# Antibiyotiklerde Terapötik İlaç Düzeyi Takibi Yeni Ne Var?

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9 Mart 2024, Antalya

*'Hakiki yenilik, daima kaynaklara dönüşle başlar'*
*Edgar Marin*

# Sunum planı

- Terapötik ilaç düzeyi takibi
  - Amacı nedir?
  - Nasıl yapılır?

- Antibiyotiklerde terapötik ilaç düzeyi takibi
  - Dünden bugüne
  - Yeni ne var?
  - Geleceğe yansımalar

# Antibiyotiklerde Terapötik İlaç Düzeyi Takibi

*Dünden bugüne…*

**Terapötik ilaç görüntülemenin amacı (TİG);**
**Gerçek zamanlı veri sağlamak**
**Kritik hastalarda yan etkiler olmaksızın optimal tedavi yanıtını sağlamak**
**Klinik yanıtı arttırmak ve mortaliteyi azaltmak**
**Antimikrobiyal direnci azaltmak ve antimikrobiyal yönetişime katkı sağlamak**

**İlaçlar**

- MRSA etkili ilaçlar
- Aminoglikozidler
- Beta laktamlar
- Anti fungaller
- Yeni nesil BL-BLI
- Antiviraller

**Hasta grupları**

- Kritik hastalar
- ECMO
- SRRT


Schneider H, et al. Ther Drug Monit 2022;44:230–240

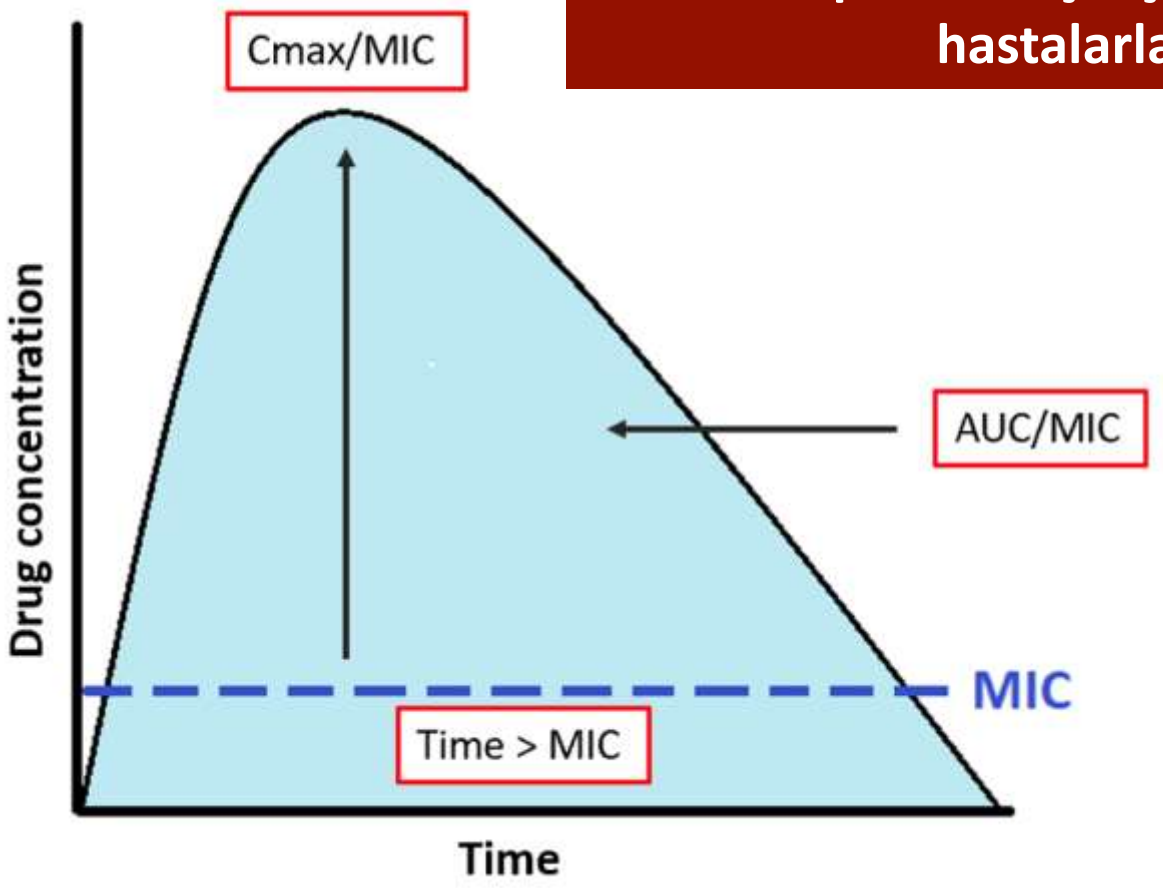
Guilhaumou R, et al. Crit Care Med. 2019;23(1):104.

Abdul-Aziz MH, et al. Intensive Care Med (2020) 46:1127–1153

# Antibiyotiklerde Terapötik İlaç Düzeyi Takibi

*Ufak bir hatırlatma…FK/FD indeksler*

**İndeksler preklinik çalışmalar, hayvan çalışmaları, sağlıklı gönüllüler ve nadiren hastalarla yapılan çalışmalardan elde edilmektedir**




**ECOFF (epidemiyolojik cut-off)**

**Zamana bağlı etki**

- T>MIK ya da %ft>MIK
- Beta-laktamlar, klindamisin, vankomisin, makrolidler

**Konsantrasyona bağlı etki**

- AUC/MIK
- Cmax/MIK
- Aminoglikozidler, florokinolonlar, azitromisin, vankomisin, tigesiklin, linezolid

CONFERENCE REPORT AND EXPERT PANEL

# Antimicrobial therapeutic drug monitoring in

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**Table 1 Pharmacokinetic/pharmacodynamic (PK/PD) indices and the magnitudes associated with antibacterial clinical efficacy and toxicity**

| Antibacterial class | PK/PD index | Pre-clinical PK/PD target for efficacy | Clinical PK/PD target for efficacy | Clinical PK/PD threshold for toxicity |
|---|---|---|---|---|
| Aminoglycosides | | | | |
| Amikacin | $AUC_{0-24}$/MIC | $AUC_{0-24}$/MIC: 80–100 | $C_{max}$/MIC ≥ 8–10 | $C_{min}$ > 5 mg/L[a] |
| Gentamicin/tobramycin | $AUC_{0-24}$/MIC | $AUC_{0-24}$/MIC: 80–100 | $AUC_{0-24}$/MIC ≥ 110 | $C_{min}$ > 1 mg/L[a] |
| Beta-lactams | | | | |
| Carbapenems | | | | |
| Cephalosporins | | | | |
| Penicillins | | | | |
| Co-trimoxazole | | | | |
| Daptomycin | | | | |
| Fluoroquinolones | | | | |
| Glycopeptides | | | | |
| Teicoplanin | | | | |
| Vancomycin | | | | |
| Linezolid | | | | |
| Polymyxins | | | | |
| Colistin | | | | |
| Polymyxin B | | | | |

$AUC_{0-24}$/MIC = the ratio of the area under the concentration–time curve duri
maximum drug concentration to minimum inhibitory concentration; $C_{min}$ = t
ratio of the area under the concentration–time curve during a 24-h period to
concentration remains above the MIC during a dosing interval; PK/PD = phar

**Table 2 Pharmacokinetic/pharmacodynamic (PK/PD) indices and the magnitudes associated with antifungal clinical efficacy and toxicity**

| Antifungal class | PK/PD index | Pre-clinical PK/PD target for efficacy | Clinical PK/PD target for efficacy | Clinical PK/PD threshold for tox- |
|---|---|---|---|---|
| Echinocandins | $AUC_0$ | | | |
| Fluconazole | $AUC_0$ | | | |
| Flucytosine | $fT_{>MIC}$ | | | |
| Isavuconazole | $AUC_0$ | | | |
| Itraconazole | $AUC_0$ | | | |
| Posaconazole | $AUC_0$ | | | |
| Voriconazole | $AUC_0$ | | | |

$AUC_{0-24}$/MIC = the ratio of the area ur
concentration; $C_{min}$ = trough drug cor
a 24-hour period to minimum inhibito
PK/PD = pharmacokinetic/pharmacoc

**Table 3 Pharmacokinetic/pharmacodynamic (PK/PD) indices and the magnitudes associated with antiviral clinical efficacy and toxicity**

| Antivirals | PK/PD index | Pre-clinical PK/PD target for efficacy[a] | Clinical PK/PD target for efficacy | Clinical PK/PD threshold for toxicity |
|---|---|---|---|---|
| Aciclovir/valaciclovir | Unclear | Unclear | Unclear | Unclear |
| Foscarnet | Unclear | Unclear | Unclear | No data |
| Ganciclovir/valganciclovir | AUC | Unclear | AUC: 40–60 mg h/L (Prop) | Unclear |
| Oseltamivir/oseltamivir carboxylate | Unclear | Unclear | Unclear | Unclear |
| Ribavirin | AUC | Unclear | $AUC_{0-4}$ > 1755 mg h/L<br>$AUC_{0-12}$ > 3014 mg h/L<br>$C_{min}$ ≥ 2 mg/L | $C_{min}$ > 2.3 mg/L[b] |

AUC = area under the concentration–time curve; $AUC_{0-4}$ = the ratio of the area under the concentration–time curve during a 4-h period; $AUC_{0-12}$ = the ratio of the area under the concentration–time curve during a 12-h period; $C_{min}$ = trough drug concentration; PK/PD = pharmacokinetic/pharmacodynamic; Prop = prophylaxis

[a] Whilst in vitro concentrations at which viral replication is inhibited by 50% (i.e. $EC_{50}$ representing antiviral activity) have been widely determined, there are no/limited data which correlate these values with in vivo pharmacokinetic parameters (e.g. AUC) to describe magnitudes required for pre-clinical efficacy

[b] Mostly related to anaemia

Abdul-Aziz MH, et al. Intensive Care Med (2020) 46:1127–1153

# Clinical Practice Guideline for the Therapeutic Drug Monitoring of Voriconazole in Non-Asian and Asian Adult Patients: Consensus Review by the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring

Yoshio Takesue, MD, PhD[1,2,#]; Yuki Hanai, PhD[3,#]; Kazutaka Oda, PhD[4]; Yukihiro Hamada, PhD[5]; Takashi Ueda, PhD[1]; Toshihiko Mayumi, MD, PhD[6]; Kazuaki Matsumoto, PhD[7]; Satoshi Fujii, PhD[8]; Yoshiko Takahashi, PhD[9]; Yoshitsugu Miyazaki, MD, PhD[10]; and Toshimi Kimura, PhD[11], on behalf of the Japanese Antimicrobial Therapeutic Drug Monitoring Guideline Committee

**Table II. Recommendations for voriconazole TDM in non-Asian and Asian patients.**

| CQ | Non-Asians | Asians |
|---|---|---|
| CQ1. PK/PD parameter | Trough level (II) | Trough level (II) |
| CQ2. Indication for TDM | TDM is generally recommended mainly to prevent subtherapeutic concentrations (II) | TDM is strongly recommended, mainly because of the risk for supratherapeutic concentrations (I) |
| CQ3. TDM timing | Day 3 after start of therapy (III-A) | Days 3–5 after start of therapy (III-A); if patient condition allows, delaying TDM until day 5 is suggested |
| CQ4. Target trough level | | |
| To improve efficacy outcome | ≥1 μg/mL (I) | ≥1 μg/mL (I) |
| To prevent adverse effects | <5.5 μg/mL is generally recommended (II) | <4 .0 μg/mL is strongly recommended (I) |
| CQ5. Dosing regimen | | |
| Loading dose for initial day | 6.0 mg/kg q12h (I) | 6.0 mg/kg q12h (I) |
| Maintenance dose | 4 mq/kg q12h (II) | 3 mq/kg q12h is suggested to prevent overdose (III-A) |

CQ = clinical question; PK/PD = pharmacokinetic/pharmacodynamic; q12h = every 12 hoursTDM = therapeutic drug monitoring.

# Antibiyotiklerde Terapötik İlaç Düzeyi Takibi

*Nasıl yapılır?*

- Geleneksel yöntem: **Cmin, Cmax**
- Simülasyonlar: Monte Carlo, Bayesian istatistik, **AUC/MIK, ft/MIK**

**TİG yapılabilmesi için;**
**Geçerliliği doğrulanmış bir yöntem şarttır**
**Bireyler arası FK değişkenliğinin belirlenmiş olması gerekir**
**Serum konsantrasyonu ile etki/toksisite ilişkisinin tanımlanmış olmalıdır**
**Terapötik indeksin dar olması gerekmektedir**

Gomez-Lopez A. Clinical Microbiology and Infection 26 (2020) 1481e1487

# Therapeutic Drug Monitoring of Ganciclovir: Where Are We?

**TABLE 1.** Characteristics of the Evaluated Assays for the Determination of Ganciclovir and Its Derivatives

| Author, Year | Analytes | Instrument | Detection | Sample | Ru |
|---|---|---|---|---|---|
| Chan et al, 1998[25] | Ganciclovir | HPLC | Spectrofluorimeter ($\lambda_{ex}$ = 278 nm; $\lambda_{em}$ = 380 nm) | Serum and heparinized human plasma | ≤ |
| Merodio et al, 2000[26] | Ganciclovir | HPLC | Diode array λ = 254 nm | Albumin nanoparticles; human corneal fibroblasts | 8 |
| Tsuchie et al, 2001[27] | Ganciclovir | HPLC | Spectrofluorimeter ($\lambda_{ex}$ = 365 nm; $\lambda_{em}$ = 512 nm) | Human serum | 7. (re t |
| Kishino et al, 2002[28] | Ganciclovir | HPLC | Pulsed amperometer | Plasma samples from transplant recipients | 6.2 |
| Hosseini et al, 2002[39] | Ganciclovir | Raman spectroscopic system | Raman spectrometer | Rabbit eye | |
| Saleh and Hempel 2006[38] | Ganciclovir | Electrophoresis | UV | Human plasma | |
| Perrottet et al, 2007[29] | Ganciclovir | HPLC | Spectrofluorimeter ($\lambda_{ex}$ = 260 nm; $\lambda_{em}$ = 380 nm) | Plasma from SOT patients receiving valganciclovir as prophylaxis | 1. (re t |
| Xu et al, 2007[32] | Valganciclovir, ganciclovir | LC-MS/MS | Tandem mass spectrometer | Human plasma | 5. |
| Weller et al, 2008[30] | Ganciclovir | HPLC | UV | Plasma | 8 |
| Singh et al, 2011[33] | Ganciclovir, valganciclovir | LC-MS/MS | Tandem mass spectrometer | Human plasma | 2. |
| Padullés et al, 2012[31] | Ganciclovir | UPLC | UV λ = 254 nm | Human plasma | 2. |
| Rigo-Bonnin et al, 2014[40] | Ganciclovir | UPLC-MS/MS | Tandem mass spectrometer | Plasma | 2. |
| Billat et al, 2015[34] | Ganciclovir and its derivatives in cells | LC-MS/MS | Tandem mass spectrometer | Whole blood healthy volunteers | |
| Gunda et al, 2015[35] | Ganciclovir, valganciclovir, tyrosine-valganciclovir | LC-MS/MS | Tandem mass spectrometer | Rat plasma samples | <3 |
| Märtson et al, 2018[36] | Ganciclovir | LC-MS/MS | Tandem mass spectrometer | Human serum | 4. |

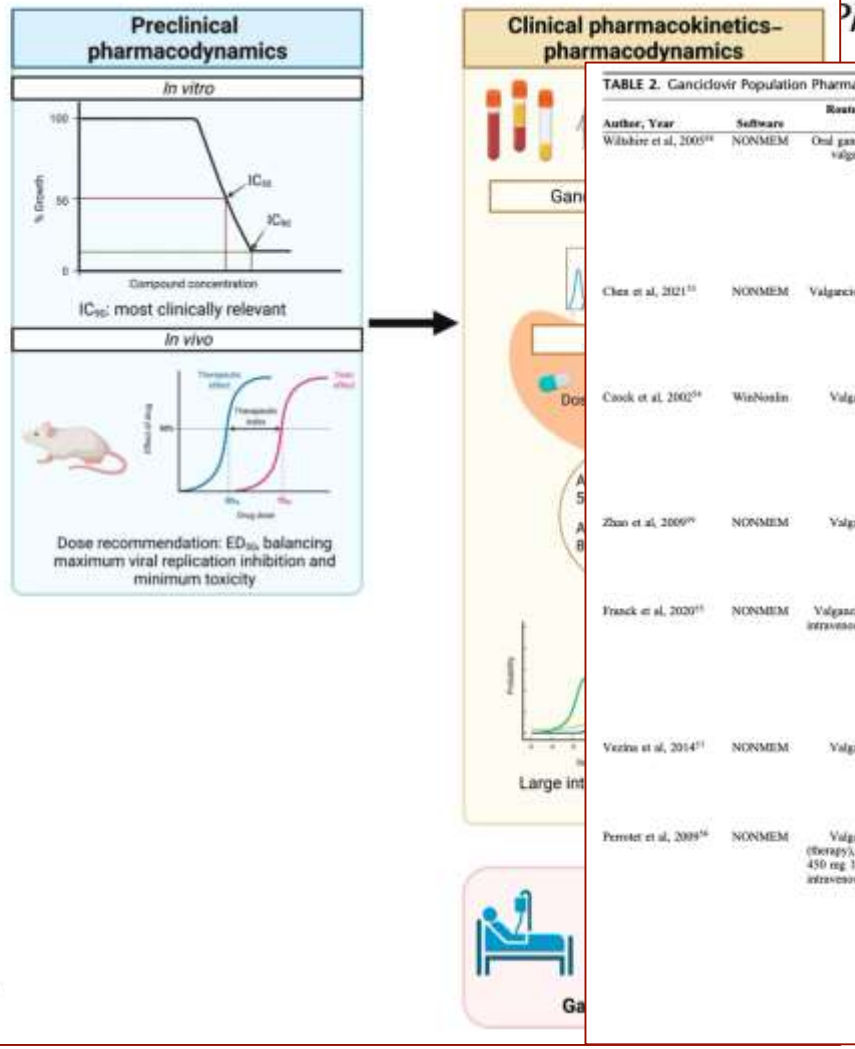



**FIGURE 2.** Preclinical and clinical PK/PD and TDM of ganciclovir.

**TABLE 2.** Ganciclovir Population Pharmacokinetic Models

| Author, Year | Software | Route of Administration or Formulation | Population (n), Country | Final Model |
|---|---|---|---|---|
| Wiltshire et al, 2005[55] | NONMEM | Oral ganciclovir 1000 mg 3dd and valganciclovir 900 mg 1dd | SOT recipients aged 13 yr and older with a CMV serostatus of D+/R− (n = 364); United Kingdom | CL (L/h) = 12.4 × ($CL_{CR}$/median)$^{0.505}$ × (WT/79.6)$^{0.725}$<br>$CL_{CR}$ median males = 80.4 mL/min<br>females = 65.8 mL/min<br>Vc (L) = 25<br>Vp (L) = 49<br>Inter-tissue CL (L/h) = 12 tlag (h) = 0.883<br>Ka ($h^{-1}$) = 0.128 |
| Chen et al, 2021[53] | NONMEM | Valganciclovir 450 mg and 900 mg 1dd | Adult kidney transplant recipients (n = 70); China | CL (L/h) = 7.09 × (1 + $CL_{CR}$/68.3 × 1.08)<br>Vc (L) = 10.8<br>Q (L/h) = 5.96<br>Vp (L) = 174<br>Ka (L/h) = 0.23 tlag (h) = 0.93 |
| Crook et al, 2002[54] | WinNonlin | Valganciclovir 900 mg 1dd | HIV-positive and CMV-positive patients (n = 32), healthy volunteers (n = 12); Germany and England | K10 ($h^{-1}$) = 0.022<br>K12 ($h^{-1}$) = 1.44<br>K21 ($h^{-1}$) = 0.66<br>Vc (L/kg) = 0.213<br>F = 0.63 tlag (h) = 0.77<br>$tau_{half}$ (h) = 5.5<br>Kbd ($h^{-1}$) = 0.57 |
| Zhao et al, 2009[56] | NONMEM | Valganciclovir 900 mg 1dd | Pediatric renal transplant recipients (n = 22); France | CL (L/h) = 8.04 × ($CL_{CR}$/89)$^{1.01}$ × 3.62 × (WT/28)<br>Vc (L) = 5.2<br>Vp (L) = 30.7 tlag (h) = 0.743<br>Ka ($h^{-1}$) = 0.369 |
| Franck et al, 2020[57] | NONMEM | Valganciclovir 10 mg/kg 2dd and intravenous ganciclovir 5 mg/kg 2dd | Pediatric solid-organ and stem cell transplant recipients (n = 50); Canada | CL × WT/26.7 × $CL_{CR}$/149.8 (L/h) = 6.9<br>Vc × WT/26.7 (L) = 9.7<br>Vp × WT/26.7 (L) = 7.6<br>Q × WT/26.7 (L) = 10.9 tlag (h) = 0.33<br>Ka ($h^{-1}$) = 0.73<br>F (%) = 43 |
| Vezina et al, 2014[52] | NONMEM | Valganciclovir 900 mg 1dd | Pediatric and adult SOT recipients (n = 82 adults and 13 children); USA | CL/F (L/h) = 14.5 × (($CL_{CR}$/60) × (70/WT)$^{0.692}$ × (WT/70)$^{0.75}$<br>Vc/F (L) = 87.5 × (WT/70)<br>Vp/F (L) = 42.6 × (WT/70)<br>Q/F (L/h) = 4.8 × (WT/70)$^{0.75}$ |
| Perrottet et al, 2009[58] | NONMEM | Valganciclovir 900 mg 2dd (therapy), 900 mg 1dd (prophylaxis), 450 mg 1dd (renal impairment), and intravenous ganciclovir 5 mg/kg 2dd | Adult SOT recipients (n = 65); Switzerland | CL (L/h) = $\theta_{CrCl_{TBW}}$ × $GFR_{MDRD}$ × $\theta_{female}$<br>$\theta_{kidney}$ 1.68<br>$\theta_{heart}$ 0.86<br>$\theta_{lung/liver}$ 1.17<br>$\theta_{female}$ 1.21<br>Vc (L) = 24 × (WT/70 kg)·$\theta_{female}$<br>$\theta_{female}$ 0.78<br>Vp (L) = 22<br>Q (L/h) = 4.1<br>F = 0.6<br>Ka ($h^{-1}$) = 0.56 |

# Antibiyotiklerde Terapötik İlaç Düzeyi Takibi

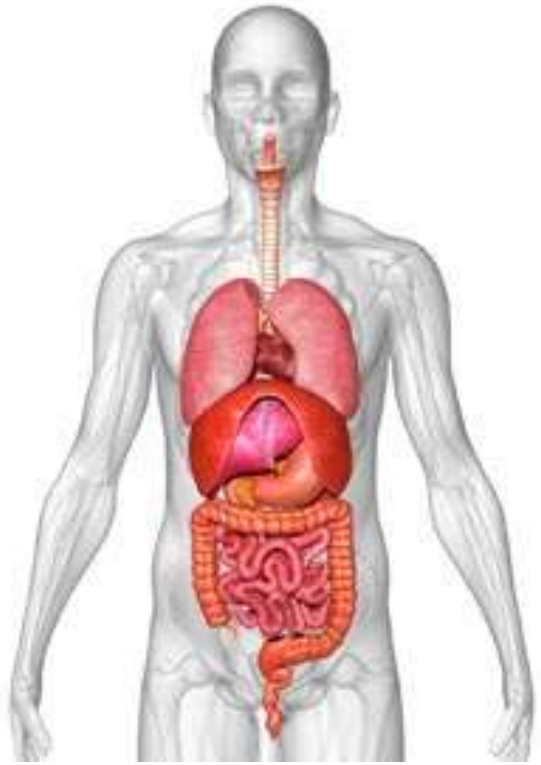
## *Kısıtlılıklar*

- Daha kısa sürede sonuç verecek yeni bir altın standart teste ihtiyaç var!
- Yalnız serum düzeyi ölçülebiliyor!
- İnfeksiyon bölgesindeki ilaç düzeyini ölçebilecek yöntemlere ihtiyaç var!
- Kolay kullanılabilir modellere ihtiyaç var!

Abdul-Aziz MH, et al. Intensive Care Med (2020) 46:1127–1153

# Kritik hastalar
## *FK/FD indeksler nelerden etkilenir?*

- Dağılım hacmi değişimi
  - Endotelyal disfonksiyon, kapiller kaçak, sıvı yükündeki artış- Hidrofilik antibiyotikler
  - Hipoalbuminemi-Proteinlere yüksek oranda bağlanan antibiyotikler
- Klirens değişikliği
  - Artmış renal klirens
    - %14-80, Mekanizma net değil
  - SRRT, ECMO



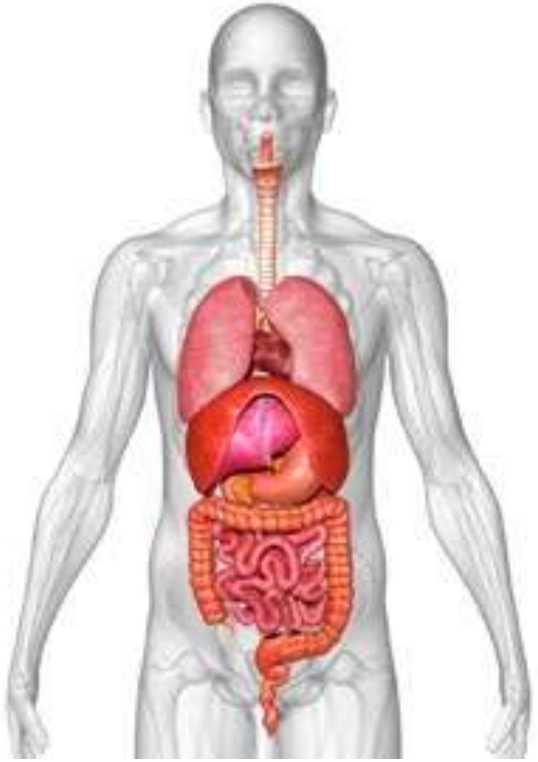
**DALI [defining antibiotic levels in intensive care unit patients] çalışmasında kritik hastaların %20-50'sinde hedeflenen FK/FD hedef değerlere ulaşılamadığı gösterilmiştir**

Abdul-Aziz MH, et al. Intensive Care Med (2020) 46:1127–1153.
Roberts JA, et al. BMC Infect Dis. 2012 Jul 6;12:152.

# Kritik hastalar

## *FK/FD indeksler nelerden etkilenir?*

- Yaş
- Cinsiyet
- Vücut ağırlığı
- Etnik köken
- İnfeksiyon odağı
- Organ disfonksiyonu
- Kan pH'sı
- Doku perfüzyonu
- Diğer ilaç kullanımı



**Başta meropenem olmak üzere karbapenem düzeyi ölçümünden en çok böbrek fonksiyon bozukluğu olan hastaların fayda görmesi beklenmektedir**

Steffens NA, et al. J Clin Pharm Ther. 2021;46:610–621.
Matusik E et al. BMC Nephrology (2022) 23:48
Matusik E. Ther Drug Monit. 2021

# SRRT


SRRT: Sürekli renal replasman tedavisi

- Kritik hastaların takibi sırasında hastaların >%30'unda akut böbrek yetmezliği görülmektedir
  - Bu hastaların %19.2'sinde RRT ihtiyacı gelişmektedir
- Septik şok ile izlenen hastalarda RRT ihtiyacı %3-36 arasında değişmektedir
- Sürekli venovenoz hemodiyaliz
- Sürekli venovenoz hemofiltrasyon
- Sürekli venozvenoz hemodiafiltrasyon
- Yavaş devamlı ultrafiltrasyon

Clec'h C, et al. Crit Care. 2011;15:R128.
Iwagami M, et al. Nephrol Dial Transpl. 2018;33:1354–1362.
Poukkanen M, et al. Crit Care. 2014;18:R26.
Matusik E. Ther Drug Monit. 2021

# SRRT


SRRT: Sürekli renal replasman tedavisi

- Sıvı ve kan aynı yönde hareket eder
- Kan kompartmanında basınç daha yüksektir

- Difüzyon
- Konveksiyon
- Adsorpsiyon

- Sıvı akış hızı

Clec'h C, et al. Crit Care. 2011;15:R128.
Iwagami M, et al. Nephrol Dial Transpl. 2018;33:1354–1362.
Poukkanen M, et al. Crit Care. 2014;18:R26.
Matusik E. Ther Drug Monit. 2021

# SRRT

**TABLE 2.** Practical Recommendations for Therapeutic Drug Monitoring of Antibiotics in Patients Receiving RRT

| Antibiotics | TDM Recommendation | PK/PD Target | Time from Therapy Onset or Dose Change to TDM | Suggested Sampling Strategy | Drug Administration in Patients Undergoing Intermittent RRT |
|---|---|---|---|---|---|
| Aminoglycosides | TDM recommended | Cmax/MIC ≥8–10<br>AUC: 80–120 mg·h/L<br>Safety target:<br>Cmin amikacin <2.5 mg/L<br>Cmin gentamicin/tobramycin/netilmicin <0.5 mg/L | After the first dose | Cmax:<br>30 min after the end of infusion<br>Cmin: Just before the next infusion and before the intermittent RRT session | Administration after the intermittent RRT session on dialysis day<br>An additional half-dose after the end of the session may be administered on dialysis day preceding 72 h interdialytic period |
| Beta-lactams | TDM recommended | *f*Cmin or *f*Css ≥ 1 MIC (*f*T > MIC = 100%)<br>Safety target: Piperacillin: Cmin <361 mg/L<br>Piperacillin/tazobactam: Css <157 mg/L<br>Cefepime: Cmin <20–22 mg/L or Css <35 mg/L meropenem: Cmin <64 mg/L | 24–48 h | | |
| Vancomycin | TDM recommended | Cmin:10–20 mg/L<br>Css: 20–25 mg/L<br>AUC/MIC ≥400 mg/L·h<br>Safety target:<br>AUC <600 mg/L·h | 24–48 h (loading dose required) | Cmin: Just before the | Administration during |
| Teicoplanin | TDM recommended | Cmin ≥15–40 mg/L | 48–72 h (loading do required) | | |
| Fluoroquinolones | TDM suggested in critically ill patients | AUC/MIC ≥100–125<br>Cmax/MIC ≥8–12 | 48–72 h | | |
| Linezolid | TDM recommended | Cmin of 2–7 mg/L | 48–72 h | | |
| Daptomycin | TDM suggested in critically ill patients | AUC/MIC ≥666<br>Safety target:<br>Cmin <24 mg/L | 48–72 h | | |
| Tigecycline | TDM suggested in critically ill patients | AUC/MIC ≥17.9<br>AUC/MIC ≥12.8<br>AUC/MIC ≥6.96 | 96 h | AUC-based monitoring: Cmin + Cmax 0.5–1 h after the intermittent infusion | NS |
| Colistin | TDM recommended | Cmin ~2 mg/L | 48–72 h | Cmin immediately before the next infusion<br>48–72 h and just before the intermittent RRT session | RRT sessions at the end of the dosing interval<br>An additional dose after the end of the session may be administered<br>Loading dose |

[a]Times to the first TDM indicated are those necessary to achieve steady-state exposure in most situations. Earlier sampling is possible when a model-based TDM is used (see text).

72 h interdialytic period

Matusik E. Ther Drug Monit. 2021

# SRRT
## *Meropenem*


Sanford: 8 saatte bir 750 mg

Schatz ML, et al. Antimicrobial Agents and Chemotherapy . 2023.

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

PHARMACOLOGY

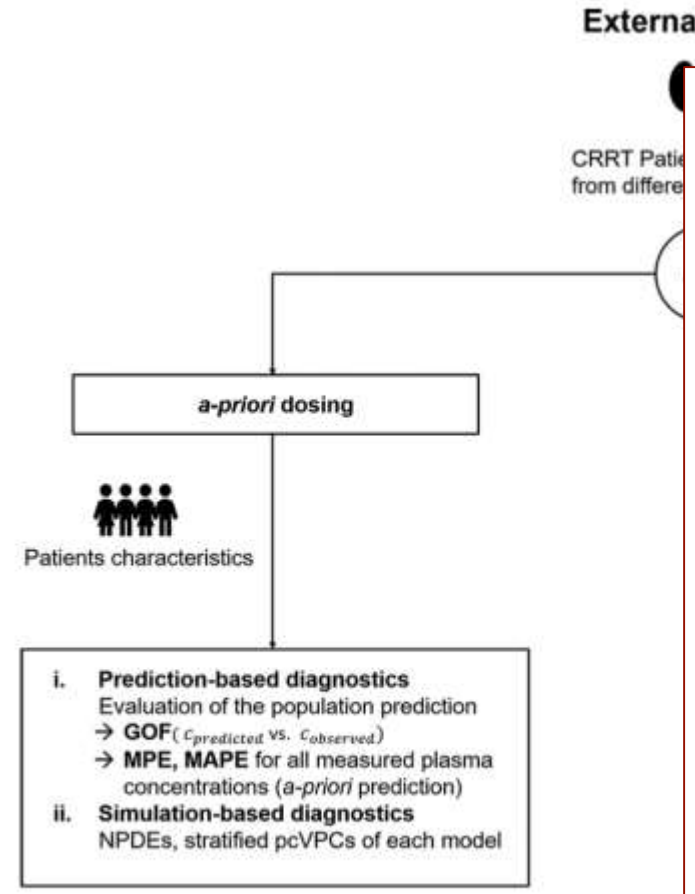



**FIG 3** Model evaluation workflow for model-informed precisio
fit-plots; MPE, median prediction error; MAPE, median absolut
prediction-corrected visual-predictive-check.

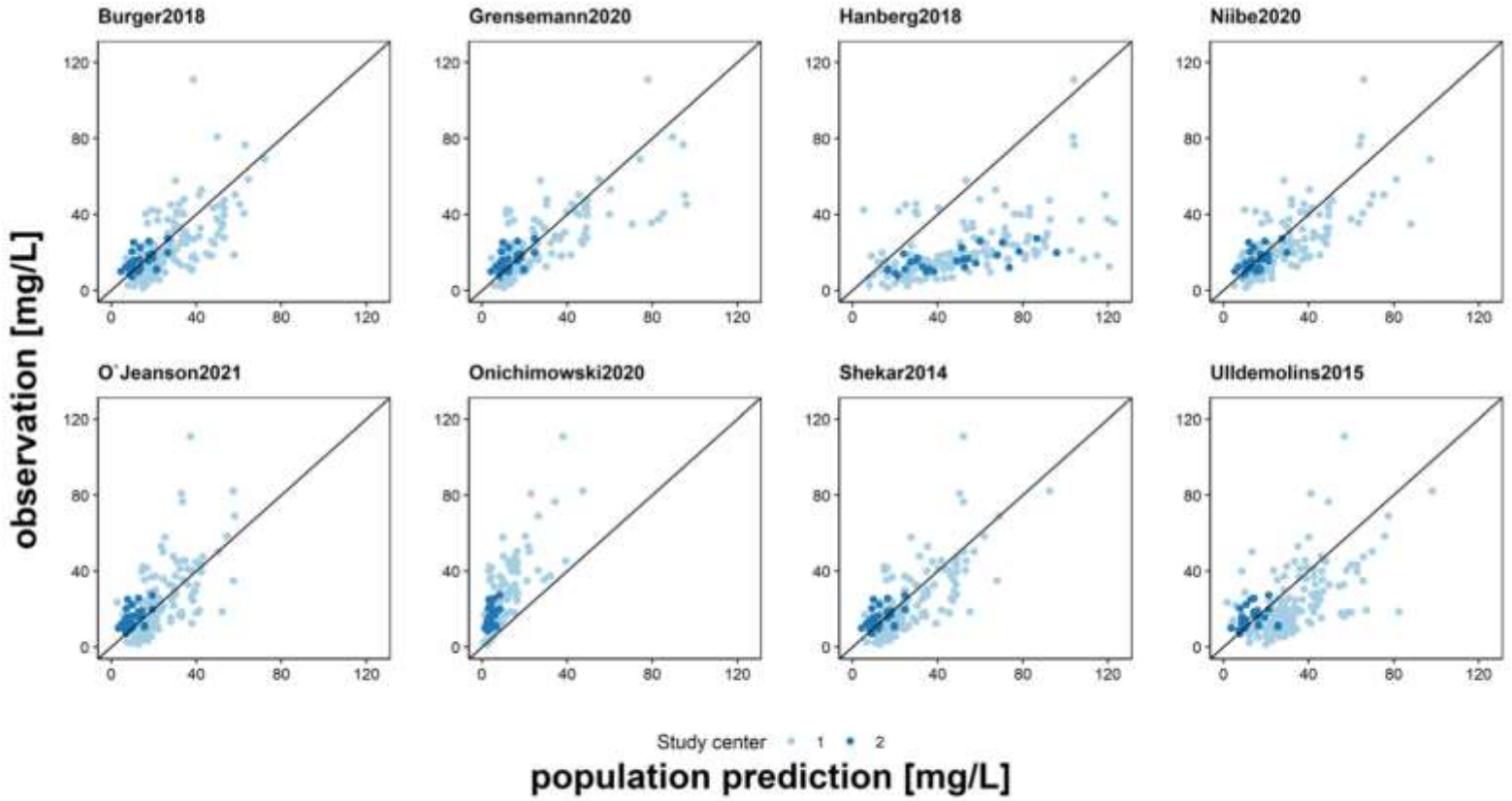
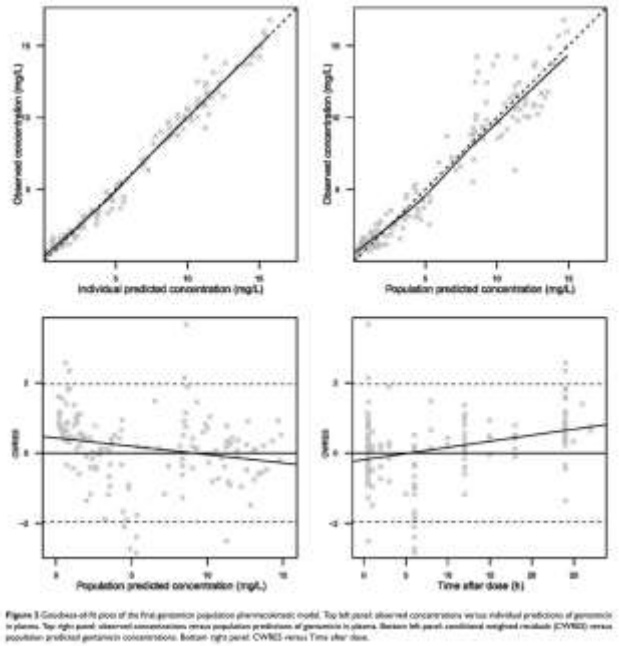



**FIG 1** Goodness-of-fit plot: population predictions of the investigated models versus observations of all measured meropenem plasma concentrations. Black line: line of identity.

Schatz ML, et al. Antimicrobial Agents and Chemotherapy . 2023.

# SRRT
## *Gentamisin*

- Etkililik: Cmax/MIK >8-10, AUC/MIK>100
- Toksisite: Cmin<1-2 mg/l
- SRRT alan kritik hastalarda dağılım hacminin sağlıklı gönüllülerden %56 daha fazla olduğu bildirilmiştir
  - Öneri: SRRT Cmax'ın azalmasına neden olacağından hedef değere ulaşmak için ilaç miktarının arttırılması gerekmektedir



**Bir popülasyon FK model çalışmasında 40 ml/kg/h SRRT alan hastalarda MIK<1 mg/ml olan suşlar için gentamisin dozu 24 saatte 7 mg/kg önerilmiştir**

He S, et al. Drug Design, Development and Therapy 2022:16 13–22

# SRRT
## *Polimiksin B*

**Population pharmacokinetics and limited sampling strategies of polymyxin B in critically ill patients**

**Meng-Ying Pi[1,2]†, Chang-Jie Cai[3]†, Ling-Yun Zuo[3]†, Jun-Tao Zheng[1], Miao-Lun Zhang[1,2], Xiao-Bin Lin[1], Xiao Chen[1], Guo-Ping Zhong[4] and Yan-Zhe Xia[1]***

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**Objectives:** To characterize the pharmacokinetics (PK) of polymyxin B in Chinese critically ill patients. The factors significantly affecting PK parameters are identified, and a limited sampling strategy for therapeutic drug monitoring of polymyxin B is explored.

**Methods:** Thirty patients (212 samples) were included in a population PK analysis. A limited sampling strategy was developed using Bayesian estimation, multiple linear regression and modified integral equations. Non-linear mixed-effects models were developed using Phoenix NLME software.

**Results:** A two-compartment population PK model was used to describe polymyxin B PK. Population estimates of the volumes of central compartment distribution (V) and peripheral compartment distribution (V2), central compartment clearance (CL) and intercompartmental clearance (Q) were 7.857 L, 12.668 L, 1.672 L/h and 7.009 L/h. Continuous renal replacement therapy (CRRT) significantly affected CL, and body weight significantly affected CL and Q. The $AUC_{0\text{-}12h}$ of polymyxin B in patients with CRRT was significantly lower than in patients without CRRT. CL and Q increased with increasing body weight. A limited sampling strategy was suggested using a two-sample scheme with plasma at 0.5h and 8h after the end of infusion ($C_{0.5}$ and $C_8$) for therapeutic drug monitoring in the clinic.

**Conclusions:** A dosing regimen should be based on body weight and the application of CRRT. A two-sample strategy for therapeutic drug monitoring could facilitate individualized treatment with polymyxin B in critically ill patients.

- **Sanford: Doz ayarlaması önermez**
- **Polimiksin B klirensi vücut ağırlığı ve SRRT ile değişmektedir**
- **SRRT alan hastalarda AUC azalmaktadır**
- **TİG verileri sınırlıdır**
  - **C0.5h ve C8h ölçümü (ikili şema) önerilmiştir**

# SRRT
## *Seftazidim-avibaktam*

- Sanford: 8 saatte bir 1.25 gram

- *K. pneumoniae* ilişkili infeksiyonlar nedeniyle seftazidim-avibaktam ile tedavi edilen kritik hastalarda SRRT tedavi altında direnç gelişimi ve klinik yanıtsızlıkla ilişkilendirilmiştir

- Karbapenemlere dirençli Gram-negatif kan dolaşımı infeksiyonu nedeniyle seftazidim-avibaktamın devamlı infüzyonla verildiği 10 hastanın ikisinde mikrobiyolojik yanıtsızlık görülmüş ve ikisinin de SRRT aldığı belirlenmiştir

- Hedef değerler?
  - Cmin/MIK 1-4
  - Kritik hastalarda %100 fT > 4XMIC

Shields RK, et al. Antimicrob Agents Chemother. 2018;62(5):e02497-e02417.
Wenzler E, et al. Antimicrob Agents Chemother. 2017;61(7):e00464–17.
Bakdach D, et al. J Clin Med. 2022;11(23):6898.
Delattre IK, et al. Expert Rev Anti Infect Ther. 2017;15(7):677-688.
Gatti M, et al. Int J Antimicrob Agents. 2023;61(1):106699.
Gatti M, et al. J Crit Care. 2023;76:154301.

# SRRT
## *COVID-19?*

International Journal of Antimicrobial Agents 63 (2024) 106997

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Short Communication

### High concentrations of nirmatrelvir/ritonavir in critically ill patients receiving continuous renal replacement therapy

Rong Dong[a,b], Yizhen Huang[a,c], Xiao Ling[a,d], Lu Li[a], Wenqiao Yu[e,*], Saiping Jiang[a,*]

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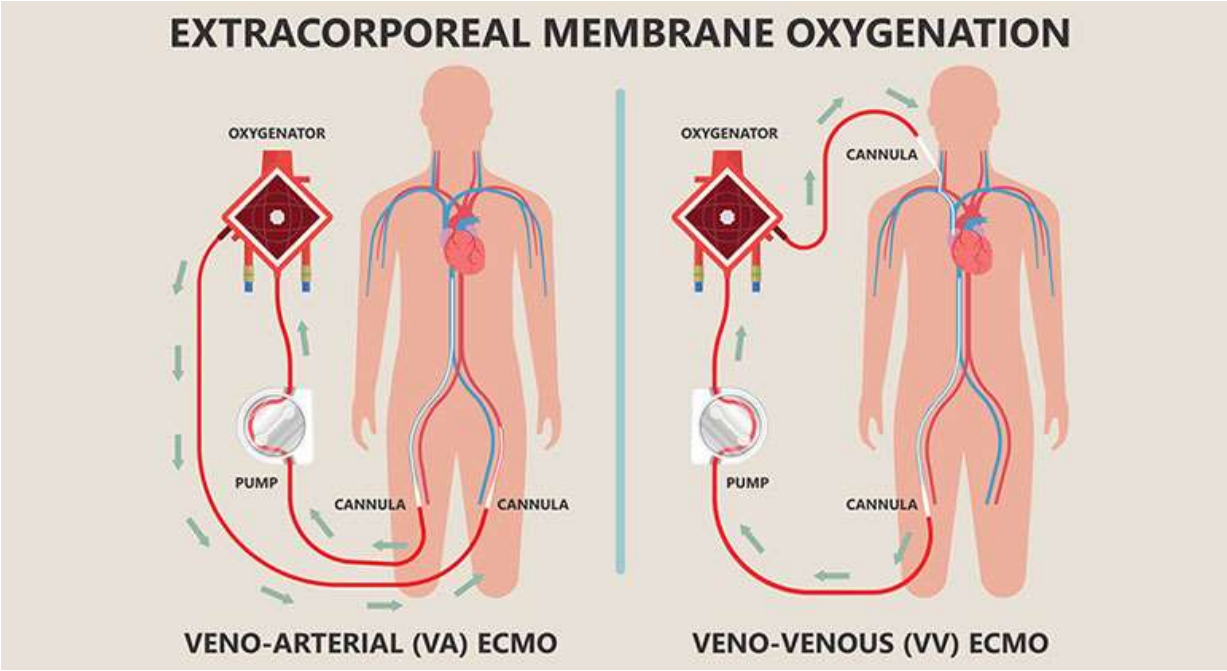
[b] Department of Clinical Pharmacy, Key Laboratory of Clinical Cancer Pharmacology and Toxicology Research of Zhejiang Province, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, 310006, China
[c] Department of Pharmacy, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, Zhejiang, 321000, China
[d] Department of Pharmacy, The People's Hospital of Yuhuan, Taizhou, Zhejiang, 317600, China
[e] Department of Hepatobiliary and Pancreatic Surgery and Intensive Care Unit, The First Affiliated Hospital, Zhejiang University, School of Medicine, Hangzhou, 310021, China

- **CRRT ihtiyacı olan sekiz COVID-19 hastasında kübe göre kullanılan nirmatrelvir/ritonavirin normal böbrek fonksiyonu olan hastalara göre 7 kat, hemodiyaliz ihtiyacı olan hastalara göre 2 kat daha yüksek olduğu bildirilmiştir**

# ECMO




ECMO: Ekstrakorporal membran oksijenizasyonu

- Veno-venöz=Solunum desteği
- Veno-arteriyel=Kardiyak ve/veya solunum desteği
- Kanül
  - Hastanın venöz sisteminden kanı drene eder
  - Veno-arteriyel ECMO'da kanı tekrar hastaya götürür
- Oksijenatör
- Isıtıcı
- Mekanik pompa

# ECMO

**Ekstrakorporal Yaşam Destek Organizasyonu (ELSO) ECMO desteği alan hastalarda tüm yaş gruplarında infeksiyon hızı**
**1000 ECMO gününde 15 bildirmişlerdir**
**Bu infeksiyonlar nedeniyle hastaların %56-68'i kaybedilmektedir**

**Extracorporeal Life Support Organization Registry report: international summary. 2016**

- İlaçlar önemli bir zaman diliminde ekstrakorporal alanda ve çeşitli yabancı yüzeylerle temas halindedir
- Çoğu hastada end organ disfonksiyonu nedeniyle klirens azalır ancak;
  - Dağılım hacmi artar
  - Sıvı miktarı artar
  - Serum konsantrasyonu azalır
- Proteinler devreye bağlanmaktadır

Ha MA, Sieg AC. Pharmacotherapy 2017;37(2):221–35.
Cheng V, et al. J Thorac Dis 2018;10(Suppl 5):S629–41.
Shekar K, et al.. J Crit Care. 2012;27(6):741.e9–741.e18.
Varghese JM, et al. Curr Opin Anaesthesiol 2010;23(4):472–8.

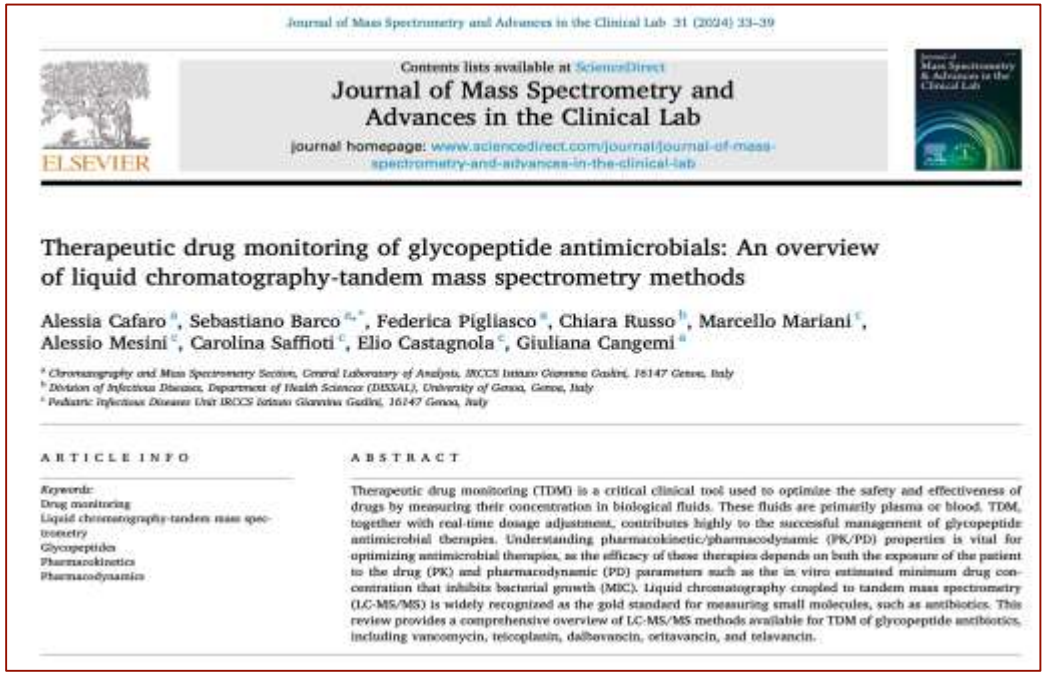
# Vankomisin

PHARMACOTHERAPY

SPECIAL ARTICLE

**Executive Summary: Therapeutic Monitoring of Vancomycin for Serious Methicillin-Resistant *Staphylococcus aureus* Infections: A Revised Consensus Guideline and Review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists**

Michael J. Rybak[1,2,3*] Jennifer Le,[4] Thomas P. Lodise,[5,6] Donald P. Levine,[2,3] John S. Bradley,[7,8] Catherine Liu,[9,10] Bruce A. Mueller,[11] Manjunath P. Pai,[11] Annie Wong-Beringer,[12] John C. Rotschafer,[13] Keith A. Rodvold,[14] Holly D. Maples,[15] and Benjamin M. Lomaestro[6]



Journal of Mass Spectrometry and Advances in the Clinical Lab 31 (2024) 33–39

Contents lists available at ScienceDirect

Journal of Mass Spectrometry and Advances in the Clinical Lab

journal homepage: www.sciencedirect.com/journal/journal-of-mass-spectrometry-and-advances-in-the-clinical-lab

**Therapeutic drug monitoring of glycopeptide antimicrobials: An overview of liquid chromatography-tandem mass spectrometry methods**

Alessia Cafaro [a], Sebastiano Barco [a,*], Federica Pigliasco [a], Chiara Russo [b], Marcello Mariani [c], Alessio Mesini [c], Carolina Saffioti [c], Elio Castagnola [c], Giuliana Cangemi [a]

[a] Chromatography and Mass Spectrometry Section, Central Laboratory of Analysis, IRCCS Istituto Giannina Gaslini, 16147 Genoa, Italy
[b] Division of Infectious Diseases, Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy
[c] Pediatric Infectious Diseases Unit IRCCS Istituto Giannina Gaslini, 16147 Genoa, Italy

ARTICLE INFO

*Keywords:*
Drug monitoring
Liquid chromatography-tandem mass spectrometry
Glycopeptides
Pharmacokinetics
Pharmacodynamics

ABSTRACT

Therapeutic drug monitoring (TDM) is a critical clinical tool used to optimize the safety and effectiveness of drugs by measuring their concentration in biological fluids. These fluids are primarily plasma or blood. TDM, together with real-time dosage adjustment, contributes highly to the successful management of glycopeptide antimicrobial therapies. Understanding pharmacokinetic/pharmacodynamic (PK/PD) properties is vital for optimizing antimicrobial therapies, as the efficacy of these therapies depends on both the exposure of the patient to the drug (PK) and pharmacodynamic (PD) parameters such as the in vitro estimated minimum drug concentration that inhibits bacterial growth (MIC). Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) is widely recognized as the gold standard for measuring small molecules, such as antibiotics. This review provides a comprehensive overview of LC-MS/MS methods available for TDM of glycopeptide antibiotics, including vancomycin, teicoplanin, dalbavancin, oritavancin, and telavancin.

- **AUC/MIK >400-600, Bayesian model**
- Cmin 15-20 mg/l
  - MRSA ilişkili ciddi infeksiyonlarda önerilmemektedir: Etkililik, nefrotoksisite
  - Mevcut kanıtlar MRSA dışı infeksiyonlarda kullanımı için önermeye yeterli değildir

- Vankomisin ölçümü sıklıkla immunoassaylerle yapılmaktadır
  - Duyarlılık ve özgüllüğü likit kromatografiden daha düşüktür

# ECMO
## *Vankomisin*

- Literatürde ECMO tedavisinin vankomisin farmakokinetiğine etkisini değerlendiren çok sayıda çalışma bulunmaktadır
  - Bu çalışmaların sonuçları birbirinden farklılık göstermektedir
  - Çalışmaların bazılarında vankomisin kinetiğinin etkilenmediği, bazılarındaysa ECMO tedavisi alan hastalarda belirgin biçimde değiştiği bildirilmiştir


Amaker RD, et al. Antimicrob Agents Chemother. 1996.
Mulla H, Pooboni S. Br J Clin Pharmacol. 2005 10.1111/ j.1365-2125.2005.02432.x.
Hoie E, et al. Clin Pharm. 1990;9:711–5. [PubMed: 2225752]
Moore JN, et al. 2016 10.1002/psp4.12112.
Donadello K, et al. Crit Care. 2014 10.1186/s13054-014-0632-8.
Park SJ, et al.. PLoS ONE. 2015 10.1371/ journal.pone.0141016.

# ECMO
## *Meropenem*

- Saito J ve ark.
  - Meropenem populasyon farmakokinetik modelleme çalışması
  - WinBUGS v.1.4.3 programı, Bayesian istatistik
  - ECMO ile tedavi edilen kritik hastalarda %100 fT>MIC ve %100 fT>4MIC hedeflerine ulaşmak için ilaç dozunu dört kat arttırmak ve ilacı uzun infüzyonla vermek gerekmektedir

Saito J, et al. Journal of Global Antimicrobial Resistance 22 (2020) 651–655

# ECMO
## *İmipenem*

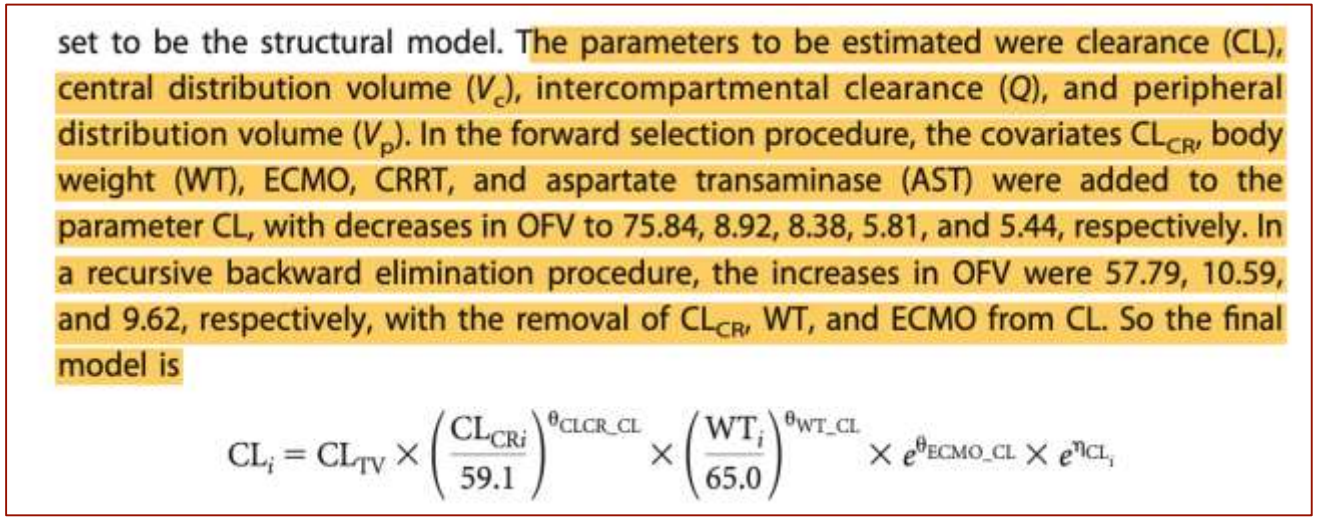
AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

PHARMACOLOGY

**Imipenem Population Pharmacokinetics: Therapeutic Drug Monitoring Data Collected in Critically Ill Patients with or without Extracorporeal Membrane Oxygenation**

Wenqian Chen,[a] Dan Zhang,[a] Wenwen Lian,[a] Xiaoxue Wang,[a] Wenwen Du,[a] Zhu Zhang,[b] Dongjie Guo,[a] Xianglin Zhang,[a] Qingyuan Zhan,[b] Pengmei Li[a]

[a]Department of Pharmacy, China-Japan Friendship Hospital, Beijing, China
[b]Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China



set to be the structural model. The parameters to be estimated were clearance (CL), central distribution volume ($V_c$), intercompartmental clearance ($Q$), and peripheral distribution volume ($V_p$). In the forward selection procedure, the covariates $CL_{CR}$, body weight (WT), ECMO, CRRT, and aspartate transaminase (AST) were added to the parameter CL, with decreases in OFV to 75.84, 8.92, 8.38, 5.81, and 5.44, respectively. In a recursive backward elimination procedure, the increases in OFV were 57.79, 10.59, and 9.62, respectively, with the removal of $CL_{CR}$, WT, and ECMO from CL. So the final model is

$$CL_i = CL_{TV} \times \left(\frac{CL_{CRi}}{59.1}\right)^{\theta_{CLCR\_CL}} \times \left(\frac{WT_i}{65.0}\right)^{\theta_{WT\_CL}} \times e^{\theta_{ECMO\_CL}} \times e^{\eta_{CL_i}}$$

İmipenem popülasyon farmakokinetik çalışması
Monte-Carlo simülasyonu
1000 hasta
NONMEM programı

**ECMO ile tedavi edilen hastalarda imipenem 6 saatte bir 750 mg verildiğinde tedavi başarı hızı daha yüksektir**

# ECMO
## *Teikoplanin*

- Ciddi infeksiyonların tedavisinde tedavisinde teikoplanin Cmin >15 mg/ml olması önerilmiştir

Harding I, et al. J Antimicrob Chemother 2000;45:835e41.

Journal of the Formosan Medical Association (2020) 119, 1086–1092

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

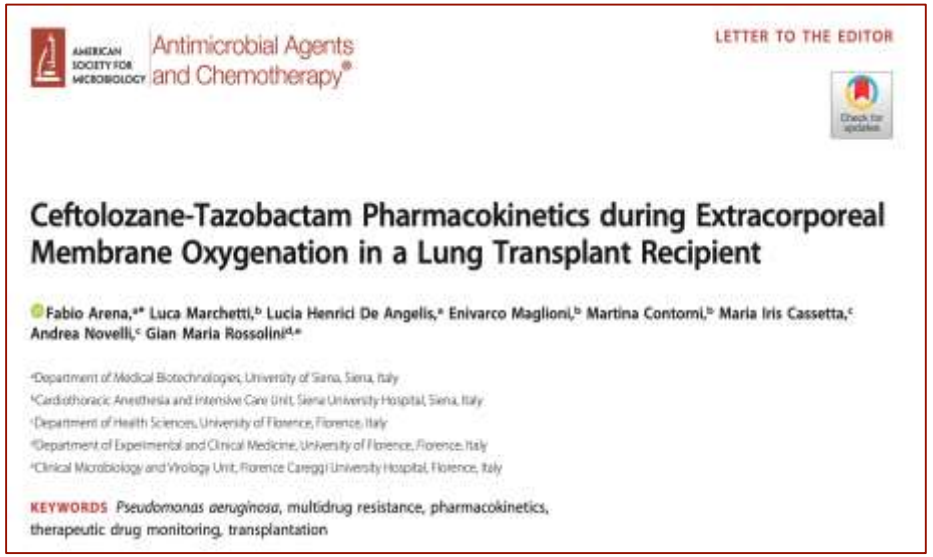
Original Article

**Therapeutic drug monitoring of the teicoplanin trough level after the loading doses in patients receiving venoarterial extracorporeal membrane oxygenation**

Guan-Jhou Chen [a], Shu-Wen Lin [b,c,d], I-Lin Tsai [e,f], Ching-Hua Kuo [c,d,g], Jann-Tay Wang [h], Szu-Min Hsieh [h,*]

**VA-ECMO ile tedavi edilen 11 hasta Teikoplanin ilk üç dozu 12 saat arayla ve dördüncü doz üçüncü dozdan 24 saat sonra ve tüm dozlar 12 mg/kg verildiğinde hastaların %90.9'unda hedef değerlere ulaşılabilmiştir**

# ECMO
## *Seftolozan tazobaktam*



Antimicrobial Agents and Chemotherapy®

LETTER TO THE EDITOR

**Ceftolozane-Tazobactam Pharmacokinetics during Extracorporeal Membrane Oxygenation in a Lung Transplant Recipient**

Fabio Arena,[a]* Luca Marchetti,[b] Lucia Henrici De Angelis,[a] Enivarco Maglioni,[b] Martina Contorni,[b] Maria Iris Cassetta,[c] Andrea Novelli,[c] Gian Maria Rossolini[d,e]

[a]Department of Medical Biotechnologies, University of Siena, Siena, Italy
[b]Cardiothoracic Anesthesia and Intensive Care Unit, Siena University Hospital, Siena, Italy
[c]Department of Health Sciences, University of Florence, Florence, Italy
[d]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
[e]Clinical Microbiology and Virology Unit, Florence Careggi University Hospital, Florence, Italy

KEYWORDS *Pseudomonas aeruginosa*, multidrug resistance, pharmacokinetics, therapeutic drug monitoring, transplantation

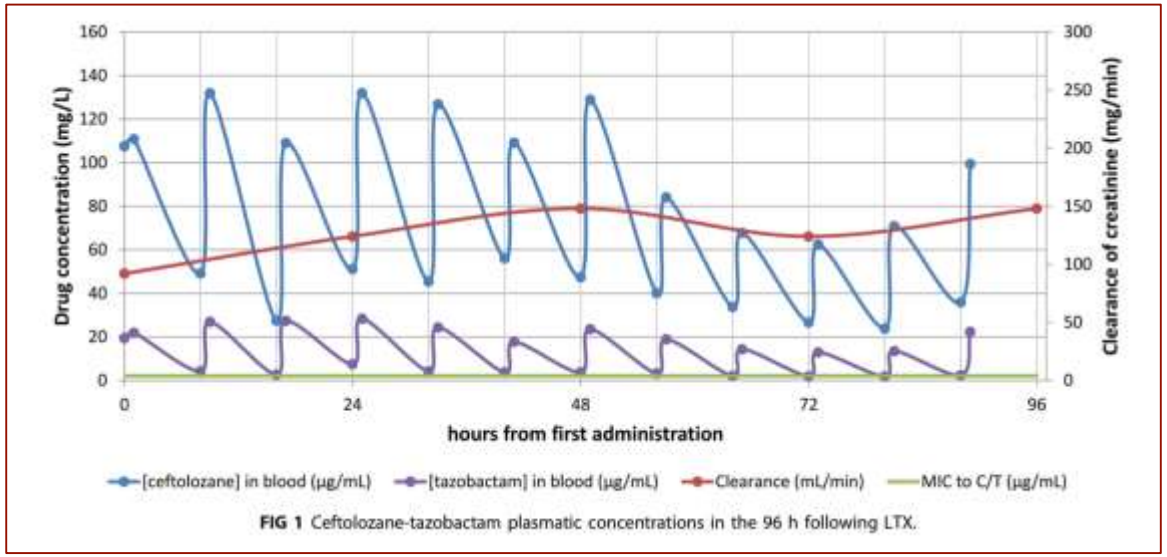



FIG 1 Ceftolozane-tazobactam plasmatic concentrations in the 96 h following LTX.

**Tedavi süresince seftolozan ve tazobaktam düzeyleri MIK (4mg/ml) değerinin üzerinde seyretmiştir**
**Cmax ve Cmin değerleri sabit düzeye tedavinin 96. saatinde ulaşmıştır**

# ECMO
## *Diğer antibakteriyeller*

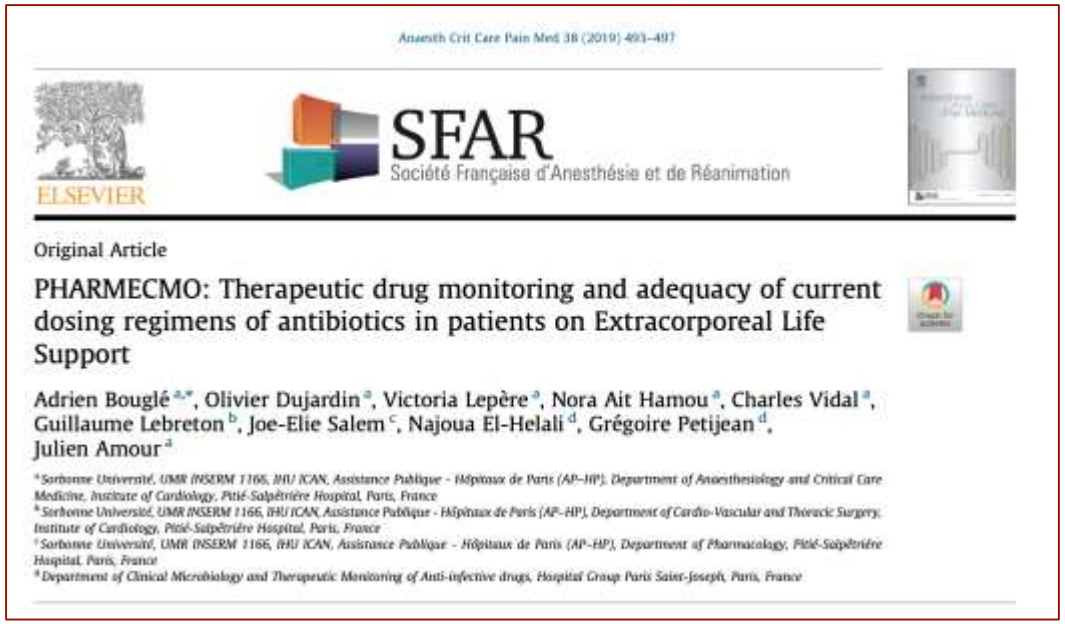
Kühn et al. Crit Care (2020) 24:664
https://doi.org/10.1186/s13054-020-03397-1

Critical Care

RESEARCH Open Access

Antibiotic therapeutic drug monitoring in intensive care patients treated with different modalities of extracorporeal membrane oxygenation (ECMO) and renal replacement therapy: a prospective, observational single-center study

Dennis Kühn[1,2†], Carlos Metz[2†], Frederik Seiler[2], Holger Wehrfritz[2], Sophie Roth[1], Mohammad Alqudrah[2], André Becker[2], Hendrik Bracht[3], Stefan Wagenpfeil[4], Mathias Hoffmann[5], Robert Bals[2], Ulrich Hübner[6], Jürgen Geisel[6], Philipp M. Lepper[2*†] and Sören L. Becker[1*†]



Anaesth Crit Care Pain Med 38 (2019) 493–497

ELSEVIER

SFAR
Société Française d'Anesthésie et de Réanimation

Original Article

PHARMECMO: Therapeutic drug monitoring and adequacy of current dosing regimens of antibiotics in patients on Extracorporeal Life Support

Adrien Bouglé[a,*], Olivier Dujardin[a], Victoria Lepère[a], Nora Ait Hamou[a], Charles Vidal[a], Guillaume Lebreton[b], Joe-Elie Salem[c], Najoua El-Helali[d], Grégoire Petijean[d], Julien Amour[a]

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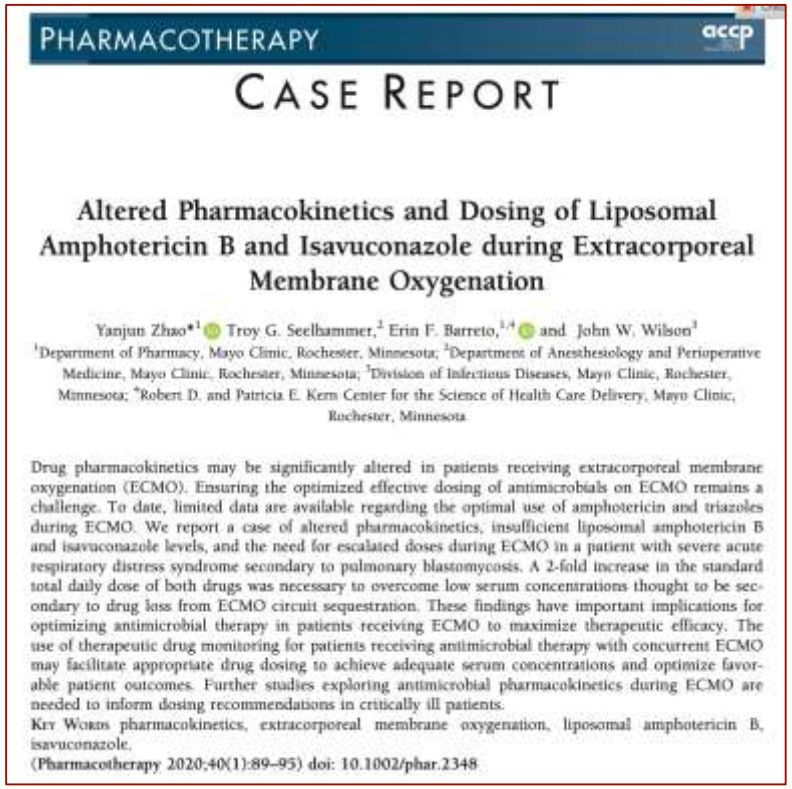
[b] Sorbonne Université, UMR INSERM 1166, IHU ICAN, Assistance Publique - Hôpitaux de Paris (AP-HP), Department of Cardio-Vascular and Thoracic Surgery, Institute of Cardiology, Pitié-Salpêtrière Hospital, Paris, France
[c] Sorbonne Université, UMR INSERM 1166, IHU ICAN, Assistance Publique - Hôpitaux de Paris (AP-HP), Department of Pharmacology, Pitié-Salpêtrière Hospital, Paris, France
[d] Department of Clinical Microbiology and Therapeutic Monitoring of Anti-infective drugs, Hospital Group Paris Saint-Joseph, Paris, France

- **Standart doz linezolid, piperasilin-tazobaktam ve amikasin tedavileri ECMO ile tedavi edilen hastalarda hedeflenen FK/FD değerlerine ulaşamamıştır**
- **Bu hastalarda rutin TİG önerilmiştir**

# ECMO
## *Lipozomal amfoterisin B*

- Amfoterisin-B düzey ölçümü rutin olarak önerilmemektedir ve hedef değerler belirlenmemiştir

Gomez-Lopez A. Clinical Microbiology and Infection 26 (2020) 1481e1487



PHARMACOTHERAPY accp

CASE REPORT

**Altered Pharmacokinetics and Dosing of Liposomal Amphotericin B and Isavuconazole during Extracorporeal Membrane Oxygenation**

Yanjun Zhao*[1] Troy G. Seelhammer,[2] Erin F. Barreto,[3,4] and John W. Wilson[3]
[1]Department of Pharmacy, Mayo Clinic, Rochester, Minnesota; [2]Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota; [3]Division of Infectious Diseases, Mayo Clinic, Rochester, Minnesota; [4]Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, Minnesota

Drug pharmacokinetics may be significantly altered in patients receiving extracorporeal membrane oxygenation (ECMO). Ensuring the optimized effective dosing of antimicrobials on ECMO remains a challenge. To date, limited data are available regarding the optimal use of amphotericin and triazoles during ECMO. We report a case of altered pharmacokinetics, insufficient liposomal amphotericin B and isavuconazole levels, and the need for escalated doses during ECMO in a patient with severe acute respiratory distress syndrome secondary to pulmonary blastomycosis. A 2-fold increase in the standard total daily dose of both drugs was necessary to overcome low serum concentrations thought to be secondary to drug loss from ECMO circuit sequestration. These findings have important implications for optimizing antimicrobial therapy in patients receiving ECMO to maximize therapeutic efficacy. The use of therapeutic drug monitoring for patients receiving antimicrobial therapy with concurrent ECMO may facilitate appropriate drug dosing to achieve adequate serum concentrations and optimize favorable patient outcomes. Further studies exploring antimicrobial pharmacokinetics during ECMO are needed to inform dosing recommendations in critically ill patients.

KEY WORDS pharmacokinetics, extracorporeal membrane oxygenation, liposomal amphotericin B, isavuconazole.
(Pharmacotherapy 2020;40(1):89–95) doi: 10.1002/phar.2348

**Eşlik eden komorbiditesi olmayan 44 yaşında erkek hasta Blastomikoz ilişkili akciğer infeksiyonu nedeniyle ECMO ile tedavi altında alınmış**

**Merkezin kendi belirlediği hedef değerlere ulaşmak için lipozomal amfoterisin B ve isavukonazol dozunu normalin iki katına arttırmaları gerekmiş**

# Yan etki
## *Daptomisin*

- Cmin ≥20 $\mu$g/mL kreatin fosfokinaz artışıyla ilişkilendirilmiştir
  - Cmin < 20 $\mu$g/mL olduğunda da daptomisin statinler ve antihistaminiklerle birlikte verildiğinde enzim artış riski bulunmaktadır
- Hayvan çalışmalarının sonuçları MRSA bakteriyemisi için hedef değerlerin AUC/MIC 666 ve üzerinde tutulmasını desteklemektedir

Matsumoto K, et al. Biol. Pharm. Bull. 45, 824–833 (2022).
Safdar N, et al. Antimicrob. Agents Chemother., 48, 63–68 (2004).
Falcone M, et al. J. Infect. Chemother., 19, 732–739 (2013).
Galar A, et al. Int. J. Anti- microb. Agents, 53, 40–48 (2019).

# Linezolid
## *Yan etki*

- Linezolidi nasıl biliriz?
  - Oral biyoyararlanımı %100
  - Böbrek ve karaciğer fonksiyon bozukluğunda doz ayarlaması gerekmez

- Hedef değerler
  - AUC/MIK: 80-120
  - T>MIK: %85
  - Cmin: 2-7 mg/l
    - Cmin>10 mg/l olduğunda trombositopeni riskinin %50 arttığı bildirilmiştir

Heidari S, et al. European Journal of Clinical Pharmacology (2023) 79:195–206

# Linezolid
## *Yan etki-karaciğer yetmezliği*

- Luque ve ark.
  - Siroz hastaları standart doz linezolid tedavisi aldığında supra-terapötik plazma düzeyi nedeniyle daha ciddi advers reaksiyonlar yaşamaktadır
- Zhang ve ark.
  - Karaciğer fonksiyon bozukluğu olan 45 hastanın 163 plazma örneği
  - Tek-kompartmanlı farmakokinetik modelleme
  - Standart doz tedavi supra-terapötik düzeyle ilişkilendirilmiştir
  - **Etkin ve güvenli hedef değere ulaşmak için 12 saatte bir 300 mg tedavi daha uygundur**
  - **MIK<2 mg/l olduğunda günlük 400 mg linezolid yeterlidir**

Heidari S, et al. European Journal of Clinical Pharmacology (2023) 79:195–206.
Luque S, et al. (2019) Ther Drug Monit 41:732–739.
ZhangSH, et al. (2020) Antimicrob Agents Chemother 64(6):e00133-e220.

# Linezolid

## *Neden trombositopeni yapar? Hipotezler?*

- Olgun megakaryoblastlardan trombosit gelişiminin inhibisyonu
- Trombositlere oksidatif hasar
- Trombositlerin immün yıkımı
- Mitokondriyal protein sentez inhibisyonu
- Metabolitlerin birikimi (PNU-142300, PNU-142386)

- İleri yaşta ve düşük vücut ağırlığına sahip hastalarda linezolid ilişkili trombositopeni daha sık görülmektedir


Dong HY, et al. Eur J Clin Microbiol Infect Dis. 2014; 33(6):1029-1035.
Niwa T, et al. Diagn Microbiol Infect Dis. 2014;79(1):93-97.
Wu VC, et al. Clin Infect Dis. 2006;42(1):66-72.
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# Linezolid
## *Yan etki-trombositopeni*

- Bir derlemede linezolid ile tedavi edilen hastalarda trombositopeni sıklığının %8-68 olduğu bildirilmiştir

**Linezolid ilişkili trombositopeni kreatinin klirensi <60 ml/dak olan hastalarda daha sık görülmektedir**

**Linezolid ilişkili trombositopeni doz bağımlıdır**

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# Linezolid
## *Yan etki-trombositopeni*

META-ANALYSIS

BJCP BRITISH PHARMACOLOGICAL SOCIETY

**Effect of renal function on the risk of thrombocytopaenia in patients receiving linezolid therapy: A systematic review and meta-analysis**

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- **Ciddi böbrek fonksiyon bozukluğu ve hemodiyaliz ihtiyacı olan hastalarda linezolid ilişkili trombositopeni daha sık görülmektedir**
- **Tek şema tüm hastalara uymamaktadır**
- **TİG öneriliyor**

# Eve götürülecek mesajlar


*‘Cevapları olan değil, soruları olan insanları dinleyin’*
*Albert Einstein*