# Jeffrey Blumer, PhD, MD

## Ceftriaxone Pharmacokinetics and Pharmacodynamics in Acute Otitis Media



(17)

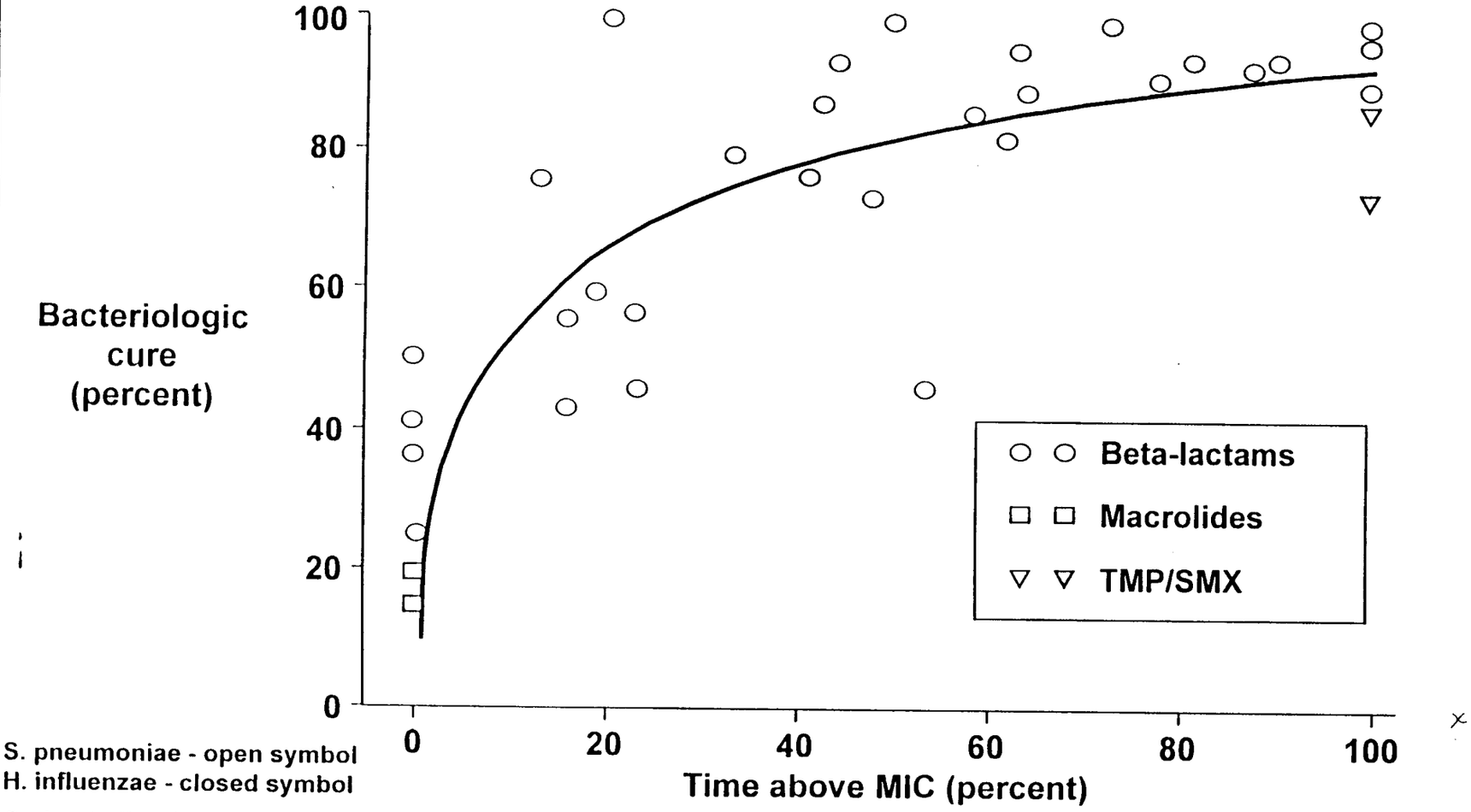
# Issues in Therapeutic Decision Making in AOM

- Treatment is empiric -- the identity of the pathogen being treated is unknown
- Overall spontaneous resolution rate is high (~60%) but varies among the individual pathogens
- Parents of symptomatic children essentially demand treatment

# Issues in Therapeutic Decision Making in AOM (cont'd)

- In the current health care environment where cost is a major force driving antibiotic selection amoxicillin remains 3 to 6 times less expensive than most other oral antibiotics
- In current health care environment there are no alternatives for children who cannot tolerate oral therapy or whose families cannot complete course of oral antibiotic

# Determinants of Antibiotic Effectiveness in Acute Otitis Media
## -- Time Above MIC --




S. pneumoniae - open symbol
H. influenzae - closed symbol

Craig, Pediatr Inf Dis J, 1996.



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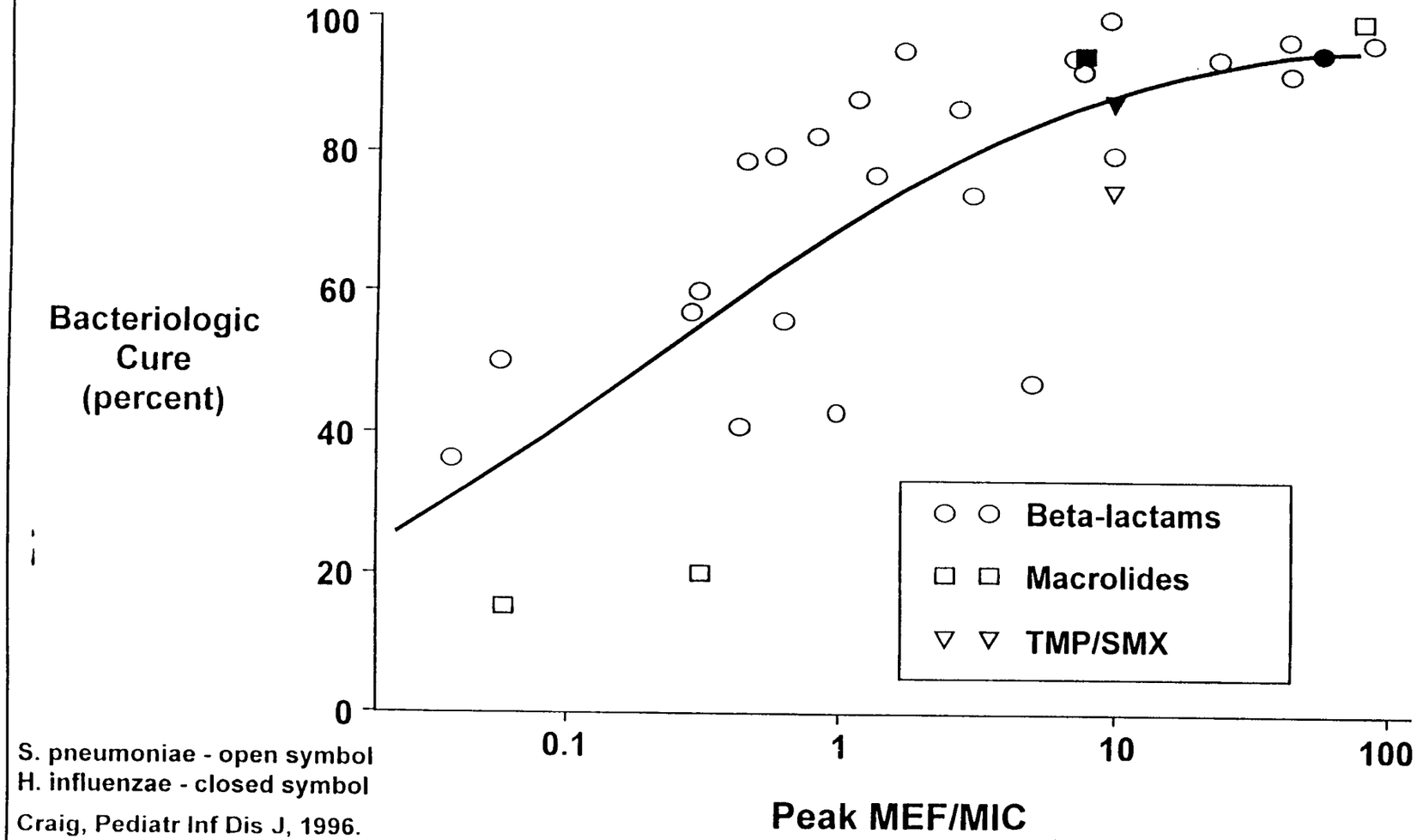
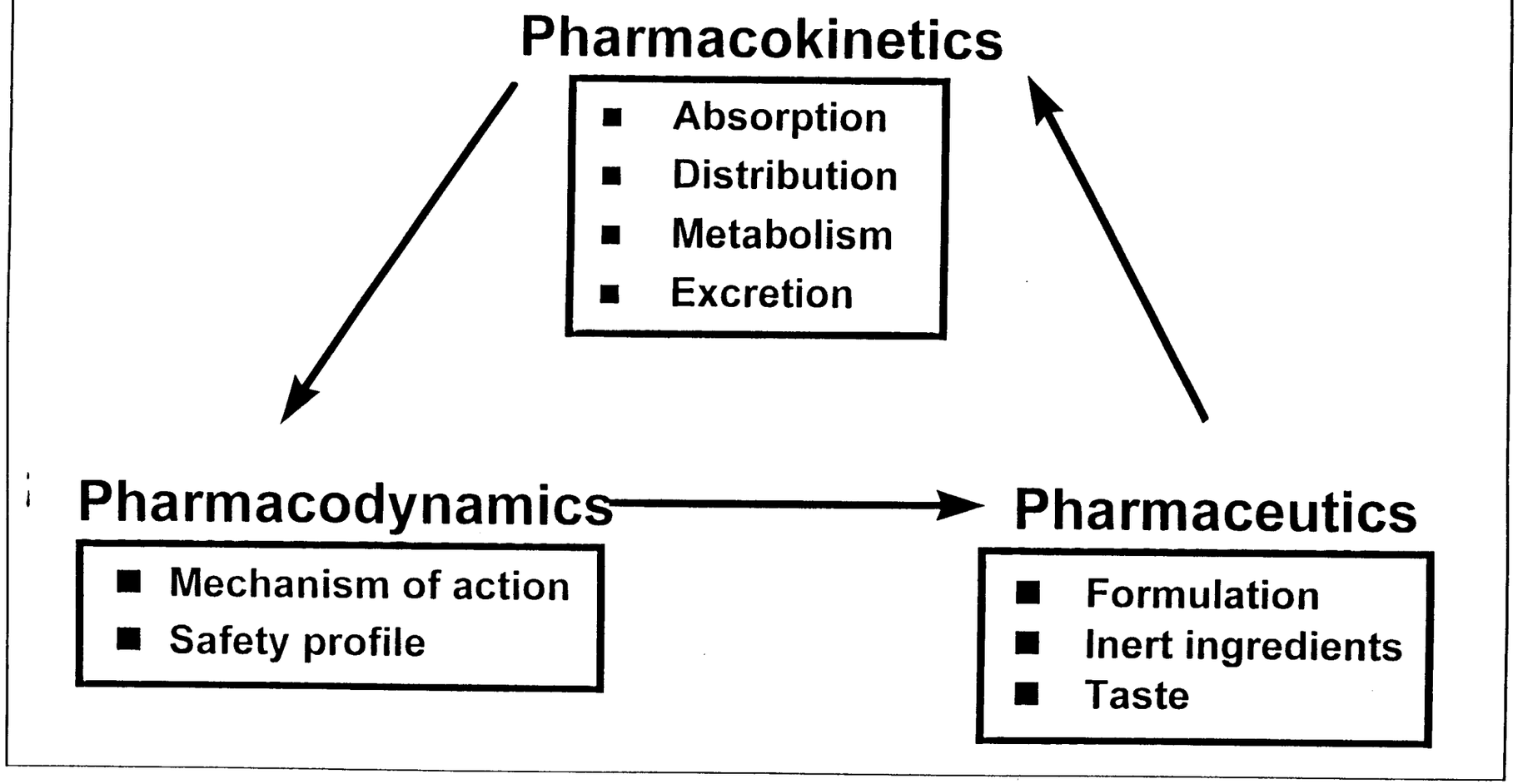
# Determinants of Antibiotic Effectiveness in Acute Otitis Media
## -- Middle Ear Fluid to MIC Ratio --




S. pneumoniae - open symbol
H. influenzae - closed symbol

Craig, Pediatr Inf Dis J, 1996.

# Determinants of Effective Therapy



# Characteristics of the Ideal Antibiotic for the Treatment of AOM

- Pharmacokinetics
  - Long elimination half-life
  - Penetration into middle ear fluid in concentrations required to inhibit bacterial replication
  - No significant metabolism
  - Renal elimination by glomerular filtration

# Characteristics of the Ideal Antibiotic for the Treatment of AOM

- Pharmacodynamics
  - Bactericidal activity against all common pathogens
  - β-lactamase stable
  - No major organ system side effects
  - Low incidence of rash and gastrointestinal side effects

# Characteristics of the Ideal Oral Antibiotic for the Treatment of Otitis Media in Children

- Pharmaceutics
  - Available in a liquid formulation
  - Palatable to young children
  - May be given with food
  - Dosing regimen which assures compliance

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# Ceftriaxone

- More than 13 years of experience in the treatment of moderate to severe infections in infants and children
- Currently the drug of choice for treatment of bacterial meningitis in children
- Extensively used in the outpatient management of presumed bacteremia in infancy (~300,000 patients/year)
- Little resistance seen among common pediatric pathogens despite intensive use

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# The Unique Pharmacokinetic Profile of Ceftriaxone Predicts Effectiveness as a Treatment for Acute Otitis Media

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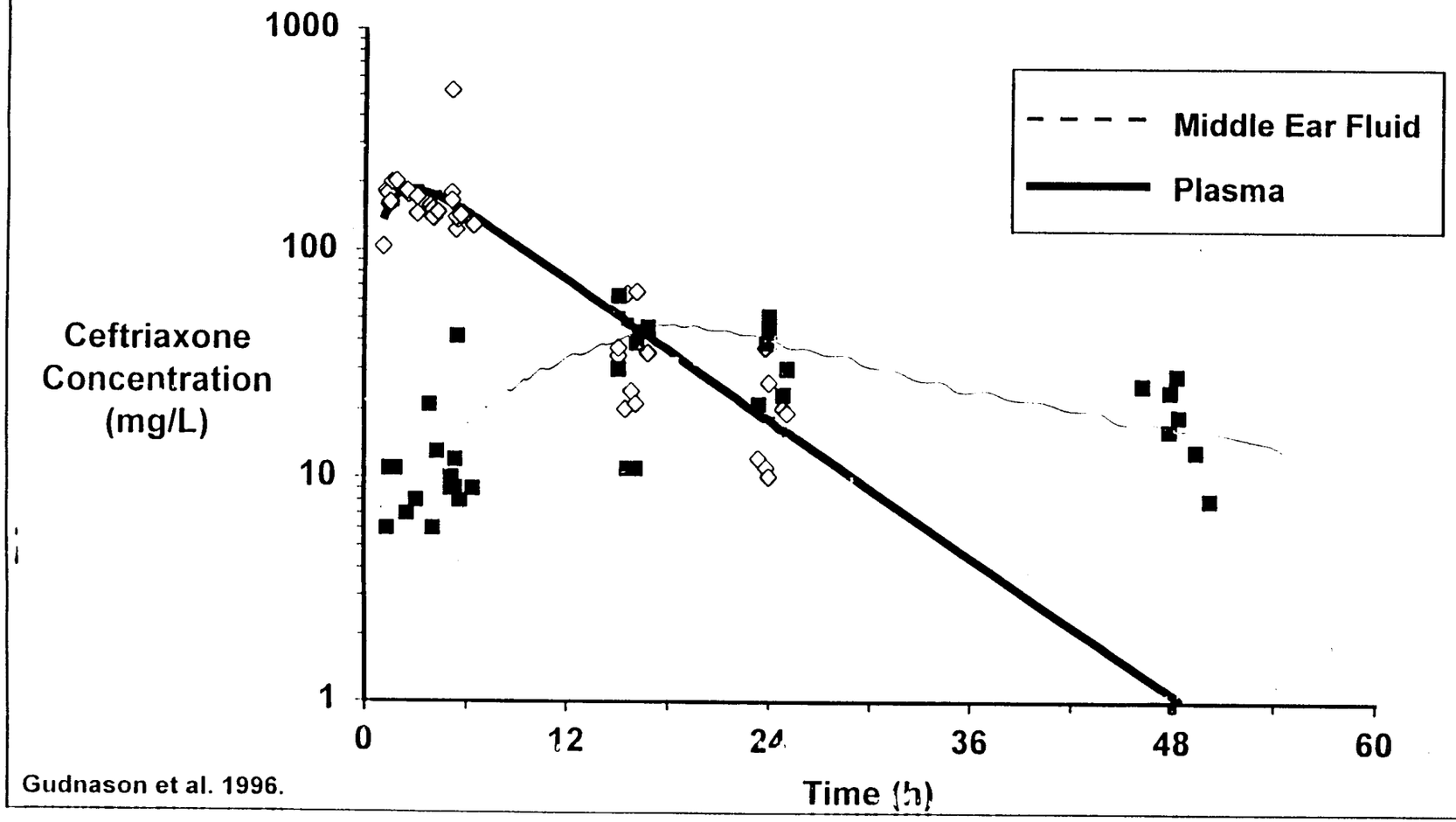
# Time-Concentrations Profiles: Plasma vs. Middle Ear Fluid




Gudnason et al. 1996.

# Pharmacokinetics of Ceftriaxone in Infants and Children

## Dose 50 mg/kg

| | Piasma | MEF |
|---|---|---|
| $C_{max}$ μg/mL | 171.0 | 35 |
| $t_{max}$ hr | 1.5 | 24 |
| $t_{1/2\beta}$ hr | 6 | 25 |

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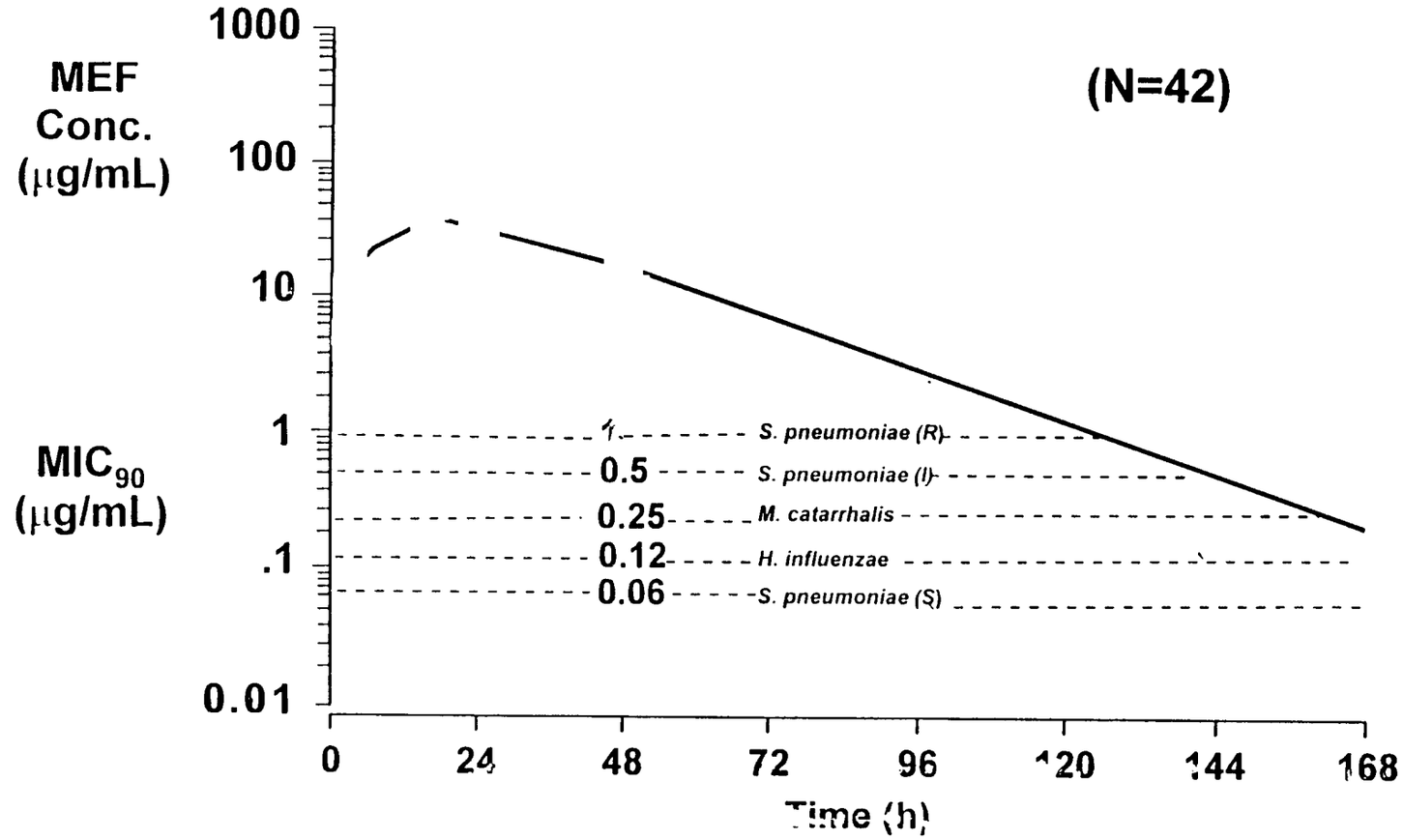
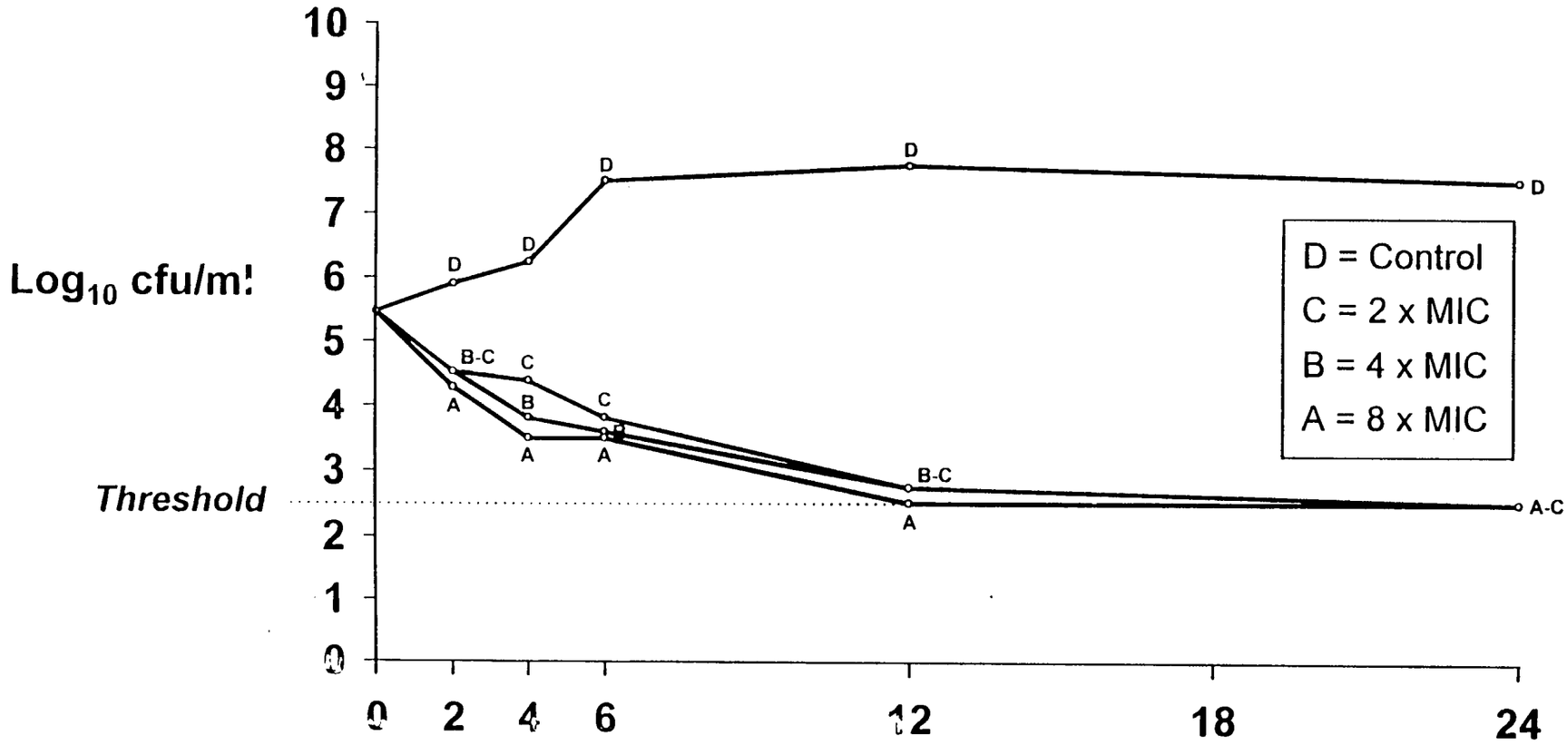
# Ceftriaxone Total Concentration in Middle Ear Fluid (MEF)




(S) = penicillin susceptible; (I) = penicillin intermediate; (R) = penicillin resistant

# Bactericidal Activity of Ceftriaxone Against Pneumococcus




Spangler S., Jacobs M.R., Applebaum P.C., A.A.C., 1997

# Concentration of Ceftriaxone in MEF Related to $MIC_{90}$ of Ceftriaxone for Three Major Pathogens Causing Otitis Media

| | *S. pneumoniae* | | | *H. influenzae* | *M. catarrhalis* |
|---|---|---|---|---|---|
| | Penicillin Sensitive ($MIC_{90}$:≤0.06μg/mL) | Intermediate Penicillin ($MIC_{90}$:0.1-1) | Penicillin Resistant ($MIC_{90}$:1-2) | | |
| Ceftriaxone $MIC_{90}$ (mg/L)* | 0.06 | 0.5 | 1 | 0.12 | 0.25 |
| Max MEF conc/$MIC_{90}$ ratio | 580 | 70 | 35 | 292 | 140 |
| Time above $MIC_{90}$ (hr)** | >200 | >150 | >100 | >150 | >150 |

* MICs obtained from Craig WA, PIDJ 1996; 15:255-259.

** Based on estimated half-life of 25 hr in MEF.

- Ceftriaxone is characterized by potent activity against the three major pathogens causing acute otitis media
- It has maintained its potency without adversely affecting microbial ecology despite widespread use in both the inpatient and outpatient setting

# Stability of Ceftriaxone Potency Against Common Pediatric Bacterial Pathogens Since Approval

| Pathogens | Ceftriaxone $MIC_{90}$ (μg/mL) | | | |
|---|---|---|---|---|
| | 1987-1991[a] | 1992-1993 | 1994-1995 | 1996 |
| *Streptococcus pneumoniae* | 0.06 | 1[b] | 1[e] | -- |
| *Haemophilus influenzae* | ≤0.007 | ≤0.12[c] | -- | -- |
| *Moraxella catarrhalis* | 0.5 | 1[d] | -- | -- |
| *Neisseria meningiditis* | -- | ≤0.002[g] | -- | ≤0.002[f] |

[a] Kessler RE, American Journal of Medicine, 1996.
[b] Goldstein FW, Journal Antimicrobial Chemotherapy, 1996.
[c] Doern GV, Journal Antimicrobial Chemotherapy, 1996.
[d] Berk SL, Journal Antimicrobial Chemotherapy, 1996.
[e] Doern GV, Antimicrobial Agents and Chemotherapy, 1996.
[f] Block et al, ICAAC, 1997.
[g] Blondeau JM, American Society for Microbiology, 1995.

# In Vitro Activity of Ceftriaxone Against Pneumococci Isolates

| | Ceftriaxone $MIC_{90}$ (μg/mL) | | |
|---|---|---|---|
| | Craig (1996) | Boken (1996) | Appelbaum (1996) |
| Penicillin susceptible (MIC ≤ 0.06 μg/mL) | 0.06 | -- | 0.06 |
| Penicillin intermediate (0.12 < MIC <1 μg/mL) | 0.5 | 0.5 | 0.5 - 1 |
| Penicillin resistant (MIC ≥ 2 μg/mL) | 1 | 1 | 1 - 2 |

Craig, Ped Infect Dis J, 1996
Boken, Ped Infect Dis J, 1996
Appelbaum, Ped Infect Dis J, 1996.

# Resistance to Antimicrobial Agents

- Microbial resistance is a natural phenomenon
  - May be intrinsic or may develop
- Complex scientific phenomenon
- Important clinical implications
- Antibiotics may exert selective pressure to favor resistant strains

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# Selective Pressure and Antimicrobial Resistance

- Antibiotics exert highly variable selective pressure
  - Influenced by MIC, pharmacokinetic profile of antibiotic
  - Sub-inhibitory concentration promotes emergence of resistant mutants in vitro
  - Sub-inhibitory trough levels in clinical dosing allow resistant organisms to emerge
  - Short-term exposure to a potent agent is less likely to select for resistant strains than long-term exposure to low antibiotic levels
  - Poor compliance in clinical settings

# Penicillin-Resistant Pneumococcal Patterns in Europe

- Correlation between antibiotic use and mode of administration
- High rate of resistance in Spain and France
  - Massive use of oral antibiotics
  - Poor treatment compliance
  - Antibiotic class
- Low rate of resistance in Italy (<5%)
  - Very low use of oral antibiotics
  - Widespread use of injectable antibiotics, including 3rd generation cephalosporins

Marchese et al.,1995. Halls et al., 1993. Baquero et a'., 1996, J. Antimicrobial Chemotherapy

# Effect of Antibiotic Treatment for Acute Otitis Media on Nasopharyngeal Colonization by Middle Ear Pathogens

| Organism | Ceftriaxone Before N=247 | Ceftriaxone After* N=230 | Ceftriaxone Change (%) | Amoxicillin/Clavulanate Before N=250 | Amoxicillin/Clavulanate After* N=235 | Amoxicillin/Clavulanate Change (%) |
|---|---|---|---|---|---|---|
| *Streptococcus pneumoniae* | 143 | 99** | 31 | 151 | 41** | 73 |
| *Haemophilus influenzae* | 98 | 68 | 3[illegible] | 98 | 77 | 21 |
| *Moraxella catarrhalis* | 134 | 95** | 29 | 143 | 24** | 83 |

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*Day 12-14 after starting treatment
**p<0.01
Cohen, 1997

# Nasopharyngeal Colonization in Children with Acute Otitis Media

| | Ceftriaxone | | Amox/Clav | |
|---|---|---|---|---|
| | Before Treatment N=247 | 10 Days After Treatment Initiation N=230 | Before Treatment N=250 | 10 Days After Treatment Initiation N=235 |
| Children carrying *S. pneumoniae* | 143 | 99 | 151 | 41 |
| Penicillin susceptible | 65 (46.6%) | 36 (36.6%) | 71 (49.0%) | 7 (17.0%) |
| Penicillin Intermediate | 37 (25.7%) | 23 (23.8%) | 32 (20.4%) | 12 (29.3%) |
| Penicillin Resistant | 41 (27.7%) | 40 (39.6%) | 48 (30.6%) | 22 (53.7%) |
| Penicillin nonsusceptible | 78 (53.4%) | 63 (63.4%) | 80 (51.0%) | 34 (83.0%) |

R. Cohen, 1997

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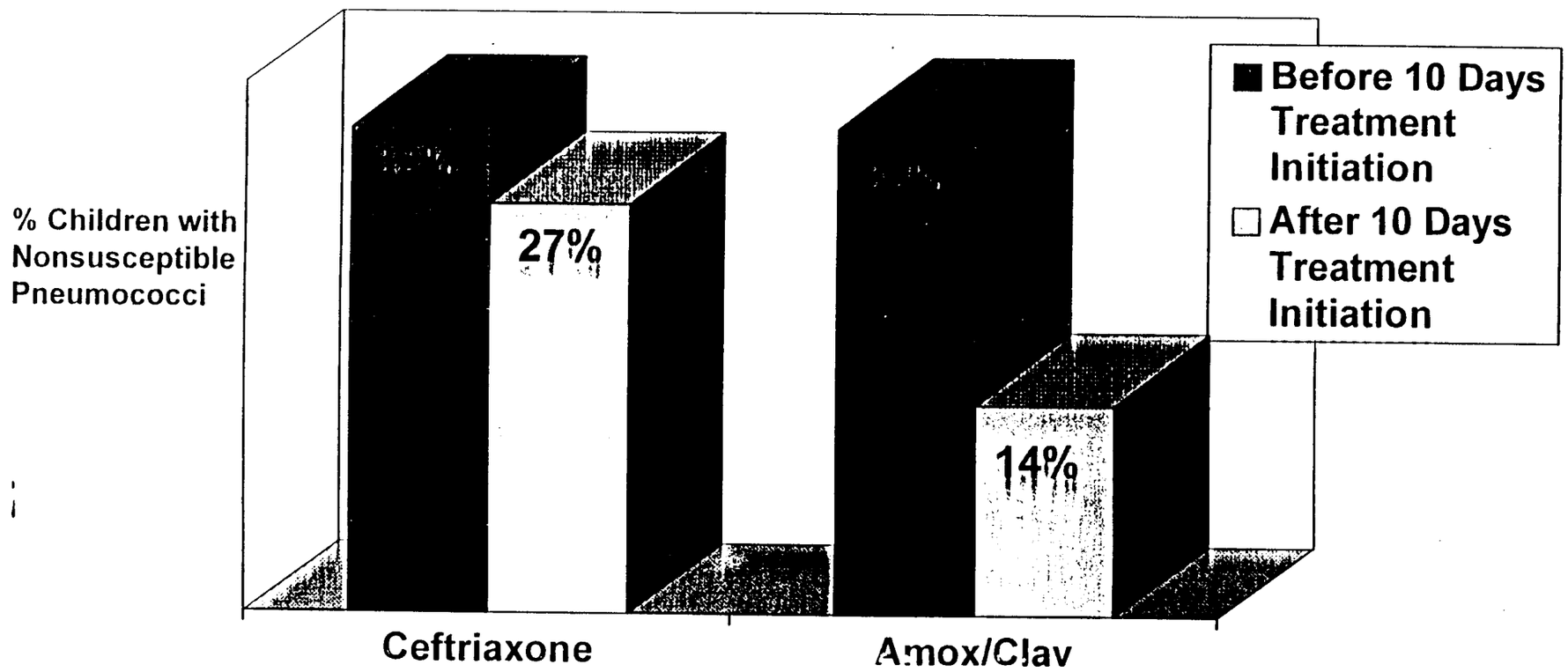
# Nasopharyngeal Colonization in Children with Acute Otitis Media




R. Cohen, 1997

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# Ecologic Impact of Ceftriaxone Use

- Aerobic bacterial flora eradicated within 24 hours*
- Stool shows *C. albicans* and enterococci as predominant resistant flora
- Recovery of normal flora starting on Day 3-10 (mean 6-7) with continued treatment
- Despite presence of resistant organisms for ~1 week after treatment, pretreatment antibiotic susceptibility patterns reestablished by 2 weeks

* Nilsson-Ehle I, Nord CE, Ursing B. Ceftriaxone: pharmacokineticcs and effect on the intestinal microflora in patients with acute bacterial infections. Scand J Infect Dis 17:77-83. 1985.

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# Treatment Failure ≠ Antibiotic Resistance

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III - 32 III - 30 III - 27 III - 29

# Pathogens Isolated from Treated Persistent and Previously Untreated Acute Otitis Media

| | Persistent N = 200 | Untreated N = 154 |
|---|---|---|
| *Streptococcus pneumoniae* | 50 (18%) | 58 (8%)** |
| *Haemophilus influenzae* | 12 (83%) | 14 (44%)* |
| *Moraxella catarrhalis* | 11 (100%) | 12 (85%)* |
| Streptococcus *pyogenes* | 10 | 9 |
| *Staphylococcus aureus* | 9 | 3 |
| No growth or nonpathogen | 105 | 56 |

* β-lactamase. ** penicillin res.

Pichichero and Pichichero. Pediatr Infect Dis J. 1995; 14:178-183.

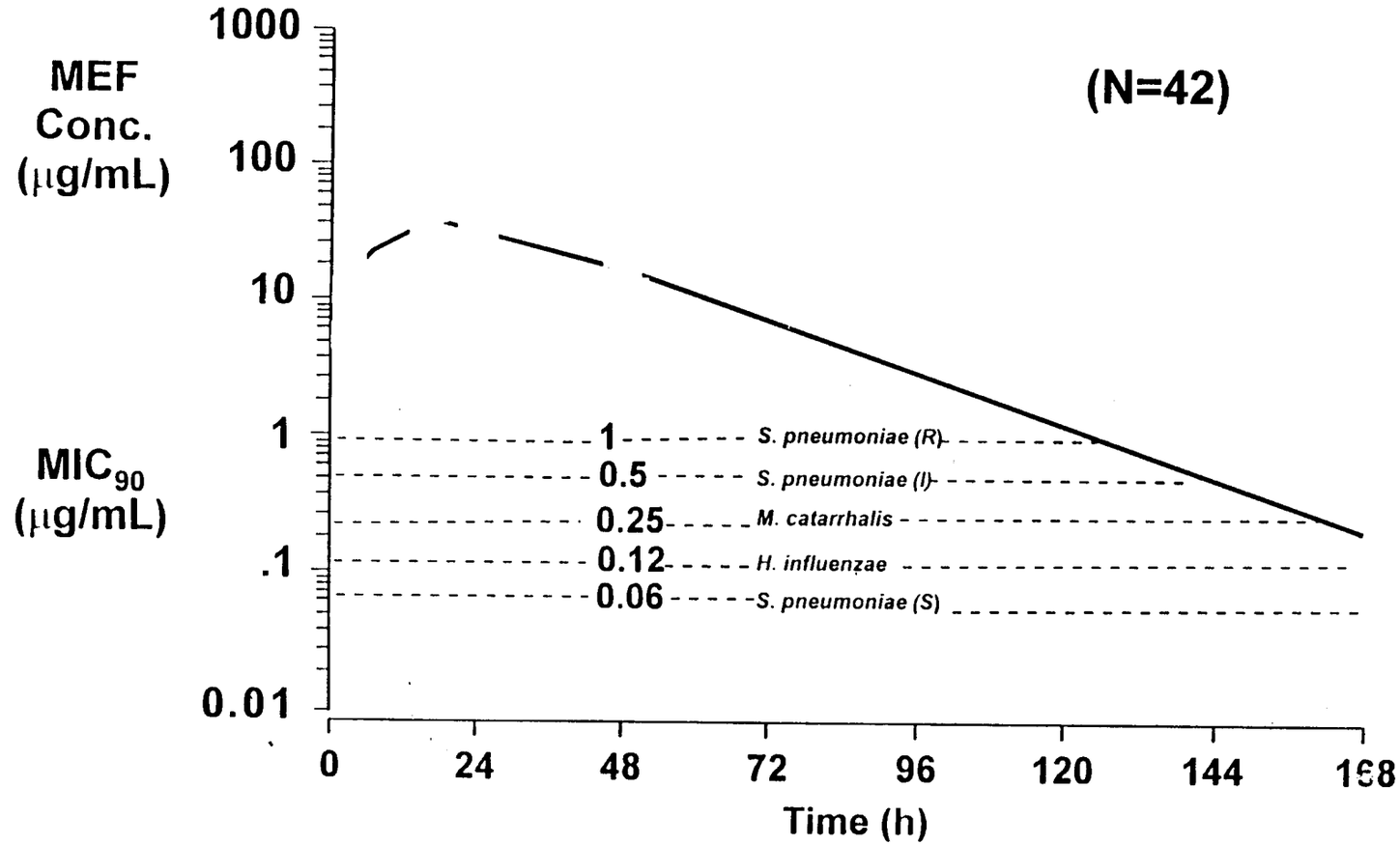
# Characteristics of Acute Otitis Media Antibiotic Treatment Failures

- Oral antibiotic treatment may fail in up to 20% of patients
- Most organisms isolated from MEF from clinical failures are susceptible to the original antibiotic prescribed
- Pre-treatment with original antibiotic results in <30% clinical success
- Successful treatment of antibiotic failures requires drug with β-lactamase stability and concentrations in MEF that are effective against *S. pneumoniae*

# Ceftriaxone and the Antimicrobial Resistance Paradigm

- Quickly bactericidal in middle ear fluid for even resistant pathogens
- Complete compliance is assured
- No sub-bactericidal trough levels
- Bactericidal for entire 4-5 day persistence in middle ear
- Therefore, less likelihood of selection in resistant strains

# Ceftriaxone Total Concentration in Middle Ear Fluid (MEF)

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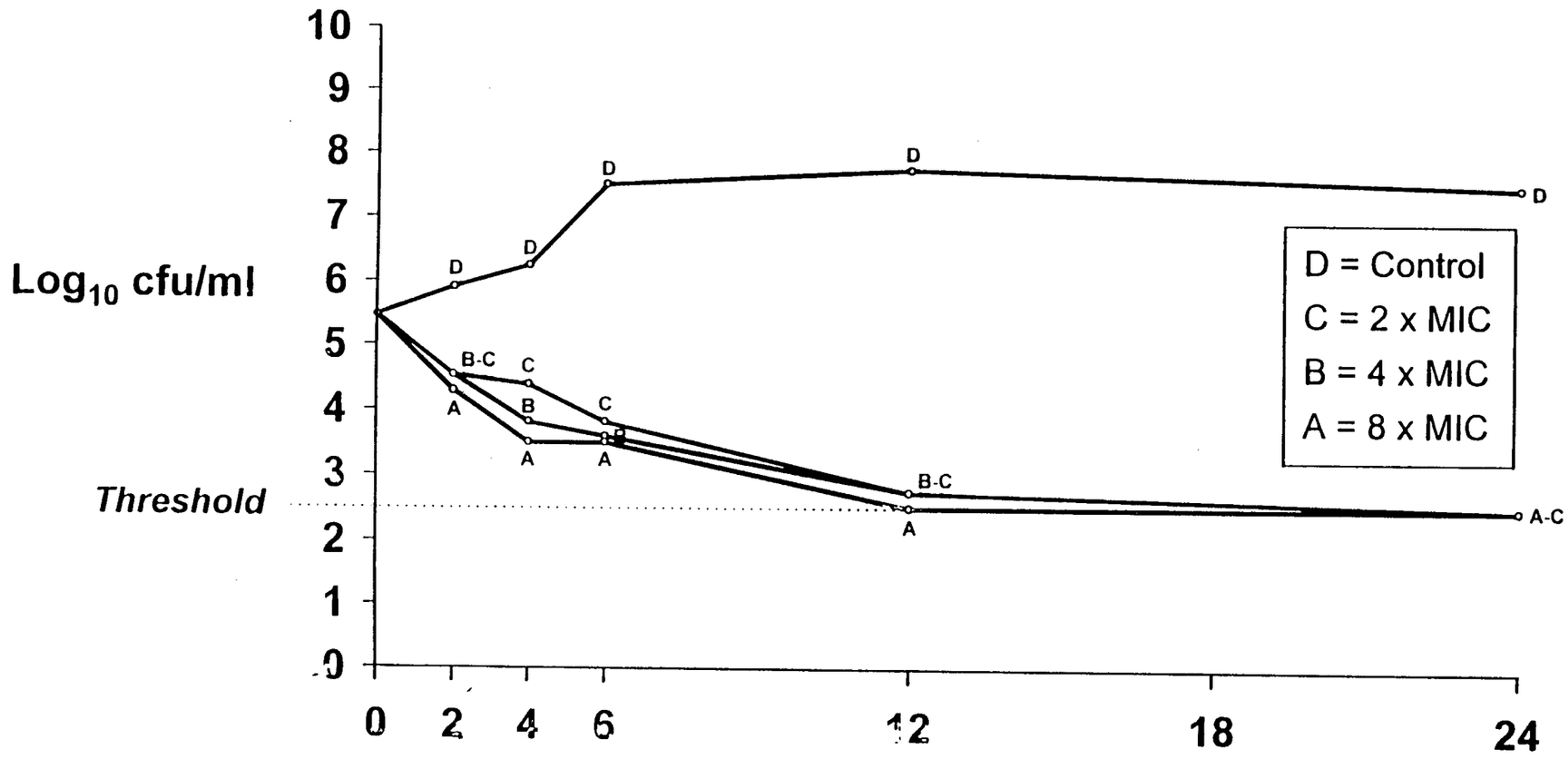
# Bactericidal Activity of Ceftriaxone Against Pneumococcus




Spangler S., Jacobs M.R., Applebaum P.C., A.A.C., 1997



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# Contrast Between Ceftriaxone and Oral Antibiotics for the Treatment of Acute Otitis Media

| | Ceftriaxone | Oral Agents |
|---|---|---|
| Effective against all three primary pathogens | + | +/- |
| β-Lactamase Stable | + | +/- |
| Effective against resistant *S. pneumoniae* | + | Variable |
| Required Doses | Single | Multiple |
| Compliance | + | Variable |
| Sub-inhibitory trough concentrations | NA | + |
| Gut flora exposure | Short | Prolonged |

# Advantages of Ceftriaxone

- Pharmacokinetics
  - Long elimination half-life in middle ear fluid √
  - Penetrates into middle ear fluid in concentrations required to inhibit bacterial replication √
  - No significant metabolism √
  - Renal elimination by glomerular filtration √
- Pharmacodynamics
  - Bacterial activity against all common pathogens √
  - β-lactamase stable √
  - No major organ system side effects √
  - Low incidence of rash and gastrointestinal side-effects √
- Pharmaceutics
  - Available in liquid formulation √
  - Palatable to young children √
  - May be given with food
  - Dosing regimen which assures compliance

# Jonathan Solsky, MD

## Efficacy and Safety of Single Dose Ceftriaxone in the Treatment of Acute Otitis Media in Children

# Clinical Development Program
## Rationale

- Need for parenteral therapy in AOM, particularly:
  - Infants and children unable to tolerate oral therapy
  - Patients at risk of pneumococcal infection
  - Problematic issue of compliance/misuse with oral therapy
- Superior bactericidal activity against three major pathogens
- Sustained high concentrations in middle ear fluid
  - Exceeds the MICs for resistant pathogens
- Excellent safety profile in pediatric population
- Guaranteed treatment and compliance

# Favorable Efficacy and Safety Demonstrated By:

- 2 bacteriology studies (US)
- 4 clinical studies (US)
- 1 clinical study (France)
- 1 pharmacokinetic study (Iceland)

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# Ceftriaxone

## Bacteriology Results

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# Bacteriology Studies Demonstrate:

- Ceftriaxone exhibits bactericidal activity against the three major causative pathogens
- Effectiveness against penicillin-resistant *S. pneumoniae* and β-lactamase producing strains of H. *influenzae* and *M. catarrhalis*

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# Comparative Bacteriology Study

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# Comparative Bacteriology Study

- Investigator-initiated trial (11/91-2/94)
- Tympanocentesis, baseline and Day 2-3
- Age range: 6 mo - 3 yrs
- Primary outcome: Bacteriologic eradication at Day 2-3 after initiation of treatment
- 203 pts enrolled: Single dose ceftriaxone IM (154 pts)
  CR-bicillin IM/ TMP-SMZ 10d (49 pts)

# Bacteriologic Cure of Baseline Pathogen
## Day 2-3

### Comparative Bacteriology Study

| Organism | Ceftriaxone (N=84) Eradicated/Total | % | Bic / TMP-SMZ (N=33) Eradicated/Total | % |
|---|---|---|---|---|
| *Streptococcus pneumoniae* | 39/39 | 100% | 17/17 | 100% |
| Penicillin-resistant | 0/0 | -- | 1/1 | 100% |
| *Haemophilus influenzae* | 39/39 | 100% | 15/18 | 83% |
| β-lactamase (+) | 12/12 | 100% | 4/6 | 67% |
| *Moraxella catarrhalis* | 25/25 | 100% | 14/15 | 93% |
| β-lactamase (+) | 14/14 | 100% | 10/11 | 91% |
| TOTAL | 103/103 | 100% | 46/50 | 92% |

# Bacteriologic Outcome by Patient
## Day 2-3

### Comparative Bacteriology Study

| Organism | Ceftriaxone (N=87) n | Ceftriaxone (N=87) % | Bic / TMP-SMZ (N=34) n | Bic / TMP-SMZ (N=34) % |
|---|---|---|---|---|
| Bacteriologic Cure | 83 | 95.4% | 29 | 85.3% |
| Eradication | 66 | 75.9% | 26 | 76.5% |
| Presumed Eradication | 17 | 19.5% | 3 | 8.8% |
| Bacteriologic Failure | 4 | 4.6% | 5 | 14.7% |
| Persisted | 0 | 0% | 4 | 11.8% |
| New infection | 3 | 3.4% | 0 | 0% |
| Superinfection | 1 | 1.1% | 1 | 2.9% |

# Bacteriologic Failure: New Infection and Superinfection

## Ceftriaxone Group - Comparative Bacteriology Study

| Baseline Tap | Day 2-3 Tap |
|---|---|
| Sterile | *M. catarrhalis*-β-Lactamase + |
| Sterile | *M. catarrhalis*-β-Lactamase + |
| Nonpathogenic organism | *M. catarrhalis* |
| *H. influenzae*<br>*S. pneumoniae* | *M. catarrhalis* |

# Noncomparative Bacteriology Study

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# Noncomparative Bacteriology Study

- Geographically diverse, prospective, multicenter trial
  - Site selection based on prevalence of resistant pneumococci (11/95-3/96)
- Tympanocentesis at baseline
  - Post-therapy tympanocentesis at ≥3 days in clinical failures
- Age range: 6 mo - 6 yrs
- Primary outcome: Presumed bacteriologic eradication at Week 2
- 108 patients enrolled; 79 patients at BL tap had 100 isolates

# Baseline Pathogens

## Noncomparative Bacteriology Study

| Organism | Ceftriaxone (N=79)<br>No. Isolates (n=100) |
|---|---|
| ***Streptococcus pneumoniae*** | ***43*** |
| Penicillin-resistant | 10 |
| Penicillin-susceptible | 33 |
| ***Haemophilus influenzae*** | ***39*** |
| β-lactamase (+) | 18 |
| β-lactamase (-) | 21 |
| ***Moraxella catarrhalis*** | ***18*** |
| β-lactamase (+) | 17 |
| β-lactamase (-) | 1 |

# Clinical Outcome by Patient
## Week 2 (ITT)
## (Presumed Microbiologic Eradication Based on Clinical Outcome)

### Noncomparative Bacteriology Study

| | N | (%) |
|---|---|---|
| Cure | 65 | (82.3%) |
| Failure | 14 | (17.7%) |

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# Clinical Outcome by Pathogen

## Week 2 (ITT)

(Presumed Microbiologic Eradication Based on Clinical Outcome*)

## Noncomparative Bacteriology Study

| Organism | Ceftriaxone (N=79) No. Isolated (Baseline) | % Cured (Week 2) |
|---|---|---|
| ***Streptococcus pneumoniae*** | ***43*** | ***81.4%*** |
| Penicillin-resistant | 10 | 60.0% |
| Penicillin-susceptible | 33 | 87.9% |
| ***Haemophilus influenzae*** | ***39*** | ***82.1%*** |
| β-lactamase (+) | 18 | 83.3% |
| β-lactamase (-) | 21 | 81.0% |
| ***Moraxella catarrhalis*** | ***18*** | ***66.7%*** |
| β-lactamase (+) | 17 | 64.7% |
| β-lactamase (-) | 1 | 100.0% |

* Two patients cultured by Week 2; two cultured by Week 4.

# Noncomparative Bacteriology Study

- Of 79 patients with baseline isolates, 82.3% presumed eradicated at Week 2
- Of 36 clinical failures at Week 2 and 4, only 4 follow-up taps
- In all 4 follow-up cultures, 100% bacteriologic eradication of baseline pathogens
  - Penicillin-susceptible pneumococci

# Bacteriologic Efficacy Against the Three Major Pathogens of Acute Otitis Media

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# Ceftriaxone

## Clinical Efficacy Results

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# Analyses Consistently Indicate, Overall, Comparable Efficacy to a Variety of the Most Commonly Used Antibiotics for Acute Otitis Media

# Clinical Development Program
## US Studies

### Single dose, Ceftriaxone 50 mg/kg IM

| | Comparator | Dose/Duration | Number of Patients |
|---|---|---|---|
| Roche | Amox/Clav | 10 d (40 mg/kg/d) TID | 649 |
| Klein | TMP-SMZ | 10 d (40 mg/kg/d) BID | 596 |
| Green | Amoxicillin | 10 d (40 mg/kg/d) TID | 261 |
| Chamberlain | Cefaclor | 10 d (40 mg/kg/d) BID | 73 |
| | | | 1579 |

- Prospective, randomized, investigator-blinded
- Age: 3 mo - 6 yrs
- Efficacy Assessments: 2 wk, 4 wk

IV-3 ~~IV-16~~ ~~IV-22~~

# Clinical Development Program
## Supportive Trials

### Single dose, Ceftriaxone 50 mg/kg IM

| | Comparator | Dose/Duration | Number of Patients |
|---|---|---|---|
| French Study | Amox/Clav | 10 d (80 mg/kg/d) TID | 513 |

- Prospective, randomized, multicenter
- Age: 4 mo - 2.5 yrs
- Efficacy Assessments: 2 wk, 4 wk

# Inclusion Criteria

## Diagnosis of Acute Otitis Media

## Signs/symptoms:

- Otalgia
- Ear Pulling
- Hearing Loss
- Evidence of Middle Ear Inflammation
- Bulging Ear Drum
- Otorrhea
- Fever
- Diarrhea
- Vomiting
- Anorexia
- Irritability
- Lethargy

**AND**

## Pneumatic otoscopy/tympanometry/acoustic reflectometry

# Clinical Evaluation
## Analysis Populations

**Intent-to-Treat (ITT)**

- All patients who received drug

**Standard (STD)**

- Exclusion
  - did not have AOM
  - received other antibiotics due to illness unrelated to AOM
  - missed the primary endpoint assessment
  - lost to follow up
  - extra dose of ceftriaxone

# Definition of Clinical Outcome

- **Cure =** Complete resolution of signs and symptoms, exclusive of effusion

- **Failure =** Lack of complete resolution of signs and symptoms, exclusive of effusion

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# Clinical Evaluation
## Statistical Methods

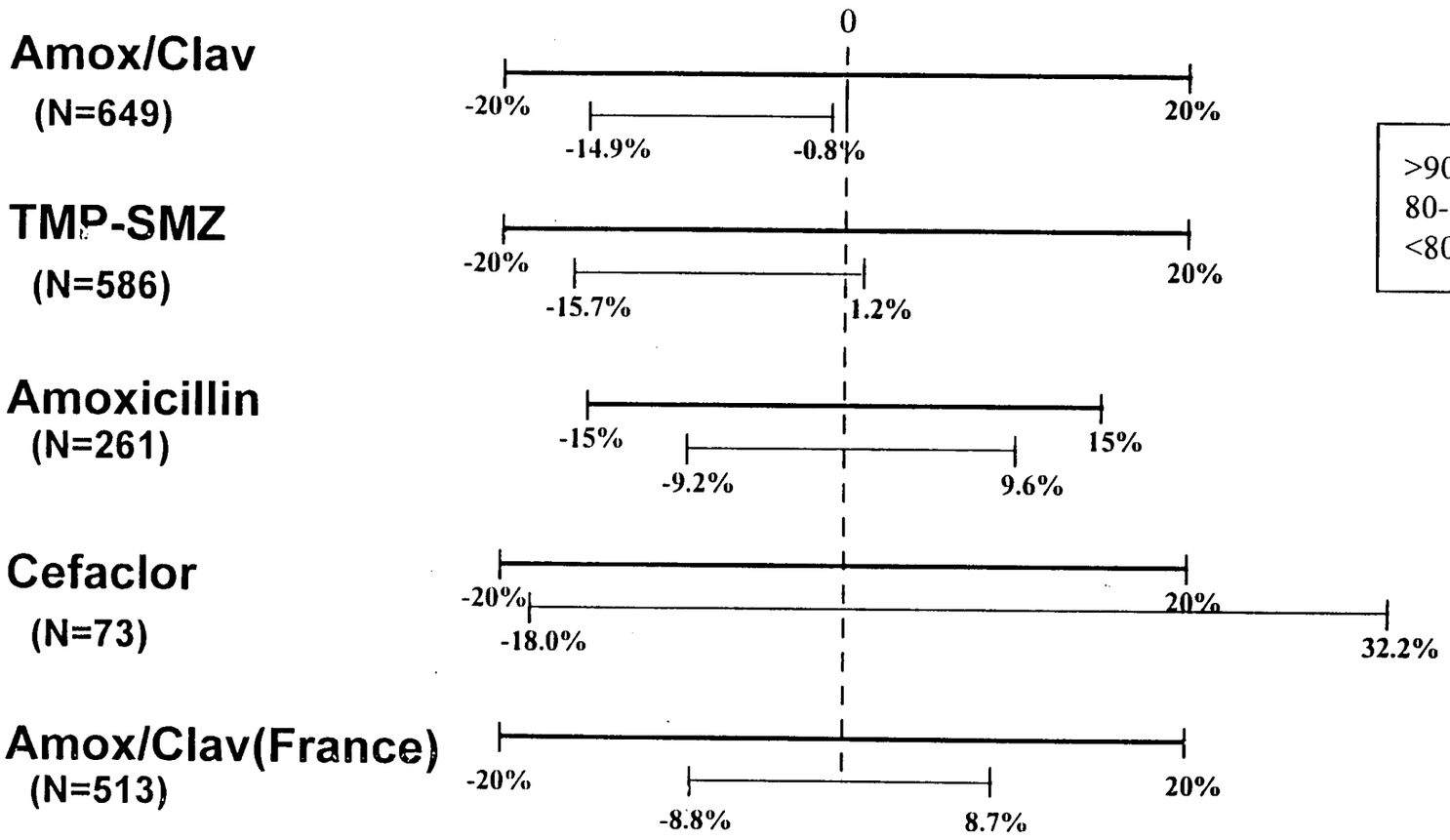
- Primary Endpoint: Week 2
- Clinical Cure Rate: $\frac{\text{Cure}}{\text{Cure + Improved + Failure}}$
- Statistical Equivalence: Two-sided 95% CI for difference in cure rate between ceftriaxone and comparator must be within pre-specified limits and include zero

# Cure Rates

## Primary Clinical End Point (ITT)

| Study | Ceftriaxone | Comparator | Confidence Interval of Difference |
|---|---|---|---|
| **US** | | | |
| Amox/Clav | 69.7% | 77.5% | (-14.9%, -0.8%) |
| TMP-SMZ | 51.6% | 58.8% | (-15.7%, 1.2%) |
| Amoxicillin | 85.2% | 85.0% | (-9.2%, 9.6%) |
| Cefaclor | 41.5% | 34.4% | (-18.0%, 32.2%) |
| **France** | | | |
| **Amox/Clav** | | | |
| Clinical Success | 74.5% | 77.1% | (-10.4%, 5.2%) |
| Cure | 62.4% | 62.4% | (-8.8%, 8.7%) |

# 95% CI for Treatment Difference of Cure Rates
## Primary Clinical End Point (ITT)




| | |
|---|---|
| >90% | ±10% |
| 80-89% | ±15% |
| <80% | ±20% |

# Comparative Trials Demonstrate that a Single Dose of Rocephin IM Exhibits Efficacy Comparable to Standard 10-day Multiple Oral Dose Treatment for Acute Otitis Media

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# Ceftriaxone

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# Safety

# Clinical and Bacteriology Trials Confirm that Single Dose Ceftriaxone IM is Well Tolerated and Safe

# Patient Demographics
## US Safety Population

| Characteristic | | Ceftriaxone—All Studies (N=1048)* |
|---|---|---|
| Sex (%) | Female | 48% |
| | Male | 52% |
| Age, months | Mean | 24.9 |
| | Range | |
| Weight, kg | Mean | 12.4 |
| | Range | |
| Race (%) | Caucasian | 60% |
| | Black | 22% |
| | Other | 16% |
| | Unclassified | 1% |

* Number may slightly vary for each variable due to missing data.

VI-2

# Number (%) of Patients Reporting Potentially Related Adverse Events

| Study | Patients Reporting AEs | | | |
|---|---|---|---|---|
| | Ceftriaxone | | Comparator | |
| | N | (%) | N | (%) |
| Amox/Clav | 100 | (31.1%) | 182 | (55.7%) |
| TMP-SMZ | 77 | (26.1%) | 47 | (15.6%) |
| Amoxicillin | 30 | (23.4%) | 16 | (12.0%) |
| Cefaclor | 11 | (26.8%) | 12 | (37.5%) |
| Comparative | 19 | (12.3%) | 10 | (20.4%) |
| Noncomparative | 10 | (9.3%) | -- | |
| Total (US) | 247 | (23.6%) | | |
| France | | | | |
| Amox/Clav | 79 | (31.0%) | 136 | (52.7%) |

# Number (%) of Patients with Most Frequently Reported Adverse Events

**(Excluding Unrelated)**
US (≥1%)

| Adverse Event | Ceftriaxone - All Studies (N=1048) | |
|---|---|---|
| | N | % |
| Diarrhea | 148 | 14.1 |
| Diaper rash | 55 | 5.2 |
| Rash | 51 | 4.9 |
| Injection site pain | 15 | 1.4 |
| Vomiting | 15 | 1.4 |

# Adverse Events Leading to Withdrawals

| Study | Comparator N | (%) |
|---|---|---|
| Amox/Clav | 9/327 | (2.7%) |
| TMP-SMZ | 5/301 | (1.7%) |
| Amoxicillin | 5/133 | (3.8%) |
| Cefaclor | 0/32 | (0%) |
| Total | 19/793 | (2.3%) |

# Adverse Events Leading to Withdrawals

## Most Frequent AEs Leading to Withdrawal

- Comparator: Diarrhea, rash, vomiting (Amox/Clav)
  rash, vomiting (Amoxicillin)
  rash (TMP-SMZ)

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# Serious Adverse Events

- 6 serious AEs (6/1048=0.57%) reported on ceftriaxone
  - 5 unrelated; 1 remotely related
- 7 serious AEs (7/842=0.83%) on comparator agents
  - 6 unrelated; 1 probably related
- All patients recovered
- No deaths reported

No unusual or unexpected adverse events were reported

The well established safety profile of ceftriaxone was confirmed in the clinical and bacteriology studies of acute otitis media

# Parental Preference for Single Dose IM Therapy

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# Parental Preference for Injection Versus Oral Treatment in Amoxicillin Study

| | Ceftriaxone + Amoxicillin (N=261) | |
|---|---|---|
| Parental Preference | n/N | % |
| Single dose injection | 108/161 | 67.1% |
| Multidose oral treatment | 19/161 | 11.8% |
| No Preference | 34/161 | 21.1% |

n/N = n is the number of patients with the specified preference; N in the total number of patients who responded.

# Parental Preference for Injection Versus Oral Treatment in Amox/Clav Study*

| | Ceftriaxone (N=268) | | Amox/Clav (N=279) | |
|---|---|---|---|---|
| Response | n | % | n | % |
| Satisfaction with antibiotic administration | | | | |
| *Satisfied* | 247 | *92%* | 246 | *88%* |
| Unsatisfied | 21 | 8% | 30 | 11% |
| Choice of route of treatment for otitis media in future | | | | |
| Oral | 25 | 9% | 69 | 25% |
| *Intramuscular* | 242 | *90%* | 209 | *75%* |

* Bauchner, Pediatrics 1996;150:396-399.

# Ceftriaxone

## Summary and Conclusion

# Summary and Conclusions

Single dose IM Rocephin for treatment of acute otitis media offers:

- Favorable pharmacokinetics, pharmacodynamics and pharmaceutics
  - Demonstrated long serum half-life in infants and children
  - Bactericidal serum levels reached within 90 minutes of administration
  - Sustained high concentrations in the middle ear fluid above $MIC_{90}$ of the 3 major pathogens
  - None of the pharmaceutical issues of oral suspension antibiotics

# Summary and Conclusions

Single dose IM Rocephin for treatment of acute otitis media offers:

- Bactericidal activity against the three major pathogens
  - Bactericidal activity in vitro demonstrated against *S. pneumoniae* including resistant strains
  - Excellent in vitro activity against *H. influenzae* and *M. catarrhalis* including β-lactamase (+) strains
  - Bactericidal eradication of resistant pneumococci was demonstrated in experimental otitis media in animals
  - Bactericidal eradication confirmed in clinical bacteriology studies

# Summary and Conclusions

Single dose IM Rocephin for treatment of acute otitis media offers:

- Possibility of increasing resistance is minimized due to PK properties, sustained duration of bactericidal activity and parenteral administration
  - Stepwise exposure of bacteria to sub-inhibitory antibiotic concentrations which may occur with oral multiple dose agents is negated with single dose Rocephin
  - Epidemiological data from Europe is suggestive that parenteral therapy in outpatients is associated with a lower incidence of resistance
  - Ceftriaxone has remained clinically effective in a changing environment of microbial resistance

# Summary and Conclusions

Single dose IM Rocephin for treatment of acute otitis media offers:

- Efficacy comparable to standard treatment
  - One dose of Rocephin exhibits efficacy comparable to standard 10-day multiple oral dose treatment of AOM

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# Summary and Conclusions

Single dose IM Rocephin for treatment of acute otitis media offers:

- Well established safety profile
  - Extensive clinical experience in pediatric population for past 13 years
  - No unexpected or unusual adverse events reported in patients treated for AOM

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# Summary and Conclusions

Single dose IM Rocephin for treatment of acute otitis media offers:

- Advantages of single dose parenteral therapy
  - Eliminates issues of refrigeration, inaccurate dosing, difficulty swallowing (vomiting), variable absorption (diarrhea) of oral agents
  - Although transient injection pain, Rocephin obviates difficulties in administering to infants/children multidose, multiple day oral therapy

# Summary and Conclusions

Single dose IM Rocephin for treatment of acute otitis media offers:

- Guaranteed 100% full course treatment and compliance
  - Inadequate compliance is common and problematic with standard multidose oral therapy potentially leading to lack of efficacy or resistance
  - Effectively eliminates concerns whether prescription filled, missed doses (day care), misuse of unused drug

# Summary and Conclusions

Single dose IM Rocephin for treatment of acute otitis media offers:

- Parental preference for single dose IM therapy
  - Two-thirds of parents surveyed prefer single dose parenteral therapy to standard oral therapy
  - Ninety percent of parents whose children received single dose IM treatment would choose the same treatment in the future

# Summary and Conclusions

**Single dose IM Rocephin for treatment of acute otitis media offers:**

- Favorable pharmacokinetics, pharmacodynamics and pharmaceutics
- Bactericidal activity against the three major pathogens
- Possibility of increasing resistance is minimized
- Efficacy comparable to standard treatment
- Well established safety profile
- Advantages of single dose parenteral therapy
- Guaranteed 100% full course treatment and compliance
- Parental preference for single dose IM therapy

- **A significant addition to the armamentarium for the treatment of acute otitis media**