

## Review

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# Current concepts in the pathogenesis and treatment of chronic suppurative otitis media

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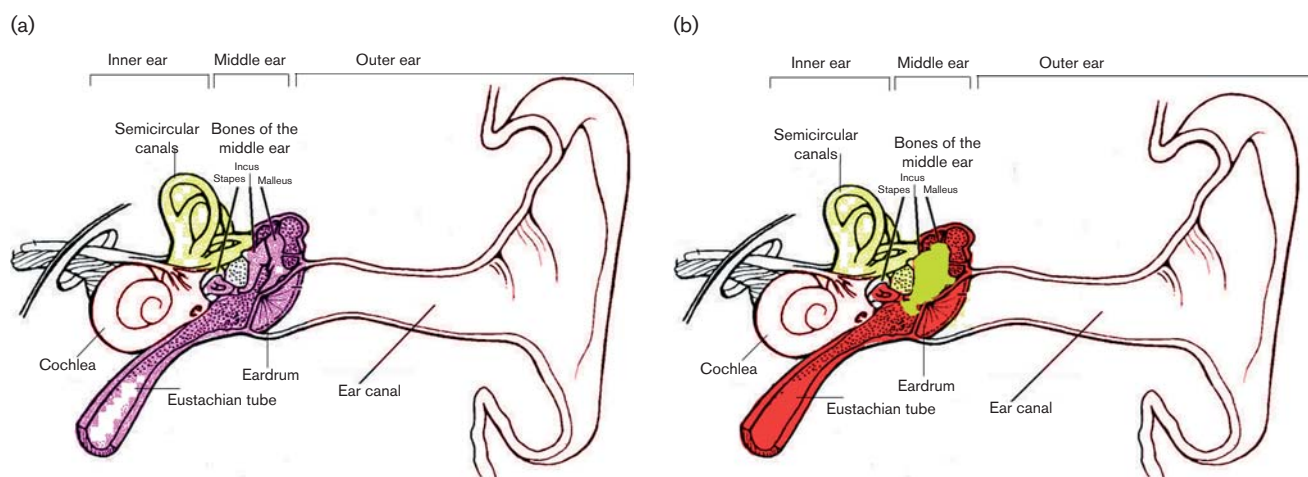
Otitis media (OM) is an inflammation of the middle ear associated with infection. Despite appropriate therapy, acute OM (AOM) can progress to chronic suppurative OM (CSOM) associated with ear drum perforation and purulent discharge. The effusion prevents the middle ear ossicles from properly relaying sound vibrations from the ear drum to the oval window of the inner ear, causing conductive hearing loss. In addition, the inflammatory mediators generated during CSOM can penetrate into the inner ear through the round window. This can cause the loss of hair cells in the cochlea, leading to sensorineural hearing loss. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most predominant pathogens that cause CSOM. Although the pathogenesis of AOM is well studied, very limited research is available in relation to CSOM. With the emergence of antibiotic resistance as well as the ototoxicity of antibiotics and the potential risks of surgery, there is an urgent need to develop effective therapeutic strategies against CSOM. This warrants understanding the role of host immunity in CSOM and how the bacteria evade these potent immune responses. Understanding the molecular mechanisms leading to CSOM will help in designing novel treatment modalities against the disease and hence preventing the hearing loss.

## Introduction

Otitis media (OM) refers to a group of complex infectious and inflammatory diseases affecting the middle ear (Dickson, 2014). OM in general is very common, as studies show that around 80 % of children should have experienced at least one episode by their third birthday (Teele *et al.*, 1989). OM has been broadly classified into two main types, acute and chronic. Acute OM (AOM) is characterized by the rapid onset of signs of inflammation, specifically bulging and possible perforation of the tympanic membrane, fullness and erythema, as well as symptoms associated with inflammation such as otalgia, irritability and fever (Pukander, 1983; Harkness & Topham, 1998). Despite appropriate antibiotic therapy, AOM may progress to chronic suppurative OM (CSOM) characterized by persistent drainage from the middle ear associated with a perforated ear drum (Wintermeyer & Nahata, 1994; Harkness & Topham, 1998). When examined by otoscope, the

middle ear looks red and inflamed with purulent discharge in CSOM patients (Figs 1 and 2). It is one of the most common chronic infectious diseases worldwide especially affecting children (Roland, 2002; Verhoeff *et al.*, 2006). Hearing impairment is one of the most common sequelae of CSOM (Aarhus *et al.*, 2015). The resultant hearing loss can have a negative impact on a child's speech development, education and behaviour (Olatoke *et al.*, 2008; Khairi Md Daud *et al.*, 2010). Mortality due to complications of CSOM is typically higher than other types of OM (Yorgancilar *et al.*, 2013a; Qureishi *et al.*, 2014). Intracranial complications like brain abscess and meningitis are the most common causes of death in CSOM patients (Dubey *et al.*, 2010; Chew *et al.*, 2012; Sun & Sun, 2014).

In this article, the recent scientific advancements in epidemiology, microbiology, pathogenesis, treatment and effect of CSOM on hearing loss are reviewed. There are only a few studies available in relation to understanding the



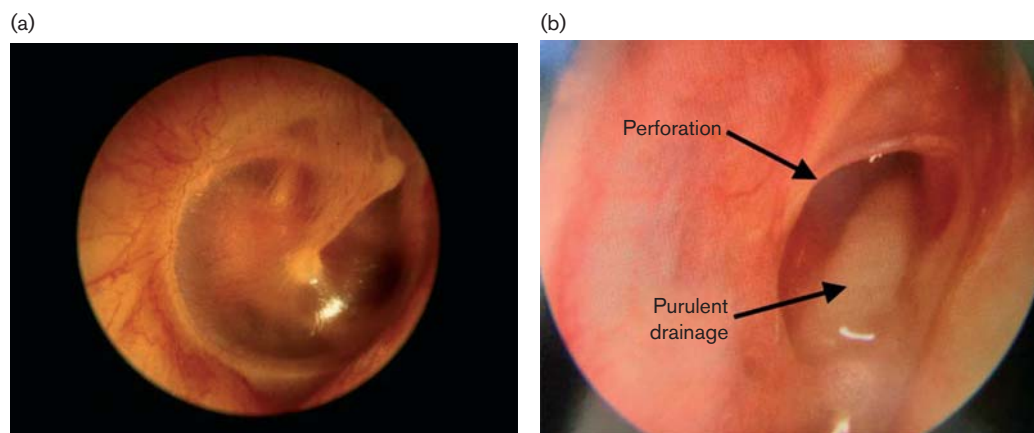
**Fig. 1.** Schematic representation of the ear under normal and CSOM conditions. (a) Under normal conditions, the middle ear cavity is clear and empty. (b) In contrast, the middle ear becomes red and inflamed with the presence of fluid under CSOM conditions. The red colour denotes inflammation, while yellow indicates fluid during CSOM.

pathogenesis of CSOM (Table 1). The present review is intended to draw the attention to the fact that there is an urgent need to conduct studies on the pathogenic mechanisms of CSOM in order to identify novel therapeutic targets beyond the antibiotic therapy. A better understanding of the underlying mechanisms and, ultimately, the discovery of more effective therapies would result in decreased healthcare costs and improved quality of life for CSOM patients.

### Incidence and epidemiology

CSOM usually develops in the first years of life but can persist during adulthood. The disease affects 65–330 million people worldwide, mainly in developing countries. It has

been estimated that there are 31 million new cases of CSOM per year, with 22.6 % in children less than 5 years old (Monasta *et al.*, 2012). The populations with the highest reported prevalence of CSOM are the Inuits of Alaska, Canada and Greenland, American Indians and Australian Aborigines (7–46 %) (Bluestone, 1998; Coates *et al.*, 2002; Couzos *et al.*, 2003). Intermediate prevalence has been reported in the South Pacific Islands, Africa, Korea, India and Saudi Arabia, ranging from 1 to 6 % (Rupa *et al.*, 1999; Zakzouk & Hajjaj, 2002). A prospective population-based longitudinal cohort study among children aged 0 to 4 years demonstrated a cumulative incidence rate of CSOM of 14 % in Greenland (Koch *et al.*, 2011). However, earlier studies have reported CSOM incidence rates of 19 and 20 % among Greenlandic children aged 3–8 years (Pedersen and Zachau-Christiansen, 1986; Homøe *et al.*, 1996).



**Fig. 2.** Otoscopic examination of the ear. (a) A normal ear from a healthy individual shows an intact eardrum and no fluid. (b) In CSOM patients, there is tympanic membrane perforation and purulent discharge.

**Table 1.** Pathophysiological findings in CSOM patients

Findings	References
Biofilm formation in the middle ear of CSOM patients	Saunders <i>et al.</i> (2011); Lampikoski <i>et al.</i> (2012); Kaya <i>et al.</i> (2013); Khosravi <i>et al.</i> (2014); Gu <i>et al.</i> , (2014)
Increased levels of IL-8 chemokine in middle ear effusion of CSOM patients	Elmorsy <i>et al.</i> (2010)
Increased transcript and protein levels of TNF- $\alpha$ , IL-6, IL-1 $\beta$ and IFN- $\gamma$ inflammatory cytokines in the middle ear mucosa of CSOM patients	Si <i>et al.</i> (2014)
Temporal bone erosion	Yorgancilar <i>et al.</i> (2013a, b)
Ossicular chain disruption	Varshney <i>et al.</i> (2010)
Hearing loss in CSOM patients	Paparella <i>et al.</i> (1984); Kolo <i>et al.</i> (2012); Luntz <i>et al.</i> (2013); Aarhus <i>et al.</i> (2014)

These studies show that CSOM is highly prevalent in Greenlandic Inuits and appears very early in life, on average before 1 year of age. The risk factors that predispose children to CSOM in Greenland include attending childcare centres, having a mother who reported a history of purulent ear discharge, having smokers in the household, a high burden of upper respiratory tract infections and being Inuit (Koch *et al.*, 2011). Although CSOM is still prevalent in developed countries, very few studies are available regarding this disease. The exact incidence of CSOM in the USA is not well documented: 70 % of US children have at least one acute middle ear infection before 3 years of age, constituting a major risk factor for the development of CSOM (Kraemer *et al.*, 1984). In the USA, CSOM has been documented to occur most often in certain ethnic groups, with an estimated prevalence of 12 % in Eskimo and 8 % in American Indian children and less frequently in the white and black population (Fairbanks, 1981; Kenna *et al.*, 1986). For the latter two groups, the exact incidence has not been documented. It has been observed that males and females are equally affected, but the cholesteatomatous form is more common among males (Matanda *et al.*, 2005). Additional epidemiological studies are required to highlight the incidence of CSOM in developed countries.

## Microbiology

The most common cause of OM is bacterial infection of the middle ear. AOM is predominantly caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* (Sierra *et al.*, 2011; Qureishi *et al.*, 2014). However, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most common aerobic microbial isolates in patients with CSOM, followed by *Proteus vulgaris* and *Klebsiella pneumoniae* (Table 2) (Sattar *et al.*, 2012; Aduda *et al.*, 2013; Prakash *et al.*, 2013). A number of studies from different countries including India, Nepal, Singapore and Nigeria have reported that *P. aeruginosa* is the most common pathogen that causes CSOM, followed by *S. aureus* (Yeo *et al.*, 2007; Sharma *et al.*, 2010; Dayasena *et al.*, 2011; Madana *et al.*, 2011; Afolabi *et al.*, 2012; Ahn *et al.*, 2012; Asish *et al.*, 2013). However, studies from Pakistan (Gilgit), Iran and Saudi Arabia reported *S. aureus* as the most predominant pathogen, followed by *P. aeruginosa* (Ettehad *et al.*, 2006; Mariam *et al.*, 2013; Ahmad *et al.*, 2013; Ahmed *et al.*, 2013). The difference in the various studies could be due to the differences in the patient population studied and geographical variation. A cross-sectional study of bacterial microbiota in middle ear, adenoid and tonsil specimens from a paediatric patient with chronic serous OM utilizing 16S rRNA gene-based pyrosequencing analysis revealed *Pseudomonas* spp. as the most common pathogen present in the middle ear, whereas *Streptococcus* spp. dominated the tonsil microbiota at relative abundance rates of 82.7 and 69.2 %, respectively (Liu *et al.*, 2011). On the other hand, the adenoid microbiota was dominated by multiple bacteria including *Streptococaceae*,

**Table 2.** A list of micro-organisms isolated from CSOM patients

Organisms	Percentage isolation	References
<b>Aerobic bacteria</b>		
<i>Pseudomonas aeruginosa</i>	22–44	Ibekwe <i>et al.</i> (1997); Nwabuisi and Ologe (2002); Sharma <i>et al.</i> (2004); Sharma <i>et al.</i> (2010); Dayasena <i>et al.</i> (2011); Afolabi <i>et al.</i> (2012); Kabir <i>et al.</i> (2012); Vishwanath <i>et al.</i> (2012); Asish <i>et al.</i> (2013); Prakash <i>et al.</i> (2013); Orji and Dike (2015)
<i>Staphylococcus aureus</i>	17–37	Dayasena <i>et al.</i> (2011); Vishwanath <i>et al.</i> (2012); Asish <i>et al.</i> (2013); Mariam <i>et al.</i> (2013); Prakash <i>et al.</i> (2013); Orji and Dike (2015)
<i>Klebsiella pneumoniae</i>	4–7	Deb and Ray (2012); Vishwanath <i>et al.</i> (2012)
<i>Proteus mirabilis</i>	3–20	Ibekwe <i>et al.</i> (1997); Madana <i>et al.</i> (2011); Deb and Ray (2012); Vishwanath <i>et al.</i> (2012); Orji and Dike (2015)
<i>Proteus vulgaris</i>	0.9–3	Vishwanath <i>et al.</i> (2012)
<i>Escherichia coli</i>	1–21	Deb and Ray (2012); Vishwanath <i>et al.</i> (2012); Orji and Dike (2015)
<i>Streptococcus pneumoniae</i>	1–3	Vishwanath <i>et al.</i> (2012); Prakash <i>et al.</i> (2013)
<i>Acinetobacter baumannii</i>	1–3	Vishwanath <i>et al.</i> (2012); Asish <i>et al.</i> (2013) Prakash <i>et al.</i> (2013)
<i>Enterobacter aerogenes</i>	0.9–4	Vishwanath <i>et al.</i> (2012); Asish <i>et al.</i> (2013)
<b>Anaerobic bacteria</b>		
<i>Bacteroides</i> spp.	4–8	Brook (2008); Vishwanath <i>et al.</i> (2012)
<i>Clostridium</i> spp.	3–6	Brook (2008); Vishwanath <i>et al.</i> (2012)
<i>Prevotella</i> spp.	1–3	Brook (2008); Vishwanath <i>et al.</i> (2012)
<i>Fusobacterium nucleatum</i>	3–4	Brook (2008)
<b>Fungi</b>		
<i>Aspergillus niger</i>	3–15	Juyal <i>et al.</i> (2014); Vishwanath <i>et al.</i> (2012)
<i>Aspergillus flavus</i>	3–20	Juyal <i>et al.</i> (2014); Vishwanath <i>et al.</i> (2012)
<i>Candida albicans</i>	0.9–23	Juyal <i>et al.</i> (2014); Vishwanath <i>et al.</i> (2012); Asish <i>et al.</i> (2013)
<i>Candida krusei</i>	2–3	Juyal <i>et al.</i> (2014)



*Fusobacteriaceae*, *Pasteurellaceae* and *Pseudomonadaceae*. *P. aeruginosa* and *S. aureus* can enter the middle ear through the external canal. *P. aeruginosa* can thrive well in the ear environment and is difficult to eradicate. It has been proposed that *P. aeruginosa* evades the host defence mechanism by taking advantage of a shell of surrounding damaged epithelium that causes decreased blood circulation to the area (Pollack, 1988). *P. aeruginosa* damages the tissues, interferes with normal body defences and inactivates antibiotics by various enzymes and toxins (Gellatly & Hancock, 2013). *Bacteroides* spp., *Clostridium* spp., *Peptococcus* spp., *Peptostreptococcus* spp., *Prevotella melaninogenica* and *Fusobacterium* spp. are anaerobic pathogens that can cause CSOM (Table 2) (Verhoeff *et al.*, 2006; Prakash *et al.*, 2013). It is possible that some of these pathogens may be just the normal microbial flora harbouring the middle ear instead of causative agents. However, no studies are available reporting the normal microflora of the middle ear. Therefore, further studies are warranted to characterize the normal microflora of the middle ear, which will help in differentiating normal ear flora from the pathogens that cause CSOM.

CSOM can also be characterized by co-infections with more than one type of bacterial and viral pathogen (Vartiainen & Vartiainen, 1996; Bakaletz, 2010). Fungi have also been identified in cultures from patients with CSOM (Ibekwe *et al.*, 1997; Khanna *et al.*, 2000; Prakash *et al.*, 2013; Asish *et al.*, 2014; Juyal *et al.*, 2014). However, the presence of fungi can be due to the treatment with antibiotic ear drops, which causes suppression of bacterial flora and the subsequent emergence of fungal flora (Schrader & Isaacson, 2003). This probably increases the incidence of fungal superinfection, and even the less virulent fungi become more opportunistic. Furthermore, there has been much disparity on the rate of isolation of fungi from CSOM patients (Table 2). This variation can be attributed to the climatic conditions, as the moist and humid environment favours the prevalence of fungal infections of the ear.

## Pathogenesis

CSOM is considered a multifactorial disease resulting from a complex series of interactions between environmental, bacterial, host and genetic risk factors (Rye *et al.*, 2012; Li *et al.*, 2013). It is important to identify the genes that contribute to CSOM susceptibility, which will provide insights into the biological complexity of this disease and ultimately contribute to improve the methods of prevention and treatment (Allen *et al.*, 2014). Innate host immune mechanisms such as the TLR4/MyD88 pathway are particularly important in eliciting protective immune responses against bacteria (Hernandez *et al.*, 2008). On the other hand, the transforming growth factor- $\beta$  pathway helps in balancing the adverse outcome of an exaggerated pro-inflammatory response (Leichtle *et al.*, 2011). The roles of these pathways have been extensively studied in AOM; however, no studies are available in relation to CSOM.

Bacterial biofilms have gained attention in the pathogenesis of CSOM. Biofilms are resistant to antibiotics and other antimicrobial compounds (Stewart & Costerton, 2001; Hall-Stoodley & Stoodley, 2009; Mah, 2012; Alhede *et al.*, 2014; Jolivet-Gougeon & Bonnaure-Mallet, 2014; Römling *et al.*, 2014). Therefore, they are difficult to eradicate and hence could lead to recurrent infections (Donelli & Vuotto, 2014; García-Cobos *et al.*, 2014). In addition, biofilms attach firmly to damaged tissue, such as exposed osteitic bone and ulcerated middle ear mucosa, or to otological implants such as tympanostomy tubes, further aggravating the problem of eradication (Wang *et al.*, 2014). Although biofilms have been demonstrated in the middle ear of CSOM patients, their precise role in the pathophysiology of the disease is yet to be determined (Saunders *et al.*, 2011; Lampikoski *et al.*, 2012; Kaya *et al.*, 2013; Gu *et al.*, 2014; Khosravi *et al.*, 2014). Furthermore, the molecular mechanisms leading to biofilm formation in the middle ear during CSOM are also poorly understood.

Cytokines have also been implicated in the pathogenesis of OM. Most of the studies addressing the role of cytokines are in relation to AOM, and there are very limited studies available demonstrating the role of cytokines in the pathogenesis of CSOM. High levels of inflammatory cytokine such as IL-8 have been demonstrated in the middle ear effusion of CSOM patients (Elmorsy *et al.*, 2010). IL-8 plays a role in the development of chronicity of OM and has also been related to bacterial growth. Increased mRNA as well as protein levels of TNF- $\alpha$ , IL-6, IL-1 $\beta$  and IFN- $\gamma$  have been found in the middle ear mucosa of CSOM patients compared with healthy individuals (Si *et al.*, 2014). The upregulation of these pro-inflammatory cytokines can cause tissue damage as well as transition from acute to chronic OM. Additional studies are warranted to investigate the role of cytokines in the pathogenesis of CSOM.

## Hearing loss

Hearing impairment is the most common sequela of CSOM (Aarhus *et al.*, 2015). CSOM can cause conductive hearing loss (CHL) as well as sensorineural hearing loss (SNHL). CHL results from the obstruction in the transmission of sound waves from the middle ear to the inner ear. CSOM is characterized by the presence of fluid (pus), which can hinder the conductance of sound to the inner ear. The amount of effusion in the middle ear has been directly correlated with the magnitude and severity of CHL (Wiederhold *et al.*, 1980). CSOM is characterized by the presence of tympanic membrane perforation, which can hinder the conductance of sound to the inner ear. The degree to which hearing is compromised has also been demonstrated to be directly proportional to the damage caused to the structures of the middle ear (Yorgancilar *et al.*, 2013b). In some cases of CSOM, there can be permanent hearing loss that can be attributed to irreversible tissue changes in the auditory cleft (Kaplan *et al.*, 1996; Sharma *et al.*, 2013). Chronic infection of the

**Table 3.** List of inflammatory mediators generated in the middle ear in response to microbial infection

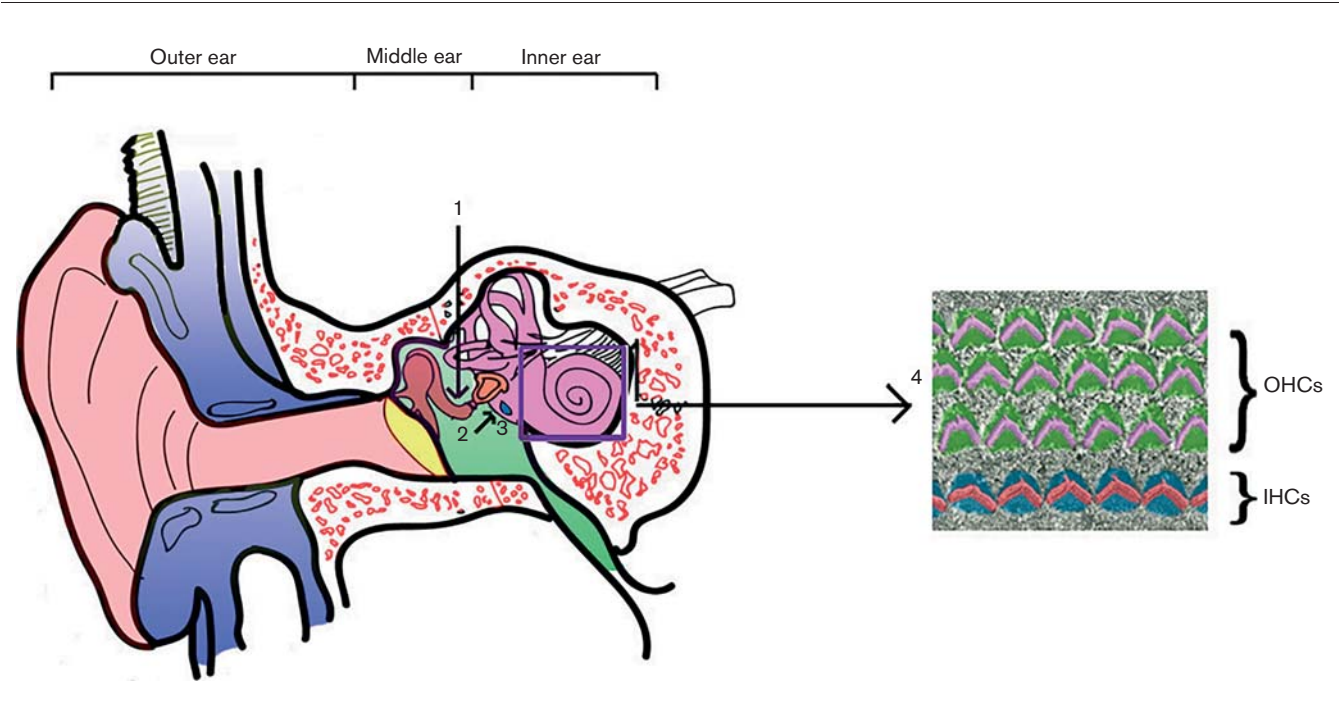
Inflammatory mediators	Possible mode of action	References
Nitric oxide	Destroys hair cells	Huang <i>et al.</i> (1990); Jung <i>et al.</i> (2003)
Reactive oxygen species	Morphological changes like cell membrane rupture, blebbing and cell body shortening	Clerici <i>et al.</i> (1995)
Arachidonic acid metabolites (prostaglandin and leukotriene)	Alteration in cochlear blood flow, hair cell damage	Jung <i>et al.</i> (1992)
Histamine	Interferes with the efferent innervations of the outer hair cells	Housley <i>et al.</i> (1988)
Cytokines	Damage to hair cells	Juhn <i>et al.</i> (2008)
Bacterial toxins	Block Na/K ATPase and change the ion concentration of endolymph; damage to hair cells	Guo <i>et al.</i> (1994)

middle ear causes oedema of the middle ear lining and discharge, tympanic membrane perforation and possibly ossicular chain disruption, resulting in CHL ranging from 20 to 60 dB (Varshney *et al.*, 2010).

SNHL results either from inner ear damage (cochlea) or injury to the nerve pathways that relay signals from the inner ear to the brain. The cochlea in mammals has three rows of outer hair cells and one row of inner hair cells. The outer hair cells help in the amplification and tuning of sound waves, whereas inner hair cells are involved in converting the mechanical energy of sound into an electrical impulse to be relayed to the auditory nerve. Any damage

to outer or inner hair cells can cause severe hearing impairment, which can be irreversible and permanent.

Recent studies have demonstrated that CSOM is able to cause SNHL in addition to CHL (Papp *et al.*, 2003; da Costa *et al.*, 2009; Kolo *et al.*, 2012; Yang *et al.*, 2014). Infection of the middle ear leads to the generation of inflammatory mediators such as nitric oxide and arachidonic acid metabolites (Table 3), which can cause functional as well as morphological changes in the auditory structures (Housley *et al.*, 1988; Jung *et al.*, 1992; Guo *et al.*, 1994; Clerici *et al.*, 1995; Jung *et al.*, 2003). These inflammatory mediators can also penetrate the round window membrane



**Fig. 3.** OM and inner ear damage. The bacterial infection of the middle ear (1) leads to the generation of inflammatory mediators (2) that can penetrate from the round window (3) to the inner ear, leading to damage to outer (OHCs) and inner (IHCs) auditory hair cells (4).

and pass into the inner ear causing cochlear damage (Fig. 3) (Morizono & Tono, 1991; Penha & Escada, 2003; Juhn *et al.*, 2008). The loss of outer and inner hair cells in the basal turn of the cochlea has been observed in CSOM patients (Huang *et al.*, 1990; Cureoglu *et al.*, 2004). The majority of SNHL in CSOM patients is in the high-frequency range and is unilateral (Jensen *et al.*, 2013). A recent study has also shown that bacterial toxins found in the middle ear during CSOM can pass into the cochlea and result in cochlear pathology (Joglekar *et al.*, 2010). These bacterial toxins can be exotoxins (proteins) produced by both Gram-positive and Gram-negative bacteria, or endotoxins (LPSs of the outer membrane of Gram-negative bacteria). These infection-associated toxins might cause direct damage to hair cells, especially those at the cochlear base where the hair cells are sensitive to high-frequency sounds (Kolo *et al.*, 2012). A significant loss of outer and inner hair cells, as well as significant atrophy of the stria vascularis in the basal turn of the cochlea, has been observed in CSOM patients. The basal turn of the cochlea also demonstrated severe pathological changes that were consistent with the high-frequency SNHL in CSOM patients (Cureoglu *et al.*, 2004; Joglekar *et al.*, 2010).

SNHL in CSOM patients is often demonstrated by higher bone conduction (BC) thresholds in the audiogram. BC thresholds in the healthy and CSOM ear differed by at least 20 dB at all of the measured frequencies (Luntz *et al.*, 2013). In a multi-centre study, 58 % of 874 patients with unilateral CSOM presented with SNHL of more than 15 dB in the affected ear (Paparella *et al.*, 1984). El-Sayed (1998) showed that, in 218 patients, the BC thresholds over a range of frequencies were increased by 9.2 to 14.1 dB in CSOM ears, with a mean difference between CSOM and normal ears of more than 10 dB in 39 % of patients and of 20 dB or more in 12 % of patients. Greater differences at 4000 Hz (5 dB) than at 500, 1000 or 2000 Hz (3 dB) were observed in 145 patients with unilateral CSOM (Eisenman & Parisier, 1998). Significant differences in BC between chronic OM and normal ears in 344 patients, ranging from 0.6 dB at 500 Hz to 3.7 dB at 4000 Hz for all frequencies have also been observed (Redaelli de Zinis *et al.*, 2005). da Costa *et al.* (2009) reported, in 150 patients, a BC difference of 5 dB between chronic OM and normal ears at 1000 and 2000 Hz, increasing to 10 dB at 3000 and 4000 Hz. The percentage of CSOM patients with higher BC thresholds tended to increase with age (Yoshida *et al.*, 2009). The site and size of the tympanic membrane perforation have been correlated with the degree of hearing loss, with posterior perforations having a greater decibel level loss, probably as a result of loss of protection of the round window membrane from impinging sound pressure waves (Vaidya *et al.*, 2014). It was suggested that all measures for an early cure, including surgery, should be considered promptly to prevent hearing loss in CSOM patients (Yoshida *et al.*, 2009).

## Treatment

The current primary treatment modality for CSOM is a combination of aural toilet and topical antimicrobial

drops. Systemic oral or parenteral antibiotics, although an option, are less commonly used due to the fact that topical antibiotics in combination with aural toilet are able to achieve significantly higher tissue concentrations than systemic antibiotics (in the order of 100–1000 times greater). Surgery, in the way of mastoidectomy, was traditionally the mainstay of therapy. However, retrospective studies have suggested that mastoidectomy is not superior to more conservative therapies such as aural toilet and topical and systemic antibiotics for uncomplicated CSOM. Reconstruction of the tympanic membrane or tympanoplasty is another surgical technique often used for persistent perforations after the active infection of CSOM has been treated. In addition, surgical eradication of cholesteatoma is indicated in chronic cholesteatomatous OM (CCOM).

## Aural toilet

The term aural toilet refers to keeping the chronically draining ear clean and dry as much as possible. Techniques include in-office mopping with cotton swabs, suctioning to remove discharge and debris, and placing an ear wick to stent open an oedematous canal (Doshi *et al.*, 2009). Some practitioners use various powders to help dry the ear, many of which include topical antibiotics. One popular example is otic insufflation powder, which consists of a mixture of chloramphenicol, sulfamethoxazol, and amphotericin B (Fungizone). There is no consensus on how often to perform aural toilet or when to use insufflation powder, but in the case of previous treatment failure, the former can be performed daily, if feasible. Some practitioners recommend at least two to three times a week, depending on the severity and duration of symptoms (Dagan *et al.*, 1992; Daniel, 2012).

A small number of randomized controlled studies have shown that aural toilet is not effective as monotherapy and should be used in combination with medical therapy, ideally ototopical antibiotics in the treatment of CSOM. Otorrhoea resolved frequently in groups treated with a combination of aural toilet, topical and systemic antibiotics, and topical boric acid compared with aural toilet alone or with no specific therapy (Melaku & Lulseged, 1999; Choi *et al.*, 2010). Another trial demonstrated that children with CSOM treated with aural toilet and intravenous antibiotics improved more frequently compared with aural toilet alone (Fliss *et al.*, 1990).

## Ototopical antibiotics

Antibiotic drops in combination with aural toilet are the mainstay of therapy for CSOM and have been shown to be the most effective in randomized controlled trials. Quinolones are the most commonly used topical antibiotics in the USA due to their established effectiveness (Aslan *et al.*, 1998; Ohyama *et al.*, 1999). Topical quinolones carry a low side-effect profile and are superior to aminoglycosides (Nwabuisi & Ologe, 2002). Quinolones are particularly



effective against *P. aeruginosa* and do not carry a potential side effect of cochleotoxicity and vestibulotoxicity, which are attributed to aminoglycosides (Dohar *et al.*, 1996). A randomized controlled trial demonstrated that ciprofloxacin is more effective compared with aminoglycoside, and another study showed the efficacy of ofloxacin topical antibiotic over oral amoxicillin-clavulanic acid in resolving otorrhoea (Yuen *et al.*, 1994; Couzos *et al.*, 2003).

Corticosteroids are sometimes used in combination with quinolones for CSOM but are not well studied. Combination ear drops can be prescribed when there is inflammation of the external auditory canal or middle ear mucosa, or when granulation tissue is present. Dexamethasone is often used in combination with ciprofloxacin for these conditions (Shinkwin *et al.*, 1996; Hannley *et al.*, 2000; Acuin, 2007).

There are several alternative topical solutions that can be used in settings in which antibiotic drops are not readily available. These are used in developed countries but are much more common in resource-limited settings due to their low cost and availability. Some of these include acetic acid, aluminium acetate (Burrow's solution), or combinations of these (Domeboro's solution), and iodine-based antiseptic solutions. Few studies exist comparing these solutions with ototopical quinolones. However, one retrospective study showed that aluminium acetate solution was as effective as gentamicin in resolving otorrhoea (Clayton *et al.*, 1990). Also, 57 % of patients in another study had resolution of otorrhoea after acetic acid irrigations to their affected ear three times weekly for 3 weeks, in the absence of any other therapy (Aminifarshidmehr, 1996). Aluminium acetate can potentially be even more effective than acetic acid because of its increased activity against many of the pathogens *in vitro* (Thorp *et al.*, 1998). Povidone-iodine-based antiseptic solution has broad-spectrum action against many organisms that can colonize the middle ear – bacteria, viruses, fungi and protozoa. One randomized controlled trial demonstrated that povidone-iodine had the same efficacy as ciprofloxacin drops in resolving otorrhoea (Jaya *et al.*, 2003). Additionally, it was shown that bacterial resistance rates were much lower for iodine solution than for ciprofloxacin (Jaya *et al.*, 2003). Further large-scale studies are warranted to confirm the safety and efficacy of these topical agents in CSOM.

### Systemic antibiotics

Upon failure of primary treatment to resolve otorrhoea after 3 weeks of therapy, alternative measures must be considered. Oral antibiotics are a second-line therapy for CSOM. Systemic therapy has not been as effective as direct delivery of topical antibiotics due to the inability to achieve effective concentrations in the infected tissues of the middle ear. Multiple factors affect drug efficacy including bioavailability, organism resistance, scarring of middle ear tissues and decreased vascularization of middle ear mucosa in chronic disease (Macfadyen *et al.*, 2006; Daniel, 2012). Topical agents such as quinolones

are the drug of choice for the second-line therapy (Lang *et al.*, 1992; Kristo & Buljan, 2011). These, however, must be used with caution in children because of the potential for growth problems related to tendons and joints, and should be reserved for organisms that are otherwise resistant to other therapies or when there is no safe alternative. Amoxicillin/clavulanic acid (Augmentin) or erythromycin/sulfafurazole (Pediazole) are other antibiotics that are recommended for children.

Intravenous antibiotics have demonstrated efficacy against CSOM but are not the first-line treatment option for several reasons. Due to the risk of systemic side effects and increased potential to breed antibiotic resistance, intravenous antibiotics should be used as the last-line medical option for CSOM patients. When possible, antibiotics should be culture directed, and an infectious disease consultation should be sought, when available. Because the most common organisms encountered in CSOM are *P. aeruginosa* and methicillin-resistant *S. aureus* (MRSA), penicillin-based antibiotics and macrolides have very limited efficacy, as organism resistance rates are high (Brook, 1994; Campos *et al.*, 1995; Park *et al.*, 2008; Choi *et al.*, 2010). The most effective antibiotics for *P. aeruginosa* and MRSA are quinolones, such as ciprofloxacin, and a combination of vancomycin and trimethoprim-sulfamethoxazole (Bactrim), respectively (Park *et al.*, 2008). Other common antibiotics that can be used against *Pseudomonas* spp. include imipenem and aztreonam (Somekh & Cordova, 2000). In one study, *P. aeruginosa* isolates resistant to ciprofloxacin also demonstrated high resistance to aminoglycosides, piperacillin-tazobactam, and ceftazidime (Jang & Park, 2004), making these drugs less-than-ideal candidates for intravenous therapy. Despite the activity against the most common infectious agents, intravenous antibiotics are certainly not a panacea in CSOM. The cure rate of patients treated with culture-directed intravenous vancomycin in MRSA CSOM was similar to those treated with aural toilet and topical acetic acid and aluminium acetate solutions (Choi *et al.*, 2010). This further demonstrates the concept that ototopical treatment combined with aggressive aural toilet is the preferred primary therapeutic modality in CSOM. Systemic antibiotics should be used for various degrees of primary treatment failure or when intracranial complications ensue during CSOM.

### Surgery

Surgery should be considered as a last-line resort after maximal medical therapy has been exhausted for cases of CSOM that are particularly recalcitrant or recurrent. Surgery in the form of tympanomastoidectomy is also indicated in cases of CSOM in which there are complications, some of which could potentially be life threatening, such as significant hearing loss, facial nerve palsy, subperiosteal abscess, petrositis, dural venous sinus thrombosis, meningitis, cerebral abscess and labyrinthine fistula, among others (Kangsanarak *et al.*, 1993; Matin *et al.*, 1997;



Taylor & Berkowitz, 2004; Matanda *et al.*, 2005; Zanetti & Nassif, 2006; Dubey & Larawin, 2007; Akinpelu *et al.*, 2008; Mostafa *et al.*, 2009). Chronic cholesteatomatous OM requires surgery, usually in the form of tympanomastoidectomy in order to eradicate cholesteatoma, a usual underlying cause of chronic infection (Shirazi *et al.*, 2006). However, some retrospective studies show that there is no difference in outcomes of graft success rate or post-operative hearing with regard to whether mastoidectomy is performed in addition to tympanoplasty (Balyan *et al.*, 1997; Mishiro *et al.*, 2001). Mastoidectomy may be indicated to reduce the burden of disease in cases with abscess formation in the mastoid, tympanoplasty or recalcitrant disease (Collins *et al.*, 2003; Angeli *et al.*, 2006).

Tympanoplasty can be performed anywhere from 6 to 12 months after resolution of the infection. A large percentage of perforations will heal on their own after resolution of infection, but in those that do not, tympanoplasty is indicated to improve hearing and to help prevent recurrence of infection by closing off the middle ear space. In addition, patients must practice dry ear precautions to help decrease the rate of recurrent infection and otorrhoea (Bluestone, 1988).

## Recurrent disease

Recurrent CSOM (patients who develop CSOM, recover from disease and develop chronic infection again) is due to one or a combination of several factors. These include treatment with oral antibiotics alone, treatment with non-antibiotic drops, non-compliance with the treatment regimen, infection with resistant bacteria such as *P. aeruginosa* or MRSA, and the presence of cholesteatoma. Disease can also be particularly recalcitrant and recurrent in patients with a distorted ear anatomy or who are prone to infections.

Recurrent disease can be managed by ototopical antibiotic therapy during the active infection and by several additional methods to prevent relapse. The most conservative of these measures are dry ear precautions and aural toilet (Bluestone, 1988). Prophylactic antibiotics have been used but are not recommended to prevent recurrent disease, as this may lead to antibiotic resistance and difficulty with treatment in the future (Arguedas *et al.*, 1994). Upon resolution of the active infection, tympanoplasty may be performed to help prevent chronic drainage by sealing off the middle ear, assisting in proper Eustachian tube function, and preventing microbial entry into the middle ear space (Rickers *et al.*, 2006; Shim *et al.*, 2010). When a child develops recurrent disease, computed tomographic imaging of the temporal bones should be sought to evaluate for potential cholesteatoma or mastoid abscess formation, as these are surgically correctable causes of recurrent or persistent CSOM.

## Conclusions

CSOM is the most common chronic infectious disease worldwide. The factors underlying the pathogenesis of

CSOM are still poorly understood. There is an urgent need to focus research studies in the area of CSOM, which will open up avenues to design novel therapeutic studies against CSOM and hence prevent hearing loss. Medical and surgical options are limited, with side effects and risks, and sometimes are not successful in eliminating disease. Topical antibiotics, which are the first-line therapy of choice, are limited only to those that are not potentially ototoxic. Additionally, surgery carries the risks of worsening hearing, as well as the potential for damage to the facial nerve and resulting facial nerve paresis.

It is likely that some of the factors involved in AOM may also be involved in CSOM; however, it is also possible that there are significant differences that need to be elucidated in further studies. There is a need to characterize the role of immunity (both innate and adaptive) as it pertains to the transition from AOM to CSOM. Establishing animal models of CSOM will help in elucidating the role of microbial biofilms and virulence factors, as well as host factors in the CSOM pathogenesis. These models will also help in evaluating the potency and efficacy of novel treatment strategies against CSOM. Recently, a mouse model of CSOM has been reported (Santa Maria *et al.*, 2015) that can be explored to understand host-pathogen interactions during CSOM and the development of novel treatment modalities against the disease. Emerging new technologies such as systems biology approaches employing high-throughput multiomics techniques (genomics, transcriptomics, proteomics and metabolomics) can be used to construct predictive models of the networks and dynamic interactions between the biological components of the complex host-pathogen system. Advances in sequencing technology have revolutionized pathogen biology and opened up unprecedented opportunities to understand the pathologies of intractable infectious diseases. Development of computational methods to probe these 'ultra-fast' 'omics' data to discover new pathogens or deconstruct the molecular network underlying host-pathogen interactions is increasingly being pursued, and is likely to catalyse the development of new clinical approaches for tackling CSOM. Bacteriophages can be a viable option for the treatment of bacterial infections due to the emergence of multidrug-resistant strains (Samson *et al.*, 2013; Viertel *et al.*, 2014; Qadir, 2015). Bacteriophages are viruses that specifically and uniquely destroy bacteria. Bacteriophages are considered safe, economical, self-replicating and effective bactericidal agents (Golkar *et al.*, 2014; Jassim and Limoges, 2014). In a small controlled clinical trial with 24 patients, bacteriophages provided efficient protection and demonstrated efficacy against chronic otitis media caused by chemoresistant *P. aeruginosa* (Wright *et al.*, 2009). Further large-scale randomized double-blind clinical trials are warranted to explore the translational potential of bacteriophages against CSOM. In addition, studies are warranted to characterize middle ear and inner ear interactions during CSOM pathogenesis. This is especially true regarding the role of

inflammatory mediators that appear to be capable of crossing the round window membrane and causing potentially permanent hearing loss via damage to auditory hair cells. The identification of genetic and prognostic markers will help in predicting CSOM-susceptible individuals and possibly even novel therapeutic strategies. Understanding the molecular mechanisms leading to CSOM will provide avenues to design novel treatment modalities against the disease and consequent hearing loss.

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