Otitis media

What’s behind the ear drum?

Emma Best

Paediatric Infectious Diseases consultant, Starship Children’s Hospital

Senior Lecturer, Department of Paediatrics
University of Auckland
What to cover?

• Common pathogens

• Medical management – antibiotics or not?

• Vaccination to prevent otitis media
  – Current NZ research
Acute Otitis Media

• A “normal part” of childhood

• 80% < 3 yrs have episode of acute otitis media

• Multifactorial risk factors
  – Eustachian tube dysfunction
    • Young infants - short and flat ET
  – Passive smoke exposure
  – Lack of breast feeding
  – Exposure to other children (sibling, day care)

Nasopharyngeal colonisation with middle ear pathogens
AOM

• Very common infection world wide
  – And a recurrent problem - 1/3 have ≥ 6 recurrences by the age of 7yrs

• Most common reason for Dr’s visit & main reason for prescription of antibiotics to children (developed countries)

Coker et al. Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review JAMA 2010
Reasons for medical/hospital presentation

• Acute OM
  – recurrent acute OM episodes, acute perforations, mastoiditis

• Chronic OM
  – persistent effusion (‘glue ear’/hearing)
  – chronic complications; cholesteatoma, mastoiditis
In New Zealand

• 63 GP practices over 12 months showed 83,000 consultations for new cases of acute OM / yr in <5yrs of age

• Antibiotics were prescribed for 50% of these cases

NZ hospital data 2013

• Acute admissions for OM related conditions - mostly static over last year

• Grommet waiting list gradual decline 2000-2010

• Rates highest for Maori & Pacific > European > Asian for both acute OM admissions and grommets

Craig E and NZ Child & Youth Health Epidemiology service report: The Health Status of Children and Young People in New Zealand 2013
Figure 26. Acute Hospital Admissions for Otitis Media and Arranged/Waiting List Admissions for Grommets in Children Aged 0–14 Years, New Zealand 2000–2010

- NZ Grommets 0–14 Years
- NZ Otitis Media 0–14 Years
Case

• 18 month old baby girl
• Immunised
• Febrile to 38.5
• Cranky and not drinking, rubbing her ears
• Runny nose, cough, wheezy chest

• Otoscopy
Dx: Acute otitis media (AOM) – abrupt onset plus pain, fever, irritability plus bulging drum/otorrhoea/limited mobility drum

Image c/- Dr Mahadevan ORL Starship
So who to treat?

- 2/3rds of acute OM - bacterial but nearly all preceded by viral infection
  - High rate of detection of viruses in nasopharynx during AOM (50%)
  - Respiratory viruses detected in middle ear fluid during acute and recurrent OM
    - rhinovirus, RSV, hbocavirus, adenovirus, parainfluenza virus, coronaviruses and influenza
The Big Three – bacterial pathogens of otitis media

- *Haemophilus influenzae* (non-typable) NTHi
- *Moraxella catarrhalis*
- *Streptococcus pneumoniae* ‘Pneumococcus’

- Uncommonly *Alloiococcus otitidis* (<10%)
- Very uncommon <1% *S. pyogenes*,
- *S. aureus*, Pseudo (true pathogens when ear drum is intact?)
< 6 months - always treat
6-24 months – treat if severe or bilateral
  - Severe = mod or severe pain or pain >48hrs or temp >39°C

Otherwise observation option for age >2yr or non severe AOM
Enrolled young children ages 6 mths – 2 or 3 yrs
Clear OM diagnoses and included all levels of severity, bilateral and unilateral

Measured ‘Time to treatment failure’ Day 3 & 8
at D3: 30/161 on antibiotics “failed versus 71/158 (18% vs 45%)

Moderate benefit of antibiotics for some number needed to treat (NNT) = 4 children

Adverse events
Diarrhoea and nappy rash
Can antibiotics reduce persistence of middle ear fluid?

• Persistent middle ear fluid after acute infection — “normal” weeks

• Generally thought that antibiotics have little or no impact on persistent middle ear effusions

• Multifactorial reasons why some children go on to have recurrent or chronic OM

Antibiotic, acute OM and risk of serious suppurative complications

Observational study - 1990’s Netherlands (2 of 4700 untreated children developed mastoiditis)

Mastoiditis rates comparable across developed countries despite large variation in antibiotic prescribing for OM
E.g. Scandanavia/ Netherlands – low prescribing compared with Australia/ UK/ Canada/ US – high prescribing
Natural history of acute otitis media

- Most acute otitis media are bacterial infection involving big 3

Natural history

@ 1-2 days 60% of kids w AOM improved

@ 3-7 days 75% acute symptoms resolve

- Resolution of middle ear fluid longer but mostly gone by 6wks (5-10% persist @ 2mths)

- Antibiotics modest effect on shortening symptoms of AOM (NNT 4 - 20)
Why not use antibiotics

Rising antimicrobial resistance: a strong reason to reduce excessive antimicrobial consumption in New Zealand

Thomas et al NZMJ 2014

Antibiotic resistance is a growing problem in NZ

- High antibiotic consumption primary cause of antibiotic-resistant bacteria
- New antibacterial drugs will not be available in the next decade
- Increasing levels of antibiotic resistance cause inconvenience and risk for patients and increased costs for the health system
Figure 2. Consumption of penicillins (defined daily doses [DDDs]/1000 population/day) by community-based patients (i.e. not hospital inpatients) during 2010, in relation to the prevalence of reduced susceptibility to penicillin in strains of *S. pneumoniae* isolated during 2010; (a) and consumption of fluoroquinolones (DDDs/1000 population/day) by community-based patients during 2010, in relation to the prevalence of resistance to ciprofloxacin in strains of *E. coli* isolated during 2010; (b) for a number of large European nations.³¹⁰
From 2005 to 2012, community-based patients antibiotic consumption increased by 43%.

*Thomas et al NZMJ 2014*
Figure 6. Per capita consumption of antimicrobials by community-based patients, in relation to patient age, during 2012, measured in prescriptions/100 population/year.
Antibiotic side effects are common and harmful

- 5-25% chance – antibiotic will cause diarrhoea
- 1 in 1000 may lead to visit to ED due to bad reaction
- Number needed to ‘harm’ – (diarrhoea) = 14

Shehah et al. Clin Inf Dis 2008 Emergency dept visits for antibiotic associated adverse events
Budnitz et al JAMA 2006
Venekamp et al Cochrane Database Rev 2013
Antibiotics in Otitis Media

Best bang for your buck – target *S. pneumoniae*

Treat if < 6mths or severe or bilateral 6mth-2 years

Amoxycillin 5-7 days Dose: 45 mg/kg/day div TDS

- 90mg/kg/day High dose - if attends child-care centre, previous abx in past 3mths
- Treat longer 7-10 days if <2 years or perforation

2nd line or alternate agent: if no response after 72 hr Tx Amox-clav (25 -50mg/kg/day of amoxyl- ?might be too low for some Spn)
Prevention of otitis media

• Vaccines role in reducing burden of otitis media
Influenza vaccine and OM

• Influenza viruses are one of more frequently found resp viruses in MEF during AOM

• Plus *S. pneumoniae* is part of Big 3 of AOM
  – And influenza virus known to predispose to pneumococcal infection
**Streptococcus pneumoniae**

- Colonises the nasopharynx < 5-10% of adults, >40% children at any one time
- Invasive disease common in young children and elderly
  - Bacteraemia, meningitis, bacteraemic pneumonia

Non invasive (mucosal) much more common
  - otitis media, sinusitis, pneumonia
>90 serotypes identified based on diff capsular polysaccharides

Capsule plays essential role in escape from phagocytosis

Capsule - focus of vaccine development
Use a proven Immunogenic protein e.g small amount of tetanus or diphtheria toxoid...
# NZ Immunisation schedule 2008

### New Zealand National Immunisation Schedule from 1 September 2008

<table>
<thead>
<tr>
<th>Age</th>
<th>DTaP-IPV-Hepl/Hib IM</th>
<th>PCV7 IM</th>
<th>Hib IM</th>
<th>MMR SC</th>
<th>DTaP-IPV IM</th>
<th>dTap IM</th>
<th>HPV IM</th>
<th>Td IM</th>
<th>Influenza IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>Infanrix® - hexa</td>
<td>Prevenar®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>Infanrix® - hexa</td>
<td>Prevenar®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 months</td>
<td>Infanrix® - hexa</td>
<td>Prevenar®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 months</td>
<td>Prevenar® (starts April 2009)</td>
<td>Hiberix™</td>
<td>MMR® II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 years</td>
<td></td>
<td></td>
<td>MMR® II</td>
<td></td>
<td>Infanrix™-IPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Boostrix®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 years²</td>
<td>(School year 8) starts in 2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gardasil®</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gardasil® ² 2 months after 1st dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gardasil® ² 4 months after 2nd dose</td>
</tr>
<tr>
<td>45 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADT®-Booster®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65 years²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADT®-Booster®</td>
<td>Influenza annually (annually)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Since introduction in conjugate pneumococcal vaccines in

- 97% efficacy against invasive pneumococcal disease caused by the vaccine serotypes (bacteraemia, meningitis)
- 30% reduction in X-ray confirmed pneumonia
- Significant protection of those not receiving the vaccine (older children > 5 years and adults)

=Herd immunity
Impact of conjugate pneumococcal vaccines on nasopharyngeal carriage

• Doesn’t change rate of carriage of *S. pneumoniae*

• Consistently shown to lessen proportion of S.pn in nasopharynx due to vaccine types (by 90%)

• **Vaccine impact on nasopharyngeal S.pn in young children**
  – *Important as basis of herd immunity - they are community reservoirs*
  – *Important part of impact on mucosal disease*
NZ carriage data – summarised: %Spn within each sample period by VT

N= 218/732
30%
2007
PCV7 serotypes
PCV 13 serotypes
Non vaccine serotypes

N= 233/927
28%
2009
Spn/total sample
Carriage rate

N= 174/450
36%
2011

Unpublished data from Childhood Resp Viruses cohort (CMDHB)
Best et al.
Serotype (and other pathogen) replacement

COMPETITION

S. aureus

pneumococci

Commensal bacteria

biofilm formation

CO-OPERATION

influenza virus

mucus layer

nasopharyngeal epithelium

CONJUGATE PNEUMOCOCCAL VACCINE

Reduced pneumococcal colonisation could make the niche more available for commensals and competing pathogens

Reduced pneumococcal colonisation could inhibit synergistic pathogens

Vaccine 2013 Dunne et al.
Many environmental, host and pathogen influences on a child’s nasopharynx...

Pneumococcal conjugate vaccine generally does not show an impact on other pathogens in the nasopharynx including S.aureus, Moraxella, Haemophilus
Impact of pneumo conjugate vaccine (PCV7) on OM

- Reduction in acute otitis media – estimated 10 - 20%
  - measured by Dr visits or hospital presentations, reduced antibiotic prescriptions, healthcare savings

*Fitzwater et al PIDJ May 2012
Taylor et al June CID 2012*
Incidence of AOM & Dr’s visits declining even before introduction of PCV7

Need to disentangle vaccination effect from other temporal trends
Impact of PCV on OM

“It’s complicated”

• Only modest reductions in incidence rates of OM since introduction of PCV7
  – Increases in non-vaccine pneumococcal serotypes
• Increases in disease due to other pathogens?
  – *H. influenzae* (NTHI) commonly reported to “increase” - ?changing aetiology or proportion shifts in dominant causative organism

– But AOM is extremely common infection
  – Even small reductions mean 1000’s of cases prevented
PCV vaccines

**Prevenar 7**
- **Serotypes**: 4, 6B, 9V, 14, 18C, 19F, 23F
- CRM$_{197}$ Diphtheria carrier protein

**Prevenar13**
- **Serotypes**: 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F
- CRM$_{197}$ Diphtheria carrier protein

**Synflorix PCV10**
- **Serotypes**: 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F
- NTHi protein D

3 + 1 schedule
6wks, 3mths, 5mths and 15 mths
PCV10

- Potential benefit over other pneumococcal conjugate vaccines
  - Particularly relevant for otitis media where NTHi one of the Big 3 causative pathogens
  - Pre licensure trials - otitis media reduced by 33% - efficacy against AOM caused both S.pn vaccine serotypes and against AOM caused by NTHi
Otitis Media Infectious Aetiology & Vaccination Impact (OMIVI)

“What's behind the ear drum?” The microbiology of otitis media and the nasopharyngeal flora in children in the era of pneumococcal vaccination

Accepted J Paeds and Child Health
OMIVI Research Team

Infectious Diseases
Emma Best (ADHB)
Tony Walls (CDHB)
David Murdoch (CDHB)

ORL surgeons:
Nikki Mills (ADHB)
Mel Souter (CDHB)
Murali Mahadevan (ADHB)
Colin Barber (ADHB)
Michel Neeff (ADHB)
Lesley Salkeld (ADHB & CMDHB)
Zahoor Ahmad (CMDHB)

Research Nurses:
Debby Sandow (ADHB)
Mandy Retter (CMDHB)
Liane Dixon & Raewyn Wright (CDHB)

Childrens Research Centre:
Gail Gillies (Nurse Manager)
Boris Mauwa (Accountant)

A+ Research Trust
Genevieve Morris

Statisticians:
John Pearson (Uni Otago)
Cameron Walker (Uni Auck)

Thanks to Nikki Mills for slides
- Prospective descriptive study < 3 y olds
- Nasopharyngeal flora
- Bacteria present in middle ear fluid
- Impact of planned vaccination change in NZ:
  Phase 1 – Apr-Nov 2011: Cohort PCV7
  Phase 2 – Apr – Nov 2014: Cohort PCV10

3 Study Centres
ADHB, CMDHB, CDHB
OMIVI Study 2011

Total 462 participants

< 3 y olds

325
Grommet patients
RAOM & OME

137
Comparison group
No sig history ear disease

Questionnaire
&
Nasopharyngeal Swab

Middle ear samples

PCR

Culture

Pneumococcal Serotyping
Cohort: PCV7 vaccine status

Median age: 22mths

97% : >1 vaccination (all centres, G’s & C’s)
72% : “up-to-date”
39% : “up-to-date” and “on time”

Diff between cohort and comparisons

– Day care attendance: 63% vs 39%
– Family History of OME: 48% vs 21%
– Antibiotic in last 4 weeks: 62% vs 38%

Not statistically significant: Gest age and weight, breast feeding, exp to smoke, family size
Ethnicity

![Graph showing the proportion of European, Maori, Pacific Island, and Other ethnicities in Grommets (n = 325) and Controls (n = 137). The graph indicates there is no significant difference (No sig diff).]
Nasopharyngeal Carriage
Grommets vs Comparison

Positive Culture
\[
\begin{array}{c|c}
\text{Organism} & \text{Culture} \\
\hline
\text{H.inf, M.cat, S.pneu} & \text{86\%} \\
\text{Comparison} & \text{76\%} \\
\end{array}
\]

\text{for} \geq 1 \text{ organism: H.inf, M.cat, S.pneu}
\text{p < 0.01}
Nasopharyngeal Carriage
Grommets vs Comparison

<table>
<thead>
<tr>
<th></th>
<th>Grommets n = 325</th>
<th>Comparisons n = 137</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.inf</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>M.cat</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>S.Pn</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
</tbody>
</table>
OMIVI Study Results: Middle ear findings

325 Grommet Patients
441 Middle ear samples
Middle Ear Findings
650 Ears

- Mucoid: 40%
- Dry: 33%
- Mucopus: 13%
- Serous: 15%
Culture: Middle Ear Effusions

428 samples: 33% positive culture for ≥ 1 organism
Culture vs PCR: Middle Ear Effusions

% of positive results for different pathogens:
- H. inf
- M. cat
- S. pneu

Comparison between Culture and PCR methods.
Pneumococcal serotyping
Nasopharynx & Ear

Only 1 incongruous result:
Ear 23B - Nasopharynx 35NT
Conclusion

- *H. influenzae* is the most prevalent organism present in the nasopharynx of <3yr olds with grommets
- Kids having grommets have higher NP carriage rate of both *H. influenzae* & *S. pneumoniae*
- *H. influenzae* is the most common organism found in middle ear fluid on culture and on PCR
- Impact of PCV10 on microbiology of middle ear fluid (currently underway)
The Northern Territory experience

• Vaccine schedule similarities to NZ
• Introduced PCV7 2001 then PCV10 – late 2009
• Children in remote aboriginal communities – high burden of ear disease

  90% have OM
  1 in 4 have tympanic perforations

Leach et al. BMC Ped Aug 2014 OM in children vaccinated during consecutive PCV7 or PCV10 schedules
Compared impact on OM wth 2 vaccines

• 900 children < 3yrs
  – 450 infants had 2 primary course of either 2 doses of PCV7
  – 450 infants had 2 × PCV10
  – (all had 1 -2 doses of another PCV age >1)
• Still had very high rates (90%) of OM
• Differences in severity: PCV10 less suppurative AOM or perforation compared with PCV7
• Concomitant 10% increase in OME in PCV10 versus PCV7

Leach et al. BMC Ped Aug 2014 OM in children vaccinated during consecutive PCV7 or PCV10 schedules
Acute & chronic ear infections

– Common problem and common reason for antibiotics
– Antibiotics are not the way to solve this and likely will us cause more problems

– Nasopharynx - a niche of competing flora that closely relates to what is behind the drum

– Conjugated pneumococcal vaccine should help – will impact on at least 1 of the Big 3