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UK RUB UNIVERSITÄTSKLINIKUM DER
RUHR-UNIVERSITÄT BOCHUM

# Einfluss der Sepsis auf die Pharmakokinetik von Antibiotika

RUB

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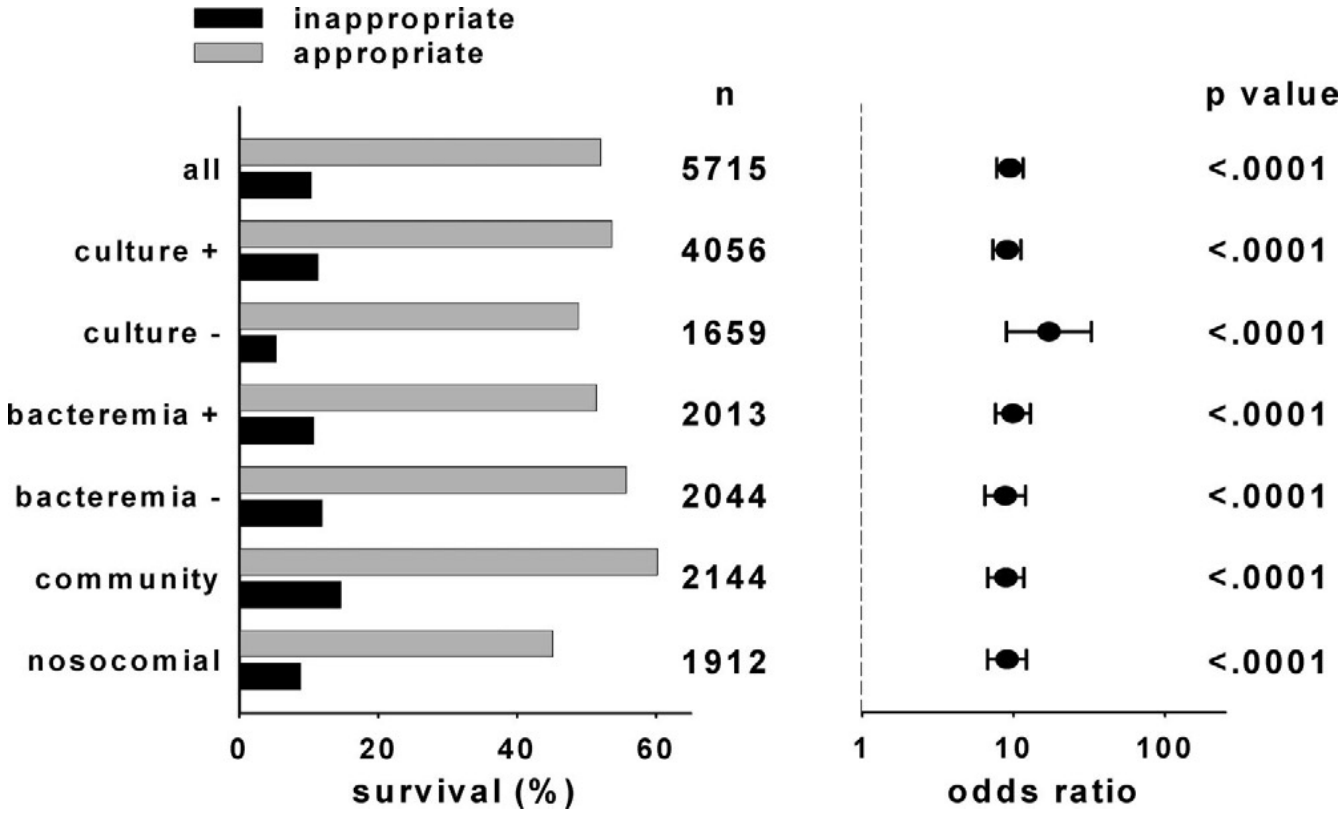
# Interessenskonflikte

**u.a. Vortragshonorare, Beratertätigkeit, Reise- und Kongressunterstützung, Forschungsunterstützung**

- Astute Medical GmbH / bioMérieux Deutschland
- Alexion Pharma Germany
- Bayer Vital GmbH
- Biotest AG
- CSL Behring GmbH
- Eumedica S.A.
- Grünenthal GmbH
- Mitsubishi Tanabe Pharma GmbH
- MSD Sharp & Dohme GmbH
- Pfizer Deutschland GmbH
- Portola Pharmaceuticals
- Shionogi GmbH

# Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock

*Anand Kumar, MD; Paul Ellis, MD; Yaseen Arabi, MD, FCCP; Dan Roberts, MD; Bruce Light, MD; Joseph E. Parrillo, MD, FCCP; Peter Dodek, MD; Gordon Wood, MD; Aseem Kumar, PhD; David Simon, MD; Cheryl Peters, RN; Muhammad Ahsan, MD; Dan Chateau, PhD; and the Cooperative Antimicrobial Therapy of Septic Shock Database Research Group**




Kumar A, et al. Chest. 2009 Nov;136(5):1237-1248.

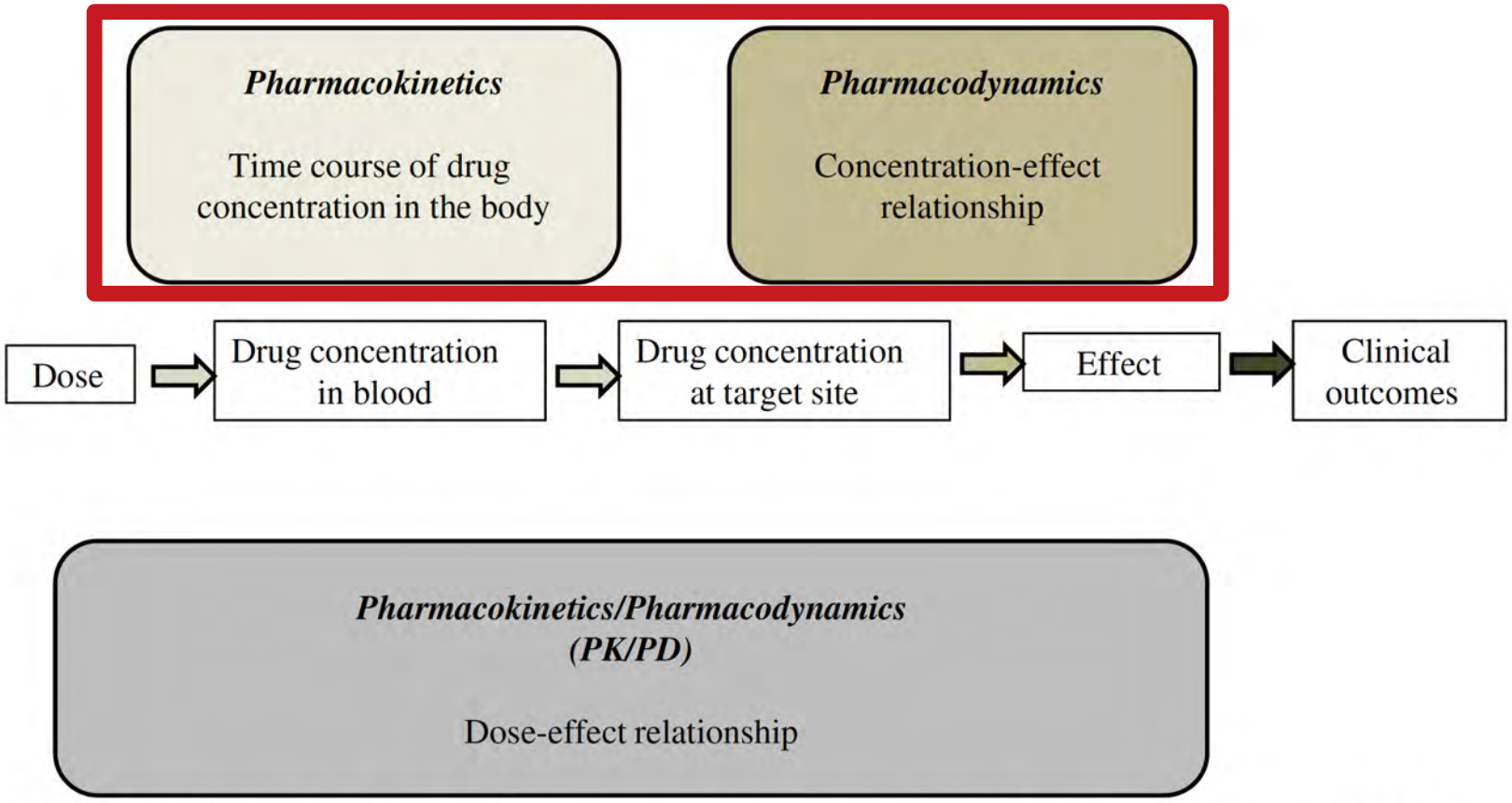



**Fig. 1.** The relationship between pharmacokinetics (PK) and pharmacodynamics (PD).

*Varghese JM, et al. Crit Care Clin. 2011 Jan;27(1):19-34.*

## Pharmakodynamik (PD)

**„Was macht das Arzneimittel mit dem Körper?“**

Dosis/Wirkungsbeziehung
Therapeutische Breite
Wirkmechanismus
Nebenwirkungen

## Pharmakokinetik (PK)

**„Was macht der Körper mit dem Arzneimittel?“**

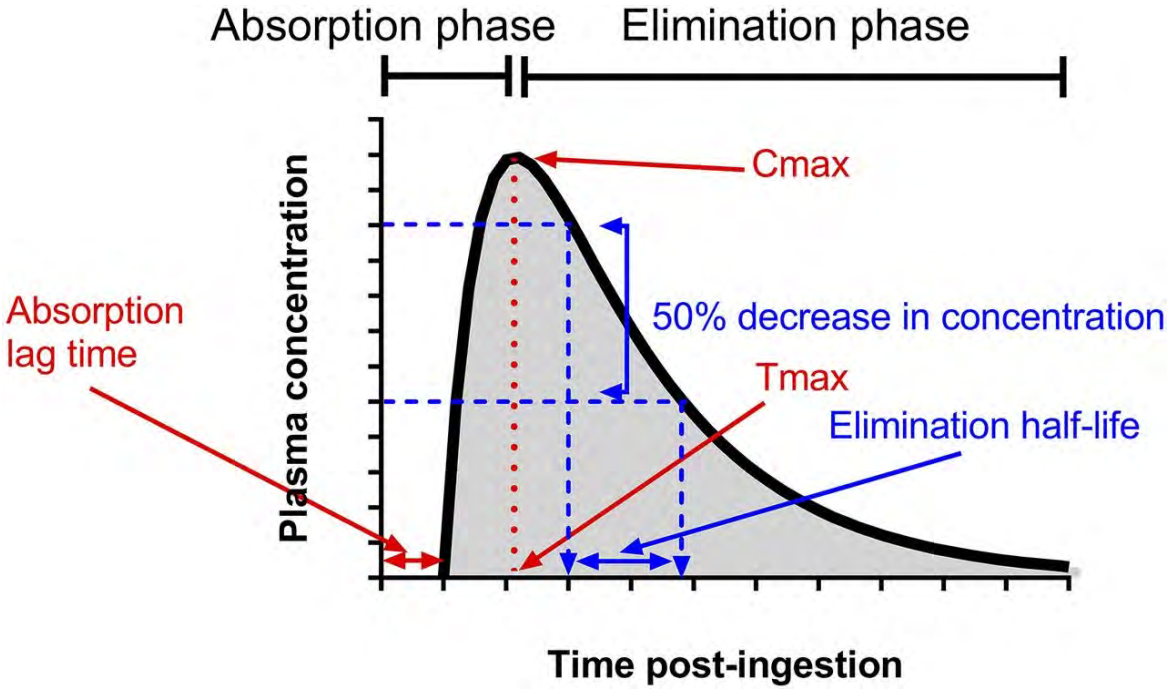
**L** – Liberation (Freisetzung)
**A** – Absorption (Aufnahme in die Blutbahn)
**D** – Distribution (Verteilung im Organismus)
**M** – Metabolisation (Verstoffwechselung)
**E** – Excretion (Ausscheidung)

# Pharmakokinetik (PK)



**Table 1**
**Relevant PK parameters for drug dosing**

| PK Parameter | Definition | Description |
|---|---|---|
| Clearance (CL) | The volume of blood cleared of drug per unit time | CL measures the irreversible elimination of a drug from the body by excretion and/or metabolism |
| Volume of distribution ($V_d$) | Apparent volume of fluid that contains the total drug dose administered at the same concentration as in the plasma | $V_d$ is the parameter that relates the total amount of drug in the body to the plasma concentration |
| Half-life ($t_{1/2}$) | Time required for the plasma drug concentration to decrease by half | Half-life is dependent on CL and $V_d$; half-life is increased with a decrease in CL or an increase in $V_d$ |
| $C_{max}$ | Peak drug concentration during a dosing interval | |
| $C_{min}$ | Minimum drug concentration during a dosing interval | |
| $AUC_{0-24}$ | Area under the concentration-time curve from 0 to 24 h | |




*Varghese JM, et al. Crit Care Clin. 2011 Jan;27(1):19-34.*
*Lea-Henry TN, et al. CJASN Jul 2018;13(7):1085-1095.*

# Pharmakodynamik (PD)



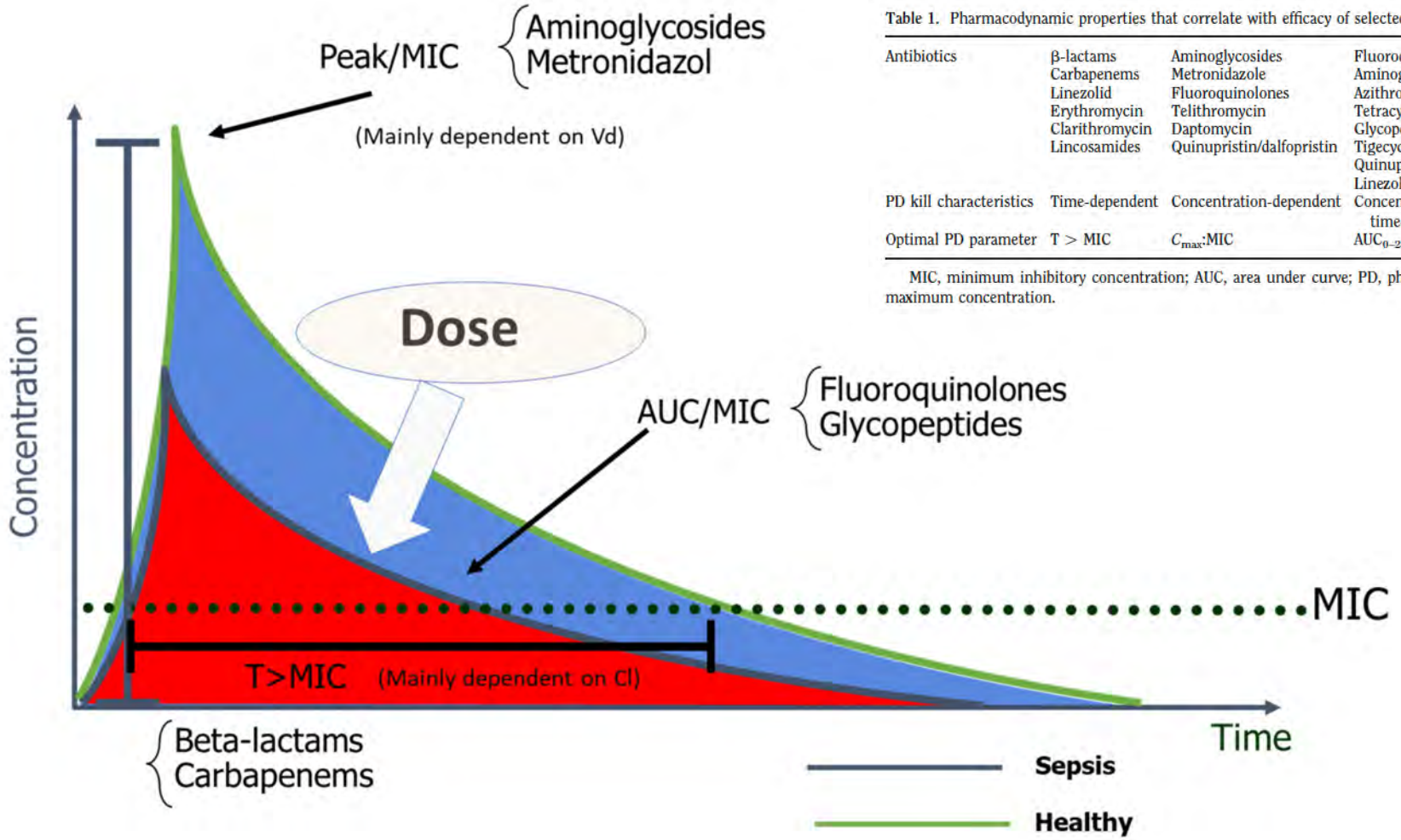



Table 1. Pharmacodynamic properties that correlate with efficacy of selected antibiotics

| Antibiotics | β-lactams<br>Carbapenems<br>Linezolid<br>Erythromycin<br>Clarithromycin<br>Lincosamides | Aminoglycosides<br>Metronidazole<br>Fluoroquinolones<br>Telithromycin<br>Daptomycin<br>Quinupristin/dalfopristin | Fluoroquinolones<br>Aminoglycosides<br>Azithromycin<br>Tetracyclines<br>Glycopeptides<br>Tigecycline<br>Quinupristin/dalfopristin<br>Linezolid |
|---|---|---|---|
| PD kill characteristics | Time-dependent | Concentration-dependent | Concentration-dependent with time-dependence |
| Optimal PD parameter | T > MIC | $C_{max}$:MIC | $AUC_{0-24}$:MIC |

MIC, minimum inhibitory concentration; AUC, area under curve; PD, pharmacodynamics; $C_{max}$, maximum concentration.

*Póvoa P, et al. Microorganisms. 2021 Jun 28;9(7):1401.*
*Roberts JA, et al. Crit Care Med 2009;37(3):840-851.*

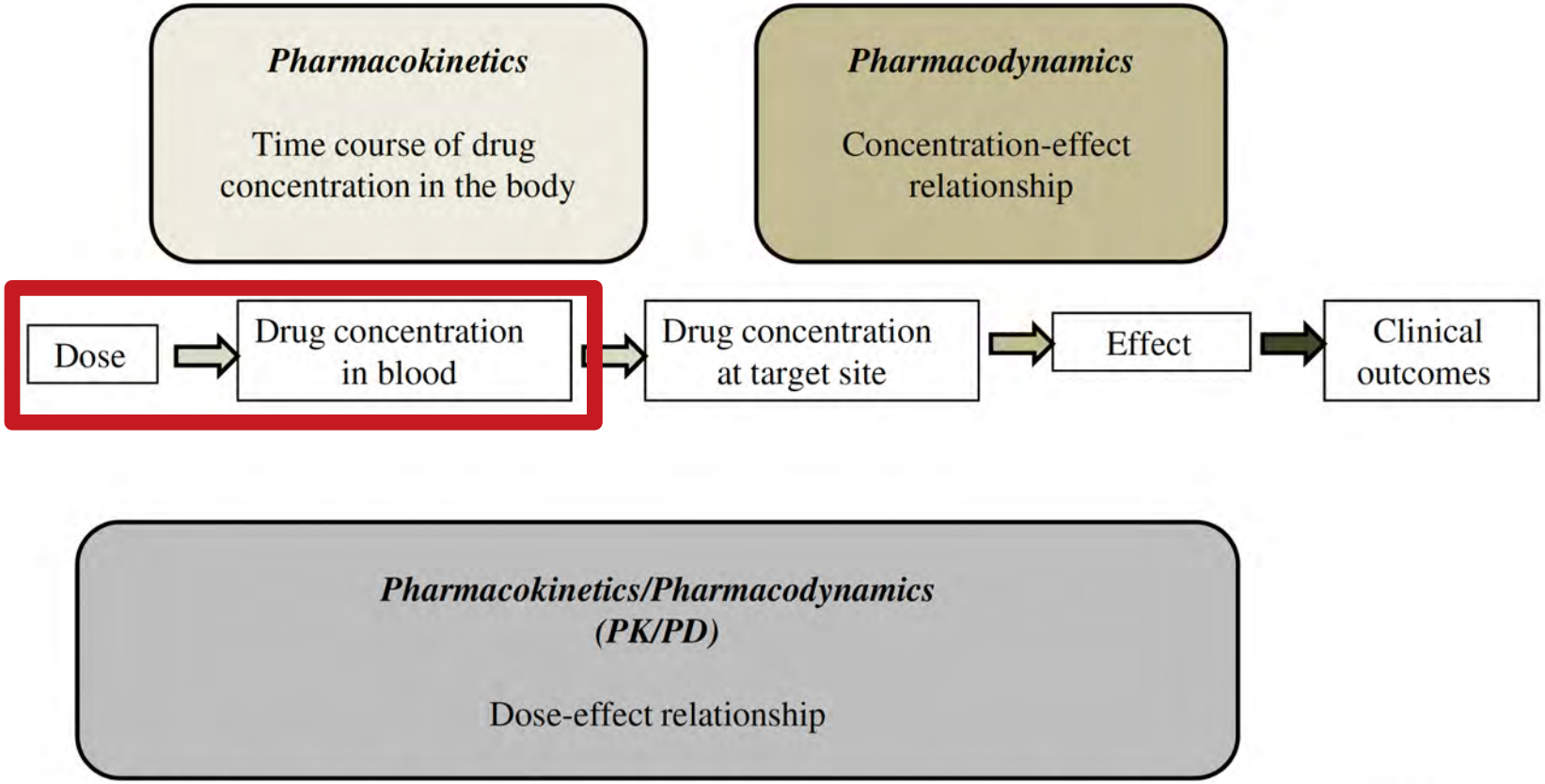
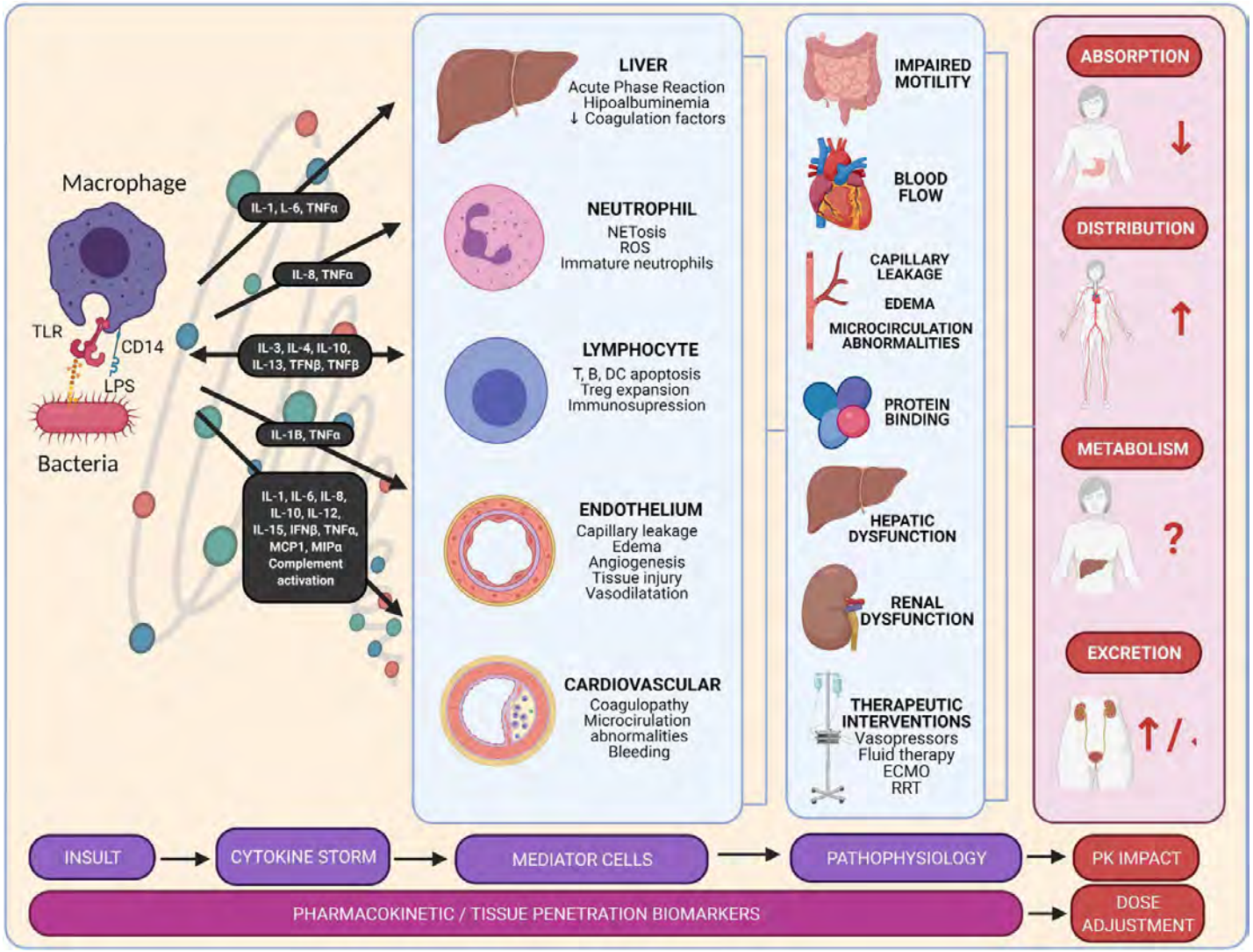



**Fig. 1.** The relationship between pharmacokinetics (PK) and pharmacodynamics (PD).

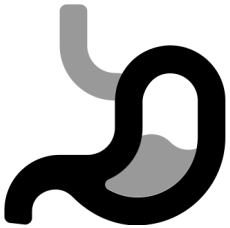
*Varghese JM, et al. Crit Care Clin. 2011 Jan;27(1):19-34.*




*Sanz Codina M et Zeitlinger M. Clin Pharmacokinet. 2022 Feb 25. Epub ahead of print.*

# Absorption *(bei nicht-parenteraler Applikation)*

*Magen*

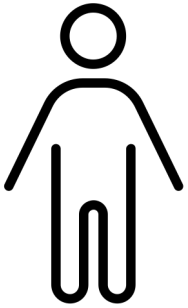


- Verzögerte gastrale Entleerung
- Hypoperfusion
- Mukosa-Ödem
- Künstliche Ernährung
- Absaugen
- pH-Alkalisierung

*Darm*

- Reduzierte Splanchnikus-Durchblutung
- Reduzierte Darmmotilität
- Chirurgische Probleme
- Ileus

*Nicht enterale Applikation*

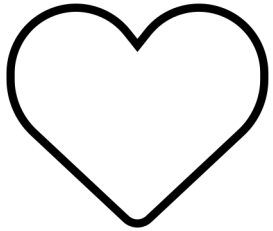


- Reduzierte Haut- und Muskeldurchblutung (Schock)
- Erhöhte Durchblutung (Fieber und periphere Vasodilatation)
- Einsatz von Vasopressoren

*Charlton M et Thompson JP. BJA Educ. 2019;19(1):7–13.*

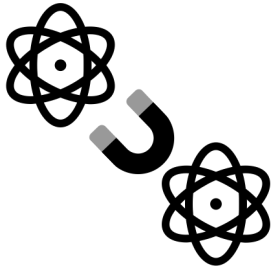
# Verteilung ($V_D$)

*Herz-Kreislauf-System*



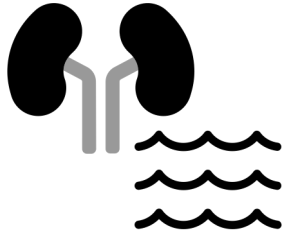
- Veränderungen des HZV
- Veränderungen der Blutverteilung
- Endothelschädigung und Kapillarleck
- Extrakorporale Kreisläufe (Organersatzverfahren)
- Reduzierte Gewebsperfusion

*Proteinbindung*



- Hypalbuminämie
- Veränderungen des pH-Wertes
- Geringere Proteinbindung
- Organinsuffizienzen (z.B. Leber)

*Wasserhaushalt*

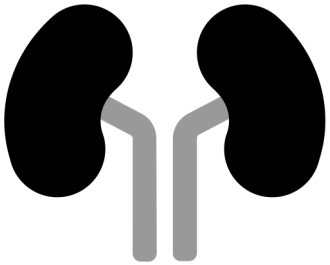


- Flüssigkeits-Therapie
- Akute Nierenschädigung
- Herzinsuffizienz
- Leberschädigung

*Charlton M et Thompson JP. BJA Educ. 2019;19(1):7–13.*

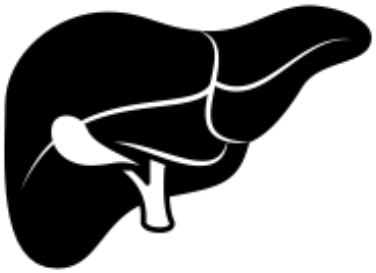
# Metabolismus und Ausscheidung

*Nieren*



- Veränderungen der glomerulären Filtrationsrate
- Organersatzverfahren (Dialyse)

*Leber*

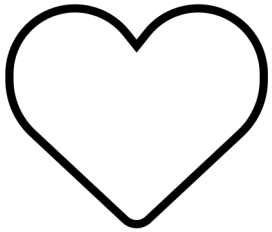


- Veränderungen der Metabolisierung
- Reduzierte biliäre Exkretion

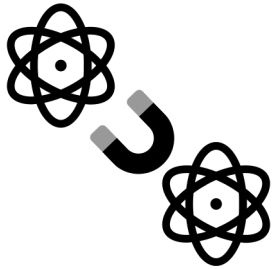
*Charlton M et Thompson JP. BJA Educ. 2019;19(1):7–13.*

# Verteilung ($V_D$)

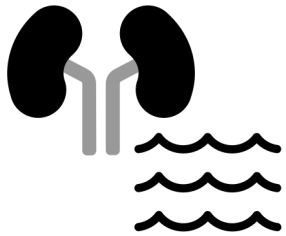
*Herz-Kreislauf-System*



*Proteinbindung*

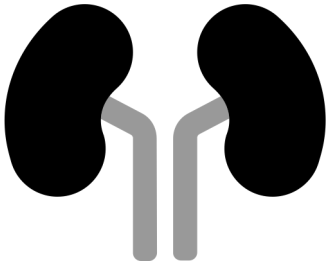


*Wasserhaushalt*



# Metabolismus und Ausscheidung

*Nieren*



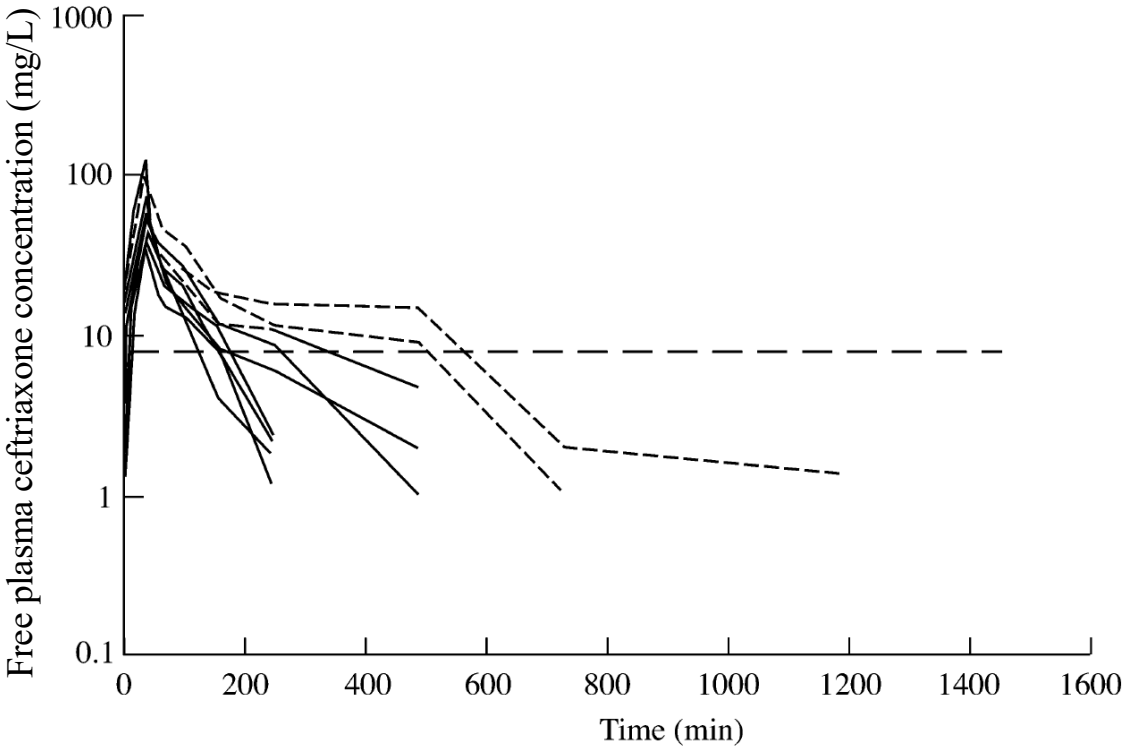
*Leber*

*Journal of Antimicrobial Chemotherapy* (2001) **47**, 421–429

JAC

# The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients

G. M. Joynt[a]*, J. Lipman[b], C. D. Gomersall[a], R. J. Young[a], E. L. Y. Wong[a] and T. Gin[a]




Joynt GM, et al. J Antimicrob Chemother. 2001 Apr;47(4):421-9.

# Ceftriaxone dosing in patients admitted from the emergency department with sepsis

Aaron J. Heffernan[1,2] · Rebecca A. Curran[3] · Kerina J. Denny[4] · Fekade B. Sime[2,5] · Claire L. Stanford[6] · Brett McWhinney[7] · Jacobus Ungerer[7,8] · Jason A. Roberts[2,5,9,10,11] · Jeffrey Lipman[5,10,11]



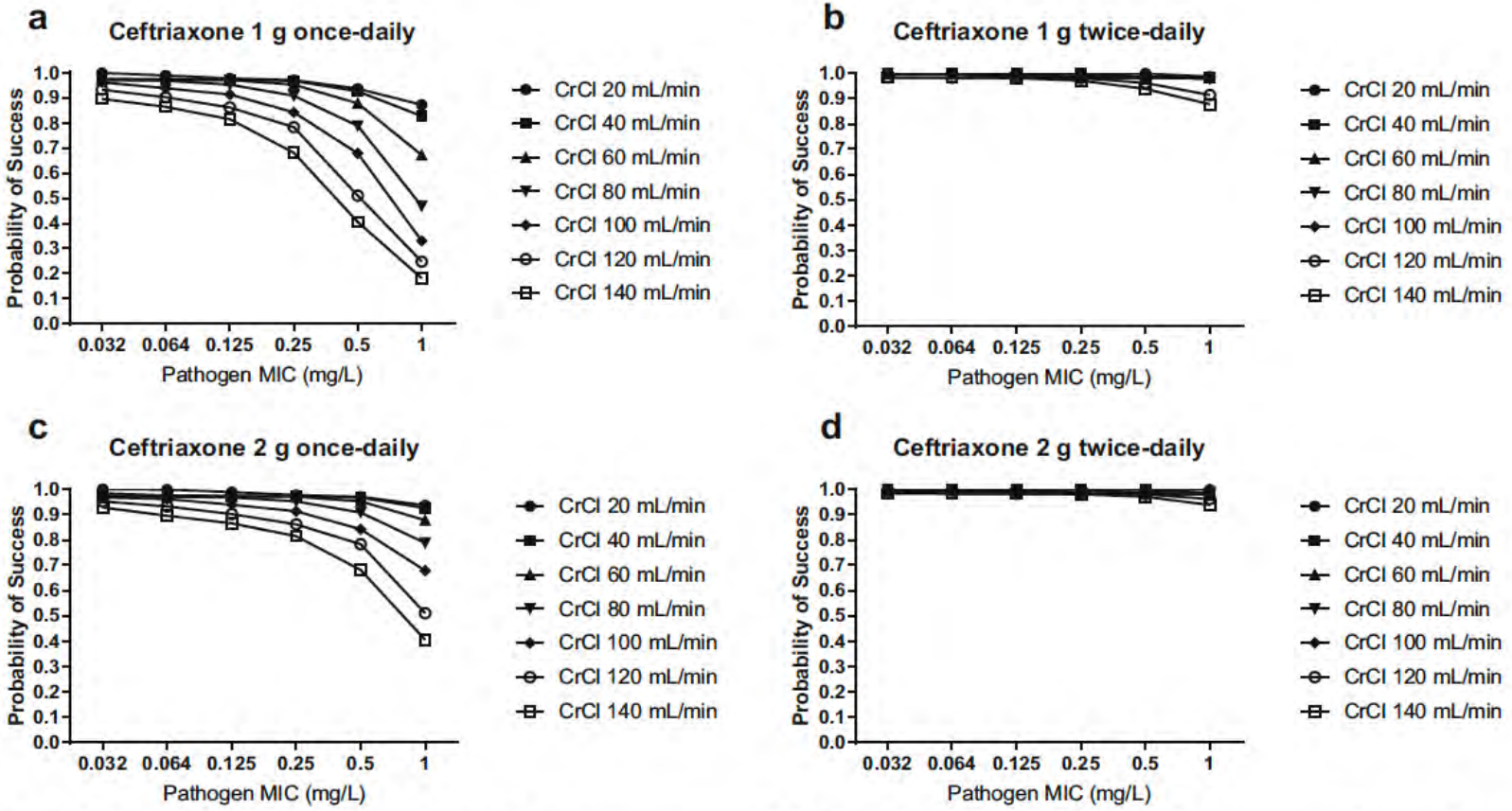
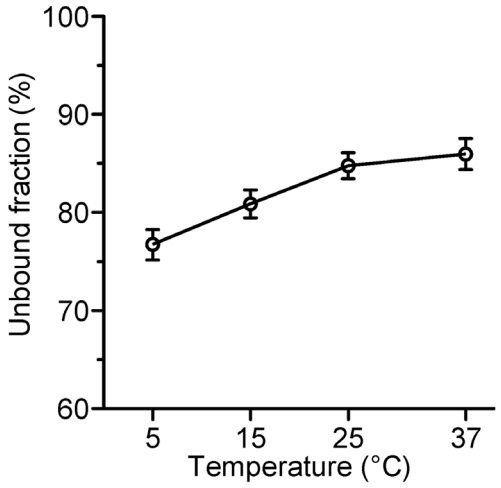


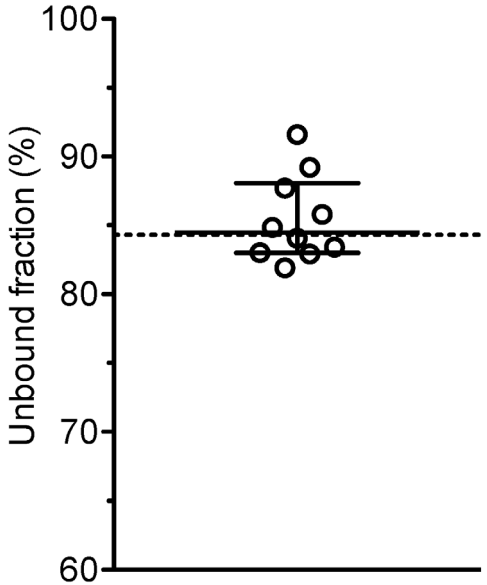

Fig. 2 Probability of target attainment (unbound ceftriaxone concentration 100% $fT_{>MIC}$) for ceftriaxone administered as a 1 g once-daily dose (**a**), 1 g twice-daily dose (**b**), 2 g once-daily dose (**c**), and 2 g twice-daily dose (**d**)

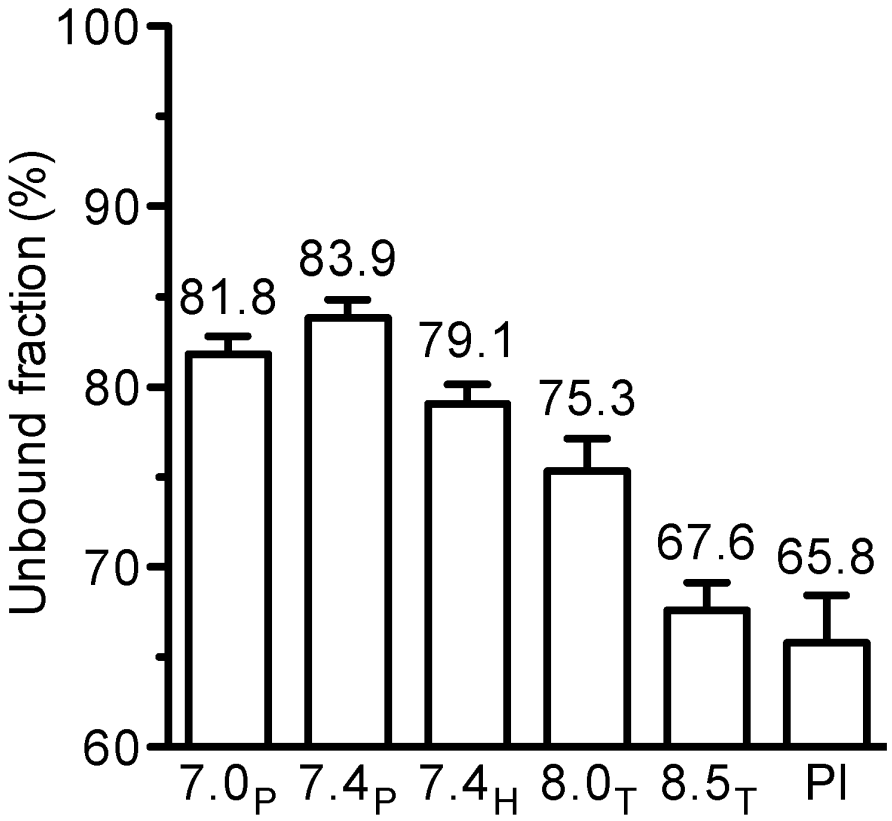
*Heffernan AJ, et al. European Journal of Clinical Pharmacology (2021) 77:207–214.*

# Decreased protein binding of moxifloxacin in patients with sepsis?

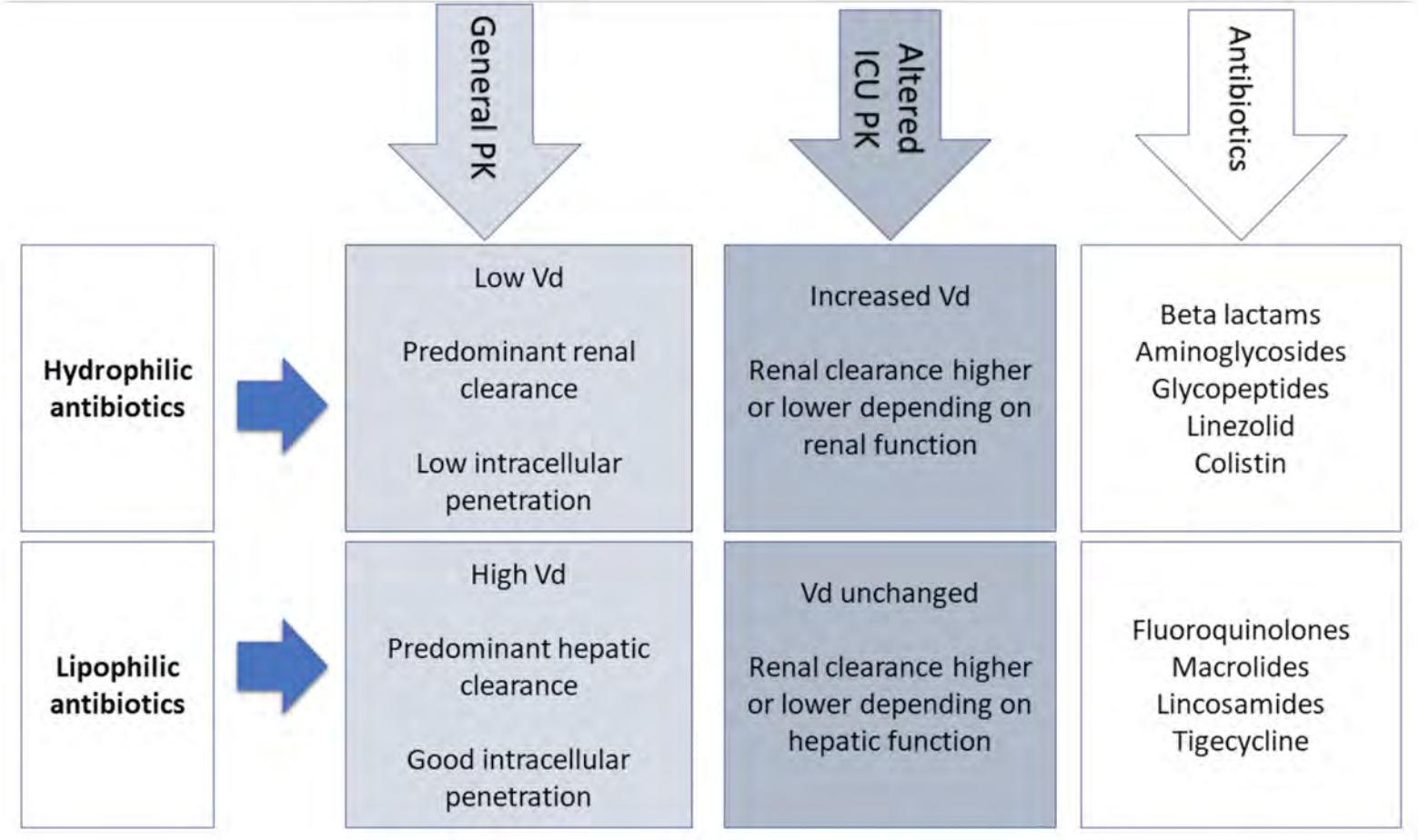





*Dorn C, Nowak H, et al. GMS Infect Dis. 2017 Feb 3;5:Doc03.*




*Póvoa P, et al. Microorganisms. 2021 Jun 28;9(7):1401.*

# Impact of cumulative fluid balance on the pharmacokinetics of extended infusion meropenem in critically ill patients with sepsis

Renata Černá Pařízková[1], Jiřina Martínková[2], Eduard Havel[3], Petr Šafránek[3], Milan Kaška[3], David Astapenko[1], Jan Bezouška[2], Jaroslav Chládek[4*] and Vladimír Černý[1]



**Table 2** Characteristics of fluid status and kidney function. Pharmacokinetic parameters of meropenem

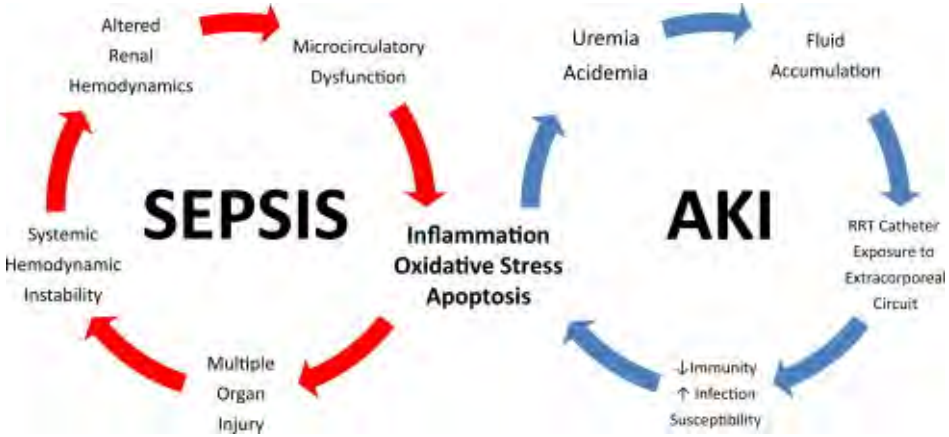
| Characteristics | Day | Fluid overload | No fluid overload |
|---|---|---|---|
| CFB = cumulative fluid balance | 1 | 11.7 (3.3)[2,3,#] | 2.4 (1.8)[#] |
| | 2 | 8.0 (4.3)[1,#] | 3.3 (1.9)[#] |
| | 3 | 6.7 (4.3)[1] | 4.1 (2.6) |
| 24-h urine output[a] (L) | 1 | 3.7 (2.1) | 2.8 (1.1) |
| | 2 | 4.0 (2.0) | 3.1 (1.6) |
| | 3 | 4.0 (2.1) | 3.1 (1.2) |
| Scr[b] (μmol/L) | 1 | 91 (46)[2,3] | 81 (36) |
| | 2 | 71 (25)[1] | 77 (27) |
| | 3 | 69 (15)[1] | 72 (28) |
| $CL_{cr}$ (L/h) | 1 | 4.9 (2.6) | 4.9 (2.2) |
| | 2 | 6.8 (2.6) | 5.4 (2.7) |
| | 3 | 6.1 (2.5) | 5.6 (2.9) |
| $CGCL_{cr}$ (L/h) | 1 | 5.7 (2.1) | 6.0 (2.1) |
| | 2 | 6.9 (2.6) | 6.3 (2.7) |
| | 3 | 7.1 (2.5) | 6.7 (2.9) |
| $CL_{me}$ (L/h) | 1 | 8.5 (3.2)[3,#] | 11.5 (3.5)[#] |
| | 2 | 10.9 (3.0) | 12.2 (3.6) |
| | 3 | 12.4 (3.8)[1] | 11.5 (2.0) |

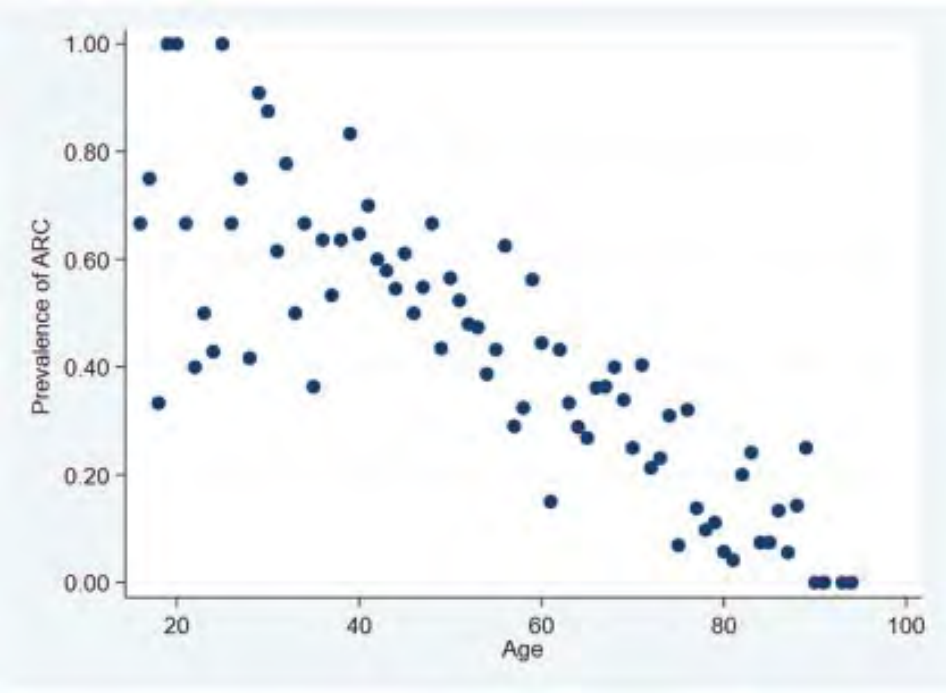
**Table 4** The PK/PD target attainment in the course of therapy with meropenem of patients with or without fluid overload on day 1

| Characteristics | Day | Fluid overload | No fluid overload |
|---|---|---|---|
| $fC_{min} > 2$ mg/L (%)[a] | 1–3 | 98 (89–100) | 93 (80–98) |
| $fC_{min} > 8$ mg/L (%)[a] | 1–3 | 67 (52–80) | 27 (20–48)*** |
| $\%fT > 2$ mg/L (%)[b] | 1 | 99 (2.3) | 99 (2.7) |
| | 2 | 100 (0.1) | 98 (1.6) |
| | 3 | 99 (1.2) | 100 (0.1) |
| $\%fT > 8$ mg/L (%)[b] | 1 | 79 (17)[#,3] | 58 (17)[#] |
| | 2 | 78 (23)[#] | 56 (13)[#] |
| | 3 | 68 (21)[#,1] | 58 (12)[#] |

*Pařízková et al. Crit Care (2021) 25:251.*

## Acute Kidney Injury (AKI) vs. Augmented Renal Clearance (ARC)



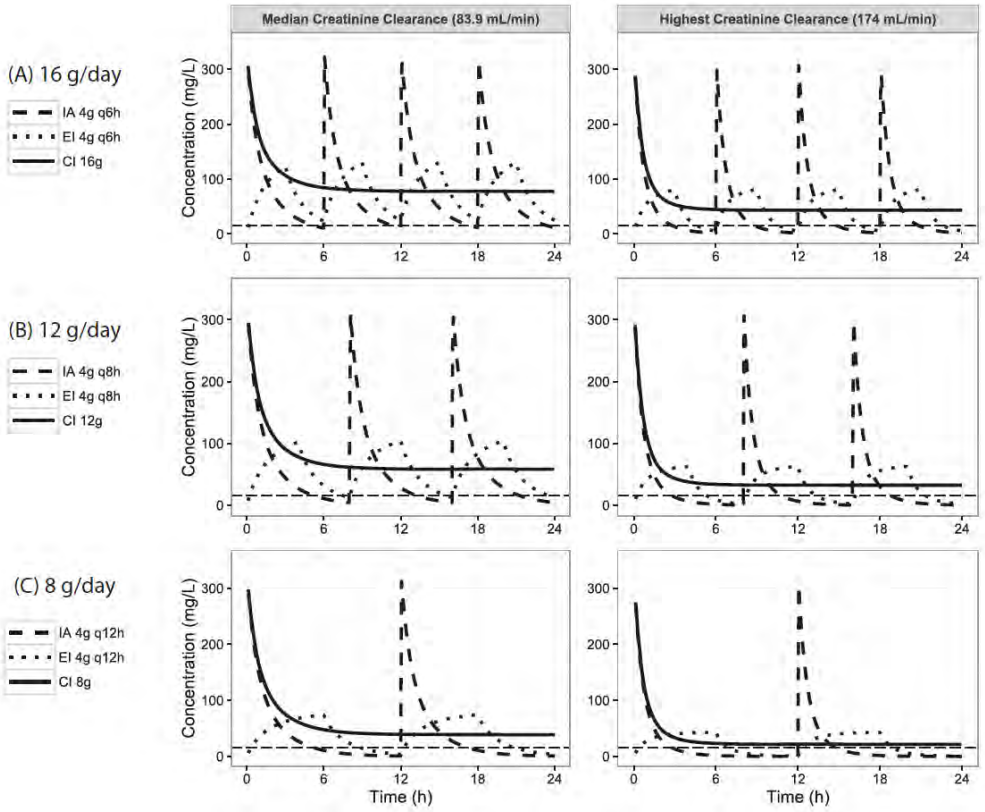



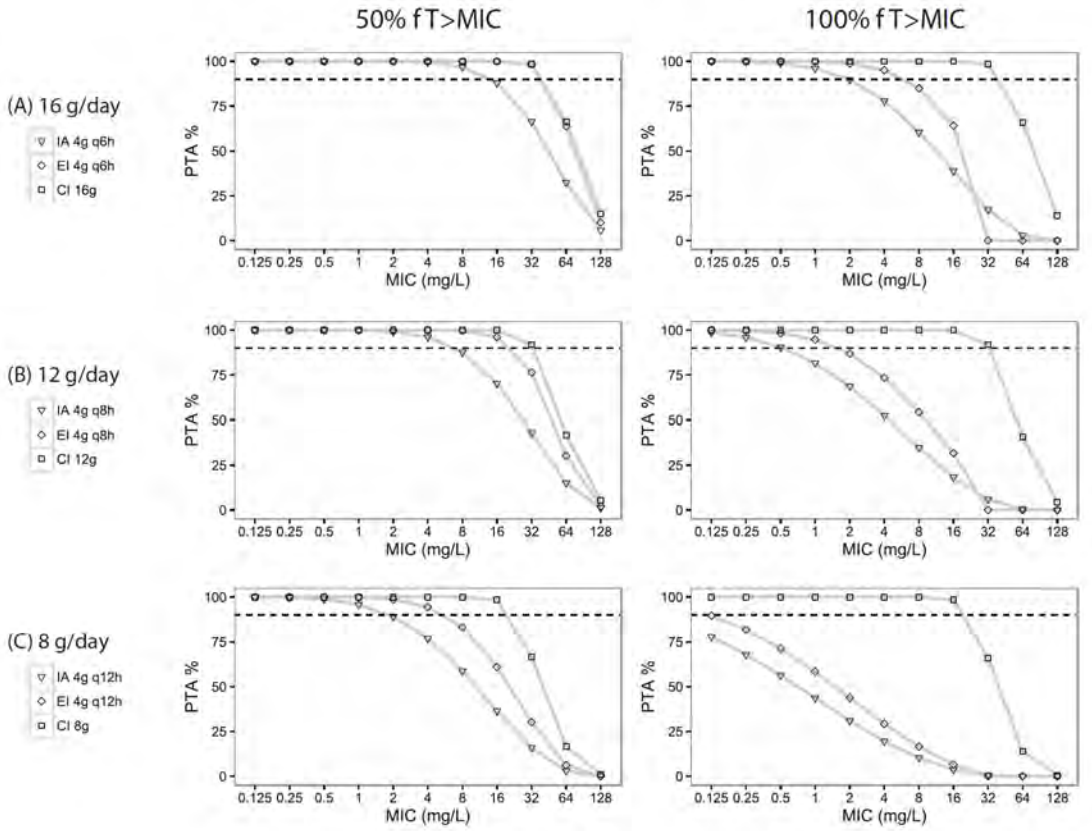

Alobaidi R, et al. Semin Nephrol. 2015 Jan;35(1):2-11.
Johnston BW, et al. J Int Med Res. 2021 May;49(5):3000605211015573.

# Population Pharmacokinetics of Piperacillin in Sepsis Patients: Should Alternative Dosing Strategies Be Considered?

Maria Goul Andersen,[a] Anders Thorsted,[b] Merete Storgaard,[a] Anders N. Kristoffersson,[b] Lena E. Friberg,[b] Kristina Öbrink-Hansen[a]






*Andersen MG, et al. Antimicrob Agents Chemother. 2018 Apr 26;62(5):e02306-17.*

# Extrakorporale Membranoxygenierung (ECMO)

**AB-Konzentration**

Einflüsse des Filters ↓

Verteilungsvolumen $V_D$ ↓

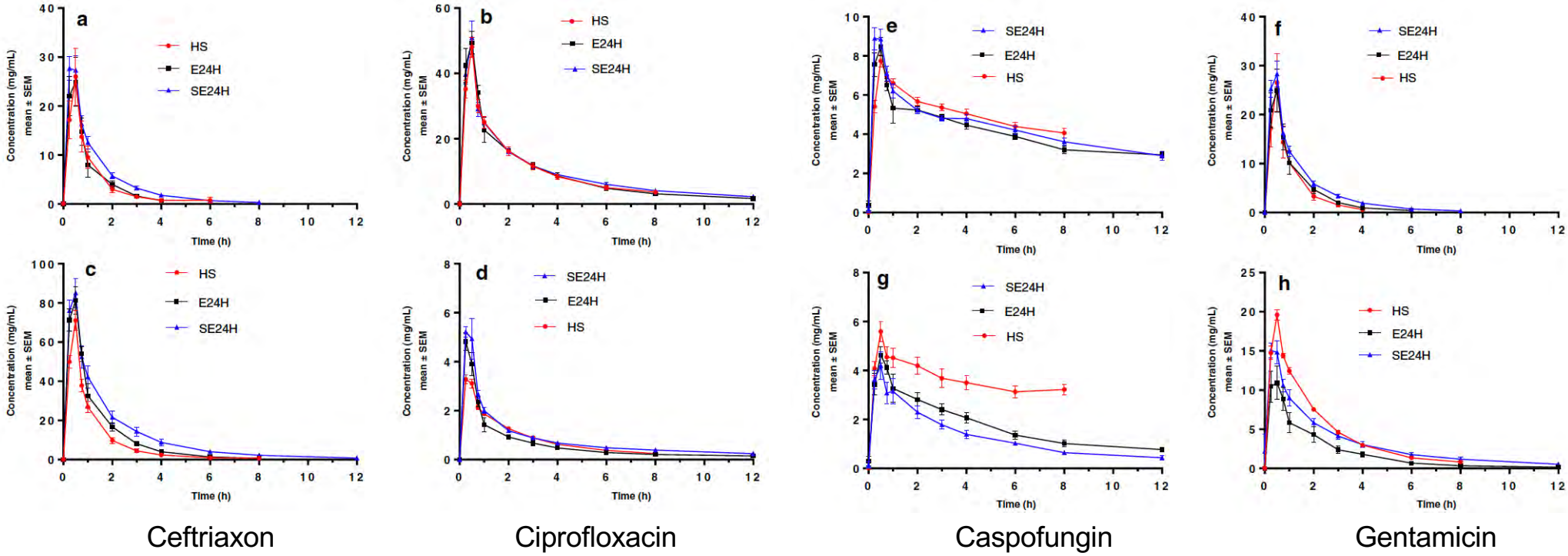
Verringerte AB-Clearance ↑

*Abdul-Aziz MH, Roberts JA. Curr Opin Anaesthesiol. 2020 Feb;33(1):71-82.*

HS =

E24H =

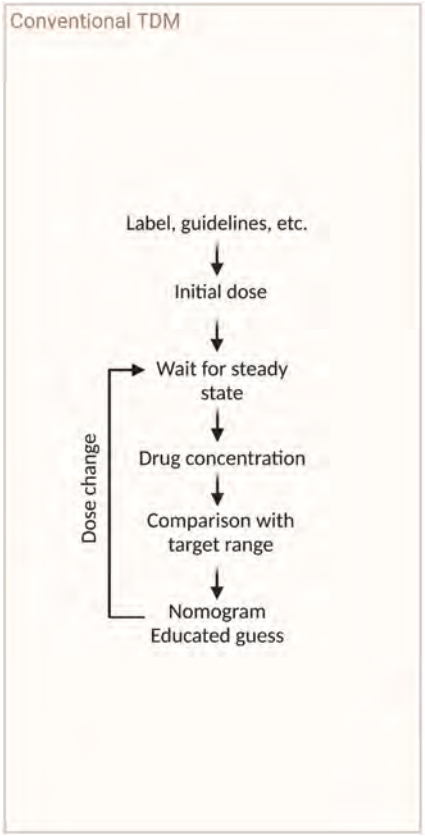
SE24H =

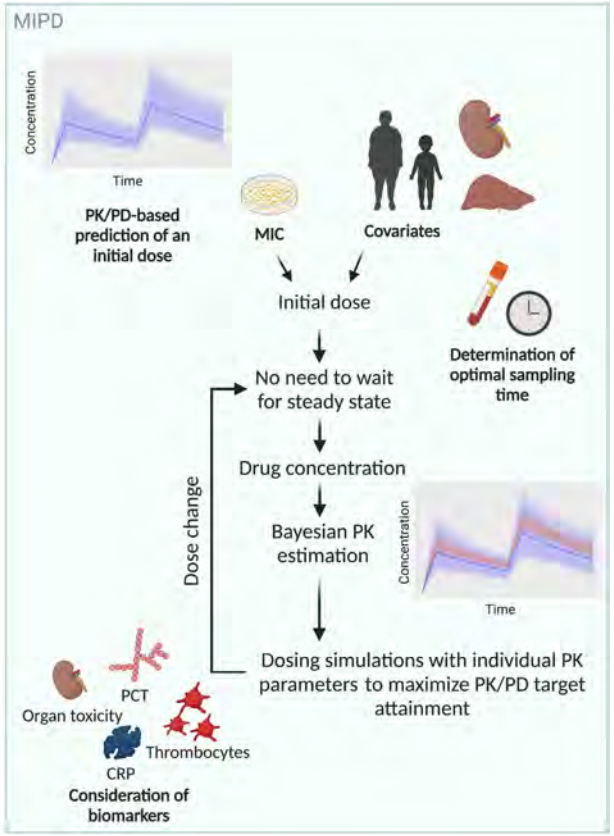


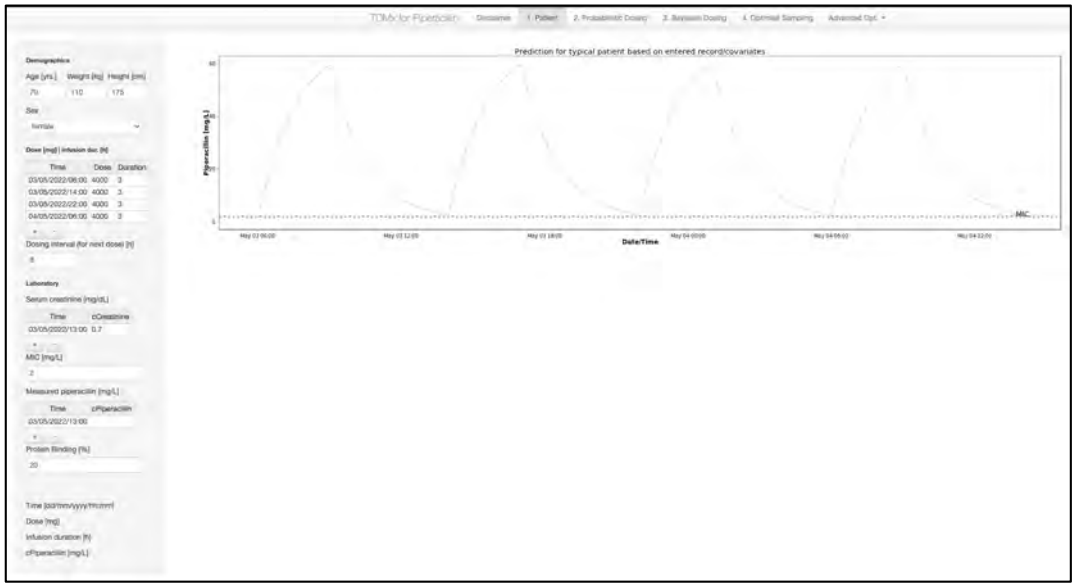

Shekar K, et al. Crit Care. 2015 Dec 15;19:437.

# From Therapeutic Drug Monitoring to Model-Informed Precision Dosing for Antibiotics

Sebastian G. Wicha[1,*], Anne-Grete Märtson[2], Elisabet I. Nielsen[3], Birgit C.P. Koch[4], Lena E. Friberg[3], Jan-Willem Alffenaar[5,6,7] and Iris K. Minichmayr[3] on behalf of the International Society of Anti-Infective Pharmacology (ISAP), the PK/PD study group of the European Society of Clinical Microbiology, Infectious Diseases (EPASG)



TDMx

www.tdmx.eu

*Wicha SG, et al. Clin Pharmacol Ther. 2021 Apr;109(4):928-941.*

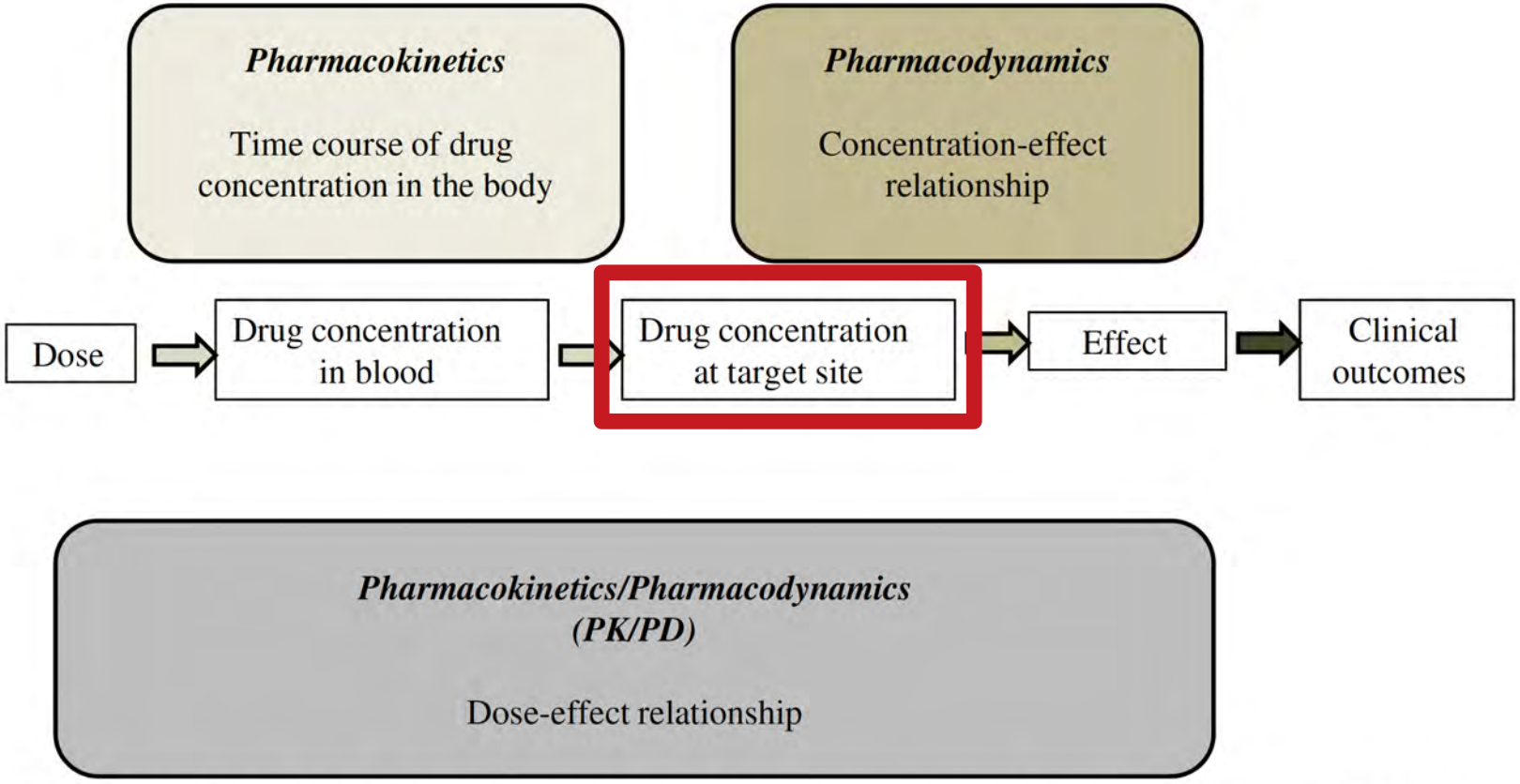



**Fig. 1.** The relationship between pharmacokinetics (PK) and pharmacodynamics (PD).

*Varghese JM, et al. Crit Care Clin. 2011 Jan;27(1):19-34.*

# Repeated determination of moxifloxacin concentrations in interstitial space fluid of muscle and subcutis in septic patients

Hartmuth Nowak[1], Caroline Weidemann[1], Stefan Martini[1], Zoe Anne Oesterreicher[2], Christoph Dorn [3], Michael Adamzik[1], Frieder Kees[4], Markus Zeitlinger[2*] and Tim Rahmel [1]

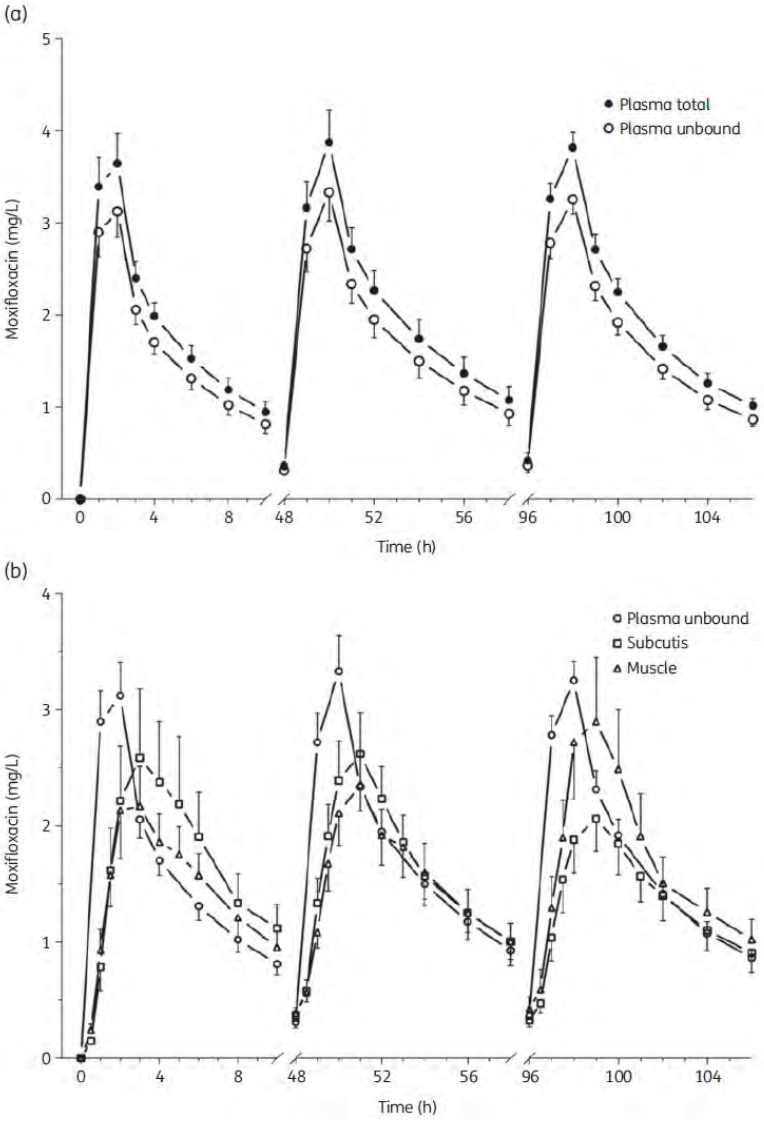



**Table 1.** Study population characteristics

| Characteristic | Value |
|---|---|
| Number of patients | 10 |
| Male, *n* (%) | 4 (40) |
| Age (years), range (median) | 44–82 (58.5) |
| BMI (kg/m$^2$), range (median) | 22.32–31.22 (26.35) |
| Focus of infection, *n* (%) | |
| lung | 9 (90) |
| hip | 1 (10) |
| ICU stay (days), range (median) | 6–38 (22) |
| 28 day mortality, *n* (%) | 0 (0) |
| SAPS II without GCS, range (median) | 15–45 (31) |
| SOFA score, range (median) | 4–12 (7) |
| APACHE II score, range (median) | 8–27 (17) |

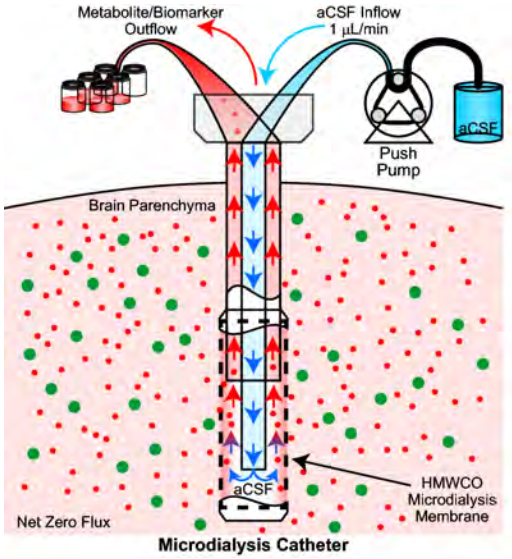



**Table 2.** Key PK parameters of moxifloxacin in plasma, subcutis and muscle of septic patients on days 1, 3 and 5 after intravenous application of 400 mg of moxifloxacin over 2 h

| Parameter | $C_{max}$ (mg/L) | $T_{max}$ (h) | $AUC_{0-\infty}$ (mg·h/L) | Elimination $t_{1/2}$ (h) | *V* (L) | CL (L/h) | $fAUC_{0-24}/MIC^a$ (h) |
|---|---|---|---|---|---|---|---|
| Day 1 | | | | | | | |
| $plasma_{total}$ | 4.1±1.0 | 1.8±0.4 | 27.4±8.5 | 5.9±1.9 | 131.1±28.7 | 16.2±5.9 | |
| $plasma_{unbound}$[b] | 3.5±0.9 | 1.8±0.4 | 23.5±7.5 | 5.9±1.9 | | | 91.6±24.8 |
| subcutis | 2.8±1.8 | 3.3±1.5 | 24.8±15.1 | 5.6±2.1 | | | 100.9±62.9 |
| muscle | 2.5±1.3 | 2.4±1.0 | 21.3±10.5 | 5.4±2.3 | | | 86.5±38.3 |
| Day 3 | | | | | | | |
| $plasma_{total}$ | 3.9±1.1 | 2.0±0.0 | 29.9±11.4 | 5.8±1.2 | 121.2±23.2 | 15.7±7.4 | |
| $plasma_{unbound}$[b] | 3.3±1.0 | 2.0±0.0 | 25.7±10.1 | 5.8±1.2 | | | 101.8±37.3 |
| subcutis | 2.7±1.1 | 2.5±0.6 | 23.5±9.9 | 5.7±1.6 | | | 96.4±40.1 |
| muscle | 2.4±0.9 | 3.0±1.4 | 24.5±11.2 | 6.4±2.2 | | | 95.0±41.2 |
| Day 5 | | | | | | | |
| $plasma_{total}$ | 3.8±0.5 | 2.0±0.0 | 28.5±6.3 | 5.7±0.8 | 118.6±39.8 | 14.9±4.2 | |
| $plasma_{unbound}$[b] | 3.3±0.5 | 2.0±0.0 | 24.3±5.8 | 5.7±0.8 | | | 97.4±22.3 |
| subcutis | 2.1±0.9 | 2.4±0.7 | 22.7±13.5 | 6.4±2.3 | | | 85.6±45.0 |
| muscle | 3.0±1.8 | 2.5±0.4 | 27.8±16.6 | 7.4±7.0 | | | 101.5±55.3 |

Values are displayed as mean±SD.
[a]MIC is the EUCAST clinical MIC breakpoint for moxifloxacin (0.25 mg/L).
[b]Calculated using mean unbound fraction of moxifloxacin at 1 and 10 h after application.

*Nowak H, et al. J Antimicrob Chemother. 2019 Sep 1;74(9):2681-2689.*

# Clinical Scoring System for the Prediction of Target Site Penetration of Antimicrobials in Patients with Sepsis

*Barbara S. Zeitlinger,[1,2] Markus Zeitlinger,[1] Irmgard Leitner,[1] Markus Müller[1] and Christian Joukhadar[1,3]*

**Table I.** Tissue penetration as determined by the calculation of the ratio of area under the concentration-time curve in tissue ($AUC_{tissue}$) to the AUC of the unbound concentration in plasma ($AUC_{plasma,free}$) assessed by use of microdialysis in patients with sepsis[a]

| Drug | Medium | $AUC_4$ (mg • min/mL) | $AUC_{tissue}/AUC_{plasma,free}$ |
|---|---|---|---|
| Cefpirome[16] | Plasma (free) | 16.04 ± 1.12 | |
| | Muscle | 9.80 ± 0.72 | 0.63 ± 0.04 |
| | Subcutis | 6.72 ± 7.60 | 0.43 ± 0.04 |
| Fosfomycin[17] | Plasma (free) | 43.06 ± 3.97 | |
| | Muscle | 30.09 ± 4.16 | 0.70 ± 0.07 |
| | Subcutis | 17.13 ± 2.28 | 0.41 ± 0.06 |
| Levofloxacin[4] | Plasma (free) | 0.90 ± 0.08 | |
| | Muscle | 0.58 ± 0.14 | 0.60 ± 0.12 |
| | Subcutis | 0.71 ± 0.08 | 0.81± 0.08 |
| Piperacillin[16] | Plasma (free) | 18.36 ± 2.76 | |
| | Muscle | 3.39 ± 6.57 | 0.19 ± 0.03 |
| | Subcutis | 1.70 ± 4.54 | 0.10 ± 0.02 |
| All | Plasma (free) | 20.46 ± 2.84 | |
| | Muscle | 12.21 ± 2.25 | 0.57 ± 0.04 |
| | Subcutis | 7.35 ± 1.31 | 0.44 ± 0.05 |

a Values are presented as mean ± SD.

**$AUC_4$** = AUC from 0 to 4 hours.

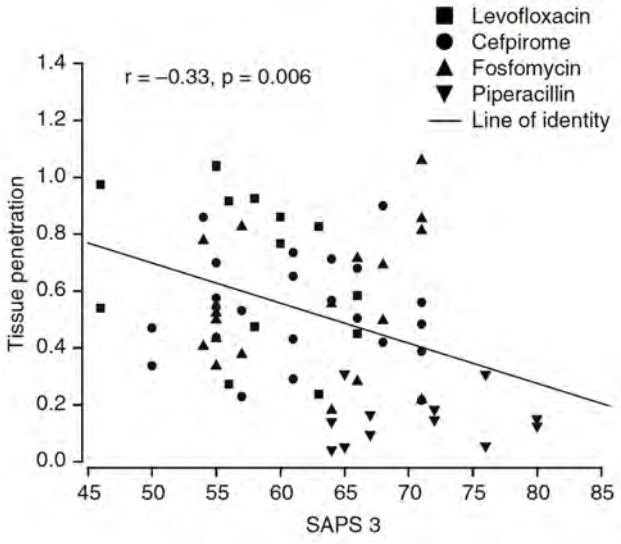



**Table II.** Spearman rank order correlations of selected parameters or scoring systems to tissue penetration. Data are shown for all tissues (sum of muscle and subcutis), and muscle and subcutis separately

| Parameter | $AUC_{tissue}/AUC_{plasma,free}$ | | | $AUC_{muscle}/AUC_{plasma,free}$ | | | $AUC_{subcutis}/AUC_{plasma,free}$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | r | p-value | n | r | p-value | n | r | p-value |
| $SaO_2$ (%) | 67 | 0.33 | 0.006 | 34 | 0.35 | 0.04 | 33 | 0.31 | 0.08 |
| Lactate (mmol/L) | 67 | −0.35 | 0.003 | 34 | −0.28 | 0.11 | 33 | −0.45 | 0.01 |
| Creatinine (mg/dL) | 67 | −0.31 | 0.01 | 34 | −0.31 | 0.07 | 33 | −0.33 | 0.06 |
| Bilirubin (mg/dL) | 67 | −0.29 | 0.02 | 34 | −0.25 | 0.15 | 33 | −0.33 | 0.06 |
| Epinephrine (adrenaline) dose (µg/kg/min) | 67 | −0.24 | 0.05 | 34 | −0.25 | 0.16 | 33 | −0.26 | 0.15 |
| Norepinephrine (noradrenaline) dose (µg/kg/min) | 67 | −0.57 | 0.0000004 | 34 | −0.54 | 0.001 | 33 | −0.64 | 0.00005 |
| SAPS | 67 | −0.12 | 0.34 | 34 | −0.09 | 0.60 | 33 | −0.12 | 0.49 |
| SAPS 2 | 67 | −0.06 | 0.64 | 34 | −0.13 | 0.46 | 33 | −0.23 | 0.21 |
| SAPS 3 | 67 | −0.33 | 0.006 | 34 | −0.22 | 0.21 | 33 | −0.43 | 0.01 |
| APACHE II score | 67 | −0.20 | 0.10 | 34 | −0.10 | 0.58 | 33 | −0.28 | 0.12 |
| APACHE III score | 67 | −0.27 | 0.03 | 34 | −0.12 | 0.50 | 33 | −0.41 | 0.02 |
| Simplified SSS | 67 | 0.09 | 0.47 | 34 | 0.29 | 0.09 | 33 | −0.10 | 0.59 |
| Complete SSS | 67 | −0.13 | 0.28 | 34 | 0.11 | 0.52 | 33 | −0.36 | 0.04 |
| SOFA | 67 | −0.32 | 0.01 | 34 | −0.32 | 0.06 | 33 | −0.36 | 0.04 |

**APACHE** = Acute Physiology and Chronic Health Evaluation; **AUC** = area under the concentration-time curve; **$AUC_{plasma,free}$** = AUC of the unbound concentration in plasma; **n** = number of profiles; **$SaO_2$** = oxygen saturation; **SAPS** = Simplified Acute Physiology Scores; **SOFA** = Sepsis-Related (or Sequential) Organ Failure Assessment; **SSS** = Septic Shock Scores.

Zeitlinger BS, et al. Clin Pharmacokinet. 2007;46(1):75-83.

**Table 5** Selected biomarkers for predicting antibiotic pharmacokinetics

| Biomarkers | Pathogenesis | Value | MW (kDa) | Peak (h) | $t_{1/2}$* | Affected drug PK | References |
|---|---|---|---|---|---|---|---|
| Inflammation biomarkers | | | | | | | |
| Cytokines/chemokines | | | | | | | |
| IL-1β | Proinflammatory cytokine | Px | 18–25 | 4 | 2 | D | [227] |
| IL-6 | Proinflammatory cytokine | Dx, Px | 21 | 6 | 2–4 | D | [228, 229] |
| IL-8 | Neutrophilic inflammation cytokine | Dx, Px | 8.4 | 4–8 | 4 | D | [230, 231] |
| IL-10 | Regulatory cytokine | Dx, Px | 18 | 12–24 | 2–4 | D | [232] |
| TNFα | Proinflammatory cytokine, neutrophilic activation | Px | 17.3 | 6 | 1–2 | D | [233] |
| IFNγ | $Th_1$ immune response | – | 17 | 6 | 2 | D | [234, 235] |
| MIP-1, -2 | Neutrophil, leukocyte activation | Px | 440 | 2 | 2.5 | D | [236, 237] |
| MCP-1 | Monocyte chemoattractant protein | Px | | | | | [238] |
| Cell markers/soluble receptors | | | | | | | |
| Presepsin | N-terminal fragment of sCD14 (LPS receptor) | Dx, Px, Tx | 13 | 3 | 4–5 | D | [239–241] |
| CD64 | Binds Fc fraction of IgG, induces phagocytosis | Dx, Tx | 43 | 4–6 | 5–17 | D | [242–244] |
| mHLA-DR | Expressed on APC, activation of T-cells | Px | – | 24 | 3–22 | D | [245, 246] |
| TLR2, TLR4 | Recognition of bacterial peptidoglycan (TLR2) or LPS (TLR4) | Dx | – | – | 3 | D | [247–249] |
| sTREM-1 | TREM-1 secreted by phagocytes | Dx, Px | 23.8 | 6 | 1.5 | D | [250–252] |
| SuPAR | Recruitment of neutrophils and monocytes | Dx, Px | – | 4 (d) | 10 (d) | D | [253–255] |
| Acute-phase reactants | | | | | | | |
| CRP | Complement activation, proinflammatory effects | Px | 20–25 | 24–48 | 19 | D | [256, 257] |
| PCT | Prohormone stimulated by IL-1, IL-6, TNFα | Dx, Px, Tx | 14.5 | 6–24 | 20–36 | D | [258, 259] |
| LBP | Connects CD14 to bacteria LPS | Dx, Px | 50 | 12 | 12–24 | D | [260] |
| Pro-ADM | Precursor of adrenomedullin, induces vasodilatation | Px | 4–5.5 | 4 | 2 | D | [261–263] |
| Pentraxin 3 | Pathogen recognition and removal | Dx, Px | 35 | – | 4 | D | [264–266] |
| C5a, C3a | Neutrophil migration, coagulopathy | Dx, Px | 190 | – | 4 | D | [267, 268] |
| Albumin | Increased vascular permeability | Px | 66.5 | NA | 21 (d) | D, M | [269–271] |
| Endotheliopathy biomarkers | | | | | | | |
| Syndecans | Glycocalyx component indicates damage | Px | 30 | NA | 0.06 | D | [272] |
| Heparan sulfate | Polysaccharide | Px | 30 | NA | 3–4 | D | [273] |
| Endocan | Soluble endothelial peptidoglycan, increases microvascular permeability | Px | 50 | NA | – | D | [94, 274, 275] |
| Ang-2/Ang-1 | Vascular integrity, Ang-2 is Ang-1 antagonist | Px | 1 | NA | 30 (s) | D | [99, 254, 276, 277] |
| sVCAM-1 | Adhesion protein expressed by endothelial cells, which binds to lymphocytes | Px | 102 | NA | 4 | D | [278, 279] |
| sICAM-1 | Intercellular adhesion molecules | Dx, Px | 76–114 | NA | – | D | [278–281] |
| E-selectin | Glycoprotein expressed in activated endothelial cells | Px | 115 | NA | 1.9 | D | [279, 281, 282] |
| P-selectin | Adhesion receptor expressed in platelets and endothelial cell | Px | 140 | NA | 2.3 | D | [283] |
| VEGF | Endothelial cells proliferation factor | Px | 23 | NA | 0.5–1 | D | [284] |
| Blood flow biomarkers | | | | | | | |
| $SO_2$ % | Oxygen saturation | Px | NA | NA | NA | D | [285] |
| MAP | Main global perfusion index | Px | NA | NA | NA | D | [286, 287] |
| CO | Cardiac output | Px | NA | NA | NA | D | [288] |

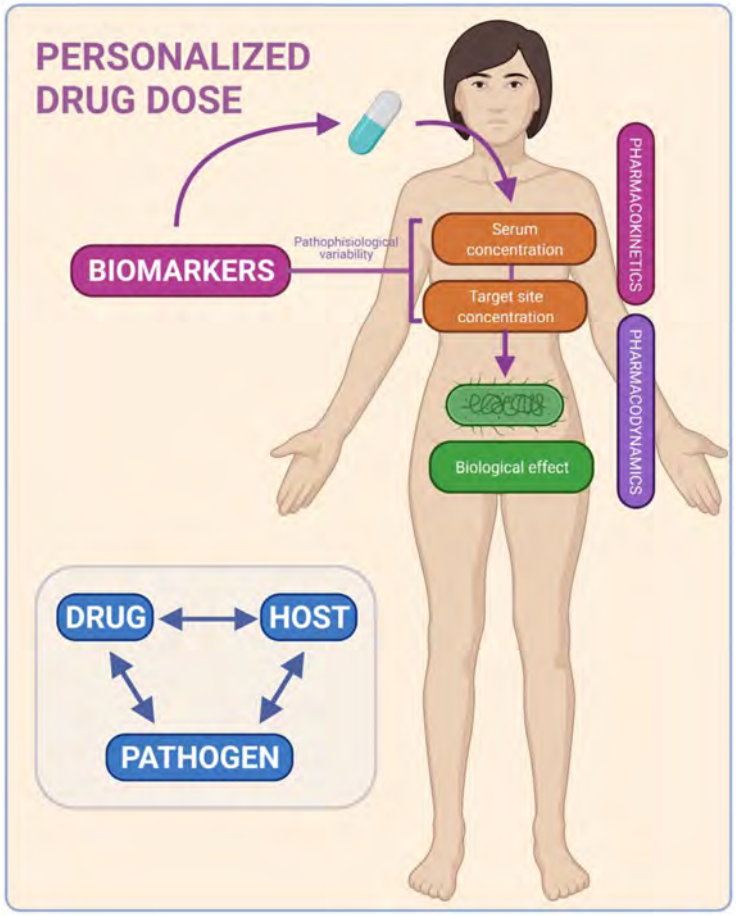



**Table 5** (continued)

| Biomarkers | Pathogenesis | Value | MW (kDa) | Peak (h) | $t_{1/2}$* | Affected drug PK | References |
|---|---|---|---|---|---|---|---|
| HR | Heart rate | Px | NA | NA | NA | D | [289] |
| $ScvO_2$ | Central venous oxygen saturation | Px | NA | NA | NA | D | [290] |
| $StO_2$ | Tissue oxygen saturation | Px | NA | NA | NA | D | [291] |
| Lactate | Anaerobic glycolysis end product | Px | 0.08 | – | 20 (m) | D | [286] |
| Coagulation biomarkers | | | | | | | |
| vWf Ag | Platelet adhesion and accumulation | Px | 5000–10,000 | NA | 4–26 | D, M | [292] |
| ADAMTS-13 activity | vWf cleaving protease | Px | 154 | NA | 48–72 | D, M | [293–295] |
| F ibrinogen | Low activation of secondary fibrinolysis | Px | 340 | NA | 100 | D, M | [296, 297] |
| PT | Consumption, depletion of endogenous haemostasis factors | Px | NA | NA | – | D, M | [298, 299] |
| aPPT | Indicative of CRP activity | Dx | NA | NA | – | D, M | [300–303] |
| AT activity | Coagulation inhibition and anti-inflammation | Px | 58 | NA | 72 | D, M | [296] |
| PF-4 | Protein secreted by activated platelets | Px | 29 | NA | | D | [304–306] |
| D-Dimer | Fibrinogen, fibrin breakdown, excessive coagulation | Px | 180 | NA | 8 | D, M | [304] |
| PAI-1 | Fibrinolysis inhibition | Px | 43 | NA | 2 | D | [304, 307] |
| Protein C | Antithrombotic action | Dx, Px | 62 | NA | 8 | D, M | [308–310] |
| Thrombomodulin | Endothelial cells glycoprotein, protein C pathway | Px | 74 | NA | 20 | D, M | [311–313] |
| Hepatic function biomarkers | | | | | | | |
| Bilirubin | Product of heme catabolism | Px | 548.67 | NA | 2–4 | M | [314–316] |
| ALT | Transaminase enzyme, indicates liver function | – | 110 | NA | 8 | M | [316, 317] |
| AST | Transaminase enzyme, indicates liver function | – | 90 | NA | 16 | M | [316, 317] |
| Ceruloplasmin | Increases as part of acute-phase response | Px | 115 | – | 15 | M | [318] |
| Hyaluronic acid | Indicates liver dysfunction | Px | 1000–8000 | NA | 4 (m) | D, M | [319] |
| Renal function biomarkers | | | | | | | |
| Creatinine | Estimate GFR | Px | 0.113 | NA | 3.85 | E | [320] |
| Cystatin C | Estimate GFR | Px | 13.3 | NA | 2 | E | [320] |
| BUN | Urea nitrogen in blood, indicative of renal function | Px | NA | NA | NA | M, E | [321–323] |
| NGAL | Indicative of kidney injury | Px | 25 | 6–12 | 15 | E | [320, 324] |
| KIM-1 | Injured kidney epithelial cells | Px | 60–90 | 12–24 | 6 | E | [320] |

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# Zusammenfassung

- Multiple Veränderungen der Pharmakokinetik von Antibiotika bei der Sepsis
  - Verteilungsvolumen
  - Proteinbindung
  - Metabolismus
  - Ausscheidung
- Dadurch Einschränkung der Wirksamkeit vs. Unerwünschte Überdosierungen
- TDM misst nur Antibiotika-Konzentrationen im Blut
- Herausforderung: Bestimmung der Konzentration im Zielgewebe

**Dr. med. Hartmuth Nowak, MSc, DESAIC**
Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie
Universitätsklinikum Knappschaftskrankenhaus Bochum
In der Schornau 23-35
44892 Bochum
eMail: hartmuth.nowak@kk-bochum.de


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# A pharmacometric approach to define target site-specific breakpoints for bacterial killing and resistance suppression integrating microdialysis, time–kill curves and heteroresistance data: a case study with moxifloxacin

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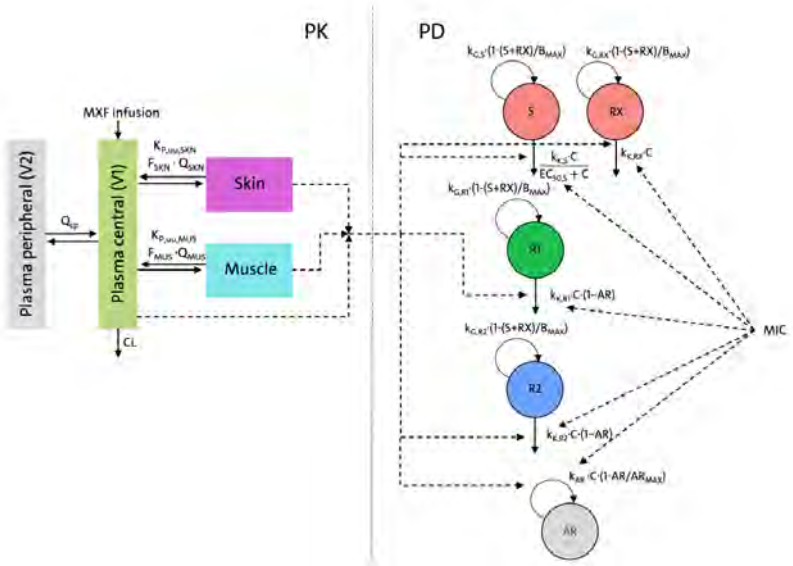


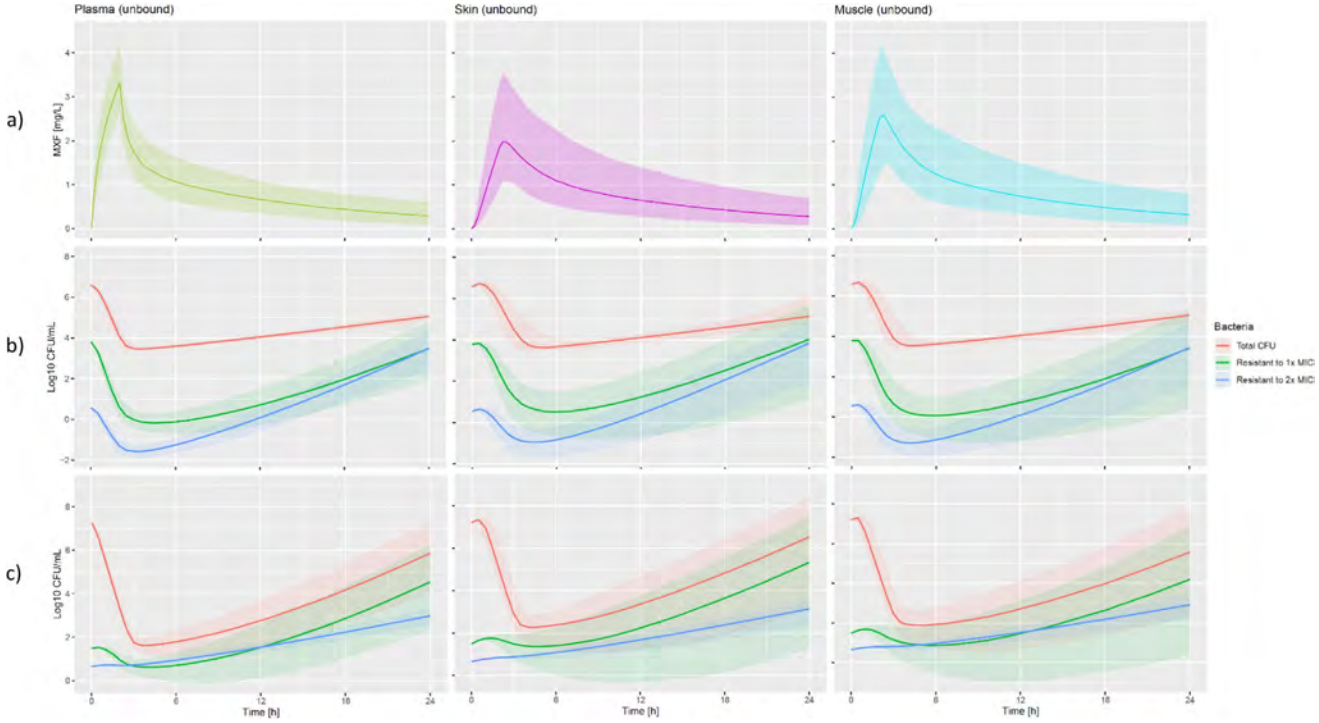


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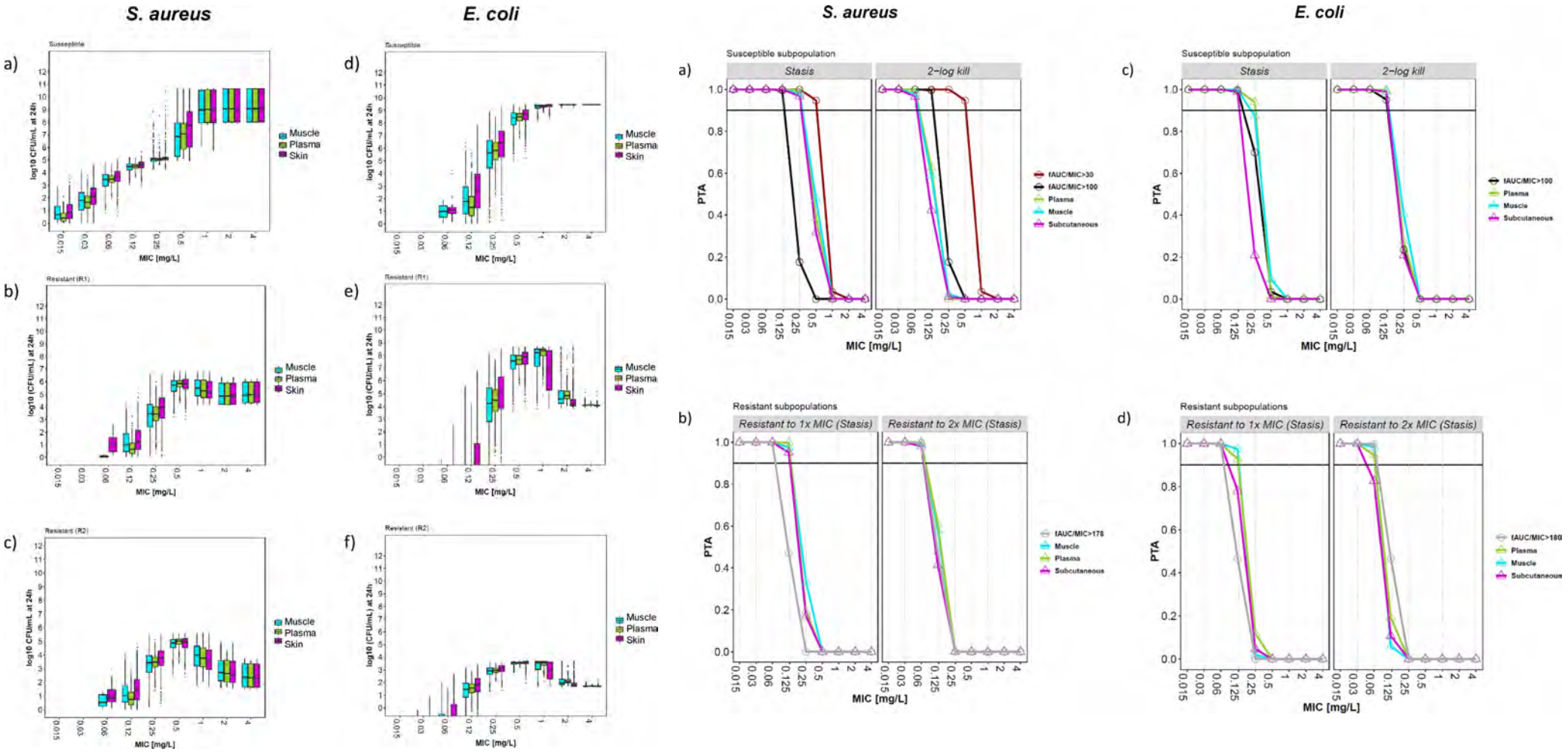


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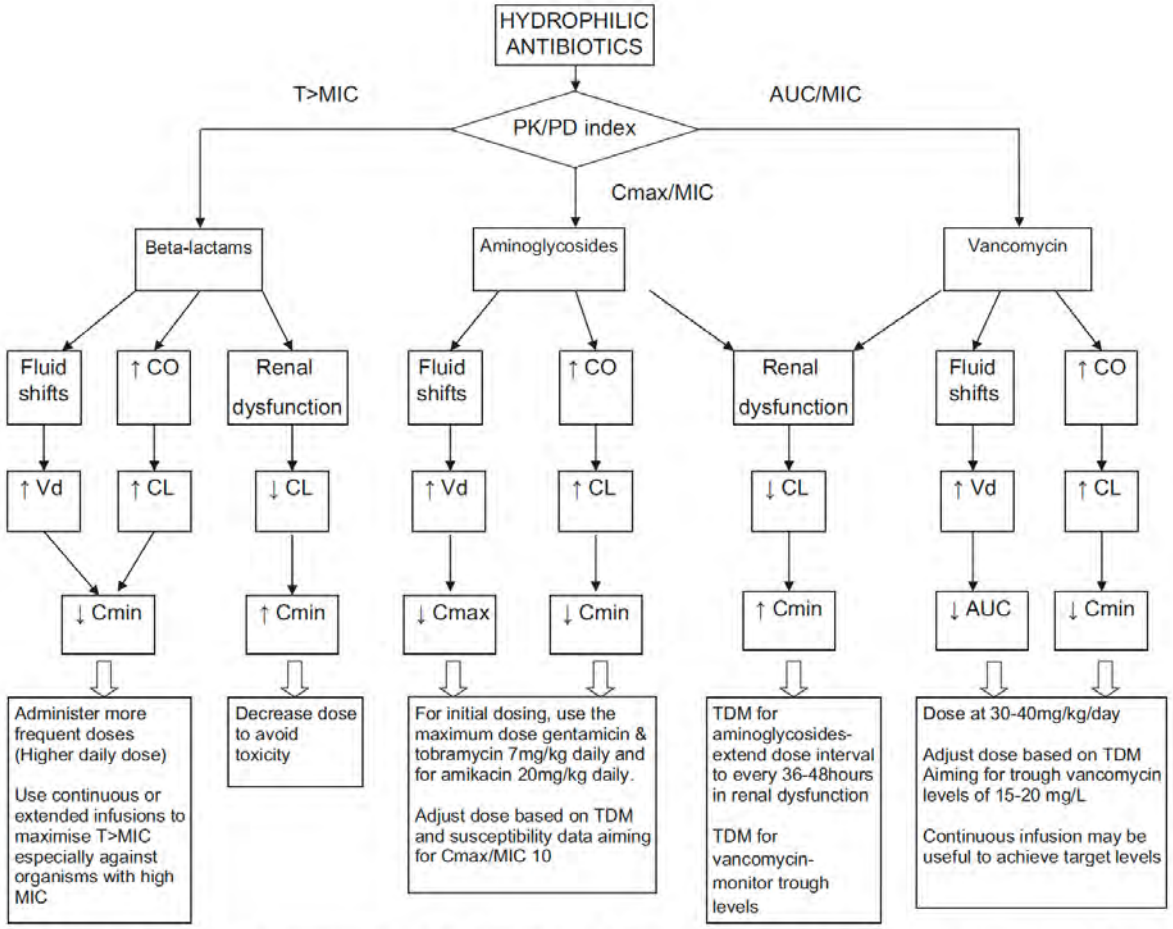


**Fig. 2.** Flow diagram summarizing the effects of pathophysiologic changes on PK/PD parameters of hydrophilic antibiotics. AUC, area under the curve; $C_{max}$, maximum drug concentration; $C_{min}$, minimum drug concentration; CL, clearance; CO, cardiac output; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic; $V_d$, volume of distribution.

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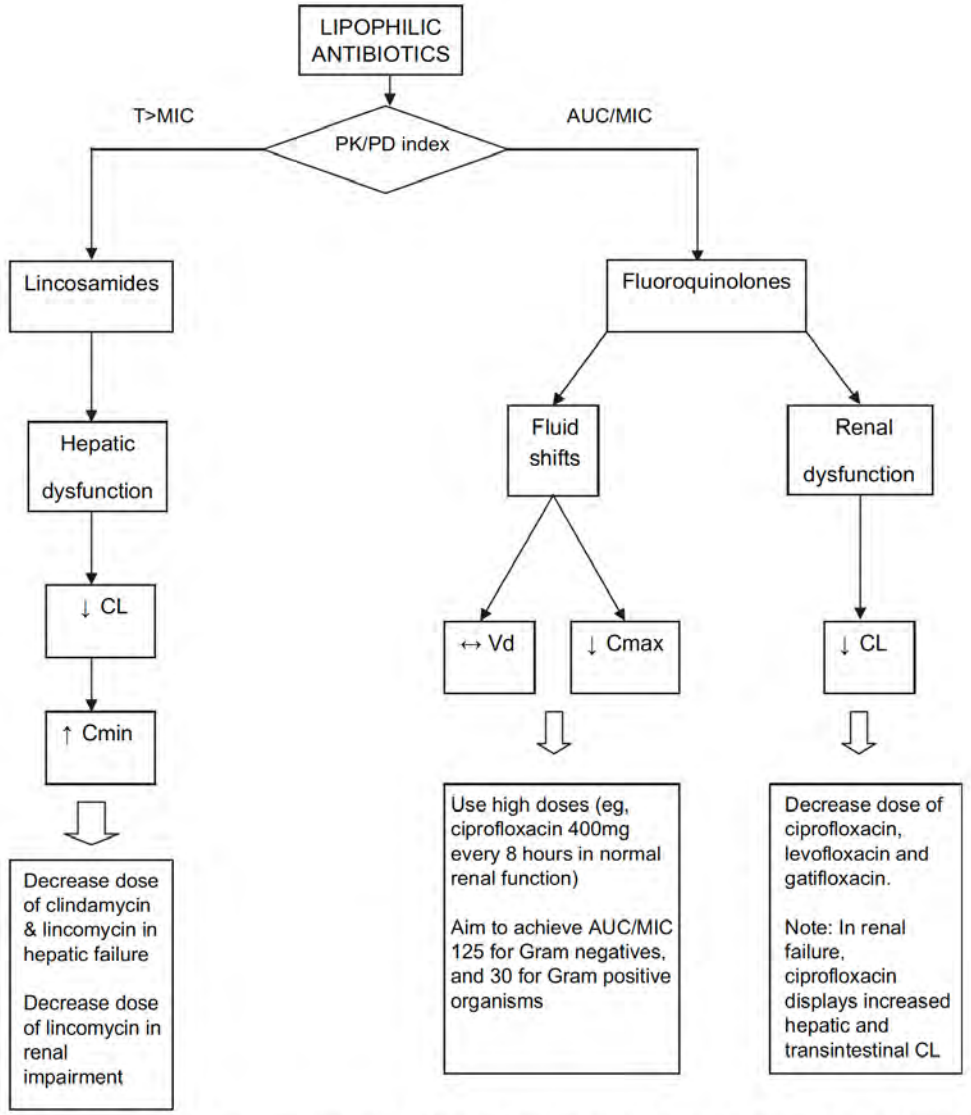


**Fig. 3.** Flow diagram summarizing the effects of pathophysiologic changes on PK/PD parameters of lipophilic antibiotics. AUC, area under the curve; $C_{max}$, maximum drug concentration; $C_{min}$, minimum drug concentration; CL, clearance; CO, cardiac output; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic; $V_d$, volume of distribution.

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