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Bench and Bedside Advances in Otitis Media

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Abstract

Purpose of review—Otitis media continues to be an important pediatric illness and requires significant expenditures in management and treatment. Despite its prevalence and importance clinicians often have significant knowledge deficits regarding the most up-to-date research or clinical thinking regarding this disease. This review aims to discuss recent and important publications related to otitis media and present an analysis of some of these findings.

Recent findings—Major basic science and clinical themes related to otitis media are discussed and include: the importance of biofilms in otitis media pathogenesis, the evidence that otitis media with effusion impacts development, the impact of otitis media treatment on quality of life, risk factors associated with otitis media and current concepts with respect to vaccine strategies and otitis media.

Summary—Important basic and clinical research in the field of otitis media continues to clarify our understanding of the pathogenesis of this disease and drive new paradigms in treatment and clinical management.

Keywords

otitis media; biofilm; development; quality of life; vaccine

Introduction

Otitis media (OM) continues to be one of the most common reasons for children to see a physician, affects virtually all children in one fashion or another and annually requires billions of dollars in health care expenditures for treatment. Antibiotic resistance has made OM treatment more challenging. Given all of these factors, there continues to be a need for significantly more research into the pathophysiology, clinical management and outcomes of therapy of this disease process. Despite the fact that OM is relatively understudied, there are a number of areas in which significant progress has been made and it is beyond the scope of this work to highlight or catalogue each of these areas. Instead, the focus of this manuscript will be to highlight some of the most important areas of recent investigation from both a basic science and clinical perspective.

Molecular Biology

In the area of basic molecular biology one of the most important advances has been the demonstration that OM, as a chronic infectious disease, represents a human pathologic condition associated with biofilm development. Although the concept that biofilms are the primary source of bacterial infection in chronic forms of OM is novel, the association of biofilms with other chronic forms of infection is certainly not ¹⁻⁴. It has long been recognized that most bacteria in nature exist in a biofilm state as opposed to the small percentage of bacteria that live in a planktonic or free-swimming state. In the planktonic state bacteria are capable of producing host responses which are generally associated with acute infections: fever, inflammation, cellular damage and leukocyte stimulation. However, pathologic conditions in which bacteria form biofilms also have numerous clinical implications. In the biofilm state, bacteria become organized, anchor to a surface and form a microcolony surrounded by a complex polymeric matrix that is constantly being remodeled that includes polysaccharides, nucleic acids, and proteins that are secreted by the bacteria themselves. Bacteria in the biofilm state maintain a low metabolic rate, are able to escape host immune surveillance and rapidly share genetic information. These characteristics make biofilm bacteria difficult to culture using standard techniques, difficult to eradicate with antimicrobial compounds and allows for the development of effective and widespread antimicrobial resistance characteristics. Evidence that chronic OM is the result of a biofilm infection has been demonstrated by a number of well-designed studies ^{5, 6}. However, recent identification of bacterial biofilms in children with recurrent acute otitis media (RecOM) and chronic otitis media with effusion (OME), and not in control populations (**), has brought this OM biofilm discussion from a basic science, theoretical discussion to a clinical one. With the demonstration of biofilms in children with chronic OM, and the likelihood that these biofilms play a role in the pathogenesis of OM, important clinical questions require additional scrutiny including: 1) what are the implications for OM treatment and pathogen eradication with a knowledge that middle ear pathogens routinely achieve biofilm formation and that this environment enhances their ability to develop and acquire antimicrobial resistance? 2) early onset of OM media increases the likelihood of developing chronic disease – what are the implications of biofilm formation in these patients and the best strategies for prevention? 3) what will be the clinical impact of anti-biofilm interventions? As middle ear biofilms likely originate in the nasopharynx this may include strategies such as reduction of nasopharyngeal biofilm through surgical (adenoidectomy), mechanical or pharmacologic (nasal irrigations or medications designed to reduce biofilm formation) means. With respect to RecOM, the somewhat unexpected finding of biofilms in each of the patients with chronic RecOM also raises important questions with respect to pathogenesis. It has been postulated that each of these recurrent infections represented a new episode caused by a unique bacterial strain ascending through the nasopharynx and Eustachian tube into the middle-ear space ⁸. However, these findings would suggest that viable bacteria are capable of residing as biofilms within the middle-ear space in between acute exacerbations of bacterial infection and that, at least in part, may be responsible for the recrudescence of these acute infections through planktonic showering of bacteria from the biofilm. Other studies would support this hypothesis and have demonstrated that approximately 30% of cases of recurrent OM result from relapses attributable to the original

organism⁸. In addition, surgical intervention with tympanostomy tubes (TT) for patients with RecOM and OME, known to be clinically efficacious, will need further examination with a biofilm concept of pathogenesis. This includes not only initial placement of TT but potential complications such as chronic otorrhea from the TT (*).

It is important to point out that the findings from these studies do not exclude other potential pathogenic factors associated with chronic OM. Important associations such as an antecedent viral upper respiratory infection, eustachian tube dysfunction, a genetically predisposed host, persistent inflammatory mediators, or exacerbation by gastroesophageal reflux could each be incorporated into the concept of facilitating biofilm formation. While these factors may also be independently associated with OM chronicity the ubiquitous presence of biofilms in patients with chronic OM would suggest that investigations aimed at linking these factors to biofilm formation may provide significant scientific advances toward understanding chronic OM and developing novel treatment regimens.

Developmental Impact, Outcomes and Quality of Life in Patients with OM

Studies examining outcomes of patients with OM have been extremely important in recent years. One of the most important areas of discussion has centered around the impact of children with chronic otitis media with effusion (OME) and the long-term impact this may have on children with respect to development. In a recently published study following children long-term (**), 6350 infants were enrolled after birth. Subsequently 429 healthy kids developed persistent middle ear effusion (MEE) and were randomized before 3 years of age to undergo bilateral tympanostomy tube placement (TT) promptly or to wait 9 months and undergo TT if the effusion was still present. Of these children 391 were then assessed for literacy, attention, social skills and academic achievement at 9-11 years of age. This study did not find a difference between patients that received prompt intervention with TT and those who received them later.

Unfortunately, the data from this study has been often misinterpreted and led to erroneous clinical assumptions not supported by the evidence presented in the study. The authors are careful to point out that their findings cannot be generalized to children who are not otherwise healthy or have disabilities such as sensorineural hearing loss, speech delay or Down's syndrome; or to children in whom effusion is consistently accompanied by greater levels of hearing loss than those in the study. And although patients with these types of characteristics are relatively rare in the general population they are quite common in the group of patients who are referred for surgical consideration. In a recent review of surgical patients, 50% of 168 children had developmental delays prior to tube placement and would have been in an at risk not eligible for the above study. In addition to this, there are a number of methodological aspects of this data set which need consideration before making the assumption that even healthy children do not benefit from early intervention with TT tubes. Only a small percentage of patients studied had bilateral MEE for more than 90 days (27%) while 60% had unilateral effusions. Obviously patients with unilateral disease would be expected to have normal hearing in the unaffected ear and these patients would not be expected to demonstrate developmental delays even if treatment were delayed. In contrast, in a recent examination of children undergoing surgical intervention for OME, these patients

had much more severe disease with 86% having bilateral MEE and an additional 10% demonstrating bilateral ear disease related to changes in the tympanic membrane associated with retraction ¹¹. An important point not evident from cursory examination of the patient set is that 50% of the patients originally randomized into the delayed group crossed over to the treatment group in less than 9 months because of parental preference. This almost undoubtedly represents a significant bias in the patient analysis given that the most likely factors influencing patient cross over would be more severe or progressive disease; removing the most severely affected patients from the observational group. In addition, it needs to be mentioned that a majority of patients (56%) that are referred for surgical intervention for OME are also affected by RecOM as an additional consideration for TT placement ¹¹. Other studies have demonstrated some likelihood that OM may affect development ^{12, 13} and, importantly, these tended to be larger population studies which did not aggressively screen for patient enrollment, therefore, more likely capturing patients that would ordinarily present to a physician with disease. One such study demonstrated that children with OM had poorer receptive and expressive language at age 2-5 yr ($p < .01$) ¹⁴. Finally, a number of studies have demonstrated conclusively that children with OM and OME benefit significantly from surgical intervention with improved quality of life (**), ¹⁶. Taken in aggregate, these data can most appropriately be summarized as: healthy children enrolled in a study with aggressive screening procedures to identify children who develop MEE and with minimal difficulty from MEE, such as unilateral fluid, and without significant other health considerations are not likely to have significant developmental delays if monitored closely without surgical intervention. However, more significantly affected children are likely to benefit from surgical intervention and have significant improvement in their quality of life. Fortunately, studies examining patients undergoing surgical intervention, which are more likely to demonstrate real-world practice patterns, indicate that referred patients and those operated upon have a much higher severity of disease and associated other medical conditions.

Surgical Outcomes

One additional area to address within the realm of outcomes is surgical outcomes. TT placement is the most common surgical procedure performed in children beside circumcision. Despite over a million procedures being performed in the US alone, very little data exists with respect to the variety of surgical techniques and procedures. As with any surgical procedure, TT placement does have the potential for morbidity. These are generally small difficulties, but this procedure has been associated with hearing loss, retained tubes which require removal, tympanic membrane perforation and cholesteatoma formation. Studies examining the risk of tympanic membrane perforation have identified that longer-lasting TT such as T-tubes present an increase risk of perforation. Additional retrospective studies have analyzed specific types of tubes which remain for a shorter period of time, such as Armstrong beveled-bobbin tubes, and have found them to be safe without any significant incidence of complication ¹⁷. However the large, prospective studies examining surgical outcomes that have been lacking are currently underway ¹⁸.

Vaccines

An additional area of fertile investigation with respect to OM is in the arena of vaccine development. This area of investigation has included both viral and bacterial vaccine development given that many episodes of bacterial OM are preceded by a viral upper respiratory tract infection. Of the major upper respiratory viral pathogens associated with OM, only the influenza vaccine has been reliably tested and demonstrated to have the potential for reduction in OM episodes¹⁹. Similarly, although there exists promise for the development of bacterial vaccines against the major OM bacterial pathogens the results to date have been somewhat limited. The only major OM pathogen to achieve successful vaccination has been for that of *Streptococcus pneumoniae*. And although the pneumococcal conjugate vaccine has provided improved immunogenicity compared with previous pneumococcal vaccines it has provided only modest reduction in OM episodes in the range of 6 to 7%²⁰. This has been related to the fact that, even in vaccinated children, the efficacy of the vaccine is somewhat lacking and a relatively high rate of infection can occur with the serotypes covered by the vaccine²¹. Additionally, the conjugate vaccine utilized in the US is only a heptavalent vaccine. Although it is designed to protect against the serotypes most likely to demonstrate antimicrobial resistance it has been demonstrated that following vaccination the nasopharynx of children becomes colonized with other serotypes of pneumococcus which also have the potential for pathogenesis and development of antimicrobial resistance (*), (**)

Of clinical importance with the widespread utilization of the pneumococcal conjugate vaccine is also the increased incidence of non-typeable *Haemophilus influenzae* (NTHi) OM infections. Given this increased incidence and the overall association of NTHi with the development of chronic OM, ongoing efforts at developing NTHi vaccines have moved forward. It is beyond the scope of this manuscript to outline all of the promising venues in this research. However, one interesting development is the utilization of protein D, which has demonstrated efficacy in limiting both pneumococcal and NTHi OM in both animals and a recent human trial²⁴ (**). It is clear that significant progress continues to be made in many other areas as well (*), (*) and that development of an effective NTHi vaccine will reach fruition, which in turn, will have a major impact on the management of OM.

Risk Factors and OM

Another area of some progress in the field of OM has been the assessment of risk factors in patients. Along with a better understanding of pathogenesis and the development of new vaccine strategies this perhaps holds the greatest promise in allowing clinicians to effectively manage patients with OM. In the discussion about which patients benefit from surgical intervention compared with watchful waiting it is clear that patients with elevated risk for developmental delay, speech delay or who have other medical problems should be managed differently than children without these difficulties. Thoughtful investigations to more clearly define the parameters around these clinical decisions are important. Additionally, the concept of risk assessment has allowed for a more individualized approach in the management of acute OM (AOM). With an understanding that a large percentage of episodes of AOM can resolve spontaneously and that there are differences in managing risks

associated with AOM based on patient age ²⁷, there has been a trend toward fewer antibiotic prescriptions and managing, especially older children, expectantly, with utilization of antimicrobial therapy in AOM for younger children and those without resolution of symptoms in one to two days.

Additionally genomic characterization of individuals holds great potential to allow clinicians to make individual decisions for patients in the future. It has been demonstrated conclusively that there is a strong genetic component to susceptibility and likely morbidity associated with OM ²⁸. Undoubtedly there are many genetic factors that are implicated in OM which will make deciphering the role of any specific gene complex. Added to this complexity is the certainty that environmental influences such as daycare attendance will interact with genetic predisposition. However, genome-wide linkage studies and investigation of specific candidate genes are providing insight into possible areas of therapeutic investigation ²⁹. Some of the most interesting investigations have included findings demonstrating that genetic polymorphisms associated with inflammatory cytokines or mucin genes, both known to be important in the pathogenesis of OM, in patients that are prone to OM ^{30, (**)} ³². This type of patient specific knowledge about genetic susceptibility will lead to an entirely new arena of individualized medicine in which specific clinical decisions about the benefits of antimicrobial therapy or surgical intervention will be possible based upon genetic predisposition characteristics.

In summary, we have highlighted a number of the recent important topics of conversation and areas of investigation with respect to OM. Given the prevalence of this disease in childhood and the diversity with which patients present and are currently managed there remains a great deal of work ahead to solidify our understanding of OM pathogenesis and optimum treatment practices. However, with continued investment in OM research to sustain current energetic investigations, and those of the future, it appears clear that there are numerous opportunities for clinical advancement on the near horizon.

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