

# Efficacy of gatifloxacin for the treatment of acute otitis media due to *Streptococcus pneumoniae* in the chinchilla animal model

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## DISCUSSION

With the ever-increasing resistance of bacteria to current antibiotics, there is a need for new agents able to eradicate microbiological diseases. Most children experience at least one episode of AOM during their childhood.<sup>1</sup> Recurrent episodes are also common. Three or more episodes of AOM by 1 year of age have been reported to occur in 10-15% of children.<sup>1</sup> By ages 3, 5, and 7, three or more episodes of AOM have been reported in 50, 65, and 75% of children, respectively.<sup>1</sup>

Empiric treatment of AOM with antibiotics is based on the presumption that one of the three species of bacteria *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* is the most likely pathogen. Amoxicillin is the antibiotic most commonly used in the treatment of AOM. However, as the number of resistant *S. pneumoniae* strains increases, there will be a directly related increase in treatment failure rates using this strategy.<sup>1</sup> Therefore, newer antibiotics that circumvent *S. pneumoniae* resistance mechanisms are in demand.<sup>2</sup>

Gatifloxacin eradicated all of the *S. pneumoniae* strains inoculated into the chinchilla ME. It sterilized the ME as well as ampicillin (150 mg/kg) without regard to penicillin sensitivity. It performed significantly better against penicillin-resistant strains than did Zithromax. If survival is combined with negative culture status as a measure of cure rate, gatifloxacin cured more than 70% of the animals. Both ampicillin and Zithromax show expected decreases in cure rates with respect to *S. pneumoniae* resistant to penicillin and erythromycin. With respect to the secondary outcome measures, otomicroscopy and tympanometry, gatifloxacin resulted in more normal MEs than did Zithromax. Contradictory results were evident in the comparison of gatifloxacin to ampicillin for these measures. It resulted in more normal MEs by otomicroscopy, but fewer by tympanometry, than ampicillin-treated animals.

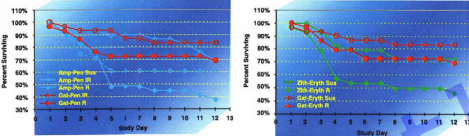
## CONCLUSION

In conclusion, the results of this study support further in vivo trials of gatifloxacin for treatment of acute otitis media. It suggests that gatifloxacin will be effective in cases of primary treatment failure or in areas with high levels of penicillin and erythromycin resistance in *S. pneumoniae*. These results argue for clinical trials to evaluate the efficacy of gatifloxacin for AOM in humans.

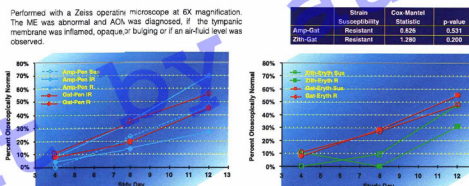
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## RESULTS: Survival



## RESULTS: Otomicroscopy



## RESULTS: Tympanometry

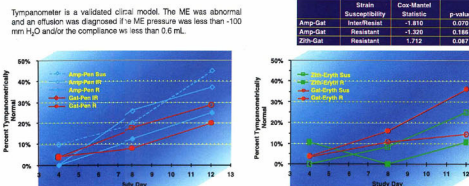


Table 1: *Streptococcus pneumoniae* Strains

CHP Number	Penicillin Resistance	Erythromycin Resistance	N
P18797	Susceptible MIC=0.03	Susceptible	18
W62415-2	Susceptible MIC=0.04	Susceptible	15
M69306-1	Intermediate MIC=0.12	Susceptible MIC=0.06	45
M69302	Intermediate MIC=0.12	Resistant MIC=0.06	45
P19441	Resistant MIC=2	Susceptible MIC=0.03	45
P19541	Resistant MIC=2	Resistant MIC=256	45

## METHODS: Data Analysis

1. Primary outcome: sterility of the ME after a 10-day course of treatment. Secondary outcomes: mortality, disease course, and resolution to penicillin.
2. For serial tympanometry and otomicroscopy, the number of days required to return to normal after being abnormal was used in the analysis. Animals that died with abnormalities or remained abnormal at the conclusion of the study were considered censored.
3. Kaplan-Meier survival analysis with Cox-Mantel comparison of survival curves was used to detect differences among treatment groups. (Bonferroni adjustment for two a priori (Gat-Amp, Gat-Zith) comparisons was used p<0.025 significant).
4. Separate analyses were performed for the culture, otomicroscopy, and tympanometry results.

## RESULTS

### RESULTS: Pharmacokinetic Study

	20 mg/kg	40 mg/kg	Middle Ear Effusion
C <sub>max</sub> , Obs. (µg/ml)	10.25	22.38	3.75
T <sub>max</sub> , Obs. (hrs)	1.5	2	6
AUC <sub>0-12</sub> (µg·hr/ml)	0.21	0.24	2.3
AUC <sub>0-24</sub> (µg·hr/ml)	0.2	0.3	15.6
AUC <sub>0-48</sub> (µg·hr/ml)	54	199	29
AUC <sub>0-72</sub> (µg·hr/ml)	53	140	29
AUC <sub>0-96</sub> (µg·hr/ml)	123.5	260	35
MRT (hr)	13.6	15.3	21.5

\*based on HPLC analysis

### RESULTS: Middle Ear Cultures

The number of middle ears culture negative at sacrifice was respect to the number of animals surviving on Study Day 12.

	Susceptible	Penicillin Intermediate	Resistant	Erythromycin Susceptible	Resistant
Ampicillin	16/22	22/28	13/15	20/22	18/19
Zithromax	16/22	12/16	20/26	20/26	3/13
Gatifloxacin	22/28	21/21	22/24	22/24	25/26

### RESULTS: Cure Rates

Percentage of middle ears culture negative with respect to the number of ears inoculated. Animals that died during the study are considered treatment failures.

	Penicillin Susceptible	Intermediate	Resistant	Erythromycin Susceptible	Resistant
Ampicillin	64%	85%	48%		
Zithromax				69%	11%
Gatifloxacin	90%	72%	0%	70%	

Comparison p=0.19 p=0.001

## INTRODUCTION

Acute otitis media (AOM) is a common infectious disease of infants and children. Annual costs for the treatment of otitis media in the United States have been estimated to exceed \$3 billion dollars.<sup>1</sup> Clinical studies document a bacterial etiology for most cases of AOM with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* representing the species most frequently recovered from the middle ear (ME) of children with the disease.<sup>2</sup> A meta-analysis confirms the efficacy of antimicrobial treatment for AOM, and empiric therapy with antibiotics remains the mainstay of treatment in the United States.<sup>3</sup>

Over the past 15 years, the frequency of antibiotic resistance *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* has increased for AOM. Because amoxicillin is the empiric first-line treatment for AOM, it is expected that the frequency of primary treatment failures will increase. *S. pneumoniae* resistance to penicillin and erythromycin is conferred by the penicillin binding proteins and efflux pumps respectively.<sup>4</sup> Therefore, antibiotics able to circumvent these resistance mechanisms will be a valuable for resolving cases of AOM that are primary treatment failures.

Gatifloxacin is a new 6-fluoro-8-methoxy quinolone.<sup>5</sup> It shows a broad range of in vitro activity against gram negative and gram positive organisms, including the most common middle ear pathogens.<sup>6</sup> Its in vitro activity against *Streptococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa* is better than ciprofloxacin and ciprofloxacin, except for ciprofloxacin's activity against *Pseudomonas aeruginosa*.

The purpose of this study was to determine if gatifloxacin, used in a standard 10-day treatment course, effectively eradicated *S. pneumoniae* in vivo and reduced the morbidity of induced otitis media in the chinchilla animal model.

## MATERIALS AND METHODS

The Animal Research and Care Committee of Children's Hospital of Pittsburgh approved this protocol. Anesthesia was a cocktail of ketamine (5.7 mg/kg), xylazine (1.1 mg/kg) and acepromazine (4.5 mg/kg). Personnel blinded to the group and subgroup assignment of the animals performed all procedures.

### METHODS: Pharmacokinetic Study

1. Middle ears (ME) of twenty-four chinchillas were inoculated transcutaneously with *K. pneumoniae* LPS (50 µg in 0.3 ml PBS).
2. Two days later a single IM dose of gatifloxacin (20 or 40 mg/kg) given.
3. At 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 hours blood (0.5 ml) and ME fluid samples (0.5, 1, 2, 4, 6, 8 and 10 hrs) were obtained.
4. ME, 4 µl per ear animal.
5. Samples were stored in 2 milliliter screw top vials (-85°C) until they were analyzed. Gatifloxacin concentration of the sera and ME fluids was determined by validated HPLC assay.

### METHODS: Efficacy Study

1. Normal ME status was verified by otomicroscopy and tympanometry in 210 adult chinchillas.
2. On Study Day 0, the right MEs of all animals were inoculated transcutaneously with 0.1 ml PBS containing approximately 10<sup>7</sup> CFU of one of six *S. pneumoniae* strains listed in Table 1.
3. On Study Day 2, animals were randomly assigned to one of the three antibiotic treatment groups: M. Ampicillin (N=70; 150 mg/kg/day TID bid to Day 10), Zithromax (N=60; 10 mg/kg/day on Day 1 for 5 mg/kg/day QD 4 days, PBS for 5 days) or gatifloxacin (N=70; 15 mg/kg/day QD).
4. Study Days 4, 8, and 12, animals were anesthetized and examined by otomicroscopy and tympanometry.
5. Study Day 12 the animals were killed by barbiturate overdose (324 mg of pentobarbital CI). Their right bulbar were opened, and effusions recovered into sterile traps. These effusions were cultured using standard microbiological techniques for the detection of *S. pneumoniae*.