinus, and total IgE level at the initial visit were similar in both groups. However, peripheral blood eosinophil counts and positivity of myeloperoxidase (MPO)-ANCA were significantly higher in the EGPA group than in the EOM group. They concluded that phenotypic characteristics of EOM closely resemble those of otitis media associated with EGPA in early stages before the appearance of vasculitis. Attention should be paid to the progression to EGPA, particularly in cases showing fluctuating hearing loss, and the peripheral blood eosinophil count and ANCA titer during the course of EOM should be checked. However, the differentiation between EGPA and EOM is sometimes difficult when EGPA patients are negative for ANCA. Morita et al. [23] reported the usefulness of assessing myeloperoxidase-DNA complex in MEE of complicated otitis media. The detection and quantification of myeloperoxidase-DNA complex in MEE can predict the activity and severity of OMAAV. They also showed its usefulness in discriminating OMAAV, such as EGPA from EOM, regardless of the serum ANCA level.

Hypereosinophilic syndrome is characterized by marked blood or tissue eosinophilia and is defined by the presence of a peripheral blood eosinophil count of $\geq 1.5 \times 10^9$/L for at least 6 months. Secondary and clonal eosinophilia should be excluded. These involve various organs including the heart, lung, liver, skin and nervous system. The middle ear is also the target organ of hypereosinophilic syndrome, characterized by formation of granulation tissue containing eosinophils [24]. These two diseases should be clearly differentiated from EOM because the pathogenesis of EGPA and hypereosinophilic syndrome is completely different from EOM.

3.2. Mucosal condition grading

Kanazawa et al. [6] classified middle ear mucosal condition into three grades; Grade 1, nearly normal or slightly edematous; Grade 2, edematous or slightly thickened; Grade 3 highly thickened or presence of granulation extending beyond the normal eardrum level. As shown in Table 1, the prevalence of COM with granulation type (Grade 3) has been reported as 32.1% [2] and 13.2% [4]. The risk factors of proceeding to the formation of granulation tissue include the presence of bacterial infection and diabetes mellitus (HbA1c ≥6.5%) [25]. The latter may lead to increased susceptibility to bacterial infection. The mechanism underlying the condition of mucosal

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thickness and formation of granulation tissue is not fully understood. Nishizawa et al. [12] demonstrated that periostin is expressed at the lamina propria of the middle ear mucosa in EOM, especially in severe EOM cases with mucosal thickening. In addition, these cases showed little response to glucocorticoid treatment [4]. Periostin is an extracellular matrix protein and a matricellular protein. As an extracellular matrix protein, periostin acts to maintain tissue structure and is involved in fibrosis. As a matricellular protein, periostin binds to the integrin receptor to transmit various signals in various cell types, such as keratinocytes and fibroblasts. Periostin may play a crucial role in Type 2 inflammation. In type 2 inflammatory diseases, such as bronchial asthma, ECRS, atopic dermatitis, and allergic conjunctivitis, periostin is strongly expressed in the diseased area [26]. Therefore, periostin may also be responsible for the formation of granulation tissue and thickened mucosa in EOM.

3.3. Severity scores

Evaluation of EOM severity in each patient is essential for treatment selection and to judge the clinical efficacy of treatment. The evaluation of severity is also necessary to investigate the risk factors of EOM progression. In 2012, Iino et al. [27] reported the efficacy of the anti-IgE antibody, omalizumab, for the treatment of EOM, and first proposed a scoring system for EOM to evaluate clinical efficacy. The severity of EOM was clinically scored on five items with scores of 0–2 points. The following three items were evaluated separately for both ears: quantity of MEE or otorrhea, condition of the middle ear mucosa using a grading system (G1–G3), and frequency of intratympanic instillation of triamcinolone acetonide. The frequency of systemic administration of corticosteroids and antibiotics to patients in the previous 3 months was also evaluated. Details of the scoring system are shown in Table 3. After this scoring system was proposed many studies have used it to evaluate treatment efficacy [14,28,29]. Kanazawa et al. [6] analyzed various clinical features in EOM patients and compared those with their severity scores. Multivariate logistic regression analysis showed the significant risk factors of EOM severity to be obesity and long-term bronchial asthma. Aspirin tolerance also tended to associate with severe EOM.

3.4. Temporal bone computed tomography (CT) scores

Temporal bone CT imaging is also very important to evaluate the status of EOM and to judge the efficacy of treatment. Recently, radiological staging of the aeration/opacification in temporal bone CT was proposed [30]. With reference to the rhinosinusitis staging system proposed by Lund et al. [33], each part of the temporal bone was scored from 0–2 points, as follows: 0 (well aerated and no abnormality), 1 (partial opacification), and 2 (complete opacification). The middle ear was divided into four parts: mesotympanum, attic, antrum, and mastoid air cells. Each side was graded separately. This radiological scoring is easy to apply and similar to the Lund-Mackay scoring system.

4. Treatment

4.1. Pharmacological treatment

The main goal of EOM treatment is to control eosinophilic/Type 2 inflammation and bacterial infection. At present, systemic and topical administration of corticosteroids is the most effective way to control Type 2 inflammation in the middle ear. Various adverse effects of long-term systemic corticosteroid use have been documented; therefore, it is recommended to use local corticosteroid application in EOM, similar to the use of inhaled corticosteroids for bronchial asthma, and the administration of systemic corticosteroids should be limited to uncontrolled EOM cases, as described below. In addition to corticosteroids, various antiallergy drugs that have inhibitory effects on eosinophilic inflammation are used, including the prostaglandin D2 and thromboxane A2 receptor antagonist, ramatoroban [32], ibudilast and an antileukotriene receptor antagonist. The clinical efficacy of a single use of these drugs is unknown as they have not been through clinical trials. Matsubara et al. [31] showed the efficacy of a combination of various antiallergic drugs for decreasing the frequency of intra-tympanic instillation of triamcinolone acetonide in EOM patients.

Neff et al. [34] reported the efficacy of interferon-α 2a or 2b in eight cases of EOM. Among them, four patients showed improvement of EOM. However, many patients showed adverse reactions.

Most EOM patients have associated bronchial asthma and ECRS (Table 1). It is also important to treat the associated bronchial asthma and ECRS using inhaled corticosteroid and steroid nasal spray. Seo et al. [35] demonstrated that EOM improved along with improved lung function when double doses of inhaled corticosteroid were administered to patients with EOM and asthma.

4.2. Local treatments

Corticosteroids should be administered topically whenever possible. The instillation of triamcinolone acetonide, a suspension of corticosteroids, into the mesotympanum was reported to be an effective treatment for patients with EOM [36]. A clinical trial comparing triamcinolone acetonide administration with betamethasone eardrops showed the effectiveness of the former was significantly higher than the latter. In patients without eardrum perforation, triamcinolone acetonide can be instilled into the middle ear cavity using a syringe with a long needle. In patients with persistent perforation, triamcinolone acetonide suspension can be applied via the eardrum perforation after the removal of effusion or otorrhea. Then, positive pressure is applied to the external auditory canal using a pneumatic otoscope to pass the suspension through the Eustachian tube. In cases with granulation tissue, the granulation of the mesotympanum can be removed via the perforation using cutting forceps and the same procedure performed [25]. Matsubara et al. [37] reported the effectiveness of topical administration of heparin. Heparin has inhibitory effects on eosinophil chemotaxis and a neutralizing effect on cyto-

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Table 3. Severity scores of eosinophilic otitis media [27]

The mucosal condition	
0	nearly normal or slightly edematous
1	edematous or slightly thickened
2	highly thickened or granulated to an extent beyond the position of a normal eardrum.
The quantity of MEE / otorrhea	
0	no MEE
1	MEE with intratympanic aeration in a case without eardrum perforation or otorrhea limited to the mesotympanum in a case with perforation
2	mesotympanum totally filled with MEE in a case without perforation or otorrhea coming out from the mesotympanum to the external auditory canal in a case with perforation
The frequency of intratympanic administration of corticosteroid	
0	none
1	once in the previous 3 months
2	two or more times in the previous 3 months
The frequencies of systemic administration of corticosteroids	
0	none
1	7 days or less in the previous 3 months
2	more than 7 days in the previous 3 months
The frequencies of systemic antibiotics	
0	none
1	7 days or less in the previous 3 months
2	more than 7 days in the previous 3 months

MEE: middle ear effusion.

toxic proteins such as ECP and major basic protein derived from eosinophils. The topical administration of heparin could reduce corticosteroid use and decrease the amount of steroids administered.

4.3. Intensive treatment

When a rapid increase in bone conduction threshold, acute exacerbation of the middle ear condition or uncontrolled otorrhea occurs, intensive treatment for EOM is required [38]. Such patients should be hospitalized, and high-dose steroid administered on a tapering schedule in accordance with the protocol for the treatment of sudden deafness, together with antibiotic administration. Patients usually receive a daily dose of 50 mg oral prednisolone, reduced by 10 mg every 2 days and then maintained at 10 mg for 1–4 weeks, depending on the condition of the middle ear.

For the granulation type of EOM, the transcanal removal of granulation tissue is performed. After intensive treatment, some patients show normalization of the eardrum and decrease of otorrhea [38]. Long-term follow-up and treatment is essential to prevent relapse of otorrhea and granulation formation.

4.4. Biologics

Recently various biologics have been administered to patients with moderate to severe bronchial asthma. They include omalizumab (anti-IgE antibody), mepolizumab and reslizumab [anti-interleukin (IL)5 antibody], benralizumab [anti-IL5 receptor (R) antibody], pitrakinra/dupilumab (anti-IL4Rα antibody) and lebrikizumab (anti-IL13 antibody). Omalizumab, metpolizumab, benralizumab and dupilumab are available for clinical use by the Japanese national insurance system for moderate to severe bronchial asthma and other limited diseases.

4.4.1. Omalizumab (anti-IgE antibody)

Omalizumab, a recombinant humanized monoclonal anti-IgE antibody, is the first anti-IgE agent to be used for the treatment of moderate to severe bronchial asthma, urticarial, and allergic rhinitis. Unfortunately, it is not available for the treatment of EOM or ECRS under the Japanese insurance system. Immunohistological studies have shown that many IgE-immunopositive cells are present in the middle ear mucosa of EOM patients. In addition, IgE levels in MEE are significantly higher in EOM patients than in control patients with common otitis media with effusion [39,40]. Therefore, omalizumab may show some benefit for improvement of EOM. Iino et al. [27] first described a prospective study using omalizumab in the treatment of EOM associated with bronchial asthma. They showed the effectiveness of long-term add-on omalizumab treatment for EOM compared with patients without omalizumab. The omalizumab studies are shown in Table 4. Two studies are case reports showing efficacy of omalizumab for EOM [41,42]. Bartier et al. [43] reported the clinical results of omalizumab in ten patients with EOM, and four patients were responders judged by global evaluation of treatment effectiveness scores. Interestingly, in the treatment of bronchial asthma using omalizumab, treatment failure was mostly associated with eosinophilic comorbidities of EOM and ECRS [44].

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Table 4. Literatures of the treatment using biologics

	No. pt	Mean age	F	M	BA	ECRS	Outcome parameter	R	non-R	Definition of responder	Study design
Omaliumab											
Iino et al. (2012) [27]	8	54	6	2	8	8	severity score, audiometry, symptom score	5	3	clinical (severity) score ≤ 5	comparative study
Okude et al. (2012) [41]	1	51	1		1	N/A	audiometry	1		hearing improvement	case report
Han et al. (2018) [42])	1	57	1		1	1	severity score, COMOT 15, audiometry	1		decrease of the scores	case report
De Corso et al (2022)[29]	1	62		1	1	1	severity score, audiometry, otoscopic finding	1		clinical (severity) score ≤ 5	case review
Bartier et al. (2022)[43]	10	52	5	5	10	10	GETE score	4	6	GETE score ≤2	case review
Mepolizumab											
Iino et al. (2019) [14]	9	66	6	3	9	6	severity score, audiometry, symptom score	6	3	clinical (severity) score ≤ 5	comparative study
Suzaki et al. (2019)[47]	1	60		1	1	1	audiometry, CT findings	1		hearing improvement, no OCS	case report
Akaba et al. (2021)[44]	6	50	2	4	6	3	otoscopic findings	3	3	resolution of MEE	case review
Breslin et al. (2021)[48]	5	N/A	N/A		5	N/A	otoscopic findings	2	3	resolution of MEE	case review
De Corso et al. (2022)[29]	1	49	1		1	1	severity score, audiometry, otoscopic findings	1		clinical (severity) score ≤ 5	chart review
Bartier et al. (2022) [43]	8	51	3	5	8	8	GETE score	2	6	GETE score ≤2	case review
Takeshita et al. (2023)[49]	1	56	1		1	1	clinical symptoms, CT findings		1	improvement of clinical symptoms	case report
Benralizumab											
Kagoshima et al. (2020)[51]	1	47	1		1	1	N/A	1			case report
Chow et al. (2020)[52]	1	24	1		1	1	symptoms, otoscopic findings	1		resolution of MEE	case report
Akaba et al. (2021)[44]	1	41	2	1	1	1	otoscopic findings	1		resolution of MEE	case review
Shimizu et al. (2021)[53]	1	50 s	1		1	1	otoscopic findings, symptoms		1	resolution of otorrhea	case report
Breslin et al. (2021)[48]	2	N/A	N/A		2	N/A	otoscopic findings	2	0	resolution of MEE	case review
De Corso et al. (2022)[29]	1	57		1	1	1	severity score, audiometry, otoscopic findings	1		clinical (severity) score ≤ 5	case review
Bartier et al. (2022)[43]	6	48	3	3	6	6	GETE score	1	5	GETE score ≤2	case review
Dupilumab											
Iino et al. (2021)[30]	3	68	1	2	3	3	severity score, temporal bone CT score	3		clinical (severity) score ≤ 5	case reports
Akaba et al. (2021)[44]	1	62	0	1	1	1	otoscopic findings	1		resolution of MEE	case review
van der Lans et al. (2021)[54]	1	40	1		1	1	otoscopic findings, audiometry	1		resolution of granulation	case reports
Shimizu et al. (2021)[53]	1	50 s	1		1	1	symptoms	1		free from symptoms	case review
De Corso et al. (2022)[29]	5	53	4	1	5	5	severity score, audiometry, otoscopic findings	5	0	clinical (severity) score ≤ 5	case review
Bartier et al. (2022)[43]	6	49	4	2	6	6	GETE score	4	2	GETE score ≤2	case review
Takeshita et al (2023)[49]	1	56	1		1	1	symptoms, temporal bone CT findings	1		temporal bone CT	case report

Pt, patients; F, female; M, male; BA, bronchial asthma; ECRS, eosinophilic chronic rhinosinusitis; R. responders; non-R, non-responders.
GETE, global evaluation of treatment effectiveness; OCS, oral corticosteroids; N/A, not applicable.

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4.4.2. Mepolizumab (anti-IL5 antibody)

Mepolizumab is a humanized anti-IL5 monoclonal antibody that was recently approved in Japan for patients with moderate to severe bronchial asthma and EGPA. Mepolizumab prevents IL5 from binding to the α-chain of the IL5 receptor complex expressed on eosinophils and, therefore, inhibits IL5 signaling, which blocks eosinophil survival, proliferation, and activation. The efficacy of mepolizumab for bronchial asthma has been demonstrated in randomized controlled clinical trials. Mepolizumab produced significant reduction in the rate of asthma exacerbation and the need for oral corticosteroids at the time of exacerbation. However, no studies have assessed the efficacy of mepolizumab for comorbid EOM.

A previous study reported that a significantly higher concentration of IL5 was detected in the MEEs of EOM patients compared with that in non-EOM otitis media patients. The concentration of eosinophilic cationic protein, an eosinophilic marker protein, was also positively correlated with that of IL5 in MEE [45,46]. Therefore, the effectiveness of mepolizumab against IL5 may occur by neutralization of IL5 in the middle ear.

Iino et al. [14] first described the improved clinical efficacy of add-on mepolizumab for EOM associated with bronchial asthma compared with control patients without the use of mepolizumab. However, the therapy showed minimal effect in patients with the granulation type of EOM. Later, the clinical efficacy of mepolizumab for EOM was reported by several authors in case reports and retrospective case reviews [29,43,44,47,48,49] (Table 4).

4.4.3. Benralizumab (anti-IL5R antibody)

Benralizumab is an IL5-receptor monoclonal antibody, which specifically binds to the a-chain of IL5R expressed on eosinophils and basophils to block signal transduction. There have been many reports concerning its efficacy for asthma because of a reduced asthma exacerbation rate and the use of oral corticosteroids. Beranilzumab can reduce peripheral eosinophil counts to 0 cells/μl in most patients. In addition, it can reduce eosinophil counts in airways and bone marrow [50], which may provide the clinical effect on eosinophilic airway diseases. There have been seven studies concerning the efficacy of benralizumab for EOM [29,43,44,48,51,52,53]. They were all case reports and retrospective case reviews; therefore, it is difficult to conclude its exact effectiveness for EOM (Table 4).

4.4.4. Dupilumab (anti-IL4Rα antibody)

Dupilumab is a fully humanized monoclonal antibody that binds specifically to IL4Rα, which shares a receptor subunit with IL13R. Therefore, it inhibits signaling of both IL4R and IL13R, key drivers of Type 2 inflammation. Dupilumab is effective in the treatment of severe and refractory atopic dermatitis, bronchial asthma and ECRS. Some trials have shown that dupilumab benefits patients with severe corticosteroid-dependent asthma, regardless of levels of blood eosinophils or any other Type 2 biomarker.

There have been seven studies concerning the efficacy of dupilumab for EOM [29,30,43,44,49,53,54]. Unfortunately, none of them were comparative studies or randomized controlled trials. However, most of the patients in the studies received other biologics and then switched to dupilumab because of poor responses to the previous biologics. Dupilumab has many inhibitory effects on Type 2 inflammatory responses, including on IgE production from B cells, migration of eosinophils to the inflammatory site, goblet cell hypersecretion, hypersensitivity of respiratory mucosa, periostin production from fibroblasts, and fibrosis of the respiratory epithelium. A recent report demonstrated that dupilumab showed a significant effect in granulation type EOM patients [30].

4.4.5. Selection of biologics

There have been several recommendations regarding the use of biologics for bronchial asthma. In 2020, "the statement of the appropriate use of biologics for adult bronchial asthma" was published by the Japanese Respiratory Society and the Japanese Society of Allergology [55]. In the statement, indication of the use of biologics was limited and only to the patients of uncontrolled asthma who are unresponsive to high doses of inhaled corticosteroid and other controllers. Omalizumab is indicated for patients positive for specific inhaled antigens (allergic asthma). Mepolizumab or benralizumab are indicated for patients who show a peripheral blood eosinophil count >150/μL, or have shown >300/μL in the past 12 months (eosinophilic asthma). Dupilumab can be used for patients with a peripheral blood eosinophil count >150/μL, fractional exhaled nitric oxide (FeNO) >25 ppb or a serum IgE level >167 IU/ml.

At present, there are no recommendations for the use of biologics for EOM. As shown in Table 4, there are no unity of outcome parameters or definition of responses in the literature. Excluding a case report of one patient, the efficacy of biologics is summarized in Table 5. IgE, IL5 and various Type 2 biomarkers can be detected in MEE of EOM [56]; therefore, dupilumab should be effective at inhibiting the production of cytokines and chemokines that cause Type 2 inflammation in the middle ear.

Recently, sequential biotherapy or cycling therapy using benralizumab and dupilumab for eosinophilic asthma with ECRS and EOM have been reported [57,58]. These therapies showed significant effect on controlling bronchial asthma as well as ECRS and EOM. Further studies are needed to clarify the efficacy of biologics for EOM using the same outcome parameters, and to identify biomarkers for the selection of biologics.

4.5. Surgical treatment

4.5.1. Myringoplasty

Eosinophilic inflammation is an endogenous pathology that can easily recur even if the diseased tissue is surgically removed. Therefore, surgical management is generally contraindicated for patients with EOM. Myringoplasty is less invasive and has a lower risk of causing inner ear damage compared with tympanoplasty/mastoidectomy. However, myringo-

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Table 5. Efficacy of biologics for eosinophilic otitis media

	Omalizumab		*Mepolizumab*		*Benralizumab*		*Dupilumab*	
	R	non-R	R	non-R	R	non-R	R	non-R
Iino et al. (2012, 2019, 2021) [14,27,30]	5	3	6	3			3	0
Akaba et al. (2021) [44]	3	3						
Breslin et al. (2021)[48]			3	2	2	0		
De Corso et al. (2022)[29]	1	0	1	0	1	0	5	0
Bartier et al. (2022)[43]	4	6	2	6	1	5	4	2
Total	13	12	12	11	4	5	12	2
	52%		52%		44%		86%	

R; responder, non-R; non-responder.

plasty is generally not indicated for ears with continuous otorrhea, severe mucosal disease in the mastoid, and total perforation. The advantages of closure of the eardrum perforation include improvement of the air conduction hearing level, reduction of bacterial infection of the middle ear via the perforated eardrum, and reduction of MEE recurrence. The Eustachian tube has been reported to be patulous rather than stenotic in patients with EOM [59]. If the eardrum is perforated, pathogenic materials can enter the middle ear to cause eosinophilic inflammation in patients with Type 2-dominant predisposition either via the Eustachian tube or via the perforated eardrum. The middle ear is thus less likely to be invaded by pathogens that can cause MEE if the perforated eardrum is closed. Indeed, Esu at al. [4] showed successful graft uptake and reduction of EOM severity score after myringoplasty in EOM patients and concluded that this may be due to protection against recurrent bacterial infections and pathogenic antigens in the middle ear. However, if MEE recurs, it is necessary to apply triamcinolone acetonide into the middle ear cavity using a syringe with a long needle, as described previously.

4.5.2. Tympanoplasty/mastoidectomy

The surveillance of EOM in Japan showed that the deterioration rate of the bone conduction hearing level in EOM was 59.1% and 5.8% of patients became deaf [3]. The incidence of deafness was significantly more frequent in patients who received tympanoplasty than in those who did not [3]. The inner ear seems to be susceptible to damage by surgical stress.

Kikuchi et al. [60] recently reported a successfully treated case by tympanoplasty and mastoidectomy with the use of dupilumab. They also assessed 24 EOM patients reported in 10 studies between 2006 and 2021who underwent tympanoplasty/mastoidectomy. All of these patients had not been diagnosed with EOM at that time of the operation and showed relapse of EOM in a relatively short period. Some of them were subsequently diagnosed with EOM and received topical and systemic corticosteroids with or without revision surgery. Now, surgical interventions for EOM are not contraindicated if patients show good response to biologics for a long period.

4.5.3. Cochlear implantation

Patients with bilateral deafness are usually indicated for cochlear implantation (CI). There have been three reports (four patients) concerning the results of CI for EOM patients [61–63]. One patient received tympanomastoidectomy and relapsed with otitis media immediately. Then the patient was subsequently diagnosed as EOM and received CI with the use of topical and systemic corticosteroids [61]. Three patients with bilateral deafness had been diagnosed as EOM prior to the CI operation [62,63]. Therefore, they received CI with the method of Rambo's operation or subtotal petrosectomy, which included closure of both the external auditory canal and Eustachian tube. It is reasonable to close the Eustachian tube and external auditory canal to prevent pathogenic materials from invading into the middle ear and recurrence of EOM on CI. Indeed, outcomes of the CI operation for the three patients were excellent with good speech perception. It is recommended to perform CI by subtotal petrosectomy with middle ear obliteration to prevent EOM relapse.

5. Conclusion

Since diagnostic criteria were established in 2011 by the Japanese EOM study group, the concept of EOM has been known worldwide. In 2017, an EOM case report appeared in the *New England Journal of Medicine* [64]. Recently the clinical and pathological features of EOM were introduced in the journal, *Head and Neck Pathology* [65]. In this article, EOM and OMAAV were added to the classification of otitis media as new entities of otitis media together with acute otitis media, chronic otitis media with effusion and chronic suppurative otitis media. With the appreciation of Type 2 inflammatory disease, EOM is no longer considered a rare disease and should be specifically treated to improve the quality of life of patients with EOM and associated bronchial asthma and ECRS. Further research should focus on clarifying the various phenotypes and endotypes of EOM and on developing treatment strategies, including the use of biologics.

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References

[1] Tomioka S, Kobayashi T, Takasaka T. Intractable otitis media in patients with bronchial asthma (eosinophilic otitis media) . In: Sanna M, ed. Cholesteatoma and Mastoid Surgery. Rome: CIC Edizioni Internazionali, 997: 851-3.
[2] Iino Y, Tomioka-Matsutani S, Matsubara A, Nakagawa T, Nonaka M. Diagnostic criteria of eosinophilic otitis media, a newly recognized middle ear disease. Auris Nasus Larynx 2011;38:456–61.
[3] Suzuki H, Matustani S, Kawase T, Iino Y, Kawauchi H, Gyo K, et al. Epidemiologic Surveillance of "eosinophilic otitis media" in Japan. Otol Jpn 2004;14:112–17 abstract in English.
[4] Esu Y, Masuda M, Yoshida Y. Periostin in middle ear mucosa according to eosinophilic otitis media severity: middle ear pathology-based treatment. Auris Nasus Larynx 2020;47:527–35.
[5] Chen T, Ashman PE, Bojrab DI, Johnson AP, Hong RS, Benson B, et al. Diagnosis and management of eosinophilic otitis media: a systematic review. Acta Oto-Laryngologica 2021;141:579–87.
[6] Kanazawa H, Yoshida N, Yamamoto H, Hara M, Hasegawa M, Matsuzawa S, et al. Risk factors associated with severity of eosinophilic otitis media. Auris Nasus Larynx 2014;41:513–17.
[7] Tokunaga T, Sakashita M, Haruna T, Asaka D, Takano S, Ikeda H, et al. Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC study. Allergy 2015;70:995–1003.
[8] Iino Y. eosinophilic otitis media: A new middle ear disease. Curr Allergy Asthma Rep 2008;8:525–30.
[9] Masuda M, Esu Y, Iino Y, Yoshida N. Risk factors for bacterial infection to cause sensorineural hearing loss in eosinophilic otitis media. Auris Nasus Larynx 2021;48:207–13.
[10] Nakagawa T, Matsubara A, Shiratsuchi H, Kakazu Y, Nakashima T, Koike K, et al. Intractable otitis media with eosinophils: importance of diagnosis and validity of treatment for hearing preservation. ORL J Otorhinolaryngol related Spec 2006;68:118–22.
[11] Iino Y, Usubuchi H, Kodama K, Takizawa K, Kanazawa T, Ohta Y. Bone conduction hearing level in patients with eosinophilic otitis media associated with bronchial asthma. Otol Neurotol 2008;29:949–52.
[12] Nishizawa H, Matsubara A, Nakagawa T, Ohta N, Izuihara K, Shirasaki T, et al. The role of periostin in eosinophilic otitis media. Acta Otolaryngol 2012;132:838–44.
[13] Nagamine H, Iino Y, Kojima C, Miyazawa T, Iida T. Clinical characteristics of so-called eosinophilic otitis media. Auris Nasus Larynx 2002;29:19–28.
[14] Iino Y, Takahashi E, Ida S, Kikuchi S. Clinical efficacy of anti-IL-5 monoclonal antibody mepolizumab in the treatment of eosinophilic otitis media. Auris Nasus Larynx 2019;46:196–203.
[15] Saliba I, Alzahrani M, Weng X, Bestavros A. Eosinophilic otitis media diagnosis using flow cytometric immunophenotyping. Acta Otolaryngol 2018;138:110–15.
[16] Fahy JV, dickey BF. Airway mucus function and dysfunction. N Engl J. Med 2010;363:2233–47.
[17] Ueki S, Konno Y, Takeda M, Moritoki Y, Hirokawa M, Matuwaki Y, et al. Eosinophil extracellular trap cell death-derived DNA traps: Their presence in secretions and functional attributes. J Allergy Clin Immunol 2016;137:258–67.
[18] Ohta N, Ueki S, Konnno Y, Hirokawa M, Kubota T, Tomioka-Matsutani S, et al. ETosis-derived DNA trap production in middle ear effusion is a common feature of eosinophilic otitis media. Allergol Int 2018;67:414–16 4.
[19] Haruna S, Yoshikawa M, Otori N, Moriyama H. Association between eosinophilic sinusitis and eosinophilic otitis media. Oto-Rhino-Laryngol. Tokyo 2003;46:472–80 abstract in English.
[20] Tay TR, Hew M. Comorbid "treatable traits" in difficult asthma: Current evidence and clinical evaluation. Allergy 2018;73:1369–82.
[21] Nagase H. Severe asthma in Japan. Allergol Int 2019;68:167–71.
[22] Fukuda A, Morita S, Nakamaru Y, Hoshino K, Fujiwara K, Homma A. Differentiation between eosinophilic otitis media and otitis media associated with eosinophilic granulomatosis with polyangiitis. Otol Neurotol 2019;40:e796–802.
[23] Morita S, Nakamaru Y, Fukuda A, Fujiwara K, Suzuki M, Hoshino K. The quantification of extracellular trap cell death-derived products as diagnostic biomarkers for otitis media with antineutrophil cytoplastmic antibody-associated vasculitis and eosinophilic otitis media. Otol Neuotol 2022;43:e337–43.
[24] Jung HJ, Yu GH, Park JH. Hypereosinophilic syndrome presenting with bilateral ear fullness. Eur Ann Otorhinolaryngol Head Neck Dis 2019;136:199–201.
[25] Esu Y, Iino Y, Masuda M, Kanazawa H, Yoshida N. Proposal of a treatment strategy for eosinophilic otitis media based on middle ear condition. Otol Neurotol 2018;39:e671–8.
[26] Izuhara K, Nunomura S, Nanri Y, Ono J, Takai M, Kawaguchi A. Periostin: An emerging biomarker for allergic diseases. Allergy 2019;74:2116–28.
[27] Iino Y, Hara M, Hasegawa M, Matsuzawa S, Shinnabe A, Kanazawa H, et al. Clinical efficacy of anti-IgE therapy for eosinophilic otitis media. Otol Neurotol 2012;33:1218–24.
[28] Esu Y, Tamii S, Masuda M, Iino Y, Yoshida Y. Effectiveness of myringoplasty in patients with eosinophilic otitis media. Auris Nasus Larynx 2021;48:368–76.
[29] De Corso E, Montuori C, Settimi S, Mele DA, Cantiani A, Corbo M, et al. Efficacy of biologics on refractory eosinophilic otitis media associated with bronchial asthma or severe uncontrolled CRSwNP. J Clin Med 2022;11:926.
[30] Iino Y, Sekine Y, Yoshida S, Kikuchi S. Dupilumab therapy for patients with refractory eosinophilic otitis media associated with bronchial asthma. Auris Nasus Larynx 2021;48:353–60.
[31] Lund VJ, Kennedy DW. Staging for rhinosinusitis. Otolaryngol Head Neck Surg 1997;117(Suppl):S35–40.
[32] Wada T, Uemaetomari I, Murashita H, Tobita T, Tsuji S, Tabuchi K, et al. Successful treatment of eosinophilic otitis media using ramatroban: report of two cases. Auris Nasus Larynx 2006;33:455–60.
[33] Matsubara A, Takahata J, Miura T, Kudo N. Tretament of eosinophilic otitis media. J Clin Cell Immunol 2018;9:538.
[34] Neff BA, Voss SG, Carlson ML, O'Brien EK, Butterfield. Treatment of eosinophilic otitis media with pegylated interferon-a 2a and 2b. Laryngoscope 2017;127:1208–16.
[35] Seo Y, Nonaka M, Yamamura Y, Pawankar R, Tagaya E. Optimal control of asthma improved eosinophilic otitis media. Asia Pac Allergy 2018;8:e5–e18.
[36] Iino Y, Nagamine H, Kakizaki K, Komiya T, Katano H, Saruya S, et al. Effectiveness of instillation of triamcinolone acetonide into middle ear for eosinophilic otitis media associated with bronchial asthma. Ann Allergy Asthma Immunol 2006;97:761–6.
[37] Matsubara A, Kuroda R, Usami S, Takahata J, Shinkawa H. The effect of topical administration of heparin to the eosinophilic otitis media. In: Takasaka T, Yuasa R, Hozawa, editors. Recent advances in otitis media. Bologna: Monduzzi Editore; 2001. p. 403–6.
[38] Kikuchi S, Sekine Y, Yoshida S, Iino Y. Clinical course of patients with eosinophilic otitis media treated by intensive care. Otol Jpn 2020;30:29–35 abstract in English.
[39] Iino Y. Role of IgE in eosinophilic otitis media. Allergol Int 2010;59:233–8.
[40] Kanazawa H, Yoshida N, Shinnabe A, Iino Y. Antigen-specific IgE in middle ear effusion of patients with eosinophilic otitis media. Ann Allergy Asthma Immunol 2014;113:88–92.
[41] Okude A, Tagaya E, Kondo M, Nonaka M, Tamaoki J. A case of severe asthma whit eosinophilic otitis media successfully treated with anti-IgE monoclonal antibody omalizumab. Case Reports in Pulmonology 2012:340525 VolumeArticle ID.
[42] Han YE, Kang YS, Cho Y, Park MK. Eosinophilic otitis media treated with anti-IgE monoclonal antibodies and a bone conduction implant. J Int Adv Otol 2018;14:144–7.
[43] Bartier S, Bequignon E, de Menonville CT, Verillaud B, Evrard D, Leger M, et al. Otitis media in severe asthma associated with chronic rhinosinusitis with nasal polyps: a new therapeutic target for biologics. J Asthma 2022 online ahead of print.
[44] Akaba T, Kodo M, Kobayashi F, Honda N, Muramatsu S, Yagi O, et al. Characteristics of patients with severe asthma who experienced

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treatment failure with omalizumab. Pulmonary Pharmacology Therapeutics 2021;68:102032.
[45] Iino Y, Nagamine H, Yabe T, Matsutani S. Eosinophils are activated in middle ear mucosa and middle ear effusion of patients with intractable otitis media associated with bronchial asthma. Clin Exp Allergy 2001;31:1135–43.
[46] Nonaka M, Fukumoto A, Ozu C, Mokuno E, Baba S, Pawankar R, et al. IL-5 and eotaxin levels in middle ear effusion and blood from asthmatics with otitis media with effusion. Acta Otolaryngol 2003;123:383–7.
[47] Suzaki I, Kimura Y, Tanaka A, Hirano K, Ishibashi A, Mizuyoshi T, Ando I, et al. Successful treatment of eosinophilic otitis media associated with bronchial asthma with an anti-IL5 monoclonal antibody, mepolizumab. Auris Nasus Larynx 2019;46:141–6.
[48] Breslin NK, Heindel NH, Haberman RS. Role of interleukin 5 inhibition in the treatment of eosinophilic otitis media. OTO-open 2021;5:2473974X21991449.
[49] Takesita Y, Tada Y, Okano M, To M, To T. dupilumab remarkably improved eustachian tub obstruction: a case of mepolizumab-resistant eosinophilic otitis media. J Investig Allergol Clin Immunol 2023;33 In press.
[50] Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, et al. Effect of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. J Allergy Clin Immunol 2013;132:1086–96 e5.
[51] Kagoshima H, Hori R, Kojima T, Okanoue Y, Taguchi A, Yamamoto H, et al. Successful treatment of eosinophilic chronic rhinosinusitis and eosinophilic otitis media using an anti-IL-5 receptor monoclonal antibody benralizumab: A case report. Respiratory Med Case Reports 2020;30:101135.
[52] Chow K, Cosetti MK. Use of IL-5 inhibitor benralizumab as a novel therapy for eosinophilic otitis meia: clinical capsule and review of literature. Otol Neurotol 2020;41:e238–40.
[53] Shimizu H, Hayashi M, Kato H, Nakagawa M, Imaizumi K, Okazawa M. IL-13 may play an important role in developing eosinophilic chronic rhinosinusitis and eosinophilic otitis media. Int J Mol Sci 2021;22:11209.
[54] van der Lans RJL, van Spronsen E, Fokkens WJ, Reitsma S. Complete remission of severe eosinophilic otitis media with dupilumab: a case report. Laryngoscope 2021;131:2649–51.
[55] https://www.jsaweb.jp/uploads/files/20200621ST.pdf
[56] Uchimizu H, Matsuwaki Y, Kato M, Otori N, Kojima H. Eosinophil-derived neurotoxin, elastase, and cytokine profile in effusion from eosinophililc otitis media. Allergol Int 2015;64:S18–23 Suppl.
[57] Hamada S, Ogino E, Yasuba H. Cycling therapy with benraliumab and dupilumab for severe eosinophilic asthma with eosinophilic chronic rhinosinusitis and eosinophilic otitis media. Allergol Int 2021;70:389–91.
[58] Chikumoto A, Oishi K, Hamada K, Hirano T, Kakugawa T, Kanesada K, et al. Sequential biotherapy targeting IL5 and IL4/13 in patients with eosinophilic asthma with sinusitis and otitis media. Biomolecules 2022;12:522.
[59] Iino Y, Kakizaki K, Saruya S, Katano H, Komiya T, Kodera K, et al. Eustachian tube function in patients with eosinophilic otitis media. Arch Otolaryngol Head Neck Surg 2006;132:1109–14.
[60] Kikuchi S, Yoshida S, Sugiyama T, Iino Y. A case of eosinophilic otitis media successfully treated by tympanoplasty with use of dupilumab. Otolaryngology Case reports 2021;21:100381.
[61] Iwasaki S, Nagura M, Mizuta K. Cochlear implantation in a patients with eosinophilic otitis media. Eur Arch Otorhinolarungol 2006;263:365–9.
[62] Kojima H, Sakurai Y, Rikitake M, Tanaka Y, Kawano A, Moriyama H. Cochlear implantation in patients with chronic otitis media. Auris Nasus Larynx 2010;37:415–21.
[63] Sugimoto H, Hatano M, Noda M, Hasegawa H, Yoshizaki T. cochlear implantation in deaf patients with eosinophilic otitis media using subtotal petrosectomy and mastoid obliteration. Eur Arch Otorhinolaryngol 2017;274:1173–7.
[64] Hugo LS, Vallejo LA. Eosinophilic otitis media. N Engl J Med 2017;376:e10.
[65] Magliocca K, Vivas EX, Griffith CC. Idiopathic, infectious and reactive lesions of the ear and temporal bone. Head and Neck Pathology 2018;12:328–49.

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