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COMMENTARY

Trends in Otorhinolaryngology
Head and Neck Surgery

Cutting the Gordian Knot: Unravelling Demographic and Pathophysiological Factors Influencing Pathogen-Specific Immune Responses in Chronic Otitis Media-Prone Children

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In Greek mythology, it is said that the impossibly tangled knot tied by Gordius, king of Phrygia, could only be unravelled by the future ruler of Asia; Alexander the Great solved this problem by cutting the knot with his sword. The phrase 'cutting the Gordian knot' is used today as a metaphor for a complex, seemingly intractable, problem to which a solution may be found only through taking decisive and bold steps [1].

This ancient legend comes to mind when considering the overlapping and interacting risk factors in the development of otitis media (OM) [2]. A greater understanding of these causal determinants will lead to targeted management strategies, more effective therapies and thus to improved patient outcomes for this global childhood illness. Foremost among topics where there is a knowledge gap are the colonization of the nasopharynx by pathogenic viruses or bacteria and the nature of the immune response that this triggers [3].

OM occurs when viral or bacterial commensals ascend the eustachian tube – the canal that connects the middle ear to the nasopharynx, which consists of the upper throat and the back of the nasal cavity – to enter the air-filled middle ear cavity located behind the eardrum (tympanic membrane). Once here, these opportunistic pathogens cause infection, inflammation, fluid accumulation, primary otalgia (earache) and possible otorrhea (external discharge of fluid, sometimes purulent, after the eardrum bursts) [4]. Of an array of pathologies that may present during middle ear infection, those most commonly observed are acute OM or chronic OM (COM), the latter often with effusion (so-called 'glue ear') [5-7].

In developed countries, OM is the most frequent reason for primary healthcare practitioner visits to, and analgesic and antibiotic treatments for, infants and young children, while it is also the second most common cause of juvenile hospitalization associated with a procedure [8,9]. The scale of this paediatric health concern can be gauged by the fact that as much as 80% of children of all backgrounds are affected by 3 years of age [10]. Associated with poverty, OM is particularly prevalent among First Nations peoples around the world, including indigenous Australian children, in whom complications and recurrence are disproportionately high [11,12]. In around half of cases a documented perforation of the tympanic membrane is evident, resulting in poor hearing and speech, thereby leading to under-developed learning and social behaviour [12].

Factors relating to the microbes, host and environment each increase the risk of contracting OM and of its disease burden [8,9]. These include: microbial factors of nasopharyngeal colonization, and inter-microbial and microbial-host relationships; host determinants of demography, anatomy, physiology and immunity; and environmental factors of overcrowded housing, poor hygiene, exposure to cigarette smoke, and limited access to medical care [11]. On a broad scale, how each of these demographic and pathophysiological factors contributes to the disease aetiology is quite well defined, yet the relationships between them and how such associations contribute to OM are understood much less clearly.

The bacterial pathogen that is most frequently implicated in OM is *Streptococcus pneumoniae*, followed by non-typeable *Haemophilus influenzae* (NTHi) and *Moraxella (Branhamella) catarrhalis*. These three organisms are responsible for more than 95% of all acute OM cases with a bacterial aetiology [4,13]. Host tolerance to microbial colonization at mucosal sites, including *S. pneumoniae* colonization of the nasopharynx, has been associated with regulatory T (Treg) lymphocytes and suppression of pro-inflammatory immune responses [14-16]. What has not been established, however, is the association of the Treg lymphocyte population with NTHi and *M. catarrhalis*, or the characteristics of local immunoregulation upon nasopharyngeal colonization by other otopathogen commensals.

This knowledge gap has been addressed recently by investigating OM in children from regional Queensland, on the northeast coast of Australia. This study undertook a detailed examination of a

cohort of 40 children between 2 and 7 years of age resident in the Rockhampton region of Central Queensland who were scheduled for elective surgical adenoidectomy [17-21]. Each child presented with a diagnosed medical history of either being or not being prone to COM, which was confirmed upon examination by a consultant ENT surgeon specializing in paediatric otorhinolaryngology. Multiple factors of demographic, environmental, nasopharyngeal bacterial carriage, lymphocyte subset proportions from the adenoids and blood, and salivary and plasma pneumococcal-specific antibody titres were assessed. Within Australia, most published studies of OM come from the Northern Territory and Western Australia and relate exclusively to indigenous children who commonly experience a greater disease burden [22], compared to non-indigenous counterparts [8,12,23-25]. OM in children from the more populous eastern states of Australia had not hitherto been investigated.

For each participating child a questionnaire was used to gather information on their household environment and family history of OM [18-20]. This information included: Aboriginal and Torres Strait Islander heritage; the number of children in the household under 15 years of age; birth order; sibling history of OM; exposure to environmental tobacco smoke; attendance at day care, kindergarten, preschool or school; and routine immunization compliance. The clinical history of all participants was obtained from their medical records, while biological samples were collected during the adenoidectomy procedure. For each child, their adenoids, samples of peripheral blood and saliva, and a nasopharyngeal aspirate (NPA) were collected in order to determine microbiological profiles, lymphocyte subset proportions and level of pneumococcal-specific antibodies [17-19].

Of all demographic, environmental, microbiological and immunological factors investigated, none increased the risk of a child's susceptibility to COM or to upper respiratory tract infections (URTI), and there were no significant differences in these factors between COM-prone and non COM-prone children, or between URTI-prone and non URTI-prone children [20,21]. Among these factors, however, there were significant associations and differences with nasopharyngeal culture. The risk of NTHi nasopharyngeal carriage increased markedly in participants who were the youngest among siblings, whereas these children had a reduced risk of *Staphylococcus aureus* positive nasopharyngeal carriage [21]. Environmental tobacco smoke exposure increased significantly the risk of *M. catarrhalis* and *S. aureus* nasopharyngeal carriage, and male children had significantly more nasopharyngeal positive culture compared to female children [21]. NPA cultures of *S. pneumoniae* were found to significantly predict S. pneumoniae colonization at the adenoids [20]. This provides a rationale for the potential use by physicians of NPA as a novel screening method to determine *S. pneumoniae* colonization at the adenoids, thereby enabling targeted antibiotic treatment to reduce *S. pneumoniae* carriage in children, while also lessening the number of inappropriate prescriptions of antibiotics.

The presence of circulating CD19+ B lymphocytes had a significant, positive association with *M. catarrhalis*, while CD3+CD8+ T lymphocytes from the adenoids had a significant, negative association with *S. aureus* [17-19]. Lymphocyte subset proportions from the adenoids and blood were not significantly different between NTHi or *S. pneumoniae* culture positive or negative children [17,18]. However, children with positive nasopharyngeal culture did have significantly increased percentages of circulating Treg lymphocytes compared to children with negative nasopharyngeal culture [18,19]. This supports the hypothesis, in regard to systemic immunity but not locally in the adenoids, that commensal bacteria within the nasopharynx are positively associated with Treg lymphocytes in the adenoids and blood of children with COM, thereby possibly contributing to host tolerance of nasopharyngeal colonization and the development of COM [3]. This is the first report globally of lymphocyte proportional changes and associations with general nasopharyngeal otopathogen culture, *M. catarrhalis, S. aureus* and NTHi culture in children.

The findings of this investigation offer an insight into the multiple factors that contribute to a child's susceptibility to COM in regional Queensland. Furthermore, when considered alongside similar studies conducted in Western Australia, the Northern Territory and New Zealand [23-26], collectively this research enables a greater understanding of OM in Australasian children. The demographic, environmental, microbiological and immunological factors that contribute to a child being prone to COM in rural and remote communities remain obscure. Furthermore, the extent of the relationships between these determinants and how they affect a child's proneness to COM also require further investigation. For instance, this might identify possible risk factors, dominant nasopharyngeal bacterial colonizers and potential microbial screening methods to target antibiotic therapies, thereby reducing the over-prescription of inappropriate antibiotics. Importantly, this information would contribute to better clinical management of COM in children from under-resourced communities such as in regional Queensland [27,28].

A deeper understanding of the relationships among nasopharyngeal otopathogens with local and systemic lymphocyte subset populations, particularly Treg lymphocytes, goes a long way to cutting the Gordian knot that is the pathophysiology of COM [3]. It also provides justification for a still deeper exploration of the functional aspects of colonization, tolerance and host immunity, and how these contribute to a child's susceptibility to COM [18-20]. Once such relationships and mechanisms are elucidated sufficiently, research may then focus on ways to manipulate such immune pathways to promote increased clearance of URTI and to reduce COM. This would have the effect of decreasing the overall incidence and severity of the disease, together with lessening complications associated with prolonged clinical manifestations. There is still much work to be done but solving big (public health) problems requires firm and focused action.

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Conflicts of interest

The author declares no competing issues of interest.

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