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# Ceftobiprole Activity Tested Against North American Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. in 2005-2007

*T.R. Fritsche, H.S. Sader, M. Janechek, R.N. Jones*
*JMI Laboratories, North Liberty, Iowa, USA*

Ronald N. Jones, MD
JMI Laboratories
345 Beaver Kreek Centre, Ste A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
e-mail: ronald-jones@jmilabs.com

## Abstract

**Background:** Ceftobiprole, an investigational parenteral cephalosporin active against methicillin-resistant *S. aureus* (MRSA), is under regulatory review for complicated skin and skin-structure infections (cSSSI). We present results assessing potency of ceftobiprole and comparator agents against Enterobacteriaceae, *Pseudomonas aeruginosa,* and *Acinetobacter* spp.

**Methods:** Nonduplicate clinically-significant isolates of Enterobacteriaceae (5865), *P. aeruginosa* (1229), and *Acinetobacter* spp. (416) were collected from >25 medical centers in North America participating in the Ceftobiprole Surveillance Program during 2005-2007. Identifications were confirmed by the central laboratory and all isolates were susceptibility (S) tested using CLSI methods and interpretations.

**Results:**

| | $MIC_{90}$ in µg/ml (% at ≤2/≤4/≤8 µg/ml) | | |
|---|---|---|---|
| Species (no. tested) | Ceftobiprole | Ceftazidime | Cefepime |
| *Escherichia coli* (2367) | ≤0.06 (97/97/97) | ≤1 (95/96/96) | ≤1 (97/98/98) |
| *Klebsiella* spp. (1585) | >8 (85/85/85) | >16 (87/87/88) | 2 (90/92/92) |
| *Enterobacter* spp. (871) | 8 (86/89/91) | >16 (72/73/75) | 2 (92/95/97) |
| *Citrobacter* spp. (152) | 2 (91/94/94) | >16 (85/86/87) | 1 (99/>99/>99) |
| *Proteus mirabilis* (258) | ≤0.06 (>99/>99/>99) | ≤1 (98/>99/100) | ≤0.12 (>99/>99/>99) |
| *Serratia* spp. (406) | 0.25 (95/96/96) | ≤1 (96/97/97) | 0.25 (97/>99/>99) |
| *P. aeruginosa* (1229) | >8 (57/69/83) | >16 (56/73/81) | 16 (49/67/83) |
| *Acinetobacter* spp. (416) | >8 (51/54/55) | >16 (15/37/44) | >16 (34/42/48) |

Ceftobiprole was similar in potency to ceftazidime and cefepime ($MIC_{50}$ values, ≤1 µg/ml) for all tested Enterobacteriaceae. Coverage against *E. coli* was nearly identical for the three agents (Table; 96-98% inhibited at ≤4 µg/ml). Whereas cefepime provided enhanced coverage against *Klebsiella* spp. (92% at ≤8 µg/ml vs 85-88% for ceftobiprole and ceftazidime), ceftobiprole and cefepime were superior to ceftazidime against *Enterobacter* spp. and *Citrobacter* spp. All were equally active against *P. mirabilis* and *Serratia* spp. Against *P. aeruginosa*, ceftobiprole was equal in potency to ceftazidime ($MIC_{50}$, 2 µg/ml) and 2-fold more potent than cefepime, although % inhibited for these agents at ≤2/≤4/≤8 µg/ml was similar (ceftobiprole, 57-83; ceftazidime, 56-81; cefepime, 49-83%). Ceftobiprole was more active than either ceftazidime or cefepime against *Acinetobacter* spp.

**Conclusions:** Ceftobiprole is a new anti-MRSA cephem with activity against commonly occurring Enterobacteriaceae and *P. aeruginosa*, similar to that of other extended-spectrum cephalosporins. These characteristics warrant continued evaluation of ceftobiprole as empiric therapy for cSSSI and nosocomial pneumonia, especially in those medical centers where MRSA and *P. aeruginosa* may be prevalent pathogens.

## Introduction

Emergence of resistance among commonly occurring bacterial pathogens has limited the utility of many penicillins and cephalosporins, driving increased utilization of carbapenems for infections caused by Gram-negative organisms and vancomycin, daptomycin, and linezolid for Gram-positive pathogens.

Ceftobiprole (formerly BAL9141), an expanded-spectrum cephalosporin with potent activity against commonly occurring Gram-positive and -negative bacterial pathogens, including resistant strains, has completed several phase 3 clinical trials for the treatment of complicated skin and skin-structure infections (cSSSI), hospital-acquired pneumonia (HAP), and community-acquired pneumonia (CAP), and is under US-FDA regulatory review for cSSSI. The compound is stable to most commonly occurring β-lactamases and has a strong affinity for penicillin-binding proteins (PBP), including PBP2a, that mediates resistance to β-lactams in methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci, making it an attractive therapeutic candidate given this unique spectrum, broad safety profile, and predominant bactericidal activities. Importantly, ceftobiprole also displays activity against most Enterobacteriaceae and *Pseudomonas aeruginosa*, similar to that of advanced generation cephems and β-lactam/β-lactamase inhibitor combinations.

Here we assessed current trends in resistance and effects of co-resistance on ceftobiprole potency against the most commonly occurring contemporary (2005-2007) clinical strains of Enterobacteriaceae and nonfermentative Gram-negative bacilli originating in the United States (USA).

## Materials and Methods

### Bacterial Isolates

- Consecutive, nonduplicate clinically significant isolates of Enterobacteriaceae (5865 isolates), *P. aeruginosa* (1229), and *Acinetobacter* spp. (416) were collected from >25 medical centers in the United States participating in a ceftobiprole surveillance program during 2005-2007.
- Isolates originated from infections of the bloodstream (77.8%), lower respiratory tract (17.0%), or skin and soft tissues (5.2%).
- Organisms were identified locally and forwarded to a central monitoring facility (JMI Laboratories, North Liberty, IA, USA) where identifications were confirmed and susceptibility testing using reference methodologies performed. Species and numbers tested during this period are found in **Table 1**.

### Susceptibility Test Methods

- Ceftobiprole and comparator agents were tested in validated broth microdilution trays (TREK Diagnostics, OH, USA) using cation-adjusted Mueller-Hinton broth according to CLSI methods (M7-A7 [2006] and M100-S18 [2008]).
- Quality control strains utilized included *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853; all MIC results for these strains were within CLSI-specified ranges.
- Categorical interpretations were by CLSI M100-S18 breakpoint criteria. Breakpoints have not been approved for ceftobiprole, although this agent is known to have pharmacokinetic and pharmacodynamic features similar to those of other advanced-generation cephalosporins.

## Results

- Among all tested Enterobacteriaceae, ceftobiprole was similar in potency to ceftazidime and cefepime ($MIC_{50}$ values, ≤1 µg/ml; **Tables 1** and **2**).
- Coverage against *E. coli* was nearly identical for the three agents (**Table 1**; 96-98% inhibited at ≤4 µg/ml).
- Whereas cefepime provided enhanced coverage against *Klebsiella* spp. (92% at ≤8 µg/ml vs 85-88% for ceftobiprole and ceftazidime, respectively), ceftobiprole and cefepime were superior to ceftazidime against *Enterobacter* spp. and *Citrobacter* spp.
- Up to 5.7% of *E. coli,* 16.0% of *Klebsiella* spp. and 2.3% of *Proteus mirabilis* were extended-spectrum β-lactamase (ESBL)-screen test positive using CLSI criteria, although none of the expanded-spectrum cephalosporins can be considered active against ESBL-producing enteric bacilli (**Table 2**).
- Carbapenem-resistant *Klebsiella* spp. were detected in this North American sample (4.5-4.7%), and reflect the ongoing epidemic of *Klebsiella pneumoniae* carbapenemase (KPC)-producing strains involving the eastern seaboard of the United States (**Table 2**).
- All three extended-spectrum cephalosporins were equally active against *P. mirabilis* and *Serratia* spp. (≥96% inhibited at 4 or 8 µg/ml).
- Against *P. aeruginosa*, ceftobiprole was equal in potency to ceftazidime ($MIC_{50}$, 2 µg/ml) and 2-fold more potent than cefepime, although the percentage of strains inhibited for these agents at ≤4 and ≤8 µg/ml was similar (ceftobiprole, 69 and 83; ceftazidime, 73 and 81; cefepime, 67 and 83%; **Tables 1** and **2**).
- Ceftobiprole was more active than either ceftazidime or cefepime against *Acinetobacter* spp. ($MIC_{50}$ values, 2, >16, and 16 µg/ml, respectively) and inhibited a greater proportion of isolates at 4 µg/ml (54%) than the other two agents achieved at 8 µg/ml (44 and 48%, respectively; **Table 1**).

**Table 1.** Frequency distributions of three cephalosporins tested against ranking US Enterobacteriaceae and nonfermentative bacilli (7510 isolates; 2005-2007)

| | MIC (µg/ml) | | Cumulative % inhibited at MIC (µg/ml)[a] | | | |
|---|---|---|---|---|---|---|
| Cephalosporin/Organism (no. tested) | 50% | 90% | ≤1 | 2 | 4 | 8 |
| Ceftobiprole | | | | | | |
| *E. coli* (2367) | ≤0.06 | ≤0.06 | 97 | 97 | 97 | 97 |
| *Klebsiella* spp. (1585) | ≤0.06 | >8 | 84 | 85 | 85 | 85 |
| *Enterobacter* spp. (871) | ≤0.06 | 8 | 83 | 86 | 89 | 91 |
| *Citrobacter* spp. (152) | ≤0.06 | 2 | 86 | 91 | 94 | 94 |
| *P. mirabilis* (258) | ≤0.06 | ≤0.06 | >99 | >99 | >99 | >99 |
| *Serratia* spp. (406) | ≤0.06 | 0.25 | 94 | 95 | 96 | 96 |
| *P. aeruginosa* (1229) | 2 | >8 | 35 | 57 | 69 | 83 |
| *Acinetobacter* spp. (416) | 2 | >8 | 47 | 51 | 54 | 55 |
| Ceftazidime | | | | | | |
| *E. coli* (2367) | ≤1 | ≤1 | 94 | 95 | 96 | 96 |
| *Klebsiella* spp. (1585) | ≤1 | >16 | 85 | 87 | 87 | 88 |
| *Enterobacter* spp. (871) | ≤1 | >16 | 69 | 72 | 73 | 75 |
| *Citrobacter* spp. (152) | ≤1 | >16 | 82 | 85 | 86 | 89 |
| *P. mirabilis* (258) | ≤1 | ≤1 | 98 | 98 | >99 | 100 |
| *Serratia* spp. (406) | ≤1 | ≤1 | 93 | 96 | 97 | 97 |
| *P. aeruginosa* (1229) | 2 | >16 | 13 | 56 | 73 | 81 |
| *Acinetobacter* spp. (416) | >16 | >16 | 4 | 15 | 37 | 44 |
| Cefepime | | | | | | |
| *E. coli* (2367) | ≤0.12 | ≤0.12 | 97 | 97 | 98 | 98 |
| *Klebsiella* spp. (1585) | ≤0.12 | 2 | 87 | 90 | 92 | 92 |
| *Enterobacter* spp. (871) | ≤0.12 | 2 | 87 | 92 | 95 | 97 |
| *Citrobacter* spp. (152) | ≤0.12 | 1 | 95 | 99 | >99 | >99 |
| *P. mirabilis* (258) | ≤0.12 | ≤0.12 | >99 | >99 | >99 | >99 |
| *Serratia* spp. (406) | ≤0.12 | 0.25 | 96 | 97 | >99 | >99 |
| *P. aeruginosa* (1229) | 4 | 16 | 22 | 49 | 67 | 83 |
| *Acinetobacter* spp. (416) | 16 | >16 | 17 | 34 | 42 | 48 |

[a]CLSI breakpoints for susceptibility of the comparison cephalosporins are ≤8 µg/ml.

**Table 2.** *In-vitro* activity of ceftobiprole in comparison to selected antimicrobial agents tested against ranking US Enterobacteriaceae and nonfermentative Gram-negative bacilli (2005-2007)

| | MIC (µg/ml) | | |
|---|---|---|---|
| Organism (no. tested)/Antimicrobial agent | 50% | 90% | % Susceptible/Resistant[a] |
| *E. coli* (2367) | | | |
| Ceftobiprole | ≤0.06 | ≤0.06 | - / - |
| Ampicillin | 16 | >16 | 49.8 / 49.3 |
| Cefepime | ≤0.12 | ≤0.12 | 98.0 / 1.8 |
| Ceftazidime | ≤1 | ≤1 | 96.4 / 2.5 (5.7)[b] |
| Ceftriaxone | ≤0.25 | ≤0.25 | 96.0 / 2.9 (5.0)[b] |
| Ertapenem | ≤0.06 | ≤0.06 | 99.9 / 0.1 |
| Imipenem | ≤0.12 | 0.25 | >99.9 / <0.1 |
| Levofloxacin | ≤0.5 | >4 | 78.6 / 20.3 |
| Meropenem | ≤0.12 | ≤0.12 | >99.9 / <0.1 |
| Piperacillin/tazobactam | 2 | 4 | 95.9 / 2.0 |
| Tetracycline | ≤2 | >8 | 74.6 / 25.2 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | >2 | 71.5 / 28.5 |
| *Klebsiella* spp. (1585) | | | |
| Ceftobiprole | ≤0.06 | >8 | - / - |
| Ampicillin | >16 | >16 | 4.5 / 77.2 |
| Cefepime | ≤0.12 | 2 | 92.4 / 5.9 |
| Ceftazidime | ≤1 | >16 | 87.5 / 11.8 (14.5)[b] |
| Ceftriaxone | ≤0.25 | 32 | 86.9 / 7.9 (16.0)[b] |
| Imipenem | 0.25 | 0.5 | 94.6 / 4.5 |
| Levofloxacin | ≤0.5 | >4 | 86.6 / 12.1 |
| Meropenem | ≤0.12 | ≤0.12 | 94.8 / 4.7 |
| Piperacillin/tazobactam | 2 | >64 | 85.8 / 11.9 |
| Tetracycline | ≤2 | >8 | 84.4 / 11.7 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | >2 | 80.7 / 19.3 |
| *Enterobacter* spp. (871) | | | |
| Ceftobiprole | ≤0.06 | 8 | - / - |
| Ampicillin | >16 | >16 | 7.2 / 84.7 |
| Cefepime | ≤0.12 | 2 | 96.9 / 2.3 |
| Ceftazidime | ≤1 | >16 | 75.4 / 20.2 |
| Ceftriaxone | ≤0.25 | >32 | 76.2 / 12.2 |
| Imipenem | 0.5 | 1 | 98.6 / 0.7 |
| Levofloxacin | ≤0.5 | 2 | 91.3 / 5.9 |
| Meropenem | ≤0.12 | ≤0.12 | 99.0 / 0.5 |
| Piperacillin/tazobactam | 2 | 64 | 80.1 / 7.8 |
| Tetracycline | ≤2 | 8 | 85.6 / 9.2 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | >2 | 87.6 / 12.4 |
| *Citrobacter* spp. (152) | | | |
| Ceftobiprole | ≤0.06 | 2 | - / - |
| Ampicillin | >16 | >16 | 13.2 / 77.0 |
| Cefepime | ≤0.12 | 1 | 99.3 / 0.0 |
| Ceftazidime | ≤1 | >16 | 86.8 / 11.2 |
| Ceftriaxone | ≤0.25 | 32 | 87.5 / 5.3 |
| Imipenem | 0.5 | 1 | 100.0 / 0.0 |
| Levofloxacin | ≤0.5 | ≤0.5 | 94.1 / 4.6 |
| Meropenem | ≤0.12 | ≤0.12 | 100.0 / 0.0 |
| Piperacillin/tazobactam | 2 | 32 | 88.8 / 3.3 |
| Tetracycline | ≤2 | >8 | 84.9 / 11.8 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | >2 | 81.6 / 18.4 |
| *P. mirabilis* (258) | | | |
| Ceftobiprole | ≤0.06 | ≤0.06 | - / - |
| Ampicillin | ≤1 | >16 | 78.3 / 21.7 |
| Cefepime | ≤0.12 | ≤0.12 | 99.6 / 0.4 |
| Ceftazidime | ≤1 | ≤1 | 100.0 / 0.0 (2.3)[b] |
| Ceftriaxone | ≤0.25 | ≤0.25 | 99.6 / 0.4 (1.9)[b] |
| Imipenem | 1 | 2 | 99.2 / 0.0 |
| Levofloxacin | ≤0.5 | >4 | 80.2 / 15.1 |
| Meropenem | ≤0.12 | ≤0.12 | 100.0 / 0.0 |
| Piperacillin/tazobactam | ≤0.5 | 1 | 100.0 / 0.0 |
| Tetracycline | >8 | >8 | 1.2 / 98.4 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | >2 | 78.7 / 21.3 |
| *Serratia* spp. (406) | | | |
| Ceftobiprole | ≤0.06 | 0.25 | - / - |
| Ampicillin | >16 | >16 | 4.9 / 86.0 |
| Cefepime | ≤0.12 | 0.25 | 99.8 / 0.0 |
| Ceftazidime | ≤1 | ≤1 | 97.3 / 2.0 |
| Ceftriaxone | ≤0.25 | 2 | 95.3 / 0.7 |
| Imipenem | 1 | 2 | 99.8 / 0.2 |
| Levofloxacin | ≤0.5 | 1 | 96.1 / 2.2 |
| Meropenem | ≤0.12 | ≤0.12 | 99.5 / 0.0 |
| Piperacillin/tazobactam | 2 | 4 | 96.8 / 0.7 |
| Tetracycline | >8 | >8 | 6.2 / 61.1 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | 1 | 96.1 / 3.9 |
| *P. aeruginosa* (1229) | | | |
| Ceftobiprole | 2 | >8 | - / - |
| Cefepime | 4 | 16 | 83.1 / 5.9 |
| Ceftazidime | 2 | >16 | 80.9 / 15.1 |
| Ceftriaxone | >32 | >32 | 9.6 / 65.6 |
| Imipenem | 2 | >8 | 80.8 / 11.9 |
| Levofloxacin | ≤0.5 | >4 | 72.6 / 21.5 |
| Meropenem | 0.5 | 8 | 85.2 / 6.7 |
| Piperacillin/tazobactam | 4 | >64 | 85.4 / 14.6 |
| Tetracycline | >8 | >8 | 4.8 / 77.8 |
| Trimethoprim/sulfamethoxazole | >2 | >2 | 15.3 / 84.7 |
| *Acinetobacter* spp. (416) | | | |
| Ceftobiprole | 2 | >8 | - / - |
| Ampicillin/sulbactam | 4 | >16 | 61.1 / 28.1 |
| Cefepime | 16 | >16 | 48.3 / 37.3 |
| Ceftazidime | >16 | >16 | 44.0 / 51.2 |
| Ceftriaxone | 32 | >32 | 24.3 / 48.6 |
| Imipenem | 1 | >8 | 69.0 / 20.0 |
| Levofloxacin | >4 | >4 | 46.4 / 50.5 |
| Meropenem | 1 | >8 | 64.9 / 28.4 |
| Piperacillin/tazobactam | 32 | >64 | 47.1 / 38.7 |
| Tetracycline | 8 | >8 | 49.8 / 41.1 |
| Trimethoprim/sulfamethoxazole | 2 | >2 | 54.3 / 45.7 |

[a]Breakpoint criteria are those of CLSI M100-S18 [2008]. - = no breakpoints established.
[b]Percentage meeting CLSI criteria for an ESBL- phenotype (≥2 µg/ml)

## Conclusions

- **Ceftobiprole is a new anti-MRSA cephem currently under regulatory review that displays activity against commonly occurring Enterobacteriaceae and *P. aeruginosa*, similar to that of other extended-spectrum cephalosporins.**
- **These characteristics warrant continued evaluation of ceftobiprole as empiric therapy for cSSSI and pneumonia, especially in those medical centers where MRSA and *P. aeruginosa* may be prevalent pathogens.**

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