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Cholesteatoma – A Potential Consequence of Chronic Middle Ear Inflammation

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Abstract

The article provides an overview on the current state-of-science of middle ear cholesteatoma, a non-neoplastic, keratinizing lesion that is characterized by the proliferation of epithelium with aberrant micro-architecture.

Pathogenetic mechanisms including morphological, immunological, epidemiological and microbiological aspects of the disease are summarized. The importance of penicillinase-expressing anaerobic bacteria and biofilm formation for maintaining the chronic middle ear inflammation is stressed. Nevertheless, the role of the isolated pathogens in the primarily non-sterile compartiment of the middle ear cavity is so far not completely understood and data on the isolated species are contradictious. Heredity was demonstated for some variants of the disease. Therefore, further studies on the etiological role of microbial agents and potential benefits of resistance-adapted antimicrobial therapy seem advisable.

Local and systemic complications of the potentially life-threatening disease like conductive and sensorineural hearing loss and cranial abscesses are reported. The prognosis is limited due to frequent recurrence in spite of surgical therapy. Further research is necessary for a better understanding of the pathogenetic mechanisms and to expand the sectrum of therapeutic options.

Keywords: Cholesteatoma; Biofilm; Chronic infection; Hyperproliferation; Complication

Introduction

Cholesteatoma is a non-neoplastic, keratinizing lesion [1], which is associated with enhanced proliferation of epithelial cells with aberrant morphologic characteristics [2]. Synonyms for cholesteatoma in the literature include epidermoid tumor, epidermoid cyst, and epithelial inclusion cyst [3]. Its first description is dated to the year 1683 [4].

While the middle ear is the most typical localization, ectopic cholesteatoma has been described for many sites, including the mastoid process [5], the petrous bone [6-8], the external auditory canal [9-14], the paranasal sinuses [15-17] with special emphasis on the frontal sinus [18-19], the genitourinary tract [20] including the ureter [21-23], the renal pelvis [21], the pyelocaliceal region [21], and the kidney [24-26], as well as the endocranium, predominantly the cerebellopontine angle [27], and the posterior cerebellar fossa [28]. Cases of bi-lateral congenital middle ear cholesteatoma have been described [29-31], some of them in association with ossicular chain abnormalities [29,31], e.g. as an aspect of branchio-oto-renal syndrome [31].

Middle ear cholesteatoma forms a keratinic mass, consisting of matrix and perimatrix [32]. Some authors consider the pathogenic entity to be 'a serious form of chronic otitis media' [33]. Without therapy, it leads to progressive destruction of the middle and the inner ear [34]. It is subdivided into acquired and congenital cholesteatoma [1,35-37].

The acquired form is attributed to inflammatory otitic pathology and becomes rarer due to progresses in treatment [4]. Acquired cholesteatoma is typically associated with a defect of the tympanic membrane [1].

Congenital cholesteatoma is regularly a disease of infants, although this entity has been described in adults as well [38,39]. It usually grows behind an intact tympanic membrane [1]. Eustachian tube dysfunction is rare [40]. Typical features include satisfactory mastoid air cells and – in about one out of three cases - associated congenital malformations with or without involvement of the otologic system [41,42]. Despite agressive growth, in particular if functioning air cells in the mastoid are present, long latency periods without clinical symptoms have been described [42].

Cholesteatoma is particularly aggressive in childhood. Clinical diagnosis can be confirmed by modern imaging including CT and MR scans [4]. Rare differential diagnoses include the chorda tympani neuroma [43].

A favorable outcome depends to a large degree on an early diagnosis, but diagnosis is delayed in most instances. Thus, complications are frequent [44].

Complications

Although cholesteatoma is considered to be a benign process, spreading to surrounding structures may lead to severe, sometimes even life-threatening complications [19]. Most of the complications are infectious [4]. Advanced disease typically occurs in older children [45].

Typical acquired middle ear cholesteatoma, regularly associated

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with otitis media, may lead to temporal bone resorption, ossicular and otic capsule destruction, mastoid infiltration, tympanic membrane rupture, otorrhea, conductive hearing loss, sensorineural hearing loss, vestibular dysfunction, neuropathies, pain, and altered mental status [2,45-48].

Congenital cholesteatoma can present as acute mastoiditis with post-auricular pain or swelling [49]. Facial nerve paresis [13,50], lateral sinus thrombosis and cervical abscess (Bezold's abscess) due to partially recurrent cholesteatoma [51-53] have been reported. Even facial nerve transection due to cholesteatoma has been described [54]. Cholesteatomas of the petrous bone and the labyrinth were shown to be associated with cutaneous fistulas [55,56].

Gradual intracranial involvement, e.g. into the posterior fossa, has been occassionally described [3,48]. Other endocranial complications include temporal lobe abscess, parietal lobe abscess, cerebellar abscess, extradural abscess, labyrinthine fistulas, invasion of the the labyrinth and fallopian canal, lateral sinus thrombophlebitis with subdural abscess, and meningitis [57-59] (Table 1).

At least infectious complications of cholesteatoma were reduced by the application of antibiotics [60].

Pathogenesis

Although keratinizing stratified squamous epithelium is well known as the pathological substrate of cholesteatoma [1], the understanding of the pathogenesis of cholesteatoma is still limited. Various animal models have been used so far in basic science to decipher the disease's pathophysiological processes [2]. In addition, immunohistochemistry of matrix and perimatrix contributed to the knowledge on pathogenesis of middle ear cholesteatoma [61].

Site	Complication
Systemic	Systemic infection
	Altered mental status
	Pain
External ear	Otorrhea
Middle ear	Temporal bone resorption
	Ossicular destruction
	Otic capsule destruction
	Tympanic membrane rupture
	Conductive hearing loss
Inner ear	Sensorineural hearing loss
	Dysequilibrium due to vestibular dysfunction
Periauricular	Local infection
	Mastoid infiltration (e.g. acute mastoiditis)
	Facial nerve paresis/transsection
	Cutaneous fistulas
	Cervical abscess (Bezold's abscess)
	Postauricular pain
	Postauricular swelling
Intracranial	Invasion of posterior fossa
	Temporal lobe abscess
	Parietal lobe abscess
	Cerebellar abscess
	Extradural abscess
	Invasion of the labyrinth and Fallopian canal
	Lateral sinus thrombosis/thrombophlebitis
	Subdural abscess
	Meningitis

Table 1: Complications of middle ear cholesteatoma.

Origin and triggering factors

Iatrogenic or non-iatrogenic tympanic membrane trauma like perforation, displacement, retraction or invagination, tympanic membrane disease, tympanic cavity mucosa disease, ear infection, and Eustachian tube dysfunction are likely to trigger acquired cholesteatoma developement [1,48,62]. Ectopic tissue immigration and retraction pockets are believed to be etiopathogenetically relevant, same as chronic inflammation [1]. Up to 10% of chronic otitis cases in children are associated with cholesteatoma [63] (Figure 1).

In contrast, congenital cholesteatoma might be explained by the postpartum persistence of a fetal epidermoid formation [1,64,65], which physiologically persists at the junction of the Eustachian tube with the middle ear near the anterior limb of the tympanic ring until the 33rd gestation week [66] (Figure 1).

Macroscopic findings

In acquired middle ear cholesteatoma, tubal dysfunction leads to a retraction pocket according to the retraction pocket theory [61]. The formation of retraction pockets is usually based on diseased mucosa [62] and facilitates the recruitment of initially planktonic bacteria due to a loss of defense mechanisms [67]. Within retraction pockets, cell debris and keratinocytes accumulate due to disturbed self-cleaning mechanisms as a consquence of local infection. However, this phenomenon is restricted to the rare cases of disturbed self-cleaning of keratinocytes, while normal migration of the squamous epithelium from the basal layers to the surface occurs in healthy individuals. Initially occuring 'micro-cholesteatomas' show confluence to the macroscopic cholesteatoma [61], which in turn leads to bone erosions [68] (Figure 1).

Micro-morphological and immunological aspects

Epithelium of cholesteatoma behaves more like 'wound-healing' than like neoplasm. There are no hints for inherent genetic instability [69]. Increased presence of fibronectin in cholesteatoma stroma has been observed [70]. Accumulating cell debris and keratinocytes of the cholesteatoma tissue are invaded by cells of the immune system including Langerhans' cells, T-cells, and macrophages [61]. The process is stimulated by an imbalance of epithelial proliferation, keratinocyte differentiation and maturation, as well as prolonged apoptosis [61]. Cell migration is replaced by hyperplasia under inflammatory conditions [62]. Hyperproliferation markers include Cytokeratin 16 (CK16), antigen Ki-67 and Proliferating Cell Nuclear Antigen (PCNA), which are overexpressed in the annulus tympanicus, adjacent meatus and tympanic regions [71]. The inflammation-driven epithelial proliferation is associated with an increased expression of lytic enzymes and cytokines including arachidonic acid, Intercellular Adhesion Molecule (ICAM), Receptor Activator Of Nuclear Factor Kappa-B Ligand (RANKL), Interleukin-1,-2 and -6 (IL-1, IL-2, IL-6), Matrix Metalloproteinase-2 and -9 (MMP-2, MMP-9) as well as Tumor Necrosis Factor-alpha (TNF-alpha), which are partly induced by bacterial antigens [61,68,72] including endotoxins like lipopolysaccharides [67]. Increased proliferative activity of epithelial cells is associated with increased nuclear content in the basal cells of colesteatoma as the morpholocial correlate of basal hyperplasia, being particularly pronounced in areas of inflammatory infiltration [73]. Mast cells are present in high numbers in cholesteatoma tissue and may contribute to chronic inflammation [74]. Histamine and Platelet-Activating Factor (PAF) lead to a disturbance of the Eustachian tube function, resulting in a disturbed mucociliary clearance. This

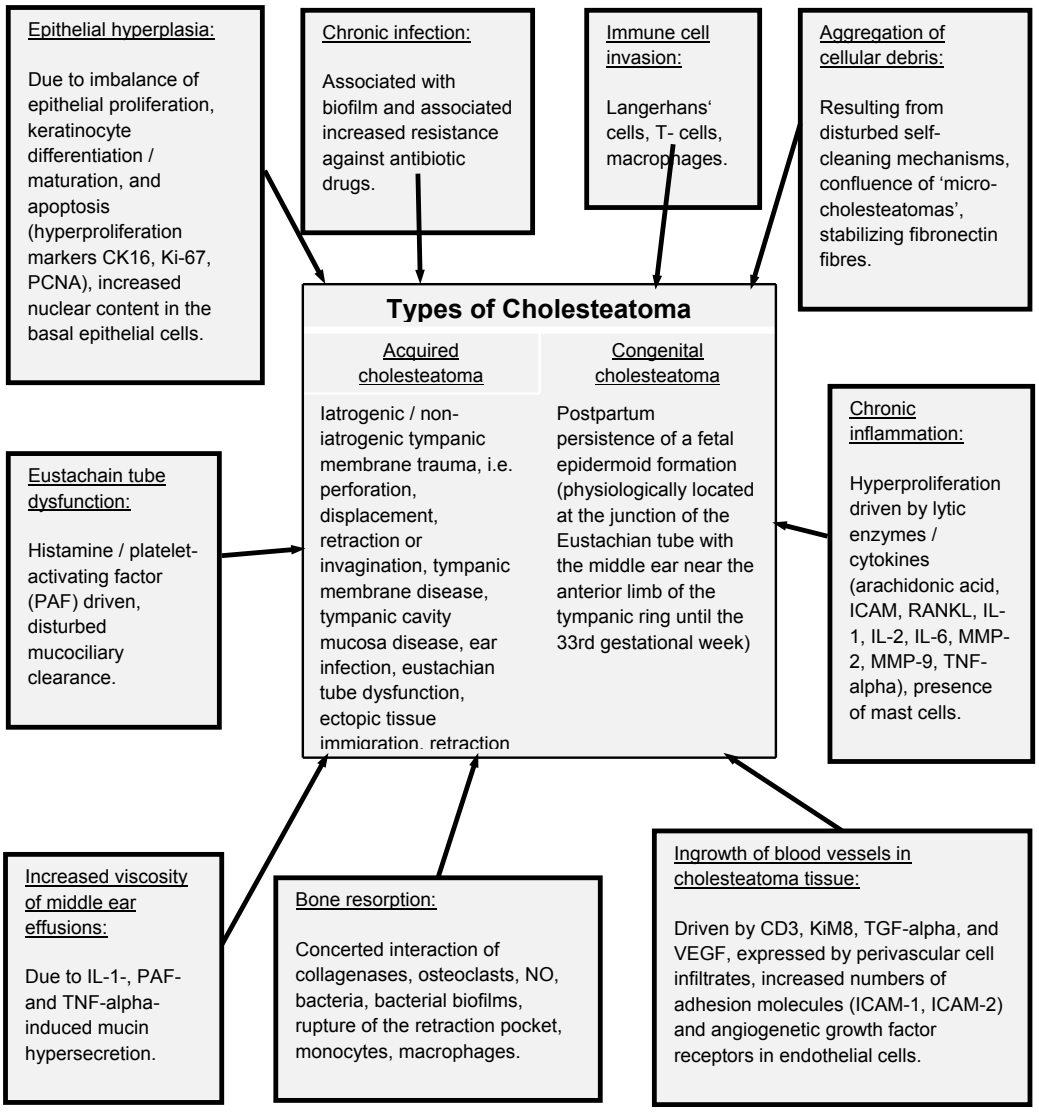

Figure 1: Pathogenesis of middle ear cholesteatoma.

process is aggravated by IL-1-, PAF- and TNF-alpha-induced mucin hypersecretion in the middle ear, leading to increased viscosity of middle ear effusions [61,75] (Figure 1).

The effector cells of released cytokines include osteoclasts, which lead to degradation of extracellular bone matrix and hyperproliferation, resulting in the macroscopically visible bone arrosion [61,68,76-78]. Other factors of importance for erosive bone depletion include collagenases, osteoclasts, nitric oxide (NO), bacteria including bacterial biofilms and rupture of the retraction pocket [32,79]. Large numbers of monocytes and macrophages accumulate in the contact area of cholesteatoma and bone, but only multi-nucleated osteoclasts are associated with disappearance of the bone surface [80] (Figure 1).

Vascular aspects

Hyperproliferative epithelial growth in cholesteatoma is supported by abundant blood vessels as a consequence of increased vascularization. Cholesteatoma stroma is characterized by numerous blood vessels with intact basal membrane, particularly in regions with abundant macrophage infiltration. Perivascular cellular infiltrates express angiogenetic factors like Cluster of Differentiation 3 (CD3), KiM8, Transforming Growth Factor-alpha (TGF-alpha), Vascular Endothelial Growth Factor (VEGF), and Human Histocompatibility Antigen (HLA-II) as a marker for cellular activation. Endothelial cells show Intercellular Adhesion Molecules (ICAM-1, ICAM-2) and angiogenetic growth factor receptors in increased numbers [81] (Figure 1).

Microbiology

As for many chronic infections, cholesteatoma was demonstrated to be associated with biofilm formation of infecting and/or colonizing bacteria [82-84]. In particular, avid biofilm-forming *Pseudomonas aeruginosa* strains have been isolated from cholesteatoma material [83]. Biofilms lead to impaired clearance, because bacteria within

biofilm formations are well protected against host defense mechanisms as well as systemic or topical antibiotic drugs [75,85].

Next to *Pseudomonas aeruginosa*, *Staphylococcus areus* and anaerobic bacteria like *Peptostreptococcus* spp., *Prevotella* spp., *Porphyromonas* spp., *Bacteroides* spp. and *Fusobacterium* spp. are believed to be of etiological relevance for cholesteatoma development [86]. Gram-positive anaerobic cocci, *Bacteroides* spp., and *Fusobacterium* spp. were found in up to 50% of analyzed cholesteatoma tissues in a previous analysis. The expression of beta-lactamases in these anaerobic bacteria is common and should be considered if antibiotic therapy or peri-operative prophylaxis is intended [87].

In a previously published work, *Pseudomonas aeruginosa* was considered as the most relevant bacterial agent in pathology of cholesteatoma, followed by *Staphylococcus aureus* and *Proteus mirabilis* [88]. In contrast, we described a broad variety of aerobic and anaerobic Gram-positive and Gram-negative bacteria and even yeasts on ossicle samples that were overgrown by cholesteatoma in a recent study [89]. In detail, *Acinetobacter baumannii*, *Aeromonas salmonicida*, *Bacillus licheniformis*, *Bacteroides urealyticus*, *Brevundimonas diminutiva*, *Burkholderia cenocepacia*, *Candida albicans*, *Clostridium bifermentans*, *Corynebacterium pseudodiphtheriticum*, *Eubacterium limosum*, *Haemophilus somnus*, *Kocuria rosea*, *Leuconostoc mesenteroides* spp. *cremoris*, *Micrococcus luteus*, *Neisseria sicca*, *Neisseria subflava*, *Propionibacterium acnes*, *Propionibacterium granulosum*, *Pseudomonas aeruginosa*, *Pseudomonas fluorescence*, *Ralstonia pickettii*, *Sphingomonas paucimobilis*, *Staphylococcus aureus*, *Staphylococcus auricularis*, *Staphylococcus capitis*, *Staphylococcus epidermidis*, *Staphylococcus hominis*, *Staphylococcus simulans*, *Streptococcus mitis*, *Streptococcus sanguinis*, *Turicella otidis*, and *Veilonella parvula* were isolated. Only half of the tested bacteria showed *in-vitro* single species biofilm formation [89]. However, discrimination of infecting pathogens and harmless colonizers in primarily non-sterile compartments like middle ear is hardly possible. The mentioned species comprise facultative pathogens or typical commensals (Table 2).

Hereditiy

A single Danish paper provides hints on potential hereditary factors that might interact with other factors in the onset of acquired cholesteatoma. A family from Greenland with an unusual accumulation of chlolesteatoma patients was described [90].

Imaging

Computed Tomography (CT) and Magnetic Resonance (MR) cross-sectional scans are used for pre-operative assessment and post-operative follow-up [4,91-96]. These techniques replaced the formerly common plain petro-mastoid views, from which the lateral with caudal tilt of the tube was considered to be the most useful as it demonstrates the extent of pneumatisation and the position of the lateral sinus and middle fossa dura [97]. The drawback of CT scanning is its low specificity, i.e. its failure to discriminate soft-tissue structures [98]. Precise diagnosis is usually based on gadolinium-enhanced T1-weighted and diffusion-weighted MRI sequences [4]. Diffusion weighted MR imaging is advicable if CT scans lead to equivocal results [99].

Further, diffusion-weighted magnetic resonance imaging scans are the method of choice to detect residual or recurrent middle ear cholesteatoma after surgery [100]. The differentiation from granulation tissue, inflammatory tissue, or fluid within the middle ear cavity and mastoid cavity is challenging [101]. Non-echo-planar imaging, e.g. half Fourier acquisition single-shot turbo spin echo sequences, yield the most reliable results for this indication [100] and outperforms traditional approaches like high-resolution computed tomography, conventional magnetic resonance imaging, and delayed contrast magnetic resonance imaging [101].

Rarely used imaging approaches include optical coherence tomography, allowing for non-invasive imaging with micrometer resolution and therefore being well-suited for the diagnosis of middle ear cholesteatoma [102].

Therapy

Surgery is the treatment of choice for cholesteatoma [103-106]. Surgical approaches should aim to avoid residual or recurrent cholesteatoma. A good functional result, including improvement of hearing, is of secondary importance [107,108]. The third aim is the restoration of ear anatomy [109]. Treatment approaches by laser showed less promising results [4]. Single-stage procedures are favored for the reconstruction of the sound conduction system [108]. The outcome is highly depending on the extent of the cholesteatoma-induced lesion [110]. Individualized approaches, taking anatomic, clinical and social factors into account, are necessary to yield optimal results, in particular in young infants [37,111,112]. The likelihood of compliance should be considered for the design of the management plan, because adherence may be a relevant problem, particularly in children [113].

Typical approaches in surgery of cholesteatoma of the mastoid include preservation or reconstruction of the posterior meatal wall with an aerated mastoid, partial or complete obliteration of the mastoid after removal of the posterior wall, and leaving the cavity open for inspection [108]. Canal wall-preserving techniques are common [101]. Cavity obliteration is important to protect vital neurovascular structures, which can be exposed during operation [50].

Though the use of autogenous ossicles leads to the best results concerning the reconstruction of the sound conducting system in cholesteatoma surgery, ingrowth of matrix epithelia often limits

Group	Isolated agents
Gram-negative aerobic bacteria	*Aeromonas salmonicida*, *Acinetobacter baumannii*, *Burkholderia cenocepacia*, *Brevundimonas diminutiva*, *Haemophilus somnus*, *Neisseria sicca*, *Neisseria subflava*, *Pseudomonas aeruginosa*, *Pseudomonas fluorescence*, *Ralstonia pickettii*, *Sphingomonas paucimobilis*,
Gram-positive aerobic bacteria	*Bacillus licheniformis*, *Corynebacterium pseudodiphtheriticum*, *Kocuria rosea*, *Leuconostoc mesenteroides* spp. *cremoris*, *Micrococcus luteus*, *Staphylococcus aureus*, *Staphylococcus auricularis*, *Staphylococcus capitis*, *Staphylococcus epidermidis*, *Staphylococcus hominis*, *Staphylococcus simulans*, *Streptococcus mitis*, *Streptococcus sanguinis*, *Turicella otidis*
Gram-negative anaerobic bacteria	*Bacteroides urealyticus*, *Eubacterium limosum*, *Porphyromonas* spp., *Prevotella* spp., *Veilonella parvula*
Gram-positive anaerobic bacteria	*Clostridium bifermentans*, *Fusobacterium* spp., *Peptostreptococcus* spp., *Propionibacterium acnes*, *Propionibacterium granulosum*
Yeasts	*Candida albicans*

Table 2: Infectious microorganisms isolated from cholesteatoma material or ossicles that were overgrown by cholesteatoma [83,86,89].

their use. High-hydrostatic pressure treatment was shown to reliably inactivate epithelial cells prior to a replantation of ossicles [114]. However, as previously shown by our group, high-hydrostatic pressure fails to completely inactivate bacteria on these ossicles. The effect is particularly reduced for biofilm formers, so only a reduction of bacterial count can be achieved [89]. The question, whether such reductions of bacterial counts may nevertheless contribute to a more favorable clinial outcome, has still to be answered in further studies.

Prognosis

Despite surgical interventions, risk of recurrence of cholesteatoma is high. Postoperative complications and recurrence are more common in acquired than in congenital cholesteatoma, with early detection being the most important predictor for a favorable outcome [40,115,116]. Recurrence rates of < 10% should be aimed [117]. Iatrogenic cholesteatoma of the neck has been described as a late complication of radical mastoidectomy to cure a cholesteatoma [118].

Postoperative follow-up is advisable in order not to miss infections, stenosis, and recurrence of cholesteatoma [13]. Second-look surgery is mandatory to exclude residual or recurrent disease, because clinical and otoscopic diagnosis is not reliable for this indication [101]. Life-long follow-up is necessary due to a high incidence of delayed recurrence [3]. Recurrence is more frequent in infants than in adults [109]. Proven risk factors of recurrence of the disease after surgical intervention include posterior mesotympanum involvement, ossicular chain interruption after disease excision, relative lack of experience of the surgeon, and presumed incomplete removal [119] (Table 3).

Prophylaxis

Due to the important role of chronic inflammation in acquired cholesteatoma, early treatment of inflammatory conditions has prophylactic effects, e.g. by preventing the development of hyperplastic papillary protrusions [1].

Discussion

Though the understanding of middle ear cholesteatoma pathogenesis advances, prognosis is limited by frequent recurrence of disease despite surgical intervention [40,116]. Inflammation due to chronic otitis is the only risk factor for the development of cholesteatoma that can be relevantly influenced [1,60,63].

However, microbiology of cholesteatoma is poorly understood. Even data regarding the causative infectious agents are contradictory [86-89], making anti-infectious therapy challenging. Anaerobic bacteria are frequently isolated [86,87] and should be considered.

Though biofilm forming bacteria were described to be of importance for the pathogenesis of cholesteatoma, we could demonstrate *in-vitro* biofilm formation in no more than a half of the isolates from ossicles that were overgrown by cholesteatoma [89]. Hypertrophic infected tonsils are a crucial factor to a reduced clearance of infectious detritus from the middle ear cavity by blocking the Eustachian tube [120]. Intra-cellular persistence of bacteria was demonstrated by our group to be of patho-etiological relevance for recurrent adentotonsillar disease [120,121]. These pathogens persisting intra-cellularly in the adenotonsills might ascent from this spatially related reservoir through the Eustachian tube to the middle ear and may lead to recurrent otitis media [121]. However, a direct role of intra-cellularly persistent bacteria in cholesteatoma tissue was not examined so far.

- Late diagnosis/surgical intervention
- Posterior mesotympanon involvement
- Interrupted ossicular chain after surgical intervention
- Lacking experience of the surgeon
- Incomplete removal of cholesteatoma material

Table 3: Unfavorable prognostic factors.

Although antibiotic therapy of chronic otitis media is generally accepted [122], acquired cholesteatoma is common, demanding futher optimization. Therefore, further studies to unveil the exact role of infection in the pathogenesis of cholesteatoma are required, same as further research on the standardization of antibiotic therapy. A better control of chronic otitis media might lead to an additional decrease in the incidence of acquired cholesteatoma.

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