Workshop on Antibacterials
Discussion on specific indications

AOM/ABS

R. Cohen

CHI Créteil, France

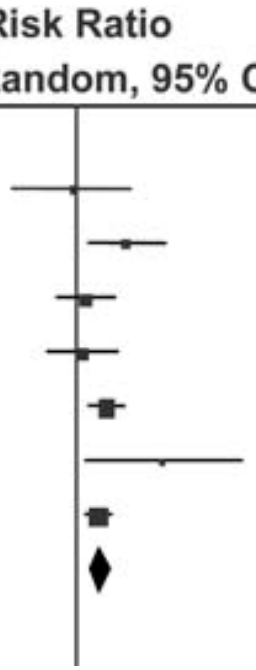
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Background

- AOM is the most frequent bacterial infection
- One of the major reason of antimicrobial use →ecological impact
- No consensus regarding the management of AOM across the Europe
  - Several guidelines : watchful-waiting strategy
  - Other guidelines : initial antibiotic treatment if young children or other conditions leading to an increased risk of unfavorable outcome
- Meta-analyses concluded that for 1 child to have relief of of symptoms, 7 to 17 children must be treated with antibiotics

Meta-Analysis of Antibiotic treatment in AOM

Study or Subgroup	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Placebo controlled trials		
Halsted 1968	3.2%	0.98 [0.75, 1.28]
Mygind 1981	6.7%	1.25 [1.05, 1.49]
van Buchem 1981 (1)	10.3%	1.04 [0.91, 1.19]
Appelman 1991	7.5%	1.03 [0.87, 1.21]
Burke 1991	19.1%	1.15 [1.06, 1.24]
Damoiseaux 2000	1.9%	1.48 [1.04, 2.13]
Le Saux 2005	22.1%	1.10 [1.03, 1.18]
Subtotal (95% CI)	**70.9%**	**1.11 [1.05, 1.18]**



Vouloumanou Journal of Antimicrobial Chemotherapy (2009) 64, 16–24

Each of the studies included in these meta-analyses had substantial flaws in study design including

- Lack of precise criteria for the diagnosis of AOM
- Participation of physicians who were not validated otoscopists
- Inadequate sample size,
- Inclusion of
  - Older children,
  - Children who had minimal or uncertain signs of disease,
- Ambiguous end points for cure or failure.

Wald Pediatr Infect Dis J, 2003;22:103–4

2 last studies…in 2011

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 13, 2011 VOL. 364 NO. 2

Treatment of Acute Otitis Media in Children under 2 Years of Age

Alejandro Hoberman, M.D., Jack L. Paradise, M.D., Howard E. Rockette, Ph.D., Nader Shaikh, M.D., M.P.H.,

The NEW ENGLAND JOURNAL of MEDICINE

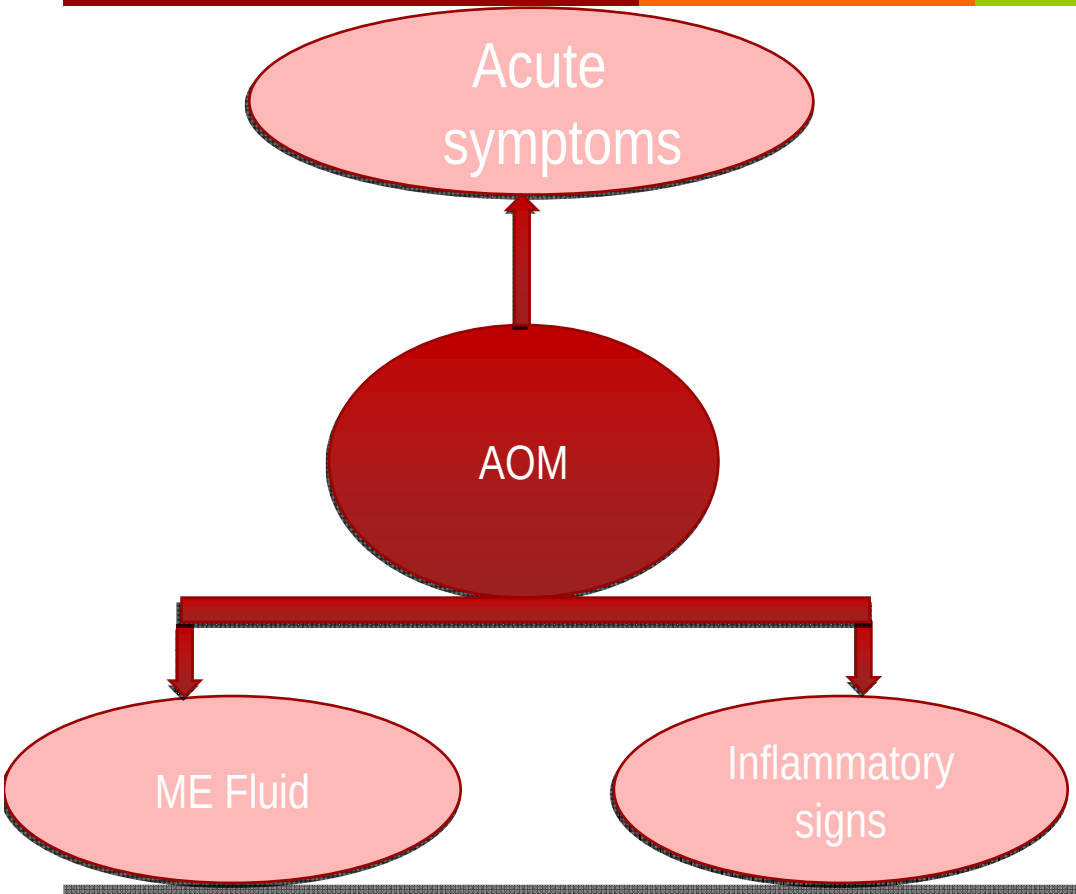
ORIGINAL ARTICLE

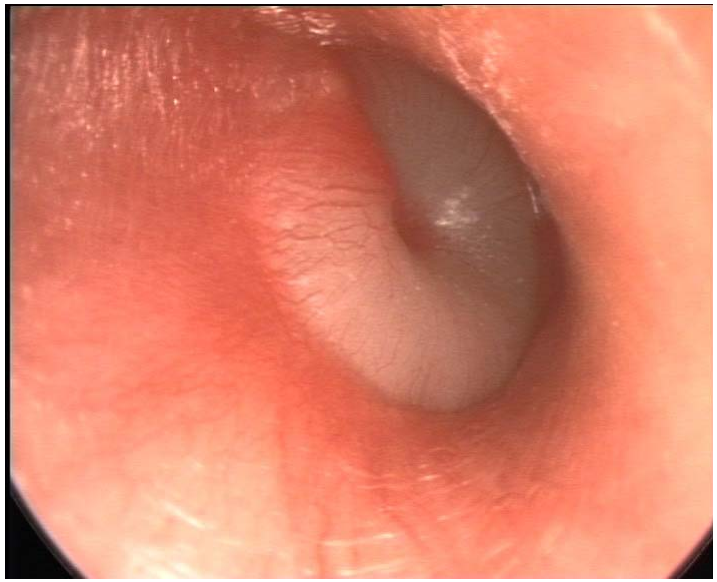
A Placebo-Controlled Trial of Antimicrobial Treatment for Acute Otitis Media

Paula A. Tähtinen, M.D., Miia K. Laine, M.D., Pentti Huovinen, M.D., Ph.D.,

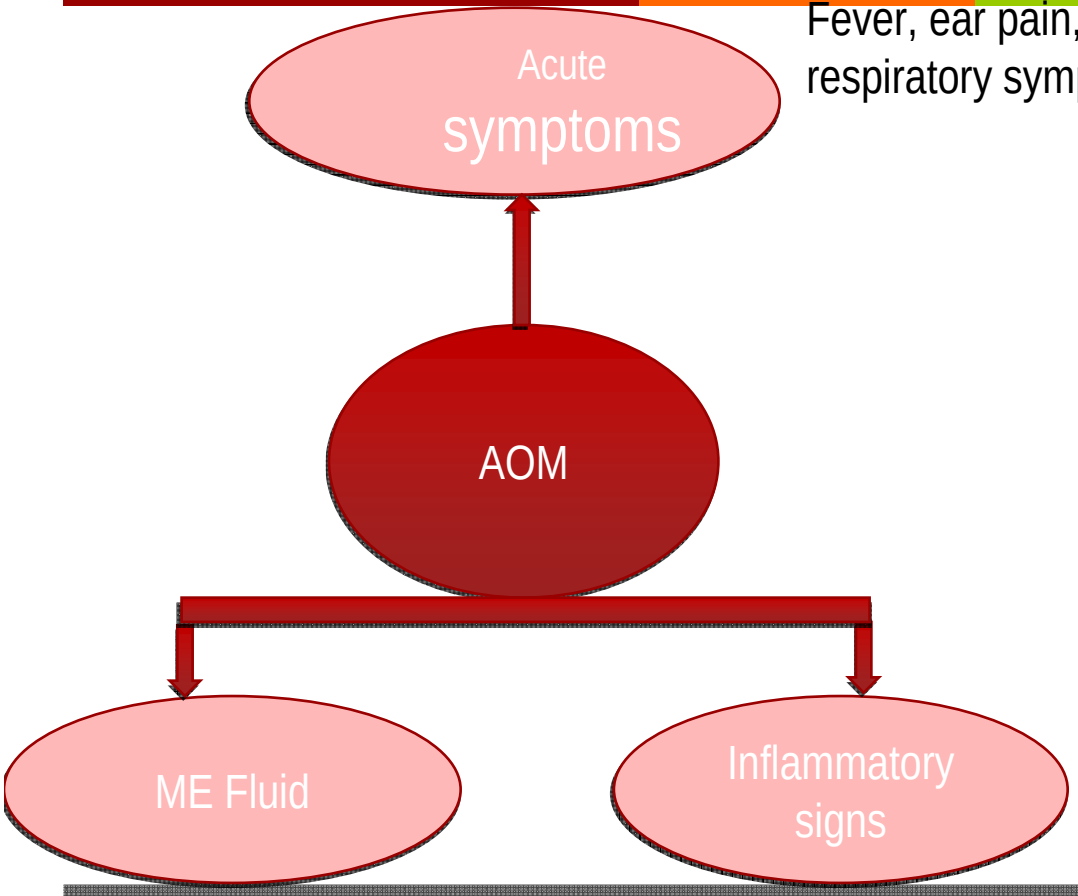
- Randomized, double blind, placebo studies
- Experienced (validated) otoscopists
- Young children
- Meticulously (clear) diagnosis of AOM
  - Acute onset of the symptoms
  - MEF
  - Inflammation

The Key : the accuracy of the diagnosis

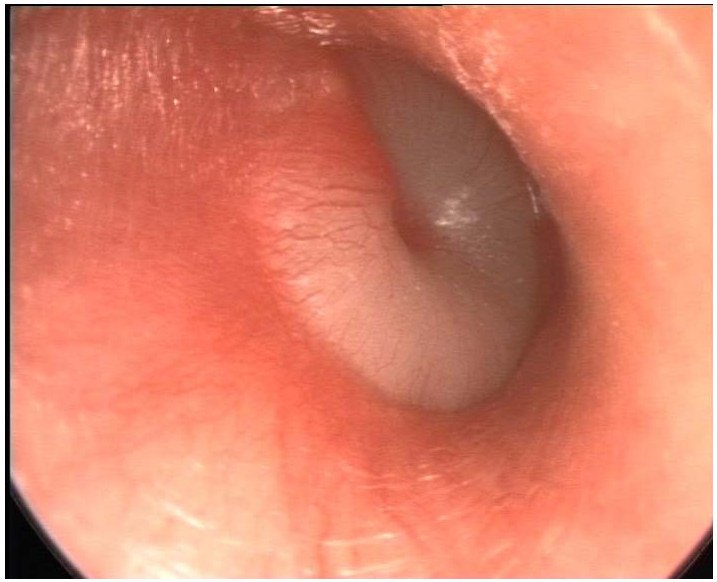




The Key : the accuracy of the diagnosis



Fever, ear pain,
respiratory symptoms



Erythematous patches, increased
vascularity, bulging or yellow tympanic mb

Bulging position, decreased of absent mobility, abnormal color or opacity

2 last studies…in 2011

Treatment of Acute Otitis Media in Children under 2 Years of Age

Alejandro Hoberman, M.D., Jack L. Paradise, M.D., Howard E. Rockette, Ph.D., Nader Shaikh, M.D., M.P.H.,

A Placebo-Controlled Trial of Antimicrobial Treatment for Acute Otitis Media

Paula A. Tähtinen, M.D., Miia K. Laine, M.D., Pentti Huovinen, M.D., Ph.D.,

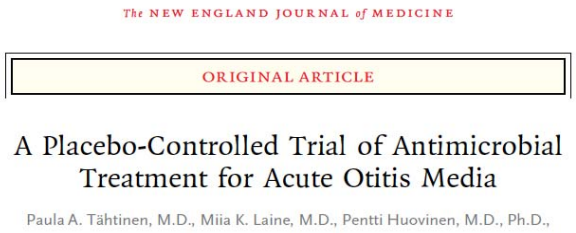
- Randomized, double blind, placebo studies
- Experienced otoscopists
- Young children
- Meticulously (clear) diagnosis of AOM
  - Acute onset of the symptoms
  - MEF
  - Inflammation

Young children with a certain diagnosis of AOM recover more frequently and more quickly with appropriate antibiotics

2 last studies…in 2011

Treatment of Acute Otitis Media in Children under 2 Years of Age

Alejandro Hoberman, M.D., Jack L. Paradise, M.D., Howard E. Rockette, Ph.D., Nader Shaikh, M.D., M.P.H.,



A Placebo-Controlled Trial of Antimicrobial Treatment for Acute Otitis Media

Paula A. Tähtinen, M.D., Miia K. Laine, M.D., Pentti Huovinen, M.D., Ph.D.,

Treatment	Placebo	Amox-clav 90mg/6.4mg bid	Placebo	Amox-clav 40mg/5.7mg bid
Duration	7 d		10 d	
Age (months) Range Mean	6-23 m ≈10 m		6-35 16 m	
N of patients	291		359	
Failures	51%	16%	44.9	18.6
	P = 0.001		P = 0.001	

2 last studies…in 2011

Treatment of Acute Otitis Media in Children under 2 Years of Age

Alejandro Hoberman, M.D., Jack L. Paradise, M.D., Howard E. Rockette, Ph.D., Nader Shaikh, M.D., M.P.H.,

A Placebo-Controlled Trial of Antimicrobial Treatment for Acute Otitis Media

Paula A. Tähtinen, M.D., Miia K. Laine, M.D., Pentti Huovinen, M.D., Ph.D.,

Treatment	Placebo	Amox-clav 90mg/6.4mg bid	Placebo	Amox-clav 40mg/5.7mg bid
Duration	7 d			
Age (months) Range Mean	6-23 m ≈10 m			
N of patients	291			
Failures	51%	16%	44.9	18.6
	P = 0.001		P = 0.001	

Prognosis factors
-3 or more children (DCC)
-Severity of the disease
-Bilateral AOM
-Bulging tympanic membrane

2 last studies…in 2011

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 13, 2011 VOL. 364 NO. 2

Treatment of Acute Otitis Media in Children under 2 Years of Age

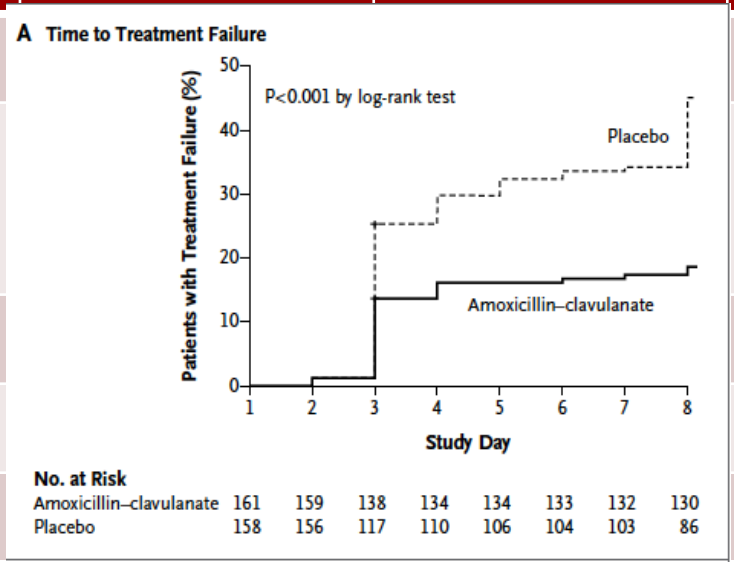
Alejandro Hoberman, M.D., Jack L. Paradise, M.D., Howard E. Rockette, Ph.D., Nader Shaikh, M.D., M.P.H.,

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

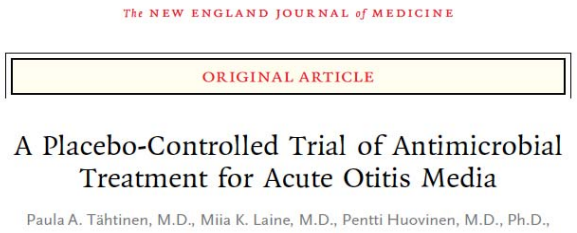
A Placebo-Controlled Trial of Antimicrobial Treatment for Acute Otitis Media

Paula A. Tähtinen, M.D., Miia K. Laine, M.D., Pentti Huovinen, M.D., Ph.D.,

Treatment	Placebo	Amox-clav 90mg/6.4mg bid	Placebo	Amox-clav 40mg/5.7mg bid
Duration			10 d	
Age (months) Range Mean			 6-35 16 m	
N of patients			359	
Failures			44.9	18.6
			P = 0.001	

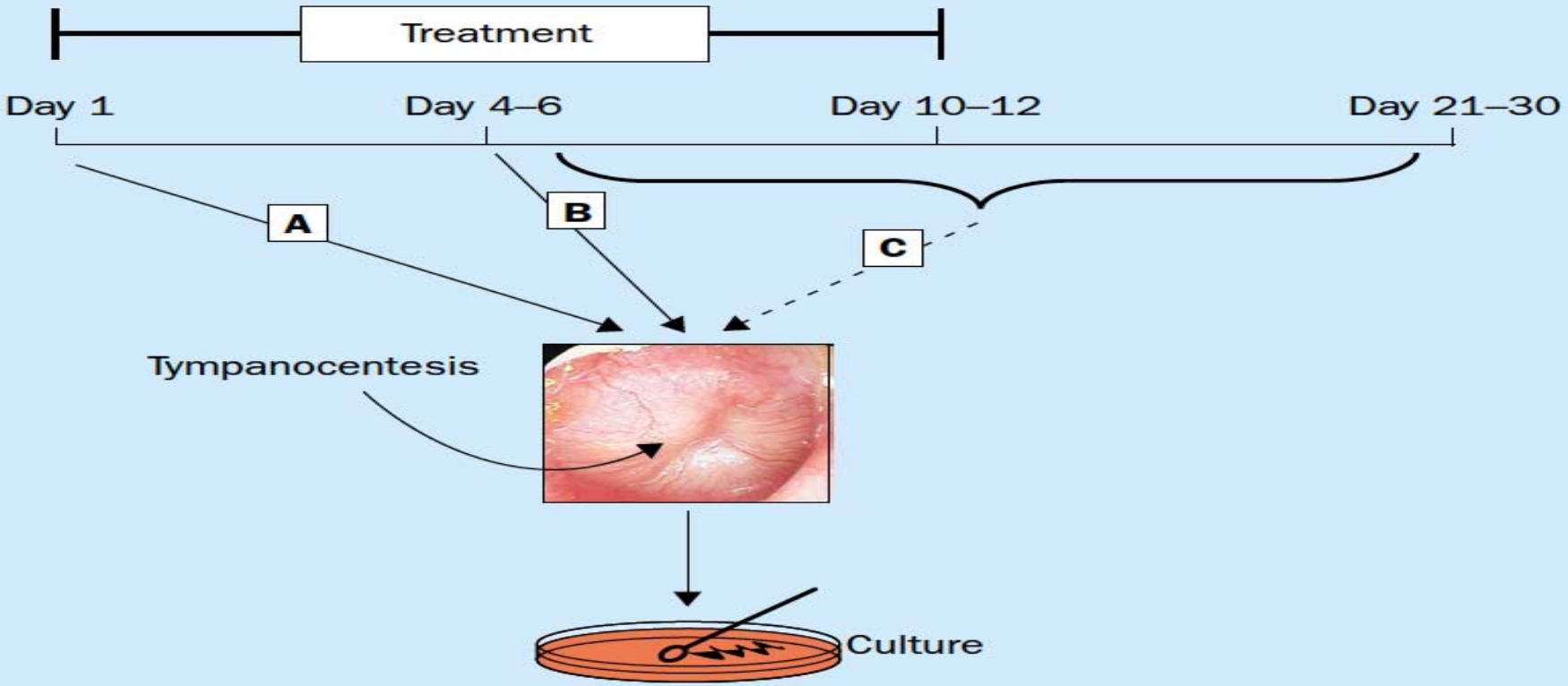


2 last studies…in 2011



Treatment	Placebo	Amox-clav 90mg/6.4mg bid	Placebo	Amox-clav 40mg/5.7mg bid
N of patients	291		359	
Perforation	6	1	5	0
Severe infection	1	0	2	0
Diarrhea (%)	7*	24*	26*	47*
Vomiting (%)	7	8		

Bacterial eradication in AOM



Dagan THE LANCET Infectious Diseases Vol 2 October 2002

Bacterial eradication in AOM

Probably the best method to assess the efficacy of antibiotics in respiratory tract infections for some resistant respiratory pathogens

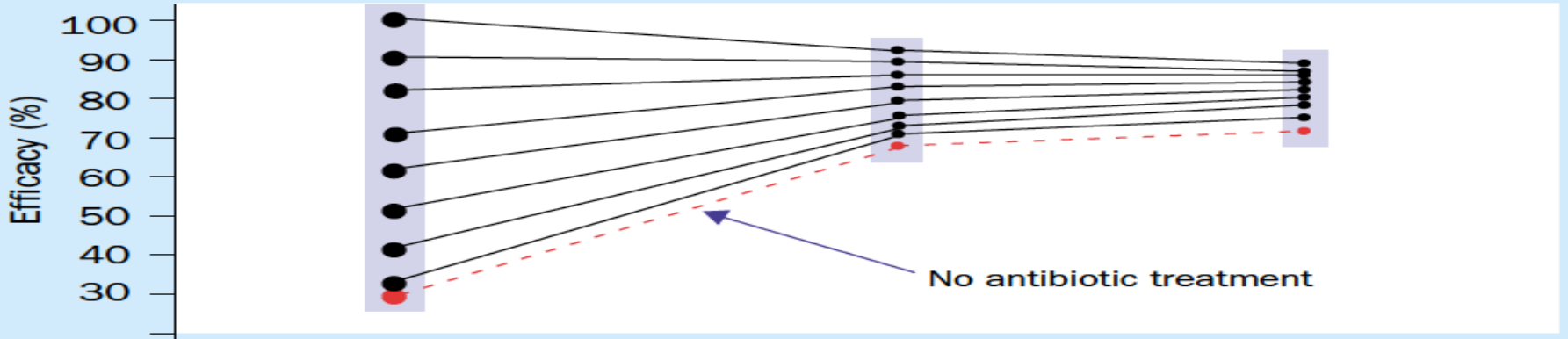
-Multidrug resistant pneumococci

-BLNAR *H. influenzae*

Dagan THE LANCET Infectious Diseases Vol 2 October 2002

Bacterial eradication in AOM

A



	(1) Bacteriological efficacy in bacteriologically proven AOM			(2) Clinical efficacy in bacteriologically proven AOM			(3) Clinical efficacy in clinical AOM		
B Sample size required to show significant differences between two drugs (drug A and drug B)	Drug A	Drug B	Sample size	Drug A	Drug B	Sample size	Drug A	Drug B	Sample size
	90	80	666	90	87	5884	87	85	15454
	90	60	100	90	81	780	87	81	1934
	90	30	30	90	72	234	87	75	542

Dagan THE LANCET Infectious Diseases Vol 2 October 2002

Systematic review of antimicrobial therapy in patients with ABS

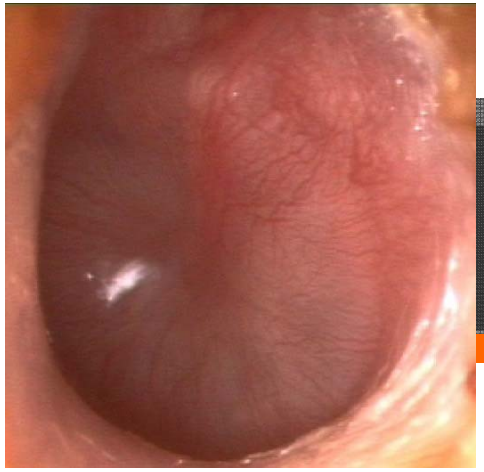
- Thirteen trials
- Placebo clinical cure rate
  - Day 3-5 8%
  - Day 7-12 35%
  - Day 14-15 45%
- Antimicrobials increased cure rates at 7 to 12 days, with an absolute rate difference of 15% (95% CI, 4%-25%).

Rosenfeld, Otolaryngol Head Neck Surg. 2007;137:S32-45.

Systematic review of antimicrobial therapy in patients with ABS

- Placebo clinical improvement
  - Day 3-5 30%
  - Day 7-12 73%
- Antimicrobials increased improvement rates at 7 to 12 days by 14% (95% CI, 1%-28%) and at 14 to 15 days by 7% (95% CI, 2%-13%).
- Over 70% of patients with acute rhinosinusitis are improved after 7 days, with or without antimicrobial therapy.
- About 7 patients must be treated to achieve one additional positive outcome at 7 to 12 days.

Rosenfeld Otolaryngol Head Neck Surg 2007;137:S32-45



Suggestions

- Placebo controlled trials are now, difficult to perform and not necessary IF a number of requirements are fulfilled
  - Double blind (single blind?)
  - Accuracy of AOM diagnosis
    - Experienced otoscopists
    - Meticulously (clear) diagnosis of AOM
      - Acute onset of the symptoms
      - MEF
      - Inflammation
  - Young children
  - Other associated risk factors
  - Calculation of the number of patients taking into account a spontaneous cure rate of 50 to 60%
- Bacterial eradication studies are probably interesting to assess the efficacy on specific resistant strains

- Placebo controlled trials are probably useful
- Improvement of accuracy of diagnosis is needed
- Bacterial eradication studies are probably interesting to assess the efficacy on specific resistant strains