Evaluation of Solithromycin (CEM-101) for Treatment of Experimental Otitis Media due to nontypeable *Haemophilus influenzae* or *Streptococcus pneumoniae*

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Background

Solithromycin (CEM-101) is a next-generation fluoroketolide with in-vitro antibacterial activity against multidrug-resistant *Streptococcus pneumoniae*, including erythromycin A-resistant (ER) isolates and both β-lactamase positive and negative nontypeable *Haemophilus influenzae* (NTHi)

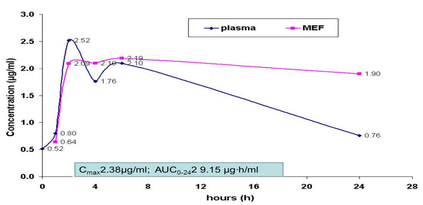
Objectives

To evaluate pharmacokinetics, middle ear fluid (MEF) concentrations, and microbiologic efficacy of solithromycin in a chinchilla model of experimental otitis media (EOM) due to isolates of *S. pneumoniae* or NTHi.
To evaluate the in vitro activity (MIC and MBC) of solithromycin against respiratory isolates of NTHi.
To evaluate in vitro activity (Time kill assays) of solithromycin against *S. pneumoniae* with *mef*E and *erm*B mechanisms of macrolide resistance.

Methods and Results

Methods: Pharmacokinetic parameters (Cmax and AUC_{0-24}) were determined in plasma and MEF after administration of 150 mg/kg daily of solithromycin via orogastric tube

Mean plasma and MEF concentrations of solithromycin on day 3 of a three-dose oral regimen 150 mg/kg/day, once a day



Methods: MIC and minimum bactericidal concentration (MBC) for NTHi and *S. pneumoniae* was determined by microtiter dilution

MIC for solithromycin and other agents against selected NTHi

Strain ID	β-lactamase	Azithromycin	Erythromycin	Amoxicillin	Amox/Clav	Solithromycin MIC/MBC
BMC1247C	neg	1.5	3	0.75	0.75	2/2
BCH1	pos	2	6	>256	24	0.5/1
BMC1213C	pos	1.5	4	>256	1.5	4/4

MIC for solithromycin and other agents against selected *S. pneumoniae*

Strain ID	Serotype	Resistance	Azithromycin	Erythromycin	Amoxicillin	Ceftriaxone	Solithromycin MIC/MBC
645	14	*erm*B	>256	>256	12	2	0.125/16
712	19F	*mef*E	>256	>256	12	3	0.5/16
331	14	-	0.2	0.064	0.064	0.047	0.064/0.125

In vitro solithromycin activity vs. 165 nontypeable *Haemophilus influenzae* respiratory isolates recovered from children in Boston 2010-2014

MICs for Nontypeable *H. influenzae* (N=165)*

	Range	MIC 50%	MIC 90%
Solithromycin	0.12-8	1	2
Telithromycin	0.12-16	1	2
Azithromycin	0.06-4	0.5	1
Erythromycin	0.12-16	2	8
Ampicillin	0.06->64	0.25	64
Amox/Clav	0.12/0.06-8/4	0.5/0.25	2/1
Cefdinir	<=0.03-2	0.25	1
Trim/Sulfa	<=0.015/0.3-32/608	0.03/0.6	8/152

*Performed by Dwight Hardy, Rochester, NY

Experimental otitis media (EOM) due to NTHi or *S. pneumoniae* in a Chinchilla Model

Methods: Isolates of NTHi or *S. pneumoniae* with specified antimicrobial susceptibility patterns were inoculated directly into the bullae of adult chinchillas and MEF quantitative cultures were performed to determine solithromycin efficacy in the treatment of EOM.

Day -2: Direct Bullae Inoculation of 35-50 cfu of NTHi or *Sp* /100 µl

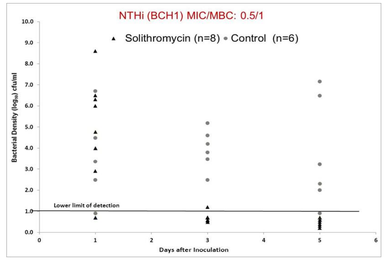
Day 1: 48-72 hours after inoculation, exam and MEF culture to determine infection prior to first dose of 3 day course of solithromycin by orogastric tube

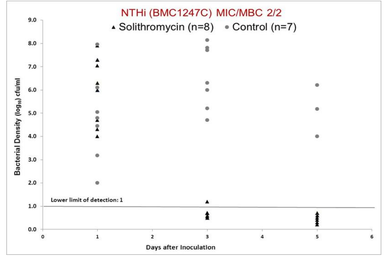
Day 2: Dose #2

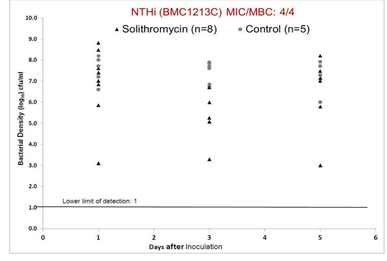
Day 3: Dose 3 (last dose), MEF cultures, plasma and MEF collection at different time points for PK studies (C_{max} , AUC_{0-24h})

Day 5: Complete therapy, exam and MEF cultures performed to determine efficacy

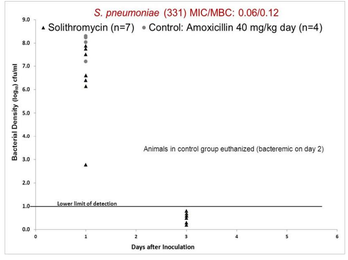
Efficacy of solithromycin (150 mg/kg/day) administered via orogastric tube against NTHI EOM

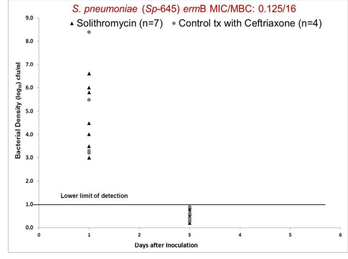


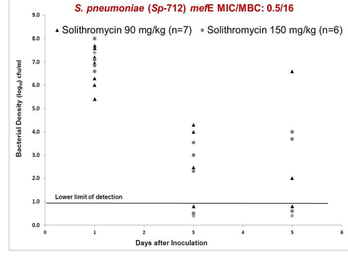




Efficacy of solithromycin at (150 mg/kg/day) administered via orogastric tube against *S. pneumoniae* EOM

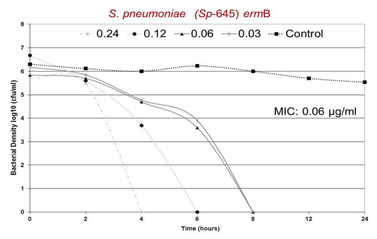


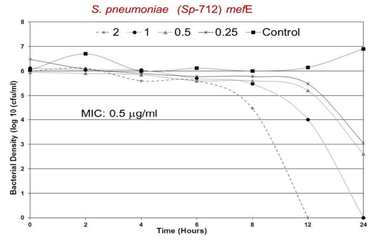




Time-kill assay for Macrolide resistant *Streptococcus pneumoniae* strains evaluated in Chinchilla model of EOM

Method : Time-kill assessment of solithromycin vs. selected *S. pneumoniae* strains was performed at one-half MIC, MIC, 2X MIC and 4X MIC.





Conclusions

- A 3-day oral regimen of solithromycin at 150 mg/kg/daily sterilized MEF in chinchillas challenged with NTHi isolates with MIC ≤2 µg/ml.
- *In vitro* studies of respiratory isolates of NTHi demonstrate MIC_{90} of 2 µg/ml.
- Solithromycin at 150 mg/kg/daily sterilized EOM due to *S. pneumoniae* with MIC ≤0.125 µg/ml; HOWEVER, only 50% of animals with disease due to *S. pneumoniae* with *mef*E resistance were sterilized at that dose.
- Differences in time to killing are observed when comparing *S. pneumoniae* with *erm*B resistance to *S. pneumoniae* with *mef*E resistance; strains with *mef*E resistance demonstrated delayed killing compared to those with *erm*B consistent with the reduced sterilization in our animal model.

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