**Title**

Faropenem for the management of infectious diseases – A systematic review of *in vitro* susceptibility tests and clinical studies

**Running title**

Faropenem in infectious disease management

**Authors**

Amitrajit Pal1\*, Dattatray Pawar1, Akhilesh Sharma1

**Affiliations**

1Medical Affairs Department, Alkem Laboratories Ltd., Mumbai, India

**\*Corresponding author**

Dr. Amitrajit Pal,

Medical Affairs Department, Alkem Laboratories Ltd., Mumbai, India

Email ID: amitrajit.pal@alkem.com

Phone number: +91-8335012814

**Supplementary Table 1:** List of clinical isolates against which minimum inhibitory concentration of faropenem was estimated

|  |  |
| --- | --- |
| Gram-negative bacteria | Gram-positive bacteria |
| *Acinetobacter baumannii*/*haemolyticus* | *Clostridium* species |
| *Bacteroides fragilis* | *Enterococcus* species |
| *Chlamydia trachomatis* | Group A Streptococci |
| *Citrobacter* species | Group B Streptococci |
| *Escherichia coli* | *Peptostreptococcus* species |
| *Haemophilus influenzae* | *Staphylococcus* species |
| *Klebsiella* species | *Streptococcus* species |
| *Moraxella catarrhalis* | β-haemolyticstreptococci |
| *Mycoplasma genitalium* |  |
| *Neisseria gonorrhoeae* |  |
| *Neisseria meningitides* |  |
| *Proteus* species |  |
| *Providentia stuartii* |  |
| *Pseudomonas* species |  |
| *Salmonella* species |  |
| *Shigella* species |  |
| *Trichomonas vaginalis* |  |

**Supplementary Table 2:** Minimum inhibitory concentrations of penicillin-susceptible or resistant strains of *Streptococcus pneumonia*

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author-year Comparators | Susceptible/ Resistant | No. of isolates tested | Faropenem | | | Comparator 1 (C1) | | | Comparator 2 (C2) | | | Comparator 3 (C3) | | |
| MIC50 | MIC90 | MIC range | MIC50 | MIC90 | MIC range | MIC50 | MIC90 | MIC range | MIC50 | MIC90 | MIC range |
| Sewell et al., 1995 [35] C1: Co-amoxiclav | S | 71 | ≤0.03 | 0.06 | ≤0.03–0.06 | ≤0.03 | ≤0.03 | ≤0.03–0.12 | NA | NA | NA | NA | NA | NA |
| R | 31 | 0.12 | 0.5 | ≤0.03–2.0 | 0.25 | 2.0 | ≤0.03–8.0 | NA | NA | NA | NA | NA | NA |
| Eliopoulos et al., 1995 [23] C1: Co-amoxiclav C2: Cefpodoxime | Sa | 15 | 0.06 | 0.12 | 0.008–0.25 | 0.06 | 0.5 | 0.03–0.5 | 0.12 | 0.5 | 0.03–0.5 | NA | NA | NA |
| R | 15 | 1.0 | 8.0 | 0.06–8.0 | 2.0 | 8.0 | 0.06–8.0 | 1.0 | 16.0 | 0.06–16.0 | NA | NA | NA |
| S | 7 | NA | NA | 0.016–0.12 | NA | NA | 0.016–0.06 | NA | NA | 0.016–0.12 | NA | NA | NA |
| R | 11 | 0.5 | 4.0 | 0.06–4.0 | 2.0 | 2.0 | 0.25–2.0 | 2.0 | 4.0 | 0.5–4.0 | NA | NA | NA |
| Mortensen et al., 1995 [15]  C1: Co-amoxiclav C2: Cefpodoxime | MIC < 0.1 | 15 | ≤0.015 | ≤0.015 | ≤0.015 | ≤0.015 | 0.03 | ≤0.015–0.03 | 0.03 | 0.03 | 0.03 | NA | NA | NA |
| MIC ≥ 0.1 | 4 | NA | NA | 0.12–2.0 | NA | NA | 0.06–4.0 | NA | NA | 0.12–16.0 | NA | NA | NA |
| Milatovic et al., 2002 [33] C1: Co-amoxiclav C2: Cefpodoxime | S | 228 | ≤0.015 | 0.03 | ≤0.015–0.12 | 0.03 | 0.03 | ≤0.015–0.12 | 0.03 | 0.06 | ≤0.015–0.5 | NA | NA | NA |
| IR | 38 | 0.12 | 0.5 | ≤0.015–0.1 | 0.12 | 1.0 | ≤0.015–2.0 | 0.25 | 2.0 | ≤0.015–2.0 | NA | NA | NA |
| R | 47 | 1.0 | 1.0 | 0.5–2.0 | 2.0 | 2.0 | 0.25–8.0 | 2.0 | 4.0 | 0.5–4.0 | NA | NA | NA |
| Critchley et al., 2002 [29] C1: Co-amoxiclav C2: Levofloxacin | S | 3078 | ≤0.004 | 0.008 | ≤0.004–12.0 | ≤0.015 | 0.03 | ≤0.015–1.0 | 1.0 | 1.0 | ≤0.004–>8.0 | NA | NA | NA |
| IR | 1154 | 0.12 | 0.25 | ≤0.004–1.0 | 0.5 | 1.0 | ≤0.015–4.0 | 1.0 | 1.0 | 0.25–>8.0 | NA | NA | NA |
| R | 493 | 0.5 | 1.0 | ≤0.004–2.0 | 2.0 | 4.0 | 0.5–16.0 | 1.0 | 1.0 | 0.25–>8.0 | NA | NA | NA |
| Decousser et al., 2003 [31] C1: Levofloxacin | Sb | 100 | 0.016 | 0.032 | 0.008–0.125 | 1.0 | 1.0 | 0.25–2.0 | NA | NA | NA | NA | NA | NA |
| IR | 75 | 0.25 | 0.25 | 0.016–0.5 | 1.0 | 1.0 | 0.5–2.0 | NA | NA | NA | NA | NA | NA |
| R | 19 | 0.5 | 0.5 | 0.25–1.0 | 1.0 | 1.0 | 1.0–2.0 | NA | NA | NA | NA | NA | NA |
| Sc | 35 | 0.016 | 0.032 | 0.008–0.25 | 1.0 | 1.0 | 0.5–2.0 | NA | NA | NA | NA | NA | NA |
| IR | 21 | 0.25 | 0.5 | 0.125–0.5 | 1.0 | 1.0 | 1.0–1.0 | NA | NA | NA | NA | NA | NA |
| R | 4 | 0.5 | 1.0 | 0.016–1.0 | 1.0 | 1.0 | 0.5–1.0 | NA | NA | NA | NA | NA | NA |
| Yamaguchi et al., 2005 [11] C1: Levofloxacin C2: Azithromycin | S | 16.0 | ≤0.06 | ≤0.06 | ≤0.06 | 0.5 | 1.0 | 0.5–1.0 | 128.0 | >128.0 | 0.25–>128.0 | NA | NA | NA |
| IR + R | 26.0 | 0.25 | 0.25 | ≤0.06–0.5 | 0.5 | 1.0 | 0.25–1.0 | 16.0 | >128.0 | 0.5–>128.0 | NA | NA | NA |
| Stone et al., 2007 [10] C1: Co-amoxiclav C2: Levofloxacin C3: Azithromycin | Sd | 154 | NA | 0.015 | ≤0.004–0.06 | NA | 0.03 | ≤0.015–0.12 | NA | 1.0 | 0.25–2.0 | NA | 0.12 | ≤0.03–≥8.0 |
| IR | 147 | NA | 0.25 | ≤0.004–0.5 | NA | 1.0 | 0.03–2,0 | NA | 1.0 | 0.25–1.0 | NA | ≥8.0 | ≤0.03–≥8.0 |
| R | 92 | NA | 1.0 | 0.25–1.0 | NA | 2.0 | 1.0–4.0 | NA | 1.0 | 0.5–1.0 | NA | ≥8.0 | ≤0.03–≥8.0 |
| Se | 133 | NA | 0.008 | ≤0.004–0.03 | NA | 0.03 | ≤0.015–0.12 | NA | 1.0 | 0.5–1.0 | NA | 0.06 | ≤0.03–>8.0 |
| IR | 24 | NA | 0.25 | 0.03–0.25 | NA | 1.0 | 0.06–1.0 | NA | 1.0 | 0.5–1.0 | NA | 8.0 | 0.06–>8.0 |
| R | 11 | NA | 0.5 | 0.25–2.0 | NA | 2.0 | 1.0–16.0 | NA | 1.0 | 0.5–1.0 | NA | 4.0 | ≤0.03–≥8.0 |

All MICs are presented in µg/mL

aIncludes penicillin susceptible or resistant strains of *Streptococcus viridans*

bClinical isolates were collected from adult patients

cClinical isolates were collected from children

dClinical isolates were collected from children in Israel

eClinical isolates were collected from children in Costa Rica

Co-amoxiclav, amoxicillin-clavulanic acid combination; S, penicillin-susceptible; IR, penicillin-intermediate resistant; R, penicillin-resistant; MIC, minimum inhibitory concentration

**Supplementary Table 3:** Minimum inhibitory concentrations of β-lactamase positive or negative strains of *Haemophilus influenzae and Moraxella catarrhalis*

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author-year  Comparators | β-lactamase positive/negative | No. of isolates tested | Faropenem | | | Comparator 1 (C1) | | | Comparator 2 (C2) | | | Comparator 3 (C3) | | |
| MIC50 | MIC90 | MIC range | MIC50 | MIC90 | MIC range | MIC50 | MIC90 | MIC range | MIC50 | MIC90 | MIC range |
| Mortensen et al., 1995 [15] C1: Co-amoxiclav C2: Cefpodoxime | *H. influenzae* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Positive | 15 | 0.25 | 0.5 | 0.12–0.5 | 1.0 | 2.0 | 0.25–2.0 | 0.06 | 0.25 | 0.03–1.0 | NA | NA | NA |
| Negative | 57 | 0.25 | 0.5 | 0.03–2.0 | 0.5 | 0.5 | 0.12–1.0 | 0.06 | 0.12 | 0.03–4.0 | NA | NA | NA |
| Fuchs et al., 1995 [24] C1: Co-amoxiclav | *H. influenzae* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Positive | 10 | 0.25 | 0.5 | 0.25–0.5 | 0.5 | 1.00 | 0.5–1.0 | NA | NA | NA | NA | NA | NA |
| Negative (AS) | 10 | 0.5 | 1.0 | 0.25–2.0 | 0.5 | 1.00 | 0.5–2.0 | NA | NA | NA | NA | NA | NA |
| Negative (AR) | 10 | 2.0 | 4.0 | 1.0–4.0 | 4.00 | 8.00 | 4.0–8.0 | NA | NA | NA | NA | NA | NA |
| Sewell et al., 1995 [35] C1: Co-amoxiclav | *H. influenzae* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Positive | 30 | 1.0 | 2.0 | 0.12–4.0 | 1.0 | 2.0 | 0.5–2.0 | NA | NA | NA | NA | NA | NA |
| Negative | 70 | 1.0 | 1.0 | 0.25–4.0 | 0.5 | 1.0 | 0.25–2.0 | NA | NA | NA | NA | NA | NA |
| *M. catarrhalis* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Positive | 70 | 0.5 | 1.0 | ≤0.03–1.0 | 0.25 | 0.5 | ≤0.03–1.0 | NA | NA | NA | NA | NA | NA |
| Negative | 30 | 0.12 | 0.5 | 0.06–1.0 | ≤0.03 | 0.5 | ≤0.03–1.0 | NA | NA | NA | NA | NA | NA |
| Marchese et al., 1999 [26] C1: Co-amoxiclav C2: Cefpodoxime C3: Azithromycin | *H. influenzae* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Positive | 14 | 0.5 | 1.0 | 0.12–2.0 | 0.5 | 2.0 | 0.12–2.0 | 0.12 | 0.12 | ≤0.03–1.0 | 1.0 | 2.0 | 0.5–2 |
| Negative | 296 | 0.5 | 1.0 | 0.12–2.0 | 0.5 | 1.0 | 0.12–2.0 | 0.12 | 0.12 | ≤0.03–0.5 | 1.0 | 2.0 | ≤0.03–2 |
| *M. catarrhalis* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Positive | 48 | ≤0.06 | 0.25 | ≤0.06–1.0 | 0.12 | 0.25 | 0.12–0.5 | 0.25 | 0.5 | 0.12–1.0 | ≤0.06 | 0.12 | ≤0.06–0.25 |
| Negative | 15 | ≤0.06 | 0.12 | ≤0.06–0.12 | ≤0.06 | 0.12 | ≤0.06–0.5 | 0.12 | 0.12 | 0.12–0.5 | ≤0.06 | 0.12 | ≤0.06–0.25 |
| Milatovic et al., 2002 [33] C1: Co-amoxiclav C2: Cefpodoxime | *H. influenzae* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Positive | 33 | 0.5 | 1.0 | 0.25–2.0 | 1.0 | 2.0 | 0.5–2.0 | 0.06 | 0.12 | ≤0.015–0.25 | NA | NA | NA |
| Negative | 361 | 0.5 | 1.0 | 0.06–2.0 | 0.5 | 0.5 | ≤0.015–2.0 | 0.06 | 0.12 | ≤0.015–0.5 | NA | NA | NA |
| Schmitz et al., 2002 [32] C1: Co-amoxiclav C2: Cefpodoxime | *H. influenzae* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Positive | 34 | 0.5 | 1.0 | 0.25–4.0 | 0.5 | 1.0 | 0.06–>4.0 | 0.12 | 0.25 | 0.06–1.0 | NA | NA | NA |
| Negative | 200 | 0.5 | 1 | 0.06–2 | 0.25 | 1 | ≤0.03–4 | 0.06 | 0.12 | ≤0.03–0.5 | NA | NA | NA |
| Critchley et al., 2002 [29] C1: Co-amoxiclav C2: Levofloxacin | *H. influenzae* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Positive | 847 | 0.25 | 0.5 | ≤0.004–4.0 | 1.0 | 2.0 | 0.03–8.0 | 0.015 | 0.015 | ≤0.004–0.06 |  |  |  |
| Negative | 1767 | 0.25 | 1.0 | ≤0.004–4.0 | 0.5 | 1.0 | ≤0.015–4.0 | 0.015 | 0.015 | ≤0.004–0.06 |  |  |  |
| *M. catarrhalis* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Positive | 1121 | 0.25 | 0.5 | 0.008–2.0 | 0.25 | 0.5 | ≤0.015–1.0 | 0.03 | 0.06 | 0.015–1.0 |  |  |  |
| Negative | 72 | 0.3 | 0.12 | 0.015–1.0 | ≤0.015 | 0.03 | ≤0.015–0.5 | 0.03 | 0.06 | 0.03–0.25 |  |  |  |
| Stone et al., 2007 [10]  C1: Co-amoxiclav C2: Levofloxacin C3: Azithromycin | *H. influenzaea* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Positive | 77 | NA | 0.25 | 0.03–4.0 | NA | 2.0 | 0.12–8.0 | NA | 0.015 | 0.008–0.03 | NA | 2.0 | 0.25–4.0 |
| Negative | 290 | NA | 0.25 | 0.015–4.0 | NA | 0.5 | 0.12–2.0 | NA | 0.015 | ≤0.004–0.03 | NA | 2.0 | 0.25–4.0 |
| *H. influenzaeb* |  |  |  |  |  |  |  | NA |  |  |  |  |  |
| Positive | 16 | NA | 0.5 | 0.06–0.5 | NA | 1.0 | 0.5–1.0 | NA | 0.015 | ≤0.004–0.12 | NA | 2.0 | 0.25–4.0 |
| Negative | 171 | NA | 0.5 | 0.008–4.0 | NA | 0.5 | 0.03–2.0 | NA | 0.015 | 0.008–1.0 | NA | 2.0 | 0.12–4.0 |

All MICs are presented in µg/mL

aClinical isolates were collected from children in Israel

bClinical isolates were collected from children in Costa Rica

Co-amoxiclav, amoxicillin-clavulanic acid combination; MIC, minimum inhibitory concentration

**Supplementary Table 4:** Minimum inhibitory concentrations of methicillin/oxacillin susceptible or resistant strains of *Staphylococcus aureus* and *Neisseria gonorrhoeae*

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author-year | Study organism/pathogen | No. of isolates tested | Faropenem | | | Amoxicillin-clavulanate | | | Cefpodoxime | | |
| MIC50 | MIC90 | MIC range | MIC50 | MIC90 | MIC range | MIC50 | MIC90 | MIC range |
| Sewell et al., 1995 [35] | *S. aureus* |  |  |  |  |  |  |  |  |  |  |
| Oxacillin sensitive | 65 | 0.06 | 0.12 | ≤0.03–0.12 | 2.0 | 2.0 | 0.06–4.0 | NA | NA | NA |
| Oxacillin resistance | 23 | 4.0 | >64.0 | 0.25–>64.0 | 16.0 | 32.0 | 4.0–64.0 | NA | NA | NA |
| Fuchs et al., 1995 [24] | *N. gonorrhoeae* |  |  |  |  |  |  |  |  |  |  |
| Penicillinase negative | 10 | ≤0.03 | ≤0.03 | ≤0.03–0.06 | 0.25 | 0.5 | ≤0.06–1.0 | NA | NA | NA |
| Penicillinase negative PR | 10 | 0.12 | 0.25 | 0.06–0.5 | 1.0 | 2.0 | 0.5–4.0 | NA | NA | NA |
| Penicillinase positive | 10 | ≤0.03 | 0.06 | ≤0.03–0.12 | 1.0 | 2.0 | 0.5–4.0 | NA | NA | NA |
| *S. aureus* |  |  |  |  |  |  |  |  |  |  |
| Methicillin sensitive | 20 | 0.06 | 0.12 | 0.06–0.12 | 0.5 | 1.0 | 0.12–1.0 | NA | NA | NA |
| Methicillin resistance | 10 | 1.0 | >16.0 | 0.25–>16.0 | 8.0 | 16.0 | 4.0–16.0 | NA | NA | NA |
| Eliopoulos et al., 1995 [23] | *S. aureus* |  |  |  |  |  |  |  |  |  |  |
| Oxacillin sensitive | 21 | 0.12 | 0.25 | 0.016–1.0 | 1.0 | 1.0 | 0.03–1 | 4.0 | 8 | 0.25–8.0 |
| Borderline oxacillin sensitive | 6 | NA | NA | 0.12–0.5 | NA | NA | 1–2 | NA | NA | 4.0–8.0 |
| Methicillin resistance | 18 | >128.0 | >128.0 | >128.0 | 32.0 | 64.0 | 32.0–64.0 | >64.0 | >64.0 | >64.0 |
| *Staphylococci* - coagulase negative |  |  |  |  |  |  |  |  |  |  |
| Methicillin sensitive | 16 | 0.12 | 0.25 | 0.03–0.25 | 0.5 | 1.0 | 0.06–1 | 2.0 | 4.0 | 0.25–4.0 |
| Methicillin resistance | 19 | 8.0 | >128.0 | 0.25–>128.0 | 4.0 | 32.0 | 1–64 | 128.0 | >128 | 1.0–>128.0 |
| Mortensen et al., 1995 [15] | *S. aureus* |  |  |  |  |  |  |  |  |  |  |
| Methicillin sensitive | 43 | 0.12 | 0.12 | 0.03–0.12 | 2.0 | 4.0 | 0.12–8.0 | 2.0 | 4.0 | 0.25–8.0 |
| Methicillin resistance | 11 | 1.0 | 2.0 | 0.06–2.0 | 8.0 | 16.0 | 2.0–16.0 | 32.0 | >32.0 | 2.0–>32.0 |
| *Staphylococcus sp.* |  |  |  |  |  |  |  |  |  |  |
| Methicillin sensitive | 30 | 0.06 | 0.25 | 0.06–4.0 | 0.5 | 2.0 | 0.03–8.0 | 1.0 | 16.0 | 0.5–>32.0 |
| Methicillin resistance | 39 | 1.0 | 4.0 | 0.06–>32.0 | 4.0 | 8.0 | 0.5–32.0 | 32.0 | >32.0 | 0.5–>32.0 |
| Woodcock et al., 1997 [14] | *S. aureus* |  |  |  |  |  |  |  |  |  |  |
| Methicillin sensitive | 30 | 0.06 | 0.12 | 0.03–0.25 | 0.5 | 0.5 | 0.12–1.0 | 2.0 | 4.0 | 1.0–4.0 |
| Methicillin resistance | 20 | 2.0 | 2.0 | 0.25–2.0 | 16.0 | 16.0 | 2.0–16.0 | >128.0 | >128.0 | 4.0–>128.0 |
| Milatovic et al., 2002 [33] | *S. aureus* |  |  |  |  |  |  |  |  |  |  |
| Methicillin sensitive | 217 | 0.12 | 0.12 | 0.06–0.5 | 0.5 | 1.0 | 0.06–2.0 | 2.0 | 4.0 | 0.5–8.0 |
| Methicillin resistance | 146 | >32,0 | >32.0 | 0.12–>32.0 | 32.0 | >32.0 | 2.0–>32.0 | >32.0 | >32.0 | 2.0–>32.0 |

All MICs are presented in µg/mL  
PR, penicillin resistant MIC, minimum inhibitory concentration