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Newer modalities in otitis media

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Abstract
Otitis media continues to be one of the most frequent causes of outpatient visits, antibiotic prescriptions, and surgery in India, but there has been little advancement in the creation of new therapies for the prevention and treatment of this disorder, highlighting the urgent need for further research into the pathophysiology of this condition. New management guidelines for acute otitis media, chronic otitis media, and tympanostomy tube implantation have just been published. Exciting new technologies are being researched into creative ways to enhance the diagnosis of otitis media, as discussed in this article. Recent developments in mucosal immunology and genetics have provided hints about the pathophysiology underlining the predisposition for otitis media. Future work aimed at altering these pathophysiologic bases, maybe through transtympanic drug delivery devices, should have a significant impact on how this illness is managed. Recent years have witnessed significant advancements in the study of innovative approaches to the pathophysiology, diagnosis, and therapy of otitis media. Within the next few years, it's expected that approaches to significantly changing the diagnosis and treatment of the ailment will be integrated into clinical practise.

Keywords: Mucin MUC5B, optical coherence tomography, otitis media diagnosis, otitis media guidelines

Introduction
Otitis media (OM) refers to an inflammation in the middle ear cleft and is accompanied by effusion of fluids into the middle ear due to infection which may be associated with the presence or absence of tympanic membrane perforation [1-2]. The prevalence rate of ASOM in India is around 17-20%, CSOM is 7.8% and of OME is not yet known [3]. Acute Otitis Media (AOM) is characterised by abrupt onset MEE and acute middle ear inflammation. It frequently manifests with constitutional signs of infection such as fever and otalgia. Otitis medium with effusion (OME) is characterised by chronic MEE, most frequently mucoid, without fever or otalgia [4]. By the time they are 10, 80% of children have experienced at least one episode of OME, making it a fairly prevalent condition. When the inflammatory process calms down and MEE persists after an AOM, OME may develop as new-onset OME [5]. The most noticeable symptom of CSOM, which is described as chronic inflammation of the middle ear and mastoid cavity, is persistent or recurrent ear discharge through a hole in the tympanic membrane or a ventilation tube [6]. CSOM damages the middle ear ossicles and results in conductive hearing loss. Additionally, it raises the risk of neurological problems and persistent sensorineural hearing loss (hearing loss brought on by injury to the inner ear) [6]. Although the frequency of this illness varies greatly between nations, it is most prevalent in low- and middle-income nations [7].

Aetiopathogenesis
Role of Eustachian tube
The long-lasting dysfunction of the ET that follows the initial AOM attack in young infants is of enormous significance. In fact, the ET's primary responsibilities include the ventilation, protection, and cleaning of the middle ears, and they are crucial in deciding whether or not AOM will return. Each time the middle ear deglutitive, the tensor velum platinum muscle contracts, ventilating the middle ear and causing the air to equalize with atmospheric pressure. A negative pressure builds up inside the middle ear due to ET blockage, causing effusion and aspiration of nasopharyngeal secretions. Poor ventilation causes PO2 to drop,

which lowers polymorphonuclear cells' capacity to kill bacteria. Impaired clearance causes both aerobic and anaerobic microorganisms to proliferate in the middle ear. On the other hand, reflux otitis happens when the ET is less compliant due to aberrant flaccidity [8-9]. ET dysfunction is a serious issue in young children; the high frequency of AOM and the numerous relapses of each viral infection are both caused by the small diameter of the ET and its horizontal orientation. This explains the poor long-term prognosis shown in a prospective research by Damoiseaux *et al*. [10] that included 210 AOM patients less than 2 years of age.

Role of bacteria and virus

RSV (respiratory syncytial virus) is often contracted by infants during the first year of life. 42 infants with bronchiolitis, ages 2 to 24 months, were included in a prospective research [11] that revealed 26 of them had AOM at enrollment or within 10 days, and another 10 had OME. Just six patients were free of both AOM and OME over the course of a 3-week observation period. These results were supported by a more recent study that revealed 31% of patients with residual RSV antigen in the middle ear effusion returned despite a successful treatment for the initial AOM episode [12]. By cultivating the middle ear fluid, microorganisms may be discovered in 70% of AOM patients [9]. Streptococcus pneumonia and Haemophilus influenzae are the most frequently isolated species [13]. Nasopharyngeal aspirate culture might provide important details on the microorganisms causing AOM [14-17].

Other risk factors

Young children cannot fight encapsulated germs due to the immaturity of their immune systems. This explains both the protracted course of AOM and the high risk of recurrence, together with ET dysfunction. Passive smoking, younger siblings attending school, and siblings who have experienced AOM in the past are additional risk factors. These characteristics were discovered in a 1997 publication of a prospective research on 2,253 kids between the ages of 2 months and 2 years [18]. At 12 months and 24 months, respectively, 79% and 91% of patients had at least one episode of OME. The most significant risk variables were a lower socioeconomic position and recurrent exposure to other children at home or in day care centers. Breastfeeding and exposure to cigarette smoke had minimal impact on the result.

Signs and symptoms of Otitis Media

Although ear pain is the most common AOM symptom, only 50–60% of affected children report it [19-20]. Ear discomfort in young, preverbal children may be worse by ear manipulation (such as pulling, stroking, or holding), prolonged screaming, or changes in the child's sleep and behavior patterns [21]. Along with fever and vomiting, these symptoms are vague and do not distinguish between children with AOM and those with URTI [22]. MEE is necessary for the diagnosis of both AOM and OME, and its absence prevents the determination of either condition [21]. Moreover, the difficulty of verifying MEE in primary care settings contributes to the widespread overdiagnosis of AOM [23-25]. AOM (with acute tympanic membrane perforation or draining ventilation tube), CSOM (with chronic tympanic membrane perforation and persistent drainage), or acute otitis externa can all cause ear discharge or visible discharge in the external ear canal (inflammation of the external ear canal). Tympanic membrane bulging, seen by otoscopy, is a crucial diagnostic trait of AOM [21].

Diagnostic Modalities

Otoscopy is used to diagnose AOM, and a symptom severity scale can be used to further evaluate the condition. The main diagnostic method for OME is pneumatic otoscopy, with otomicroscopy and tympanometry serving as supportive tests. Parents can use acoustic reflectometry to evaluate MEE. Otoscopy or otomicroscopy can be used to identify tympanic membrane perforation related to CSOM, however for accurate visualization, ear discharge may need to be suctioned out. Because to its good diagnostic accuracy, pneumatic otoscopy has been recommended as the primary diagnostic procedure for OME [26]. Without a pneumatic bulb, otoscopy alone may miss OME since the tympanic membrane may seem normal and ear-related symptoms may be mild or nonexistent. On the other hand, pneumatic otoscopy can prevent erroneous OME diagnoses brought on by tympanic membrane surface abnormalities without MEE [26]. Tympanic membrane mobility that is clearly impeded during pneumatic otoscopy is significantly prognostic of OME [20, 27] and increases diagnostic precision compared to otoscopy alone [28-29]. Nonetheless, there are regional variations in the therapeutic applications of pneumatic otoscopy. Pneumatic otoscopy training for medical residents is difficult [21], but can be improved with a systematic, computerized programme that includes static and dynamic pictures of the tympanic membrane [24]. Middle ear function and tympanic membrane mobility are both measured objectively by tympanometry [30]. Tympanometry has a reduced specificity (50-75% versus 80% for tympanometry and pneumatic otoscopy, respectively) but comparable sensitivity (range: 90-94%) to pneumatic otoscopy for the diagnosis of OME [31]. Tympanometry in primary care settings has obstacles from equipment costs and a lack of training, although it is simpler to use and more effective in treating children with OM than pneumatic otoscopy [32]. The quantity of air in front of the probe, which is typically 0.3-0.9 ml in children, is another measurement made by tympanometry. A 226 Hz tone is often used for tympanometry, but for infants under 6 months of age, a 1,000 Hz probe tone works better because the 226 Hz tone is insensitive to MEE [33].

Symptoms severity scale for AOM

To gauge the severity of AOM, many validated parent-reported symptom measures have been created. The AOM Severity of Symptoms Scale (AOMSOS) is a 7-item scale with response options of "no," "a little," or "a lot" for the frequency of fever [34], irritability, difficulty sleeping, difficulty eating, ear discomfort, and ear pulling during the last 12 hours. While these signs and symptoms might be present to variable degrees in children with normal ears [19], the aggregate AOMSOS score distinguishes between children with AOM and those without AOM. The AOM Faces Scale (AOMFS), a different severity metric, employs a scale with seven options, with the values ranging from 1 (not present, not an issue) to 7 (severe problem) [35].

Acoustic Reflectometry

Higher reflectivity indicates a larger likelihood of MEE [36], according to acoustic reflectometry, which measures the

amount of sound that is reflected off the tympanic membrane. Easy usage, the lack of a hermetic seal requirement, and the availability of an affordable consumer version are advantages over tympanometry [37]. Parents may utilise these features to accurately monitor their child's middle ear health. Reflectometry is less sensitive and specific in other experiments. Reflectometry is more effective in excluding MEE in children because to its high specificity and negative predictive values than tympanometry in detecting MEE.

Optical Coherence Tomography

Real-time imaging technology called optical coherence tomography (OCT) is used to noninvasively examine human tissues. It generates 2D and 3D structural pictures with micron-scale resolution using a low-intensity light source. Due to the scattering of the imaging signal by fluid particles, the picture created by the reflected light is evaluated and may be used to identify fluid parameters and distinguish between air and fluid [38].

Management

Bacterial resistance is becoming a greater problem as a result of the overuse of antibiotics nowadays. According to the 2013 AAP guidelines, antibiotics are recommended for very young kids younger than 2 years old who have bilateral illness or a severe disease (temperature >39.8 degree, substantial otalgia, or toxic appearance). Recent research makes it abundantly evident that antibiotics help with symptom and illness resolution in these situations [39-40], with 10 days of therapy being preferable to 5 [41]. "Watchful waiting" is advised if the patient is older than 2 years old, has non-severe otitis media, or has a dubious diagnosis. Amoxicillin at a high dose (90 mg/kg) is typically the first course of therapy. Cefdinir and cefuroxime are two oral cephalosporins that are excellent alternatives if children are amoxicillin sensitive. High-dose amoxicillin-clavulanate or intramuscular ceftriaxone are advised if there is no improvement after 72 hours. Patients should receive clindamycin (30–40 mg/kg daily in three separate doses) with or without a cephalosporin if they have a severe type I allergy to penicillins [42]. Myringotomy should be taken into consideration in situations of recurring AOM. According to the most recent recommendations, tubes should be inserted if there have been three incidents in the previous six months or four in the previous year, and if MEE is present in one or both ears and present when the otolaryngologist examines the patient [43]. Most of the time, OME gets better on its own after 3 months. An otolaryngologist referral and a hearing test are necessary if MEE persists for more than three months. Surgery should be considered if OME lasts longer than three months, especially in children who are also at risk for other developmental delays such Down syndrome, autism, speech and language delay, irreversible hearing loss, craniofacial disorders, blindness, or overall developmental delay. Children should be checked every three to six months until there is no longer a MEE, according to the 2016 recommendations. It is inappropriate to provide antibiotics [26]. There are presently no nonsurgical treatments for MEE that have been shown to be more successful than placebo and spontaneous resolution. As a result, there is still a pressing need for treatment innovation to reduce these kids' surgical needs. Hearing loss, delayed speech development, the possibility of long-term middle ear damage, and recurrent infection are all symptoms of COM [44-46]. In the short term (less than four weeks), topical quinolone has been demonstrated to be more successful than no medication therapy, topical antiseptics, and systemic antibiotics for clearing CSOM-related aural discharge [47-48]. Quinolones have the benefit of being non-ototoxic [49], although the current evidence comparing the efficacy of quinolone--containing eardrops to those without is inconclusive [48]. CSOM patients may not benefit more from a combination of systemic and topical antibiotics than they would from topical antibiotics alone, according on limited research [47]. There were fewer postoperative tympanic membrane perforations with a cartilage graft but no differences in hearing according to two reviews comparing two different autologous graft materials to repair tympanic membrane perforation (i.e., temporalis muscle fascia tympanoplasty with cartilage tympanoplasty) [50-51]. Recent improvements in our understanding of the immunologic mechanisms underlying the progression of otitis media will probably contribute to the development of novel, noninvasive treatment options for this condition. The mucin glycoprotein MUC5B is the main mucin glycoprotein present in COM effusions, according to unbiased large-scale proteomic profiling that was used to characterize MEE [52]. Additionally, MEE was primarily composed at the macromolecular level by numerous neutrophil extracellular traps (NETs), which associate with MUC5B [53]. Muc5b is crucial for middle ear and upper airway defense, as shown by the fact that Muc5b null mice exhibit severe, spontaneous middle ear and upper airway infection [54]. Interestingly, mutations in the fucose transferase FUT2 gene, crucial for the glycosylation of mucins, have recently been linked to an increased risk of developing otitis media (55), raising the possibility that mucin glycosylation affects innate immune responses in the middle ear. Despite the fact that NETs and MUC5B are useful antimicrobial defense structures, their quick removal from airway surfaces is essential for avoiding the damaging consequences of inflammation [56-57]. Middle ear NETs can integrate into bacterial biofilms, which in some situations allows bacteria to proliferate despite bactericidal antibiotic treatment or to evade immune responses [58]. Recently, a therapy plan to treat chronic otitis media has been suggested: clearing middle ear NETs using DNAse treatment [59].

Transtympanic drug delivery

Effective transtympanic medication administration in children, without the requirement for systemic antibiotics, surgery, pain, or general anesthesia, would significantly enhance, and potentially even fundamentally transform, the way that children with AOM or COME are now treated. Higher antibiotic dosages could be topically administered to the middle ear in AOM instances without causing systemic side effects. It might be possible to provide drugs that target NETS, mucin viscosity, or biofilms in COM or CSOM. In the recent past, many strategies for transtympanic medication delivery have been established. The use of chemical permeability augmentation agents to enable the filtration of medications, such as antibiotics, into the ear may be the most developed method demonstrating safety and efficacy in chinchilla models [60]. Small molecules (or medications) can be actively delivered into the middle ear in ex-vivo models, according to a different method that was just reported [61]. Lastly, some researchers have suggested a

transtympanic approach utilizing magnets to drive drug-coated magnetic nanoparticles through the tympanic membrane [62]. One or more of these methods will probably be used in clinical trials in the upcoming years.

Conclusion

Recent years have witnessed significant advancements in the study of innovative approaches to the pathogenesis, diagnosis, and therapy of otitis media. Within the next several years, it's expected that approaches to significantly changing the diagnosis and treatment of the ailment will be integrated into clinical practice.

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