Evaluating Antimicrobial Therapy
For A O M

Prof. Hesham Abdel Fattah
Otolaryngology H & N Surgery
University of Alexandria
Egypt
Community-acquired RTIs
"Current changes & challenges"

Changes

- Emerging resistance in key pathogens
  - S. pneumoniae
  - H. influenzae
  - M. catarrhalis
- Increasing number of new pathogens
- New antimicrobial agents
- Vaccinations

Challenges

Appropriate & Responsible antibacterial usage
Acute Otitis Media (AOM) in Children

AOM: Is it common?

• The most prevalent disease of childhood after RTIs.
• The most common diagnosis for children in USA.
• The second most common diagnosis in medicine overall.
• There are around 25 million yearly visits to pediatricians related to otitis media.
• 85% of children have at least one episode of AOM by 3 years of age.
• 50% of children will have 2 or more episodes of AOM by 3 years of age.
Microbiology of AOM

Studies allover the world points to 3 bacteria as the major infecting organisms in AOM:

- **Streptococcus pneumoniae**
  - Most important
  - Greatest morbidity
  - Greatest mortality

- **Haemophilus influenzae**
  - Over 35% β-lactamase positive
  - Diminished activity of:
    - cefaclor
    - loracarbef
    - cefprozil

- **Moraxella catarrhalis**

30% of MEE in clinical AOM is sterile

Since 1949 - 2005 no change in the organisms causing OM
Prevalence of Penicillin-Intermediate and Resistant Strains of S. Pneumoniae

- **San Francisco**: 17% Pen-I, 11% Pen-R
- **New York**: 13% Pen-I, 27% Pen-R
- **Cleveland**: 19% Pen-I, 19% Pen-R
- **Mexico City**: 18% Pen-I, 37% Pen-R
- **Sao Paulo**: 14% Pen-I, 0% Pen-R
- **Hong Kong**: 6% Pen-I, 56% Pen-R
- **Riyadh**: 12% Pen-I, 6% Pen-R
- **Johannesburg**: 26% Pen-I, 5% Pen-R

Prevalence of β-lactamase-producing Strains of H. Influenzae

- **San Francisco**: 34%
- **New York**: 24%
- **Cleveland**: 20%
- **Mexico City**: 18%
- **Riyadh**: 17%
- **Hong Kong**: 29%
- **Sao Paulo**: 18%
- **Johannesburg**: 6%
Penicillin-resistant S. pneumoniae (MIC ≥ 2 µg/ml)
β-lactamase-positive H. influenzae

Middle East and Africa: penicillin-resistant S. pneumoniae

Penicillin-resistant (MIC > 2 µg/mL)
Data from various sources and various years
Regional prevalence of penicillin- & macrolide-resistant *S. pneumoniae*

- **Penicillin-resistant** (penicillin MIC $\geq 2$ µg/mL)
- **Macrolide-resistant** (erythromycin MIC $\geq 1$ µg/mL)

Regional prevalence

- **UK**
- **Germany**
- **Italy**
- **Poland**
- **Belgium**
- **Switzerland**
- **South Africa**
- **Portugal**
- **Mexico**
- **Saudi Arabia**
- **USA**
- **Singapore**
- **Spain**
- **Japan**
- **France**
- **Hong Kong**


Macrolide-resistant *S. pneumoniae*

<table>
<thead>
<tr>
<th>Year</th>
<th>Alexander Project 2001</th>
<th>PROTEKT 2001</th>
<th>PROTEKT 2002</th>
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<tbody>
<tr>
<td>Isolates (%)</td>
<td>30.2</td>
<td>32.7</td>
<td>36.9</td>
</tr>
<tr>
<td>Macrolide resistant</td>
<td>18.2</td>
<td>18.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Penicillin resistant</td>
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Resistance rates in the Middle East

- β-lactam strains: 28%
- M. catarrhalis: 100%
- DRSP: 58%

H. influenzae
M. catarrhalis
Drug resistant S. pneumoniae


AOM: Risk Factors For Recurrent AOM

- Parental smoking.
- Day care attendance.
- Allergies e.g. nasal allergy.
- Infection with an antibiotic resistant strains of the major 3 pathogens.
Risk factors for being infected by a drug-resistant pathogen:

- Age less than 2 years.
- Antibiotic use in the past 3 months, particularly low doses and for more than 5 days.
- Living in a region with a relatively high prevalence of antibiotic resistance.

<table>
<thead>
<tr>
<th>Last β-lactam</th>
<th>Rate of PRSP carriage (%)</th>
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<tbody>
<tr>
<td>- No use</td>
<td>1.0</td>
</tr>
<tr>
<td>- Low dose</td>
<td>7.0</td>
</tr>
<tr>
<td>- High dose</td>
<td>0.0</td>
</tr>
<tr>
<td>- Low dose + long duration (&gt; 5 days)</td>
<td>8.0</td>
</tr>
<tr>
<td>- High dose + short duration</td>
<td>0.0</td>
</tr>
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</table>

- Carriage of penicillin resistant S. pneumoniae (PRSP) in children according to duration & dose of last antibiotic treatment.
- An odds ratio greater than 1 indicates a strong association.

Guillemot, et al. 1998
In a O M in 4728 child

(Antibiotic timing affects recurrence rate)

a. On the 3rd week recurrence ↓ by 3.2 times
b. On the 2nd week recurrence ↓ by 2.8 times
c. On the end of the 1st week recurrence ↓ by 1.7
d. On the day of diagnosis recurrence ↑ by 0.8

Marcus & Marcus 1983 Sweden

Effectiveness of antibacterial agent

• The possible principal pathogens.
• The site of infection (Penetration of antibiotic).
• The possible antibiotic sensitivity / local resistance patterns.
• The pharmacokinetics & pharmacodynamics
• Proper dosage.
• Proper duration of therapy.
• Compliance.
Outcomes Of Treatment With An Antimicrobial

• Clinical outcome:
  • Improvement/ disappearance of clinical Picture
    • Symptoms-Otalgia, fever, irritability
    • Signs-Tympanic membrane abnormalities

• Bacteriologic outcome:
  Eradication of bacteria from site of infection.

Clinical Vs Bacteriologic outcome

Clinical outcome is influenced by factors other than bacteriologic efficacy of an antibiotic.

Clinical outcome is not an index for antibiotic efficacy.
Non bacterial AOM

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Unfavorable clinical outcome

Underestimation of efficacy of an antibiotic

30 % of all AOM are non bacterial, 20 % of them shows clinical failure inspite of antibiotic therapy.

(Marcus & Marcus 1976)

Spontaneous resolution of infections

Greater number of favorable clinical outcome

Overestimation of efficacy of an antibiotic
AOM

• Highly effective agents may appear slightly worse than they are because of clinical failure due to non-bacterial AOM.

• Poorly effective agents may appear much more better than they really are because of spontaneous resolution of some cases of AOM.

AOM : Clinical outcome Vs bacteriologic outcome

• Less than 50 % of bacteriologic failures present as clinical failure.

• In other words more than 50 % of bacteriologic failure present as favorable clinical outcome.

AOM: Clinical outcome Vs bacteriologic outcome

Clinical outcome is influenced by factors other than bacteriologic efficacy of an antibiotic.

Clinical outcome is not an index for antibiotic efficacy.

Marchant CD et al. J. Pediatrics, 1992;120:72-77.
But..there are differences in bacteriological success rates

- Some drugs in use today are no better than placebo

Source: Dagan et al., various studies

**Correlation between bacterial eradication and clinical efficacy in AOM**

What is the relevance of clinical outcome studies

Take care during the interpretation of results of drugs treating AOM

AOM : Basing treatment decisions on bacteriologic outcome

Due to concerns regarding the use of clinical outcome, infectious disease experts recommend that the endpoint of studies to compare the efficacy of antibiotics should be “Bacteriologic outcome”, as measured by repeat culture of specimens from the site of infection.
AOM: Basing treatment decisions on bacteriologic outcome

(142 children with bacterial AOM)

Bacteriologic efficacy on day 4-6 of treatment:

• Amoxicillin/Clavulanate: 83%
• Azithromycin: 49%

(p< 0.001)

The “Gold Standard” for assessing bacteriology in AOM is the “Double Tap” i.e. double tympanocentesis.

Aspiration of MEE before & during treatment to confirm bacterial eradication.

However

Tympanocentesis is rarely performed in clinical settings “Double tap” studies are very limited.
Clinical Practice Guidelines

Guidelines provide a consensus opinion of a group of experts that is founded on evidence-based medicine.

It has the advantages of being:

- Dependant on reliable studies (proper study design, statistics, interpretation of data).
- Bacteriological Results are totally considered.
- Unbiased.

Which Antibiotic?

- Fluoroquinolones
- amoxicillin-clav
- Amoxicillin
- Cephalosporins
- Doxycycline
- Clindamycin
- Macrolides
Treatment guidelines for AOM - Day 0

**Antibacterial therapy within previous 4-8 weeks?**

**NO**
- amoxicillin (45-90 mg/ kg/ day)

**YES**
- amoxicillin ± clavulanate (80-90 mg/ kg/ day amoxicillin)
- cefuroxime axetil

**Treatment Failure at Day 3**

- amoxicillin + clavulanate (90 mg/ kg/ day amoxicillin)
- cefuroxime axetil
- im ceftriaxone

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“...the most effective strategy against antimicrobial resistance is to get the job done right first time - to unequivocally destroy microbes - thereby defeating resistance before it starts.”

WHO press release, June 2000: Drug resistance threatens to reverse medical progress
The future is in your hands

Thank You