İntravenöz fosfomisin

Ne zaman ?

Doç.Dr.Serhat Birengel

AÜTF Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

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03125082681, 05326342950

Sunu planı

- Fosfomisin
  - Nedir?
  - Farmasötik formları
  - Etki mekanizması
  - Etki spektrumu
  - Klinik kullanım
- Farmakokinetik/farmakodinamik
- İv. fosfomisin ne zaman ? *Nasıl?*

Fosfomisin (FOS)

Fosfoenolpürivat (PEP) analoğu

(Fosfonik asid derivesi)

1969

Streptomyces fradiae

Fosfonomisin

Hendlin D. Science 1969; 166:122–123.
Schito GC. Int J Antimicrob Agents 2003; 22(Suppl 2): 79-83.

Mevcut kullanım

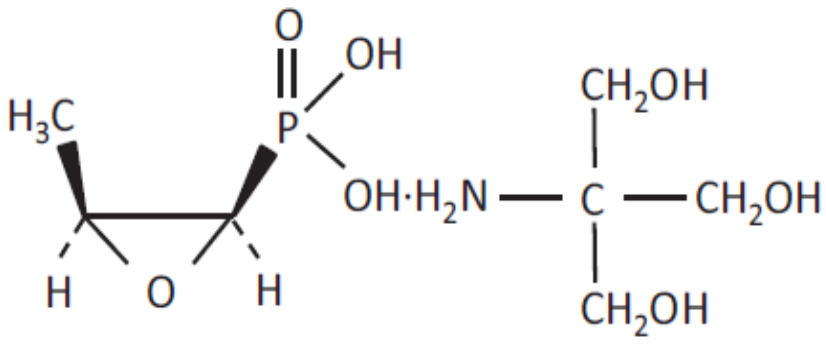
Peroral tek doz

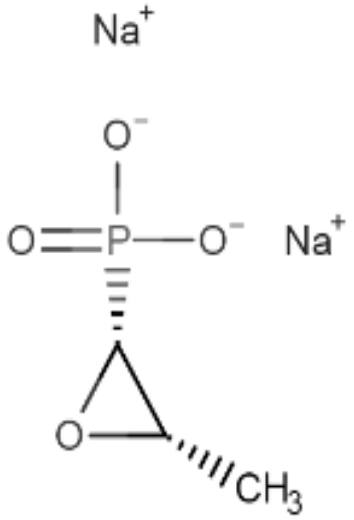
1. Komplike idrar yolu enfeksiyonları (İYE)
2. Komplike olmamış *Escherichia coli* İYE
3. Komplike olmamış enterokokkal İYE

Doz:

- İYE → 3g/gün
- Komplike İYE → 3 gün arayla 3 defa 3g/gün
- Prostatit → 3 gün arayla 7 defa 3g/gün

Farmasötik

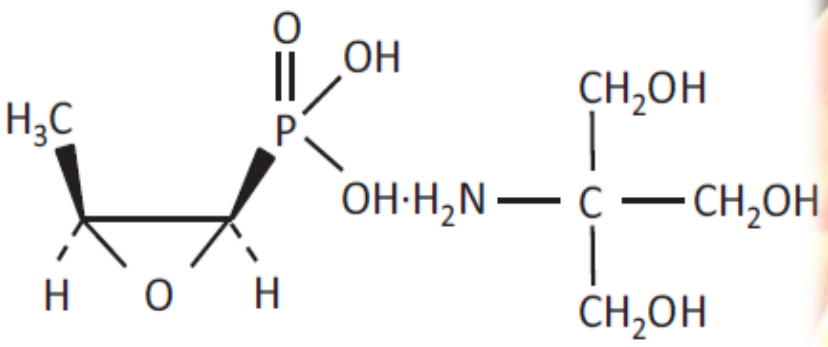


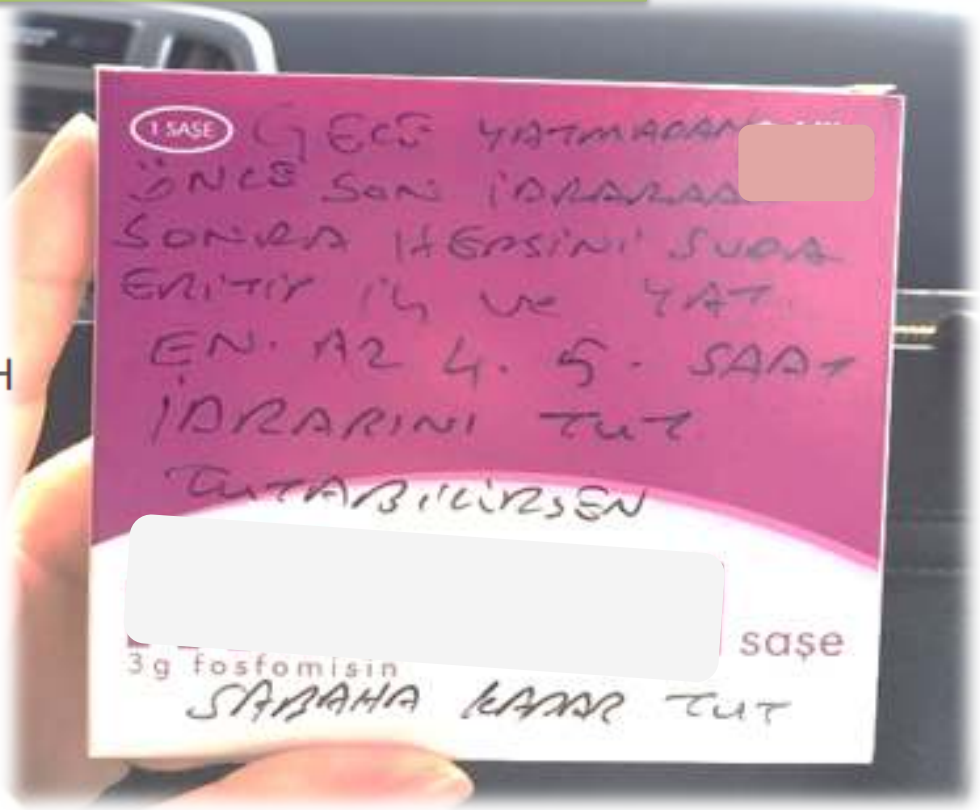


Oral form (şase, toz, kapsül)
FOS trometamin

Parenteral formlar (iv, im)
FOS disodyum

Farmasötik

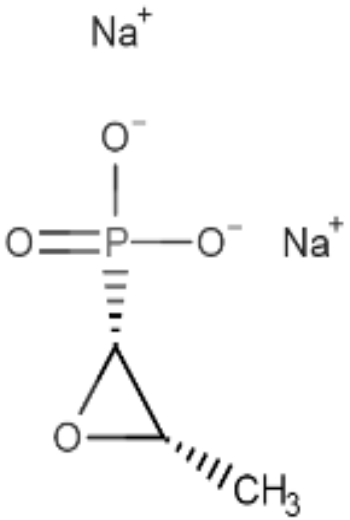




Oral form (şase)
FOS trometamin

İdrar yolu enfeksiyonları

Farmasötik



Fosfocina®
Intramuscular 1g
Fosfomicina

Fosfocina®
Intravenosa 1g
Fosfomicina

Parenteral formlar (iv, im)
Fosfomisin disodyum

?

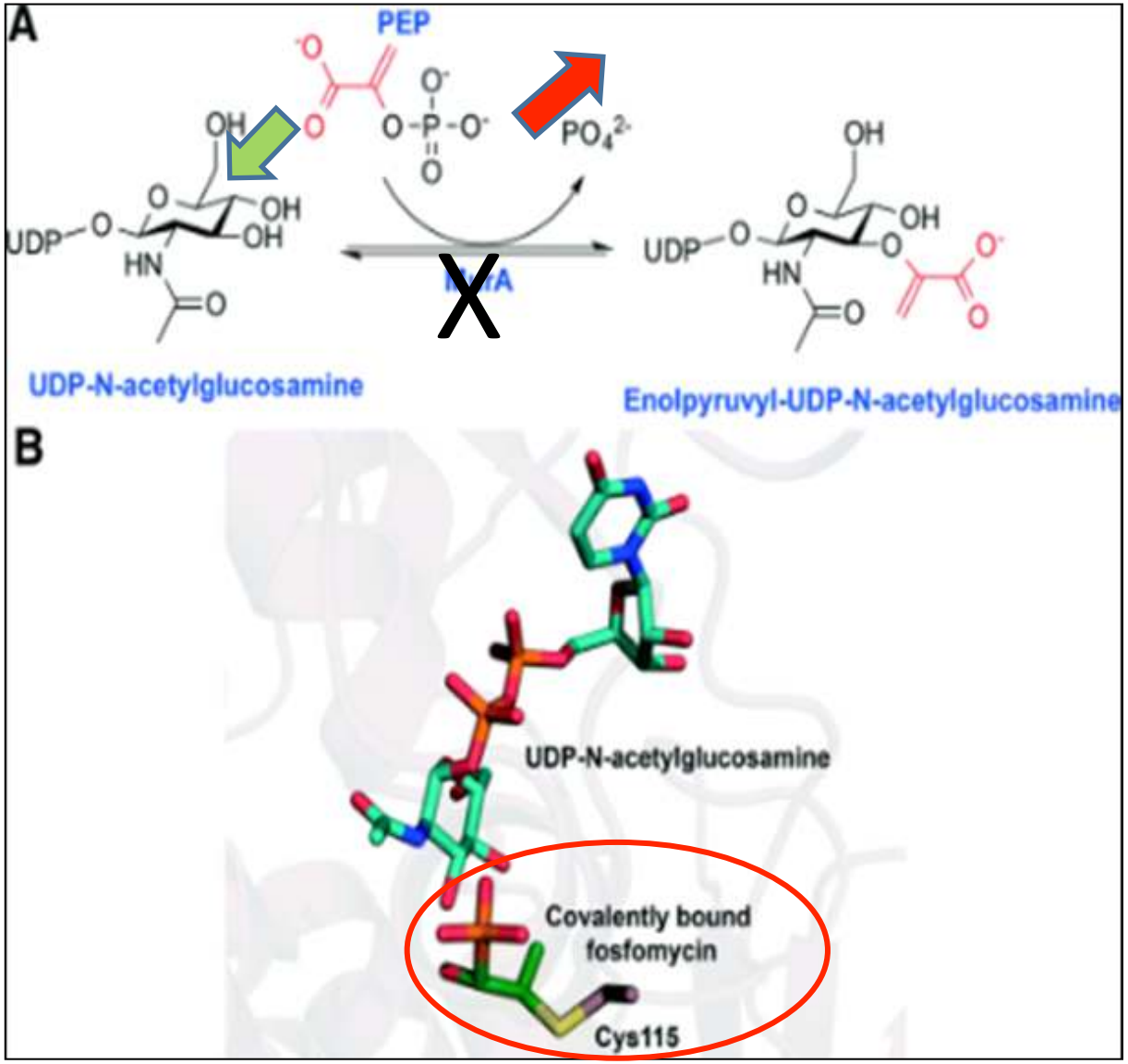
Etki mekanizması

115. sistein kalıntısına **irrevesibl** bağlanma

MurA (UDP-NAG enol piruvil transferaz)

Peptidoglikan sentezi engellenir

Bakteri ozmotik olarak parçalanır



Etki spektrumu

Gram negatifler

- E.coli (GSBL ±)
- K.pneumoniae (KPC ±)
- Enterobacter türleri
- Serratia
- Citrobacter
- Providencia
- Proteus ,…

Gram pozitifler

- MSSA, MRSA
- KNS türleri (MS,MR)
- E.faecalis
- E.faecium (VRE ±)
- …

- Pseudomonas, Acinetobacter, Stenotrophomonas maltophilia, Burkholderia cepacia,
- Staphylococcus capitis, Staphylococcus saprophyticus,
- B.fragilis dirençlidir

- İYE etkeni GSBL ± E.coli

  FOS duyarlılığı ➔ %86-100, %96-100.

- K.pneumoniae iyi etki ➔ %70-85 duyarlılık

  KPC (+) enf.da ➔ potansiyel kullanım

Sastry S. J Infect Chemother. 2016.
Saltoglu N,. Int J Clin Pract 2015;69:766-70.
Demir T. Int J Infect Dis 2013
Keating GM. Drugs 2013
Neuner EA, Antimicrob Agents Chemother 2012

INVITED ARTICLE REVIEWS OF ANTI-INFECTIVE AGENTS
Louis D. Saravolatz, Section Editor

Fosfomycin: Use Beyond Urinary Tract and Gastrointestinal Infections

Matthew E. Falagas,[1,2] Konstantina P. Giannopoulou,[1] George N. Kokolakis,[1] and Petros I. Rafailidis[1]
[1]Alfa Institute of Biomedical Sciences, Athens, Greece; and [2]Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts

The shortage of new antimicrobial agents has made the scientific community reconsider the potential value of old antibiotics. A search of the literature was performed to compile relevant evidence regarding the effectiveness and safety of fosfomycin for the treatment of patients with gram-positive and/or gram-negative bacterial infections (excluding urinary tract infection and gastrointestinal infection). Of 1311 potentially relevant studies, 62 studies were reviewed in detail. Of 1604 patients with various gram-positive and gram-negative infections of various body sites (including pneumonia and other respiratory infections; osteomyelitis; meningitis; ear, nose, and throat infections; surgical infections; obstetric and gynecological infections; arthritis; septicemia; peritonitis; cervical lymphadenitis; eye infections; diabetic foot infections; and typhoid fever) being treated with fosfomycin alone or in combination with other antibiotics, cure was achieved in 1302 (81.1%) of the patients, and improvement was noted in 47 (2.9%). In comparative perioperative prophylaxis trials that included a total of 1212 patients (mainly patients undergoing colorectal surgery), the fosfomycin-metronidazole combination led to results that were similar to those achieved with the combination of other antibiotics (doxycycline, ampicillin, or cephalothin) and metronidazole.

Parenteral FOS değişik kullanım alanları:

1971-2007 arası yayınlar analiz edilmiş

- Pnömoni, kistik fibrozis vd. alt solunum yolu enfeksiyonları
- Menenjit , sepsis, osteomiyelit, cerrahi alan enfeksiyonları, diyabetik ayak enfeksiyonları, peritonit, tifo
- Obstetrik jinekolojik enfeksiyonları
- Kulak burun boğaz enfeksiyonları, göz enfeksiyonları
- Artrit, servikal lenfadenit

%81 kür

Falagas ME. Clin Infect Dis. 2008

Susceptibility of contemporary isolates to fosfomycin: a systematic review of the literature

Konstantinos Z. Vardakas, Nikolaos J. Legakis, Nikolaos Triarides, Matthew E. Falagas

Abstract

The aim of this review was to evaluate the susceptibility of contemporary Gram-positive and Gram-negative bacteria to fosfomycin. PubMed and Scopus databases were systematically searched to identify studies published in print or electronically from January 2010 until June 2015. In total, 84 studies were selected. Susceptibility to fosfomycin of *Staphylococcus aureus* ranged between 33.2% and 100% (frequency = 91.7%, 95% confidence interval 88.7–94.9%), of *Enterococcus* spp. from 30% to 100% (*Enterococcus faecium* 92.6%, 85.2–100%; *Enterococcus faecalis* 96.8%, 92.5–100%), of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* from 81% to 100% (95.1%, 94.3–95.9%), of ESBL-producing *Klebsiella pneumoniae* from 15% to 100% (83.8%, 78.7–89.4%) and of carbapenem-resistant (CR) *K. pneumoniae* from 39.2% to 100% (73.5%, 66.4–81.4%). *Staphylococcus aureus* (including meticillin-resistant strains) and *E. coli* (including ESBL-producing strains) were the most likely to be susceptible with low minimum inhibitory concentrations (MICs). Enterococci (particularly vancomycin-resistant *E. faecium*) and *K. pneumoniae* (especially CR strains) were less susceptible with higher MIC_{50} and MIC_{90} values. Two studies reported decreasing susceptibility of ESBL-producing *E. coli* to fosfomycin. In conclusion, guided by local susceptibility data, fosfomycin could be considered for the treatment of patients with infections due to problematic multidrug-resistant bacteria.

2010-2015 arası 84 çalışma derlenmiş,

FOS duyarlılığı :

- **En sık GSBL ± E.coli ve MR ± S.aureus**
- **En az enterokoklar** (özellikle VRE) ve **K.pneumoniae** (öz. KPC üreten)

Vardakas KZ. Int J Antimicrob Agents. 2016

In Vitro Activity of Fosfomycin against *bla*$_{KPC}$-Containing *Klebsiella pneumoniae* Isolates, Including Those Nonsusceptible to Tigecycline and/or Colistin$^{\nabla}$

Andrea Endimiani,[1,2]* Gopi Patel,[3] Kristine M. Hujer,[1,2] Mahesh Swaminathan,[3] Federico Perez,[1,2] Louis B. Rice,[2] Michael R. Jacobs,[4] and Robert A. Bonomo[1,2,5,6]*

Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio[1]; Research Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio[2]; Department of Medicine, Mount Sinai School of Medicine, New York, New York[3]; Department of Pathology, Case Western Reserve University School of Medicine, Cleveland, Ohio[4]; Department of Pharmacology, Case Western Reserve University School of Medicine, Cleveland, Ohio[5]; and Department of Molecular Biology and Microbiology, Case Western Reserve University School of Medicine, Cleveland, Ohio[6]

Received 31 August 2009/Returned for modification 24 October 2009/Accepted 31 October 2009

***In vitro* activity of fosfomycin was evaluated against 68 *bla*$_{KPC}$-possessing *Klebsiella pneumoniae* (KpKPC) isolates, including 23 tigecycline- and/or colistin-nonsusceptible strains. By agar dilution, 93% of the overall KpKPC were susceptible (MIC$_{50/90}$ of 16/64 μg/ml, respectively). The subgroup of 23 tigecycline- and/or colistin-nonsusceptible strains showed susceptibility rates of 87% (MIC$_{50/90}$ of 32/128 μg/ml, respectively). Notably, 5 out of 6 extremely drug-resistant (tigecycline and colistin nonsusceptible) KpKPC were susceptible to fosfomycin. Compared to agar dilution, disk diffusion was more accurate than Etest.**

23 <u>Tigesiklin ve Kolistine dirençli KPC (+)</u> K.pneumoniae

FOS duyarlılığı

- MIC 16/64 mg/L suşlarda ➔ **%93**
- MIC 32/128 mg/L suşlarda ➔ **%87**

FOS kurtarma tedavisi ajanı olabileceği vurgulanmış.

Endimiani AAntimicrob Agents Chemother 2010;54:526-9.

Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum β-lactamase producing, Enterobacteriaceae infections: a systematic review

Matthew E Falagas, Antonia C Kastoris, Anastasios M Kapaskelis, Drosos E Karageorgopoulos

Rising rates of resistance to antimicrobial drugs among Enterobacteriaceae limit the choice of reliably active forms of these drugs. We evaluated the evidence on fosfomycin as a treatment option for infections caused by members of the family Enterobacteriaceae with advanced resistance to antimicrobial drugs, including producers of extended-spectrum β-lactamase (ESBL). We systematically reviewed studies evaluating the antimicrobial activity, or the clinical effectiveness of fosfomycin. 17 antimicrobial-susceptibility studies were found and included in our Review, accounting for 5057 clinical isolates of Enterobacteriaceae with advanced resistance to antimicrobial drugs (4448 were producers of ESBL); 11 of the 17 studies reported that at least 90% of the isolates were susceptible to fosfomycin. Using a provisional minimum inhibitory concentration susceptibility breakpoint of 64 mg/L or less, 1604 (96·8%) of 1657 *Escherichia coli* isolates producing ESBL were susceptible to fosfomycin. Similarly, 608 (81·3%) of 748 *Klebsiella pneumoniae* isolates producing ESBL were susceptible to fosfomycin. In two clinical studies, oral treatment with fosfomycin–trometamol was clinically effective against complicated or uncomplicated lower urinary tract infections caused by ESBL-producing *E coli* in, cumulatively, 75 (93·8%) of the 80 patients evaluated. Initial clinical data support the use of fosfomycin for the treatment of urinary tract infections caused by these pathogens, although further research is needed.

Lancet Infect Dis 2010; 10: 43–50

Alfa Institute of Biomedical Sciences, Athens, Greece (M E Falagas DSc, A C Kastoris MD, A M Kapaskelis MD, D E Karageorgopoulos MD); Department of Medicine, Henry Dunant Hospital, Athens, Greece (M E Falagas, A M Kapaskelis); and Department of Medicine, Tufts University School of Medicine, Boston, MA, USA (M E Falagas)

Correspondence to:

GSBL+ E.coli ve K.pneumoniae'nın da dahil olduğu,

- **İdrar yolu ve idrar dışı izolatlar çoklu ilaç direnci** (ÇİD) olan enterobakteriyase
- Fosfomisin duyarlılığı **>%90**;
- MIC değerleri ≤64 mg/ml olan üriner izolatlarda duyarlılık sırasıyla % 90 ve 81 bulunmuş.

Falagas ME, Lancet Infect Dis 2010

Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria

Konstantinos Pontikis, Ilias Karaiskos, Styliani Bastani, George Dimopoulos, Michalis Kalogirou, Maria Katsiari, Angelos Oikonomou, Garyphallia Poulakou, Emmanuel Roilides, Helen Giamarellou

11 yoğun bakımdaki kritik hastalar

çok merkezli, prospektif, vaka serileri

ÇİD ve **tüm ilaçlara dirençli P.aeruginosa ve KPC+K.pneumoniae**

- **Bakteremi ve VAP**
- **FOS 24g**/gün, ort. 14 gün + **kolistin /tigesiklin**
  - 14. gün klinik iyileşme %54.2,
  - 28. gün mortalite %37.5
  - **%56.3 bakteriyel eradikasyon**

Pontikis K Int J Antimicrob Agents. 2014

Expert Opinion on Investigational Drugs

ISSN: 1354-3784 (Print) 1744-7658 (Online) Journal homepage: http://www.tandfonline.com/loi/ieid20

Fosfomycin for the treatment of infections caused by Gram-positive cocci with advanced antimicrobial drug resistance: a review of microbiological, animal and clinical studies

Matthew E Falagas MD MSc DSc, Nikos Roussos MD, Ioannis D Gkegkes MD, Petros I Rafailidis MD MRCP UK MSc & Drosos E Karageorgopoulos MD

- **MRSA , VRE ve PR S.pneumoniae** (22 çalışma)
  - **MRSA** FOS'e duyarlılık 12 çalışmada; **kümülatif %87.9**
  - **VRE %30.3**,
  - PRSP'de %87.2
- **MRSA → pnömoni, bakteremi ve menenjit →** kombine FOS kullanımında **klinik başarı → %96.6**

Falagas ME. Expert Opin Investig Drugs 2009

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Fosfomycin plus β-Lactams as Synergistic Bactericidal Combinations for Experimental Endocarditis Due to Methicillin-Resistant and Glycopeptide-Intermediate *Staphylococcus aureus*

A. del Río,[a] C. García-de-la-Mària,[a] J. M. Entenza,[b] O. Gasch,[c] Y. Armero,[a] D. Soy,[e] C. A. Mestres,[f] J. M. Pericás,[a] C. Falces,[f] S. Ninot,[f] M. Almela,[d] C. Cervera,[a] J. M. Gatell,[a] A. Moreno,[a] P. Moreillon,[b] F. Marco,[d] J. M. Miró,[a] the Hospital Clinic Experimental Endocarditis Study Group

MRSA / GISA deneysel endokardit, invitro-invivo

FOS (3x2g)+ İmipenem(4x1g) ✓

Vs. Vankomisin 2x1g veya 4x1g

FOS (3x2g)+ **Seftriakson (2x2g)** ✓

del Río A, Antimicrob Agents Chemother. 2015

Journal of Antimicrobial Chemotherapy (2009) **64**, 574–578
doi:10.1093/jac/dkp230
Advance Access publication 3 July 2009

JAC

High fosfomycin concentrations in bone and peripheral soft tissue in diabetic patients presenting with bacterial foot infection

Michael V. Schintler[1]†, Friederike Traunmüller[1,2]†, Julia Metzler[1], Gerhard Kreuzwirt[1], Stephan Spendel[1], Oliver Mauric[2], Martin Popovic[2,3], Erwin Scharnagl[1] and Christian Joukhadar[1,2,4,5]*

MRSA'nın ciddi diyabetik ayak

FOS kemik dokuya penetrasyonu

Osteomiyelitli ve diyabetik ayaklı hastalarda metatarsal kemik ölçümleri

100mg/kg vücut ağırlığı dozunda iv. ➔ Cmax:96.4mg/L, Tmax: 3.9 saat ve 0-6 saat AUC değeri 330 mg.saat/L

FOS kemik matriksi tutan derin diyabetik ayak eneksiyonlarında etkili

Schintler MV. J Antimicrob Chemother. 2009

Fosfomisin

İdrar yolu enfeksiyonu dışında kullanım ?

Bakterisidal ✓

Mevcut ilacın yeni kullanım alanı

Antibiyotik için uygun doz seçimi ?

Farmakokinetik/Farmakodinamik (FK/FD)

FK/FD

FK ***Vücudun ilaca ne yaptığı***	**FD** ***İlacın vücutta ne yaptığı***
• Emilim • Metabolizma • Dağılım • Eliminasyon	• Zamana bağlı bakterisidal etkinlik • Konsantrasyona bağlı bakterisidal etkinlik • Konsantrasyondan bağımsız post –antibiyotik etki

Bakteri üremesinin önlenmesi

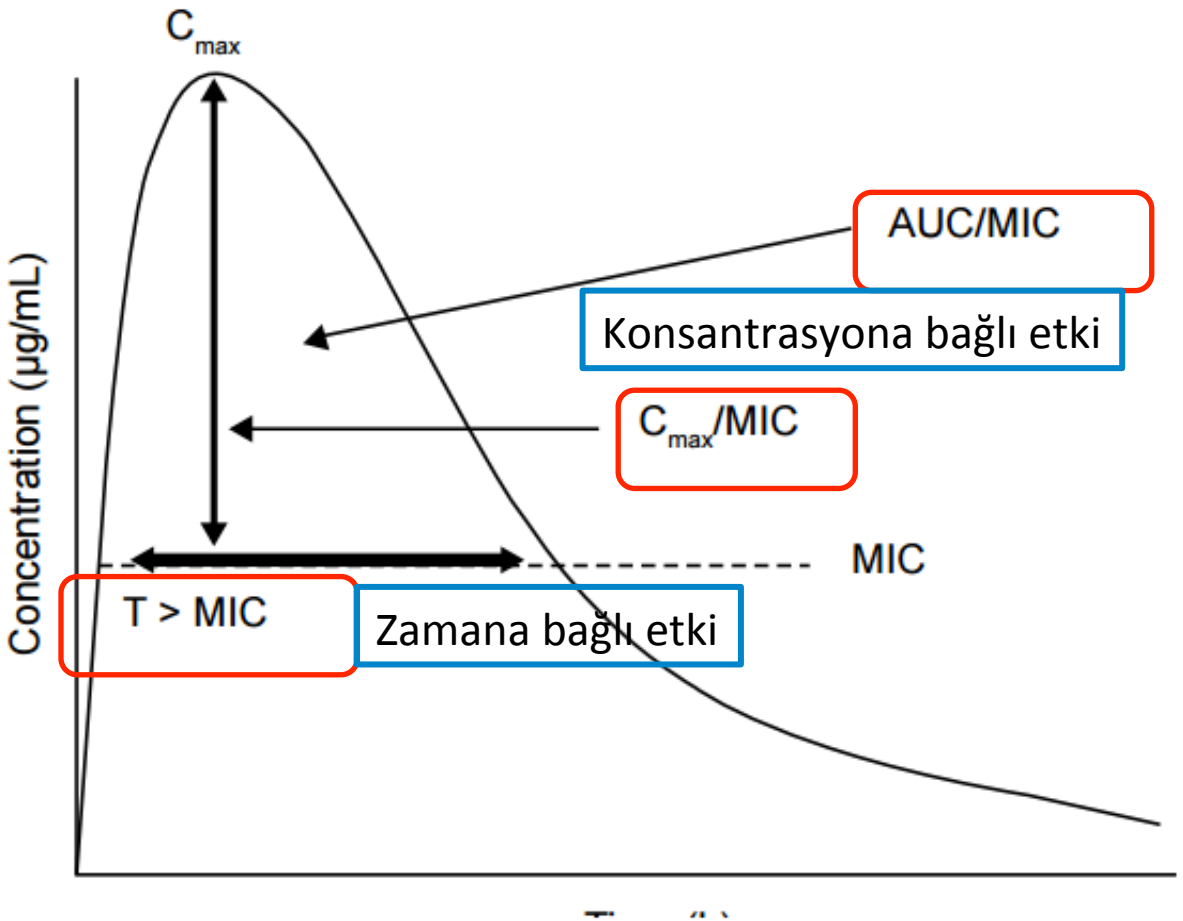


Figure 1: Pharmacokinetic / pharmacodynamic indices that describe antimicrobial effects. Cmax = maximum concentration; AUC/MIC = area under the curve / minimum inhibitory concentration; T>MIC = time above the MIC.

Connors KP. J Infect Chemoter. 2015

FOS FK/FD

Antimikrobiyal etkinliği en iyi predikte eden parametre serbest ilacın AUC_{0-24}/MIC değeridir.

FOS zamana bağlı bakterisidal etki (*f* T>MIC) ✓

- E.coli ve P.mirabilis için doza bağlıdır (İYE tek doz!)
  - **Uzamış postantibiyotik etki ➔ 3.4 ve 4.7 saat**

http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_7.1_Breakpoint_Tables.pdf (ET: 15.03.2017)

FK/FD

FK ***Vücudun ilaca ne yaptığı***	**FD** ***İlacın vücutta ne yaptığı***
• Emilim • Metabolizma • Dağılım • Eliminasyon	• **Zamana bağlı bakterisidal etkinlik** • Konsantrasyona bağlı bakterisidal etkinlik • **Konsantrasyondan bağımsız post –antibiyotik etki**

EUCAST
EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Clinical breakpoints

- Organization
- EUCAST News
- Clinical breakpoints
  - About "Clinical breakpoints".
  - Splitting MIC wild type distributions
  - When there are no breakpoints?
  - Where clinical data is lacking!
  - EUCAST setting breakpoints.
- Expert rules and intrinsic resistance
- Resistance mechanisms

Clinical breakpoints

See → information on Clinical breakpoint tables.

Breakpoint table for bacteria

Clinical breakpoints - bacteria (v 7.1) - pdf file for Printing (Update 2017-03-13)
Clinical breakpoints - bacteria (v 7.1) - excel file for screen (Update 2017-03-13)

Note: To utilize all functions in the Excel® file, use Microsoft™ original programs only.

Changes in EUCAST Breakpoint Tables v 7.1, 10 March 2017 marked in light blue. All previous Changes (between versions 6.0 and 7.0) are still marked in pale yellow).

http://www.eucast.org/clinical_breakpoints/ ET: 15.03.2017

MIC kırılma noktaları

Enterobakteriyase ve *stafilokoklar için*

- **≤32 mg/L → Duyarlı**
- **>32 mg/L. → Dirençli**

T>MIC (etkenden bağımsız)

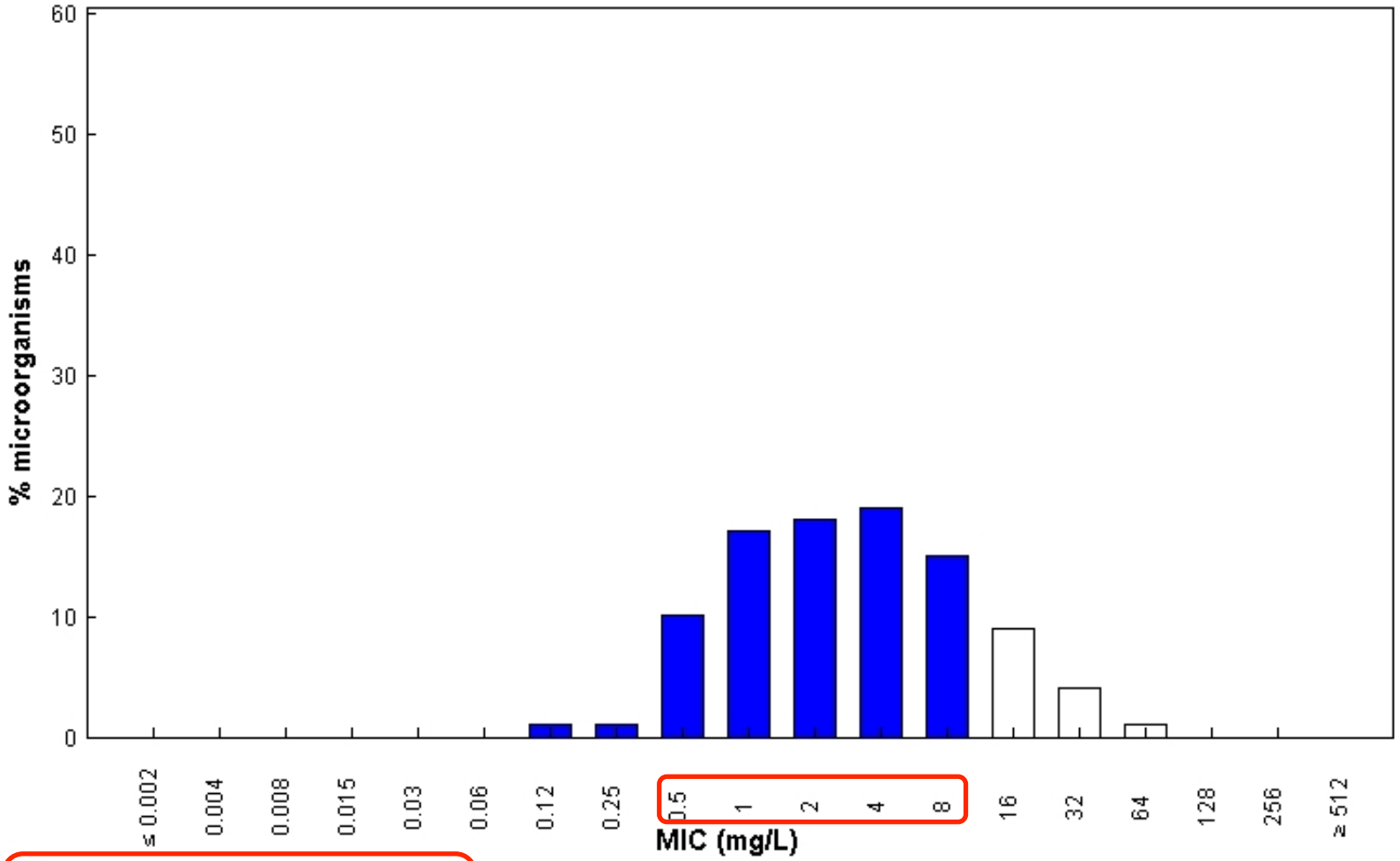
- **MIC 8-16-32 mg/L** patojenler → **%98-92-61 duyarlılık**

http://www.eucast.org/clinical_breakpoints/ ET: 15.03.2017

Fosfomycin / Escherichia coli

International MIC Distribution - Reference Database 2017-03-31

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC
Epidemiological cut-off (ECOFF): 8 mg/L
Wildtype (WT) organisms: ≤ 8 mg/L

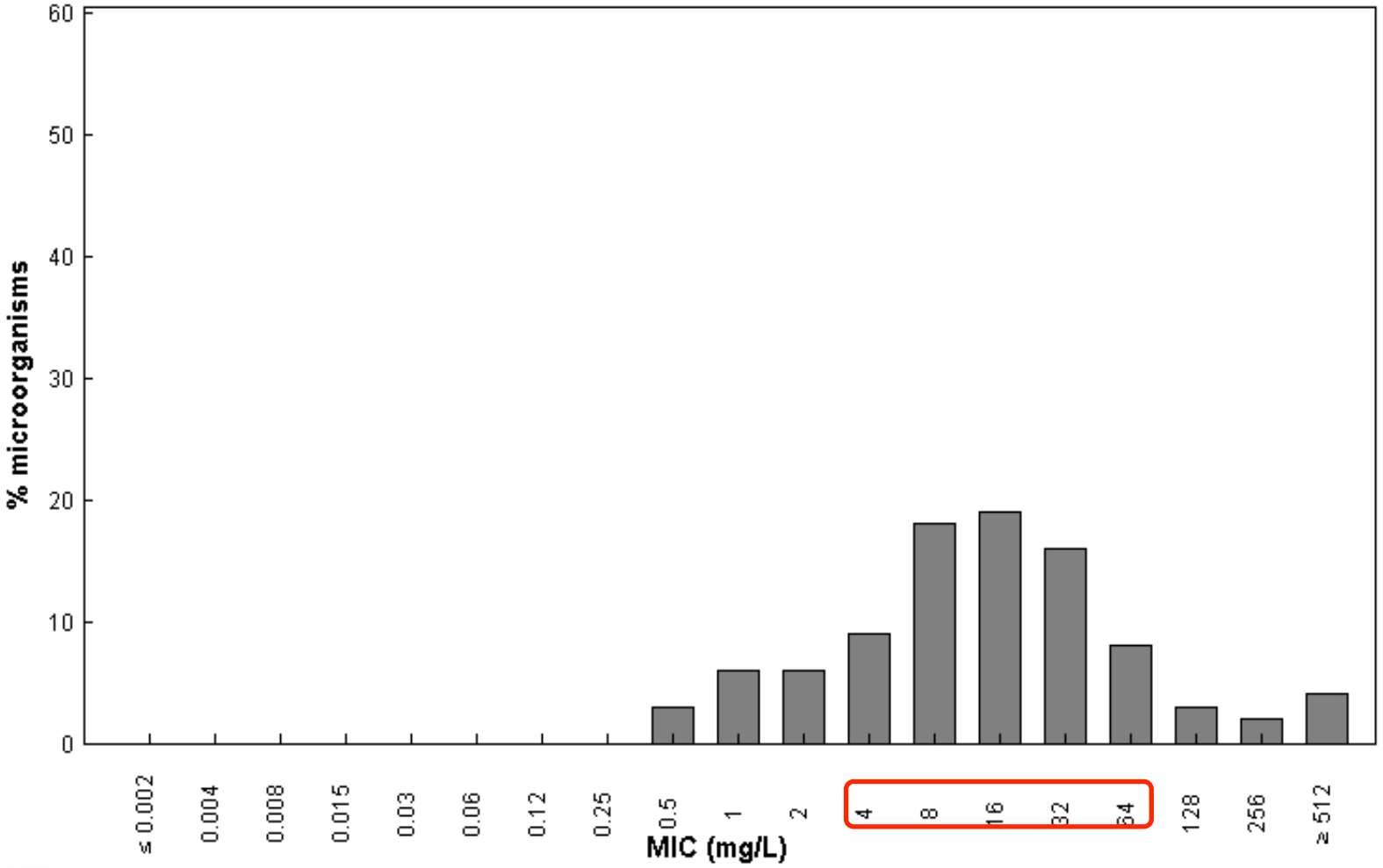
5117 observations (7 data sources)

https://mic.eucast.org/Eucast2/SearchController/regShowAll.jsp?Title=Fosfomycin#histogram_data ET: 31.03.2017

Fosfomycin / Klebsiella spp

International MIC Distribution - Reference Database 2017-03-31

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC

Epidemiological cut-off (ECOFF): -

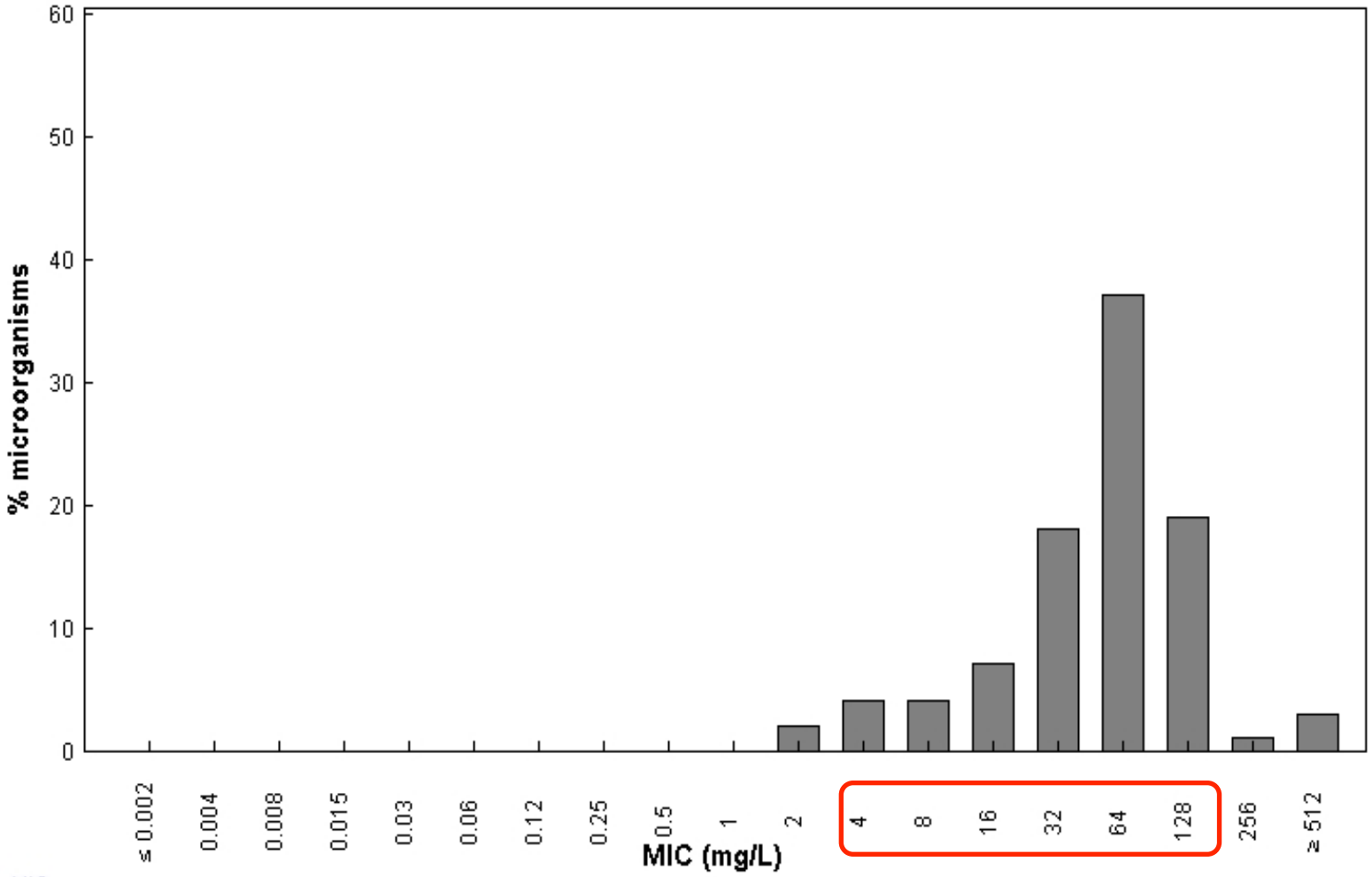
Wildtype (WT) organisms:

758 observations (7 data sources)

Fosfomycin / Pseudomonas aeruginosa

International MIC Distribution - Reference Database 2017-03-31

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC

Epidemiological cut-off (ECOFF): -

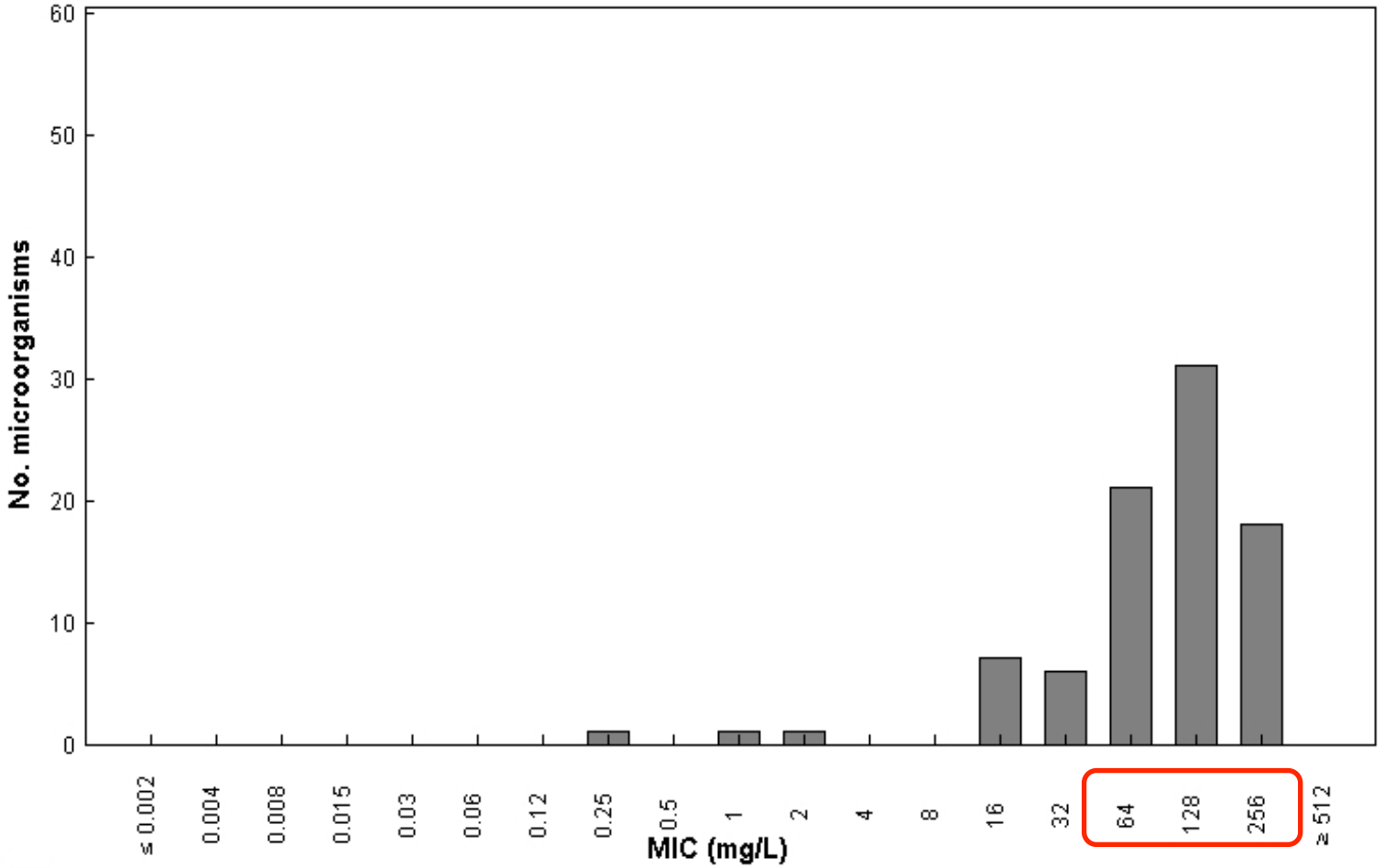
Wildtype (WT) organisms:

1250 observations (5 data sources)

Fosfomycin / Acinetobacter spp

International MIC Distribution - Reference Database 2017-03-31

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



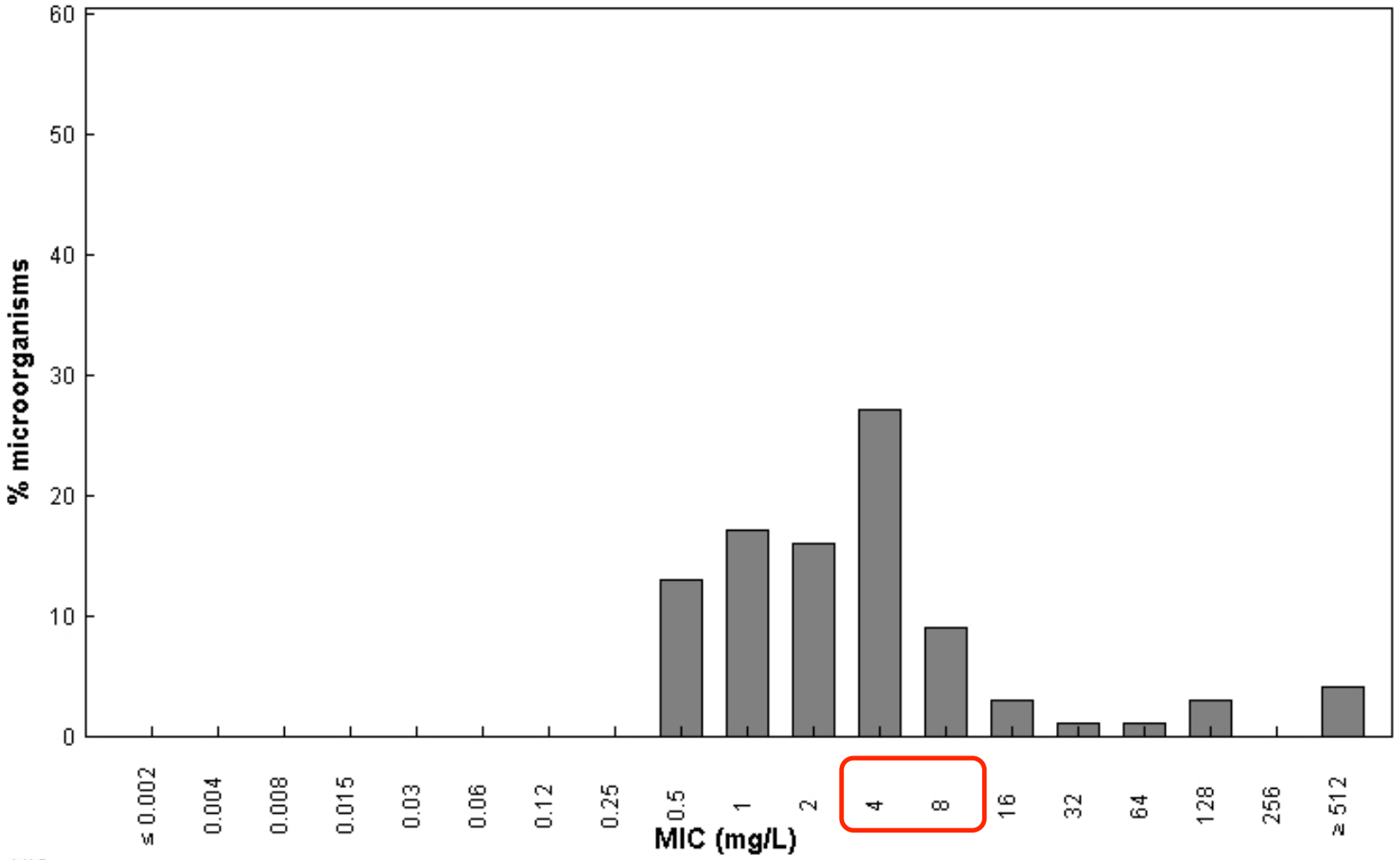
MIC
Epidemiological cut-off (ECOFF): -
Wildtype (WT) organisms:

86 observations (3 data sources)

Fosfomycin / Staphylococcus aureus MRSA

International MIC Distribution - Reference Database 2017-03-31

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

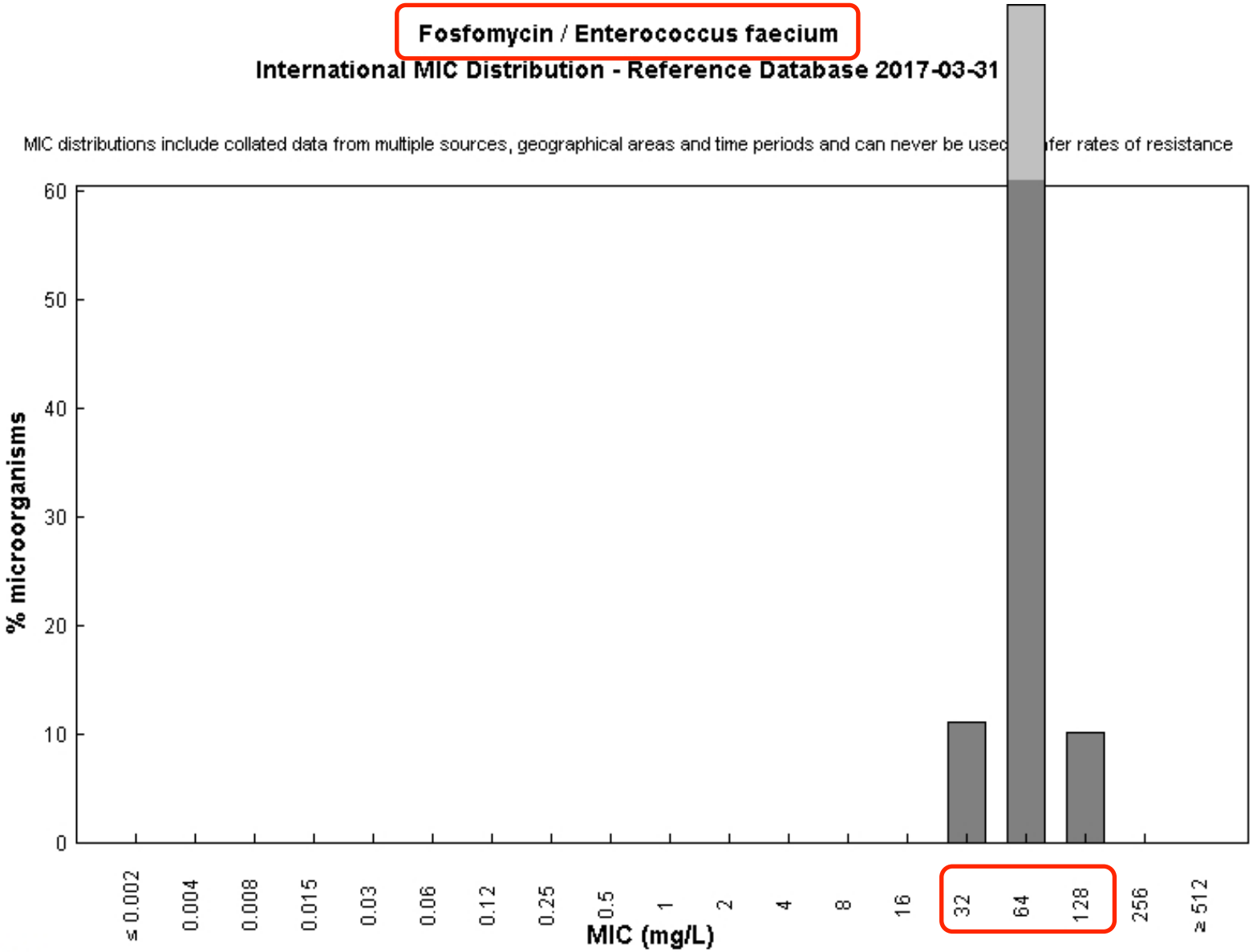


MIC

Epidemiological cut-off (ECOFF): -

Wildtype (WT) organisms:

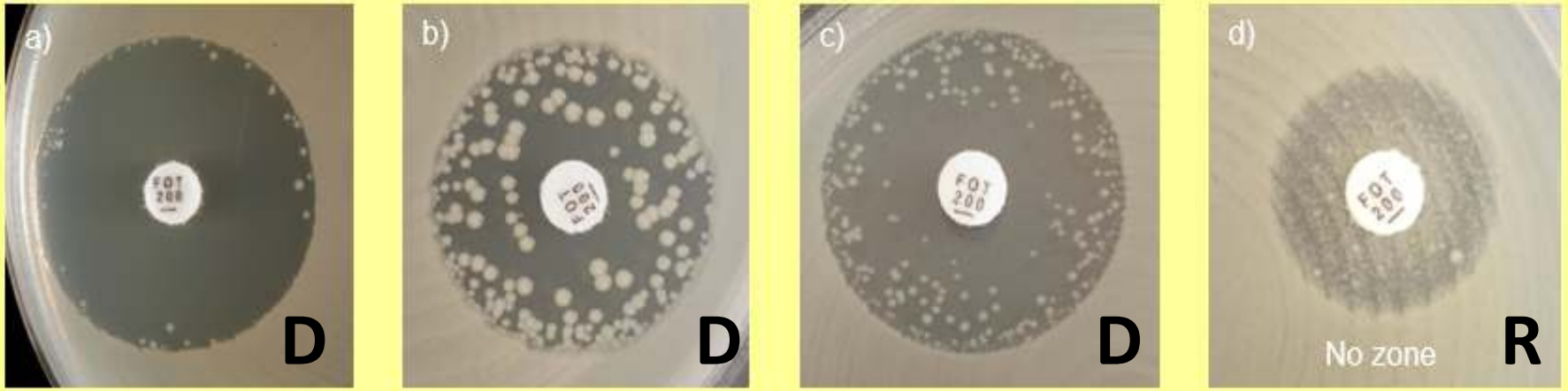
162 observations


Fosfomycin / Enterococcus faecium
International MIC Distribution - Reference Database 2017-03-31
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used
fer rates of resistance
% microorganisms
60
50
40
30
20
10
0
≤ 0.002
0.004
0.008
0.015
0.03
0.06
0.12
0.25
0.5
1
2
4
8
16
32
64
128
256
≥ 512
MIC (mg/L)
MIC
Epidemiological cut-off (ECOFF): -
Wildtype (WT) organisms:
483 observations

Disk diffüzyon değerlendirme

≤ 23mm → D

> 24 mm → R



Examples of inhibition zones for *Escherichia coli* with fosfomycin.

a-c) Ignore all colonies and read the outer zone edge.
d) Record as no inhibition zone.

http://www.eucast.org/clinical_breakpoints/ ET: 15.03.2017

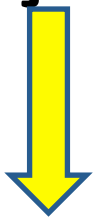
iv. FOS FK/FD

Dozaj	**4 g**
Biyoyararlanım (emilim)	
Cmax (mg/L)	**132**
Cmin (mg/L)	4.1
Total klirens (L/h)	
Ortalama yarı ömür (T $\frac{1}{2}$)	**2.25 (4-8) saat**
AUC24h (mg.h/L)	167.9-290.8
Serbest (proteine bağlanmamış) kısım	**>95%**
Dağılım hacmi (L/kg)	0.32-0.38
12. saatte idrarla >%85'i atılır.	

http://www.eucast.org/clinical_breakpoints/ ET: 15.03.2017

FOS FK/FD

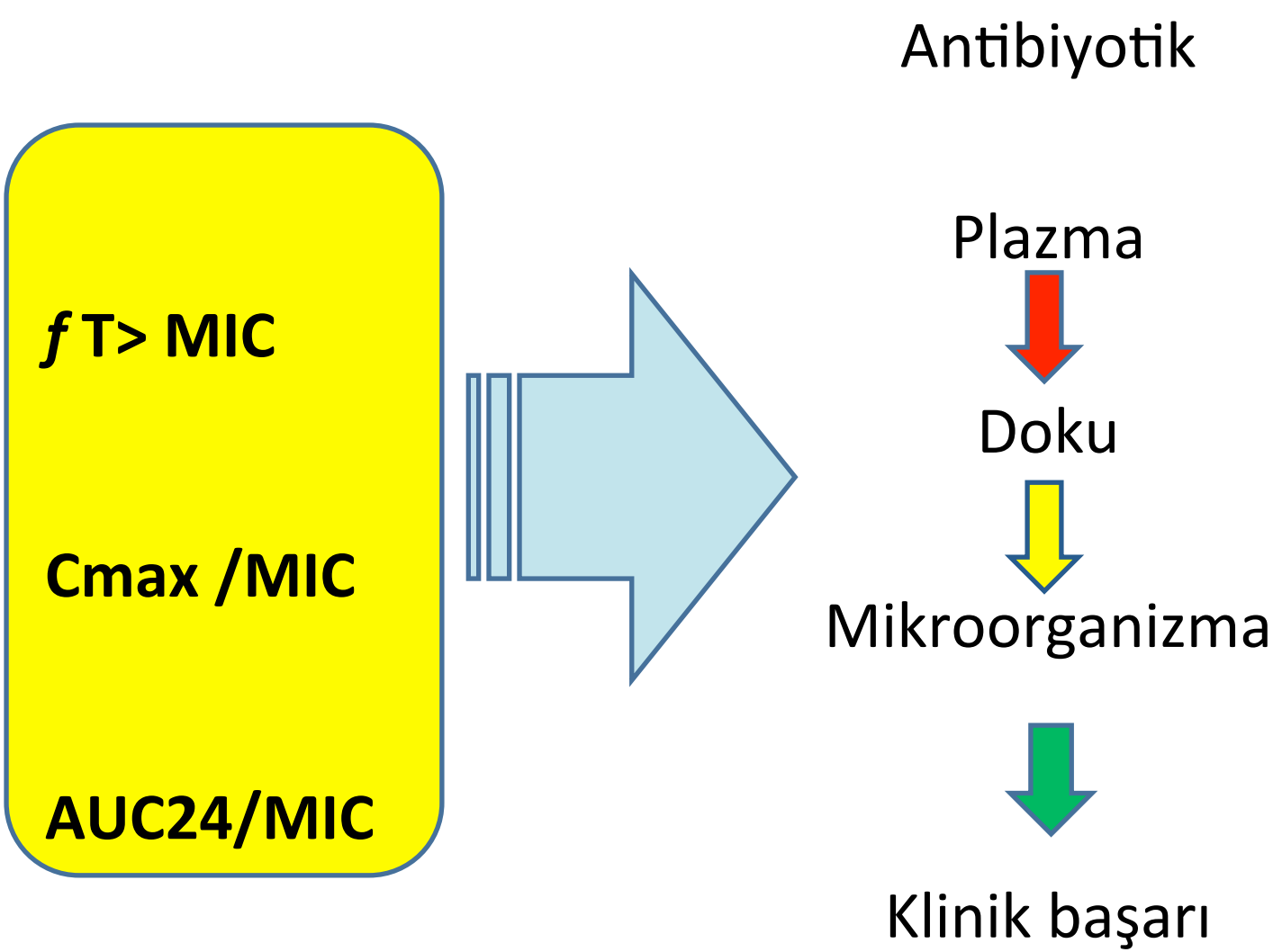
Pl.prot. düşük bağlanma



↑ Cmax, ↓ T ½

Kısa doz aralıkları

FOS FK/FD


Antibiyotik
ƒ T> MIC
Cmax /MIC
AUC24/MIC
Plazma
Doku
Mikroorganizma
Klinik başarı

- **Dokulara perfüzyonu iyi**
  - İnflame yumuşak dokuya, akuöz humor ve vireal dokuya penetrasyonu iyidir.
- **Beyin omurilik sıvısına (BOS) iyi penetre olur.**
  - 3x8 g iv FOS,
  - AUC >MIC plazma 929-280 mg saat/L,
  - BOS'ta 225-131 mg saat/L sağlar

Dosages

EUCAST Clinical Breakpoint Tables v. 7.1, valid from 2017-03-10

Tetracyclines	Standard dose	High dose
Doxycycline	0.1 g x 1 oral	0.2 g x 1 oral
Minocycline	0.1 g x 2 oral	None
Tetracycline	0.25 g x 4 oral	0.5 g x 4 oral
Tigecycline	0.1 g loading dose followed by 50 mg x 2 iv	None

Oxazolidinones	Standard dose	High dose
Linezolid	0.6 g x 2 oral or 0.6 g x 2 iv	None
Tedizolid	0.2 g x 1 oral	None

Miscellaneous agents	Standard dose	High dose
Chloramphenicol	1 g x 4 oral or 1 g x 4 iv	2 g x 4 oral or 2 g x 4 iv
Colistin	3 MU x 3 iv with a loading dose of 9 MU	None
Daptomycin	0.25 g x 1 iv	0.5 g x 1 iv
Fosfomycin iv	4 g x 3 iv	8 g x 3 iv
Fosfomycin oral	3 g x 1 oral as a single dose	None

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Exploration of the Pharmacokinetic-Pharmacodynamic Relationships for Fosfomycin Efficacy Using an *In Vitro* Infection Model

Brian D. VanScoy,[a] Jennifer McCauley,[a] Evelyn J. Ellis-Grosse,[b] Olanrewaju O. Okusanya,[a*] Sujata M. Bhavnani,[a] Alan Forrest,[a] Paul G. Ambrose[a,c]

Institute for Clinical Pharmacodynamics, Latham, New York, USA[a]; Zavante Therapeutics, Inc., San Diego, California, USA[b]; University of Oxford, Oxford, United Kingdom[c]

FOS D/R E.coli

MIC: 32-64mg/L suşları

- **Doz aralığını bulmaya yönelik invitro FK/FD çalışma**
- Mutasyon sıklığı

VanScoy BD. Antimicrob Agents Chemother . 2015

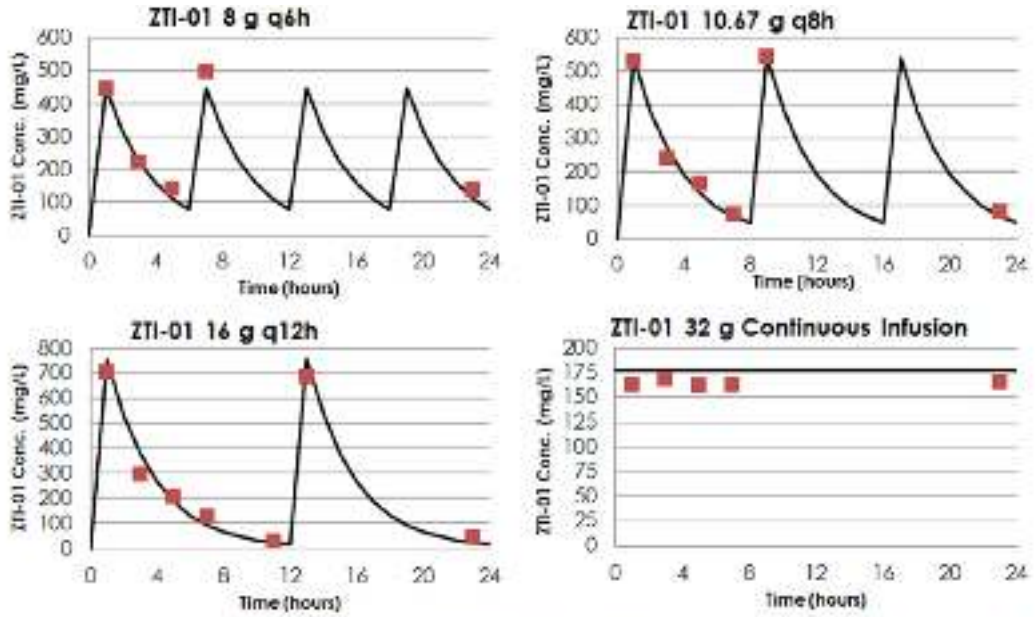

FIG 2 The targeted free-drug fosfomycin concentration-time profiles (solid lines) overlaid with the mean observed free-drug fosfomycin concentrations (red squares) for the ZTI-01 dosing regimens with a total daily dose of 32 g evaluated in the dose fractionation studies.

- *f*T>MIC, fosfomisin FK/FD için yeterli tanımlayıcı değil;
- İlaca **direçli subpopulasyonun (RIC) cevabı öngörmede dikkate alınabileceği** (*f*T>MIC yerine *f*T>RIC)

8-32g sürekli inf. FOS etkinliği ➔ maksimum sterilite !

VanScoy BD. Antimicrob Agents Chemother . 2015

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

The combination of colistin and fosfomycin is synergistic against NDM-1-producing Enterobacteriaceae in in vitro pharmacokinetic/pharmacodynamic model experiments

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Bristol Centre for Antimicrobial Research and Evaluation, Department of Medical Microbiology, North Bristol NHS Trust, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5ND, UK

- **<u>NDM-1 (+) (3'ü FOS D, 3'ü R)</u> ➔ <u>Kolistin + FOS standart doz</u>**da

- **Cmax/Cmin, T1/2**
  - **FOS ➔ 250/40 mg/L ve 2.7 saat**
  - **Kolistin ➔ 3/0.75 mg/L ve 4 saat**

1. **Kombinasyonla bakteri öldürme ↑**
2. **Sınırlı tedavi seçenekleri olan ÇİD ➔ Kolistin + FOS**

Albur MS. Int J Antimicrob Agents. 2015

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Pharmacodynamic Evaluation of the Potential Clinical Utility of Fosfomycin and Meropenem in Combination Therapy against KPC-2-Producing *Klebsiella pneumoniae*

James Albiero,[a] Sherwin K. B. Sy,[b] Josmar Mazucheli,[b] Silvana Martins Caparroz-Assef,[c] Bruno Buranello Costa,[a] Janio Leal Borges Alves,[a] Ana Cristina Gales,[d] Maria Cristina Bronharo Tognim[a]

Departamento de Ciências Básicas da Saúde, Universidade Estadual de Maringá, Maringá, PR, Brazil[a]; Programa de Pós-Graduação em Bioestatística, Departamento de Estatística, Universidade Estadual de Maringá, Maringá, PR, Brazil[b]; Departmento de Farmacologia e Terapêutica, Universidade Estadual de Maringá, Maringá, PR, Brazil[c]; Laboratório Alerta, Divisão de Doenças Infecciosas, Departamento de Medicina Interna, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil[d]

KPC-üreten K. pneumoniae

MEM ± FOS

⇩

FOS ➔ **4x6g** veya **3x8g / gün**

3 saatlik infüzyon

⇩

MIC 64-512mg/L ➔ Duyarlılık MIC50 ¼, MIC 90 için 1/8 -1/16 artmış

Albiero J. Antimicrob Agents Chemother. 2016

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Review

Fosfomycin for the treatment of infections caused by multidrug-resistant non-fermenting Gram-negative bacilli: a systematic review of microbiological, animal and clinical studies

Matthew E. Falagas[a,b,c,*], Antonia C. Kastoris[a], Drosos E. Karageorgopoulos[a], Petros I. Rafailidis[a,b]

23 çalışma, 1859 suş

ÇİD P. aeruginosa %30.2 FOS duyarlı;

FOS + AG/FQ/Beta Laktam → sinerjik (%53,5)

Kistik fibrozis alevlenmesi → %91 iyileşme

İnfektif endokardit (hayvan) → FOS +Gentamisin iyi cevap

A.baumannii (ÇİD) invitro FOS duyarlılığı %3,5

Falagas ME, Int J Antimicrob Agents 2009; 34:111–120.

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

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

O. Asuphon [a], P. Montakantikul [b], J. Houngsaitong [b], P. Kiratisin [c], P. Sonthisombat [a,*]

Kritik hastalarda 120 Karbapenem rezistan MIC 90 (Etest)

- **ÇİD (+) P.aeruginosa** → >1024, 1024, **>32, 32mg/L**
- **ÇİD (-)** P.aeruginosa → 512, 128, **8 ve 3** mg/L

FOS (+KBP)→ Uzamış infüzyonla 16-24g/gün

Asuphon O,. Int J Infect Dis. 2016

- Karbapenem➔ P.aeruginosa ➔ uzun PAE➔ FOS ile uzamış infüzyonla klinik başarı daha anlamlı

- **Biyofilm tabakasına penetre** FOS, P. aeruginosa kistik fibrozlu
  - FOS + FQ ve AG ➔ anaerobik şartlarda daha etkin

Sastry S, J Infect Chemother. 2016 May;22(5):273-80.

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Journals.ASM.org

Fosfomycin-Daptomycin and Other Fosfomycin Combinations as Alternative Therapies in Experimental Foreign-Body Infection by Methicillin-Resistant *Staphylococcus aureus*

C. Garrigós,[a] O. Murillo,[a] J. Lora-Tamayo,[a] R. Verdaguer,[b] F. Tubau,[b] C. Cabellos,[a] J. Cabo,[c] J. Ariza[a]

Laboratory of Experimental Infection, Infectious Diseases Service,[a] and Departments of Microbiology[b] and Orthopaedic Surgery,[c] IDIBELL, Hospital Universitari de Bellvitge, Barcelona, Spain

The efficacy of daptomycin, imipenem, or rifampin with fosfomycin was evaluated and compared with that of daptomycin-rifampin in a tissue cage model infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Strain HUSA 304 was used. The study yielded the following results for MICs (in μg/ml): fosfomycin, 4; daptomycin, 1; imipenem, 0.25; and rifampin, 0.03. The study yielded the following results for minimum bactericidal concentration (MBC) (in μg/ml): fosfomycin, 8; daptomycin, 4; imipenem, 32; and rifampin, 0.5. Daptomycin-rifampin was confirmed as the most effective therapy against MRSA foreign-body infections. Fosfomycin combinations with high doses of daptomycin and rifampin were efficacious alternative therapies in this setting. Fosfomycin-imipenem was relatively ineffective and did not protect against resistance.

Daptomisin-rifampisin **Vs** daptomisin-imipenem /rifampisin **+FOS**

MRSA yabancı cisim enfeksiyonu hayvan modeli

En iyi etkinlik, dap-rif

Yüksek doz FOS+dap+rif de etkili

Ancak FOS-rif invivo antagonistik !

Garrigós C. Antimicrob Agents Chemother. 2013

Kombinasyon gerekli

Ciddi enfeksiyonlar için **her zaman kombine** kullanılması önerilir

- Meropenem, imipenem, doripenem
- Seftriakson
- Kolistin
- Tigesiklin
- Amikasin
- FQ
- Aztreonam
- Rifampisin
- Daptomisin, vankomisin, telavansin

Kritik hasta, renal bozukluk

- **Kritik hastalarda dağılım hacmi ↑** kapiller geçirgenliğin artması nedeniyle artacağından, FOS doz aralarında serum konsantrasyonu düşebilecektir. Bu nedenle **24-48 saat boyunca daha sık ve yüksek dozlarda FOS**

Ancak

- **CrCl <30 ml/dk ➔** maksimum FOS dozu 12g/gün olmalı

Tobudic S. Antimicrob Agents Chemother. 2012 Jul;56(7):3992-5.

Diyaliz

- Diyaliz → FOS %80'i diyalizata geçer→ **hemodiyaliz sonrası doz**

- Peritonit gelişmemiş otomatik periton diyalizi yapılan hastalardaki FK çalışmada, **intraperitoneal FOS > iv.** üstün.

Tobudic S, is. Antimicrob Agents Chemother. 2012 Jul;56(7):3992-5.

Yan etki

Yan etkiler **çok nadirdir**;

- Gastrointestinal +cilt sorunları

– **Ciddi bulantı ve nötropeni çok nadir➔ ted kestirecek**

<u>Yan etki riskini azaltıcı özellik</u>

– **FOS + AG ➔ nefrotoksisite ↓**

– FOS + sisplatin ➔ ototoksisite ve nefrotoksisite ↓

Direnç

- Nadir ➔ %3
  - **Dirençli suş seleksiyonu 10^{-4} to 10^{-5}**
  - Çapraz direnç nadir.
- Mekanizma
  1. Hücre duvarından FOS transportunda azalma
  2. Enzimatik inaktivasyon

- Hayvan deneylerinde ÇİD E.coli suşları arasında **transpozon benzeri yapılarla taşınan fosA3 ilişkili FOS direnci** dikkati çekmiştir.

Ho P.L. , et al. Journal of Applied Microbiology. 2012; 114, 695-702.

- **Kritik hasta➔ GSBL +E.coli ➔** parenteral kombine ➔ <u>invivo fosfomisin dirençli suş !</u>

- **KPC(+) KP kısa sürede ciddi direnç➔** Acilen sıkı kontrol politikaları gerekli

Perez LRR. Hosp Epid 2016, pp. 748-9.

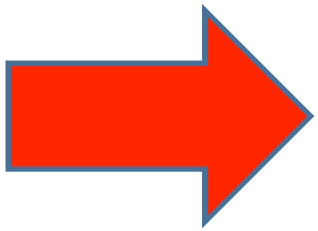
- **<u>TKP</u> GSBL ± E.coli artışı ile FOS R korele ➔** FOS klinikte kullanıldıkça direncin artacağı öngörülmekte

Oteo J. J Antimicrob Chemother. 2010;65: 2459-63

Özet ve sonuç

İv. fosfomisin

- **Sinerjik, bakterisidal etki** gösterdiği,
- Klinik etkinliği artırdığı,
- Dirençli suş seleksiyonunu azalttığı,
- Yan etki riskini azalttığı ve
- İyi bir FK/FD profili olduğu için



Özet ve sonuç

- Tedavi başarısızlığı yaşanmış
- Antibiyotiğe intoleran
- Yoğun bakım hastaları
- **Dirençli** bakterilerin neden olduğu **ciddi enfeksiyonlarda :**

GSBL ve ÇİD (+) E.coli ve KPC ± K.pneumoniae başta

ASYE, sepsis, menenjit, osteomiyelit

↓

Kurtarma tedavisi seçeneği

↓

Kombine , yüksek doz, sık /uzamış infüzyon uygulama

TEŞEKKÜR EDERİM

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