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In Vitro Activity of Lefamulin against a Collection of Respiratory Pathogens from Pediatric Patients In US (SENTRY Surveillance 2015)

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ABSTRACT (amended)

Background: Lefamulin is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans and is currently in Phase 3 trials for the treatment of CABP in adults. Lefamulin effectively and selectively inhibits bacterial translation by binding to the A- and P-site of the peptidyl transferase center (PTC) via an induced fit mechanism whereby nucleotides in the PTC shift and tighten the binding pocket around lefamulin. [1,2] In addition to its potent activity against typical respiratory pathogens, lefamulin also covers atypical respiratory pathogens including *Mycoplasma pneumoniae, Chlamydophila pneumoniae* and *Legionella pneumophila*.[3-5] This study investigated the susceptibility of respiratory pathogens collected in 2015 from pediatric patients to lefamulin and comparator agents commonly used to treat CABP.

Methods: A total of 776 unique bacterial isolates were collected in the US from pediatric patients (≤17 years old) with community-acquired respiratory tract infections (CARTI; 477), hospitalized with pneumonia (282), bloodstream infections (14) or other infections (3). Lefamulin and comparators were tested by CLSI broth microdilution methods, and susceptibility was determined using the CLSI (2017) breakpoints. [7] MIC distributions for lefamulin were also compared to those obtained from isolates collected from adults as part of the 2015 SENTRY program.

Results: Lefamulin displayed potent antibacterial activity, inhibiting all *S. pneumoniae* (n=360) isolates at ≤0.25 mg/L ($MIC_{50/90}$, 0.06/0.12 mg/L) and all *H. influenzae* (n=85) isolates at ≤2 mg/L ($MIC_{50/90}$, 0.5/1 mg/L). Lefamulin showed potent activity against *M. catarrhalis* (n=85) and *S. aureus* (n=246) with MIC_{90} and MIC_{99} of 0.06 mg/L and 0.12 mg/L, respectively. *S. pneumoniae* were susceptible (S) to levofloxacin (LEV, 100%), ceftriaxone (CTR, 98.1%) and amoxicillin/ clavulanic acid (AMC, 95.3%) but showed reduced susceptibility to azithromycin (AZM, 53.1%) and penicillin (59.4%–at ≤0.06 mg/L). *H. influenzae,* of which 27.1% were ß-lactamase positive, were S to AMC (100%), LEV (100%) and AZM (100%), while 21.2% displayed resistance to trimethoprim/sulfamethoxazole. *S. aureus* (28.9% MRSA) were 100% S to vancomycin and linezolid, but only 54.1% and 78.0% were S to AZM and LEV, respectively. Lefamulin's activity was not affected by resistance to other antibiotics.

Conclusion: Lefamulin demonstrated potent *in vitro* antibacterial activity against respiratory pathogens collected in the US from pediatric patients and was not affected by resistance to the other antibiotics tested. These results, as well as the tolerability profile of lefamulin, support the continued clinical development of lefamulin to treat CABP in pediatric patients.

INTRODUCTION

Pneumonia is the most common infectious cause of death in children worldwide accounting for over 2 million deaths annually and 15% of all deaths in children under 5 years old in 2015.[6] The two most common causes of bacterial pneumonia are *S. pneumoniae* and *H. influenzae*, which show increasing resistance to commonly used antibiotics, particularly macrolides class.[7] In addition, use of the fluoroquinolones and tetracyclines is limited in children due to potential adverse effects.[6]

This study investigated the susceptibility of respiratory pathogens collected in 2015 to lefamulin and comparator agents commonly used to treat CABP.

METHODS

As part of the SENTRY surveillance 776 unique bacterial isolates were collected from pediatric patients (≤17 years old) in the US in 2015. Susceptibility testing was conducted using the CLSI broth microdilution method and susceptibility was calculated using CLSI 2017 breakpoints.[7] QC reference organisms were tested concurrently for lefamulin and comparator agents.

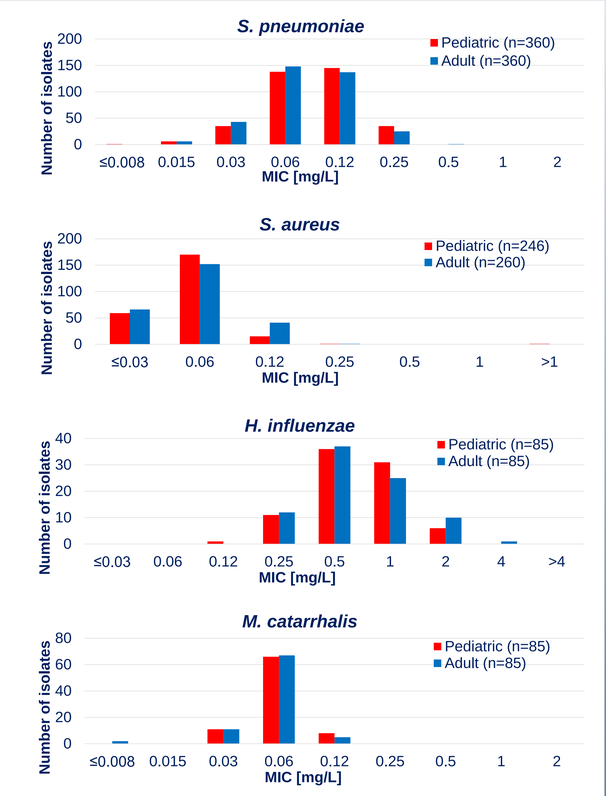

Figure 1. Lefamulin MIC distributions for isolates collected from pediatric and adult patients.

RESULTS

- Lefamulin demonstrated potent activity against this contemporary collection of bacterial isolates collected from pediatric patients in 2015.
- MIC distributions of lefamulin for isolates collected from pediatric and adult patients are shown in Figure 1. $MIC_{50/90}$ and summarized in Table 1.

Table 1. *In vitro* activity [mg/L] of lefamulin and comparators against respiratory pathogens collected from pediatric patients

Organism (*N*)	MIC_{50}	MIC_{90}	Range	% S[a]	% R[a]
***S. pneumoniae* (360)**					
Lefamulin	0.06	0.12	≤0.008 to 0.25		
Amoxi/Clav	≤0.03	2	≤0.03 to >4	95.3	1.9
Azithromycin	0.12	>4	≤0.03 to >4	53.1	46.7
Ceftriaxone	0.03	1	≤0.015 to >2	98.1	1.1 [b]
Clindamycin	≤0.12	>1	≤0.12 to >1	88.1	11.9
Levofloxacin	1	1	0.5 to 2	100.0	0.0
Linezolid	1	1	0.12 to 2	100.0	-
Penicillin	≤0.06	1	≤0.06 to 4	59.4	8.9 [b]
Vancomycin	0.25	0.25	≤0.03 to 0.5	100.0	-
***S. aureus* (246)**					
Lefamulin	0.06	0.06	≤0.03 to >1	-	-
Azithromycin	0.5	>4	0.06 to >4	54.1	43.5
Ceftaroline	0.25	0.5	≤0.06 to 1	100.0	0.0
Clindamycin	≤0.25	>2	≤0.25 to >2	85.8	14.2
Levofloxacin	0.25	>4	0.06 to >4	78.0	20.7
Linezolid	1	1	0.5 to 2	100.0	0.0
Oxacillin	0.5	>2	≤0.25 to >2	71.1	28.9
Vancomycin	0.5	1	0.25 to 1	100.0	0.0
***H. influenzae* (85)**					
Lefamulin	0.5	1	≤0.12 to 2	-	-
Amoxi/Clav	0.5	2	≤0.12 to 4	100.0	0.0
Ampicillin	0.25	>8	0.12 to >8	72.9	25.9
Azithromycin	1	2	0.25 to 4	100.0	-
Cefepime	0.06	0.12	≤0.015 to 2	100.0	-
Levofloxacin	≤0.015	≤0.015	≤0.015 to 0.25	100.0	-
Trimethoprim-sulfa	0.06	>4	≤0.03 to >4	76.5	21.2
***M. catarrhalis* (85)**					
Lefamulin	0.06	0.06	0.03 to 0.12	-	-
Amoxi/Clav	0.12	0.25	≤0.03 to 0.25	100.0	0.0
Azithromycin	0.015	0.03	0.015 to 0.03	100.0	-
Ceftriaxone	0.25	0.5	≤0.015 to 1	100.0	-
Levofloxacin	0.03	0.03	≤0.015 to 1	100.0	-

[a], Criteria as published by CLSI [2017]; [b], Non-meningitis breakpoints applied;

- Lefamulin displayed potent antibacterial activity with 100% of all *S. pneumoniae* inhibited at concentrations of ≤0.25 mg/L and 100% of *H. influenzae* isolates at ≤2 mg/L (Table 1, Figure 2).
- Lefamulin demonstrated potent activity against pediatric *M. catarrhalis* and *S. aureus* (including MRSA) with MIC_{99} of 0.12 mg/L for both organisms.
- *S. pneumoniae* isolates were highly susceptible to levofloxacin (100%), amoxicillin/clavulanic acid (95.3%) and ceftriaxone (98.1%) but showed reduced susceptibility to azithromycin (46.7%).
- *H. influenzae* isolates were susceptible to amoxicillin/clavulanic acid, azithromycin, and levofloxacin (all 100%), while 21.2% of the isolates had resistance to trimethoprim/ sulfamethoxazole.
  - 25.9% of *H. influenzae* isolates were ß-lactamase positive
- *S. aureus* isolates (28.9% MRSA) were 100% susceptible to vancomycin and linezolid. The susceptibility to azithromycin was 54.1%, to clindamycin 85.8% and to levofloxacin 78.0%, respectively
  - Among MRSA (*n*=71), susceptibility to azithromycin (18.3%), clindamycin (66.2%) and levofloxacin (38.0%) was lower than among MSSA.

CONCLUSIONS

- **Lefamulin displayed potent, *in vitro* antibacterial activity consistently across all respiratory pathogens that cause CABP in pediatric patients in the US.**
- **MIC distributions of pediatric isolates were similar to those from isolates collected from adults and not affected by the resistance to other antibiotic classes.**
- **The results of this study support the continued clinical development of lefamulin for the treatment of RTI, including CABP in adults and pediatric patients.**

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