Abstract: Abstract:
* Otitis media (OM) typically presents as either an acute infection (AOM) with symptoms including fever, otalgia, otorrhea or irritability and short duration or as otitis media with effusion (OME) which is often asymptomatic and characterised by accumulation of fluid in the middle ear.
* Diagnostic certainty of OM is challenging, given the young age of patients and symptom variability.
* OM predominantly occurs as coincident to viral upper respiratory tract infections and/or bacterial infections.
* Common viruses that cause upper respiratory tract infection are frequently associated with AOM and new onset OME. These include respiratory syncital virus, rhinovirus, adenovirus, parainfluenza and coronavirus.
* Predominant bacteria that cause OM are non-typeable Haemophilus influenzae, Streptococcus pneumoniae and Moraxella catarrhalis.
* Antibiotics often do not significantly benefit most patients for AOM but long term prophylactic antibiotics can reduce the risk of OM recurrence for children at high risk.
* In Australia, 84% of AOM is treated using antibiotics, which contributes to development of antibiotic resistance.
* Vaccine development is a key future direction for reducing world burden of disease but requires polymicrobial formulation and ongoing monitoring and modification to ensure sustained reduction in disease burden.
25 August 2009

Dr Martin B Van Der Weyden
Editor
The Medical Journal of Australia

Dear Dr Van Der Weyden

Re. Otitis Media; viruses, bacteria, biofilms and vaccines

Please find attached our revised manuscript showing “tracked changes”. A clean copy is also attached.

We have addressed the reviewer’s comments

1. The reference to the statement beginning “The viruses most commonly …” has been relocated to be more obvious.
2. A concluding paragraph has been added.

In addition, we have

1. Updated the review with respect to the availability of the 10-valent polysaccharide conjugated vaccine (Synflorix®).
2. Corrected a number of minor typographical errors.

The copyright form is being forwarded by mail.

Yours sincerely

[Signature]

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**Otitis Media**

Otitis media (OM) is inflammation of the middle ear which may present as either acute otitis media (AOM) or otitis media with effusion (OME). AOM exhibits rapid onset, middle ear effusion and signs and symptoms of middle ear inflammation including fever, otalgia, otorrhea, or irritability\(^1\), whereas OME is middle ear effusion in the absence of symptoms of acute infection.\(^2\)

Clearly, on the basis of likelihood of presentation for treatment in non-Indigenous children, AOM maybe over-reported, by 22\%-50\%.\(^3,4\) whilst OME maybe under-reported. In a recent prospective study, it was demonstrated that the frequency of AOM episodes is age related, with an average of 1.97, 1.67 and 1.07 episodes occurring per year for children 6-11 months of age, 12-23 months of age and 24-35 months of age respectively.\(^5\). For older children, the frequency of new onset OME is greater than that reported for AOM. In a cohort of 242 children aged 1-8.6 years, the frequency of new onset OME was 4-fold greater than AOM\(^6\) and this finding is consistent with previous data indicating 50\% of OME occurred subsequent to AOM.\(^7\)

**Diagnostic challenge**

OM and upper respiratory tract infections (URTIs) share many common symptoms and are often coincident, increasing the variability of diagnosis for AOM. AOM is temporally associated with upper respiratory tract infections or cold-like illnesses in 50-70\% of all new AOM cases\(^8,9\) whilst between 29\%-61\% of all cases of URTI may develop into OM.\(^5,10,11\) In clinical practice, URTI symptoms and either rhinitis or cough were observed by French general practitioners in almost 90\% of suspected or diagnosed AOM.\(^3\)
OM can be difficult to confirm since otoscopic observation of tympanic membrane changes including bulging, erythema or opacity of the tympanic membrane\textsuperscript{12,13} are not always characteristic of AOM. Successful otoscopic examination of very young distressed children, often on repeated occasions, further increases the diagnostic challenge for clinicians since the peak incidence for AOM is between 6 and 18 months of age.\textsuperscript{14,15}

The uncertainty of clinical diagnosis of AOM is demonstrated by a US study in which general practitioners stated certainty of their diagnosis for AOM in only 58\% of infant cases, 66\% of toddler cases and 73\% of AOM cases in older children.\textsuperscript{16} Furthermore, although 78\% of diagnoses of AOM in children 1-4 years of age were shown to be consistent between the general practitioner and otolaryngologists, up to one third of the incorrect diagnoses were identified as normal ears by the otolaryngologists.\textsuperscript{3}

\textbf{Otitis media; a polymicrobial disease}

OM is a multifactorial disease\textsuperscript{17} with an extensive causal basis, including demographic, social, environmental, immunological and microbial risk factors.\textsuperscript{18} The development and growth of the eustachian tube in the first two years favours episodes of tubal blockage, often exacerbated by pollutants, allergies and viral infections.\textsuperscript{19} Abnormality of the eustachian tube is a contributing factor to a child’s susceptibility to recurrent episodes of AOM and OME.\textsuperscript{20} Equalisation of middle ear pressure through reopening the eustachian tube insufflates nasopharyngeal bacteria into the tympanic cavity. It is important to note that clinically healthy middle ears may also contain bacteria or evidence of bacterial biofilms,\textsuperscript{21} possibly resulting from transfer from the nasopharynx during normal events such as sniffing.\textsuperscript{22} OM occurs when viruses and bacteria evade the host mucociliary and immune responses and
inflammation is established within the middle ear. Complex interactions occur between the otopathogens which are thought to modify the colonisation dynamics of the nasopharynx and increase susceptibility for OM.

**Role of viruses**

AOM is associated with viruses that cause upper respiratory tract infection (URTI) alone in up to 30% of cases. The extent of this association has been recently strengthened by two, 12 month prospective research studies of healthy children, incorporating comprehensive clinical examination and improved viral detection techniques. Chonmaitree and co-workers reported that 97% of the children experienced one or more URTI’s per year, for children 6 months to three years of age, at an average of 5.4 infections over the 12 month period. Nearly 10% of the children less than three years of age suffered more than 10 URTIs per year. Otitis media was identified in 61% of URTIs reported, with AOM being present in almost one-third of these children and OME present in almost a quarter of URTI’s reported. Children in the study experienced an average of 1.7 episodes of AOM per child per year and child age was the strongest predictor of AOM development after URTI, after controlling for sex, race and ethnicity. Both of the recent prospective studies of healthy children in the US confirmed that a range of respiratory viruses, causal for URTI, are highly coincident with new episodes of OM, with between 20-73% of AOM and new-onset OME coincident with infection with one or more upper respiratory tract viruses.

The viruses most commonly coincident with OM were adenovirus (70%), influenza virus types A and B (65.5%), respiratory syncitial virus (RSV) (63.2%), enterovirus (62.5%), coronavirus (55.6%), rhinovirus (55.6%) and parainfluenza virus (types
Interestingly, AOM and OME were associated with different viruses, with AOM most frequently associated with coronavirus (50%), RSV (47.4%) and adenovirus (46.5%), whilst new onset OME occurred with influenza virus (34.5%) and enterovirus (34.4%). Alper and co-workers also confirmed the high frequency of association of OM with rhinovirus (44%) and RSV (56%). In unwell children attending hospital for AOM, viruses common for URTI were detected in 35% patients acutely ill with AOM. In these children, the most commonly identified viruses, using viral culture, were RSV (41%), influenza (types A, B and C combined) 23% and adenovirus (17%).

Improved viral detection has also resulted in identification of a broader range of respiratory viruses including human metapneumonia virus (hMPV), corona virus (HCoV-NL63), and bocavirus as causal for either URTIs or OM, although their relative contribution to OM is yet to be determined. Caution regarding these viruses and their potential association with OM and URTIs is necessary since these viruses can also be detected in asymptomatic children or, in the case of rhinovirus, over a prolonged period.

The failure to detect URTIs symptoms in only 2-3% of AOM episodes in otherwise healthy children may potentially indicate that the AOM arose through bacterial or other inflammatory pathogenesis. The association of OME and URTIs is reflected in the observation that only 0.6% of new onset OME episodes were diagnosed 30 days prior to URTI establishment.

Table 1 provides a summary of the contribution of viral infections to AOM.


**Role of bacteria**

Bacterial co-infection with upper respiratory tract viruses, rather than viral or bacterial pathogenesis alone predominates and is reported to range from 28% to 70% in the middle ear and nasopharynx. The three most commonly recovered bacteria associated with OM are *Staphylococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, which are all commensal within the nasopharynx, with the majority of *H. influenzae* isolated being non-typeable.

Bacteria are recovered in up to 90% of hospital reported cases of AOM, with *S. pneumoniae* (57%), *H. influenzae* (52%) and *M. catarrhalis* (56%) identified in nasopharyngeal secretions or less frequently from bacterial culture of the middle ear fluid (MEF), 22%, 21% and 4% respectively. Non-cultivable forms of *S. pneumoniae* and *H. influenzae* can also stimulate immune response and result in OME and may occur in up to 36% of nasopharyngeal secretion samples.

Nasopharyngeal colonisation with *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* and the early onset of OM are closely correlated. Indigenous Australian children, who are at high risk of OM, are colonised with these bacteria and *Staphylococcus aureus* by 3 weeks of age. For children at low risk of OM, first episodes of AOM, involving *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, peak in the first year of life and AOM from all causes has a peak incidence between 6 and 12 months of age as determined from culture of the middle ear fluid. In contrast, Indigenous Australian children at high risk of OM, experience high rates of AOM between 3-6 weeks of age, with tympanic membrane perforation occurring in about 20% (2) of children. Overall, 9 out of 10 Aboriginal children aged 6-30 months had clinical signs of OM and tympanic membrane perforation had occurred in 40% of
children by 18 months of age. Unfortunately, in these older children, AOM is often asymptomatic until discharge from the ear is visible.\textsuperscript{38, 39,40} OM exhibits a high rate of recurrence, with three or more episodes of AOM reported in 50% of children aged three years rising to 65% for children aged 5 years of age whilst OME recurs in 50% of children within 24 months\textsuperscript{14}. For Indigenous Australian children at high risk of OM, the rate of recurrence of AOM and OME is better described as persistent AOM. For these children, despite antibiotic treatment, AOM episodes do not typically present as acute in onset or short in duration. Indeed, persistent suppuration remained present for 77% of children for up to 14 days after initial diagnosis.\textsuperscript{41}

In the first few years of life, approximately 20% of children that experience AOM will not respond to antibiotic therapy\textsuperscript{42,43} and in these children, AOM may continue to either persist or recur\textsuperscript{42}. There is ongoing controversy as to whether this ongoing AOM results from persistence of the original infection or establishment of new infection, however it has been reported that new infections may cause up to 54% of recurrent AOM episodes, within one month of antibiotic treatment whilst bacterial relapse of the original infection comprised approximately 28% of all cases.\textsuperscript{43}

Early clinical recurrence of AOM within three weeks of initial treatment is associated with nasopharyngeal carriage of \textit{S. pneumoniae}\textsuperscript{44} although \textit{H. influenzae} is clearly associated with recurrent AOM\textsuperscript{37} and was the most prevalent pathogen (42%) observed in both bilateral and unilateral OM.\textsuperscript{45} Extensive geographical variation has been observed in bacterial carriage\textsuperscript{46} and disease,\textsuperscript{47} as well as the pneumococcal serotypes\textsuperscript{48} and the relative proportion of \textit{S. pneumoniae}.
pneumoniae, H. influenzae and M. catarrhalis that are responsible for OM. This variation adds to the complexity of developing an efficacious vaccine against OM. The proportion of AOM cases attributable to bacteria is summarised in Table 1.

Biofilms

Bacterial biofilms, microbial communities that attach to the mucosal surface and produce their own 3-dimensional structures covered in an exopolysaccharide matrix, are involved with a number of otolaryngological conditions. Pneumococcal biofilms have been visualised in 92% of middle ear mucosal biopsy samples from children symptomatic for OME and H. influenzae isolates obtained from patients with recurrent AOM, form biofilms in vitro. It is important to recognise that middle ear biofilms maybe present in up to 9% of healthy ears without provoking symptoms. Biofilms are hypothesised to cause chronic suppurative otitis media and to explain the condition’s resistance to antibiotic treatment. Recent evidence has demonstrated that pneumococcal biofilms with a high biofilm forming index exhibit greater resistance to azithromycin. Effective eradication of biofilm infections requires killing both the bacteria and destruction of the matrix to minimise persistence of the viable organism. Thus, persistent OM infections may arise from the failure to completely eradicate the original bacterial infection, or the presence of biofilms or, most recently, intracellular bacterial infection of the middle ear mucosal cells, particularly mucous secreting cells.

Host response

The immune response in the middle ear to infection is characterised predominantly by an inflammatory response, which in the acute phase normally, results in clearance of
microorganisms from the middle ear cavity. The polymicrobial nature of the disease explains\textsuperscript{17}, at least in part but not entirely, why recurrent acute infection occurs. However there are some children who are at higher risk of recurrent and chronic disease. The immune mechanisms important for protection against OM are poorly understood. Some studies have suggested that children who are prone to OM may have one of a number of immune perturbations although none of these studies are conclusive with respect to causal linkage. It has also been suggested that the mucosal immune response may be down regulated by persistent high nasopharyngeal carriage.\textsuperscript{59}

OM development is often preceded by viral URTI which may predispose to secondary bacterial infections through mucosal epithelial damage, impaired mucociliary function and up regulated inflammatory cytokine responses.\textsuperscript{60} Adenoid mucosa associated lymphoid tissue aids the local immune protection against bacteria and viruses by local production of secretory antibodies that inhibit antigen uptake and block attachment and colonisation of microbes. Absence or lack of secretory IgA (sIgA) increases bacterial adherence to epithelia and bacterial colonisation of the nasopharynx.\textsuperscript{61} Therefore the observation that children who are prone to OM may have lower levels of IgA and certain IgG subclasses, particularly IgG2, is not that unexpected.\textsuperscript{62,63,64,65} However, there does not appear the be any overall deficit in the antibody response to routine paediatric vaccines.\textsuperscript{66} An effective immune response to upper respiratory tract viral infections is dependent on the induction of a number of immunoregulatory cytokines such as interleukin (IL)-2, IL-10, transforming growth factor beta and allergy associated cytokines including IL-4, IL-5, granulocyte-macrophage colony-stimulating factor.\textsuperscript{67} A recent study examining cytokine polymorphisms demonstrated that high production IL-10 phenotypes were
more frequent in children with new OM episodes coincident with RSV and rhinovirus infection, whilst low production IL-6 and high production TNF-α phenotypes contribute to OM risk during rhinovirus infection.68 The association of certain genetic polymorphisms in TNFα, IL6, IL10, and TLR4 genotypes with increased susceptibility for otitis media68,69,70 would suggest that characteristics of the initial inflammatory response to infection may be crucial in setting the course for recurrent disease. Importantly a number of environmental factors such as exposure to cigarette smoke and breastfeeding may further modify genetic risk.69

**Management OM and antimicrobial resistance**

Australian Therapeutic guidelines recommend antibiotics at initial consultation for infants diagnosed with AOM who are less than 6 months of age and for all Indigenous Australian children with AOM.71 However, given the high rate (80%) of self resolving episodes and minimal benefit of antibiotic treatment72 in children who are not at high risk of developing complications, the prudent use of antibiotics is proposed73 to minimise the rate of development of antibiotic resistant bacterial strains. Typically, a “wait and watch” approach, using analgesia to reduce acute pain is recommended for low risk children over 2 years of age74 since 90% of children with AOM, treated with analgesia alone, recover in a few days.75 Middle ear effusion normally resolves within 7 days in 40% of cases and 75-90% resolution occurs within 4 weeks.6 Unfortunately, in practice, despite an overall reduction (24.3%) in the use of antibiotics in Australian general practice between 1990-1991 and 2002-2003, the overall rate of antibiotic prescription for AOM in children increased, with antibiotics prescribed for 77.6% of cases in 1990-1991 rising to 84.4% in 2002-2003.76
The continued high rate of antibiotic prescription is not justifiable on the basis of prophylactic administration to reduce the prevalence of OME since only marginal improvement (4%) has been observed in low risk children. Children at high risk of OME such as Indigenous Australian children, are benefitted by increased return of normal middle ear function (9.6%) and reduced risks of tympanic perforation (14%) and pneumococcal carriage (12%). Over-prescription of antibiotics within a community increases development of antibiotic resistant S. pneumoniae. This was clearly demonstrated in a recent study where antibiotic resistance was highly correlated with the use of antibiotics geographically across Europe. Increasing antibacterial resistance has been demonstrated in all of the three most common bacterial OM otopathogens, S. pneumoniae, H. influenzae and M. catarrhalis and indeed may negate the small vaccination protective effect against OM that has been observed with the pneumococcal conjugate vaccine.

Vaccines, now and in the future

OM is a polymicrobial disease with 4 otopathogens predominating – S. pneumoniae, H. influenzae, M. catarrhalis and RSV. Hence vaccine strategies should be initially directed at these microbes. For S. pneumoniae the vaccine will need to include the major serotypes responsible for disease. Currently, three pneumococcal vaccines are available; a 7 valent polysaccharide conjugated vaccine using a non-toxic mutant of diphtheria toxin as a carrier protein (Prevenar®); a 10-valent polysaccharide conjugated vaccine using Protein D as the main carrier protein (Synflorix®); and a 23 valent polysaccharide formulation (Pneumovax 23®). All of these vaccines have been primarily developed for immunisation against invasive pneumococcal disease. Pneumovax 23® has been shown to be relatively efficacious (56-81%) in preventing invasive pneumococcal disease in individuals over 2 years of age but has not been
demonstrated to be efficacious for use in children against recurrent AOM when used as a booster to pneumococcal conjugate vaccination. Immunisation with the 7 valent pneumococcal vaccine reduces the occurrence of AOM episodes by 6-7% but performs better against AOM due to vaccine-type pneumococci where the reduction of episodes due to these serotypes is around 55%. Of concern is the relative increase in the proportion of disease arising from non-vaccine serotypes of \textit{S. pneumoniae} and other bacterial pathogens. Newer vaccine formulations incorporating a greater number of \textit{S. pneumoniae} serotypes and particularly one incorporating a protein antigen from \textit{H. influenzae}, Protein D (Synflorix ®) should improve vaccine efficacy against otitis media. Indeed, studies of an earlier vaccine formulation containing this protein, PCV11-\textit{HiD}, conferred protection against AOM caused \textit{H. influenzae} (~35%) in addition to that observed for the pneumococcal serotypes (~53%) present in the vaccine. Based on animal model studies the possibility of developing a tribacterial (\textit{S. pneumoniae}, \textit{H. influenzae} and \textit{M. catarrhalis}) vaccine in the future is not beyond reality. The inclusion of viral components in a future polymicrobial vaccine will come later.

Experience from studies to date, suggest that the microbial ecology of the nasopharynx may be altered by vaccination particularly as the microbes targeted are often part of the normal commensal flora. In addition, with the introduction of pneumococcal conjugate vaccines it is generally accepted that with a decrease in vaccine serotypes there has been an overall reduction in the rate of detection of antibiotic resistance. However, there is some evidence of an increase in the antibiotic resistance of non-vaccine pneumococcal serotypes which could reduce the overall impact of pneumococcal conjugate vaccination on antibiotic resistance.
Hence, it will be necessary to establish ongoing surveillance studies to monitor any changes in the otopathogen profile and to continue to prescribe antibiotics cautiously for the treatment of OM.

Conclusion

Otitis media occurs frequently in young and very young children and results from infection of the middle ear by bacteria, viruses or both. Predominant bacteria causal for OM included: *S. pneumoniae, H. influenzae* and *M. catarrhalis* whilst viruses most commonly associated with OM include respiratory syncitial virus, coronavirus, adenovirus, and influenza virus.

Currently in Australia, non-adherence to the therapeutic guidelines has resulted in the excessive use of antibiotics for treatment of AOM who are not at risk of developing complications, increasing the rate of development of antimicrobial resistance to treatment. Early and prophylactic antibiotic use is of benefit to children at high risk of developing OM, such as Australian Indigenous children.

Future development of vaccines including a greater number of pneumococcal serotypes and antigens from *H. influenzae* and *M. catarrhalis* are needed. The development of therapeutic prevention strategies is complicated in that these bacteria may be able to evade antimicrobial therapy and host immune responses through the formation of biofilms and the capacity to reside intracellularly in middle ear mucosal cells. The development of protein based vaccines with antigenic components from both the three predominant causative bacteria and common upper respiratory tract viruses is a more distant possibility.
References


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