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Nicola Principi & Susanna Esposito

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Unsolved Problems and New Medical Approaches to Otitis Media

Nicola Principi[1], Susanna Esposito[2]

[1]Professor Emeritus of Pediatrics, Università degli Studi di Milano, via Festa del Perdono 7, 20122 Milan, Italy; [2]Pediatric Clinic, Pietro Barilla Children's Hospital, Department of Medicine and Surgery, University of Parma, Via Gramsci 14, 43126 Parma, Italy

Correspondence and requests for reprints should be addressed to:

Susanna Esposito

Pediatric Clinic

Pietro Barilla Children's Hospital

Department of Medicine and Surgery

University of Parma

Via Gramsci 14, 43126 Parma, Italy

E-mail: susanna.esposito@unimi.it

ABSTRACT

Introduction: Otitis media (OM) is a spectrum of infectious and inflammatory diseases that involve the middle ear. It includes acute otitis media (AOM), otitis media with effusion (OME) and chronic suppurative otitis media (CSOM).

Areas covered: This manuscript discusses some of the emerging and unsolved problems regarding OM, and some of the newly developed prophylactic and therapeutic medical measures.

Expert opinion: In recent years, considerable progress in the knowledge of OM physiopathology has been made. However, although extremely common, diseases included under OM have not been adequately studied, and many areas of development, evolution and possible treatments of these pathologies are not defined. It is necessary that these deficiencies be quickly overcome if we want to reduce the total burden of a group of diseases that still have extremely high medical, social and economic relevance.

Keywords: acute otitis media; antibiotic therapy; chronic suppurative otitis media; otitis media with effusion; vaccine.

ARTICLE HIGHLIGHTS

- Otitis media (OM) is a spectrum of infectious and inflammatory diseases that involve the middle ear. It includes acute otitis media (AOM), otitis media with effusion (OME) and chronic suppurative otitis media (CSOM). AOM is an acute disease, and OME can be both acute and chronic, whereas CSOM is a chronic condition.
- Alternative diagnostic and therapeutic approaches to identify and cure these cases have been proposed. Unfortunately, the best therapeutic solution for the various clinical manifestations has not yet been identified, and further studies are needed before new therapeutic proposals can be accepted.
- Although extremely common, diseases included under OM have not been adequately studied, and many areas of development, evolution and possible treatments of these pathologies are not defined. It is necessary that these deficiencies be quickly

overcome if we want to reduce the total burden of a group of diseases that still have extremely high medical, social and economic relevance.

- Probably closer is the advent of more effective prophylaxis measures that, directly addressed to OMA prevention, may also have positive implications on the incidence of OME and CSOM. New pneumococcal conjugate vaccines containing a greater number of pneumococcal serotypes and universal influenza vaccines based on conserved proteins are in advanced stages of development.

1.0 INTRODUCTION

Otitis media (OM) is a spectrum of infectious and inflammatory diseases that involve the middle ear [1]. It includes acute otitis media (AOM), otitis media with effusion (OME) and chronic suppurative otitis media (CSOM). AOM is an acute disease, and OME can be both acute and chronic, whereas CSOM is a chronic condition. All of them, particularly AOM and OME, are extremely common in children, particularly the youngest, due to the immaturity of the immune system, the high frequency of upper respiratory tract infections and the characteristics of the Eustachian tubes (smaller and more horizontal than in adults) [2]. Each of these middle ear diseases has different clinical manifestations and requires specific diagnostic, prophylactic and therapeutic approaches.

Despite their high frequency and the great number of studies specifically devoted to the identification of the most effective prophylaxis and treatment for AOM, OME and CSOM, several problems remain unsolved and are debated. Guidelines prepared by international scientific societies to rationalize approaches to OM diseases are frequently conflicting [3, 4]. Moreover, the need for more satisfactory prophylaxis and therapy of AOM, OME and CSOM has led to the development of a few new interventions, some of which have been tested in clinical practice [5, 6], though their clinical importance is not yet precisely defined.

In this paper, some of the emerging and unsolved problems regarding OM will be discussed, and some of the newly developed prophylactic and therapeutic medical measures will be evaluated.

2.0 ACUTE OTITIS MEDIA (AOM)

More than 70% of AOM cases are caused by bacteria as detection of viruses as the only cause of disease in children with AOM is relatively uncommon. However, viruses play

a relevant role in AOM development as episodes of AOM are almost systematically preceded by a viral upper respiratory tract infection (URTI). AOM is extremely common, as almost all children experience at least one episode of AOM before entering the school and many of them suffer from recurrent episodes in the same period [7, 8, 9, 10]. This causes important medical, social and economic effects and justifies the various attempts to prevent AOM, especially recurrences, that have been put into practice over time [11].

2.1 Acute otitis media (AOM) prevention

It was thought that the introduction of vaccines effective against some of the infectious agents that are directly or indirectly related to AOM development, such as pneumococcal conjugate vaccines (PCVs) and influenza vaccines (IVs), could significantly reduce AOM incidence. Unfortunately, the results were at least in part disappointing, as the total AOM incidence remained high and reduction was lower than expected [12**, 13]. Despite with differences among the studies [14, 15, 16], main reasons for reduced PCV efficacy were the development of serotype replacement, i.e., the emergence of pneumococcal serotypes not included in PCVs and the evidence that a number of AOM cases were due to nonencapsulated Streptococcus pneumoniae [17, 18], The poor influenza vaccination coverage [19*], together with the reduced efficacy of IVs in same influenza seasons [20], have profoundly limited the expected vaccine prevention of AOM.

In addition to vaccines, several other measures for AOM prophylaxis have been suggested [11]. None of them can be considered effective in all children, and in some cases, the real effectiveness of suggested measures is not definitively proven. Elimination or reduction of environmental factors that favour URTIs and AOM (passive smoking, crowded living conditions, living in areas with high air pollution, use of pacifiers, absence of breastfeeding, day-care attendance) can be effective [21*, 22], but they are very difficult to put into practice, particularly when several negative conditions occur simultaneously. On

the other hand, other factors associated with AOM development cannot be completely removed. Craniofacial abnormalities, neuromuscular disease, altered immunity and genetic mutations are stable conditions that cannot be modified or can be only marginally influenced [21*, 22]. Recently, a possible role of vitamin D (VD) in AOM prophylaxis has been suggested. Starting from the evidence that VD is actively involved in the regulation of innate and adaptive immune responses [23] and that low-VD status is associated with an increased occurrence of AOM [24], it was put forth that VD supplementation could be effective in reducing the risk of new AOM episodes in AOM-prone children. The validity of this supposition seems to have been confirmed by the results of a randomized, double blind, placebo-controlled trial performed in 116 children aged < 5 years with a history of recurrent AOM [25]. These patients were assigned to receive orally 1,000 IU of VD per day or placebo for 4 months, starting from the beginning of the winter season, and were monitored for 6 months. The number of patients who had at least one new episode of AOM during the study period was significantly lower among supplemented children than among those receiving placebo (44.8% vs 65.5%; p=0.03). However, subgroup analysis revealed that VD supplementation was effective only in children with a history of uncomplicated AOM, whereas it was ineffective in patients who had suffered from recurrent AOM with tympanic membrane perforation (TMP). Moreover, several factors indicate that, while interesting, the results of the study cannot be considered the basis for systematic VD supplementation in the attempt to prevent AOM, at least in children without recurrent TMP. The study enrolled white, healthy children and was carried out during the winter season in a country of the industrialized world with a temperate climate. Consequently, the results cannot be generalized because the VD requirement depends on season, skin pigmentation, sun exposure, consumption of vitamin D-fortified foods, body mass index, and the coexistence of certain medical conditions [26]. Moreover, controversies regarding the definition of hypovitaminosis and the choice of the most

reliable marker to establish VD status further complicate VD supplementation and its potential use for AOM prevention [27].

A second suggested prophylactic measure about which no definitive conclusions can be drawn is administration of probiotics given topically or by mouth. According to the WHO definition, probiotics are bacteria that confer a health benefit on the host when administered in adequate amounts [28]. The most commonly used are some species of *Lactobacillus, Bifidobacterium, Streptococcus* and *Saccharomyces*. The results of studies carried out in experimental animals and, more rarely, in humans seem to indicate that oral probiotics may reverse gut and respiratory tract dysbiosis, reduce or eliminate pathogens through competition for nutrients or adhesion sites on cell surfaces, produce bactericidal substances and modulate immune function [29]. However, their use in the prevention of AOM remains debated. A recent Cochrane review [30*] that included 16 randomized controlled trials showed that probiotics were effective in AOM prevention (relative risk [RR] 0.77, 95% confidence interval [CI] 0.63-0.93), but efficacy could be demonstrated only in children not prone to AOM (RR 0.64, 95% CI 0.49-0.84), whereas no effect was shown in children with recurrent AOM (RR 0.97, 95% CI 0.85-1.11). The authors concluded that, due to the inconsistency of the subgroup analyses, caution in interpreting these results had to be used.

Caution should also be used in the evaluation of the studies that have measured whether the topical administration of probiotics could prevent AOM. Most of them have significant methodological flaws and do not give reliable information. In one without methodological problems in which *Streptococcus salivarius* 24SMB was sprayed in the nasopharynx, efficacy was demonstrated only in a minority of children, those in whom treatment led to persistent colonization with the sprayed bacterial strain [31]. Finally, poorly evaluated is the use of prebiotics, i.e., non-digestible food ingredients that promote the

growth of probiotics [32], to prevent AOM. However, in this case, no definitive conclusions can be drawn. Studies are few and in some cases have negative results [33].

2.2 Acute otitis media (AOM) treatment

Although most AOM cases heal spontaneously in a few days, drug therapy in some children is essential to favour AOM resolution and avoid complications. Among these, OME and tympanic membrane perforation (TMP) are the most common. However, very severe clinical problems, such as mastoiditis, meningitis, brain abscess, and facial paralysis, can follow AOM [34]. As AOM is mainly due to bacteria, antibiotics effective against the pathogens that are commonly detected in the middle ear fluid as the cause of disease (*Streptococcus pneumoniae*, non-typeable (nt) *Haemophilus influenzae, Moraxella catarrhalis* and *Streptococcus pyogenes*, this last pathogen with wide variations in prevalence according to the geographic area were studies are performed [35, 36, 37, 38, 39, 40, 41] are the drugs of choice to treat AOM. However, to avoid antibiotic overuse and related problems, an accurate selection of children with AOM for whom an immediate antibiotic prescription is mandatory is recommended by several scientific societies [35, 36, 37, 38, 39, 40, 41]. Antibiotics are generally recommended in severe (moderate to severe otalgia and/or fever ≥39°C) or complicated cases, regardless of patient age and disease laterality. For mild cases, antibiotics are suggested in children aged 6-23 months with bilateral infection. In older children or in children aged 6-23 months with unilateral disease, antibiotic therapy or additional observation are possible choices. The decision depends on the parents/caregiver consent and the activation of a mechanism capable of ensuring follow-up and begin antibiotics if the child worsens or fails to improve within 48 to 72 hours of AOM onset. Considering that *S. pneumoniae* remains the most common cause of AOM and the aetiologic agent of the most severe cases [42], amoxicillin is indicated as the drug of choice for AOM treatment, eventually with higher-than-usual dosages in those

geographic areas where increased minimal inhibitory concentrations (MIC) of amoxicillin for this pathogen have been reported [42]. Use of amoxicillin-clavulanic acid or, in case of penicillin allergy, cefdinir, cefpodoxime, cefuroxime or ceftriaxone, is recommended in subjects who have received amoxicillin in the previous 30 days, in case of failure, in the presence of concurrent purulent conjunctivitis or when there is a history of recurrences that do not respond to amoxicillin. In these cases, AOM is mainly associated with beta-lactamase-producing pathogens, although beta-lactamase-nonproducing strains play a relevant role in some geographic areas [43]. Acetaminophen or ibuprofen is added to treat otalgia and fever. No other selection of AOM cases and no other drug are suggested. However, these guidelines can be debated, as some recent studies seem to indicate that for some AOM cases, a different approach could be followed. The dosages and route of administration of suggested antibiotics can be different from those usually prescribed [36, 37, 38] and other pharmacologic measures can play a role in favouring AOM resolution.

Two examples highlight the need for a revision of the current guidelines for AOM therapy. The first regards recurrent cases. As previously reported, these cases should be treated with a systemic beta-lactamase-resistant antibiotic at the usual dosage. However, recurrent AOM cases are frequently associated with bacteria, mainly nt *H. influenzae*, which can form biofilms [44, 45]. This structure makes eradication of pathogens significantly more difficult mainly because antibiotics and components of immunity cannot penetrate biofilms and reach pathogens in adequate concentrations [46]. This seems to suggest that in cases of frequent recurrence, to eradicate the infecting bacteria and avoid new episodes, adequate microbiological evaluations [47] could be made, and if biofilm is detected, local antibiotic therapy capable of reaching effective antibiotic concentrations in the middle ear could be prescribed. Alternatively, or in association, systemic therapy at higher dosage should be prescribed, but only if the increase is not a risk for drug-related adverse events [48]. Further advantages could be given by the inhibition of biofilm

formation or eradication of established biofilm. Measuresto inhibit biofilm formation have been proposed [49*], including the use of degrading enzymes, lytic phages, and vaccines against nt *H. influenzae* components that play a fundamental role in bacterial virulence and biofilm formation [49*, 50]. Unfortunately, these measures are presently only experimental and deserve evaluation in clinical trials before use in children. A potential positive effect could be obtained with N-acetylcysteine (NAC), which has good antibacterial properties and has been found able to interfere with biofilm formation in several *in vitro* studies. Unfortunately, clinical studies on the use of NAC in disruption of biofilm formation are few and not conclusive, although there is some evidence that NAC alone or in combination with antibiotics can decrease the risk of exacerbations of chronic bronchitis, chronic obstructive pulmonary disease, and rhinosinusitis [51].

The second example is the cases of AOM complicated by TMP. AOM with TMP seems a particular type of AOM even though in the official guidelines AOM with TMP is not differentiated from the uncomplicated AOM case. Children with AOM and TMP are at increased risk of further AOM episodes with this complication [52]. Compared to in children with recurrent uncomplicated AOM, in children with recurrent AOM and TMP, prevention of new AOM episodes with the influenza vaccine [53] or VD supplementation [25] is significantly less effective. Moreover, a genetic contribution to TMP development is strongly suggested by the evidence that several genetic polymorphisms in genes that encode factors of immunity have been identified in children with AOM and repeated TMP [54]. Finally, it has been shown that, contrarily to uncomplicated AOM, for which *S. pneumoniae* is the most common pathogen, nt *H. influenzae* is the most common aetiologic agent of AOM with TMP, particularly in recurrent episodes [52]. All these findings suggest that attention should be paid to AOM with TMP. In particular, as the incidence of resistance to amoxicillin among nt *H. influenzae* clinical isolates is generally high [55], the use of a beta-lactamase-resistant drug since the first TMP episode could be

recommended. Moreover, as nt *H. influenzae* can form biofilms, all the measures previously suggested to treat cases complicated by this microbiological problem could be considered.

Among the new therapeutic measures, the use of antibiotic preparations able to penetrate the inflamed but intact tympanic membrane, reaching in the middle ear concentrations higher than the MIC of the infecting bacteria, has been proposed. Nanovesicles and nanoliposomes containing antibiotics, mainly fluoroquinolones, have been developed and found to be effective in experimental animals [56]. Moreover, the use of bacteriophages or peptides identified through the phage [57] has been suggested. Despite being interesting, both of these solutions are only in a very early stage of development and cannot be considered for AOM therapy [58**].

3.0 OTITIS MEDIA WITH EFFUSION (OME)

OME, also named glue ear, secretory otitis media or nonsuppurative otitis media, is an inflammatory condition characterized by the presence of fluid in the middle ear without signs or symptoms of active infection [59, 60]. Although sometimes diagnosed in adults [58], it is considered a typical paediatric disease because approximately 90% of children suffer from OME before school entry [60], with the greatest frequency during the first two years of age, when the prevalence in the paediatric population is more than 60% [60, 61]. OME can be acute and is usually diagnosed during or immediately after a URTI, mainly AOM. Fortunately, in most patients, acute OME tends to solve spontaneously within 3 months and does not cause significant sequelae. However, at least 25% of acute OME episodes do not resolve within this period. Middle ear fluid is not reabsorbed and persists longer. Moreover, approximately one third of the patients with a first episode of OME have recurrences within a short time. This means that many children suffer from chronic or recurrent OME that can lead to hearing loss lasting several months and, in the most

enduring cases, to ear discomfort, vestibular and behavioural problems, poor school performance, speech abnormalities and reduced quality of life [62]. The risk of developmental difficulties is greater in subjects who already suffer from developmental or craniofacial disorders but is also relevant in otherwise healthy subjects. However, even in chronic cases, spontaneous healing can occur without sequelae.

Because of the possibility of a spontaneous resolution, the therapeutic approach is largely debated. A good example in this regard is the strong discrepancies between clinical practice and expert recommendations in the use of drugs and surgery to treat OME [63]. Drugs not recommended by official guidelines are overused by paediatricians and otolaryngologists. Adherence to recommendations for tympanostomy tube insertion and adenoidectomy is poor [64, 65]. However, guidelines do not always allow us to decide what is the best for the individual patient. It is well defined that children with the first OME episode should be managed with watchful waiting for 3 months. It is equally clear that medical therapy based on steroids, antibiotics, antihistamines or decongestants is not recommended, as the efficacy of these drugs is considered of questionable clinical significance, they bring a risk of adverse events, and they are not cost-effective [66]. No mention of auto-inflation is made in American guidelines [67], whereas this measure is recommended in European guidelines [68] because considered effective on the base of some randomized studies [69]. Indications for surgery in children with persistent or recurrent (i.e., three episodes in 6 months or 4 episodes in one year with one episode in the preceding 6 months) OME are poorly detailed. Myringotomy and especially tympanostomy tube insertion are strongly recommended based on auditory tests, the child's context and overall hearing difficulties, although much discretion is left to the surgeon [67]. Moreover, the real importance of these therapeutic measures remains undefined. Efficacy is very variable because it is strongly influenced by several factors, including current age, age at first diagnosis, frequency of URTIs, and day care admission.

However, criteria for the differentiation of children who are likely to benefit from surgery are not precisely defined. A recent meta-analysis has shown that tubes are effective only as long as they remain in place [70]. Unfortunately, they are frequently extruded within a few months, and long-term effects are not maintained. This explains why in children with tubes it has been found that ear thresholds are improved at one-three months but are much like those found in untreated children by one to two years after surgery. Substantial long-term changes in ear function and delays in language, cognition and behaviour have not been demonstrated. Finally, tympanostomy tube insertion is not free from adverse events. Although the incidence of surgery-related problems significantly differs among studies, cases of otorrhea, myringosclerosis, atrophy, atelectasis or retraction of the tympanic membrane following tube insertion have been repeatedly reported in a relevant number of patients with OME treated with surgery [71].

If the present approach to OME cannot be considered satisfactory, what are the potential improvements? First, it must be highlighted that the use of measures that can reduce the incidence of AOM can inevitably lead to reduced OME incidence. Moreover, a more in-depth analysis of factors that are associated with OME development could offer some suggestions for a different and potentially more effective treatment of OME. Drugs such as antibiotics, steroids and antihistamines could be revalued. Recurrent OME episodes or chronic OME frequently occur in children who suffer from repeated URTIs and/or hypertrophic, chronically inflamed adenoids [72]. In both cases, biofilm could play a role in conditioning recurrences and poor response to antibiotic treatment. Although with exceptions [73], nasopharyngeal and adenoidal biofilm has been documented more frequently in children with OME than in subjects without [74, 75]. Moreover, studies carried out with molecular methods have shown that, contrary to what was thought when traditional culture methods were used, OME was not a bacteriologically sterile condition. Otopathogenic biofilms colonizing the middle ear could be demonstrated in a significant

number of children with this disease [76]. Moreover, it has been recently reported that *Pseudomonas aeruginosa* can be detected in the middle ear fluid of children living in the tropical and humid regions [77]. This seems to suggest that, at least in subjects in whom biofilms are detected in the middle ear, attempts to dissolve biofilm with appropriate topical antibiotic therapy and non-antibiotic measures could be effective for OME treatment, as previously reported for recurrent AOM.

Further evidence of the potential effectiveness of antibiotic administration in selected OME cases is given by the potential association between the middle ear effusion microbiome and secretory mucin production leading to OME. Although mucins are part of the innate immune system, as they entrap pathogens [78], excessive production becomes harmful because it alters middle ear fluid characteristics and reduces bacterial clearance. The expression of mucin genes, mainly MUC5B, is more elevated in patients with OME than in those without and is strictly associated with effusion viscosity and middle ear inflammation [79]. Multiple ear infections are associated with a gradual transformation of the epithelium of the middle ear that becomes capable of secreting mucins, the most predominant components of the middle ear effusion. Secretion is triggered by bacteria and proinflammatory cytokines [80], and it has been demonstrated that the middle ear effusion microbiome of children with OME and hearing loss has a specific composition that leads to mucin production and OME [81]. Starting from this evidence, it could be supposed that measurement of *MUC5B* expression could allow the identification of subjects at greatest risk of OME development, for whom an early evaluation of middle ear microbiome characteristics and effective antibiotic administration could be potentially effective in reducing this risk. Moreover, intervention for mucin production could be considered a possible future approach to OME treatment [82].

A reassessment of the role of steroids and antihistamines could start from the evidence that OME is frequently associated with respiratory allergy [83, 84, 85, 86, 87].

Studies specifically planned to measure the importance of these drugs to treat OME were generally negative, and this led health authorities to strongly recommend their use in OME. However, in most of the studies evaluating the impact of steroids [88, 89, 90, 91] and antihistamines [92, 93, 94] in children with OME, the allergy status of the enrolled patients was not assessed, and this could have strongly influenced the final results and led to incorrect conclusions. Studies enrolling only children with demonstrated allergies are urgently needed to definitively determine the role of steroids and antihistamines for OME treatment.

Finally, the supplementation of VD to treat OME has uncertain efficacy. Some studies seem to indicate that VD deficiency is significantly more common among OME children than in healthy controls, but no definitive conclusion can be drawn on the real efficacy of supplementation on OME resolution [95].

4.0 CHRONIC SUPPURATIVE OTITIS MEDIA (CSOM)

CSOM, also named chronic otitis media (COM), is a chronic inflammation and infection of the middle ear and mastoid cavity, characterized by otorrhea through a TMP. The duration of discharge that defines chronicity is not precisely established, as some authors consider 2 weeks, others 6 weeks and still others 3 months [96]. It has been calculated that CSOM has a global incidence of 31 million episodes per year, of which approximately 25% of the cases are in children < 5 years, mainly in middle- and low-income countries [97].

CSOM is one of the leading causes of acquired and preventable hearing loss [98]. Previous AOM, especially recurrent AOM, is the basis for CSOM development. It is highly likely that at least some of the risk factors for AOM development play a role in CSOM determination and that measures that can contribute to AOM prevention can also be effective for CSOM prophylaxis. *P. aeruginosa* and *S. aureus* are the most common

aetiologic agents. Conservative management is the initial choice for all CSOM cases. Surgery is reserved for patients who do not respond to medical treatment or when complications arise. Topical antibiotics with or without steroids, systemic antibiotics, topical antiseptics and aural toileting can be used to treat CSOM [99]. Each of these measures can be used alone or in combination with one or more of the others. What is the best solution to achieve pathogen eradication and complete drying of the ear is not precisely defined, although antibiotics remain a fundamental component of drug therapy. It seems well supported that, although local discomfort, ear pain or itching may accompany putting ear drops into the ear, local antibiotic administration should be preferred to systemic administration, except in cases with small TMP and difficult-to-remove pus. Quinolones (ciprofloxacin, ofloxacin, levofloxacin) and aminoglycosides (gentamicin, neomycin, polymyxin B) are the drugs most frequently prescribed. Preference for local therapy is based on the evidence that it can be carried out in the outpatient setting, is less expensive and is considered generally more effective than systemic therapy [99]. This last advantage seems related to the higher antibiotic concentrations obtained in the middle ear, where the pathogens are, and is confirmed by the conclusions of a meta-analysis including randomized controlled trials [100] showing the superiority of local quinolones over systemic therapy.

However, several aspects of local antibiotic therapy of CSOM are presently unsolved. The duration of treatment is not codified. In most cases, 1-2 weeks are sufficient, but it is not known whether a longer duration can reduce the risk of recurrences [101]. Moreover, the superiority of quinolones over aminoglycosides is debated [101]. Finally, it is not definitively established whether, how and when antibiotics should be given together with antiseptics or ear cleaning. The worth of topical steroids is also unresolved. They are given with the intent of reducing inflammation of the middle ear mucosa to prevent bacterial colonization and to prevent allergic sensitivity to antibiotics. However, the

results of clinical trials are conflicting. In some cases, an advantage has been found with a more rapid normalization of the middle ear picture [101]. In other cases, outcomes were not improved [102], or fungal overgrowth was evidenced [103]. Finally, ear cleaning, although considered essential as if the ear canal is blocked by secretion topical antibiotics cannot reach the site of the infection, is not precisely defined. How, when and whether alone or in association with drugs is not clarified. On the other hand, the need for establishing the importance of the various treatment options is needed, so a series of comparative Cochrane meta-analyses regarding all the drugs and measures usually considered for CSOM has been planned. The results are not yet available, but it is likely that it will be able to clarify at least some of the unsolved problems regarding the CSOM approach [104].

5.0 CONCLUSIONS

In recent years, considerable progress in the knowledge of OM physiopathology has been made. This has allowed us to understand, at least in part, the reasons why the official guidelines on prophylaxis and therapy of inflammatory/infectious middle ear diseases are not always satisfactory. Although the role of polymicrobial interactions, bacterial response to host innate immune components, host environmental influences, and bacterial adaptation and evolution in conditioning development and persistence of OM is not precisely defined, recent studies have clearly evidenced that not all cases of AOM and OME have similar clinical characteristics and that in some cases, the traditional therapeutic approach is not effective. Examples of recurrent AOM, AOM with TMP and chronic OME with an altered middle ear microbiome are significant in this regard.

Alternative diagnostic and therapeutic approaches to identify and cure these cases have been proposed. Unfortunately, the best therapeutic solution for the various clinical manifestations has not yet been identified, and further studies are needed before new

therapeutic proposals can be accepted. Moreover, it has clearly emerged that in some cases, most of the problems that should be solved because antibiotic therapy can be effective are not actually clearly defined. An example of AOM and OME due to biofilm-forming bacteria and CSOM is paradigmatic in this regard. Biofilm increases the MIC of pathogens, and antibiotics have to be administered at higher concentrations or directly in the middle ear to be effective. The addition of measures that favour biofilm eradication can improve antibiotic efficacy. Regarding CSOM, suggestions for antibiotic choice and administration are coarse, mainly because there are not adequate studies capable of indicating which are the most effective short-term and long-term therapies.

In general, it seems clear that, although extremely common, diseases included under OM have not been adequately studied, and many areas of development, evolution and possible treatments of these pathologies are not defined. It is necessary that these deficiencies be quickly overcome if we want to reduce the total burden of a group of diseases that still have extremely high medical, social and economic relevance.

6.0 EXPERT OPINION

Recent studies indicate that all the diseases that are globally defined as OM remain a relevant clinical problem with important social and economic consequences. The new prophylactic and therapeutic measures that take into account what has been recently discovered on the pathophysiology of individual middle ear diseases can make a significant contribution to the resolution of many problems. However, it should be considered that many new therapeutic proposals, although extremely interesting, have not yet been tested in adequate clinical trials in humans, and therefore, if effective, they will be available for clinical use only many years from now. The example of cases in which biofilm formation plays a relevant role in conditioning a poor response to usually recommended antibiotic therapy, increased risk or recurrence and greater probability of chronicity clearly

illustrates the difficulties of implementing therapies that effectively address emerging needs. Attempts to intervene in all stages of biofilm development have been made. Strategies to prevent microbial adhesion to host cells, to block the synthesis of the extracellular polymeric substance (EPS) matrix, and to favour EPS degradation were put in place, in several cases with satisfactory results. However, most of the studies were carried out *in vitro* and in experimental animals, and only a few clinical trials have been performed. However, none of them was carried out in children with OM [105].

Probably closer is the advent of more effective prophylaxis measures that, directly addressed to OMA prevention, may also have positive implications on the incidence of OME and CSOM. New pneumococcal conjugate vaccines containing a greater number of pneumococcal serotypes are in advanced stages of development [106*, 107**]. To definitively overcome the replacement-related problems, the development of vaccines based on conserved pneumococcal protein antigens could potentially provide protection against all the *S. pneumoniae* serotypes [108]. Preparations containing pneumolysin toxoid and pneumococcal histidine-triad protein D have already been tested in children in phase II clinical trials and were found to be immunogenic and well tolerated. Simultaneous administration with other routinely administered paediatric vaccines did not influence the immune response of any vaccine preparation [109]. Similar conclusions could be drawn for the prevention of viral infections that directly or indirectly cause AOM. Universal influenza vaccines based on conserved proteins can overcome the risk of poor matching between strains included in the vaccine and circulating viruses, thus reducing vaccine effectiveness [110]. Additionally, in this case, studies are advanced, and it is thought that within 10 years, an affordable universal vaccine will be available [111]. Further reduction of viral URTIs could be obtained by the introduction of vaccines against respiratory syncytial virus [112, 113].

Awaiting the new potentially effective prophylactic and therapeutic measures, presently available guidelines and recommendations for OM approach remain essential. Although largely perfectible, they still represent the best solution to ensure an acceptable approach to OM, improving its diagnosis, reducing antibiotic abuse and misuse and avoiding unneeded surgery.

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