Rocephin® (ceftriaxone) IM for Otitis Media

Anti-infective Drugs Advisory Committee
November 20, 1997

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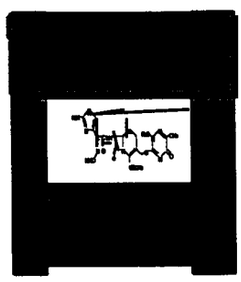
Outline

- NDA supplement for Rocephin® IM for the treatment of otitis media
- Issues in reviewing this supplement for therapy of otitis media
- Questions for the committee

Otitis Media as an indication

- Currently all anti-infective agents approved for AOM are oral therapies.

Ceftriaxone



- Cephalosporin antibiotic
- Serum $t_{½}$ of approximately 6.4 h
- Activity in vitro against Gram-positive and Gram-negative organisms commonly infecting patients with otitis media

Ceftriaxone: Current Label

Approved indications*:

- Bacterial Septicemia
- Bone and Joint Infections
- Intra-Abdominal Infections
- Meningitis
- Surgical Prophylaxis
- *due to susceptible strains of designated microorganisms
- Lower Respiratory Tract Infections
- Skin and skin structure infections
- Urinary Tract Infections
- Uncomplicated gonorrhea
- Pelvic Inflammatory disease

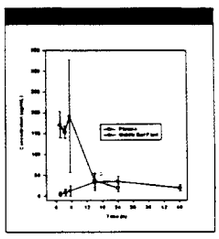
Ceftriaxone IM for Otitis Media: Proposed labeling

- Proposed addition to labeling
  - "Acute Bacterial Otitis Media caused by Streptococcus pneumoniae,(including penicillin-resistant strains). Haemophilus influenzae (beta-lactamase positive and negative strains), and Moraxella catarrhalis."
- Proposed Dosage
  - "For the treatment of acute bacterial otitis media, a single intramuscular dose of 50 mg/kg (not to exceed 1 gram) is recommended."

The studies

- Data submitted in this supplement were as follows
  - 8 trials
    - » 1 pK
    - » 5 clinical
    - » 2 bacteriologic

Icelandic pK study



- children with otitis were dosed with im ceftriaxone and plasma and middle ear fluid samples were obtained at various time points.
- Middle ear concentrations
  - levels
    - » @1.5h level approximately 4mcg/mL
    - » peak level @24h of 35 mcg/mL
    - » @48 h 19 mcg/mL
  - estimated half life -- 25 h
  - exceeded MICs -- up to 6 days as determined from simulation

5 Clinical trials

- 1 conducted by Roche under the U.S. IND
- 3 single investigator
- 1 multicenter French trial

The Green Clinical Study

- Design:
  - 261 patients
    - » 210 FDA evaluable
    - » 21 Sponsor not evaluable
      - lost to follow up and intercurrent illness
    - » 30 FDA not evaluable
      - 25 did not have sn/sx of AOM, 5 rec OM
  - randomized, double-blind, double-dummy
  - comparator - Amoxicillin
- Results Clinical Success
  - d10
    - » 90% Ceftriaxone
    - » 95%Amoxicillin
    - » [-13.3%, 2.7%]
  - and d30
    - » 71.0% Ceftriaxone
    - » 79.2% Amoxicillin
    - » [-20.8%, 4.5%]
- Issues:
  - exclusion
  - retrospective eval(d10,d30)
  - inclusion

Green study: baseline data based on FDA evaluable patients

	Ceftria--xone (n=108)	Amox--icillin (n=102)	Over--all
Otoscopy			
Discoloration	82.4%	91.6%	88.6
Opacity	63.0%	56.7%	61.0
Bulging	41.7%	39.7%	41.4
Tympanometry♣	100%	100%	100%

♣-low compliance,high pressure or low pressure

The Chamberlain Clinical Study

- Design
  - 73 patients
    - » 51 FDA evaluable
    - » 20 Sponsor not evaluable
      - lost to follow-up, negative tympanogram
    - » 2 FDA not evaluable
      - recurrent OM
- Issues
  - under powered (640 planned enrollment)
  - blinding lost 30%
  - 2nd f/u b/w d14-d197
- Results: Clinical Cure
  - Success :
    - » 57% Ceftriaxone
    - » 48% Cefaclor
    - » [-22.1%,40.7%]

Regulatory framework
Points to Consider

- Suggests 2 trials:
  - 1 clinical trial
    - » statistically adequate
    - » well-controlled
    - » multicenter trial
    - » rigid case definition
  - 1 micro trial
    - » open label study
    - » tympanocentesis
    - » micro should include :
      - 25 with *S. pneumoniae*
      - 25 with *H. influenzae*
      - 15 with *M. catarrhalis*

Regulatory Framework
Divisional Evaluability Criteria

- Clinically evaluable patients:
  - clinical diagnosis of AOM
    - » history
    - » physical examination
    - » pneumatic otoscopy
    - » tympanometry
- Microbiologically evaluable
  - microbiological dx of AOM obtained by tympanocentesis

Regulatory Framework
Divisional Evaluability Criteria

- " Test - of - Cure -- This visit should occur approximately 1 to 2 weeks after the completion of therapy..."

Establishing lower bounds in therapeutic equivalency trials(PTC)

for success rates	lower bound of the CI
->=90%	-10%
->=80%	-15%
->=70%	-20%

Review strategy for ceftriaxone IM for otitis media

- To analyze both intent-to-treat and per protocol subsets
- To examine data from multiple perspectives by analyzing differences in:
  - Clinical/microbiologic response to single dose ceftriaxone vs. traditional regimens
  - Need for modification of anti-microbial regimen
    - » Patients who received 2 injections of ceftriaxone

Inclusion criteria

- **All enrolled patients :**
- between 3m and 6 years at study entry
- diagnosis of otitis media (using evaluability criteria)
  - one or more specific symptoms (otalgia,fever,ear pulling etc)
  - signs
    - » full/bulging/erythema
  - pneumatic otoscopic finding (/impaired mobility)

Exclusion criteria

- **All enrolled patients who:**
- unable unwilling to provide informed consent.
- treatment with a systemic antibiotic within the last 7 days.
- Other source of infection requiring treatment with an antibiotic other than the test med.
- Otorrhea or a perforation of the tympanic membrane.
- Tympanostomy tubes
- A known allergy to cephalosporins or lidocaine.
- not brought back to the investigational site for all required evals.
- predisposition to recurrent ear infections such as an anatomical or physiologic defect of the ear or oro-nasopharynx (ie, cleft palate), immunodeficiency, or other serious underlying disease.
- Taken an oral steroid within 24 hours or an injection of decadron within 30 days.
- Recently received an investigational drug.
- Previously participated in this trial.
- unable to understand and follow instructions.

Exclusion criteria

- **All enrolled patients who:**
- Hx of recurrent otitis media (defined as
  - 4 episodes per year for the last 2 years or
  - 3 episodes in a child who is 12 months old or under).
- A history of acute otitis media within 30 days of entry into the study.

IM Ceftriaxone for otitis media:Randomized trials

NAME/ #PTS	STUDY DESIGN	COMPARATOR	EFFICACY ENDPOINTS
Roche/ 649	**ProspectivexR, IB, MC. Age range, 3 mo - 6 yr.**	**Amoxicillin-clavulanate po for 10 d (40 mg/kg/d)**	**Clinical response @wk2 and wk4**

Roche Clinical study

- Study Population
  - n=649
  - FDA evaluable=598
  - Sponsor not evaluable =47
    - » lost to follow up
    - » sn/sx not AOM
  - MO not evaluable = 0
- Trial Design Issues
  - none

Results: Roche Clinical Study Evaluable Population

Efficacy Parameter	Cure Rate		95% CI
	Ceftriaxone	Augmentin	
week 2	74% (220/296)	82% (247/302)	[-14.4%, -0.5%]
week 4	58% (167/288)	67% (200/297)	[-17.5%, -1.2%]

IM Ceftriaxone for otitis media:Randomized trials

NAME/ #PTS	STUDY DESIGN	ROCEPHIN® IM 50 mg/kg	COMPARATOR	EFFICACY PARAMETERS
Klein/ 596	**Prospective, R, IB,SC. Age range, 3 mo - 3 yr.**	**Single IM injection ; second injection after Day 2-3 discretionary (23 patients)**	**TMP-SMZ po for 10 d (40 mg SMZ/kg/d)**	**Clinical response @wk2 and wk4**

Klein Clinical study

- Study population
  - n=596
  - FDA evaluable=416
  - Sponsor not evaluable =132
    - » no baseline effusion
    - » lost to follow up
    - » sn/sx not AOM
  - MO not evaluable = 28
    - » recurrent OM
    - » OM <30 days prior
- Trial Design Issues
  - added some exclusions
  - 2nd dose patients (23)

Results: Klein Clinical Study Evaluable Population

Efficacy Parameter	Cure Rate		95% CI
	Ceftriaxone	TMP-SMZ	
week 2	53.8% (113/210)	60.2% (124/206)	[-16.4%,3.6%]
week 4	35.4% (73/206)	45.4% (93/205)	[-19.9%,-0.003]

IM Ceftriaxone for otitis media:Randomized trials

NAME/ #Pts	STUDY DESIGN	ROCEPHIN ® IM 50 mg/kg	COMPARATOR	EFFICACY PARAMETER
French/ 513	Prospective, R, Open, Parallel Group,MC. Age range, 4 mo - 30mo.		Amoxicillin-clavulanate po for 10 d (80 mg/kg/d)	Clinical response w2, w4

French Clinical study

- Study population
  - n=513
  - FDA evaluable=463
  - Sponsor not evaluable =50
    - » AE causing termination
    - » inappropriate time of 2nd visit
    - » non-compliance with meds
  - MO not evaluable = 0
- Issues
  - high dose Augmentin
  - np swabs
  - not blinded
  - tympanograms were completed at wk4 not at baseline

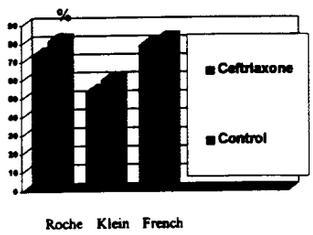
Results: French Clinical Study Evaluable Population

Efficacy Parameter	Cure Rate		95% CI
	Ceftriaxone	Augmentin	
week 2	79.1%	82.5%	[-10.9%, 4.3%]
week 4	59.0%	55.1%	[-6.7%, 14.6%]

Evaluable population demographics

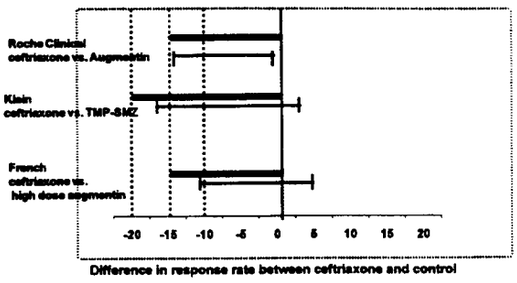
- Treatment arms balanced with respect to:
- Age, weight, sex, race
- signs and symptoms of otitis media
- tympanogram results
- pneumatic otoscopic exam

Response rates of the week 2 clinically evaluable patients

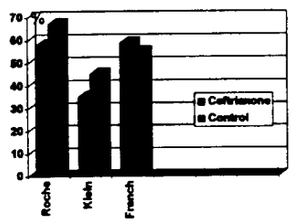


Clinical Only Studies

95% confidence intervals (evaluable subset wk 2) in the clinical studies

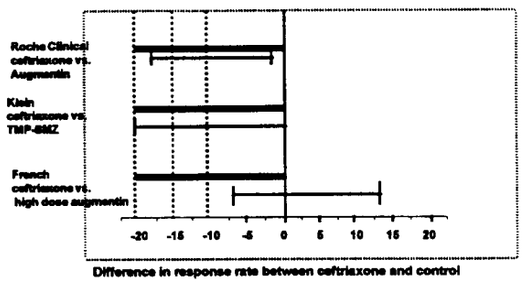


Response rates of the week 4 clinically evaluable patients



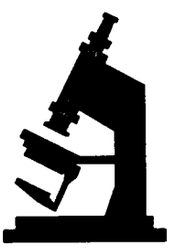
Clinical Only Studies

95% confidence intervals (evaluable subset wk 4) in the clinical studies



2 studies with microbiologic data

- **1 multicenter (U.S.)**
- **1 single investigator (U.S.)**



IM Ceftriaxone for otitis media:Bacteriologic Studies

NAME/ #PTS	STUDY DESIGN	ROCEPHIN® IM 50 mg/kg	COMPARATOR	EFFICACY PARAMETERS
Roche Bacteriologic/ 108	Prospective, Non-comparitive, open-label. Age range, 6 mo - 6 yr.	1x IM injection	None	Bacte. erad.on wk2 and wk4

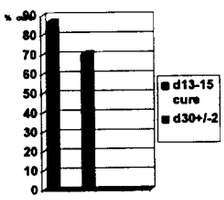
Roche Bacteriologic study

- Evaluable population
  - n=108
  - FDA evaluable=69
  - Sponsor not evaluable =29
    - » no pathogen
    - » entry violation
  - MITT=10
    - » lost to follow up
    - » sn/sx not AOM
  - MO not evaluable = 0
- Issues
  - none

Summary of bacteriologic eradication in the Roche bacteriologic study

	Day 13-15		Day 30±2	
Organism	**No. Analyzed**	**No. Erad. (%)**	**No. Analyzed**	**No. Erad. (%)**
S. PNEUMONIAE	38		35	
Penicillin Resistant	8	5 (65.2)	8	3 (37.5
Penicillin Susceptible	30	27 (90.0)	27	22 (81.5
H. INFLUENZAE				
Beta Lac (+)	33		33	
Beta Lac (-)	15	13 (86.7)	13	9 (69.2
M. CATARRHALIS	18	15 (83.3)	18	13 (72.2
Beta Lac (+)	15		15	
Beta Lac (-)	14	11(78.6)	14	8(57.1
	1	1(100.0)	1	1(100.0

Summary of cure rate for the Roche bacteriologic study



- 108 patients
- response eval d3-5,d13-15,d30+/-2d

IM Ceftriaxone for otitis media:Bacteriologic Studies

NAME/ #PTS	STUDY DESIGN	ROCEPHIN® IM 50 mg/kg	COMPARATOR	EFFI--CACY PARA--METER
Howie/ 203	Prospective, OL, SC. Age range, 6 mo - 3 yr.	1x IM injection ; 2nd injection after Day 2-3 discretionary	1x IM injection CR Bicillin followed by TMP-SMZ po for 10 d (50 mg/kg) SMZ	Bacterio--logic erad. d2-3 wk2 and wk4

Howie Bacteriologic study

- Study population
  - n=150*
  - FDA evaluable=125
  - Sponsor not evaluable =10
    - » lost to follow up
    - » consent withdrawn
  - MO not evaluable =15
    - » recurrent OM
    - » OM <30 days prior

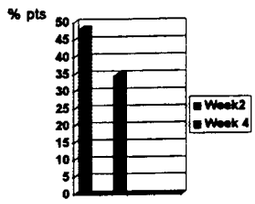
*patients who were not randomized were not analyzed at week 2

- Issues
  - 2nd dose
  - 2nd tap d2- 3
  - exclusions

Howie Bacteriologic Study

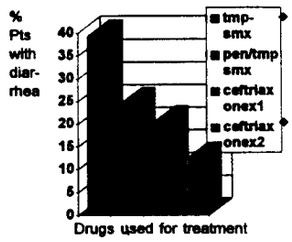
Summary of Efficacy Results: Clinical Cure rates and CIs for STD analysis	Ceftriaxone single injection (n=101)	pen/TMP-SMZ 10-day (n=49)
Cure rate at week 2	44.7%	74.4%
Cure rate at week 4	33.7%	48.8%
95% CI: Ceftraxone vs. pen/TMP-SMZ at week 2	[-48.3%, 11.2%]	
95% CI: Ceftraxone vs. pen/TMP-SMZ at week 4	[-35.2%, 5.1%]	

Subpopulation analysis: Pooled cure rates for patients who received 2 doses of ceftriaxone



- 33 patients from the Howie study
- 23 patients from the Klein study
- paradoxical decrease in efficacy
  - Perhaps explained by viral OM

Safety analysis



- No difference between ceftriaxone and controls for morbidity from total adverse events or drug related adverse events
- significant increase in diarrhea in those patients that received a second injection of ceftriaxone(Kleins' and Howies' study pooled patients.) (23+33=56)

Problematic issues which arise in the review of this drug for otitis media

- Lack of Investigator Consensus on:
- (Evaluability criteria) :
  - Inclusion and exclusion criteria
- Endpoints:
  - 1° efficacy endpoint
  - 2° efficacy endpoints

Questions

- 1. Do the safety and efficacy data presented support the approval of Rocephin® for the treatment of pediatric patients with acute otitis media (AOM)?
  - If no, what additional safety or efficacy data is necessary?
- 2. Are there recommendations that the committee would make regarding the appropriate use of Rocephin for the treatment of children with AOM?
- 3. Are there any issues that should be addressed in phase 4 studies?

36

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37

Otitis media: Antimicrobial susceptibility of major pathogens

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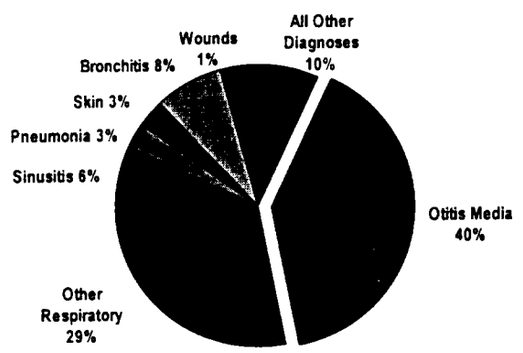
10/31/97

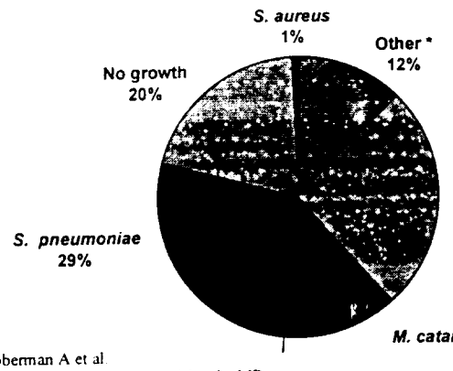
1996 Pediatric Antibiotic Usage by Diagnosis



Source: Physician Drug and Diagnosis Audit (PDDA), Scott-Levin, a division of Scott-Levin PMSI Inc.
(These data represent patients seen at an office location in 1996.)

Otitis media is one of the most frequent reasons for pediatric office visits, and is the

Key Pathogens in Acute Otitis Media



* Includes *Viridans* streptococci 0.4%, *S. pyogenes* (Group A) 2%

Adapted from Hoberman A et al
Pediatr Infect Dis J 1996;15:955-962; and Jacobs MR.
Poster presented at 35th ICAAC, 1995, E29.

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Streptococcus pneumoniae

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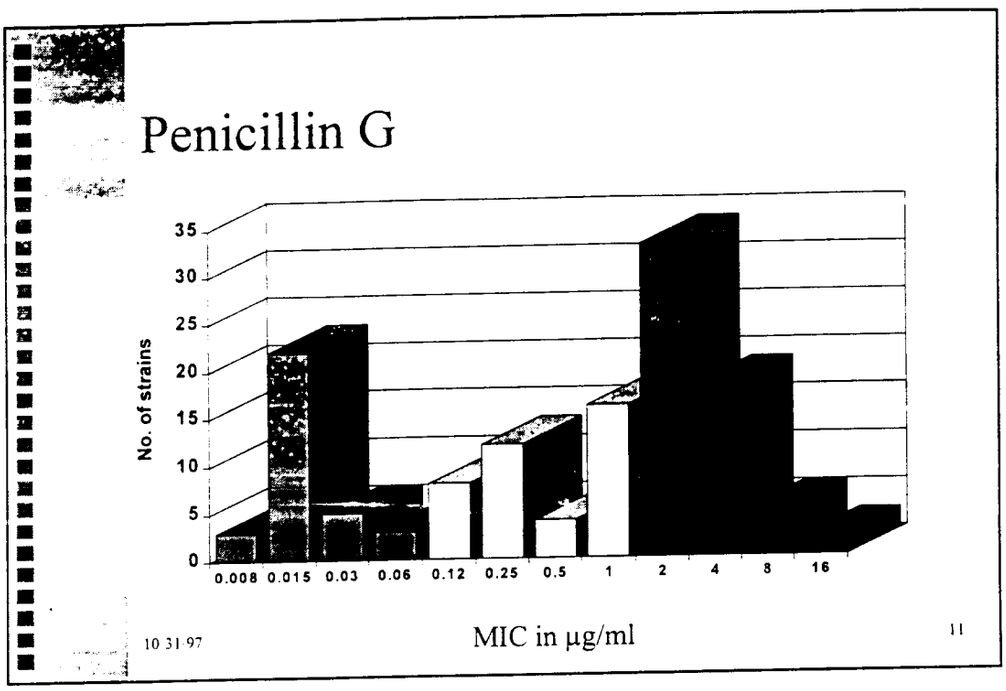
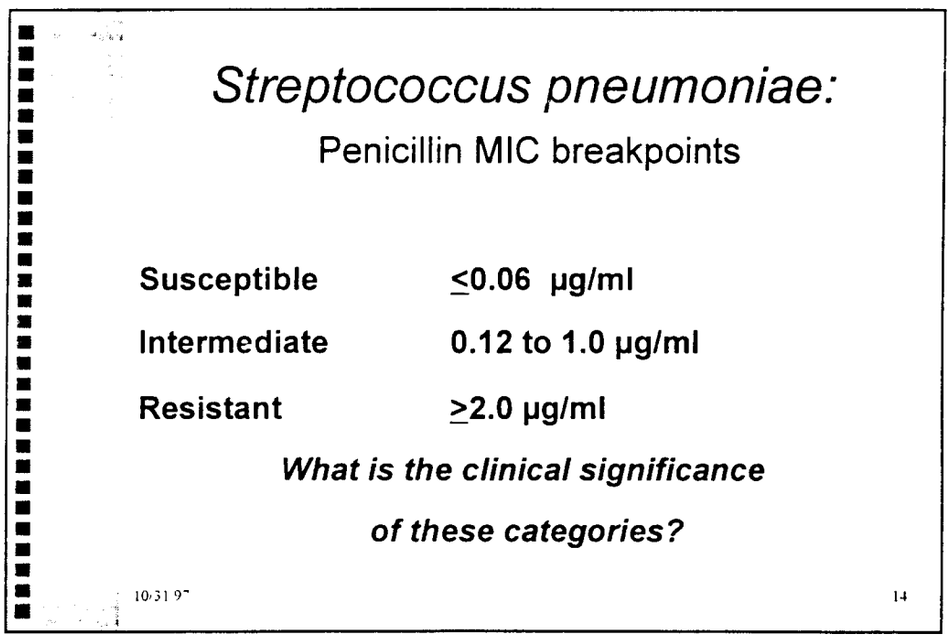
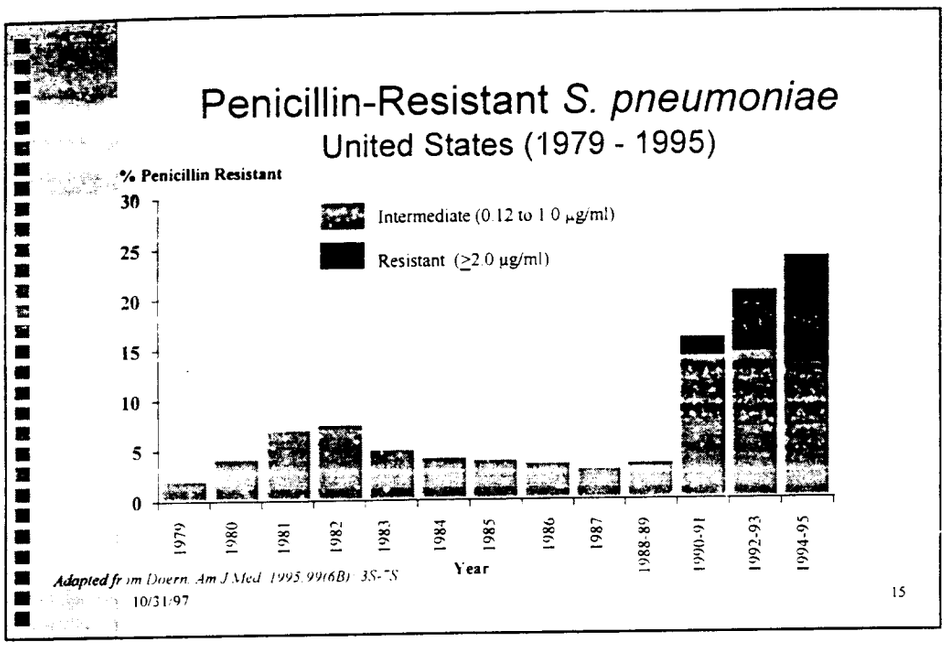
8

S. pneumoniae used to be one of the most





At the time these penicillin-susceptibility



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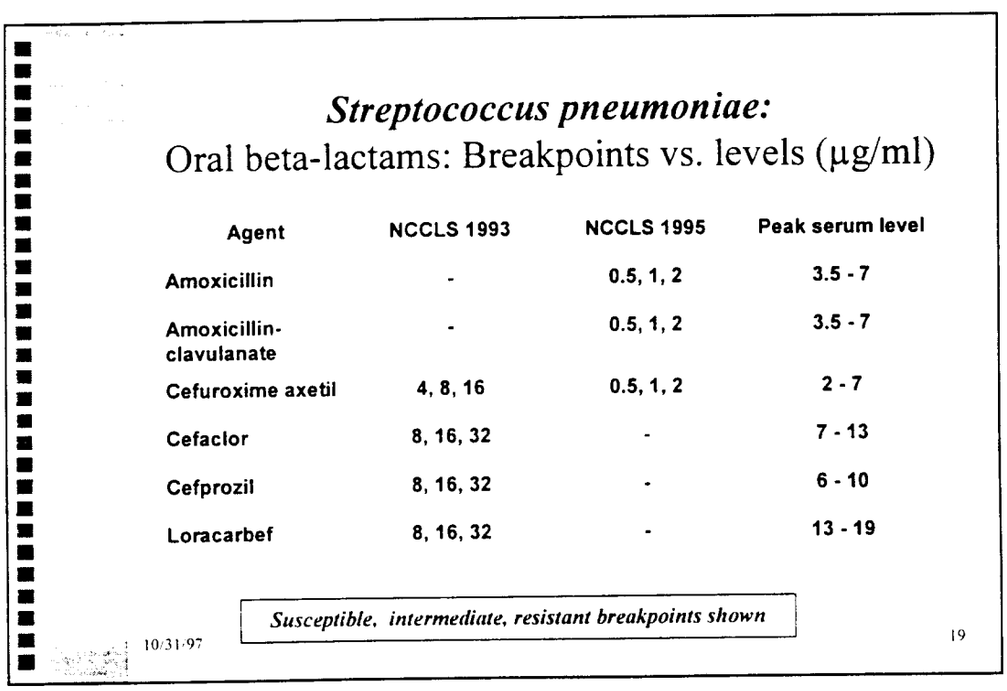
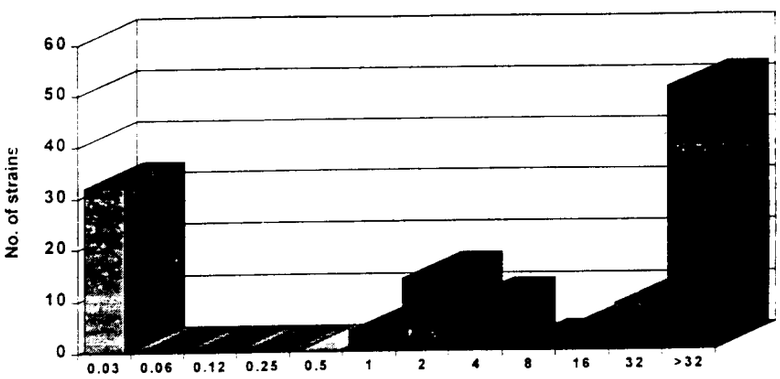


Based on the data presented, the clinical

Erythromycin

MICs by agar dilution method



From Fasola et al., Antimicr. Agents Chemother. 1997, 41:129-134

10/31/97

Macrolides: Breakpoints (µg/ml)

Agent	Susceptible	Intermediate	Resistant
Azithromycin	≤ 0.5	1	≥ 2
Clarithromycin	≤ 0.25	0.5	≥ 1
Erythromycin	≤ 0.25	0.5	≥ 1

Macrolide breakpoints apply to microdilution incubated aerobically

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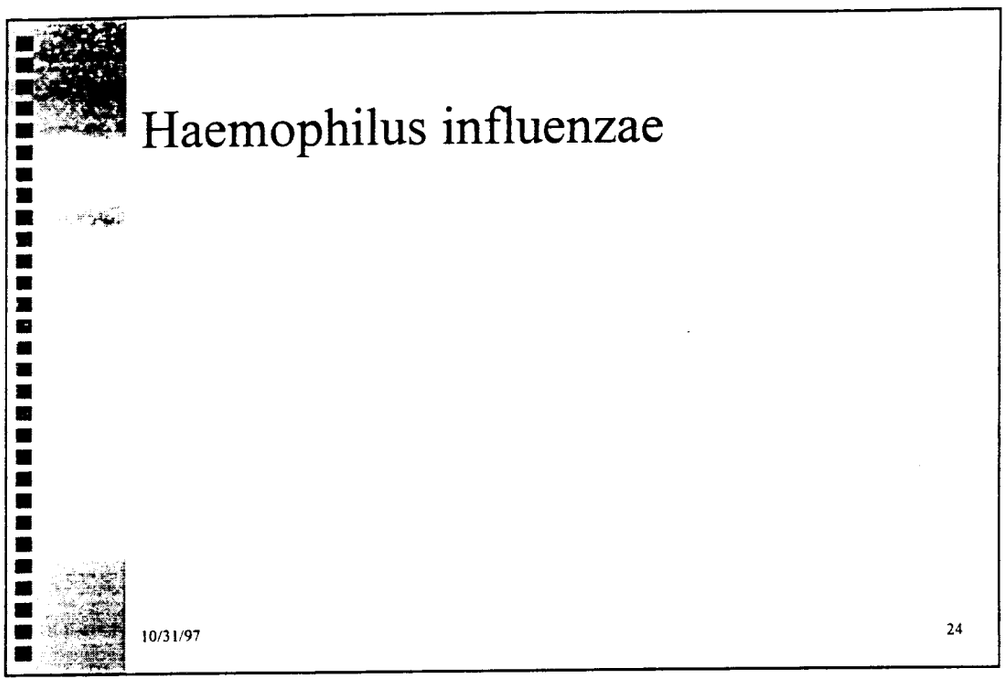
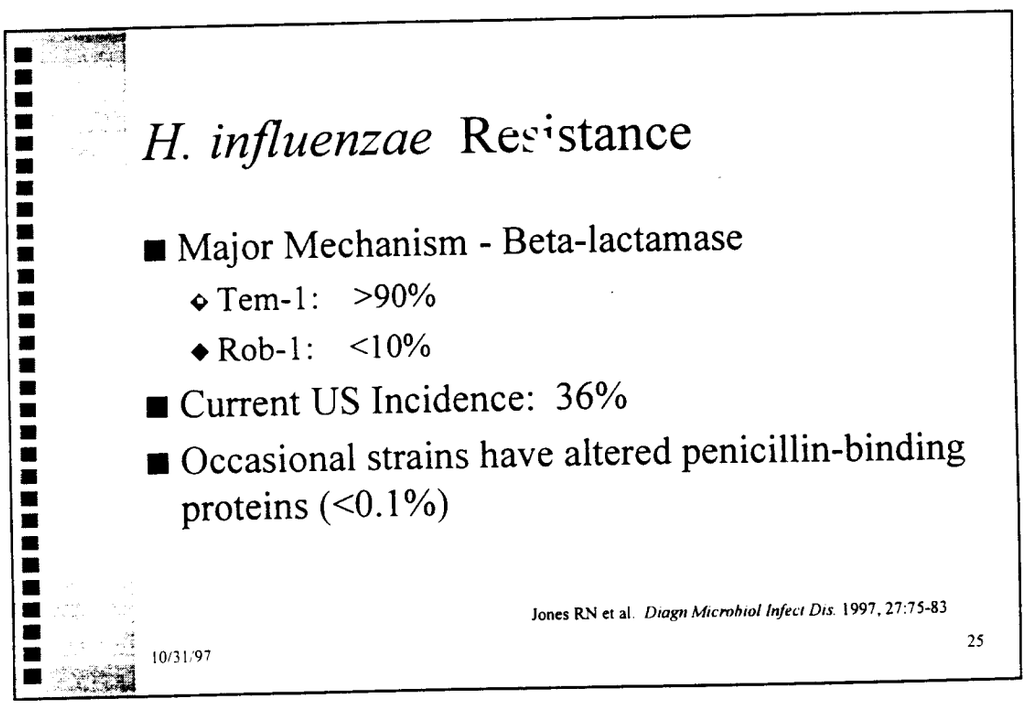
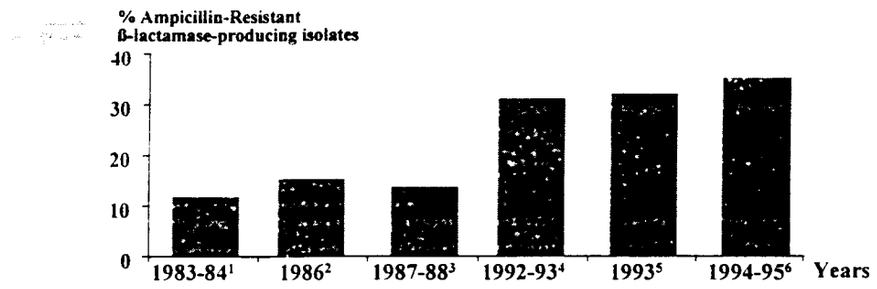
Pneumococcal-specific breakpoints for





Beta-lactam resistance in HI is predominantly due to production of beta-lactamases, which

Prevalence of ß-lactamase-producing, Ampicillin-Resistant, Non-typeable *Haemophilus influenzae* in the US



No of Centers	22	30	15	19	5	187
No of Isolates	2200	2054	564	890	5750	2278

1 Doern et al. Diagn Microb Infect Dis 1986; 4: 95
2 Doern et al. Antimicrob Agents Chemother 1988; 32: 180
3 Jorgensen et al. Antimicrob Agents Chemother 1990; 34: 2075
4 Barry et al. Antimicrob Agents Chemother 1994; 38: 2419
5 Rittenhouse et al. Diagn Microb Infect Dis 1995; 21: 223-225
6 Jones et al. Diagn Microb Infect Dis 1997; 27: 75-83

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Rates of Resistance to Selected Oral Antibiotics among Isolates of *Haemophilus influenzae*

Rate	%	Agents
Low	<1	Amoxicillin/clavulanate Cefpodoxime proxetil, Cefixime
Moderate	1 to 5	Cefuroxime axetil
High	>5	Clarithromycin, Cefprozil, Cefaclor, Loracarbef, Ampicillin

Haemophilus influenzae Susceptibility Program National Study Surveillance Data, Inc. 1995

This slide shows resistance rates of common oral agents based on current interpretative

Haemophilus influenzae:
Oral beta-lactams: Breakpoints vs. levels (µg/ml)

Agent	NCCLS 1997	Peak serum level	Agent	NCCLS 1997	Peak serum level
Amoxicillin-clavulanate	4, -, 8	3.5 - 7	Cefpodoxime	2, -, -	2.4
Cefuroxime (axetil)	4, 8, 16	2 - 7	Cefprozil	8, 16, 32	6 - 10
Cefaclor	8, 16, 32	7 - 13	Ceftibuten	2, -, -	11.2-13.3
Cefixime	1, -, -	2.8-4.4	Loracarbef	8, 16, 32	13 - 19

Susceptible, intermediate, resistant breakpoints shown

11/15/97

57

Macrolides: *Haemophilus* breakpoints (µg/ml)

Agent	Susceptible	Intermediate	Resistant
Azithromycin	< 4	-	-
Clarithromycin	< 8	16	> 32
Erythromycin	-	-	-

Macrolide breakpoints apply to microdilution incubated aerobically

11/15/97

58

33

E104

MICS OF AMOXICILLIN-CLAVULANATE AND CEFUROXIME ON INTERPRETATION OF SUSCEPTIBILITY OF *HAEMOPHILUS INFLUENZAE* TO THESE AGENTS

MICHAEL R. JACOBS

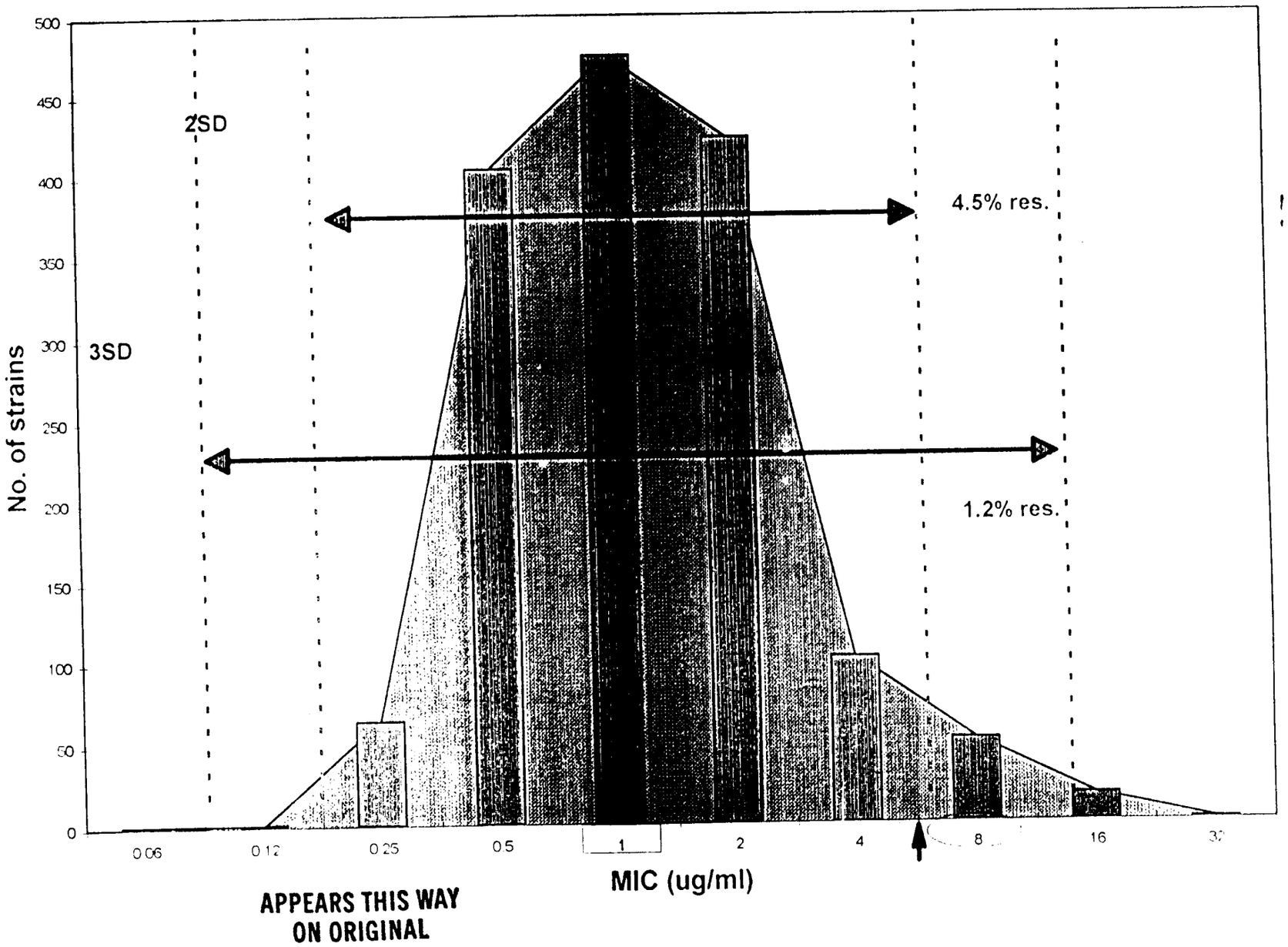
Case Western Reserve University, Cleveland, OH

The effect of distribution of MICs on interpretation of susceptibility of unimodal populations of *Haemophilus influenzae* was investigated by analysis of population distributions and confidence intervals of data from four studies to determine if susceptible and non-susceptible populations could be differentiated statistically. Data sources were 1) Doern et al., AAC 1997, 41:292; 2) Jacobs DMID 1997, 28:105; 3) Doern at al., JAC 1996, 38A:59; and 4) Jones et al. DMID 1997, 27:75. Numbers of strains in the data sets were 1539, 154, 2718 and 1910 respectively. Test methods were broth microdilution with HTM (1, 2 and 4), and MHB-LHB-NAD (3).

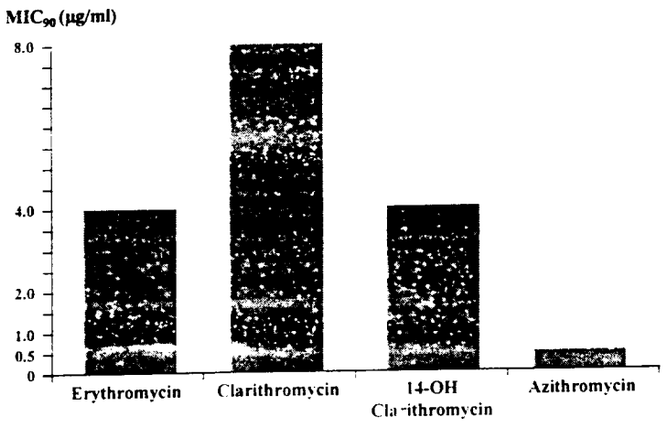
	Amoxicillin-clavulanate				Cefuroxime			
Data source	1	2	3	4	1	2	3	4
MIC_{50}/MIC_{90} (μg/ml)	1/8	0.5/4	0.5/1	0.5/2	1/4	0.5/2	1/4	1/4
Mean MIC (μg/ml)	1.15	0.6	0.6	0.5	1.23	0.66	1.16	0.9
SD (doub. dilutions)	1.2	1.15	0.68	1.6	1.25	1.24	1.0	1.23
MIC range ±2 SD (μg/ml)								
MIC range ±3 SD (μg/ml)								
% I or R	4.5	2.6	0	0.7	6.4	3.2	3.6	3.4
% I or R and beyond 2 SD	3.3	0	0	0.7	4.9	0	3.5	3.4
% I or R and beyond 3 SD	1.2	2.6	0	0.1	1.5	3.2	0.15	1.4

Geometric mean MICs were within one doubling dilution for both agents in the three studies. However, analysis of population distributions showed that, while all had poisson distributions, standard deviations (SD) varied considerably, and 95% (±2 SD) and 99.7% (±3 SD) confidence limits were very different, and overlapped the susceptible breakpoints for these agents ($\leq$4 μg/ml) in many cases. These population effects reduced raw resistance rates of up to 6.4% to $\leq$4.9% at 95% CI and $\leq$3.2% at 99.7% CI. The reasons for these variations in MIC ranges from different studies are unknown, but may be due to true population differences or to variations in methods. Categorical susceptibility interpretations may therefore not be statistically valid if population distribution analysis is not taken into consideration for populations with unimodal MIC distributions.

Amoxicillin-clavulanate Study ' (N=1539)



In Vitro Activity of Macrolides Against *H. influenzae*

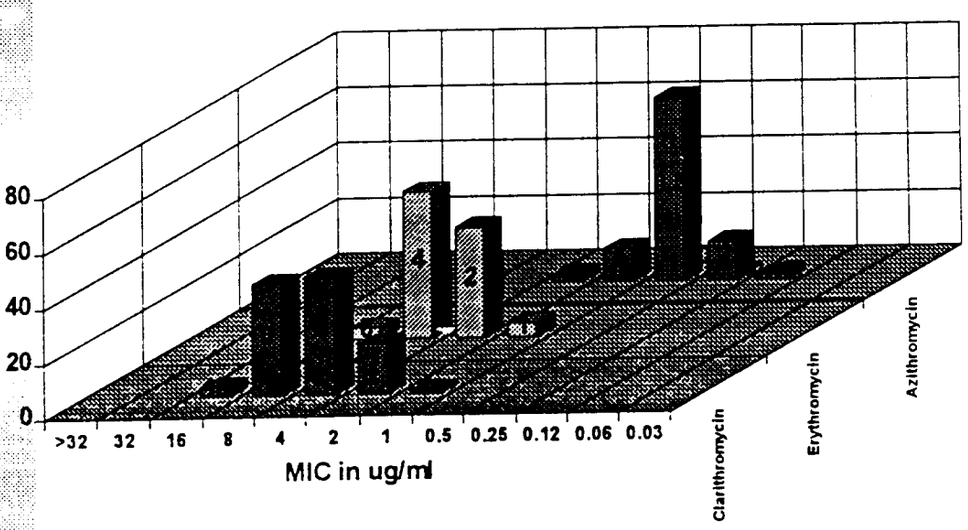


Adapted from Hardy et al. Antimicrob Agents Chemother 1988; 32: 1710-1719

10/31/97

32

H. influenzae - Macrolide MICs by microdilution

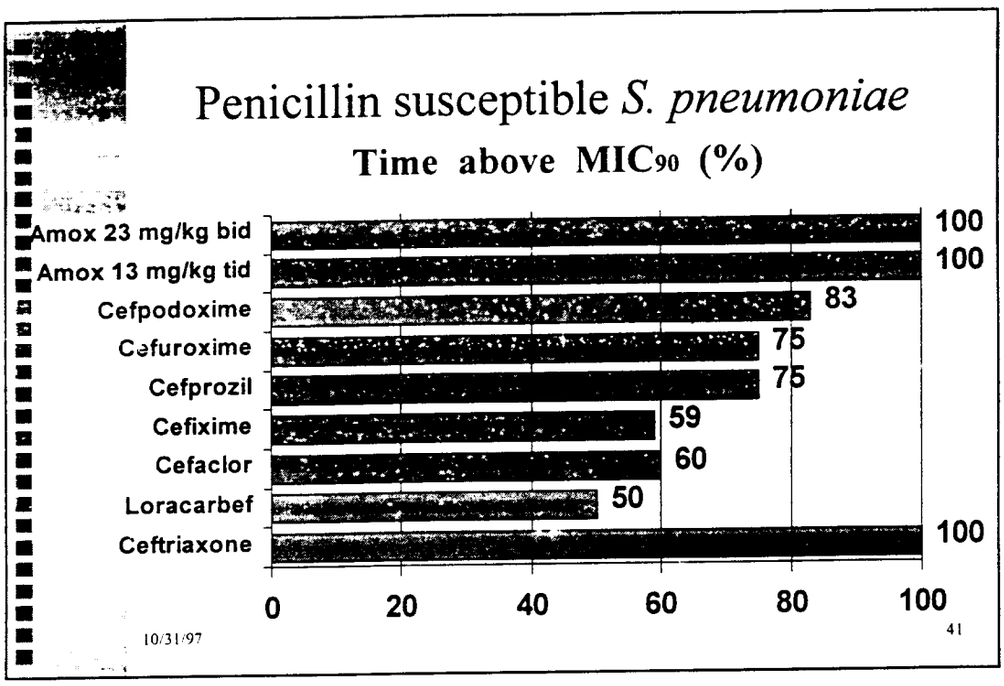


11/15/97

From Doern et al. 1996. JAC 38A:59

63

34



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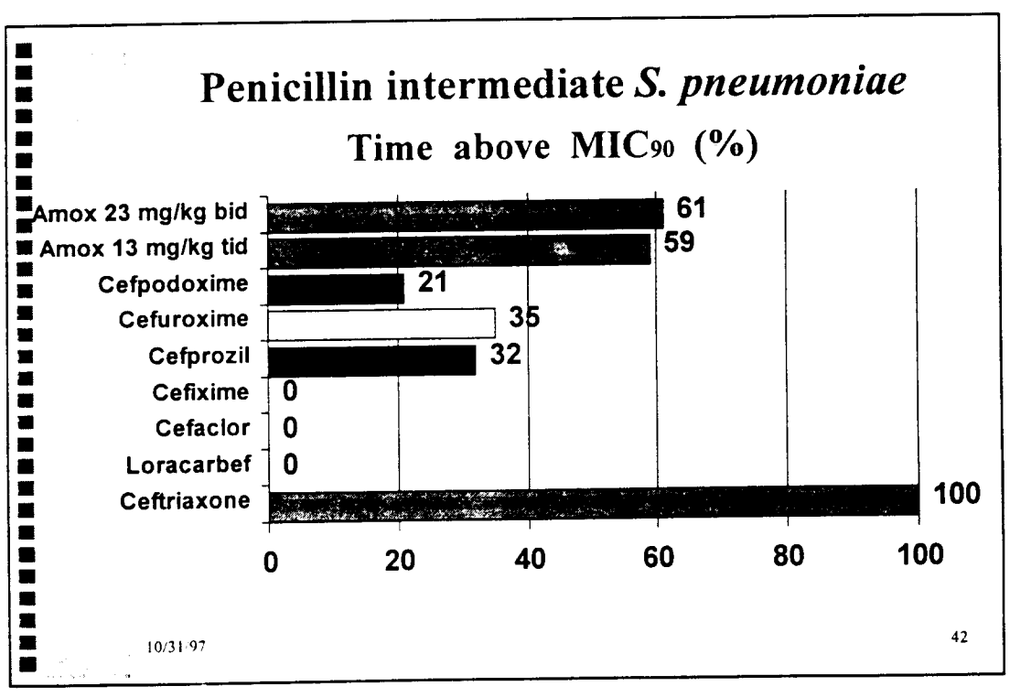
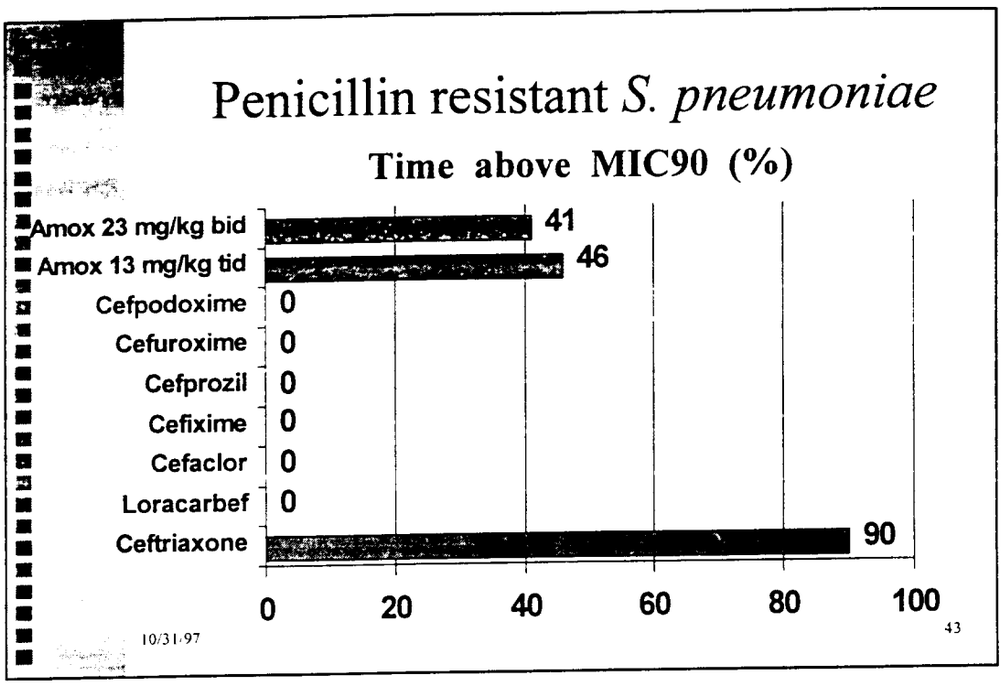


This situation changes dramatically with penI



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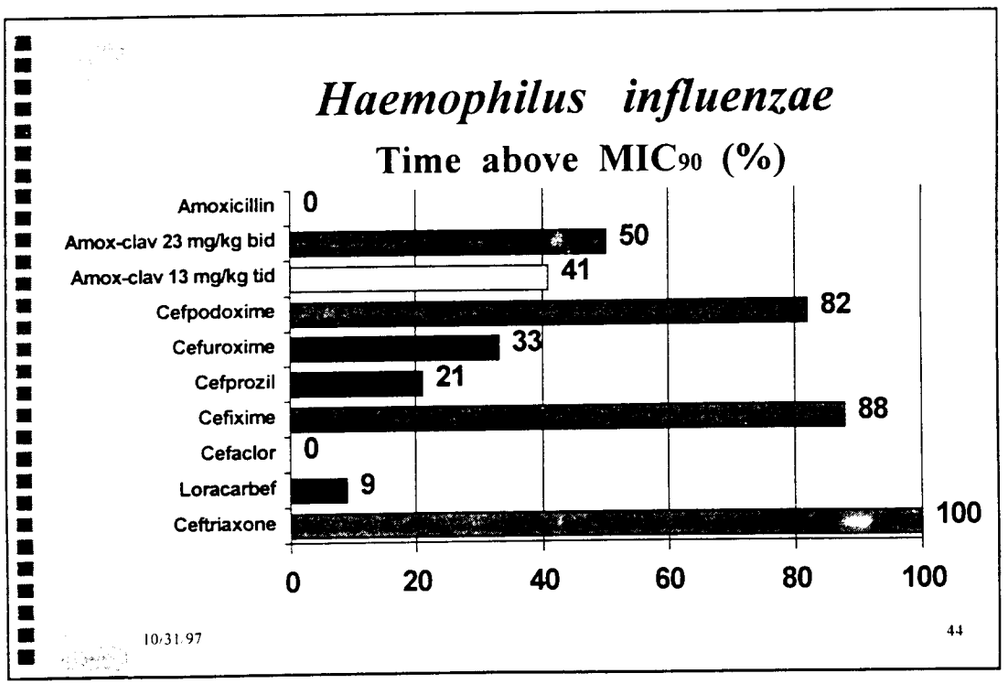
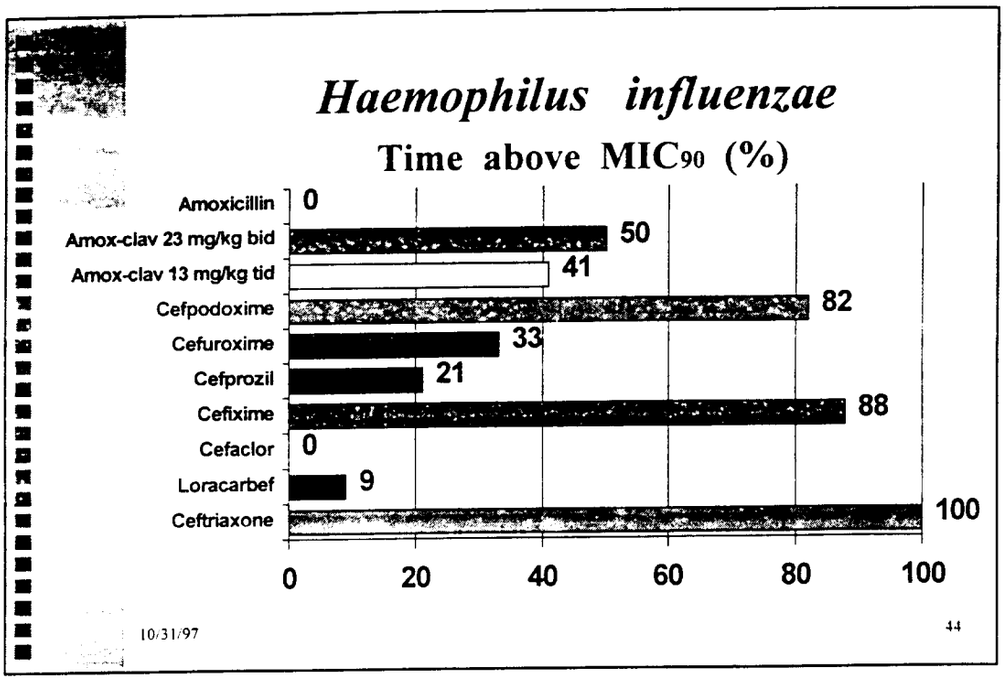
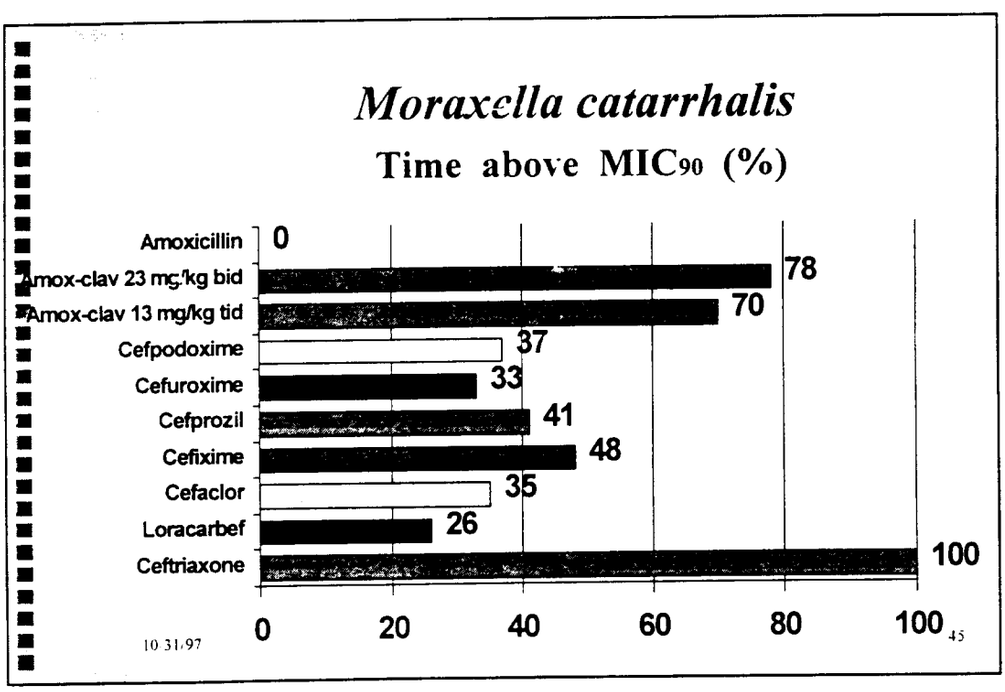


For HI, these calculation show that amox-



10/31/97



For M cat, these calculation show that amox-clav, cefprozil, cefixime and IM ceftriaxone

FLOXIN Otic
Ofloxacin Otic Solution (0.3%)

November 20, 1997
Cheryl L. McDonald, M.D.
Medical Officer

FLOXIN Otic Solution Requested Clinical Indications

- Otitis Externa in adults and children.
- Acute Otitis Media in children with tympanostomy tubes.
- Chronic Suppurative Otitis Media in adolescents and adults with perforated tympanic membrane.

Clinical Studies

- Otitis Externa (OE)
  - PRT-002 Adult Otitis Externa
  - PRT-003 Pediatric Otitis Externa
- Acute Otitis Media (AOM)
  - PRT-008 Acute Otitis Media in Children with Tympanostomy Tubes (Active Comparator)
  - PRT-007 Acute Otitis Media in Children w/ TT (Historical and Current Practice)
- Chronic Suppurative Otitis Media (CSOM)
  - PRT-006 Chronic Suppurative Otitis Media

Otitis Externa: Study 002

- Multicenter, randomized, evaluator-blinded
- Ofloxacin otic solution 0.5ml BID vs. Cortisporin 0.2ml QID for 10 days
- Age $\geq$ 12 years
- Diagnosis of acute otitis externa
- 314 subjects enrolled

FDA's Evaluable Patient Population

Study 002	Ofloxacin	Cortisporin	Total
Total Enrolled	158	156	314
Applicant's Clinically Eval.	126	121	256
Medical Officer's Clinically Eval.	99	98	197

Study 002: Clinical Cure Rates

	Ofloxacin	Cortisporin	95% C.I.
Applicant's Clinical Cure Rate	103/126 (82%)	101/121 (84%)	(-12.0, 8.5)
Medical Officer's Clinical Cure Rate	76/99 (77%)	79/98 (81%)	(-16.3, 8.6)

Study 003: Clinical Cure Rates

	Ofloxacin	Cortisporin	95% C.I.
Applicant's Clinical Cure Rate	112/116 (97%)	105/111 (95%)	(-4.3, 8.2)
Medical Officer's Clinical Cure Rate	78/81 (96%)	72/78 (92%)	(-4.5, 12.4)

13

Microbiological Eradication Rates Per Pathogen

Study 003	Ofloxacin	Cortisporin
P. aeruginosa	28/28 (100%)	35/35 (100%)
S. aureus	1/1 (100%)	4/4 (100%)
P. mirabilis	0/0	1/1 (100%)
E. faecalis	1/1 (100%)	2/2 (100%)
K. pneumoniae	0/0	1/1 (100%)
E. cloacae	3/3 (100%)	0/0

14

Overall Clinical/Microbiological Success Rates: Study 003

Study 003	Ofloxacin	Cortisporin
Applicant's Success Rates	44/45 (98%)	53/53 (100%)
Medical Officer's Success	33/33 (100%)	44/44 (100%)

15

Study 003: Safety Results

- Most Adverse Events were of mild to moderate intensity.
- Similar Rates of Adverse Events between treatment groups.
  - 35% (50/143) ofloxacin subjects vs. 26% (37/144) Cortisporin subjects had an AE

16

Study 003: Most Common Adverse Events

	Ofloxacin N=143	Cortisporin N=144
Earache	8%	4%
Otitis Media	8%	4%
Fever	6%	6%
Rhinitis	6%	6%
Coughing	4%	5%

17

Summary of Efficacy

	Ofloxacin	Cortisporin	95% C.I.
Adults	77%	81%	(-16.3, 8.6)
Pediatrics	96%	92%	(-4.5, 12.4)

18

Acute Otitis Media (AOM) in Children with Tympanostomy Tubes: Study 008

- Multicenter, randomized, evaluator-blinded
- Ofloxacin otic solution 0.25 mL BID vs. Augmentin 40 mg/kg/day for 10 days
- Age ≥ 1 year < 12 years
- Tympanostomy tube
- 474 subjects enrolled

25

FDA's Evaluable Patient Population

	Ofloxacin	Augmentin
Total Enrolled	228	246
Applicant's Clinically Evaluable	140	146
Medical Officer's Clinically Evaluable	135	145

26

Study 008: Clinical Cure Rates

	Ofloxacin	Augmentin	95% C.I.
Applicant's Clinical Cure Rate	107/140 (76%)	101/146 (69%)	(-3.8, 18.2)
Medical Officer's Clinical Cure Rate	103/135 (76%)	99/145 (68%)	(-3.1, 19.2)

27

Microbiologic Eradication Rates Per Pathogen

Study 008	Ofloxacin	Augmentin
P. aeruginosa	9/9 (100%)	3/7 (43%)
S. aureus	29/30 (97%)	15/29 (52%)
H. influenzae	28/30 (93%)	30/39 (77%)
S. pneumoniae	36/36 (100%)	34/39 (87%)
M. catarrhalis	13/14 (93%)	9/10 (90%)

28

Clinical Cure Rates Per Pathogen

	Ofloxacin	Augmentin
P. aeruginosa	6/9 (67%)	3/7 (43%)
S. aureus	23/28 (82%)	13/28 (46%)
H. influenzae	21/30 (70%)	26/39 (67%)
S. pneumoniae	29/36 (81%)	29/39 (74%)
M. catarrhalis	10/14 (71%)	9/10 (90%)

29

Overall Clinical/Microbiological Success Rates

Study 008	Ofloxacin	Augmentin
Applicant's Success Rates	64/83 (77%)	61/93 (66%)
Medical Officer's Success Rates	66/85 (78%)	64/96 (67%)

30

Study 007: Microbiological Efficacy

- Overall Clinical/Microbiological Success
  - "Success" only if Overall Clinical Response was "Cure" AND the
  - Overall Microbiological Response was "Eradication"
    - Ofloxacin 86% (92/107)

37

Study 007: Safety Results

- Data collected only for the ofloxacin-treated subjects
- Similar to safety findings in Study 008

38

Question: Acute Otitis Media in Children with Tympanostomy Tubes

- Are the data adequate to support the safety and efficacy of ofloxacin otic solution for the treatment of Acute Otitis Media in children with tympanostomy tubes?

39

Chronic Suppurative Otitis Media in Adolescents and Adults: Study 006

- Multicenter
- Open-label
- Historical and current practice groups
- Ofloxacin 0.5 mL BID for 14 days
- Age $\geq$ 12 years
- Purulent or mucopurulent otorrhea with chronic perforation of the tympanic membrane

40

Study 006: Open-Label Study

- No approved treatment regimen
- Inclusion/Exclusion Criteria were the same for all three arms: Ofloxacin, HP, and CP.
- Information on HP & CP groups was collected retrospectively
  - no data collected on baseline disease characteristics or treatment regimen used

41

Study 006: Clinical Success Rates ITT vs. Clin. Eval. per MO

	ITT Population	Clinically Evaluable
Ofloxacin Success Rate ("Dry Ear")	157/207 (76%)	148/163 (91%)
HP Success Rate ("Dry Ear")	140/220 (64%)	124/185 (67%)
CP Success Rate ("Dry Ear")	42/63 (67%)	38/54 (70%)

42

DAIICHI HANDOUT NDAC#62
11-20-97
FLOXIN

Ofloxacin Otic Solution 0.3%
FDA Advisory Committee

November 20, 1997

Elyane E. Lombardy, M.D.
Executive Director
Research & Development
Daiichi Pharmaceutical Corporation

1

Agenda & Speakers

- Rationale for Development of Ofloxacin Otic Solution 0.3%
  Elyane E. Lombardy, M.D.
  Executive Director, Research & Development
  Daiichi Pharmaceutical Corporation

- Design and Outcome of Clinical Trials
  Mindell Seidlin, M.D.
  Senior Director, Clinical Development
  Daiichi Pharmaceutical Corporation

2

Agenda & Speakers (Continued)

- Evaluation of Otic Safety
  - Professor George A. Gates, M.D.
  - Director, Virginia Merrill Bloedel
  - Hearing Research Center
  - University of Washington

- Role of a New Ototopical Therapy in Pediatric Practice
  - Professor Jerome O. Klein, M.D.
  - Professor of Pediatrics
  - Boston University School of Medicine

Rationale for Development of Ofloxacin Otic Solution 0.3%

- Indications
- Rationale for Topical Therapy
- Rationale for Selection of Ofloxacin
- Preclinical Safety Profile
- Rationale for Development of Ofloxacin Otic Solution 0.3%

Ofloxacin Otic Solution 0.3%
Proposed Indications

- Otitis Externa (OE) in Adults and Children
- Acute Otitis Media (AOM) in Children with Tympanostomy Tubes
- Chronic Suppurative Otitis Media (CSOM) in Adolescents and Adults with Perforated Tympanic Membranes

Rationale for Topical Therapy

- Local Treatment for Localized Infections
- High Concentrations at Site of Infection
  - ✧ May prevent emergence of resistance
- Minimal Systemic Exposure
  - ✧ Minimizes risk of systemic toxicity
  - ✧ Permits quinolone administration to children

Rationale for the Selection of Ofloxacin

- Safe and Effective in the Treatment of Many Infections
  - ✧ Including infections due to P. aeruginosa
- Broad Antibacterial Spectrum
- In Vitro Efficacy Against Resistant Pathogens
  - ✧ Effective against methicillin-resistant S. aureus and penicillin-resistant S. pneumoniae
  - ✧ Lack of cross-resistance with other classes of antibiotics

Ofloxacin Otic Preclinical Safety Profile

- Low Systemic Exposure
- No Skin Sensitization
- No Local Irritation
- No Local Toxicity to Middle and Inner Ear

Rationale for Development of a New Ototopical Therapy

- Advantages Over Available Therapies
  - ✧ None labeled for use in patients with open tympanic membranes
  - ✧ Many potentially ototoxic

9

Advances in the Treatment of Otitis Externa in Adults and Children

1. Monotherapy
2. Twice a Day Use
3. Otic Safety
   - ✧ Even for those patients with an undetected tympanic membrane perforation

10

Advances in the Treatment of
Acute Otitis Media in Children with
Tympanostomy Tubes
and
Chronic Suppurative Otitis Media in Adolescents
and Adults with Perforated Tympanic Membranes

1. Coverage of all Relevant Pathogens Including P. aeruginosa
2. Elimination of the Need for Systemic Antibiotic Therapy
3. Otic Safety

11

Ofloxacin Otic Solution 0.3% Design and Outcome of Clinical Trials

Mindell Seidlin, M.D.

Senior Director, Clinical Development, Anti-Infectives

Daiichi Pharmaceutical Corporation

12

Indications in Proposed Labeling

- Otitis Externa (OE) in Adults and Children 1 Year and Older
- Acute Otitis Media (AOM) in Children 1 Year and Older With Tympanostomy Tubes
- Chronic Suppurative Otitis Media (CSOM) in Adolescents 12 Years and Older and Adults With Chronic Perforations of the Tympanic Membrane

13

Subject Enrollment by Indication

		Ofloxacin	Cortisporin®	Augmentin®	Historical	Current
OE (Protocols 002, 003)	Adults and Children	301	300	0	0	0
CSOM (Protocol 006)	Adults	207	0	0	220	63
AOM (Protocols 007, 008)	Children	454	0	246	309	68
Total		962	300	246	529	131

Otitis Externa in Adults and Children

Protocols 002 and 003

15

APPEARS THIS WAY
ON ORIGINAL

Otitis Externa: Two Adequate and Well-Controlled Trials

- One trial in adults and one in children
- No known differences between adults and children in the pathophysiology or microbiology of infection
- Dose differed because of volume of the ear canal

16

Otitis Externa: Study Design

- Multicenter, randomized, evaluator-blinded
- Ofloxacin Otic Solution v. Cortisporin® Otic Solution
- Primary endpoint: Comparison of clinical response 7-10 days after completion of therapy
- Clinical cure: complete resolution of tenderness, edema, secretions and exudate

17

Summary of Studies in Otitis Externa

Protocol	Ofloxacin-Treated Subjects (n)	Dose / Duration of Ofloxacin	Cortisporin®-Treated Subjects (n)	Dose/ Duration of Cortisporin®
002 Adults	158	0.5 ml b.i.d. 10 Days	156	0.2 ml q.i.d. 10 Days
003 Children	143	0.25 ml b.i.d. 10 Days	144	0.15 ml q.i.d. 10 Days

18

OE: Populations Analyzed

	Ofloxacin	Cortisporin®
Intent-to-Treat	158	156
	143	144
Clinically Evaluable	126	121
	116	111
Microbiologically Evaluable	48	50
	45	53

Protocol 003- Children

19

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Overall Clinical Cure Rates in OE
Clinically Evaluable Subjects

Protocol	Ofloxacin		Cortisporin®		p-value	95% C.I.
	n	(%)	n	(%)		
002 Adults	103/126	(81.7)	101/121	(83.5)	0.560	-12.0%; 8.5%
003 Children	112/116	(96.6)	105/111	(94.6)	0.482	-4.3%; 8.2%

20

OE: Possible Explanations for Differences in Cure Rates Between Children and Adults

- Differences in mean duration of OE before enrollment
- Differences in the proportion of subjects with exacerbating OE at enrollment
- Differences in who administered the drug to the subject
- Possible decreased penetration through the ear canal in adult men

21

OE Protocol 002: Overall Microbiological and Clinical Response by Pathogen

(Adults)

	Microbiological Eradication		Clinical Cure	
Pathogen	Ofloxacin	Cortisporin®	Ofloxacin	Cortisporin®
P. aeruginosa	32/32 (100%)	39/40 (98%)	28/32 (88%)	35/40 (88%)
S. aureus	6/6 (100%)	8/8 (100%)	6/6 (100%)	8/8 (100%)
P. mirabilis	3/3 (100%)	8/8 (100%)	2/3 (67%)	8/8 (100%)
E. faecalis	6/6 (100%)	5/5 (100%)	5/6 (83%)	5/5 (100%)
K. pneumoniae	5/5 (100%)	2/2 (100%)	4/5 (80%)	2/2 (100%)
E. cloacae	3/3 (100%)	2/2 (100%)	1/3 (33%)	1/2 (50%)

22

OE Protocol 003: Overall Microbiological and Clinical Response by Pathogen

(Children)

	Microbiological Eradication		Clinical Cure	
Pathogen	Ofloxacin	Cortisporin®	Ofloxacin	Cortisporin®
P. aeruginosa	35/36 (97%)	42/42 (100%)	35/36 (97%)	42/42 (100%)
S. aureus	3/3 (100%)	8/8 (100%)	3/3 (100%)	8/8 (100%)
P. mirabilis	5/5 (100%)	3/3 (100%)	5/5 (100%)	3/3 (100%)
E. faecalis	1/1 (100%)	3/3 (100%)	1/1 (100%)	3/3 (100%)
K. pneumoniae	2/2 (100%)	1/1 (100%)	2/2 (100%)	1/1 (100%)
E. cloacae	3/3 (100%)	1/1 (100%)	3/3 (100%)	1/1 (100%)

OE: Overall Microbiological Assessment by Pathogen

	Protocol 002		Protocol 003	
	Ofloxacin	Cortisporin®	Ofloxacin	Cortisporin®
Eradication	47/48 (98%)	49/50 (98%)	57/58 (98%)	74/74 (100%)
Persistence	0	1/50 (2%)	1 (2%)	0
Recurrence	1/48 (2%)	0	0	0

OE Protocol 002: Summary of Adverse Events During the Study

	Ofloxacin Subjects n= 158	Cortisporin® Subjects n= 156	p-value
Treatment-Related Adverse Events	25 (15.8%)	18 (11.5%)	0.325
Serious Adverse Events	3* (1.9%)	2** (1.3%)	
Withdrawals due to Adverse Events	4† (2.5%)	2†† (1.3%)	

* 1 treatment-related
** 1 treatment-related
† 1 treatment-related
†† 2 treatment-related

25

OE Protocol 003: Summary of Adverse Events During the Study

	Ofloxacin Subjects n= 143	Cortisporin® Subjects n= 144	p-value
Treatment-Related Adverse Events	4 (2.8%)	5 (3.5%)	1.000
Serious Adverse Events	2 (1.4%)	0 (0%)	
Withdrawals due to Adverse Events	2 (1.4%)	5† (3.5%)	

† 1 treatment-related

26

OE: Most Common Treatment-Related Adverse Events

Protocol 002-Adults

Protocol 003-Children

Adverse Event	Ofloxacin n	Ofloxacin %	Cortisporin® n	Cortisporin® %
Pruritus	10	6.3%	6	3.8%
	0	0.0%	1	0.7%
Application Site Reaction	6	3.8%	6	3.8%
	0	0.0%	3	2.1%
Vertigo	2	1.3%	0	0.0%
	0	0.0%	0	0.0%
Earache	2	1.3%	3	1.9%
	1	0.7%	1	0.7%
Dizziness	1	0.6%	2	1.3%
	1	0.7%	0	0.0%
Rash erythematous follicular	1	0.6%	1	0.6%
	1	0.7%	0	0.0%

There were no statistically significant differences between treatment groups [27]

Conclusions Regarding Otitis Externa in Children and Adults

- Ofloxacin otic solution b.i.d. is as effective and as well tolerated as Cortisporin® Otic solution q.i.d.

[28]

Acute Otitis Media in Children with Tympanostomy Tubes

Protocols 007 and 008

29

AOM in Children with Tympanostomy Tubes

- Otorrhea is the key symptom
- Fever and otalgia are uncommon
- Pathogens access the middle ear either from the eustachian tube or the external auditory canal
- Must rule out other causes of otorrhea

30

Issues in the Design of Trials for AOM in Children with Tympanostomy Tubes

- No therapy is specifically approved for this indication
- Placebo controlled trials were considered unethical
- Oral and/or topical therapies are the standard of care
- No oral anti-pseudomonas agent is labeled for pediatric use
- Available ototopical and ophthalmic agents currently in use are potentially ototoxic

31

Specific Objectives of the AOM Clinical Program

- Demonstration of efficacy against the typical AOM pathogens as well as P. aeruginosa and S. aureus
- Demonstration of general safety and otic safety by audiometry
  - Data to be presented by George A. Gates, M.D.

32

Strategy in Design of the AOM Program

- One open-label trial (Protocol 007) to demonstrate efficacy against P. aeruginosa and S. aureus as well as typical AOM pathogens
- One comparative trial (Protocol 008) which would permit
  - comparison of safety and efficacy to an oral agent effective and labeled for usual AOM pathogens
  - comparison of audiometric safety to an oral agent known to be non-ototoxic

Summary of Studies in AOM in Children with Tympanostomy Tubes

Protocol	Ofloxacin-Treated Subjects (n)	Dose / Duration of Ofloxacin	Comparator-Treated Subjects (n)	Dose / Duration of Comparator
007	226	0.25 ml b.i.d. 10 Days	-	-
008	228	0.25 ml b.i.d. 10 Days	246	Augmentin® 40 mg/kg/day (t.i.d.) 10 Days

AOM Protocol 007: Study Design

- Multicenter, open label
- Ofloxacin 0.25 ml b.i.d. for 10 days
- Efficacy assessed at 7-10 days post-treatment
- Historical and Current Practice controls
- Primary Endpoint - comparison of cure in clinically evaluable ofloxacin and historical practice subjects with follow-up
- Clinical Cure: complete resolution of otorrhea (dry ear)

AOM: Purpose of Historical and Current Practice Control Groups

- To provide a context for interpretation of efficacy data of the prospective arm
- Historical Practice Subjects more numerous but Current Practice Subjects may reflect most recent trends in microbial resistance and drug therapy
- Historical and Current Practice Subjects with a record of a follow-up visit were clinically evaluable
- No data on treatment prescribed or adverse events were collected

AOM Protocol 008: Study Design

- Multicenter, randomized, evaluator-blinded
- Ofloxacin otic solution 0.25 ml b.i.d.

or

Augmentin® 40mg/kg/day for 10 days

- Primary endpoint: Clinical response 7-10 days after completion of therapy
- Clinical Cure: complete resolution of otorrhea (dry ear)

37

AOM Protocol 008: Inclusion/Exclusion Criteria

Identical to Protocol 007

Except

- Subjects with P. aeruginosa as their sole pathogen were withdrawn from both arms and were not clinically evaluable

38

AOM Protocol 007: Populations Analyzed

	Ofloxacin	Historical Practice	Current Practice
Intent-to-Treat	226	309	68
Clinically Evaluable	143	218	48
Microbiologically Evaluable	107	NA*	NA*

* NA= Not Applicable

39

AOM Protocol 008: Populations Analyzed

	Ofloxacin	Augmentin®
Intent-to-Treat	228	246
Clinically Evaluable	140	146
Microbiologically Evaluable	83	93

40

Exclusions From Clinical Evaluability Because of P. aeruginosa as Sole Pathogen (AOM Protocol 008)

- Ofloxacin Arm 20/228 subjects (9%)
- Augmentin® Arm 27/246 subjects (11%)

41

AOM Protocol 007: Overall Clinical Cure Rates in Clinically Evaluable Subjects

	Ofloxacin Otic n=143	Historical Practice n=218	Current Practice n=48
Cure	121/143 (85%)	140/218 (64%)	34/48 (71%)
		$p \leq 0.001$	$p = 0.035$

Note: p-value for Historical Practice vs. Current Practice = 0.383

42

AOM Protocol 008: Overall Clinical Cure Rates in Clinically Evaluable Subjects

	Ofloxacin Otic n=140	Augmentin® n=146	95% C. I.
Cure	107/140 (76%)	101/146 (69%)	p = 0.169 -3.7%, 18.2%

43

AOM Protocol 007: Overall Microbiological and Clinical Response by Pathogen:

Microbiologically Evaluable Ofloxacin-Treated Subjects

	Microbiological Response	**Clinical Response**
Pathogen	Eradication	Cure
P. aeruginosa	32/34 (94%)	30/34 (88%)
S. aureus	26/26 (100%)	25/26 (96%)
H. influenzae	30/30 (100%)	25/30 (83%)
S. pneumoniae	28/29 (97%)	24/29 (83%)
M. catarrhalis	15/15 (100%)	13/15 (87%)

44

AOM Protocol 008: Overall Microbiological and Clinical Response by Pathogen:
Microbiologically Evaluable Subjects

	Microbiological Response Eradication		Clinical Response Cure	
Pathogen	Ofloxacin	Augmentin®	Ofloxacin	Augmentin®
P. aeruginosa†	9/9 (100%)	3/7 (43%)	6/9 (67%)	3/7 (43%)
S. aureus††	27/28 (96%)	12/25 (48%)	23/28 (82%)	11/25 (44%)
H. influenzae	26/28 (93%)	30/39 (77%)	19/28 (68%)	26/39 (67%)
S. pneumoniae	36/36 (100%)	33/38 (87%)	29/36 (81%)	29/38 (76%)
M. catarrhalis	13/14 (93%)	9/10 (90%)	10/14 (71%)	9/10 (90%)

† p-value for microbiological response = 0.006
†† p-values for both microbiological and clinical responses < 0.001 and 0.005, respectively

AOM: Overall Microbiological Assessment by Pathogen

	Protocol 007	Protocol 008	
	Ofloxacin	Ofloxacin	Augmentin®
Eradication	157/160 (98%)	138/142 (97%)	100/140 (71%)
Persistence	3/160 (2%)	2/142 (1.4%)	36/140 (26%)
Recurrence	0	2/142 (1.4%)	4/140 (3%)

Changes in Ofloxacin MIC for Persistent or Recurrent Pathogens in AOM Ofloxacin-Treated Subjects

Protocol	Persistent/Recurrent Pathogens	Change in MIC (ug/ml)
007	P. aeruginosa (2)	none
		4→8
	S. pneumoniae	none
008	H. influenzae (2)	none
	M. catarrhalis	none
	S. aureus	0.25→0.5

47

AOM Protocol 007: Summary of Adverse Events During the Study

	Ofloxacin 0.25 ml b.i.d. n=226
Treatment-Related Adverse Events	29 (13%)
Serious Adverse Events	3* (1%)
Withdrawals Due To Adverse Events	6† (3%)

* None treatment-related
† 1 treatment-related

48

AOM Protocol 008: Summary of Adverse Events During the Study

	Ofloxacin Subjects n =228	Augmentin® Subjects n = 246	p-value
Treatment-Related Adverse Events	13 (6%)	77 (31%)	< 0.001
Serious Adverse Events	0 (0%)	2† (1.0%)	
Withdrawals Due To Adverse Events	9* (4%)	19†† (8%)	

* 1 treatment-related
† None treatment-related
†† 15 treatment-related

AOM Protocol 007: Most Common Treatment-Related Adverse Events

Adverse Event	Ofloxacin 226	
	n	%
All Treatment-Related Adverse Events	29	(13%)
Earache	5	(2%)
Taste perversion (bitter taste)	5	(2%)
Otorrhagia (bleeding)	3	(1%)
Rash	3	(1%)
Tinnitus	2	(1%)
Fever	2	(1%)
Paraesthesia	2	(1%)

AOM Protocol 008: Most Common Treatment-Related Adverse Events

Adverse Event	Ofloxacin 228		Augmentin® 246		p-value
	n	(%)	n	(%)	
All Treatment-Related Adverse Events	13	(6%)	77	(31%)	<0.001
Diarrhea	3	(1%)	66	(27%)	<0.001
Taste perversion (bitter taste)	3	(1%)	1	(0.4%)	0.355
Earache	2	(1%)	0		0.231
Rash	2	(1%)	11	(5%)	0.022
Paraesthesia	2	(1%)	0		0.231
Abdominal pain	1	(0.4%)	2	(1%)	1.000
Vomiting	1	(0.4%)	6	(2.4%)	0.124
Moniliasis	0		7	(3%)	0.015

51

Conclusions Drawn from AOM Protocols 007 and 008

- Ofloxacin otic solution is superior to Augmentin® in eradicating P. aeruginosa and S. aureus
- Ofloxacin otic solution is as effective as Augmentin® in eradication of S. pneumoniae, H. influenzae and M. catarrhalis
- Ofloxacin otic solution is clinically equivalent to Augmentin® in treatment of AOM in children with tympanostomy tubes

52

Conclusions Drawn from AOM Protocols 007 and 008 (Continued)

- Ofloxacin otic solution is associated with fewer treatment-related adverse events than Augmentin®
- Ofloxacin otic solution provides effective empiric coverage for all pathogens associated with AOM in children with tympanostomy tubes
- Ofloxacin otic solution is safe and effective for the treatment of AOM in children with tympanostomy tubes

Chronic Suppurative Otitis Media in Adolescents and Adults

Protocol 006

54

Chronic Suppurative Otitis Media

- Patients with chronically perforated tympanic membranes
- Have chronic or intermittent otorrhea
- Pathogens access the middle ear either from the eustachian tube or the external auditory canal
- Must rule out other causes of otorrhea
  - cholesteatoma and other tumors
  - mastoiditis
  - foreign body

55

CSOM: Rationale for a Single, Open Label Study

- No comparative agent with labeling for this indication
- Similarity in pathophysiology and microbiology to AOM in children with tympanostomy tubes
- Trials in these two indications support each other
- Few subjects with CSOM in the US due to aggressive therapy of AOM in childhood and prevalence of tympanoplasty

56

CSOM: Study Design

(Protocol 006)

- Multicenter, open label
- Ofloxacin 0.5 ml b.i.d. for 14 days
- Efficacy assessed at 7-10 days post-treatment
- Historical and Current Practice controls
- Primary Endpoint - comparison of cure in clinically evaluable ofloxacin and historical practice subjects with follow-up
- Clinical Cure: complete resolution of otorrhea (dry ear)

57

CSOM: Populations Analyzed

	Ofloxacin	Historical Practice	Current Practice
Intent-to-Treat	207	220	63
Clinically Evaluable	162	185	54
Microbiologically Evaluable	99	NA*	NA*

* NA = Not Applicable

58

Overall Clinical Cure Rates in CSOM Clinically Evaluable Subjects

	Ofloxacin Otic n=162	Historical Practice n=185	Current Practice n=54
Cure	148/162 (91%)	124/185 (67%)	38/54 (70%)
		p <0.001	p <0.001

Note: p-value for Historical Practice vs. Current Practice = 0.713

59

CSOM: Most Common Baseline Pathogens: Microbiologically Evaluable Population

P. aeruginosa	39
S. aureus	40
P. mirabilis	15
E. faecalis	7
E. cloacae	4
K. pneumoniae	2

All pathogens were eradicated

60

CSOM: Summary Of Adverse Events During the Study

	Ofloxacin-Treated Subjects n= 207
Treatment-Related Adverse Events	47 (23%)
Serious Adverse Events	0
Withdrawals Due To Adverse Events	5* (2%)

* All of these adverse events were considered treatment-related

61

CSOM: Most Common Treatment-Related Adverse Events

Adverse Event	Ofloxacin 207	
	n	(%)
All Treatment-Related Adverse Events	47	(23%)
Taste perversion (bitter taste)	35	(17%)
Dizziness	5	(2%)
Pruritus	5	(2%)
Mouth dry	3	(1%)
Vertigo	3	(1%)
Earache	2	(1%)
Paraesthesia	2	(1%)

62

Conclusions Regarding CSOM in Adults and Adolescents with Chronic Perforations of the TM

- Ofloxacin otic solution is effective in resolution of otorrhea and eradication of relevant pathogens
- Transient bitter taste (taste perversion) is the most common treatment-related adverse event
- Ofloxacin otic solution is well tolerated with no serious adverse event

63

Otic Safety of Ofloxacin Otic Solution

Professor George A. Gates, M.D.
Virginia Merrill Bloedel Hearing Research Center
University of Washington

64

Incidence of Otorrhea

- Over 750,000 children receive tympanostomy tubes each year to improve hearing and decrease recurrent middle ear infections
- One-third develop AOM with otorrhea at some time and nearly all have at least one episode of AOM if the tube remains for > 1 year

65

Therapeutic Approaches to Otorrhea

- Physicians rely heavily on ototopical medication to treat otorrhea due to CSOM and AOM
- Treatment of otorrhea with topical antibiotics is confounded by concerns about ototoxicity from aminoglycoside agents

66

Concerns Regarding Ototopical Aminoglycoside Therapy

- Local and systemic use can cause auditory and vestibular toxicity
- Data from guinea pig and chinchilla models show:
  - histologic damage to cochlear hair cells when drops are administered to the middle ear with most severe damage to basal turn of the cochlea
  - auditory brainstem response testing shows high frequency hearing loss

67

Non-Clinical Studies in the Guinea Pig

Objective

- To determine the effect of ofloxacin otic solution upon the structure and function of the middle ear, ossicles and cochlea.
  - Barlow, et al: 1.0% ofloxacin solution (7 days)
  - Schaefer: 0.3% and 1.0% ofloxacin solution (30 days)

68

One Month Ototoxicity Study of Ofloxacin Otic Solution in the Guinea Pig (Schaefer)

0.3% Ofloxacin Otic Solution

Middle Ear

- No effect on mucosa
- No effect upon the ossicles

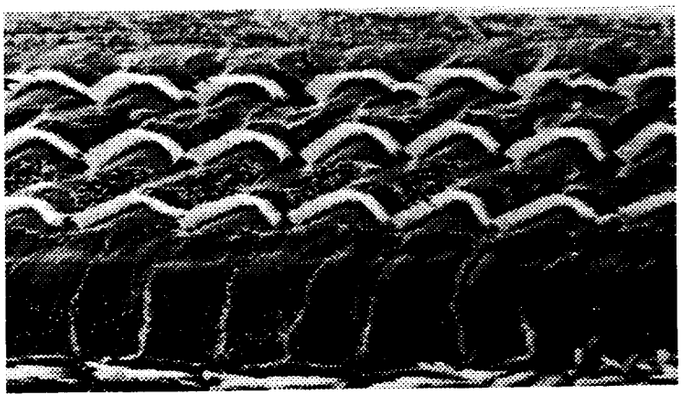
Inner Ear

- No effect upon the auditory brainstem response
- No effect upon the morphology of the cochlea

69

Ototoxicity of Ototopical Antimicrobial Agents
Cochlea - 1.0% Ofloxacin Solution (Barlow, et al.)

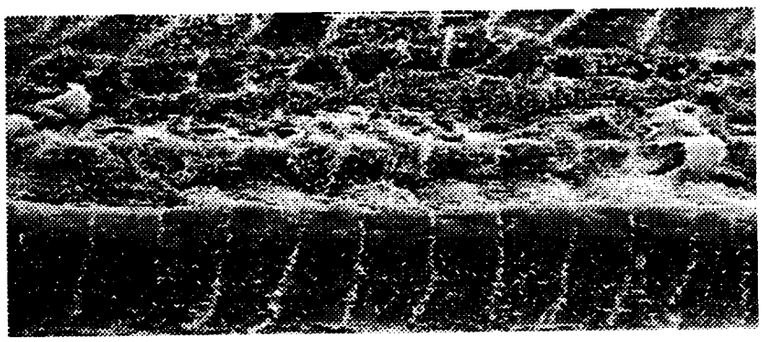
Normal appearing inner and outer hair cells (X 2000)



70

Ototoxicity of Topical Otomicrobial Agents
Cochlea - Cortisporin® Otic Suspension (Barlow, et al.)

Complete hair cell loss (x 2400)



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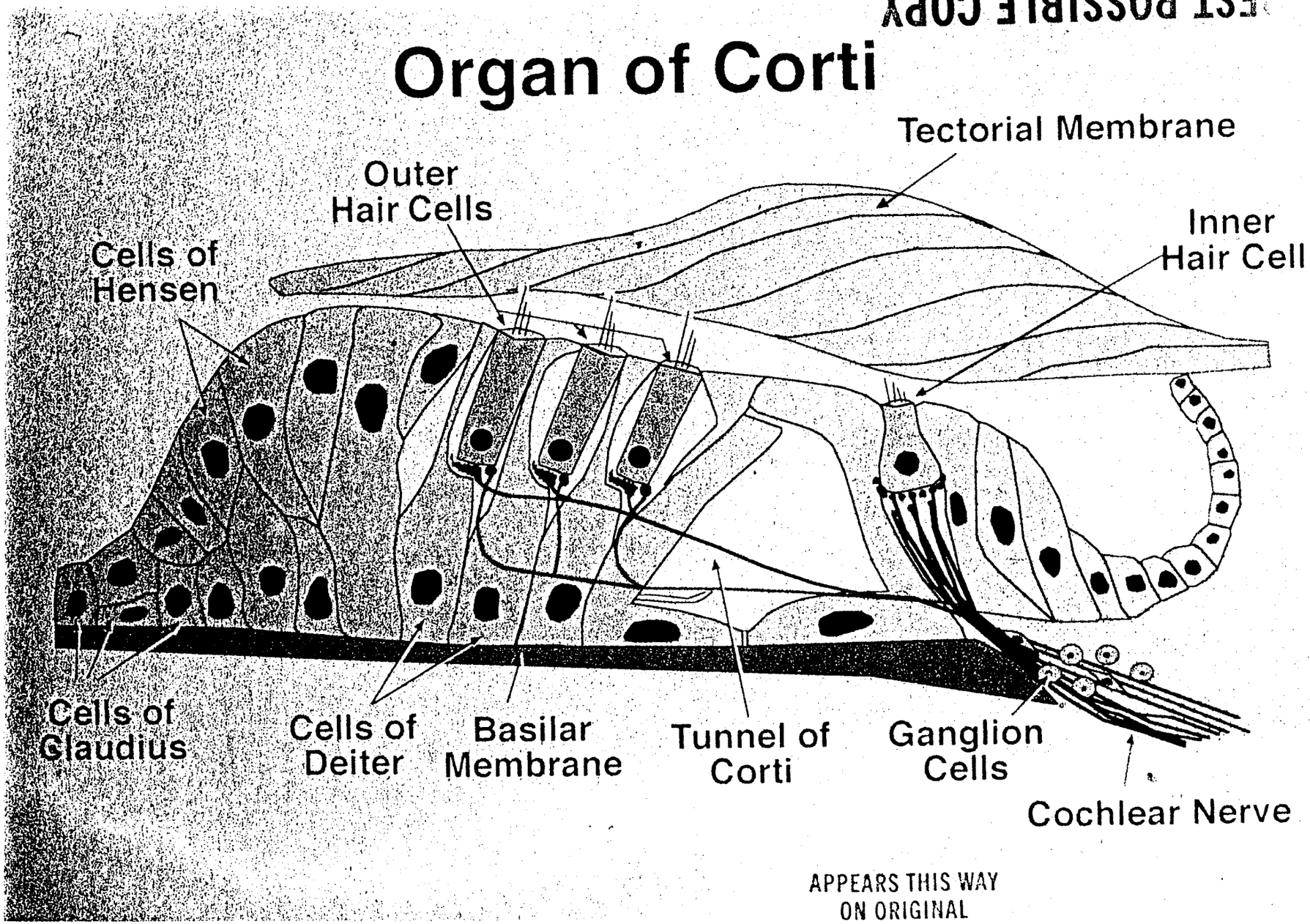
Organ of Corti



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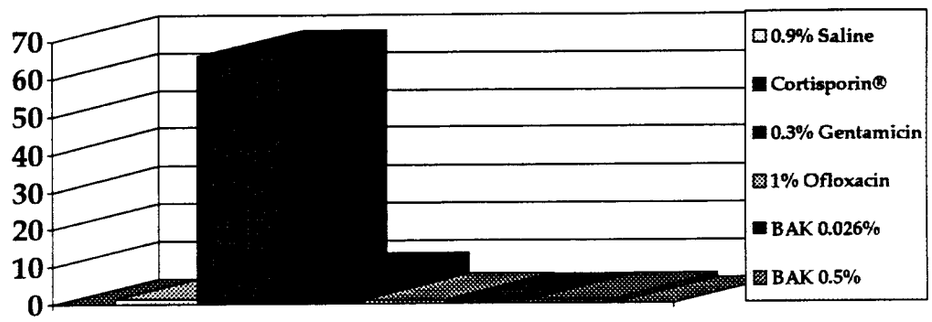
Ototoxicity of Topical Otomicrobial Agents (Barlow, et al.)

Middle Ear - Mean % Cochlear Hair Cell Loss



72

Ototoxicity of Topical Otomicrobial Agents Auditory Brainstem Response (ABR) Results (Schaefer)

Mean Threshold Shift from Baseline (in dB)
Frequency

	4 kHz		10 kHz		20 kHz	
	Day 14	Day 28	Day 14	Day 28	Day 14	Day 28
Vehicle	-2.5	-3.5	-5.5	-5.7	-4.0	-5.0
0.3% ofloxacin	-1.4	+3.4	-6.3	-0.8	-5.5	+4.4
1.0% ofloxacin	-6.7	-2.3	-7.2	-4.0	-14.6	-9.5
10% neomycin	-39.5	-41.3	-35.0	-36.8	-47.8	-47.0

73

Summary of Studies of Ototopical Use of Ofloxacin in Animals

- Demonstrate the lack of local irritation in spite of high levels of the drug achieved locally.
- Demonstrate the lack of local adverse effects on the mucosa and ossicles of the middle ear and the inner ear in developing animals by
  - histologic measurements
  - functional measurements

74

Audiometry Data

Protocol 008

AOM Subjects with Tympanostomy Tubes

75

Audiometrically Evaluable Subjects from AOM Protocol 008

- Subjects ≥ 4 years old
- No pre-existing sensorineural hearing loss
- Testing conducted at pre-therapy and failure or test-of-cure visits
- Testing at octave intervals from 500-4000 Hz

76

AOM Protocol 008: Audiometric Endpoints

- A change of 10 dB hearing loss is the minimum clinically significant change
- The primary audiological endpoint was change in air and bone conduction pure tone average (PTA) at 500, 1000 and 2000 Hz
- Change in threshold at 4000 Hz was also measured
- Positive change = Improvement
- Negative change = Worsening

77

Target Ear (Reference Ear)

- The more severely affected ear in subjects with bilateral infection was designated as the target (reference ear)
- If both ears were equally affected, the right ear was designated as the target ear
- Audiometric testing was completed in both ears for all subjects

78

AOM Protocol 008: Change from Baseline in Bone Conduction PTA

Ofloxacin

	Negative Change (Worse)	No Change (Same)	Positive Change (Better)	Total
Target Ear	0	25 (100%)	0	25
Non-Target Ear	0	25 (96%)	1 (4%)	26

No significant difference between treatment arms

79

AOM Protocol 008: Change from Baseline in Bone Conduction PTA

Augmentin®

	Negative Change (Worse)	No Change (Same)	Positive Change (Better)	Total
Target Ear	0	23 (96%)	1 (4%)	24
Non-Target Ear	0	22 (100%)	0	22

No significant difference between treatment arms

AOM Protocol 008: Change from Baseline in Air Conduction PTA

Ofloxacin

	Negative Change (Worse)	No Change (Same)	Positive Change (Better)	Total
Target Ear	2 (7%)	7 (25%)	19 (68%)	28
Non-Target Ear	1 (4%)	25 (89%)	2 (7%)	28

AOM Protocol 008: Change from Baseline in Air Conduction PTA

Augmentin®

	Negative Change (Worse)	No Change (Same)	Positive Change (Better)	Total	p-value
Target Ear	1 (4%)	16 (62%)	9 (35%)	26	0.029
Non-Target Ear	0	19 (76%)	6 (24%)	25	0.167

Conclusions

Administration of ofloxacin otic solution 0.3%

- is not associated with changes to the ossicles in the guinea pig model
- is not associated with functional or histologic changes in the middle ear or inner ear in the guinea pig model
- did not adversely impact on hearing in children participating in Protocol 008

Ofloxacin Otic Solution 0.3%
FDA Advisory Committee

November 20, 1997

Elyane E. Lombardy, M.D.
Executive Director
Research & Development
Daiichi Pharmaceutical Corporation

1

Agenda & Speakers

- Rationale for Development of Ofloxacin Otic Solution 0.3%
  Elyane E. Lombardy, M.D.
  Executive Director, Research & Development
  Daiichi Pharmaceutical Corporation

- Design and Outcome of Clinical Trials
  Mindell Seidlin, M.D.
  Senior Director, Clinical Development
  Daiichi Pharmaceutical Corporation

2

Role of a New Ototopical Therapy in Pediatric Practice

Jerome O. Klein, M.D.
Professor of Pediatrics
Boston University
School of Medicine

84

Use of Ototopical Preparations for Infants and Children

- Indications
  - Otitis externa
  - Acute otitis media with perforation and otorrhea
  - Acute otitis media with tympanostomy tube
- Available Preparations
  - Cortisporin® Otic Solution (polymyxin B, neomycin and hydrocortisone)
  - Coly-Mycin® S-Otic (neomycin and hydrocortisone)
  - Tobradex® Ophthalmic (tobramycin, dexamethasone)
    Garamycin® Ophthalmic Solution (gentamicin)

Acetic Acid used

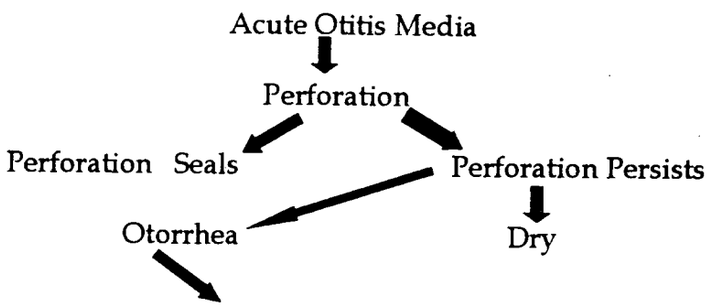
85

Use of Ototopical Preparations for Infants and Children (Continued)

- Concerns with Available Preparations:
  - Potential ototoxicity
  - "Should be used with care when the integrity of the" tympanic membrane is in question..." (Cortisporin® Otic Solution package insert)
  - Dosage schedule - 3-4x/day

86

Pathogenesis of Otorrhea Following Acute Otitis Media



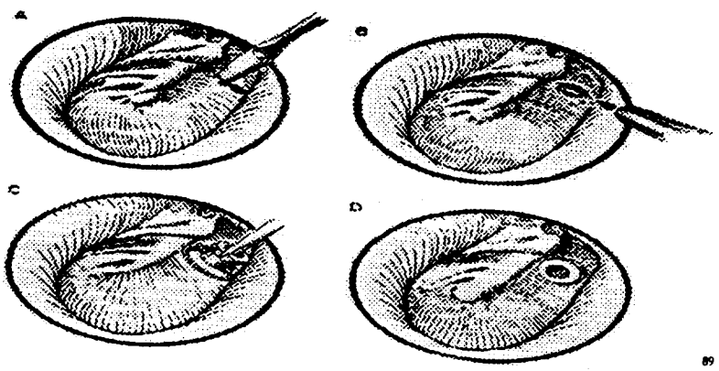
87

Management of Otorrhea

- Ototopical Medication
- Daily Cleansing of Ear Canal
- Oral Antibiotics
  - Amoxicillin (+/- clavulanate), trimethoprim-sulfamethoxazole
- Parenteral Antibiotics
  - Ticarcillin (+/- clavulanate), piperacillin or ceftazidime
- Surgery

88

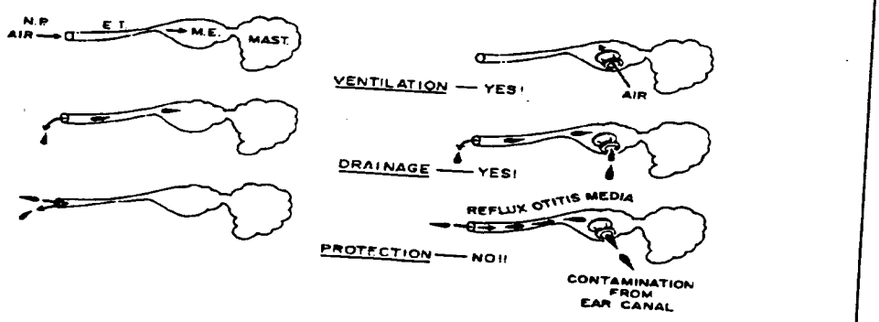
Procedure for Insertion of Tympanostomy Tube



89

Bluestone CD, Klein JO, "Otitis Media in Infants and Children", WB Saunders Co., 2nd edition 1995

Pathogenesis of Acute Otitis Media with Tympanostomy Tube



Bluestone CD, Klein JO, "Otitis Media in Infants and Children", WB Saunders Co., 2nd edition 1995

Why Would Pediatricians be Interested in Ofloxacin Otic Solution?

- In vitro efficacy against organisms acquired from the naso-pharynx or external ear canal
- Clinical efficacy and safety for:
  - otitis externa
  - chronic suppurative otitis media
  - acute otitis media with tympanostomy tube
- Less concern for ototoxicity than available preparations
- Has been studied specifically in pediatric infections

Why Would Pediatricians be Interested in Ofloxacin Otic Solution? (Continued)

- b.i.d. dosing likely to increase compliance compared with t.i.d. and q.i.d. schedules of available preparations
- Efficacy of ofloxacin otic solution for acute otitis media with tympanostomy tube likely to lead to decreased use of oral antimicrobial agents
- Ofloxacin otic solution is the first drug demonstrated to be effective and safe in children and adults with non-intact tympanic membranes

92

Safety Review
NDA 50-753

Marianne Culkin Mann, M.D.
Medical Officer, FDA

FDA Safety Concerns

Ototoxicity (cochlear toxicity)
Shifts in MIC values for
Pseudomonas aeruginosa isolates

Aminoglycoside-Induced Ototoxicity: Background

- Loss of cochlear hair cells (direct vs toxic metabolite): often a delayed phenomenon
- Can occur AFTER therapy is withdrawn
- Has been noted after oral administration, pleural/peritoneal instillation
- Hearing losses initially noted at frequencies of 8000 Hz or above
- Can be unilateral or bilateral

Risk Factors for Aminoglycoside Induced Ototoxicity

- Duration of therapy more than 10 days
- Severe underlying illness
- Decreased pure tone sensitivity at baseline
- Elevated peak and trough serum levels

Evaluations of Ototoxicity

1. Symptoms of Deafness
2. Audiology Evaluations
3. Symptoms of Tinnitus

Symptoms of Deafness

- 4 TOBI and 3 Placebo Patients
- 4 TOBI
  - -mild to moderate in severity
  - -audiograms done in three patients did not reveal hearing loss
  - -otitis media in one patient, rock concert in another
  - -all had normal hearing at end of study

Audiology Evaluations
Sponsor's Criteria for Ototoxicity

- "Bilateral, high frequency hearing loss of 15 decibels or greater at two consecutive frequencies"
- No patients met this criteria

Audiology Evaluations
FDA Criteria for Otoxicity

- "10 decibel hearing loss in at least three consecutive frequencies in either ear or...
- "15 decibel hearing loss in at least two consecutive frequencies in either ear or...
- "20 decibel hearing loss at any frequency in either ear"
- 6 TOBI and 10 placebo patients met these more sensitive criteria

Symptoms of Tinnitus

"Tinnitus is often the initial symptomatic manifestation of cochleotoxicity, and is usually high-pitched and continuous, reflecting cochlear hair damage in the basilar turn."

Black and Peznecker
Otolaryngology Clinics of North America, 1993

Tinnitus

- 8 TOBI patients had 16 episodes of tinnitus versus no placebo patients
- 6 Female/2 Male, age range 15 to 31
- Both Bilateral and Unilateral Tinnitus Occurred
- No relation to Cycle of TOBI treatment, but 12 of 16 episodes began while "on" TOBI treatment

Tinnitus

- Severity was judged moderate in 3 subjects and mild in 5 subjects
- Duration was less than 1 week for 13 of the 16 episodes; one patient had an episode lasting 10 days, and one patient had 2 episodes lasting 22 and 40 days, respectively

Tinnitus

- Serum tobramycin levels (not obtained at time of event) were less than 2 ug/mL in all subjects, and exceeded 1 ug/mL in only two subjects
- Audiograms (not obtained at time of event) did not reveal hearing loss
- Two patients were taking daily ibuprofen and two were on concurrent intravenous tobramycin

FDA Safety Summary: Ototoxicity

- No signs of ototoxicity regarding complaints of deafness or by standard audiograms to 8000 Hz
- BUT: 8 TOBI patients had 16 episodes of tinnitus; tinnitus may be an early manifestation of cochlear toxicity
- What effects might longer term TOBI therapy have on cochlear function?

Changes in MIC for *Pseudomonas aeruginosa*

- Primary FDA analyses:
  Baseline MIC to Visit 10 MIC
  Baseline MIC to Visit 11 MIC
  Baseline MIC to Final MIC

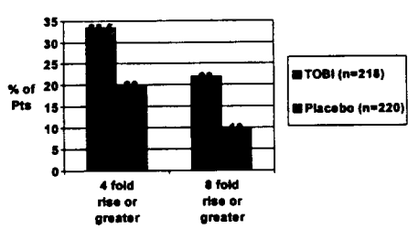
Shifts In MIC from Baseline toVisit 10 and 11

- Used Valid MIC values only
- Maximum MIC value at Visit 3, Visit 10, and Visit 11 were recorded for each patient

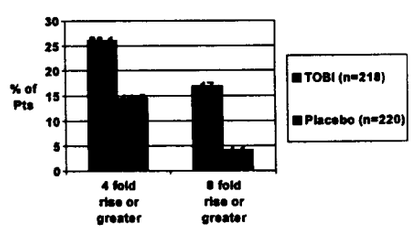
Shifts in MIC from Baseline to Visit 10 and 11

- Patients with a valid baseline, valid Visit 10, and valid Visit 11 MIC data were included (218 TOBI and 220 Placebo)
- Shifts from baseline to Visit 10, and baseline to Visit 11 were calculated for each patient
- Analyses compared relative % patients in each arm with:
  ≥ 4 fold rise in MIC
  ≥ 8 fold rise in MIC

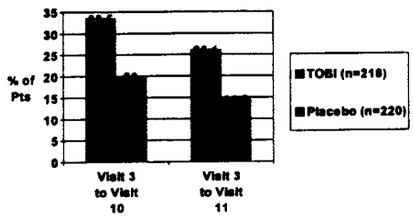
Shifts in MIC From Baseline to Visit 10



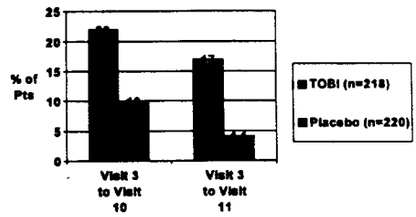
Shifts in MIC from Baseline to Visit 11



Summary:
% Patients with ≥ 4-fold Rise in MIC



Summary:
% Patients with ≥ 8-fold Rise in MIC



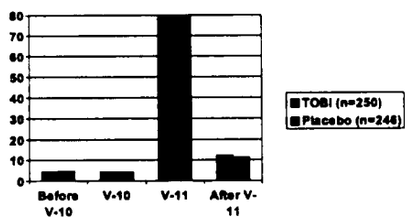
Shifts in MIC from Baseline to Final Valid MIC

- Used Valid MIC values only
- Maximum MIC value at Visit 3 and Maximum MIC value at the Final Study Visit were recorded for each patient

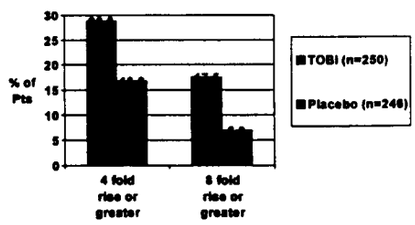
Shifts In MIC from Baseline to Final Valid MIC

- Patients with a valid baseline and valid MIC after Visit 5 were included (250 TOBI and 246 Placebo)
- Shifts from baseline to last available MIC were calculated for each patient
- Analyses compared relative % patients in each arm with:
  - ≥ 4 fold rise in MIC from baseline to last visit
  - ≥ 8 fold rise in MIC from baseline to last visit

Last Visit With Valid MIC Data



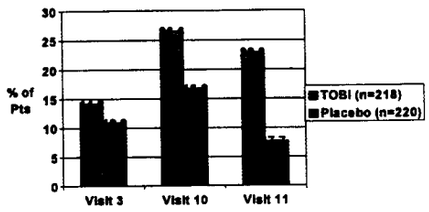
Shifts From Baseline to Final MIC



Additional FDA Analyses Regarding MIC Values

- Relative % of Patients with MIC values > 8 ug/mL at Visits 3, 10, and 11 for each Treatment Arm
- Only patients with Visit 3, Visit 10, and Visit 11 MIC data were included (218 TOBI and 220 placebo patients)

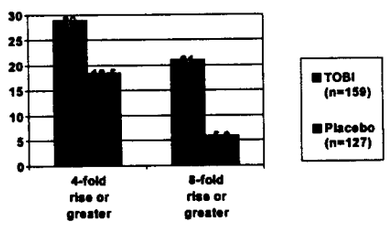
% Pts with MIC Values > 8 ug/mL At Visit 3, 10 and 11



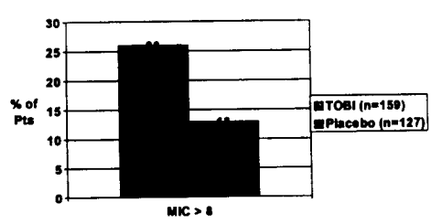
Additional FDA Analyses Regarding MIC Values

- Subset Analysis in Patients Who Did Not Receive Systemic Antipseudomonal Antibiotics During the Study
- 150 TOBI and 129 placebo patients met this criteria and had a baseline MIC value and a maximum MIC value at Visit 10 or 11

FDA Subset Analysis of Patients Not Exposed to Systemic Antipseudomonal Antibiotics: Changes from Baseline MIC to Visit 10 or Visit 11



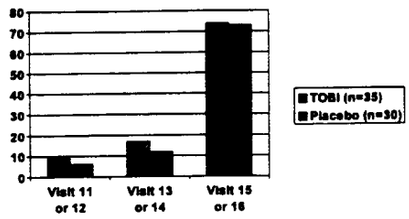
FDA Subset Analysis of Patients Not Exposed to Systemic Antipseudomonal Antibiotics: % of Patients with MIC > 8 ug/mL at Visit 10 or 11



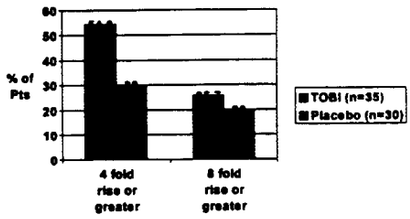
What About Longer Term Exposure to TOBI?

- 68 subjects entered open-label trial:
  - 35 TOBI/TOBI: all 35 had a valid baseline and valid MIC during open-label
  - 33 Placebo/TOBI: 30 had a valid baseline and a valid MIC during open-label

Last Visit with Valid MIC During Open Label Study



Shifts in MIC from Baseline to Final MIC Open-Label Trial



Is Clinically Significant Resistance Occurring? Data from the Parallel Studies

- % predicted FEV-1 improved
- CFU counts decreased, although this effect was less remarkable with each successive cycle of TOBI treatment
- Time to IV Antibiotic Use was Delayed (Both trials)
- Time to Hospitalization was Delayed (One trial)
- 4 deaths: All in Placebo Arm

Is Clinically Significant Resistance Occurring? Patients Who Withdrew from Parallel Trials

- 21 placebo patients withdrew prematurely

  No patients withdrew due to clinical concerns of resistant pneumonias

  Four patients had *P. aeruginosa* isolates with MIC $\geq$ 8 at the final study visit and one of these four also had *S. maltophilia* at the final study visit with an MIC 256

Is Clinically Significant Resistance Occurring? Patients Who Withdrew from Parallel Trials

- 16 TOBI patients withdrew prematurely

  One withdrew due to a clinical concern of "Resistant *Pseudomonas aeruginosa* pneumonia"

  Six patients had *P. aeruginosa* isolates with MIC $\geq$ 8 at the final study visit

  Three patients had *S. maltophilia* with MIC $\geq$ 32 at the final study visit

  One patient had *A. xylosoxidans* with MIC 512 at the final study visit

Is Clinically Significant Resistance Occurring? Data from the Open-Label Studies

- Placebo/TOBI Patients (n=33)

  6 patients withdrew prematurely

  2 due to "resistant organisms"

  1 due to "increased respiratory symptoms" and had an MIC for *P. aeruginosa* of 128 ug/mL at last Visit

Is Clinically Significant Resistance Occurring?
Data from the Open-Label Studies

- **TOBI/TOBI Patients (n=35)**

  7 patients withdrew prematurely

  3 due to "resistant organisms"

  1 "felt no better on TOBI" and had a final MIC for *P. aeruginosa* of 32

  1 "had no improvement" and had *S. maltophilia* noted from Visit 5 on, with MIC 2048 at last visit

FDA Safety Summary: MIC Values

- **Upward Shifts in MIC values for *Pseudomonas aeruginosa* isolates were more marked in the TOBI arm over time**
- **Overall, there is little evidence that these shifts were of clinical relevance during the 6 month studies**
- **Patients who withdrew prematurely, however, (particularly from open-label) may have had resistance as a contributing factor**

FDA Safety Summary: MIC Values

- **Will rises in MIC continue to occur with longer term TOBI therapy and will this have an impact on clinical outcome?**

Cystic Fibrosis Foundation

PUBLIC PRESENTATION

Robert J. Beall, Ph.D.
President and Chief Executive Officer
Cystic Fibrosis Foundation

to

The Food and Drug Administration
Anti-Infective Drugs Advisory Committee
on TOBI™ for Management of Cystic Fibrosis Patients

November 21, 1997

Foundation Office
6931 Arlington Road Bethesda, Maryland 20814
(301) 951-4422 (800) FIGHT CF Fax (301) 951-6378 www.cff.org

Robert J. Beall, Ph.D., President and CEO
Cystic Fibrosis Foundation
November 21, 1997

I appreciate the opportunity to represent the Cystic Fibrosis Foundation and the 30,000 individuals affected by cystic fibrosis at this important meeting. Let me assure you that the thoughts and hopes of these young individuals with cystic fibrosis (CF), and their families, are here with this deliberative body today.

There has been a dramatic improvement in the life expectancy of cystic fibrosis patients over the last three decades. However, with the exception of the introduction of Pulmozyme® in 1994, the treatment regimen for cystic fibrosis has remained essentially the same. We use antibiotics to treat infections, postural drainage to remove excess secretions, and aggressive enzyme replacement therapy to offset pancreatic problems. These strategies have been, and for the immediate future will remain, the cornerstone of cystic fibrosis therapy.

The improvement in life expectancy for these patients may be attributed to three factors: a network of Cystic Fibrosis Foundation-supported care centers that deliver specialized care, the availability of new antibiotics, and more aggressive nutritional intervention. For the most part, physicians have been limited to improving tools that are already available to treat cystic fibrosis. The unfortunate fact remains that despite increases in life expectancy, every child born with this disease faces a premature death sentence. And, each faces a quality of life which would be considered unacceptable by everyone in this room.

The prospect for treating the causes of CF through gene therapy and other pharmacological means has never been as hopeful as it is now. Currently, there are nine clinical trials underway that are treating the root cause of the disease—a defective gene. Other trials are underway to use drugs to correct the protein product of the defective gene. In the meantime, as these therapies are being refined, fighting the chronic lung infections and the consequent inflammatory response remain of critical importance.

Despite our efforts to identify new antibiotics during the early 80s, with the exception of the quinolones, it became apparent that no pipeline of new antimicrobial agents existed that could effectively treat CF-related infections. So we asked ourselves, "Can we improve what is already available?". The first drug candidate was an obvious one. Intravenous aminoglycosides had probably contributed more to the improved life expectancy than any other type of antibiotic.

In addition, during the 1980s, as with many groups desperate for more effective therapies, CF physicians and patients began to ask the question, "Could aminoglycosides be administered directly to the lungs via aerosol, in higher concentrations, and without

seeing the resulting side effects observed in traditional intravenous administration?". Convenience, rather than scientific method dictated the selected dosage. In fact, the patients basically took what was in the intravenous vial, and then added one or two vials to the nebulizer and went on from there. Concerns regarding dose, and preservatives in the preparation were not apparent in this early stage of aerosol usage.

In 1986, the Foundation, along with Drs. Arnold Smith and Bonnie Ramsey, began to ask some critical questions related to the use of aerosol antibiotics in CF patients. We asked whether or not aerosol antibiotics could be effective, and, if so, what was the optimal dosage and optimal delivery method? The study designed to find the answers resulted in *The New England Journal of Medicine* article, published in 1993.

But those results still did not get a drug to market. At that time, the Foundation went to PathoGenesis, and asked them to consider taking the product development to the next step. Their response to that request is why we are here today.

The pace at which this drug has moved through the subsequent developmental phases has been remarkable. The formula for this incredible feat has included: 1) a network of patients who are eager, or more appropriately described, desperate, to participate in research to treat cystic fibrosis; 2) the availability of a cystic fibrosis care center network comprised of dedicated teams of caregivers who are committed to conducting and evaluating new therapies for cystic fibrosis; 3) a company enthusiastic to develop new products, not just blockbuster drugs, but also therapies designed for a smaller patient population like cystic fibrosis; and 4) dedicated staff at the FDA. This FDA review staff has worked effectively with the private sector to evaluate and review this new drug product.

Our partnership is unique—a private foundation, a pharmaceutical company, and a regulatory agency—all working together to promptly evaluate new products. We hope that this cooperative effort will continue to strengthen and will serve to expedite future developments in cystic fibrosis research.

You, the members of this panel and staff, have sorted through reams and reams of paper documenting FEV_1s, antibiotic usage, hospitalization rates, etc. I believe, however, that one of the most significant outcomes of the study may not be found in this objective data. It is the fact that the patients on this drug reported "feeling better." To "feel better" is something that cystic fibrosis patients dream about—to not struggle for every single breath, to be able to walk up a flight of stairs without having to stop halfway. These simple things, that you and I take for granted, can dramatically change a patient's outlook on life—to change from a feeling of despair and hopelessness to one of optimism and hope.

In addition, many of these patients as a result of the aerosol drug delivery, did not have to go to the hospital for the time-consuming "clean outs," as they are called, that frequently force people to miss school and work time. The convenience of aerosol has clearly made

a difference in not only how they feel, but in allowing them the opportunity to resume efforts of education, career development, and raising families.

Not only are the patients excited about TOBI™, but physicians too are excited about having a new therapy approach. We already know that 34.3% of CF patients reported use of inhaled antibiotics in 1995. The results from the Phase III study indicate that TOBI™ could be applicable to thousands of patients who have been diagnosed with cystic fibrosis. The availability of such an innovative and well studied drug may unlock the handcuffs that have frustrated our caregivers for decades. They finally will have a new tool that may reduce morbidity and possibly mortality while providing a better quality of life for their patients. In addition, we are already applying the same rigorous process that we applied to the development TOBI™ to explore other aerosol antibiotics.

Today, the entire scientific community also is anxiously watching the landmark experiments in gene therapy for cystic fibrosis, the most likely route to a cure for CF. While everyone awaits the results of these studies, TOBI™ must be made available now. We need it to treat young individuals with cystic fibrosis so that they can better manage their disease until we achieve the ultimate cure. Clearly, TOBI™ will become a major weapon in our fight to control the progressive daily destruction of this disease.

The deliberations about to take place during the next few hours will profoundly impact the lives of individuals with cystic fibrosis. We appreciate the opportunity to represent them. We also appreciate the dedication of the scientists, the cystic fibrosis physicians, the FDA staff and the hundreds of patients who have participated in these extensive studies. We look forward to the day when we can reflect back on this meeting and identify it as truly historical. It will represent an important milestone in the long, treacherous, and sometimes painful trail that we have followed to accomplish our ultimate goal, a cure for cystic fibrosis.

Thank you.

Note: Because of the pivotal role that the Cystic Fibrosis Foundation played in the initial studies of aerosolized Tobramycin, it has a payback agreement and a royalty agreement with PathoGenesis Corporation on this product.

TOBI: EFFICACY RESULTS

JOHN ALEXANDER, M.D.
MEDICAL OFFICER
FDA

PC-TNDS-002 AND -003

A Phase III Placebo Controlled Clinical Trial to Study the Safety and Efficacy of Tobramycin Solution for Inhalation in Patients with Cystic Fibrosis

INCLUSION CRITERIA

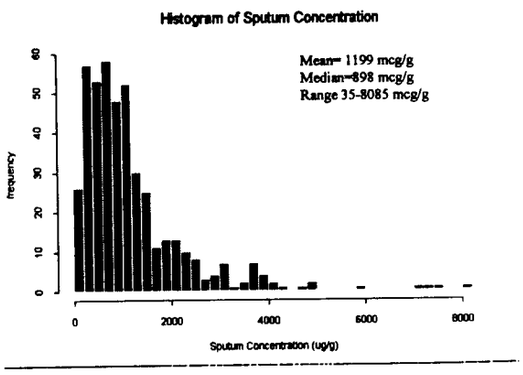
- **≥ 6 years of age.**
- **FEV_1 ≤75% and ≥25% of predicted,** based on gender, age and height
- ***P. aeruginosa*** **present in a sputum/throat culture within 6 months of screening and a minimum of one screening visit.**

Exclusion Critera

- **History of sputum culture or throat swab culture yielding *B. cepacia* in the previous two years and/or sputum or throat swab culture yielding *B. cepacia* at screening (Visit 1 or 2)**

DOSE SELECTION

TOBI: 300mg BID via Aerosol with Pari LC Plus Jet Nebulizer



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[redacted]

AEROSOLIZED DRUG

[redacted]

SPUTUM CULTURES

SPUTUM DRUG CONCENTRATION

PULMONARY FUNCTION TESTS

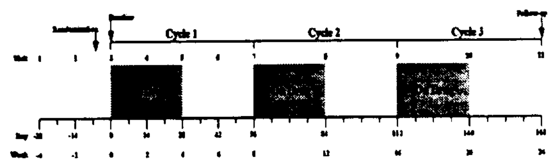
APPEARS THIS WAY ON ORIGINAL

[redacted]

LUNG DISTRIBUTION
EFFECT ON *PSEUDOMONAS* IN LOWER AIRWAYS
MECHANISM OF ACTION

Study Design

- Visits 1 and 2--Screening Visits
- Visit 3--Baseline Measurements
- Visit 10--Primary Endpoint Analysis



STUDY RESULTS

DEMOGRAPHIC DATA

Number (%) of Patients	TOBI	Placebo	TOBI	Placebo
Number of Patients	109	114	149	148
Sex				
Male	63 (57.8)	59 (51.8)	86 (57.7)	73 (49.3)
Female	46 (42.2)	55 (48.2)	63 (42.3)	75 (50.7)
Age (years)				
Mean (STD)	20.5 (9.33)	19.8 (10.16)	21.0 (9.59)	21.2 (9.84)
Age Group				
6 - < 13 years	26 (23.9)	30 (26.3)	29 (19.5)	31 (20.9)
13 - < 18 years	24 (22.0)	32 (28.1)	39 (26.2)	35 (23.6)
≥ 18 years	59 (54.1)	52 (45.6)	81 (54.4)	82 (55.4)
Race				
White	105 (96.3)	109 (95.6)	145 (97.3)	142 (95.9)
Black	0 (0.0)	2 (1.8)	1 (0.7)	5 (3.4)
Hispanic	3 (2.8)	2 (1.8)	3 (2.0)	0 (0.0)
Asian[1]	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)
American Indian[1]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
FEV_1, % Predicted				
< 50%	50 (45.9)	56 (49.1)	72 (48.3)	72 (48.6)
≥ 50%	59 (54.1)	58 (50.9)	77 (51.7)	76 (51.4)
rhDNase Therapy				
No	24 (22.0)	28 (24.6)	36 (24.2)	30 (20.3)
Yes	85 (78.0)	86 (75.4)	113 (75.8)	118 (79.7)
Tobramycin MIC (P. aeruginosa)				
< 8 µg/mL	95 (87.2)	98 (87.5)	123 (82.6)	125 (84.5)
≥ 8 µg/mL	14 (12.8)	14 (12.5)	26 (17.4)	23 (15.5)

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PRIMARY EFFICACY ENDPOINTS

- Mean Relative Change in % Pred. FEV1
- Change in Log (CFU/g)
- Mean Relative Change in % Pred. FVC

What is a mean relative change in % Predicted FEV1 ?

$$\text{RC in \%P FEV1} = \frac{\text{Visit 10 - Visit 3}}{\text{Visit 3}}$$

Mean Relative Change

- Has the tendency to inflate absolute changes from the baseline value
- Looks only at baseline and endpoint data

Why not use Raw FEV1 measurements for comparison?

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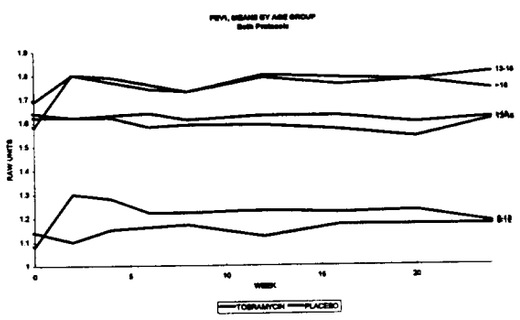
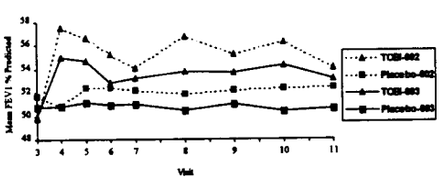


FEV1 % Predicted



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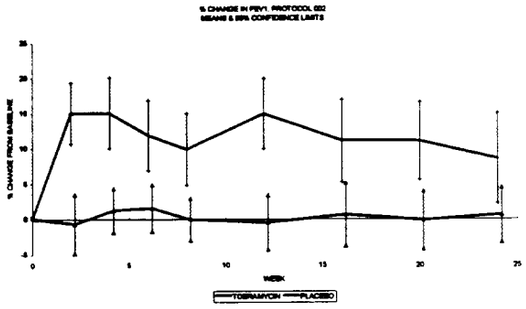
Change in % predicted FEV1

- 12% tx effect = 6% change in %FEV1
- 8% tx effect = 4.5% change in %FEV1



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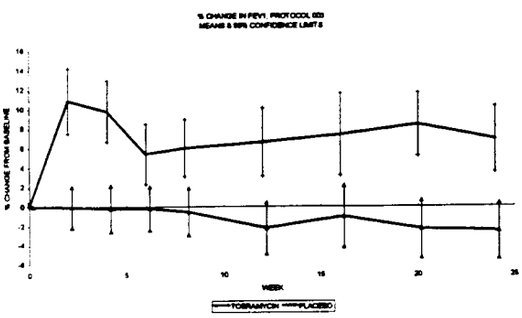

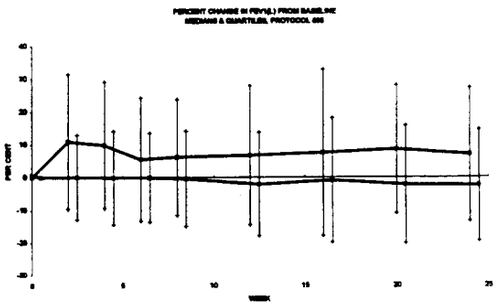

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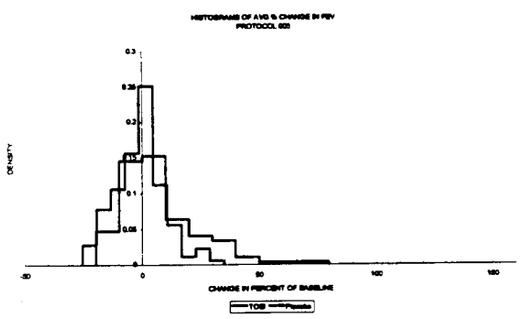
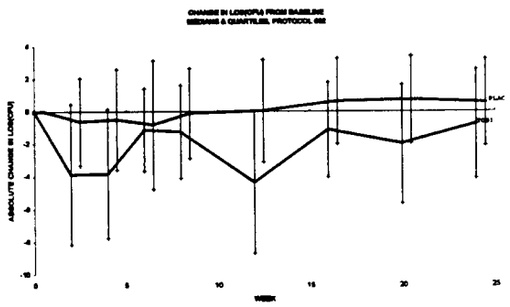
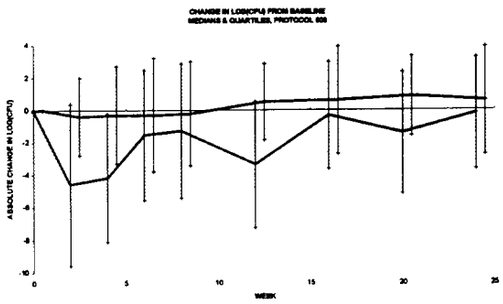




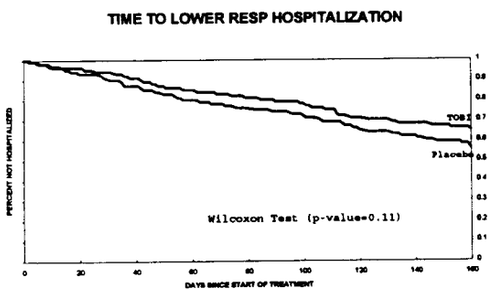


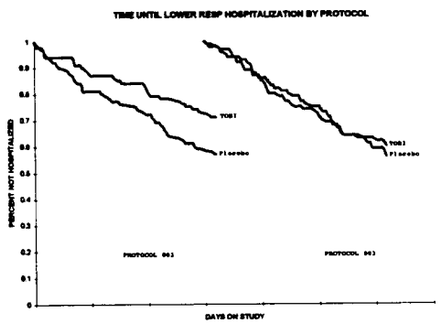
SECONDARY ENDPOINTS

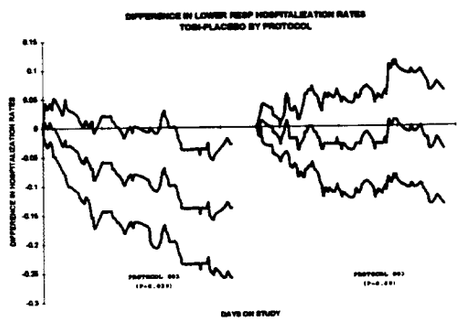
LOWER RESPIRATORY HOSPITALIZATION

SPONSOR'S RESULTS

- Results of pooled studies were shown
- Percent of Subjects Hospitalized
  37% TOBI vs. 45% Placebo
- Relative Risk=0.74 (0.567-0.975)
- Mean Days of Hospitalization (p=0.001)
  5.1 d for TOBI vs. 8.1 d for Placebo







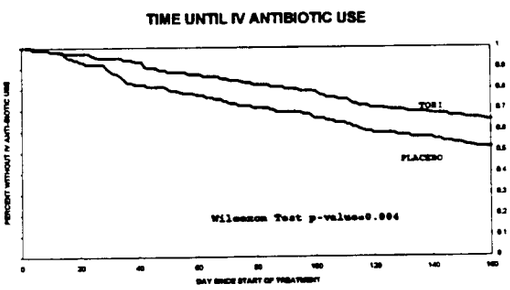
HOSPITALIZATION BY PROTOCOL

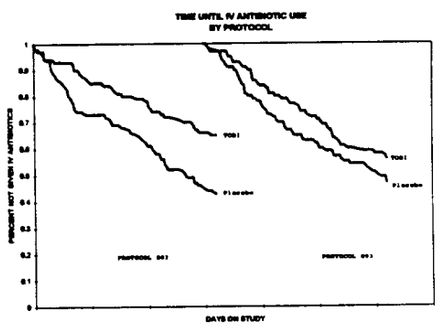
	PC-TNDS-002	PC-TNDS-003
PERCENT OF SUBJECTS HOSPITALIZED	28% TOBI vs 45% Placebo	43% TOBI vs 45% Placebo
RELATIVE RISK (95% CI)	0.557 (0.356-0.871)	0.891 (0.631-1.258)
MEAN DAYS HOSPITALIZED p-value	4.6d TOBI vs 9.1d Placebo 0.004	5.5d TOBI vs. 7.4d Placebo 0.53

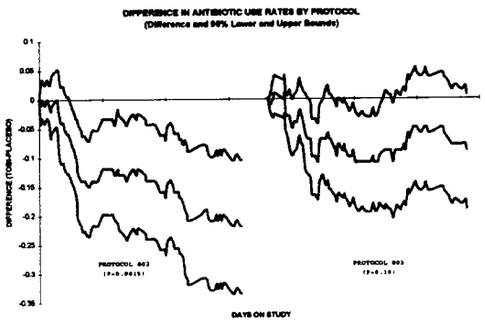
ANTIBIOTIC USE

SPONSOR'S RESULTS

- Results of pooled studies were shown
- Percent of Subjects with Antibiotic Use
  39% TOBI vs. 52% Placebo
- Relative Risk=0.64 (0.494-0.830)
- Mean Days of Antibiotics ($p<0.001$)
  9.6 d for TOBI vs. 14.1 d for Placebo

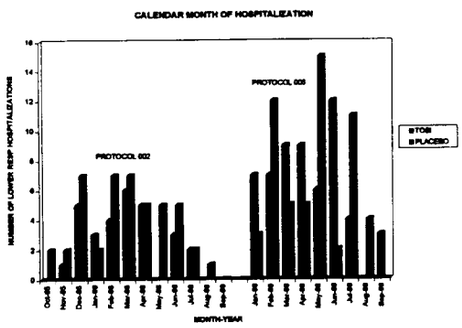


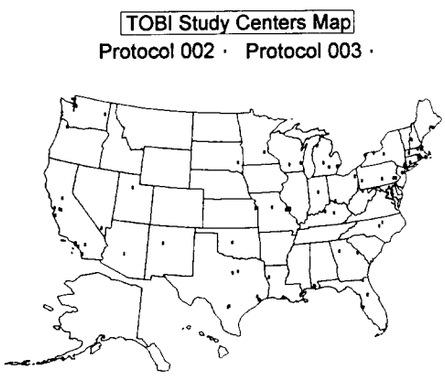




ANTIBIOTIC USE BY PROTOCOL

	PC-TNDS-002	PC-TNDS-003
PERCENT OF SUBJECTS WITH ANTIBIOTIC USE	33% TOBI vs. 54% Placebo	43% TOBI vs. 50% Placebo
RELATIVE RISK (95% CI)	0.512 (0.339-0.773)	0.746 (0.533-1.045)
MEAN DAYS OF ANTIBIOTIC USE	8.8d TOBI vs. 14.6d Placebo	10.1d TOBI vs. 13.7d Placebo
p-value	0.010	0.039





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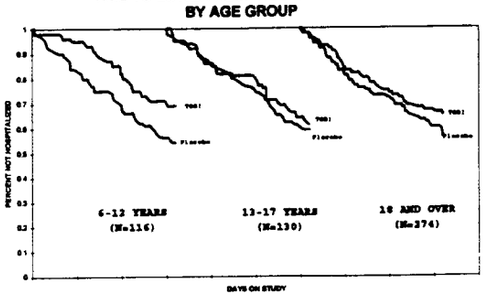
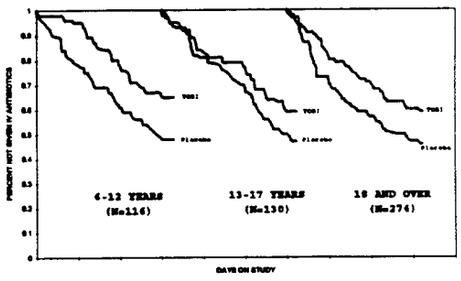
CENTER EFFECTS ?

SUBSET ANALYSES

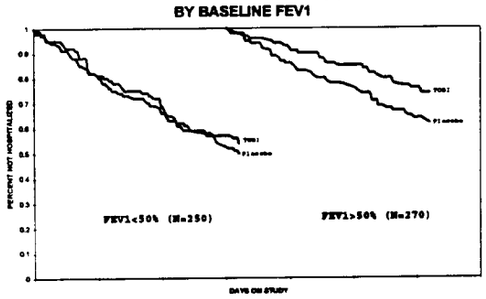
TIME TO LOWER RESP HOSPITALIZATION
BY AGE GROUP



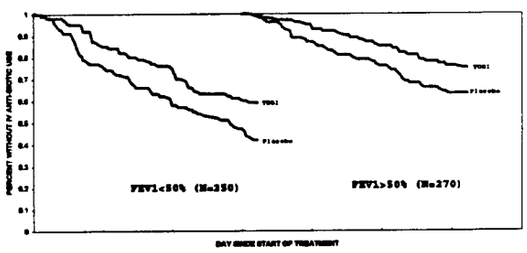
TIME UNTIL IV ANTIBIOTIC USE
SORTED BY AGE GROUP



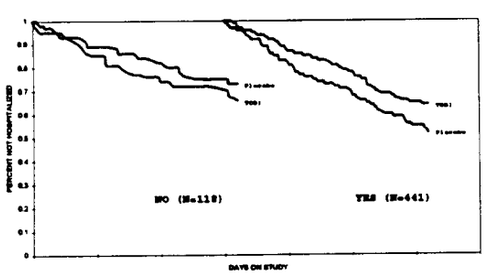
TIME TO LOWER RESP HOSPITALIZATION
BY BASELINE FEV1



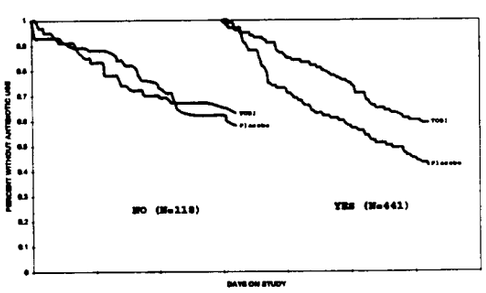
TIME UNTIL IV ANTIBIOTIC USE
SORTED BY BASELINE FEV1



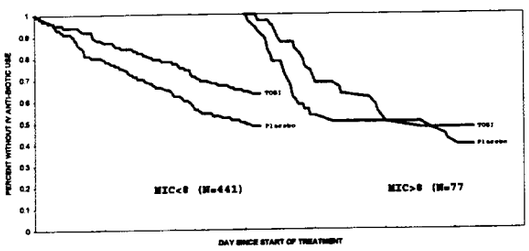
TIME TO LOWER RESP HOSPITALIZATION
BY DNASE USE



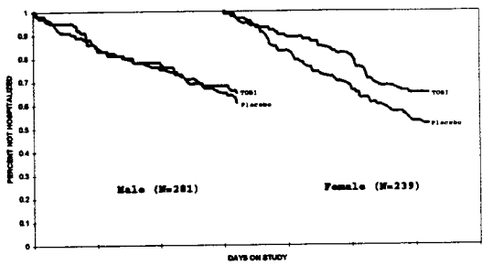
TIME TO IV ANTIBIOTIC USE BY DNASE USE



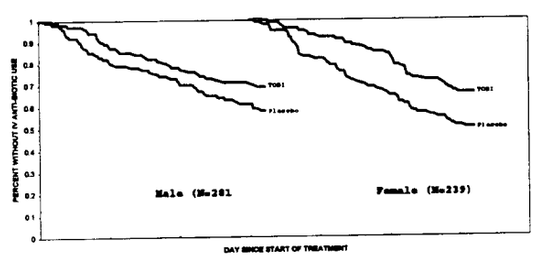
TIME UNTIL IV ANTIBIOTIC USE
SORTED BY BASELINE MIC



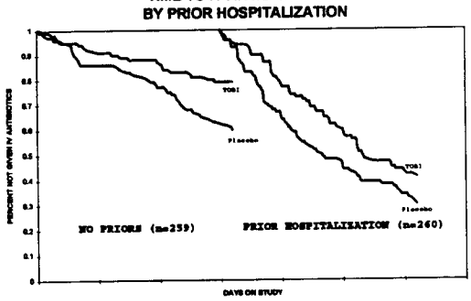
TIME UNTIL LOWER RESP HOSPITALIZATION
BY GENDER



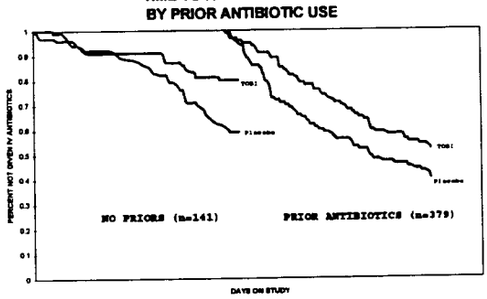
TIME UNTIL IV ANTIBIOTIC USE
SORTED BY GENDER



TIME TO IV ANTIBIOTIC USE
BY PRIOR HOSPITALIZATION

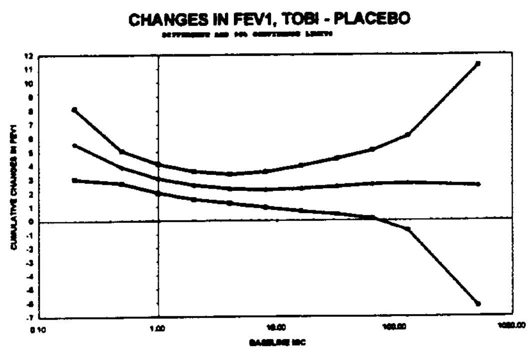


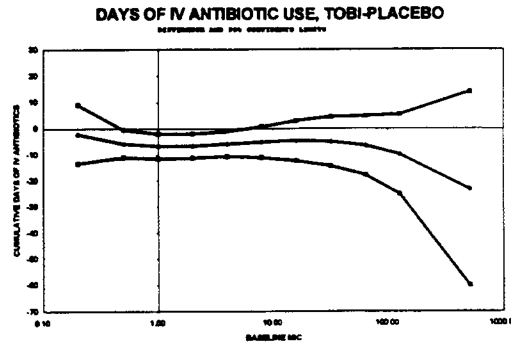
TIME TO IV ANTIBIOTIC USE
BY PRIOR ANTIBIOTIC USE

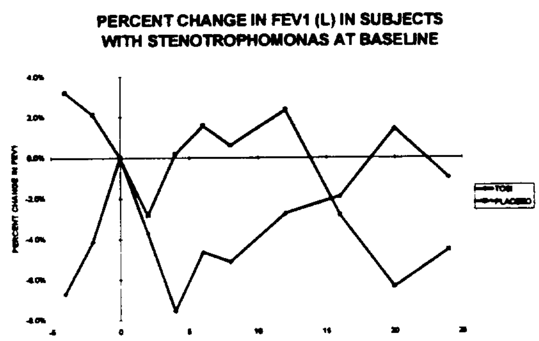


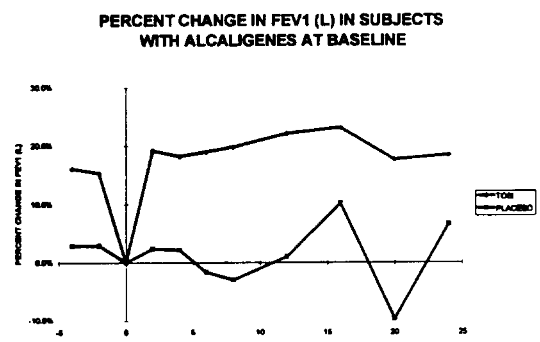
Organisms with High MIC's

- *Pseudomonas aeruginosa*
- *Stenotrophomonas maltophilia*
- *Alcaligenes xylosoxidans*









BEST POSSIBLE CO

Patient/Parent Treatment Assessment

CYCLE 1	Better	Unchanged	Worse
TOBI	80	39	15
Placebo	40	74	33
Cycle 1--Comparison of Row Means by Cochran-Mantel-Haenszel			p=0.001
CYCLE 2	Better	Unchanged	Worse
TOBI	53	56	10
Placebo	33	74	33
Cycle 2--Comparison of Row Means by Cochran-Mantel-Haenszel			p=0.020
CYCLE 3	Better	Unchanged	Worse
TOBI	57	80	16
Placebo	35	72	20
Cycle 3--Comparison of Row Means by Cochran-Mantel-Haenszel			p=0.012