New horizons: otitis media research in Australia

Peter S Morris, Peter Richmond, Deborah Lehmann, Amanda J Leach, Hasantha Gunasekera and Harvey L C Coates

ABSTRACT

- Otitis media affects nearly all children worldwide. Despite an enormous amount of research, our understanding of this common condition continues to be challenged.
- New pathogens involved in otitis media are still being identified. The importance of interactions between viral and bacterial infection and the role of new vaccines need to be clarified.
- The proposal that bacteria can become more resistant to therapy through biofilm formation and intracellular infection could have important implications for treatment.
- The most important clinical research findings have been summarised in systematic reviews. In developed countries, research supporting "watchful waiting" of otitis media with effusion and acute otitis media have had most impact on evidence-based clinical practice guidelines.
- Indigenous Australian children remain at risk of more severe otitis media. Research programs targeting this population have been well supported. Unfortunately, interventions that can dramatically improve outcomes have remained elusive.
- For children at high risk of otitis media, health care services should concentrate on accurate diagnosis, antibiotic treatment of suppurative infections, and scheduled follow-up of affected children.
- Despite the lack of recent studies, strategies to minimise the impact the hearing loss associated with otitis media are important. Improvements in education, hygiene practices, and living conditions are likely to reduce the incidence and severity of otitis media. Studies of these types of interventions are needed.

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There is a substantial amount of research on otitis media currently available. Even when considering specific conditions, such as otitis media with effusion (OME), acute otitis media (AOM) or chronic suppurative otitis media (CSOM), the amount of information available can be overwhelming. This means that it can be difficult for clinicians to keep up to date.

Advances in our understanding of the genetics, aetiology, pathogenesis and treatment of otitis media and its sequelae have been significant. Unfortunately, despite the large amount of research available, important clinical questions remain unanswered. In 2001, a systematic review of research relevant to otitis media among Indigenous Australian children had over 900 citations.[1] Evidence-based guidelines produced alongside the review had over 90 recommendations.[2] However, over 50% of these recommendations were not based on high-quality evidence, because none was available.

Methods of literature review

To inform this article, we searched MEDLINE using PubMed from 1 January 2000 (search terms "otitis media AND '2000/01/01'[PDAT] : '2009/04/30'[PDAT]" yielded 6271 hits). One of us (P S M) scanned all the titles to identify important themes of recent research. Those described in this article were agreed on by consensus of all authors.

We also searched for the most clinically relevant articles in the recent overseas literature (search terms "otitis media AND 'clinical trial'[pt] OR 'systematic'[sb] AND '2000/01/01'[PDAT] : '2009/04/30'[PDAT]" yielded 725 hits) and any otitis media research conducted in Australia (search terms "otitis media AND Australia* AND '2000/01/01'[PDAT] : '2009/04/30'[PDAT]" yielded 161 hits). All English language original research articles or systematic reviews were eligible for inclusion. Our search identified over 50 systematic reviews and over 100 clinical trials. Around 80 publications were linked to research studies conducted in Australia.

Important research findings

At the most basic level, there have been some important developments in our understanding of the pathophysiology of otitis media. Polymerase chain reaction (PCR) methods are now being widely applied. The sensitivity of these methods compared with culture-based approaches has led to an appreciation that small numbers of bacteria and viruses (previously unrecognised) are often present in middle ear fluid; truly sterile effusions are unusual. Although this is interesting, the fact that PCR-positive, culture-negative bacterial mucosal infections are milder than culture-positive infections makes the clinical significance of PCR results uncertain.[3]

New pathogens such as human metapneumovirus[4,5] and *Alloiococcus otitidis*[6-9] have been identified. The importance of interaction between viruses and bacteria (and between bacterial species) is recognised. However, translating this knowledge into better health outcomes is not straightforward.

Several publications have reported the finding of bacterial biofilm (an aggregate of organisms held together by an extracellular matrix) on the middle ear mucosa of children with OME and CSOM.[10,11] Modalities to break down this biofilm matrix include physical destruction, enzymes, calcium ion inhibitors, and agents that interfere with quorum sensing (a communication method used by bacteria to coordinate gene expression).[12] It has been proposed that "collateral damage" from the host inflammatory response might account for the chronicity of inflammation in longstanding OME. The finding of bacteria intracellularly in the mucosal lining cells of the middle ear in children with OME and recurrent AOM (RAOM) creates another dilemma — which came first, the biofilm or intracellular infection?[13] Current research by this group is focusing on the correlation between intracellular bacteria found in the adenoids with those found in the middle ear (Harvey Coates, Clinical Professor, University of Western Australia, personal communication). The findings of significant carriage of intracellular bacteria within the adenoids of children with RAOM and OME could lead to further trials to assess the role of adenoidectomy at the time of drainage of the middle ear fluid.

Clinical research studies have documented changing patterns of antibiotic resistance and pneumococcal serotype replacement following the introduction of the 7-valent pneumococcal conjugate

vaccine. Although the impact of this vaccine on invasive pneumococcal disease has been substantial, well designed, large randomised controlled trials have shown that the reduction in risk of AOM is minimal.[14] An important trial of an alternative 11-valent pneumococcal conjugate vaccine (now 10-valent) suggested that AOM caused by non-typeable *Haemophilus influenzae* may be (to an extent) a vaccine-preventable disease.[15] If the *Haemophilus* protein D carrier protein is confirmed to be protective against non-typeable *H. influenzae* disease, this would stimulate more work on otitis media vaccines based on bacterial surface proteins. The role of viral vaccines in the prevention of otitis media has been documented for seasonal influenza infection. Other vaccines in development (such as a respiratory syncytial virus vaccine) could also have an impact.

A large number of randomised controlled trials examining treatment of otitis media have been summarised in systematic reviews and evidence-based guidelines.[16] Importantly, "watchful waiting" has emerged as an appropriate management strategy for OME and AOM in developed countries. Trials of "wait and see" prescribing have shown that provision of a prescription (for antibiotic treatment if the child does not improve spontaneously) can reduce the need for antibiotic therapy without compromising clinical care.[17,18]

Individual patient data meta-analyses have provided further important information. Although children under 2 years of age with bilateral AOM or otorrhoea are most likely to benefit from antibiotic treatment, subgroups of children most likely to benefit from surgery for chronic OME have not yet been identified.[19,20] Despite the ready availability of high-quality evidence, studies suggest that there has been no reduction in active treatment strategies used by Australian doctors.[21,22]

The Australian contribution

Australian research into otitis media includes:

- studies of animal models assessing potential vaccine candidates and pathogen interactions;[23,24]
- microbiological assessment of specimens from the nasopharynx, middle ear, and ear discharge;[25-27]
- mathematical modelling of otitis media pathogen interactions;[28]
- prevalence surveys;[29]
- epidemiological studies of risk factors;[30]
- research into features of mastoiditis[31,32] and cholesteatoma;[33,34]
- reported management of otitis media;[35,36]
- clinical assessment of video-otoscopy;[37]
- the effect of swimming pools on otitis media;[38]
- measurement of speech comprehension in children with a history of otitis media;[39]
- the impact of CSOM on sense of smell;[40]
- the effect of fruit consumption;[41]
- the effects of surgery, including insertion of ventilation tubes,[42,43] adenoidectomy,[44] and myringoplasty;[45,46]
- the effects of antibiotic therapy;[47-49] and
- the impact of the newly introduced 7-valent conjugate pneumococcal vaccine.[50]

Early onset of nasopharyngeal colonisation with *Streptococcus pneumoniae*, *H. influenzae*, and *Moraxella catarrhalis* is an important feature of severe disease in Aboriginal children.[25,51] An increased density of these bacterial pathogens is associated with more severe disease.[52] The presence of these bacteria on the hands of young children explains why transmission rates are likely to be high.[53]

One of the earliest reports of *Pseudomonas* biofilm in otitis media came from an Aboriginal child with CSOM.[54] Similarly, two Australian groups noted high recovery of a slow-growing aerobic gram-positive bacterium, *Alloiococcus otitidis*, in 20%–60% of middle ear effusions on PCR assay or on special culture.[9,13,55] A study of middle ear effusions in 39 ears from 25 children, using 16S ribosomal RNA sequencing of extracted DNA, showed that 35% of organisms isolated were *A. otitidis*.[55] Further studies to determine the pathogenicity of the organism are warranted.

The Kalgoorlie Otitis Media Research Project found the measurement of otoacoustic emissions in 1–3-month-old Aboriginal children could predict children at risk for subsequent otitis media,[56] and noted high rates of early nasopharyngeal bacteria carriage,[51] and that environmental tobacco smoke was a risk factor in otitis media.[30] A follow-up study will evaluate otitis media screening and an awareness program regarding passive smoking and hand hygiene.

Australian researchers have been very active in supporting evidence-based practice for treatment of otitis media.[57] Many contribute as authors and editors of systematic reviews published in the Cochrane Library. Efforts are made to ensure that all resources useful in the management of otitis media among Indigenous Australians are freely available on the Australian Indigenous HealthInfoNet (http://www.healthinfonet.ecu.edu.au/other-health-conditions/ear). Australian researchers also contribute to better health interventions by conducting randomised controlled trials. Four Australian randomised controlled trials of otitis media management have been published since the year 2000, and others are in progress (or awaiting publication). Most of the trials (3/4) have addressed antibiotic use in Aboriginal children (topical ciprofloxacin ear drops for CSOM[47,48] and long-term amoxycillin prophylaxis for infants).[49] One trial assessed the use of topical lignocaine for children with AOM.[58] A CSOM study contributed to a change in clinical practice, with topical ciprofloxacin drops now approved for use in Aboriginal and Torres Strait Islander children.[47] The findings of the trials on long-term antibiotics and local anaesthetics could also be applied clinically.

Clinical implications

It is important to recognise that only a small proportion of the medical literature should be applied in clinical practice. Clinical epidemiologists have estimated that approximately 2% of publications are methodologically rigorous and useful to clinicians.[59] Clinicians caring for children with otitis media are most interested in studies that assess the accuracy of diagnostic tests or the potential health benefits of interventions. A recent Australian review summarised the findings of systematic reviews relevant to clinical practice.[60] The key points were summarised as follows:

- pneumatic otoscopy and/or tympanometry are the only reliable methods for detecting the presence of middle ear effusion;
- Australian Indigenous children have the highest burden of otitis media of any children in the world;
- immediate antibiotic treatment is optional for non-Indigenous children with AOM;
- non-Indigenous children with OME can be observed safely for 3–6 months; and
- children with CSOM need ear cleaning and topical antibiotics until the discharge resolves.[60]

Overall, the results of systematic reviews of studies conducted overseas will be applicable to Australian children. The potential

exception would be Indigenous children at high risk, among whom perforation of the tympanic membrane and subsequent CSOM is common. Importantly, there are also important contextual issues to be considered in remote communities.[61] It is likely that Australian studies would also be needed to clarify the most appropriate health care interventions.

New initiatives

Research into otitis media in Australia has been well supported by the National Health and Medical Research Council (NHMRC) and the Australian Government Department of Health and Ageing. Most research in Australia has focused on potential vaccines[62] and reducing the burden of otitis media among Indigenous children.[26,63] Studies of the pathophysiology of disease are still underway. They include an assessment of the role of viruses in determining tympanic membrane perforation, mathematical modelling of transmission and ear state dynamics, and intensive molecular investigation of nasopharyngeal swabs to identify the full range of colonising pathogenic and non-pathogenic organisms. Improvements in technology have made the assessment of genetic risk factor studies feasible.[64] Two studies examining the genetics of RAOM are being conducted in Western Australia. One study is looking for genetic indicators and their immunological correlates of RAOM in children 3 years and under. The other is examining familial history and DNA testing of 1000 children with RAOM (and their close relatives), seeking to identify the genes associated with the disease.

Important new randomised controlled trials in progress include:

- maternal immunisation with pneumococcal vaccine during pregnancy;
- antibiotics for the treatment of asymptomatic bulging of the tympanic membrane identified on screening;
- family support by Indigenous health brokers;
- enhanced family support via telephone, fax, email and mail; and
- smoking cessation strategies for parents.

Other ongoing studies include surveillance of pneumococcal and *H. influenzae* carriage and presence in middle ear effusions in the era of pneumococcal vaccination and changing antibiotic use; and an assessment of the association between swimming pools in remote communities and otitis media.

Surveillance of nasopharyngeal carriage organisms is complementary to routinely collected data on rates of invasive pneumococcal disease, and is ongoing in the Northern Territory and WA. This should help predict the potential impact of new vaccines. Other potential randomised controlled trials that are yet to receive funding include assessments of the effect of maternal immunisation with influenza vaccine, the role of combining two different conjugate pneumococcal vaccines, and surgical interventions for chronic OME.

To date, there is no evidence that screening for otitis media or hearing loss due to middle ear disease is associated with substantial health benefit (or harm).[65] For Aboriginal children, the high rates of poor outcomes provide a persuasive argument for more active surveillance of at-risk children.[66] A program of active surveillance is currently being evaluated in the Goldfields region of WA. However, determining whether identified children will benefit from subsequent action is important. Potential interventions include medical or surgical treatments and assistance with hearing and communication. It is likely that randomised controlled trial designs will be needed for many of these types of questions. Improvements in medical record management may also improve quality of care. New medical record documentation applications, such as MMEx (Medical Message Exchange), that are being utilised in Aboriginal health services in WA allow a patient's medical history, audiometry results, and video-otoscopic images to be emailed to distant experts.

Patients in Australia may also benefit from the results of more innovative research studies. The use of non-pathogenic bacteria and xylitol gum may have a role in treatment.[67,68] New concepts of biofilm and intracellular bacteria in middle ear disease may lead to changes in our clinical approach (eg, use of mechanical irrigation methods for treating CSOM) and preference for antibiotics (eg, azithromycin or ciprofloxacin) that are concentrated intracellularly. New research into surgical interventions may lead to biodegradable grommets, totally implantable hearing aids and tissue-engineered tympanic membranes. Japanese investigators have successfully performed 30 myringoplasties using tissue growth factors and fibrin glue, with a primary healing of 73%, a further 20% with the second application and total success at the third procedure.[69] It remains to be seen whether these outpatient procedures are appropriate interventions for the significant number of Indigenous adults and children with CSOM.

The interface between medicine and education is critical in dealing with otitis media and its complications. Unfortunately, there has been little recent research addressing this issue in Australia. Caregivers who deal directly with affected children and their families (whether they are teachers, Aboriginal health workers, community nurses, or general practitioners) must educate families regarding the effect of hearing loss on speech, language and education. All schools with high numbers of children with hearing impairments should have classroom sound field systems with wireless infrared technology. Support for training speech pathologists, audiologists, and teachers of the deaf to work in regional and remote Australia is needed to address a chronic shortage of these important professionals. All these professions should offer programs that increase the number of practising Indigenous clinicians.

Conclusions

Research in Australia is making an important contribution to the literature worldwide. Systematic reviews and studies of a high-risk population (Indigenous children) have been most informative. As "watchful waiting" becomes the preferred standard of care in developed countries, Australian researchers are ideally placed to determine the health benefits (and harms) of interventions for populations with high rates of suppurative complications. Over the next 10 years, identification of subgroups of patients most likely to benefit from more active management will probably be the most significant development worldwide. New therapies are unlikely to be as important as the more appropriate application of currently available interventions. At this point in time, Aboriginal Medical Services should concentrate on accurate diagnosis, antibiotic treatment, and scheduled follow-up of affected children. Strategies to minimise the impact of hearing loss are equally important. Crucially, advocates for Indigenous child health recognise that improvements in education, hygiene practices, and living conditions are likely to reduce the prevalence and severity of otitis media.

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Competing interests

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Author details

Peter S Morris, MB BS, FRACP, PhD, Associate Professor,[1] and General Paediatrician[2]
Peter Richmond, MB BS, FRACP, Associate Professor, School of Paediatrics and Child Health[3]
Deborah Lehmann, MB BS, MSc, Epidemiologist[4]
Amanda J Leach, MAgSci, PhD, Associate Professor[1]
Hasantha Gunasekera, DCH, FRACP, MIPH(Hons), General Paediatrician,[5] and Clinical Lecturer[6]
Harvey L C Coates, AO, MS, FRACS, Clinical Professor,[3] and Senior Ear, Nose and Throat Surgeon[7]

1 Child Health Division, Menzies School of Health Research, Darwin, NT.
2 NT Clinical School, Flinders University, Darwin, NT
3 University of Western Australia, Perth, WA.
4 Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, Perth, WA.
5 Children's Hospital at Westmead, Sydney, NSW.
6 University of Sydney, Sydney, NSW.
7 Princess Margaret Hospital for Children, Perth, WA.
Correspondence: peterm@menzies.edu.au

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