# LABORATUVARDAN KLİNİĞE

Dr.Füsun Can
Koç Üniversitesi
Tıp Fakültesi
Mikrobiyoloji AD

# Bugün Hangi Konularda Konuşmayacağız:

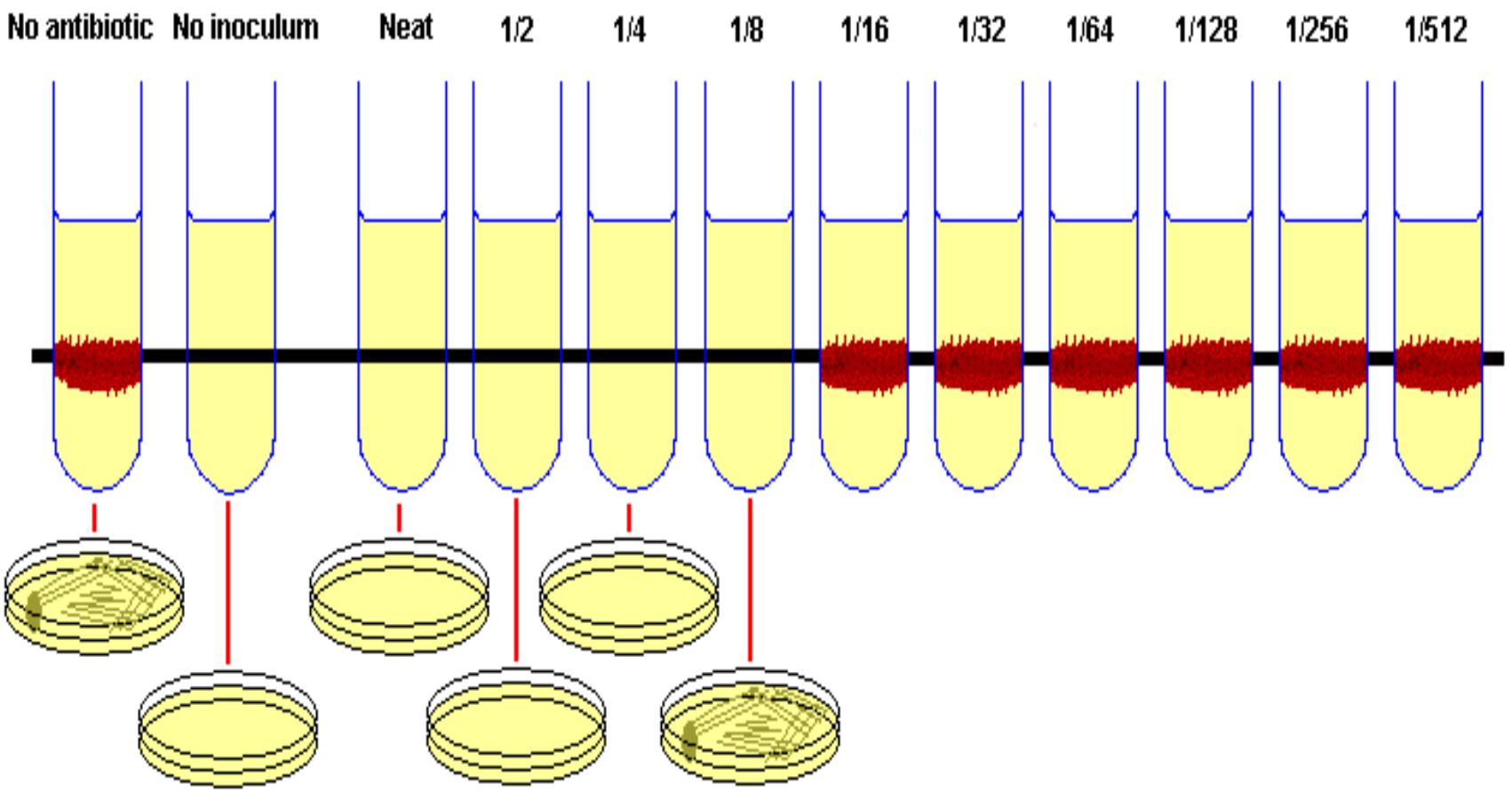
1) Sinerji Testleri
2) Otomatize sistemler ile Tiplendirme
3) Otomatize sistemler ile antibiotik duyarlılık testleri
4) HIV ilaç direnci
5) Tularemi, şarbon vakalarında optimal tedavi

# Bu sunumda

1) Minimal İnhibitör Konsantrasyon (MİK) değerlerinin *in vivo* önemi
2) MIK değerlerine göre antibiyotik seçiminin klinik yanıta etkileri
3) PK/PD parametreler, niye önem kazandı
   - Etkin tedavi doz ve uygulamalarının belirlenmesinde katkıları
   - Dirençli mutantların seçilmesinin önlenmesi
4) CLSI ve EUCAST ne düşünüyor?
5) Biz neler yapabiliriz?

# *Rutin Antibiyotik duyarlılık metodu olarak en sık disk difüzyon kullanılır*

# Minimum inhibitör konsantrasyon (MİK) testleri kantitatif testlerdir



# Antibiyotik duyarlılık testleri otomatizasyon ile yapılabilir

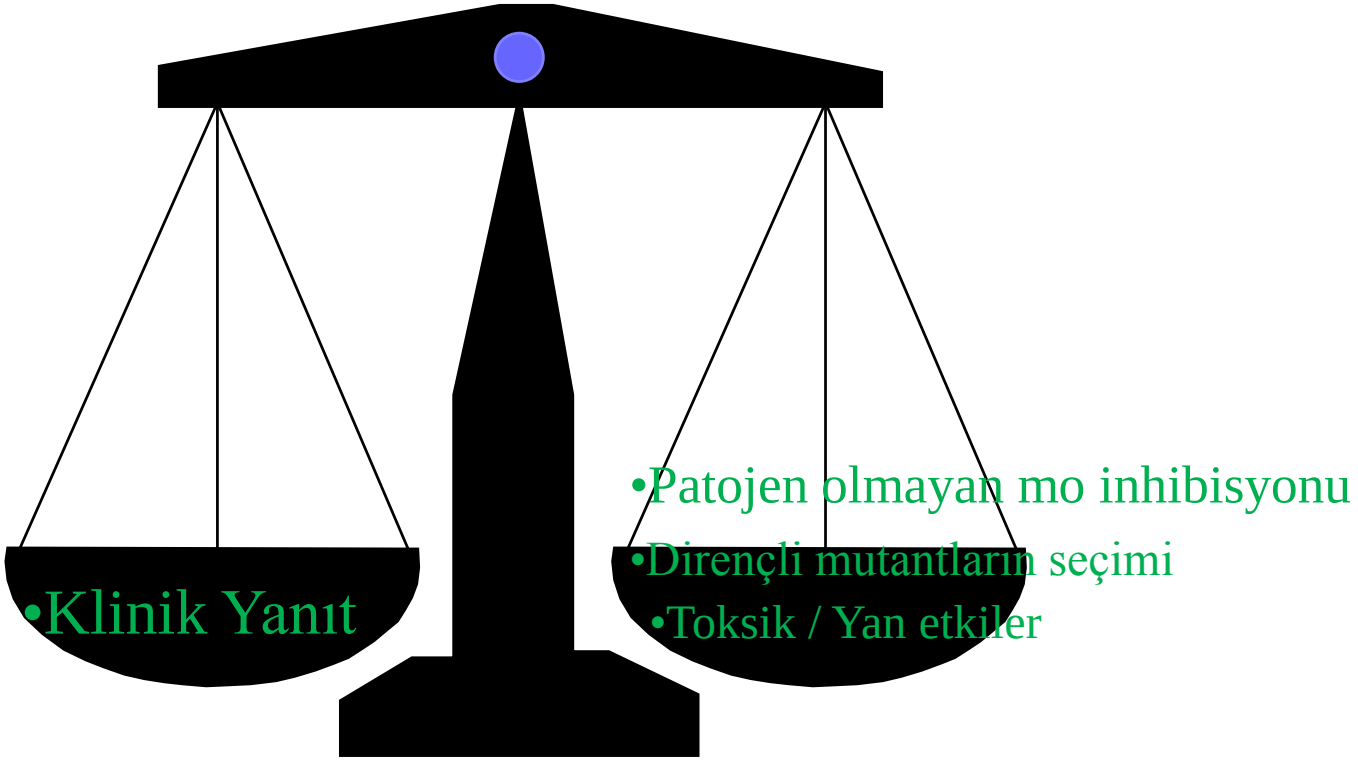
"By the year 2000, nearly all experts agree that bacterial and viral diseases will have been virtually wiped out…"

(Time magazine, february 25, 1966)

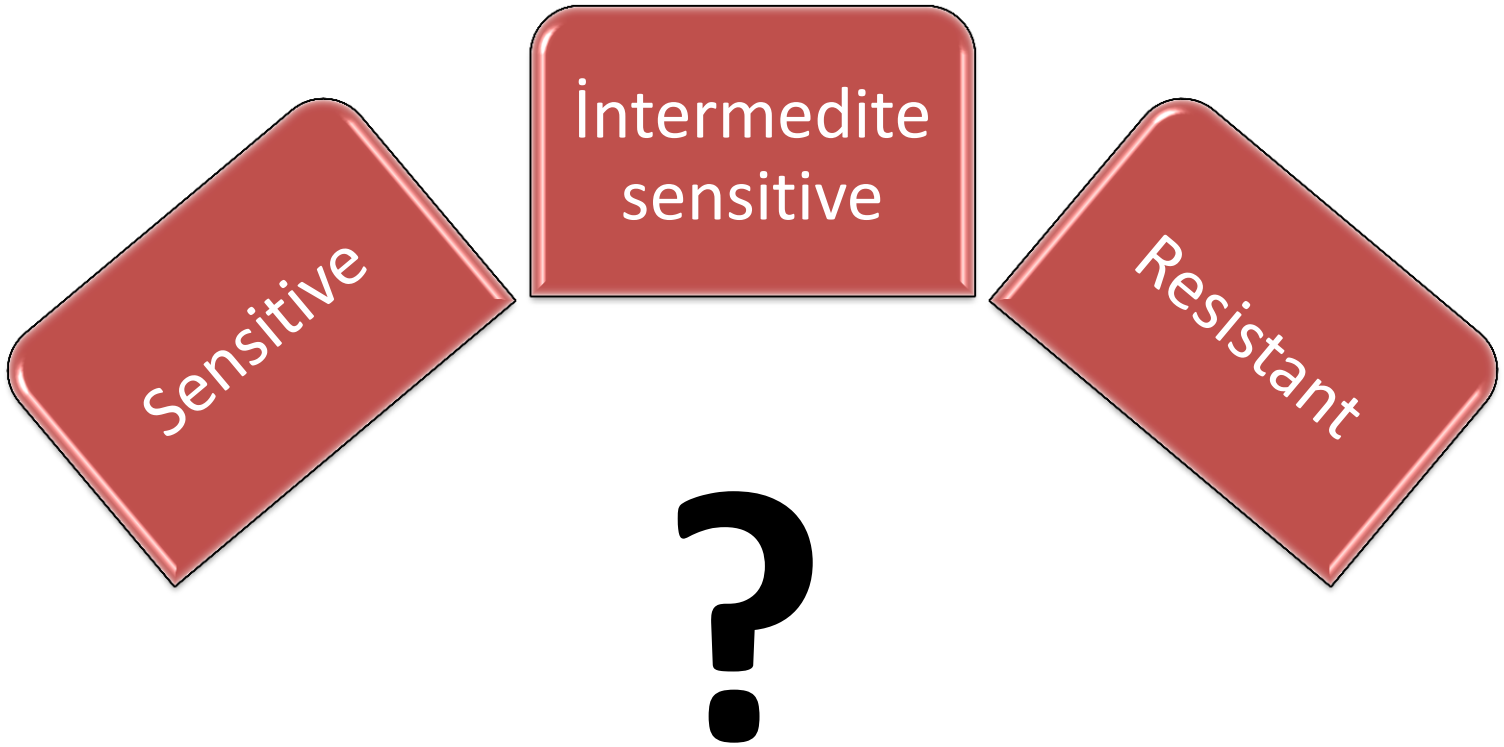
"The time has come to close the book on infectious diseases" (1969)

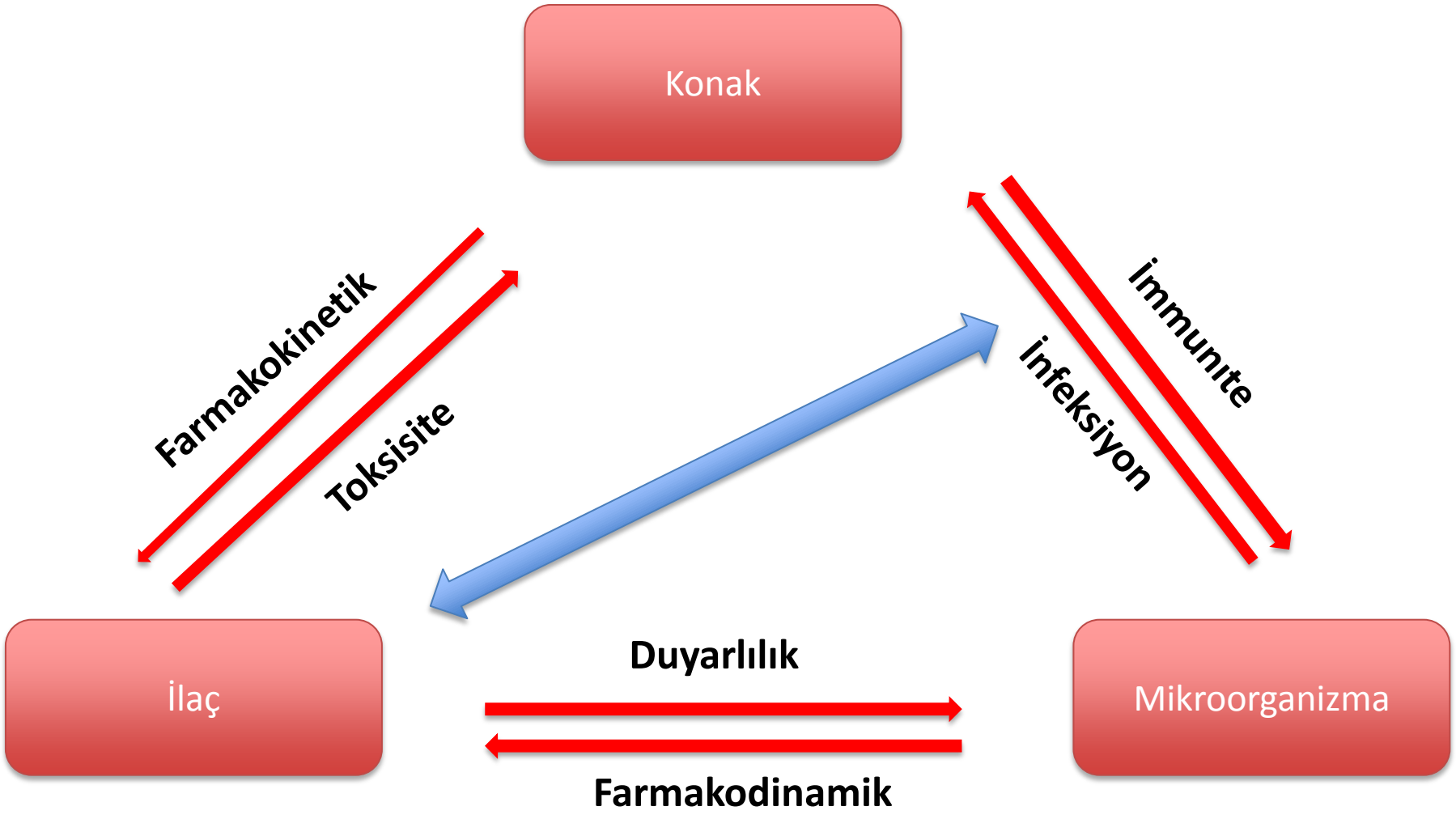
William Stewart (USA)

# Antibiyotik Kullanım İlkeleri

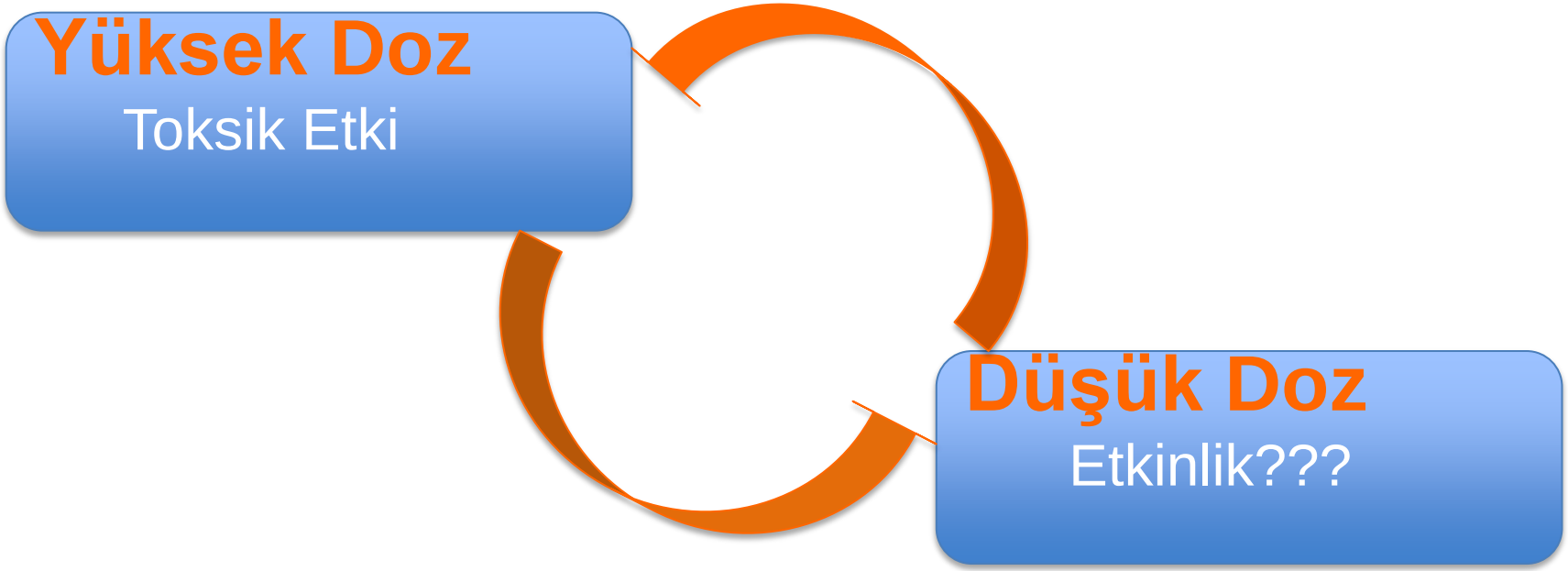



- Mümkün olan en dar spektrum
- Bakterisidal
- Aynı grup içinde MİK değeri  en düşük olan


Sensitive
İntermedite sensitive
Resistant
?


Konak
Farmakokinetik
Toksisite
İmmunite
İnfeksiyon
İlaç
Duyarlılık
Farmakodinamik
Mikroorganizma

# Sophie’nin Seçimi




- PK/PD analizleri
- Bazı hastaların gereksiz ilaç toksisitesinden korunmasına
- Etkin dozda ilaç kullanımına yardımcı

# Pharmakokinetik

Problemler:

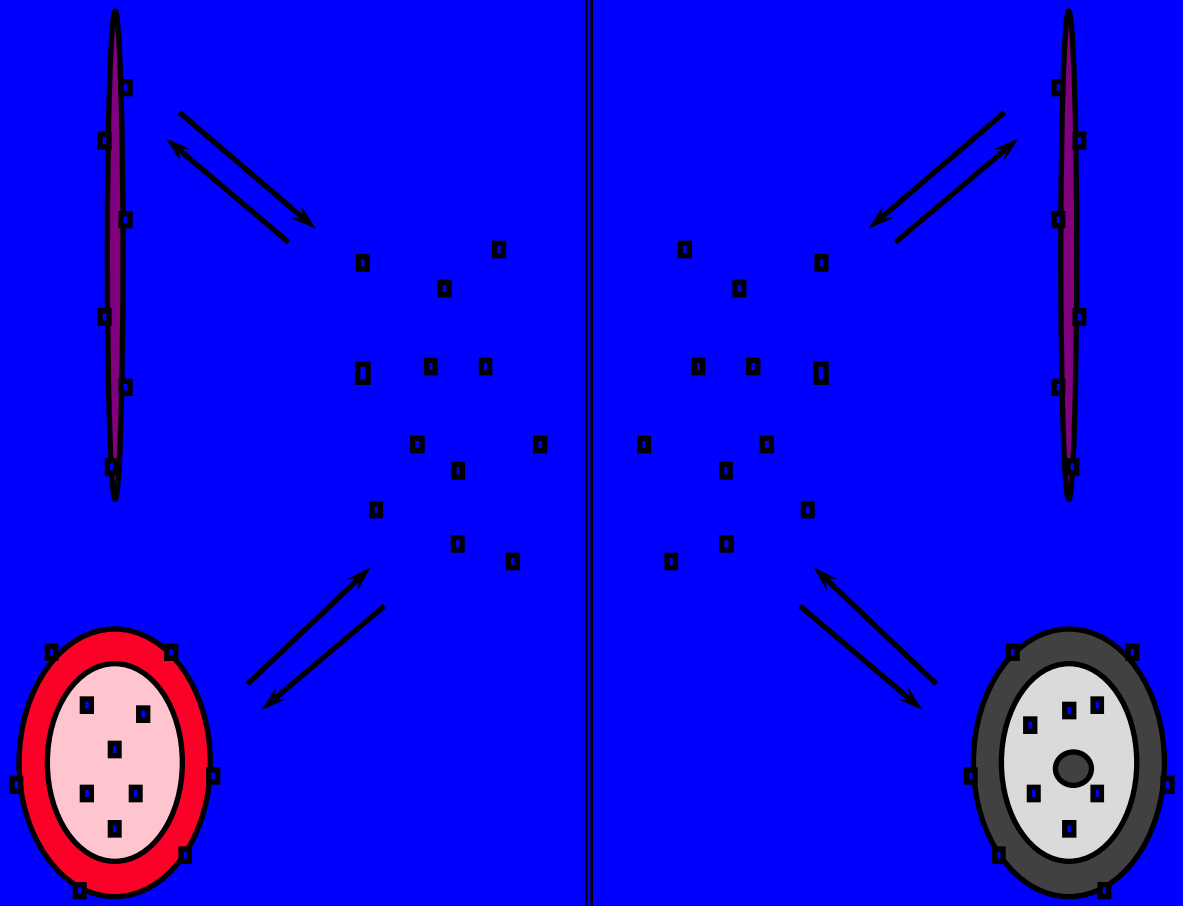
- Protein Bağlanması
- Doku Dağılımı

vascular space

extravascular space

plasma protein binding

binding to extracellular biological material



blood cell binding,

diffusion into blood cells,

binding to intracellular biological material

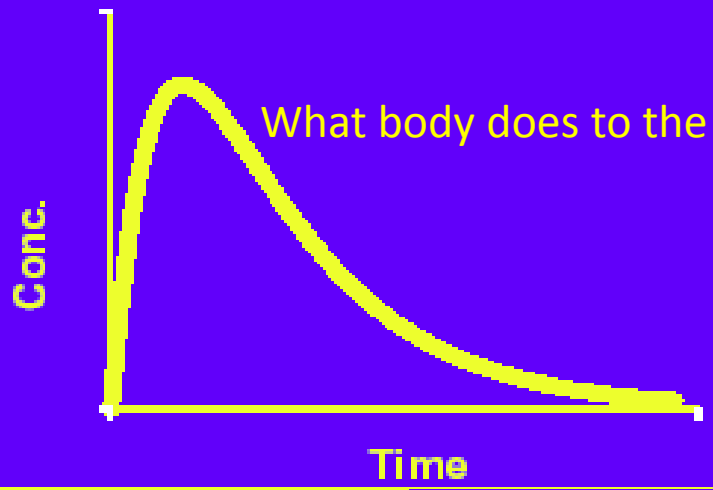
tissue cell binding,

diffusion into tissue cells,

binding to intracellular biological material

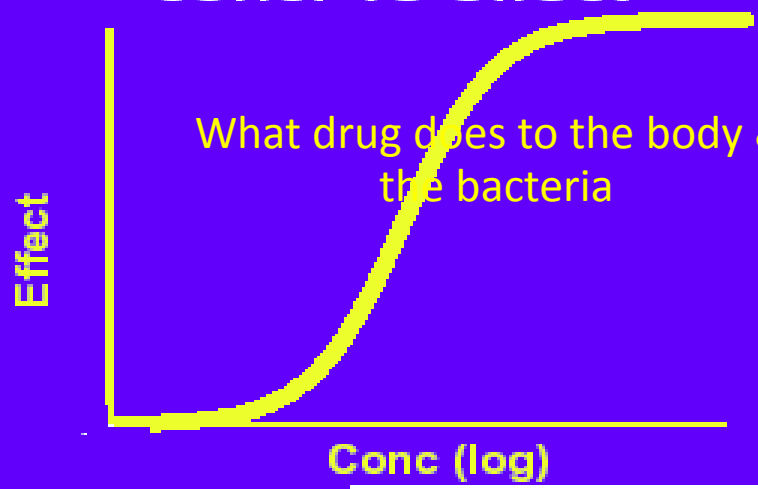
# Pharmacokinetics

conc. vs time



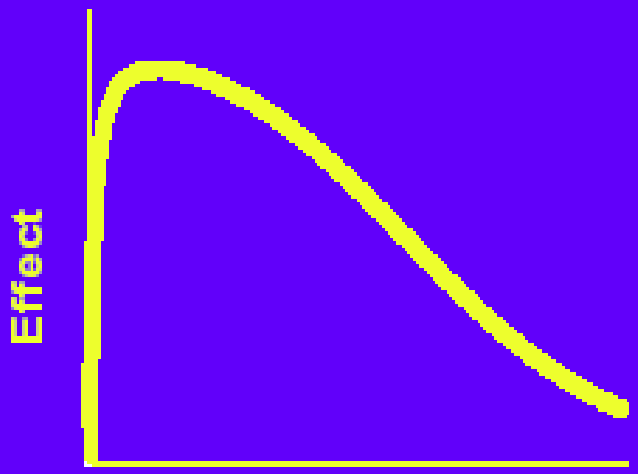

# Pharmacodynamics

conc. vs effect



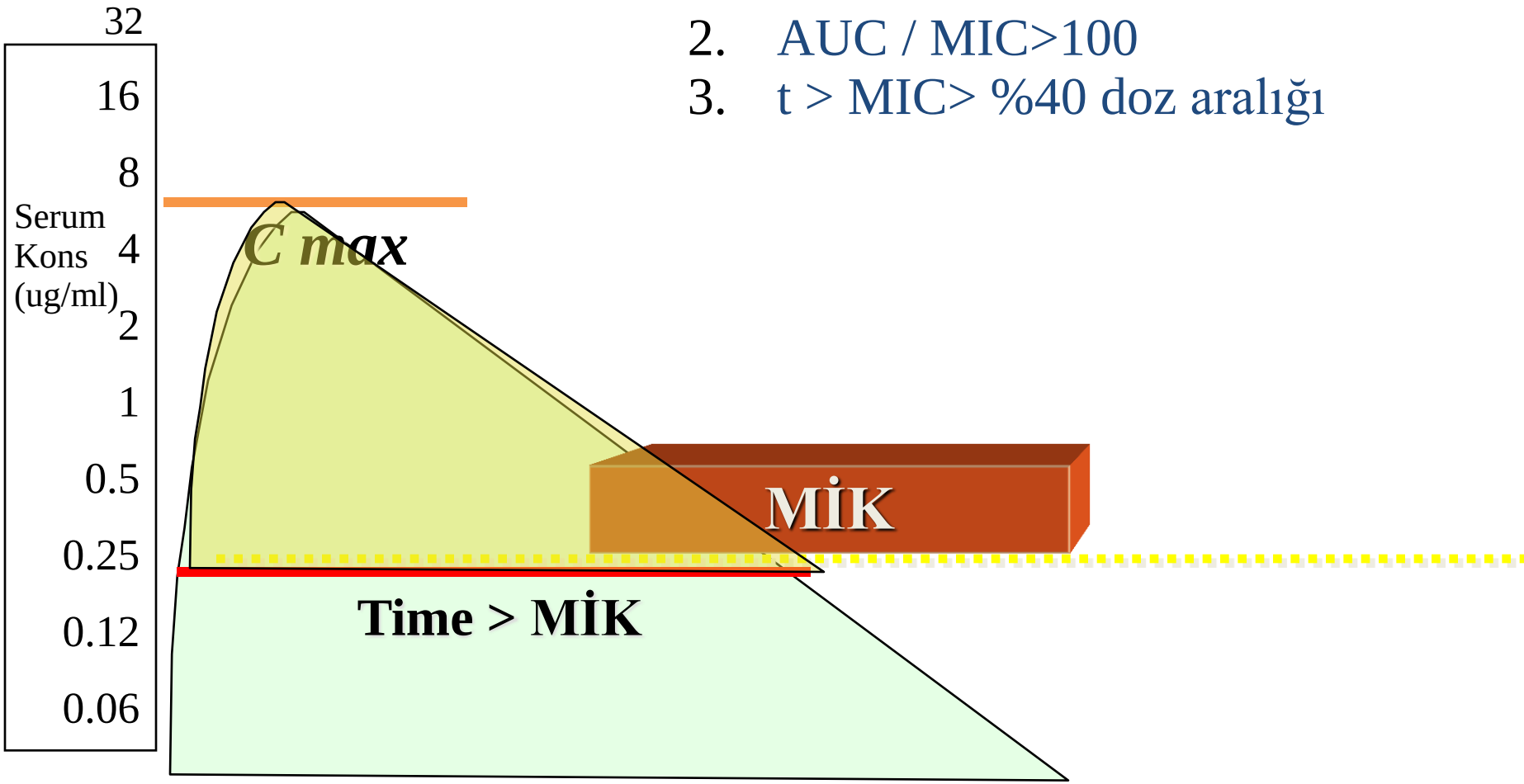

# PK/PD

effect vs time

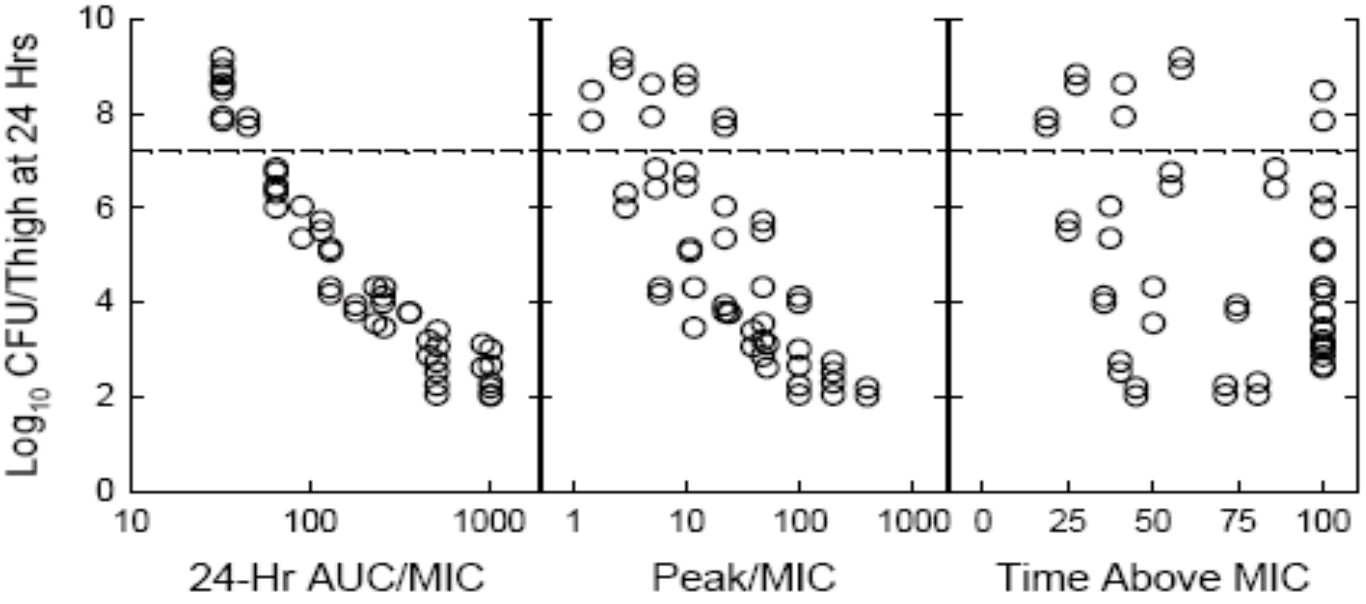


# PK/PD & MİK Etkisi

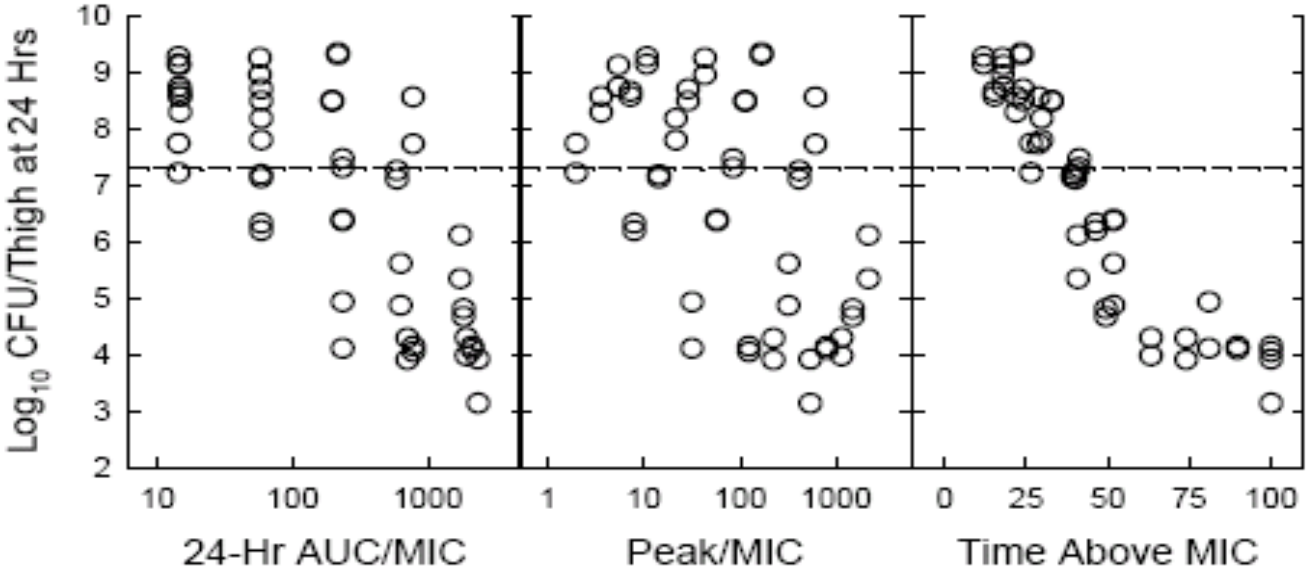
1. C max/ MIC>10
2. AUC / MIC>100
3. t > MIC> %40 doz aralığı



# PK/PD ilişkisi antibiyotik sınıfına göre değişiyor




levofloxacin




ceftazidime

2

# PK/PD correlation with efficacy

- **T > MIC**
  - –Penicillin
  - –Cephalosporins
  - –Carbapenems
  - –Monobactam
  - –Macrolides
  - –Clindamycin
  - –Oxazolidinones
  - –Glycylcyclines
  - –Flucytosine

- **AUC or Cmax/MIC**
  - –Aminoglycosides
  - –Fluoroquinolones
  - –Metronidazole
  - –Daptomycin
  - –Ketolides
  - –Azithromycin
  - –Streptogramin
  - –Glycopeptides
  - –Amphotericin
  - –Fluconazole

INVITED ARTICLE ANTIMICROBIAL RESISTANCE

George M. Eliopoulos, Section Editor

# Pharmacokinetics-Pharmacodynamics of Antimicrobial Therapy: It's Not Just for Mice Anymore

**Paul G. Ambrose,[1] Sujata M. Bhavnani,[1] Christopher M. Rubino,[1] Arnold Louie,[2] Tawanda Gumbo,[2] Alan Forrest,[1] and George L. Drusano[2]**

[1]Institute for Clinical Pharmacodynamics and [2]Emerging Infections and Fungal Pharmacodynamics Laboratory, Ordway Research Institute, Albany, New York

**Since the advent of the modern era of antimicrobial chemotherapy in the 1930s, animal infection models have allowed for the in vivo evaluation of antimicrobial agents for the treatment of experimentally induced infection. Today, animal pharmacokinetic-pharmacodynamic (PK-PD) infection models serve as a cornerstone of the preclinical assessment process for antibacterial agents and dose and dosing interval selection, as decision support for setting in vitro susceptibility breakpoints**

# PK-PD and Monte Carlo Simulation

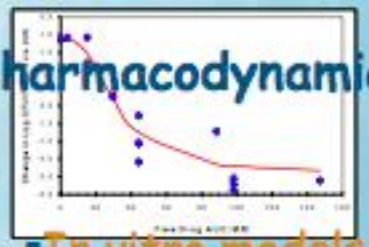
## *Powerful Tool with Drug Development, Regulatory and Clinical Application*


- Animal
- Phase-I
- Phase-II
- Patient Population


- Local Surveillance
- National Surveillance

### Mathematical Model

$$Cp^t = \left( \frac{A \bullet e^{-\alpha t}}{1 - e^{-\alpha \tau}} + \frac{B \bullet e^{-\beta t}}{1 - e^{-\beta \tau}} + \frac{C \bullet e^{-\delta t}}{1 - e^{-\delta \tau}} \right) \bullet fu$$




- In vitro models
- Animal models
- Human data

# MONTE CARLO SIMULATION RESULTS
## *Cefotaxime PK-PD Target Attainment Rate*

**CEFOTAXIME**

| | Every 6 Hrs | | | | Every 8 Hrs | | | | Every 12 Hrs | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| % T>MIC | 40 | 50 | 60 | 70 | 40 | 50 | 60 | 70 | 40 | 50 | 60 | 70 |
| hrs >MIC | 2.4 | 3 | 3.6 | 4.2 | 3.2 | 4 | 4.8 | 5.6 | 4.8 | 6 | 7.2 | 8.4 |
| **1 g** | | | | | | | | | | | | |
| **MIC:** | | | | | | | | | | | | |
| 0.25 | 100 | 99.9 | 99.7 | 98.9 | 99.9 | 99.2 | 96.4 | 88.4 | 96.4 | 82.4 | 60.6 | 37.8 |
| 0.5 | 100 | 99.8 | 98.9 | 95.5 | 99.4 | 97 | 88.6 | 73.4 | 88.6 | 64.5 | 38.6 | 18.7 |
| 1 | 99.8 | 99 | 94.6 | 84.9 | 98 | 88.9 | 71.4 | 49 | 71.4 | 39.4 | 17.1 | 6.1 |
| 2 | 99.1 | 93.1 | 79.4 | 61.4 | 89.7 | 67.1 | 40.8 | 21.9 | 40.8 | 14.6 | 4 | 1.1 |
| 4 | 90.7 | 69.5 | 43.9 | 23.9 | 61.9 | 29.2 | 11.2 | 3.6 | 11.2 | 1.9 | 0.4 | 0.1 |
| 8 | 50.3 | 21.2 | 7.4 | 1.9 | 15 | 3 | 0.7 | 0.2 | 0.7 | 0.1 | 0 | 0 |
| 16 | 2.5 | 0.3 | 0.2 | 0 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 32 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **2 g** | | | | | | | | | | | | |
| **MIC:** | | | | | | | | | | | | |
| 0.5 | 100 | 100 | 99.8 | 98.9 | 100 | 99.4 | 95.9 | 88.3 | 95.9 | 83.5 | 60.9 | 38 |
| 1 | 100 | 99.8 | 98.8 | 95.6 | 99.6 | 96.8 | 89.1 | 73.9 | 89.1 | 65.7 | 38.2 | 19.5 |
| 2 | 99.9 | 98.9 | 94.7 | 85.7 | 98.1 | 89.5 | 72 | 51 | 72 | 40.6 | 17.5 | 6.8 |
| 4 | 99.2 | 99.4 | 80.2 | 61.6 | 90.6 | 67.7 | 42.2 | 21.7 | 42.2 | 14.7 | 4.2 | 1.3 |
| 8 | 91.6 | 70.3 | 45.1 | 24.1 | 62.8 | 30.8 | 12.3 | 4.1 | 12.3 | 2.3 | 0.3 | 0 |
| 16 | 50.9 | 50.9 | 8 | 2.3 | 15.5 | 3.8 | 0.6 | 0 | 0.6 | 0 | 0 | 0 |
| 32 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Recommend:**

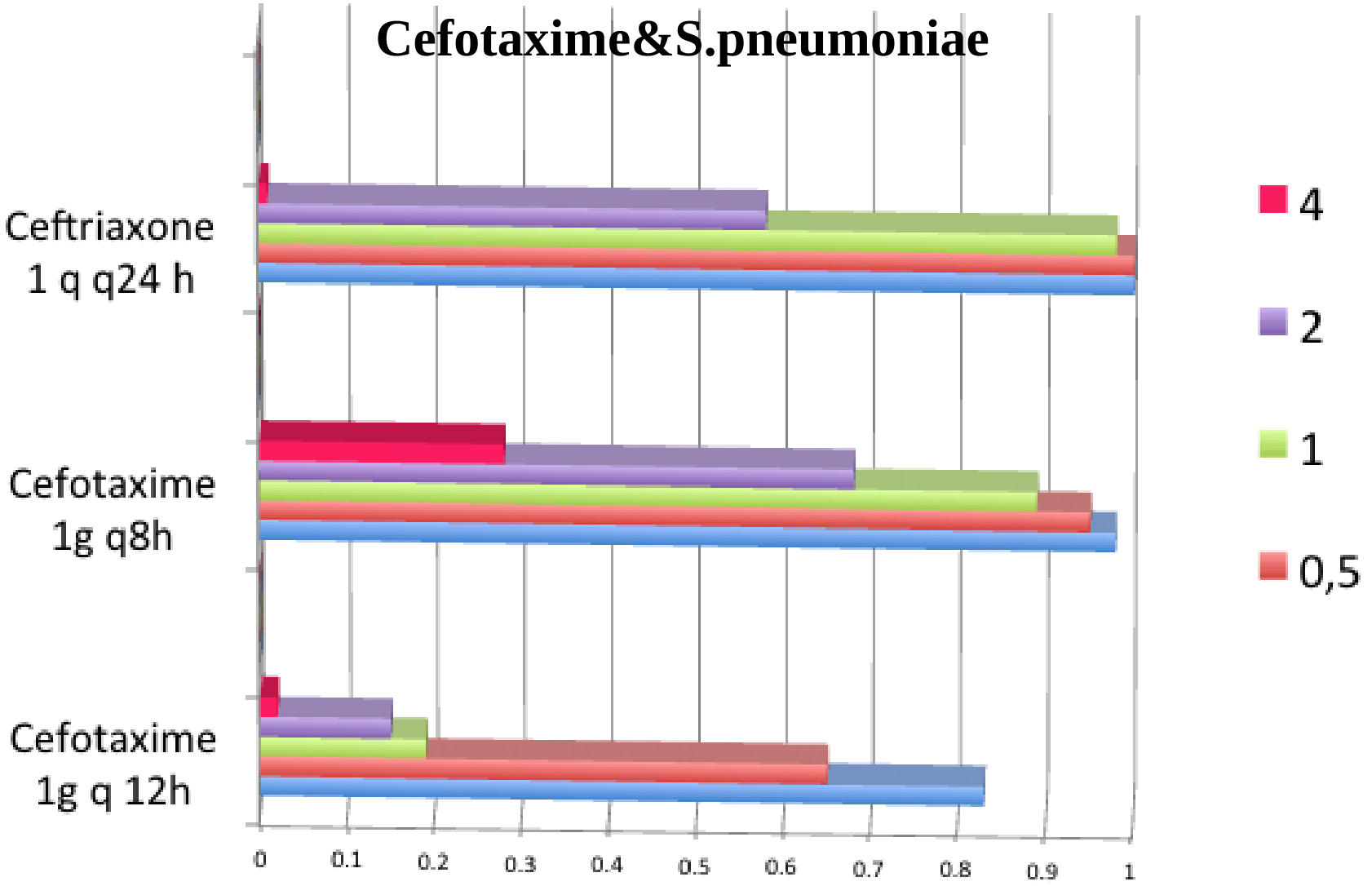
| S | I | R |
|---|---|---|
| 0.5 | 1 | 2 |

***Rationale/comments:***

Most frequent clinical use 1 g Q 8 h dosing

2 g dose covers intermediate range

Paul G. Ambrose/Mike N. Dudley




PK/PD hedefine erişim olasılığı

MİK 1 g/l belirlendi

Ambrose PG.PHARMACOTHERAPY Volume 26, Number 1, 2006

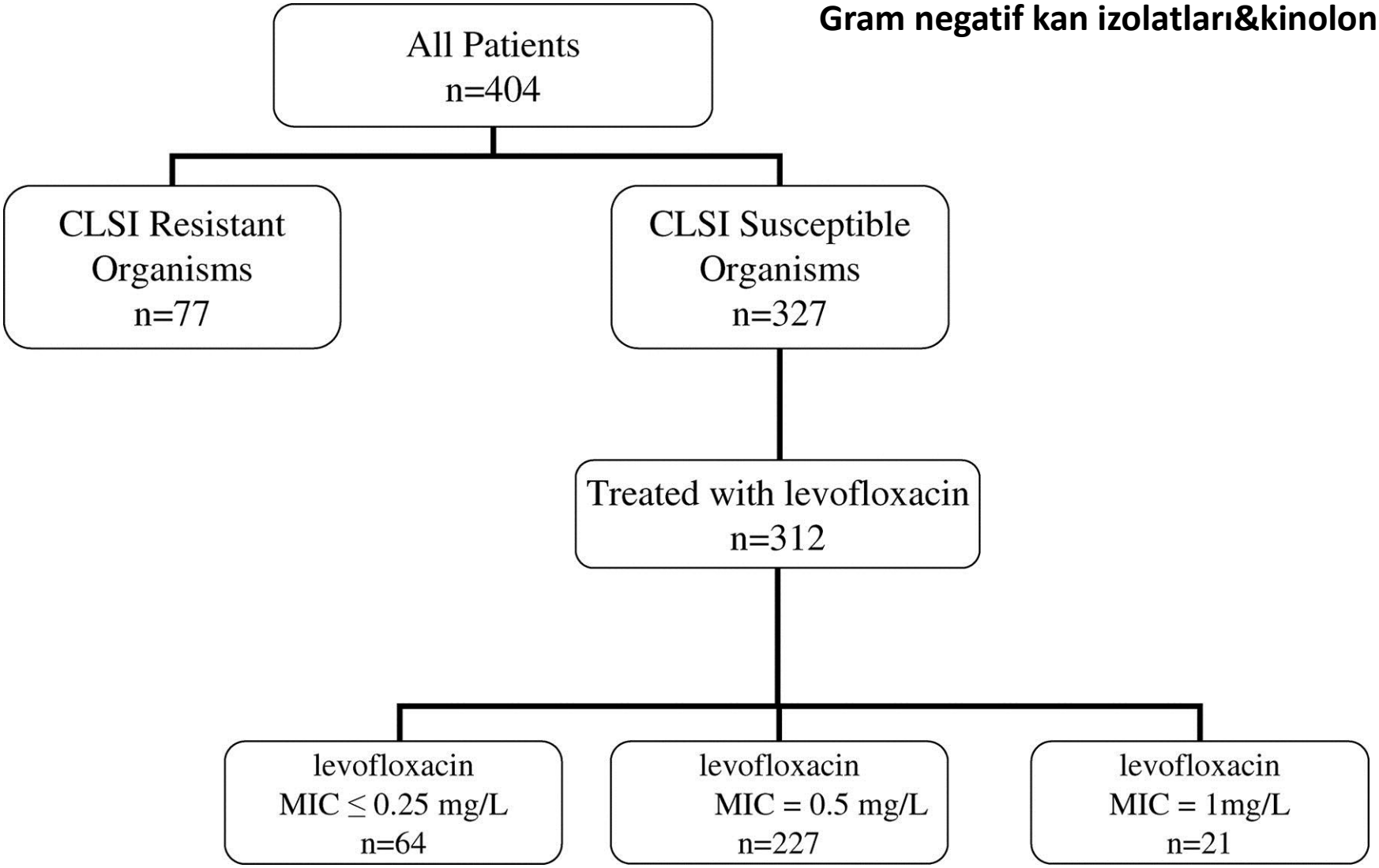
Experience is simply the name we gave our mistakes

Oscar Wilde

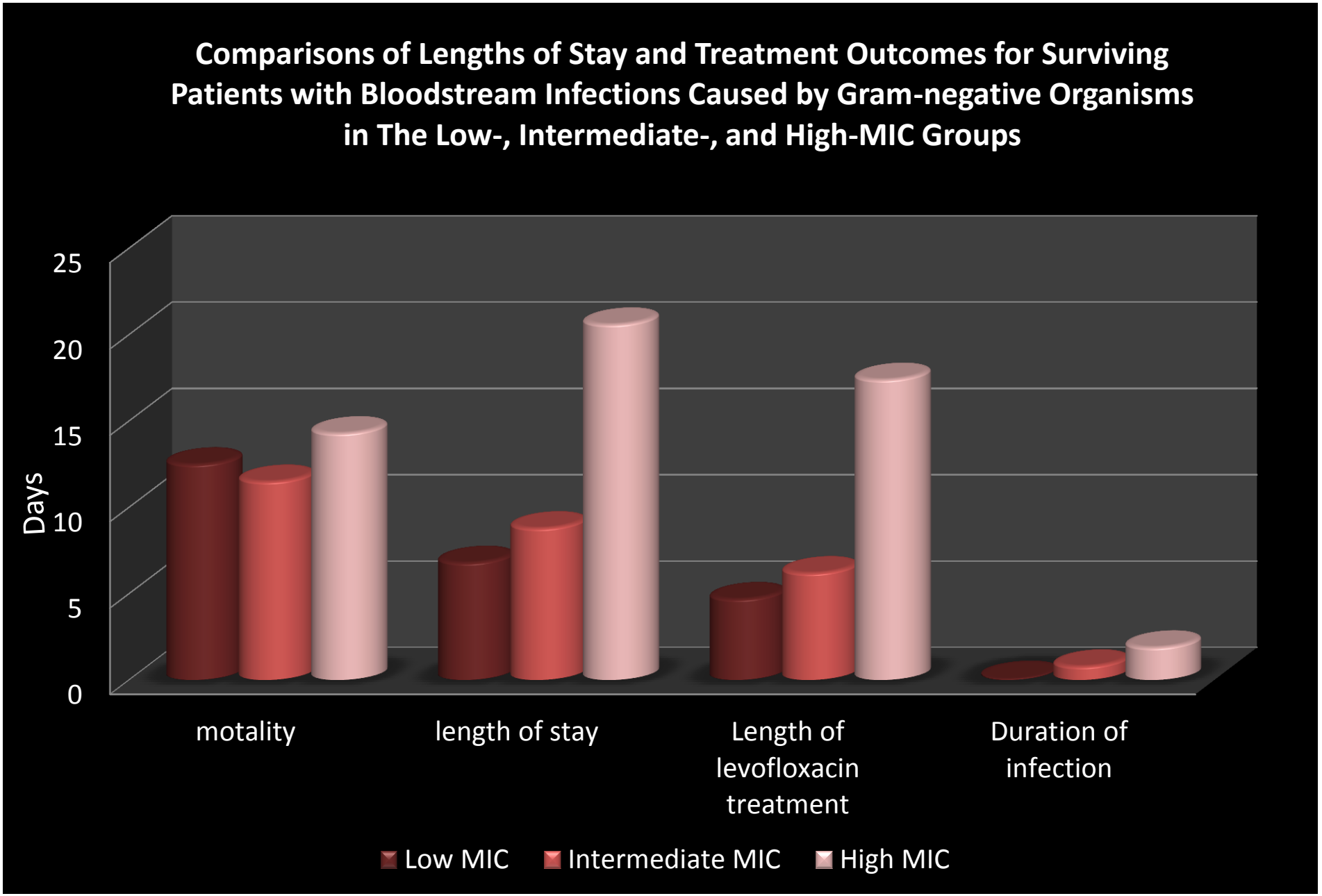
# MİK sonuçları klinik yanıt ile ne kadar uyumlu

# MİK sonuçları klinik yanıt ile her zaman uyumlu mu?

**Gram negatif kan izolatları&kinolonlar**




DeFife R et al. Antimicrob. Agents Chemother. 2009;53:1074-1079




R. Fife, M.H. Scheetz, J.M. Feinglass, M.J. Postelnick, and K.K. Scarsi. 2009. Effect of differences in MIC values on clinical outcomes in patients with bloodstream infections caused by gram-negative organisms treated with levofloxacin. Antimicrob. Agents Chemother. 53:1074-1079.

# Hastanede yatış süresini etkileyen diğer faktörler

- Mikroorganızmanın tipi
  - P.aeruginosa
- Kültür önceki süre
- Kombine ab kulanımı

R. Fife, M.H. Scheetz, J.M. Feinglass, M.J. Postelnick, and K.K. Scarsi. 2009. Effect of differences in MIC values on clinical outcomes in patients with bloodstream infections caused by gram-negative organisms treated with levofloxacin. Antimicrob. Agents Chemother. 53:1074-1079.

1) MİK değerleri antibiyotik seçiminde yararlı olabilir

2) Ancak etkin antiyotik tedavisi için antimikrobiyal ajanın farmakokinatikve farmakodinamik özelliklerinin bilinmesi gereklidir
3) Betalaktam veya kinolon gibi konsantrasyon bağımlı antibiyotiklerde doz aralıklarında antibiyotiğin dokuda MİK düzeyi üzerinde olması klinik yanıt üzerinde çok etkilidir
4) Bu çalışma kinolonların MİK değerlerinin yeniden gözden geçirilmesi gerektiğini gösteren ilk çalışmadır

**Antibiyotik seçiminde MİK sonucundan fazlasına ihtiyaç vardır**

# Gram negatif kan enfeksiyonları ve Karbapenem MİK sonuçları

AAC
Journals.ASM.org

## Evaluation of Clinical Outcomes in Patients with Bloodstream Infections Due to Gram-Negative Bacteria According to Carbapenem MIC Stratification

**John S. Esterly,[a,b] Jamie Wagner,[c] Milena M. McLaughlin,[a,d] Michael J. Postelnick,[a] Chao Qi,[e] and Marc H. Scheetz[a,d]**

Department of Pharmacy, Northwestern Memorial Hospital, Chicago, Illinois, USA[a]; Department of Pharmacy Practice, Chicago State University, Chicago, Illinois, USA[b]; Midwestern University, Chicago College of Pharmacy, Downers Grove, Illinois, USA[c]; Department of Pharmacy Practice, Midwestern University, Chicago College of Pharmacy, Downers Grove, Illinois, USA[d]; and Department of Pathology, Clinical Microbiology Division, Northwestern Memorial Hospital, Chicago, Illinois, USA[e]

**Predictive modeling suggests that actual carbapenem MIC results are more predictive of clinical patient outcomes than categorical classification of the MIC as susceptible, intermediate, or resistant. Some have speculated that current CLSI guidelines' sug-**

**Esterly J S et al. Antimicrob. Agents Chemother. 2012;56:4885-4890**

# Karbapenemlere klinik yanıt MIK breakpoint ile uyumlu mu??

**Node 0**
**All Patients**

| | % | n |
|---|---|---|
| Survived | 72.5 | 50 |
| Died | 27.5 | 19 |
| Total | 100 | 69 |

Imipenem MIC

**Node 1**
**MIC 1, 2 mcg/mL**

| | % | n |
|---|---|---|
| Survived | 83.9 | 47 |
| Died | 16.1 | 9 |
| Total | 100 | 56 |

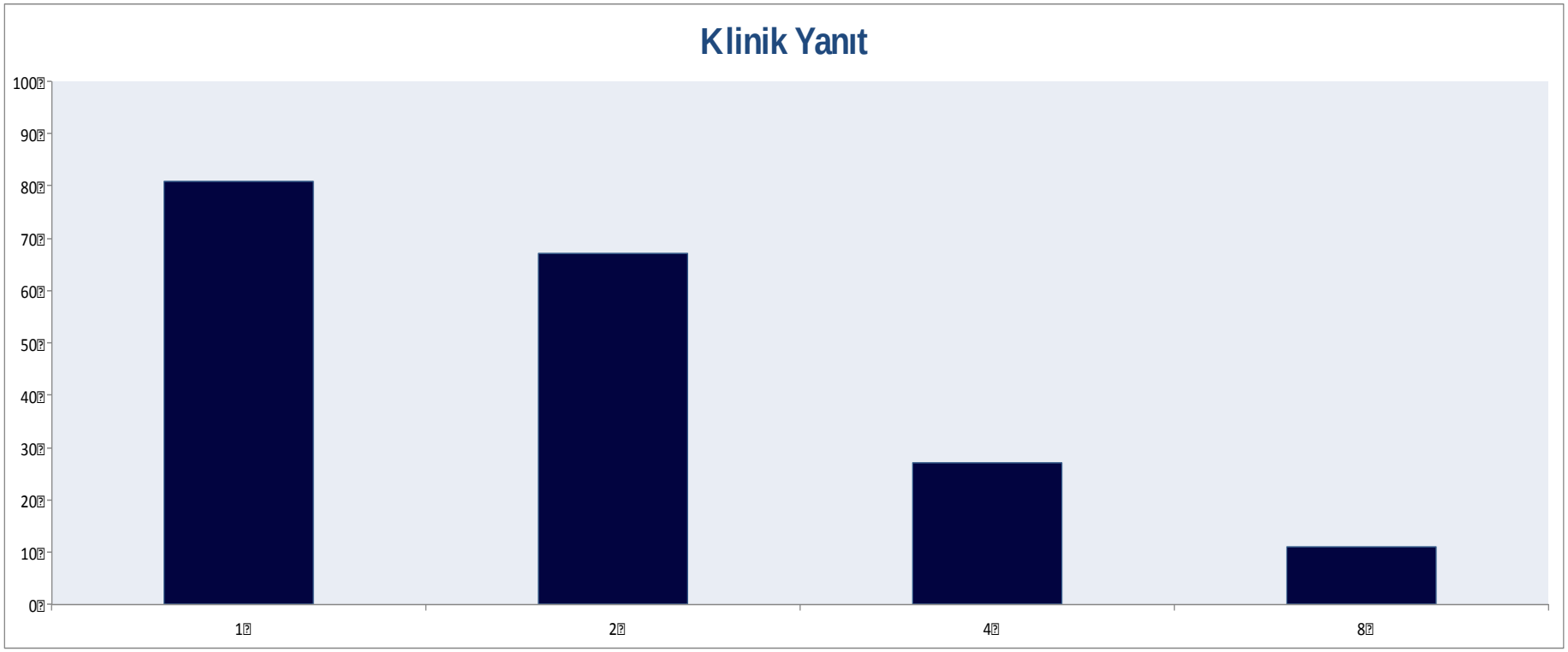
p≤0.01

**Node 2**
**MIC 4, 8, 16 mcg/mL**

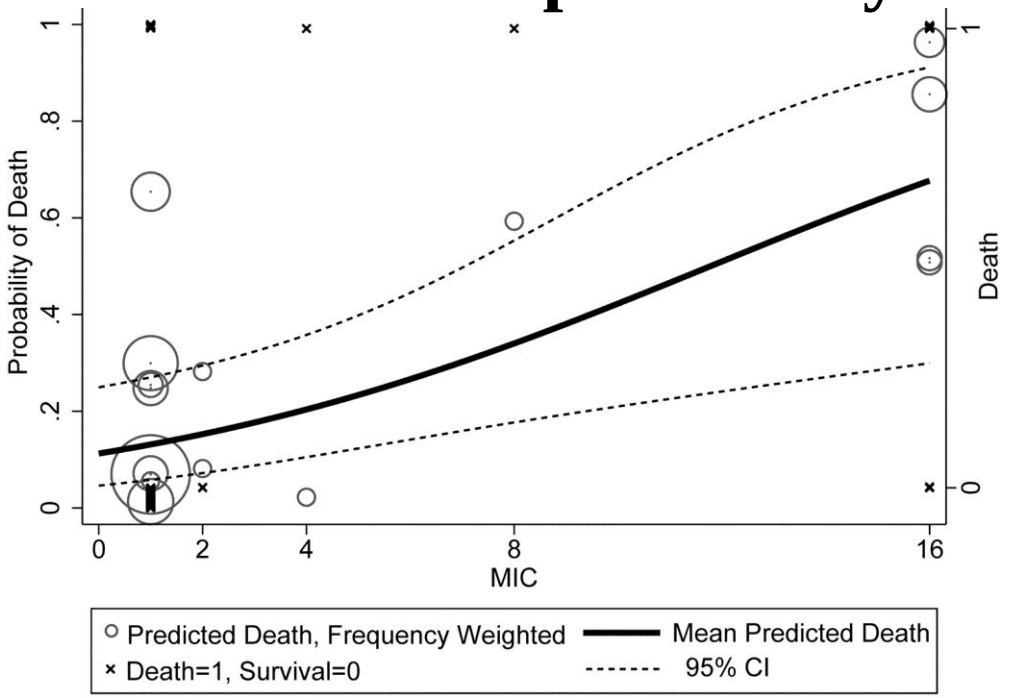
| | % | n |
|---|---|---|
| Survived | 23.1 | 3 |
| Died | 76.9 | 10 |
| Total | 100 | 13 |

Esterly J S et al. Antimicrob. Agents Chemother. 2012;56:4885-4890

# Karbapenemlere klinik yanıt MIK breakpoint ile uyumlu mu??



# Karbapenemlere klinik yanıt MIK breakpoint ile uyumlu mu??




1. MIK>4 g/l klinik yanıt kötü
2. MİK>4 mortalite oranları yüksek
3. MIK breakpointler düşürülmeli

| MIC (mg/L) | Unadjusted Actual Values Died (n,%) | Sensitivity for a cutpoint equal to or greater than the MIC | Specificity for a cutpoint equal to or greater than the MIC |
|---|---|---|---|
| 1 | 9/54, 16.7% | 100% | 0% |
| 2 | 0/2, 0% | 52.6% | 90% |
| 4 | 1/1, 100% | 52.6% | 94% |
| 8 | 1/1, 100% | 47.4% | 94% |
| 16 | 8/11, 72.7% | 42.1% | 94% |

Esterly J S et al. Antimicrob. Agents Chemother. 2012;56:4885-4890

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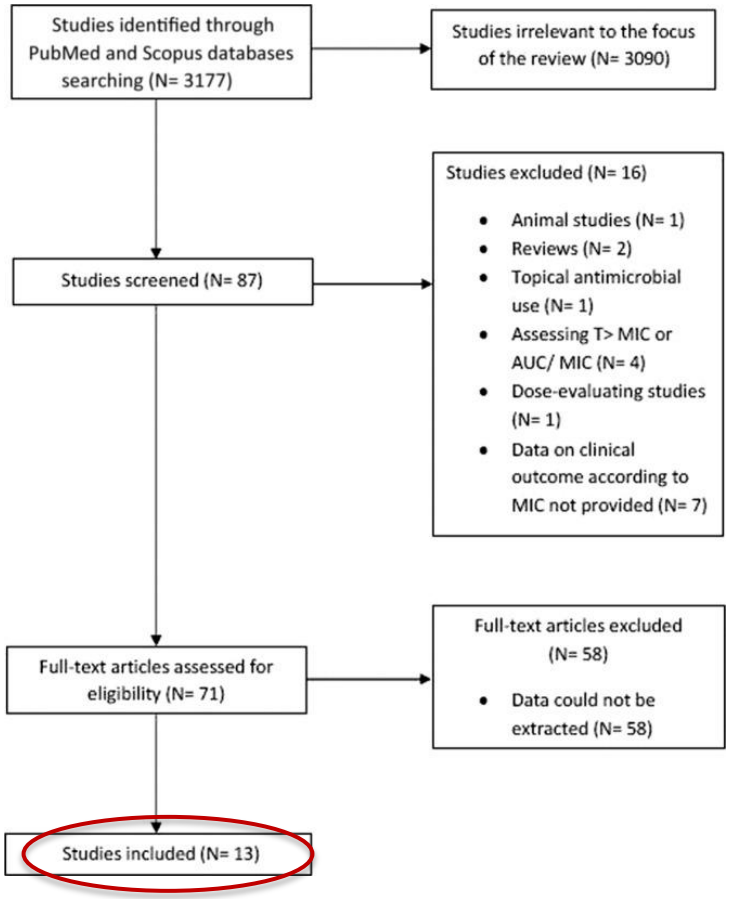
Journals.ASM.org

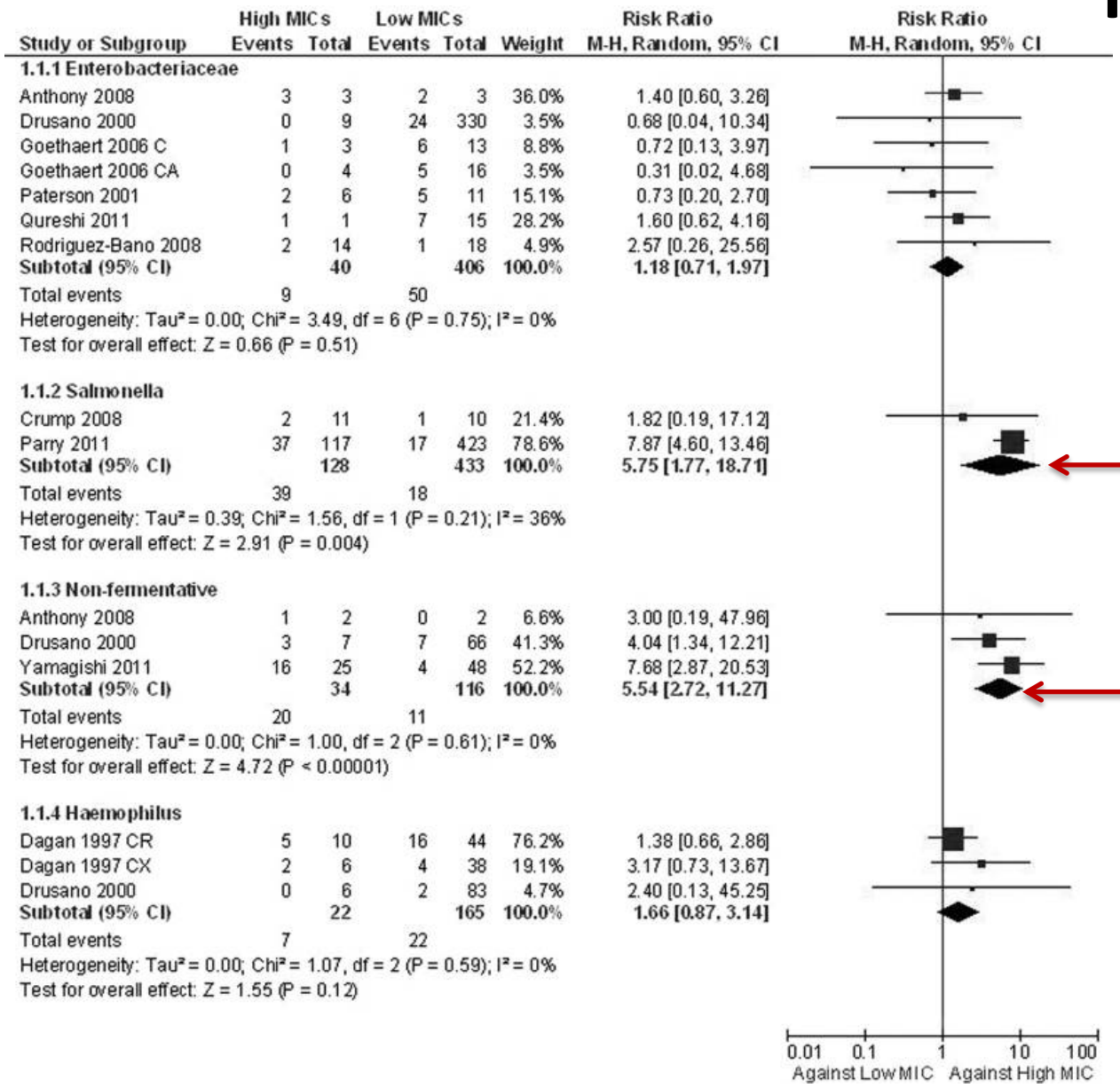
# Impact of Antibiotic MIC on Infection Outcome in Patients with Susceptible Gram-Negative Bacteria: a Systematic Review and Meta-Analysis

**Matthew E. Falagas,[a,b,c] Giannoula S. Tansarli,[a] Petros I. Rafailidis,[a,b] Anastasios Kapaskelis,[a] and Konstantinos Z. Vardakas[a,b]**

Alfa Institute of Biomedical Sciences, Athens, Greece[a]; Department of Medicine, Henry Dunant Hospital, Athens, Greece[b]; and Tufts University School of Medicine, Boston, Massachusetts, USA[c]



# Tedaviye yanıt



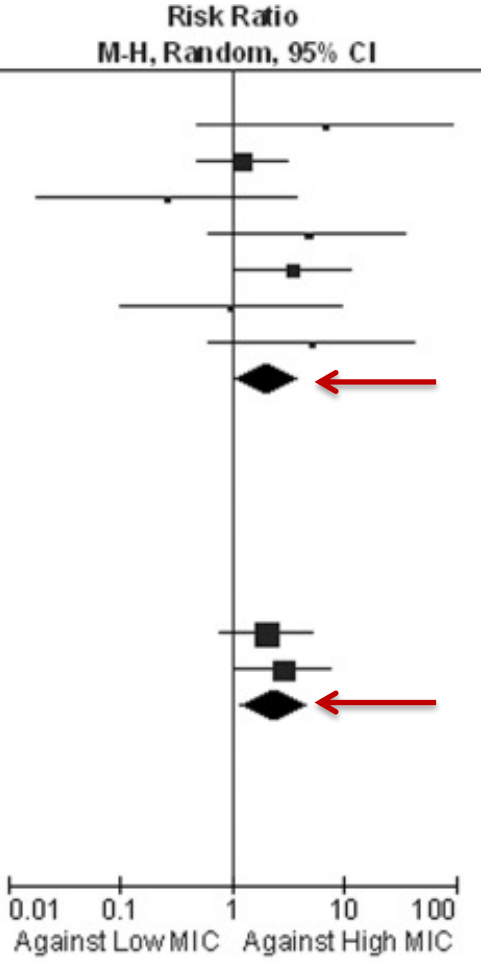

Kinolon MİK>0.125 g/l klinik yanıt kötü

P.aeruginosa piprerasilin-tazobaktam MİK>32 tedavi başarısı düşük

# Mortalite

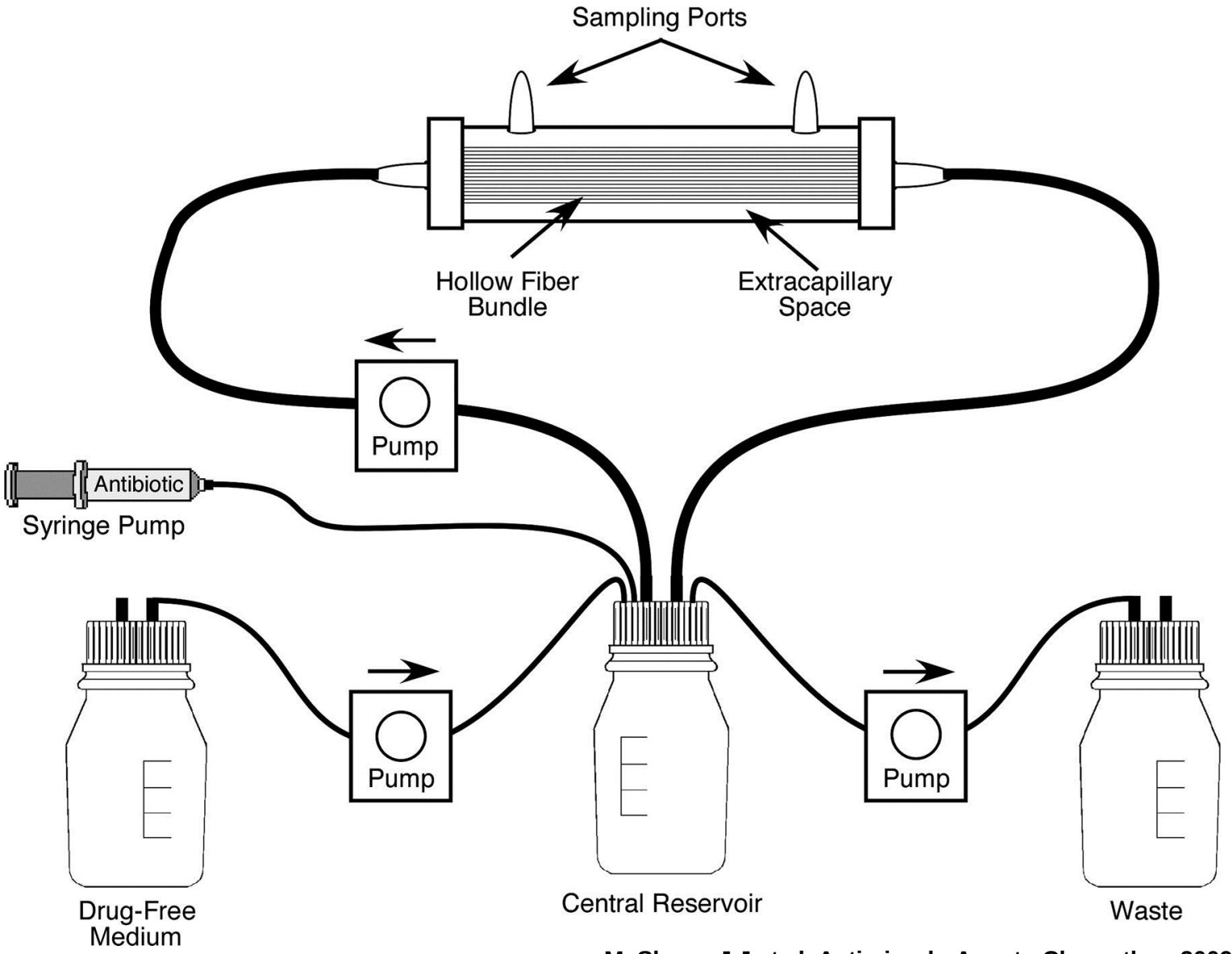
| Study or Subgroup | High MICs Events | Total | Low MICs Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **2.1.1 Enterobacteriaceae** | | | | | | |
| Anthony 2008 | 2 | 2 | 0 | 3 | 6.0% | 6.67 [0.47, 93.58] |
| Goethaert 2006 C | 2 | 3 | 7 | 13 | 37.5% | 1.24 [0.48, 3.19] |
| Goethaert 2006 CA | 0 | 4 | 6 | 16 | 5.7% | 0.26 [0.02, 3.88] |
| Paterson 2001 | 3 | 7 | 1 | 11 | 9.6% | 4.71 [0.60, 36.81] |
| Qureshi 2011 | 1 | 1 | 3 | 15 | 24.6% | 3.43 [1.01, 11.66] |
| Rodriguez-Bano 2012 A/C | 2 | 25 | 1 | 12 | 7.8% | 0.96 [0.10, 9.57] |
| Rodriguez-Bano 2012 P/T | 3 | 13 | 1 | 22 | 8.8% | 5.08 [0.59, 43.88] |
| **Subtotal (95% CI)** | | **55** | | **92** | **100.0%** | **2.03 [1.05, 3.92]** |
| Total events | 13 | | 19 | | | |
| Heterogeneity: Tau² = 0.07; Chi² = 6.52, df = 6 (P = 0.37); I² = 8% | | | | | | |
| Test for overall effect: Z = 2.11 (P = 0.03) | | | | | | |
| **2.1.2 Non-fermentative** | | | | | | |
| Anthony 2008 | 0 | 2 | 0 | 2 | | Not estimable |
| Bhat 2009 | 9 | 19 | 4 | 17 | 50.7% | 2.01 [0.76, 5.36] |
| Tam 2008 | 6 | 7 | 3 | 10 | 49.3% | 2.86 [1.06, 7.72] |
| **Subtotal (95% CI)** | | **28** | | **29** | **100.0%** | **2.39 [1.19, 4.81]** |
| Total events | 15 | | 7 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.45 (P = 0.01) | | | | | | |

Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%



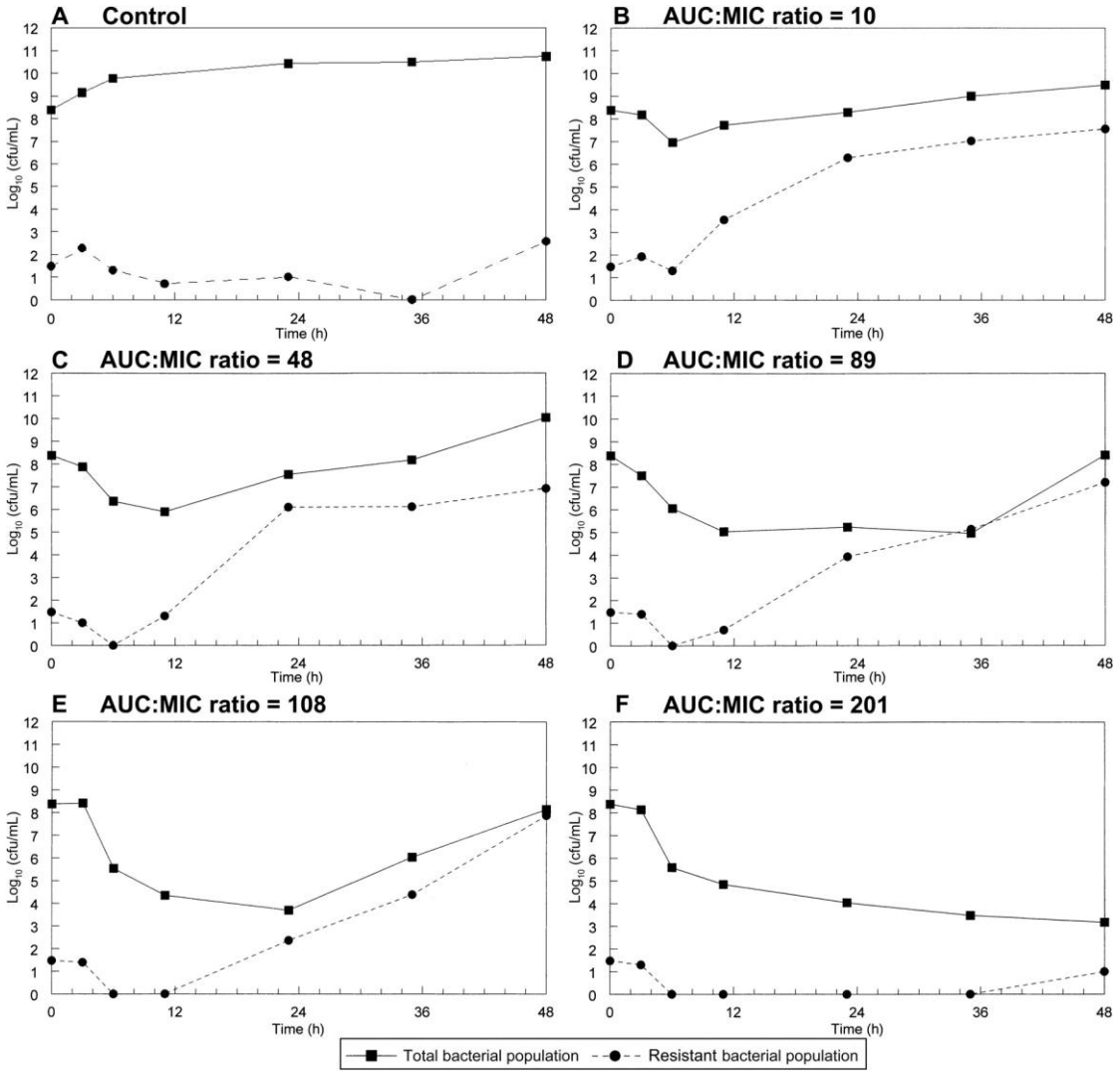
**MİK değerlerine göre antibiyotik tedavisi dirençli mutantların seçimine neden olabilir mi???**

# Antimikrobiyal testlerin dinamik çalışılmasında uygulanan Hollow Fiber Modeli




McSharry J J et al. Antimicrob. Agents Chemother. 2009;53:129-135

# Pseudomonas aeruginosa'da direnç baskılanması




**Bacterial-population responses to drug-selective pressure: examination of garenoxacin's effect on Pseudomonas aeruginosa.**

**Tam V H et al. J Infect Dis. 2005;192:420-428**

# Hollow Fiber Model klinikte direnç gelişiminin supresyonu ile uyumlu mu?

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3406–3412 Vol. 55, No. 7
0066-4804/11/$12.00 doi:10.1128/AAC.01559-10


# Meropenem Penetration into Epithelial Lining Fluid in Mice and Humans and Delineation of Exposure Targets[▽]

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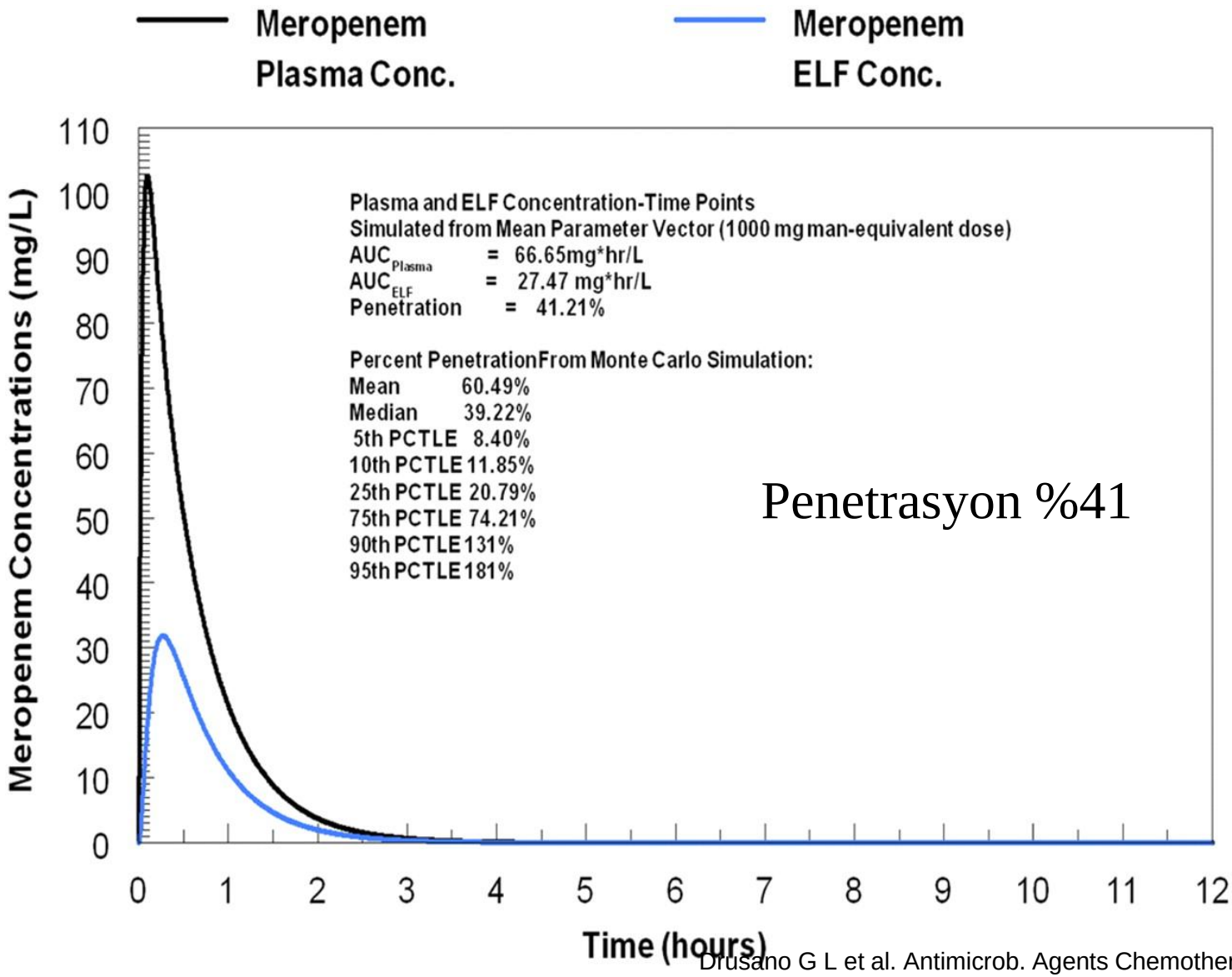
***Pseudomonas aeruginosa*** **pneumonia remains a most-difficult-to-treat nosocomial bacterial infection. We used mathematical modeling to identify drug exposure targets for meropenem in the epithelial lining fluid (ELF) of mice with *Pseudomonas* pneumonia driving substantial [2 to 3 $\log_{10}$ (CFU/g)] killing and which suppressed**

# Pseudomonas aeruginosa enfeksiyonunda dirençli mutantların baskılanması




Drusano G L et al. Antimicrob. Agents Chemother. 2011;55:3406-3412

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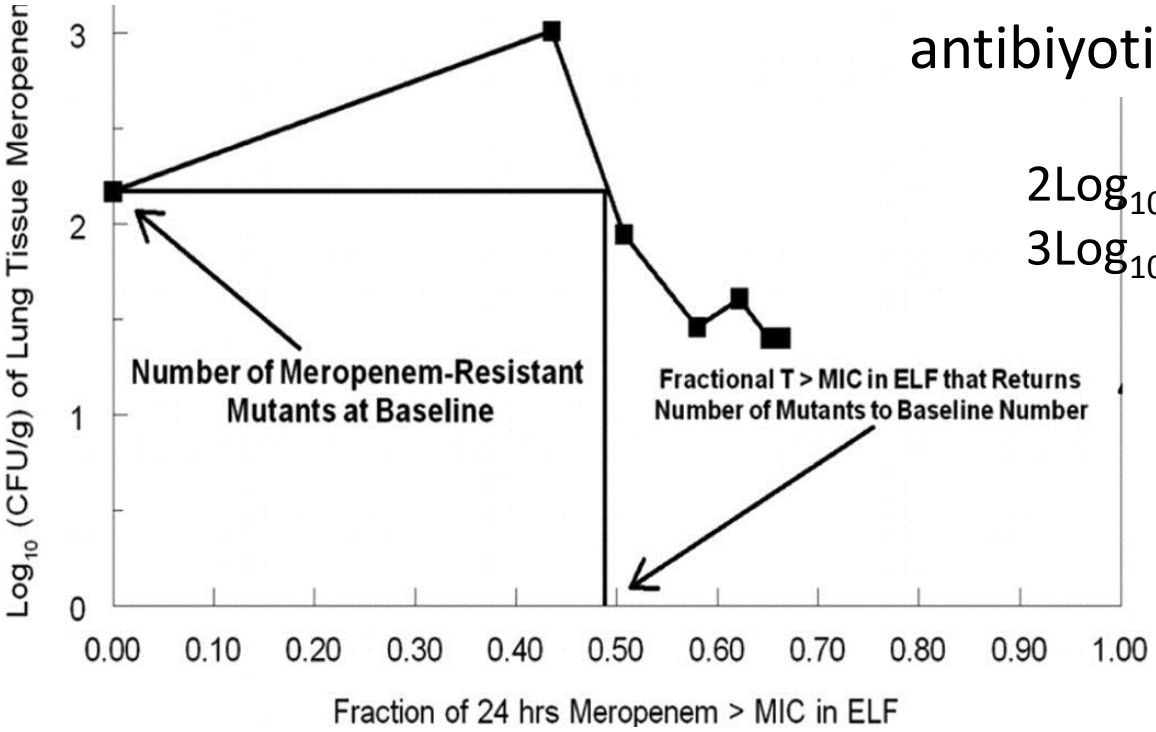


Modelden yapılan hesaplama ile;
Total killing etki için ELF de gerekli antibiyotik konsantrasyonu

$2Log_{10}$(CFU/g)Kill= 0.317 of 24 hr
$3Log_{10}$ (CFU/g)Kill= 0.496 of 24 hr

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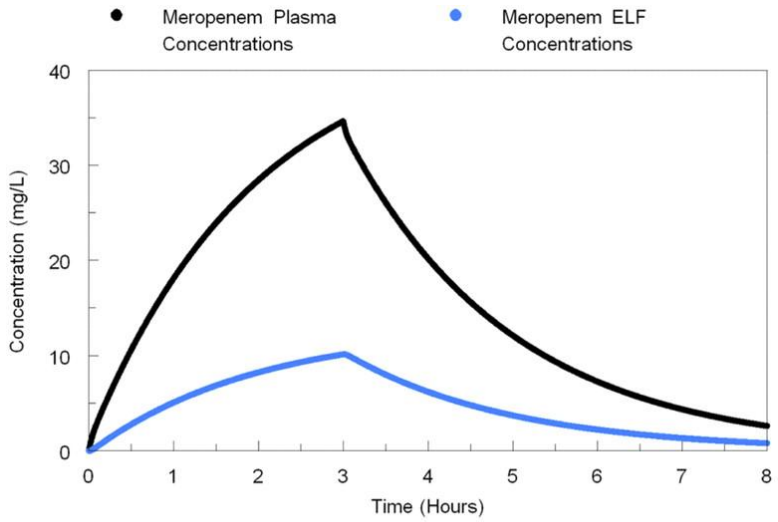



**Observed-Predicted Regressions After the Bayesian Step**

**Plasma**

Observed = 0.998 * Predicted +0.919

$r^2 = 0.962$; $p << 0.001$

**ELF**

Observed = 1.0014 * Predicted – 0.0024

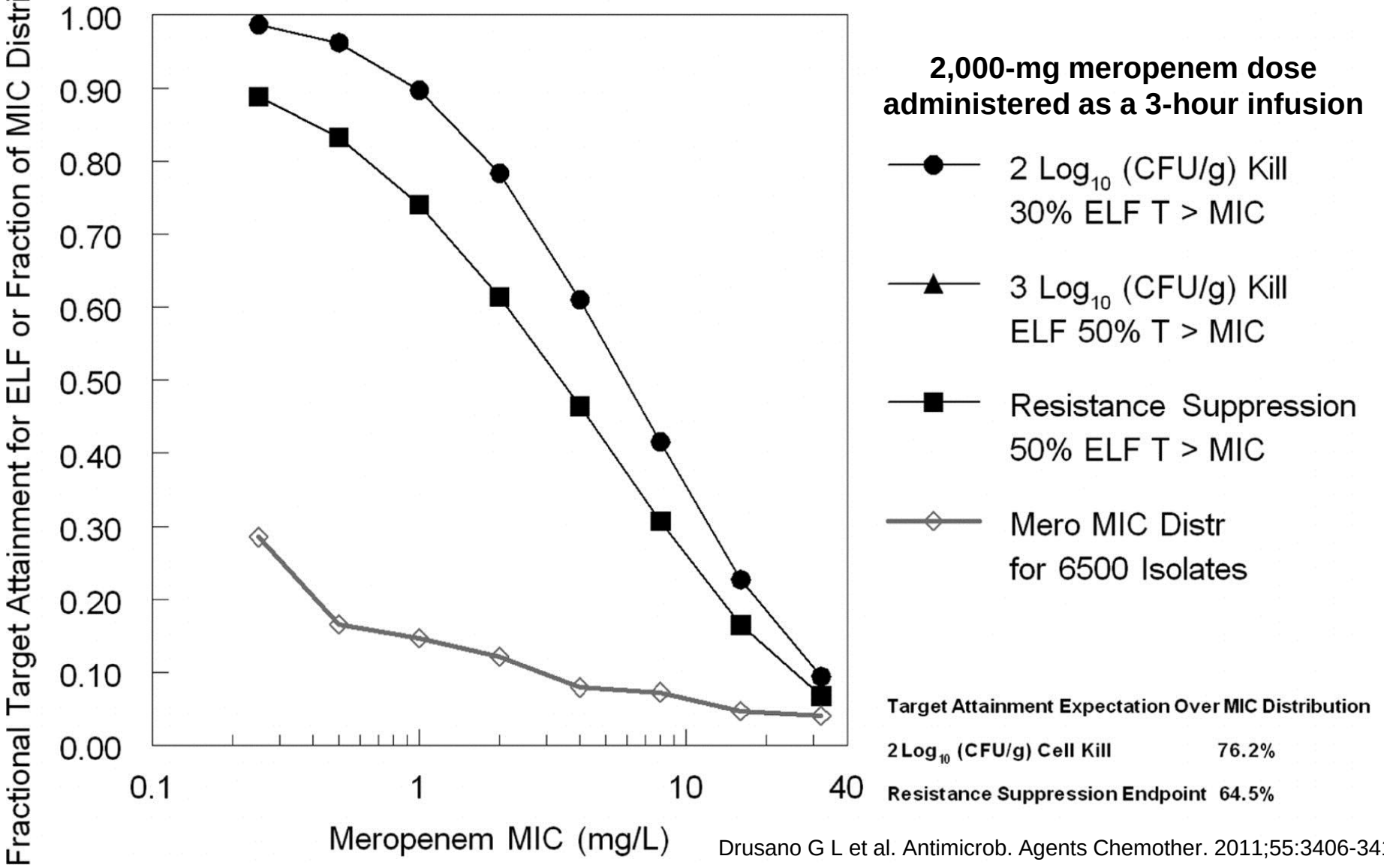
$r^2 = 0.999$; $p << 0.001$

| | $AUC_{PL}$ (mg*h/L) | $AUC_{ELF}$ (mg*h/L) | PENETRATION Fraction |
|---|---|---|---|
| Mean | 150.8 | 82.3 | 0.816 |
| Median | 130.9 | 35.0 | 0.254 |
| 5th Pctle | 51.6 | 2.75 | 0.021 |
| 10th Pctle | 63.9 | 4.76 | 0.037 |
| 25th Pctle | 90.1 | 12.5 | 0.090 |
| 75th Pctle | 189.3 | 92.1 | 0.701 |
| 90th Pctle | 262.1 | 204.7 | 1.779 |
| 95th Pctle | 315.7 | 315.3 | 3.153 |

**Penetration of meropenem into epithelial lining fluid (ELF) in 39 patients with ventilator-associated pneumonia.**

**Drusano G L et al. Antimicrob. Agents Chemother. 2011;55:3406-3412**

# Pseudomonas aeruginosa enfeksiyonunda dirençli mutantların baskılanması

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# Pseudomonas aeruginosa enfeksiyonunda dirençli mutantların baskılanması

1) Meropenem *invitro* etkinliği mükemmel bir ilaç
2) Ancak, infeksiyon bölgesindeki penetrasyona bağlı özellikle MİK>1 izolatlarda 2 $\log_{10}$ (CFU/ml) inhibisyon ve dirençli mutantların supresyonunda problem var
3) Kombine Tedavi??

CLSI ve EUCAST MIK değerlerinin PK/PD değerlere göre yeniden belirlenmesinin gerekli olduğunu belirtti

**Kişiye özel doz hedef**

# Biz Ne Yapabiliriz?

- MİK yüksek izolatların takibi
- Gram negatif enfeksiyonlar çalışma grubu
- Multidisipliner araştırmalar