## Fosfomycin

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Inconvenients</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Broad spectrum</td>
<td>□ Broad spectrum</td>
</tr>
<tr>
<td>□ Effective on MDR/XDR</td>
<td>□ Optimal dosage unknown</td>
</tr>
<tr>
<td>□ Few cross resistance</td>
<td>□ Combination recommended</td>
</tr>
<tr>
<td>□ Low level of emergence of resistance</td>
<td>□ Adverse events with high dose</td>
</tr>
<tr>
<td>□ Intracellular activity</td>
<td>□ Multiple infusion</td>
</tr>
<tr>
<td>□ Biofilm penetration</td>
<td>□ Few clinical experience</td>
</tr>
<tr>
<td>□ Good penetration in difficult to access tissues</td>
<td>□ Oral form only for UTI</td>
</tr>
</tbody>
</table>

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Areas of uncertainty

- Optimal dosage?
- Combination necessary? Which associated drug?
- Microbiological threshold susceptibility?
- Medium for susceptibility testing?
- Efficacy of oral form for severe/febrile UTI (MDR/XDR)?
- Oral fosfomycin for prophylaxis?
- Concentration or time dependent killing?
Indications

- **Gram negative:**
  - Carba sparing
  - Option for MDR, XDR, PDR infections especially in ICU (No trials, cohorts >> dosage? Combination?)

- **Gram positive:**
  - Difficult to treat infections such as IE, BJI, CNS infection especially with foreign device
Medical needs / indication

- **Empirical use**: MDR/XDR suspicion, difficult-to-treat infections (BJI), foreign body infection, CNS infection

- **Targeted indication**: ....the same? = infectious disease challenge
My own opinion

- Indications: difficult to treat infections
  - MRSA
  - BJI, Implant associated infections

- Combination !!

- Dosage: 16 to 20 g. per day
CONCLUSIONS
SYNERGY / INTERACTION WITH OTHER ANTIMICROBIALS
Evaluation of double drug combinations

- In vitro synergy against 100 MDR Gram negative pathogens
Synergy of fosfomycin with carbapenems, colistin, netilmicin, and tigecycline against multidrug-resistant *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa* clinical isolates

G. Samonis · S. Maraki · D. E. Karageorgopoulos · E. K. Vouloumanou · M. E. Falagas

Table 4 Synergy of fosfomycin combinations against the 50 serine carbapenemase-producing *Klebsiella pneumoniae* isolates studied according to the minimum inhibitory concentration (MIC) of each of the carbapenems tested or the susceptibility status to the other antibiotics tested.

<table>
<thead>
<tr>
<th>Antibiotic in combination with fosfomycin</th>
<th>Isolates exhibiting synergy, n/N (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenem MIC, mg/L</td>
<td></td>
</tr>
<tr>
<td>≤4</td>
<td>4&lt;MIC≤8</td>
</tr>
<tr>
<td>Imipenem</td>
<td>1/3</td>
</tr>
<tr>
<td>Mecopenem</td>
<td>2/5</td>
</tr>
<tr>
<td>Doripenem</td>
<td>7/11 (63.6)</td>
</tr>
<tr>
<td>Susceptibility status</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>1</td>
</tr>
<tr>
<td>Colistin</td>
<td>13/36 (36.1)</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>0/4</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>13/43 (30.2)</td>
</tr>
</tbody>
</table>

Abbreviations: I: intermediate susceptible; S: susceptible; R: resistant.

*Percentages are given only when the denominator is at least 10*
Comments

- Frequent *in vitro synergy* with other antimicrobials against MDR Gram negative pathogens
- Fosfomycin/Carbapenems seems to be the best combination
- Use of *triple-drug combination* with another active agent such as colistin, tigecyclin, aminoglycosides could be considered
- Fosfomycin inhibits the *first* committed enzymatic step in peptidoglycan synthesis while beta lactams mainly act on the *latest* stage

Samonis et al. EJCMID 2011
TISSUE PENETRATION
Intensive Care Unit

Fosfomycin levels in plasma and muscle tissue in critically ill patients (fosfomycin 8g/d)

Septic patients: ≈ 90% of plasma levels

Joukhadar et al. JAC 2003
Extracellular concentrations of fosfomycin in lung tissue of septic patients

Veronika Matzi¹, Jörg Lindenmann¹, Christian Porubsky¹, Sylvia A. Kugler², Alfred Maier¹, Peter Dittrich³, Freyja M. Smolle-Jüttner¹ and Christian Joukhadar¹,2,4,5

- Dosage by microdialysis of fosfomycin in infected and healthy lung tissue
- 6 ICU patients
- Dosage from 15g to 24g/day

Figure 1. Mean pharmacokinetic profiles of fosfomycin in plasma, infected lung tissue and healthy lung tissue in eight patients after single intravenous administration of 4.0 g. Error bars are standard deviations. Horizontal lines indicate different MICs ranging from 8 to 32 mg/L.

Matzi V et al. JAC 2010
Cerebrospinal fluid

- 8 patients with drain associated ventriculitis
- Fosfomycin 3gX8 iv per day
- Cerebrofluid levels measured with microdialysis
- Susceptible bacteria are covered
- Good tolerability of high dose

Plausler B et al. JAC 2004
Bacterial activity of fosfomycin

MSSA

Concentration in CSF of a patient

In vitro PK/PD simulation
Activity of fosfomycin in a rabbit model of experimental pneumococcal meningitis

Roland Nau*, Gregor Zysk*, Ralf Rene’ Reinert*, Hamparzum Mergeryan*, Helmut Eiffert* and Hilmar W. Prange*

- Pneumococcal experimental meningitis rabbit
- Fosfomycin tested at different dosages
- Bacterial count at 2, 5 and 8 hours after initiation of treatment
- High dose needed
- Bactericidal activity < ceftriaxone
- Could be used in combination

concentrations of at least ten times the MIC were necessary. Co-administration of both drugs (1 mg/kg/h ceftriaxone + 40 mg/kg/h fosfomycin) tended to be more active than either drug alone (in-vivo drug interaction = 1.3).

In conclusion, fosfomycin at very high doses reduced bacterial counts in CSF. However, fosfomycin CSF concentrations usually observed in patients with meningitis receiving fosfomycin were not bactericidal in this model. At all doses tested the bactericidal rate was lower than that of ceftriaxone. Fosfomycin is therefore unsuitable as a single agent but may be used as a rescue antibiotic in the British Society for Antimicrobial Chemotherapy (Working Party Report, 1988) and the NCCLS guidelines do not list breakpoints for fosfomycin. Applying the manufacturer’s criteria, all except one of the strains tested would be considered fully susceptible to fosfomycin.

The MIC of fosfomycin of the S. pneumoniae type 3 strain used in the animal studies was 4 mg/L and the MBC was 3 dilutions higher (32 mg/L). This compares well with

Nau R et al. JAC 1995
Bactericidal Activity of Cefotaxime and Fosfomycin in Cerebrospinal Fluid During the Treatment of Rabbit Meningitis Experimentally Induced by Methicillin-resistant Staphylococcus aureus

- CTX + FOS experimental meningitis model MRSA
- Bacteria surviving in CSF
  - CTX 4.35%
  - FOS 0.20%
  - CTX + FOS 0.19%
- Quick bactericidal effect of CTX+FOS

Introduction
When a methicillin-resistant Staphylococcus aureus (MRSA) meningitis occurs, mainly in neurosurgery, it creates therapeutic problems on account of bacterial resistance to antibiotics commonly used in meningitis therapy and poor diffusion into CSF of some antibiotics effective alone and in combination in rabbit meningitis perimenterially induced by MRSA.

Materials and Methods
Infecting organism: The S. aureus strain used in this study was MRSA.

Prof. A. Kazmierczak, M.D., A. Pechinot, Ph. D., J. M. Duez, E. Kohli, Ph. D., Service de Microbiologie Médicale, Centre Hospitalier Universitaire, Strasbourg, France

Figure 3: CSF concentrations of fosfomycin (mean ± SD) in experimental rabbit meningitis after two infusions of 100 mg/kg i.v. over 3 h.

It would have been interesting to know the CSF desacetyl-cefotaxime.
Activities of Fosfomycin, Tigecycline, Colistin, and Gentamicin against Extended-Spectrum-β-Lactamase-Producing *Escherichia coli* in a Foreign-Body Infection Model

Stéphane Corvec, Ulrika Furustrand Tafin, Bertrand Betrisey, Olivier Borens, Andrej Trampuz

- Implant-associated infection due CTX-M15 *E. coli*
  - Tigecyclin: unchanged at 0.5 and 1xMIC, decreased 1 log at 4xMIC
  - Gentamicin: regrowth at 0.5 and 1xMIC, rapid bactericidal activity at 4xMIC
  - Colistin: maximum decrease at 3.1 logCFU/mL
  - Fosfomycin: rapid bactericidal activity independent of drug concentration above MIC

- Fosfomycin + colistin >> synergy

FIG 1: Time-kill curves with 0.5, 1, and 4X the MIC of tigecycline (TIG), colistin (COL), fosfomycin (FOS), and gentamicin (GEN) against *E. coli* in log growth phase (inoculum, 10⁸ CFU/mL). Values are means ± SD. The experiments were performed in triplicate. GC, growth control.
Conclusion

Fosfomycin + colistin:

• significant synergism
• highest biofilm activity
• no bacterial growth

« In conclusion, fosfomycin + colistin is a promising treatment option for implanted-associated infections caused by fluoroquinolones-resistant Gram-negative bacilli. »

Corvec et al. AAC 2013
Orthopaedic infection due to *Enterococcus faecalis*

Fosfomycin and biofilm

- Only fosfomycin + gentamycin was able to cure a significant amount of *E. faecalis* infected foreign bodies
- No other effective therapy
**E. coli** biofilm

- Fosfomycin: excellent activity against biofilm and suppressed heat production at MIC or below
- Tigecyclin and colistin suppressed heat production only at high concentration (128 and 32 µg/mL)
- Gentamicin intermediate activity against *E. coli* biofilm

**TABLE 2** Activity against *E. coli* Bj HDE-1 biofilms on glass beads, evaluated by microcalorimetry

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>3-h biofilm</th>
<th>12-h biofilm</th>
<th>24-h biofilm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosfomycin</td>
<td>0.12</td>
<td>&lt;0.12</td>
<td>&lt;0.12</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>128</td>
<td>128</td>
<td>128</td>
</tr>
<tr>
<td>Colistin</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>8</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

Von Ah et al. BMC microbiol 2009
Fosfomycin is an hydrophilic molecule with low level serum protein binding, leading to high tissue penetration, especially in soft tissue, bone, central nervous system, lung, and heart valves. Time-dependent mechanism > concentration-dependent mechanism for fosfomycin. When doses > 16 g, monitoring of sodium level and hypokalemia.
MICROBIOLOGICAL RESISTANCE
Emergence of resistance under fosfomycin

- Unique mechanism of action >> Uncommon cross resistance (Falagas M et al. CMR 2016)

- But:
  - Fosfomycin MIC is not a good efficacy predictor: highly resistant mutants may appear, depending on other pre-existing mutations with no impact on MIC (Ballestero Tellez et al. JAC 2016)
  - Higher inoculum used in the microdilution method enriched the initial inoculum with resistant subpopulations and could partially explain the fosfomycin MIC discrepancies with respect to the agar dilution method (Ballestero Tellez et al. CMI 2017)
Molecular insights into fosfomycin resistance in Escherichia coli

M. Ballestero-Téllez1,2,†, F. Docobo-Pérez2,4,†, I. Portillo-Calderón1,2, J. M. Rodríguez-Martínez2,4, L. Racero1,
M. S. Ramos-Guelfo3, J. Blázquez2,5, J. Rodríguez-Baño1,2,6 and A. Pascual1,4

Table 2. Fosfomycin MIC and mutant frequency, selecting at fosfomycin concentrations of 64 and 256 mg/L, for single- and double-gene deletion mutant strains

<table>
<thead>
<tr>
<th>Strain</th>
<th>Fosfomycin MIC (mg/L)</th>
<th>Fosfomycin mutant frequency (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>selecting at 64 mg/L</td>
<td>selecting at 256 mg/L</td>
</tr>
<tr>
<td>BW25113</td>
<td>2</td>
<td>&lt;10⁻⁹</td>
</tr>
<tr>
<td>ΔgptT</td>
<td>2</td>
<td>1.3 x 10⁻³ ± 1.3 x 10⁻⁵</td>
</tr>
<tr>
<td>ΔuhpT</td>
<td>64</td>
<td>9.7 x 10⁻³ ± 7 x 10⁻⁴</td>
</tr>
<tr>
<td>ΔacyA</td>
<td>8</td>
<td>2.9 x 10⁻⁵ ± 1.6 x 10⁻⁵</td>
</tr>
<tr>
<td>ΔptsI</td>
<td>2</td>
<td>4.7 x 10⁻⁵ ± 4.2 x 10⁻⁵</td>
</tr>
</tbody>
</table>

Table 3. Changes in susceptibility to fosfomycin and mutations found in recovered strains after the time-kill experiments using fosfomycin concentrations of 64 and 307 mg/L

<table>
<thead>
<tr>
<th>Strain</th>
<th>Time-kill fosfomycin concentration (mg/L)</th>
<th>MIC (mg/L)</th>
<th>Mutation found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>original</td>
<td>final</td>
<td></td>
</tr>
<tr>
<td>ΔgptT</td>
<td>64</td>
<td>&gt;1024</td>
<td>uhpT 136delT frameshift</td>
</tr>
<tr>
<td>ΔuhpT</td>
<td>64</td>
<td>&gt;1024</td>
<td>crp 301_341del</td>
</tr>
<tr>
<td>ΔacyA</td>
<td>307</td>
<td>&gt;1024</td>
<td>uhpB 146delT frameshift</td>
</tr>
<tr>
<td>ΔptsI</td>
<td>64</td>
<td>&gt;1024</td>
<td>uhpC G48A Tn221stop</td>
</tr>
<tr>
<td>ΔgptT-uhpT</td>
<td>64</td>
<td>&gt;1024</td>
<td>uhpT (G103T Gln341stop)</td>
</tr>
<tr>
<td>ΔgptT-cyaA</td>
<td>64</td>
<td>&gt;1024</td>
<td>uhpC 81I 548del</td>
</tr>
<tr>
<td>ΔgptT-ptsI</td>
<td>64</td>
<td>&gt;1024</td>
<td>uhpB (C784T Gln262stop)</td>
</tr>
<tr>
<td>ΔuhpT-cyaA</td>
<td>307</td>
<td>&gt;1024</td>
<td>uhpC A2314C, Thr72Pro</td>
</tr>
<tr>
<td>ΔptsI-ptsI</td>
<td>64</td>
<td>&gt;1024</td>
<td>uhpB A543G Trp181stop</td>
</tr>
<tr>
<td>ΔgptT-cyaA</td>
<td>64</td>
<td>&gt;1024</td>
<td>gptT 659_724del</td>
</tr>
<tr>
<td></td>
<td>307</td>
<td>&gt;1024</td>
<td>gptT 659_724del</td>
</tr>
<tr>
<td>ΔptsI-cyaA</td>
<td>64</td>
<td>&gt;1024</td>
<td>uhpB (T654A Leu219Stop)</td>
</tr>
</tbody>
</table>

Ballestero Tellez et al. JAC 2016
Role of inoculum and mutant frequency on fosfomycin MIC discrepancies by agar dilution and broth microdilution methods in Enterobacteriaceae

M. Ballesteros-Téllez 1,2,6, F. Docobo-Pérez 2,3,4,*, 6 J.M. Rodríguez-Martínez 2,3,4, M.C. Conejo 3, M.S. Ramos-Guelfo 1, J. Blázquez 2,4, J. Rodriguez-Baño 1,2,4,5, A. Pascual 1,2,3,4

![Graph showing mutant frequency at different concentrations of Escherichia coli and Klebsiella pneumoniae.](image)

**Fig. 2.** Fosfomycin mutant frequency at different concentrations of 21 Escherichia coli (MIC = 1 mg/L) and 21 Klebsiella pneumoniae (MIC = 15 mg/L) clinical isolates. Horizontal bars and whiskers represent the mean and SD, respectively. Open grey circles denote each independent result.

![Graph showing subpopulation growth over time at different initial bacterial inocula.](image)

**Fig. 3.** Subpopulation growth concerning over time, at different initial bacterial inocula. Total bacterial population (res fosfomycin) is shown by red lines. Resistant subpopulations able to grow at 4 mg/L (blue lines) and 8 mg/L (green lines) of fosfomycin (4 x and 8 x MIC) are shown for Ec42, Ec148, Ec162, Ec271, Ec2974 and Escherichia coli ATCC 25922 strains (all with MIC = 1 mg/L). Each line represents the growth of a single experiment. Experiments were carried out in triplicate using the same overnight inoculum.
Use of a hollow fiber infection model: 3 clinical ESBL-producing *E. coli* strains with different fosfomycin MICs

- Human fosfomycin pharmacokinetic profiles simulated over 4 days: different regimens from 12 g/day to 36 g/day.
- No efficacy observed against the Ec42444 strain (fosfomycin MIC, 64 mg/L) at doses of 12, 24, or 36 g/day
- Synergy with combination meropenem + fosfomycin for bacterial killing
- Fosfomycin susceptibility breakpoints (≤64 mg/L according to CLSI [for *E. coli* urinary tract infections only]) should be revised for the treatment of serious systemic infections.

Docobo-Perez *et al.* AAC 2015
Parallel increase in community use of fosfomycin and resistance to fosfomycin in extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*

Jesús Oteo 1, Verónica Bautista 1, Noelia Lara 1, Oscar Cuevas 1, Margarita Arroyo 1, Sara Fernández 1, Edurne Lázaro 2, Francisco J. de Abajo 3 and José Campos 1,4* on behalf of the Spanish ESBL-EARS-Net Study Group†

- Susceptibility to fosfomycin among ESBL *E. coli*
- 27 Spanish hospitals

**Figure 1.** Trends in fosfomycin resistance and ESBL production in urinary *E. coli*.

**Figure 3.** Occurrence of fosfomycin resistance in ESBL-EC causing UTIs (years 2005–09), plotted against outpatient use of fosfomycin (years 2004–08) in Spain, including 95% confidence intervals.

Oteo J et al. JAC 2010
MRSA sensitivity against fosfomycin

Figure 16: Sensitivity of methicillin-resistant *Staphylococcus aureus* to fosfomycin in Germany. Longitudinal data from the German Paul Ehrlich Society for Chemotherapy and the “the antibiotic resistance monitoring services of Antiinfective Intelligence in Germany” (ZARS).
ADVERSE EVENTS
### Adverse Events Associated with Fosfomycin Use: Review of the Literature and Analyses of the FDA Adverse Event Reporting System Database

Dmitri Iarikov · Ronald Wassel · John Farley · Sumathi Nambar

#### Table 6: Adverse events associated with oral fosfomycin in 28 comparative trials [33–59, 71]

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Fosfomycin N = 2743 n (%)</th>
<th>Comparator N = 2863 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>219 (8%)</td>
<td>229 (8%)</td>
</tr>
<tr>
<td>GI disorders (nausea, vomiting, diarrhea, abdominal pain)</td>
<td>179 (6.5%)</td>
<td>177 (6%)</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>13 (0.5%)</td>
<td>23 (1%)</td>
</tr>
<tr>
<td>Central nervous system (headache, dizziness)</td>
<td>10 (&lt;0.5%)</td>
<td>13 (&lt;0.5%)</td>
</tr>
<tr>
<td>Rash</td>
<td>11 (&lt;0.5%)</td>
<td>9</td>
</tr>
<tr>
<td>Other (asthenia, dyspnea, cough, joint pain)</td>
<td>6 (&lt;0.5%)</td>
<td>8 (&lt;1%)</td>
</tr>
<tr>
<td>Hepatic function abnormal</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>
Comments

- Safe profile
- Phlebitis and gastrointestinal disorders (>1/100 to <1/10)
- Sodium load: 1g Fosfomycin >> 14 mmol/L of sodium
- Fosfomycin is well dialysed
COMBINATION?
Combination?

- Medication mainly as a combination therapy
  
  - *In vitro* studies showed possible association with drug resistance (Falagas *et al.* CID 2008)
  
  - Experimental model in rat of MRSA endocarditis: Treatment with FOS resulted in development of resistant strains in 36% (Thauvin *et al.* AAC 1988)
SUSCEPTIBILITY?
# Definitions

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Organism(s) and delivery route</th>
<th>MIC (mg/liter)</th>
<th>Zone diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td>EUCAST</td>
<td><em>Enterobacteriaceae</em></td>
<td>$\leq 32$</td>
<td>$&gt;32$</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>$\leq 32$</td>
<td>$&gt;32$</td>
</tr>
<tr>
<td></td>
<td>Oral$^c$</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas</em> spp.</td>
<td>$\leq 32$</td>
<td>$&gt;32$</td>
</tr>
<tr>
<td></td>
<td>Intravenous$^d$</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus</em> spp.</td>
<td>$\leq 32$</td>
<td>$&gt;32$</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>CLSI$^f$</td>
<td><em>E. coli</em></td>
<td>$\leq 64$</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td><em>E. faecalis</em></td>
<td>$\leq 64$</td>
<td>128</td>
</tr>
</tbody>
</table>

Ffalagas M et al. CMR 2016
CNS INFECTIONS
Penetration of fosfomycin into the parenchyma of human brain: a case study in three patients

- Plasma to brain distribution of fosfomycin
- 3 patients needed neurosurgical intensive care treatment
- Fosfomycin concentrations in brain interstitium measured by microdialysis brain catheters >> variable

Figure 1: Fosfomycin concentrations in plasma (▲) and brain tissue (▼) following i.v. bolus administration of 4 g fosfomycin to two neurosurgical patients. In the third patient fosfomycin could not be quantified. (The dotted line indicates estimated fosfomycin concentrations in a peripheral tissue based on data from Frossard et al. [5]).
Recruiting

Fosfomycin i.v. for Treatment of Severely Infected Patients

Conditions: Bacterial Infections; Bone Diseases, Infectious; Osteomyelitis; Central Nervous System Bacterial Infections; Meningitis, Bacterial; Encephalitis; Brain Abscess; Urinary Tract Infections; Respiratory Tract Infections; Pneumonia, Bacterial; Skin Diseases, Bacterial; Soft Tissue Infections; Intraabdominal Infections; Sepsis; Bacteremia; Endocarditis, Bacterial

Intervention:
整形外科領域における慢性肺感染症の例について、抗生
物質（カルシウム塩）を投与した。これらの症例の年齢、
性、疾患名は Table 2, 3 および 4 に示したとおりであ
る。また、本剤使用に先立って各患者からの承諾を得て
いる。

なお、本症例群は、すべて病巣から菌を検出したもの
であるが(Table 4, 5), これらが果して感染の原因菌で
あるとの証明はできなかった。また、以上の菌の各種抗生
物質に対する感受性は Table 6 に示したとおりである。

| Pseudomonas aeruginosa A-128 | 3.13 | 3.13 |
| Pseudomonas aeruginosa B-125 | 3.13 | 3.13 |

method: Agar plate method, 37°C, 20 hrs
medium: Nutrient agar (Difco)

<table>
<thead>
<tr>
<th>Table 2 Case (fosfomycin cap.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yrs.</td>
</tr>
<tr>
<td>0−9</td>
</tr>
<tr>
<td>10−19</td>
</tr>
</tbody>
</table>

Other questions?
FOS single drug regimen for cUTI and AP

- Information from press release by Zavante Therapeutics
- Fosfomycin met the primary endpoint of statistical non-inferiority to piperacillin/tazobactam in the pivotal ZEUS™ clinical trial in patients with complicated urinary tract infections (cUTI), including acute pyelonephritis
- 465 patients randomized
  - 6 grams ZOL YD as a one-hour intravenous infusion / 8h (18 grams daily)
  - 4.5 grams IV piperacillin/tazobactam as a one-hour IV infusion three times daily 7 days (14 if bacteremia)
- No oral relay
- Overall success rate: 64.7% (119/184 patients) vs 54.5% (97/178 patients)
- Non inferiority demonstrated
Oral fosfomycin and UTI
Is Fosfomycin a Potential Treatment Alternative for Multidrug-Resistant Gram-Negative Prostatitis?

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**Background.** Multidrug-resistant gram-negative bacterial (MDR-GNB) infections of the prostate are an increasing problem worldwide, particularly complicating transrectal ultrasound (TRUS)-guided prostate biopsy. Fluoroquinolone-based regimens, once the mainstay of many protocols, are increasingly ineffective. Fosfomycin has reasonable in vitro and urinary activity (minimum inhibitory concentration breakpoint ≤64 μg/mL) against MDR-GNB, but its prostatic penetration has been uncertain, so it has not been widely recommended for the prophylaxis or treatment of MDR-GNB prostatitis.

**Methods.** In a prospective study of healthy men undergoing a transurethral resection of the prostate for benign prostatic hyperplasia, we assessed serum, urine, and prostatic tissue (transition zone [TZ] and peripheral zone [PZ]) fosfomycin concentrations using liquid chromatography–tandem mass spectrometry, following a single 3-g oral fosfomycin dose within 17 hours of surgery.

**Results.** Among the 26 participants, mean plasma and urinary fosfomycin levels were 11.4 ± 7.6 μg/mL and 571 ± 418 μg/mL, 565 ± 149 minutes and 581 ± 150 minutes postdose, respectively. Mean overall prostate fosfomycin levels were 6.5 ± 4.9 μg/g (range, 0.7–22.1 μg/g), with therapeutic concentrations detectable up to 17 hours following the dose. The mean prostate to plasma ratio was 0.67 ± 0.57. Mean concentrations within the TZ vs PZ prostate regions varied significantly (TZ, 8.3 ± 6.6 vs PZ, 4.4 ± 4.1 μg/g; P=.001). Only 1 patient had a mean prostatic fosfomycin concentration of <1 μg/g, whereas the majority (70%) had concentrations ≥4 μg/g.

**Conclusions.** Fosfomycin appears to achieve reasonable intraprostatic concentrations in uninfamed prostate following a single 3-g oral dose, such that it may be a potential option for prophylaxis pre–TRUS prostate biopsy and possibly for the treatment of MDR-GNB prostatitis. Formal clinical studies are now required.

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**Figure 1.** Mean fosfomycin prostate concentrations by time after single oral 3-g dose.
Fosfomycin for Treatment of Prostatitis: New Tricks for Old Dogs

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(See the Editorial Commentary by Falagas and Rafailidis on pages 1144–6.)

Treatment options for prostatitis caused by multidrug-resistant gram-negative bacilli are limited. We report two cases cured with oral fosfomycin and provide a pharmacokinetic analysis of fosfomycin predose concentrations during treatment.
Efficacy and Safety of Oral Fosfomycin for Urinary Tract Infections in Hospitalized Patients


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Optimizing intravenous fosfomycin dosing in combination with carbapenems for treatment of *Pseudomonas aeruginosa* infections in critically ill patients based on pharmacokinetic/pharmacodynamic (PK/PD) simulation

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**ABSTRACT**

**Objective:** The purpose of the study was to determine the optimal dosing regimen of intravenous fosfomycin for the treatment of *Pseudomonas aeruginosa* (PA) based on PK/PD targets.

**Method:** A total of 120 PA isolates were recovered from various clinical specimens at university hospital in Thailand. Minimum Inhibitory Concentrations (MICs) of all the isolates were determined by the E-test method. PK parameters were obtained from a published study. Monte Carlo simulation was performed to calculate the percentage of target attainment (PTA) and cumulative fraction of response (CFR).

**Results:** MIC\textsubscript{90} of fosfomycin alone, fosfomycin in combination with carbapenem, carbapenems alone and carbapenems in combination with fosfomycin were >1,024, 1,024, >32 and 32 μg/ml, for multidrug resistant (MDR)-PA and 512, 128, 8 and 3 μg/ml respectively, for non-MDR PA. Approximately 40\% of the non-MDR PA were carbapenem-resistant strains. For non-MDR PA with CRPA, fosfomycin 16 g continuous infusion in combination with carbapenems provided %PTA of approximately 80 and %CFR of > 88. While, %PTA and %CFR > 90 were achieved with fosfomycin 24 g/day prolonged infusion in combination with carbapenem.

**Conclusions:** Prolonged infusion of fosfomycin 16 - 24 g combined with extended carbapenem infusion could be used in non-MDR PA treatment with CRPA.
Figure 2. The probability of target attainment (%PTA) of fosfomycin monotherapy achieve more than 70% time above MIC.
%CFR of fosfomycin (FOF) - carbapenems combination regimens ((doripenem (DOM), imipenem (IPM), meropenem (MEM)) of non-MDR PA.

<table>
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<th>IPM 1 g q 8 h</th>
<th>IPM 1 g in 3 h q 8 h</th>
<th>DOM 1 g q 8 h</th>
<th>DOM 1 g in 4 h q 8 h</th>
<th>MEM 1 g q 8 h</th>
<th>MEM 1 g in 3 h q 8 h</th>
<th>MEM 2 g q 8 h</th>
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*The CFR ≥ 90% was considered optimal against a bacterial population, whereas a CFR between 80% and 90% was associated with moderate probabilities of success.