# Dávkování léků při CRRT - co nového?

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## Obsah

- Obecné principy
- Vliv CRRT
- Praktický postup

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## Faktory ovlivňující dávkování léků

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- Farmakokinetická charakteristika farmaka
- Farmakodynamická charakteristika farmaka

Pacientské faktory
- Kritický stav
- Akutní selhání ledvin

Vliv eliminační metody
- Vlastní metoda CRRT a její provedení

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## Lékové faktory

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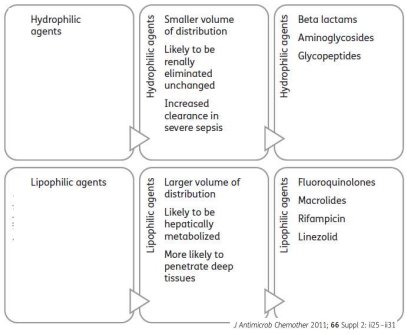
## I. Lipofilní vs hydrofilní charakter




J Antimicrob Chemother 2011; 66 Suppl 2: ii25–ii31

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## Rozdělení ATB dle velikosti Vd

Vd na úrovni ECT
- Betalaktamy
- Aminoglykosidy
- Roxithromycin

Vd vyšší než ECT
- Chinolony
- Ostatní makrolidy
- Rifampicin
- Linezolid
- Tigacyclin

van Dalen R, Vree TB: Pharmacokinetics of antibiotics in critically ill patients. Intensive Care Med, 1990, 16, s. 235-238

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## II. Vazba na bílkoviny

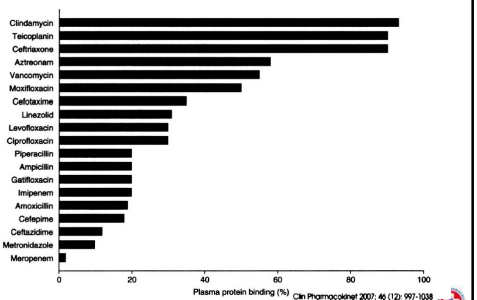


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**Table 2 Pharmacokinetic data of antibiotics for 70 kg patient receiving CVVH 35 ml/kg per hour**

| Drug | PB % | $V_d$ (l/kg) | $Cl_{total}$ (ml/min) | $Fr_R$ (%) | $Cl_{NR}$ (ml/min) | $Cl_{CVVH}$ (ml/min) | $Fr_{CVVH}$ |
|---|---|---|---|---|---|---|---|
| Acyclovir | 15 | 0.69 | 405 | 75 | 101 | 35 | 0.26 |
| Amikacin | <10 | 0.27 | 91 | 98 | 2 | 39 | 0.95 |
| Amphotericin | >90 | 0.76 | 35 | 2.5 | 31 | 4 | 0.12 |
| Amoxicillin | 18 | 0.21 | 180 | 86 | 25 | 34 | 0.57 |
| Cefotaxime | 36 | 0.23 | 260 | 50 | 130 | 26 | 0.17 |
| Ceftazidime | 21 | 0.23 | 125 | 84 | 20 | 32 | 0.62 |
| Ceftriaxone | 90–95 | 0.16 | 17 | 46 | 9 | 4 | 0.31 |
| Cefuroxime | 33 | 0.19 | 110 | 96 | 4 | 27 | 0.87 |
| Cilastatin | 30 | 0.24 | 230 | 98 | 3 | 29 | 0.91 |
| Ciprofloxacin | 40 | 1.8 | 420 | 65 | 147 | 25 | 0.14 |
| Clavulanic acid | 9 | 0.21 | 252 | 43 | 143 | 37 | 0.21 |
| Clindamycin | 93 | 1.1 | 329 | 13 | 286 | 3 | 0.01 |
| Erythromycin | 84 | 0.78 | 637 | 12 | 75 | 7 | 0.01 |
| Fluconazole | 12 | 0.7 | 21 | 75 | 5 | 36 | 0.87 |
| Ganciclovir | <5 | 0.6 | 300 | 90 | 30 | 39 | 0.56 |
| Gentamycin | <10 | 0.25 | 95 | >90 | 4 | 37 | 0.90 |
| Imipenem | <10 | 0.31 | 245 | 52 | 116 | 37 | 0.24 |
| Itroconazole | 99 | 11 | 300 | <1 | 300 | 0.4 | 0 |
| Linezolid [19] | 30 | 0.8 | 123 | 35 | 80 | 29 | 0.27 |
| Meropenem | 2 | 0.2–0.3 | 280 | 0.65–0.8 | 77 | 40 | 0.34 |
| Metronidazole | 10 | 0.74 | 91 | 10 | 82 | 37 | 0.31 |
| Ofloxacin | 10 | 2 | 250 | 86 | 35 | 37 | 0.51 |
| Penicillin | 60 | 0.3 | 205 | 85 | 30 | 16 | 0.35 |
| Piperacillin | 16 | 0.18 | 180 | 71 | 52 | 34 | 0.40 |
| Rifampicin | 89 | 0.97 | 245 | 7 | 228 | 5 | 0.02 |
| Sulfamethoxazole | 62 | 0.21 | 22 | 14 | 19 | 16 | 0.45 |
| Teicoplanin | 90 | 0.8 | 18 | 66 | 6 | 4 | 0.41 |
| Tobramycin | <10 | 0.33 | 90 | >90 | 4 | 37 | 0.90 |
| Trimethoprim | 44 | 1.8 | 154 | 69 | 48 | 23 | 0.32 |
| Vancomycin | 30 | 0.39 | 95 | 80 | 19 | 29 | 0.60 |

The pharmacokinetic parameters are taken from [20], unless otherwise indicated. $Cl_{CVVH}$, CVVH clearance; $Cl_{NR}$, nonrenal clearance; $Cl_{total}$, total body clearance; CVVH, continuous veno-venous hemofiltration; Fr, fraction unchanged by the kidney; $Fr_{CVVH}$, fractional CVVH clearance; PB, protein binding; $V_d$, volume of distribution.

Curr Opin Crit Care 14:654–659

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## III. Výchozí způsob eliminace

**Table 3: Pharmacokinetic and pharmacodynamic parameters of antimicrobial agents[25-30]**

| Drug | Concentration versus time-dependent | Vd (l/kg) | PBC (%) | Main elimination route | $T_{1/2}$ for normal renal function (h) | Target trough level (mg/l)[a] | Comments |
|---|---|---|---|---|---|---|---|
| Gentamycin | Concentration | 0.2-0.3 | <30 | Renal | | | Optimal $C_{max}$/MIC ≥8-10 |
| Tobramycin | Concentration | 0.2-0.3 | <30 | Renal | | | |
| Amikacin | Concentration | ~0.25 | 0-11 | Renal | | | |
| Cefazolin | Time | ~0.14 | 74-86 | Renal | | | 2× increase in Vd in critically ill reported* |
| Cefepime | Time | 0.23-0.29 | 16-20 | Renal | 2.1 | 8 | |
| Cefotaxim | Time | 0.15-0.55 | 27-38 | Renal | 1 | 8 | |
| Ceftazidime | Time | 0.23 | 17-21 | Renal | 1.6 | 8 | |
| Ceftriaxone | Time | 0.09-0.2 | 85-95 | Hepatic | 8 | 8 | |
| Cefuroxime | Time | | 33-50 | Renal | | | |
| Ciprofloxacine | Concentration | 1.8-2.7 | 20-40 | Renal | 4.1 | 1 | Optimal AUC 24/MIC >125 for Gram-negative, >40 for Gram-negative |
| Levofloxacine | Concentration | 1.05-1.6 | 24-38 | Renal | 7-8 | 2 | Vd is not increased in critically ill* |
| Moxifloxacine | Concentration | 1.7-2.7 | 50 | Hepatic | 12 | 2 | |
| Ampicillin | Time | 0.29 | ~28 | Renal | 1.2 | 8 | |
| Clavulanate | - | 0.3 | 30 | Hepatic | 1 | NA | |
| Vancomycin | Time/ concentration | 0.4-1.0 | 50-55 | Renal | 6 | 10 | |
| Piperacillin | Time | 0.18 | 16 | Renal | 1 | 16 | |
| Tazobactam | Time | 0.18-0.33 | 20-23 | Renal | 1 | 4 | |
| Sulbactam | Time | 0.25-0.50 | 38 | Renal | 1 | 1-4 | |
| Imipenem | Time | 0.23 | 20 | Renal | 1 | 4 | Vd is not increased in critically ill* |
| Meropenema | Time | 0.21-0.29 | 2 | Renal | 1 | 4 | MIC ≤2 mg/l MIC=4 mg/l or meningitis* |
| Linezolid | Time/ concentration | 0.57-0.71 | 31 | Hepatic | 4.8-5.4 | 4 | Optimal AUC 24/MIC~50 for *S. pneumoniae* and 82 for *S. aureus* |
| Daptomycin | Concentration | 0.1-0.13 | 90-93a | Renal | 8 | 4 | 84-88% for CrCl <30 l/min* |
| Fluconazolea | Time | 0.6-0.65 | 11 | Renal | 30 | 8-16d | ¶ undergoes postfiltration reabsorption therefore in anuric patients on CRRT its clearance ↑ necessitating dose ↑* |
| Itraconazole | Time | 10 | >99 | Hepatic | 21 | 0-1.25-0.25[c] | |
| Voriconazol* | Time | 4.6 | 58 | Hepatic | 12 | 0.5 | |
| Acyclovir | Time | 0.6 | 15 | Renal | 2-4 | NA | |
| Aztreonam | Time | 0.2 | 56 | Renal | 1.7-2.9 | 8 | |
| Clindamycin | Time | 0.6-1.2 | 60-90 | Hepatic | 3 | 2 | |
| Colistin | Concentration | 0.34 | 55 | Renal | 2 | 4 | |

DOI: 10.4103/0972-5229.151018

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## Pacientské faktory

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## I. Vliv kritického stavu

Zvýšení distribučního objemu
- Retence tekutin
- Snížená hladina albuminu

Zvýšení clearence - Augmented (Renal) Clearence
- Zvýšení srdečního výdeje
- Zvýšený průtok krev játry a ledvinami
- Snížená hladina albuminu, zvýšení volné frakce
- CRRT (non-renální indikace)

Snížení clearence
- Stupeň orgánové dysfunkce

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## II. Důsledky akutního selhání ledvin

- Zvýšení distribučního objemu
  - Retence tekutin, ztráty, compartmentalizace…
- Snížení renální clearence
  - Úprava dávkování léků eliminovaných převážně renálně
- Zvýšení non-renální clearence
  - Adaptace v čase (CHRI)
  - Interindividuální variabilita

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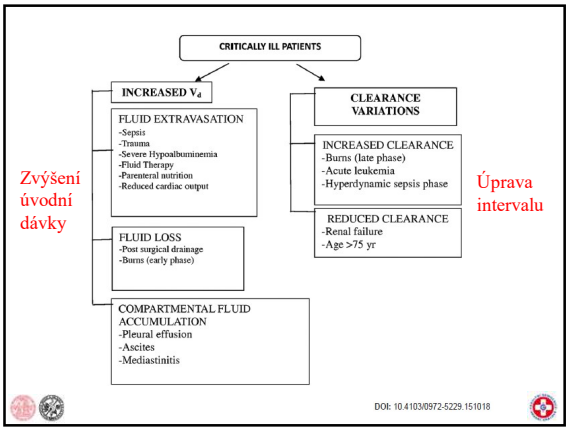


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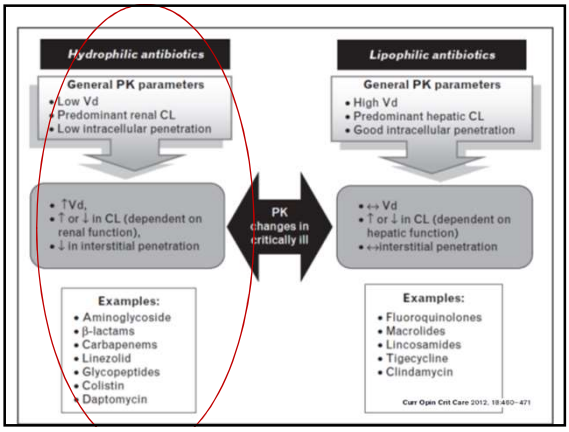


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## Změny Vd u nemocných s AKI na CRRT

**Table 1** | Volume of distribution data from pharmacokinetic studies in adults

| Antibiotic | Healthy volunteers (l/kg) | Patients with AKI receiving RRT (l/kg) |
|---|---|---|
| *Lipophilic drugs* | | |
| Ciprofloxacin | 1.98[76] | 1.60,[77] 1.65[78] |
| Levofloxacin | 0.96,[79] 1.13[80] | 1.02,[81] 1.51[82] |
| *Hydrophilic drugs* | | |
| Amikacin | 0.18[83] | 0.44[84] |
| Daptomycin | 0.10[85] | 0.23[26] |
| Meropenem | 0.17,[86] 0.18,[87] 0.27[88] | 0.26,[89] 0.35,[28] 0.37[29] |
| Piperacillin | 0.15[90] | 0.14,[91] 0.18[92] |
| Vancomycin | 0.39,[93] 0.59,[94] 0.63[95] | 0.57,[96] 0.65[97] |

Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy.

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## Pk/Pd I

| Antibacterials | Killing characteristics | Pharmacokinetic targets |
|---|---|---|
| β-Lactams | time dependent | 40–100% of dosing interval >MIC or 40–100% of dosing interval >5 times MIC [47] |
| Aminoglycosides | concentration dependent | $C_{max}$:MIC 8–10 [53] |
| Fluoroquinolones | concentration dependent/ time dependent | $C_{max}$:MIC 6–8, $AUC_{24}$:MIC 100–125 (Gram-negatives), 34 (*S. pneumoniae*) [87, 91] |
| Vancomycin | concentration dependent | $AUC_{24}$:MIC ≥400 (vs. *Staphylococcus aureus*) [77] |
| Linezolid | concentration dependent | $AUC_{24}$:MIC 50 (*S. pneumoniae*), $AUC_{24}$:MIC 82 (*S. aureus*) [92] 200 (Enterokoky) |
| Macrolides, azalides, ketolides | concentration dependent | probably $AUC_{24}$:MIC (drug concentration at target site). Relevance of plasma concentrations doubtful given the fact that drugs are concentrated in tissue [90] |
| Metronidazole | concentration dependent | not established |

Blood Purif 2010;30:195–212
DOI: 10.1159/000321488

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## Pk/Pd II

**Table 1. Antibiotic killing characteristics and pharmacokinetic/pharmacodynamic target**

| Antibiotic classification | Definition of PK/PD target | PK/PD target |
|---|---|---|
| Concentration-dependent | Ratio of the peak antibiotic concentration to the MIC of the pathogen ($C_{max}$/MIC) | Aminoglycoside: $C_{max}$/MIC 8–10 [13], daptomycin: $C_{max}$/MIC 8–10, $AUC_{0-24}$/MIC 100 [14,15] |
| Time-dependent | Percentage of time during dosing interval for which the free plasma concentration of the antibiotic remains more than the MIC of the pathogen (%$fT_{>MIC}$) | β-Lactams: 50–70% $fT_{>MIC}$ [14]; carbapenems: ≥40% $fT_{>MIC}$ [14]; linezolid: 40–80% $fT_{>MIC}$ [16,17] |
| Concentration-dependent with time-dependent | Ratio of the area under the concentration–time curve (AUC) during a 24h period to the MIC of the pathogen ($AUC_{0-24}$/MIC) | Fluoroquinolones: $C_{max}$/MIC 10, $AUC_{0-24}$/MIC 125* (Gram negatives) [18,19]; Glycopeptides: $AUC_{0-24}$/MIC ≥400* (*Staphylococcus aureus*) [20]; colistin: $AUC_{0-24}$/MIC 53–141 (*Pseudomonas aeruginosa*) [21] |

AUC, area under the curve; $C_{max}$, maximum concentration; $fT_{>MIC}$, unbound plasma concentration above the minimum inhibitory concentration of the pathogen; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic.
*Ciprofloxacin.
**Vancomycin.

Curr Opin Crit Care 2012, 18:460–471

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## Farmakodynamická charakteristika antibakteriálního účinku antibiotik

| | | Optimální PD parametr |
|---|---|---|
| Aminoglykosidy<br>Metronidazol<br>Fluorochinolony<br>Kolistin | Vrcholová koncentrace v séru | $C_{max}$/MIC<br>>8-10 |
| Fluorochinolony<br>Azitromycin<br>Tetracykliny<br>Glykopeptidy<br>Linezolid<br>Kolistin | Vrcholová koncentrace v plasmě + čas po který je sérová hladina vyšší než MIC | $AUC_{24}$/MIC<br>>100-125<br>>400 |
| Beta-laktámy<br>Karbapenemy<br>Linezolid<br>Erytromycin<br>Klaritromycin<br>Klindamycin | Čas po který je plasmatická koncentrace vyšší než MIC | T>MIC<br>100%T>MIC<br>100%T>4-5x MIC |

Chytra I, ČSARIM 2015

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Optimization of the treatment with beta-lactam antibiotics in critically ill patients—guidelines from the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique—SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Société Française d'Anesthésie et Réanimation—SFAR)

Romain Guilhaumou[1], Sihem Benaboud[2], Youssef Bennis[3], Claire Dahyot-Fizelier[4], Eric Dailly[5], Peggy Gandia[6]

**R2.2. We suggest targeting a free plasma beta-lactam concentration between four and eight times the MIC of the causative bacteria for 100% of the dosing interval (fT ≥ 4–8 x MIC = 100%) to maximize bacteriological and clinical response in critical care patients.**

Guilhaumou et al. Critical Care (2019) 23:104
https://doi.org/10.1186/s13054-019-2378-9

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## Vliv eliminační metody

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## Vliv způsobu prováděné CRRT

- Princip zvolené metody CRRT
  - Dialýza vs hemofiltrace
- Vlastní nastavení použité metody
- Materiál filtru, velikost filtru
- Doba provádění metody/24h
- Vlastnosti farmaka (velikost molekuly, vazba na bílkoviny, Vd, vazba na membránu)
- Další faktory

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## Faktory ovlivňující eliminaci farmak v průběhu CRRT

| | Odhadnutelné | Variabilní |
|---|---|---|
| Vlastnosti látky | Distribuční objem<br>Tzv. sieving koeficient | Vazba na bílkoviny (interakce s bilirubinem, dalšími látkami, vliv změn pH |
| Vlastnosti filtru | Materiál (cut-off, vazebná kapacita)<br>Velikost povrchu | Srážení krve ve filtru<br>Precipitace bílkovin na membráně |
| Vliv metody | Průtok filtrátu/dialyzátu<br>(Prediluce vs postdiluce)<br>(Průtok krve) | Žilní přístup (srážení krve, recirkulace krve)<br>Trvání přerušení metody |

Krueger WA, Schroeder TH, Hansen M: Pharmacokinetics of antibiotics during continuous renal replacement therapy. In: Vincent JL (ed) Yearbook of intensive care and emergency medicine 2005. Springer Verlag, Berlin, 2005, s. 349-359.

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Drug Dosing During Continuous Renal Replacement Therapy

Mariann D. Churchwell* and Bruce A. Mueller†
*Department of Pharmacy Practice, University of Toledo, College of Pharmacy, Toledo, Ohio, and †Department of Clinical, Social and Administrative Sciences, University of Michigan College of Pharmacy, Ann Arbor, Michigan

- Orientační kalkulace clearence na základě sieving koeficientu a součtu dializátu a ultrafiltrátu
- Clearence CVVH > CVVHDF > CVVHD, rozdíl narůstá s velikostí molekuly
- High flux membrany mají větší clearence u látek s molekulovou hmotností nad 1500 daltonu (vanko, daptomycin)
- Vliv mebrány (adsorpce)
- Vliv stáří filtru

Seminars in Dialysis—Vol 22, No 2 (March–April) 2009
pp. 185–188
DOI: 10.1111/j.1525-139X.2008.00541.x

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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2008, p. 1009–1013 Vol. 52, No. 3
0066-4804/08/$08.00+0 doi:10.1128/AAC.00858-07


Adsorption of Amikacin, a Significant Mechanism of Elimination by Hemofiltration▽

Qi Tian,[1] Charles D. Gomersall,[1]* Margaret Ip,[2] Perpetua E. Tan,[1] Gavin M. Joynt,[1] and Gordon Y. S. Choi[1]

*Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, N.T., Hong Kong,[1] and Department of Microbiology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, N.T., Hong Kong[2]*

Received 30 June 2007/Returned for modification 9 September 2007/Accepted 9 December 2007

**We used an in vitro model of continuous venovenous hemofiltration (CVVH) to characterize amikacin adsorption by polyacrylonitrile (PAN) and polyamide filters. A blood-crystalloid mixture dosed with amikacin was pumped from a reservoir through a hemofiltration circuit and back to the reservoir. All ultrafiltrate was also returned to the reservoir. The level of adsorption was calculated from the fall in the amikacin concentration. The dose and the initial concentration of amikacin were varied, as were the pH, the type of hemofilter, and the hemofilter surface area. The reversibility of adsorption and the effect of repeated dosing were also studied. The level of adsorption by 0.6-m$^2$ PAN filters was significantly greater than that by 0.6-m$^2$ polyamide filters. Adsorption was increased by increasing the dose of amikacin even when the initial concentration was unchanged. It was unaffected by the pH (pH 6.8 or 7.4) or the hemofilter surface area (0.6 m$^2$ or 0.9 m$^2$). Repeated doses of amikacin resulted in further adsorption. In a saturation experiment, the maximum adsorptive capacity of 0.6-m$^2$ PAN hemofilters was at least 546.9 mg (range, 427.6 to 577.5 mg). The adsorption of amikacin by hemofilters is irreversible and was associated with the dose and the hemofilter material but not the hemofilter surface area. Close monitoring of peak amikacin levels should be considered for patients receiving CVVH with PAN hemofilters.**

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## Jak postupovat prakticky?

- Tabulka dávkování léků na pracovišti
  - Unifikace metody
  - Unifikace dávky
- Literární/webové zdroje
  - Přehledové
  - Farmakokinetické studie – metoda, dávka, filtr, …
- TDM ve vybraných případech
  - Vankomycin
  - Aminoglykosidy
  - Další (linzeololid, batalactamy, colistin, ..)

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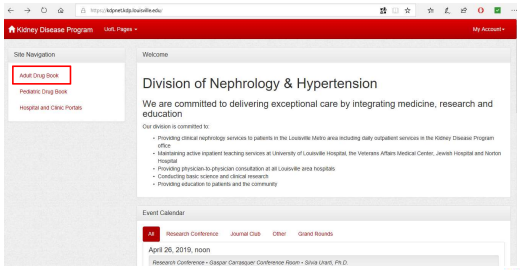
## „renal drugbook“

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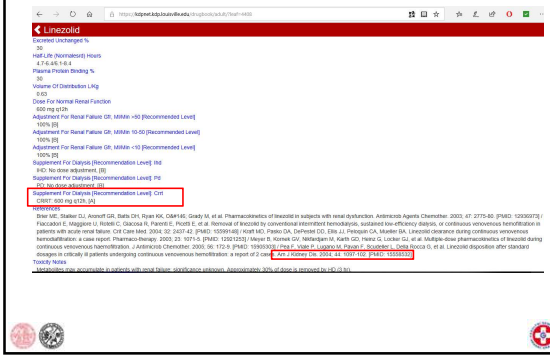


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## Effects of continuous renal replacement therapy on linezolid pharmacokinetic/ pharmacodynamics: a systematic review

Gianluca Villa[1*], Paola Di Maggio[1], A. Raffaele De Gaudio[1], Andrea Novelli[2], Riccardo Antonioli[3], Enrico Fiaccadori[3] and Chiara Adembri[1]

**Results:** Among 68 potentially relevant articles, only 9 were considered eligible for the analysis. Across these, 53 treatments were identified among the 49 patients included (46 treated with high-flux and 3 with high cut-off membranes). Continuous veno-venous hemofiltration (CVVH) was the most frequent treatment performed amongst the studies. The extracorporeal clearance values of linezolid across the different modalities were 1.2–2.3 L/h for CVVH, 0.9–2.2 L/h for hemodiafiltration and 2.3 L/h for hemodialysis, and large variability in PK/PD parameters was reported. The optimal area under the curve/minimum inhibitory concentration (AUC/MIC) ratio was reached for pathogens with an MIC of 4 mg/L in one study only.

Villa et al. Critical Care (2016) 20:374
DOI 10.1186/s13054-016-1551-7

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## Variability of linezolid concentrations after standard dosing in critically ill patients: a prospective observational study

Michael Zoller[1], Barbara Maier[2], Cyrill Hornuss[1], Christina Neugebauer[1], Gundula Döbbeler[1], Dorothea Nagel[2], Lesca Miriam Holdt[3], Mathias Bruegel[3], Thomas Weig[1], Béatrice Grabein[3], Lorenz Frey[1], Daniel Teupser[3], Michael Vogeser[2] and Johannes Zander[2*]

**Table 3 Distribution of patients in relation to the target range of linezolid**

| Patient groups, number of patients | Number (percentage) of linezolid patients | | | | | |
|---|---|---|---|---|---|---|
| | $AUC_{24}$ mg*h/L[a] | | | $C_{min}$ mg/L[b] | | |
| | <200 | 200 to 400 | >400 | <2 | 2 to 10 | >10 |
| Total patients, n = 30 | 19 (63) | 9 (30) | 2 (7) | 15 (50) | 13 (43) | 2 (7) |
| Male patients, n = 20[c] | 13 (65) | 5 (25) | 2 (10) | 11 (55) | 7 (35) | 2 (10) |
| Female patients, n = 10 | 6 (60) | 4 (40) | | 4 (40) | 6 (60) | |
| On CRRT, n = 5[d] | 2 (40) | 1 (20) | 2 (40) | | 3 (60) | 2 (40) |
| Not on CRRT, n = 25 | 17 (68) | 8 (32) | | 15 (60) | 10 (40) | |
| On ECLA, n = 7[e] | 5 (71) | 2 (29) | | 5 (71) | 2 (29) | |
| Not on ECLA, n = 23 | 14 (61) | 7 (30) | 2 (9) | 10 (43) | 11 (48) | 2 (9) |
| After liver transplantation, n = 5[f] | 2 (40) | 1 (20) | 2 (40) | | 3 (60) | 2 (40) |
| After lung transplantation, n = 10[g] | 6 (60) | 4 (40) | | 6 (60) | 4 (40) | |
| No transplantation, n = 15 | 11 (73) | 4 (27) | | 9 (60) | 6 (40) | |

Zoller et al. Critical Care 2014, 18:R148
http://ccforum.com/content/18/4/R148

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## Colistin

**Continuous Renal Replacement Therapy-Related Strategies to Avoid Colistin Toxicity: A Clinically Orientated Review**

Patrick M. Honore[1*] Rita Jacobs[1] Olivier Joannes-Boyau[1] Stijn Lochy[1] Willem Boer[1] Elisabeth De Waele[1] Viola Van Gorp[1] Jouke De Regt[1] Vincent Collin[1] Herbert D. Spapen[1]

- Hydrofilní
- Dominantně non-renální eliminace
- GF do primární moči, z 80% reabsorbován, jen malá část je vyloučena močí
- Účinek je závislý na dosažené koncentraci, nejlépe reprezentuje $AUC_{0-24}$/MIC
- Vysoká úvodní dávka je předpokladem baktericidního účinku

Blood Purif 2014;37:291–295
DOI: 10.1159/000363495

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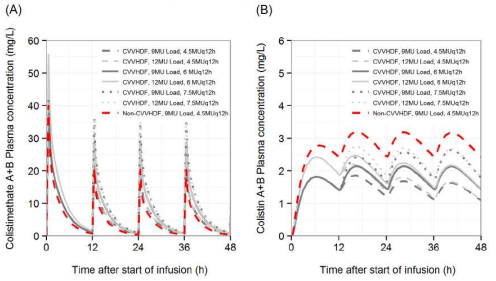
## Challenge for higher colistin dosage in critically ill patients receiving continuous venovenous haemodiafiltration

Ilias Karaiskos [a,*], Lena E. Friberg [b], Lambrini Galani [a], Konstantinos Ioannidis [c], Emmanouela Katsouda [d], Zoe Athanassa [d], Harris Paskalis [d], Helen Giamarellou [a]

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## Continuous Renal Replacement Therapy-Related Strategies to Avoid Colistin Toxicity: A Clinically Orientated Review

Patrick M. Honoré[a] Rita Jacobs[a] Olivier Joannes-Boyau[d] Stijn Lochy[a]

- Konvekce vs adsorpce
- Úvodní dávka 9 - 12 mil.j.
- 4,5 mil. j. 3x denně

AN69 ST (acrylonitrile 69 surface treated)

Blood Purif 2014;37:291–295
DOI: 10.1159/000363495

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## Modified Colistin Regimen for Critically Ill Patients with Acute Renal Impairment and Continuous Renal Replacement Therapy

Pierantonio Menna[a] Emanuela Salvatorelli[b] Alessia Mattei[c] Dario Cappiello[c] Giorgio Minotti[a,b] Massimiliano Carassiti[c]

- Úvodní dávka 9 mil. j./30 min
- Udržovací dávka 3 mil, j. á 8h, zahájená 12 h po úvodní dávce
- CVVHDF, BF 200 ml/min, Dialyzát 2500 ml/h, UF 600-900 ml/h

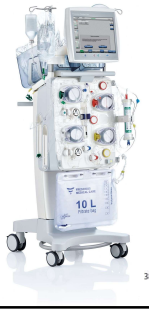


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Table 3. "Look-up" Table of Daily Doses of Colistimethate for a Desired Target colistin $C_{ss,avg}$ of 2 mg/L for Narrow Windows of Creatinine Clearance

| Creatinine clearance, mL/min | Dose of Colistimethate for $C_{ss,avg}$ of 2 mg/L[a] | |
|---|---|---|
| | CBA, mg/d | Million IU/d |
| 0 | 130 | 3.95 |
| 5 to <10 | 145 | 4.40 |
| 10 to <20 | 160 | 4.85 |
| 20 to <30 | 175 | 5.30 |
| 30 to <40 | 195 | 5.90 |
| 40 to <50 | 220 | 6.65 |
| 50 to <60 | 245 | 7.40 |
| 60 to <70 | 275 | 8.35 |
| 70 to <80 | 300 | 9.00 |
| 80 to <90 | 340 | 10.3 |
| ≥90 | 360 | 10.9 |

MAJOR ARTICLE

Dosing Guidance for Intravenous Colistin in Critically Ill Patients

Table 2. Suggested Loading and Daily Doses of Colistimethate for a Desired Target colistin $C_{ss,avg}$ of 2 mg/L in Various Categories of Critically ill Patients

| Dose | Category of Critically Ill Patient | Dosing Suggestions[a] |
|---|---|---|
| Loading dose | All patient categories | Equation 1: Loading dose of CBA (mg) = $C_{ss,avg}$ target (mg/L) × 2.0 × ideal body weight (kg) To achieve a $C_{ss,avg}$ of 2 mg/L in a patient with an ideal body weight of 75 kg, the loading dose would be 300 mg CBA (9 million IU), the suggested maximum loading dose. The 1st regular daily dose should be administered 12 h later. |
| Daily dose[b] | Not receiving RRT | Equation 2[c]: Daily dose of CBA (mg) = $C_{ss,avg}$ target (mg/L) × $10^{(0.0068 \times CrCl + 1.929)}$ See Table 3 ("look-up" table) for the daily dose to target a plasma colistin $C_{ss,avg}$ of 2 mg/L, depending on the patient's creatinine clearance. |
| | Receiving RRT | The baseline daily dose of colistimethate for a $C_{ss,avg}$ of 2 mg/L in a patient with creatinine clearance of 0 mL/min is 130 mg/d of CBA (3.95 million IU/d) (see Table 3)[d]; the supplement to the baseline daily dose needed during receipt of RRT is 10% of the baseline dose per 1 h of RRT. |
| | Intermittent hemodialysis | Nondialysis day: CBA dose of 130 mg/d (3.95 million IU/d), ie, baseline dosing for a $C_{ss,avg}$ of 2 mg/L; dialysis day supplement: add 30% or 40% to baseline daily dose after a 3- or 4-h session, respectively.[e] The dialysis session should occur toward the end of a colistimethate dosing interval, and the supplement to the baseline inondialysis daily dose should be administered with next regular dose, after the dialysis session has ended. |
| | SLED | During SLED: add 10% per 1 h of SLED replacement to baseline daily dose for a $C_{ss,avg}$ of 2 mg/L[f]; for a patient receiving a 10-h nocturnal SLED session each day and receiving colistimethate every 12 h, the dose would be baseline CBA dose of 130 mg/d for a patient with creatinine clearance of 0 mL/min + supplemental dose comprising 10% of the baseline dose per h × 10 h; ie, for this case the CBA dose would be 260 mg/d (7.9 million IU/d). It is suggested that the SLED session begin 1–2 h after the afternoon/evening dose; in such a case, it may be most convenient and safe to administer 130 mg CBA (3.95 million IU) every 12 h. |
| | CRRT | During CRRT: add 10% per 1 h of CRRT to the baseline daily dose for a $C_{ss,avg}$ of 2 mg/L[g]; the suggested CBA dose is 440 mg/d (~13 million IU/d). |

Clinical Infectious Diseases® 2017;64(5):565–71

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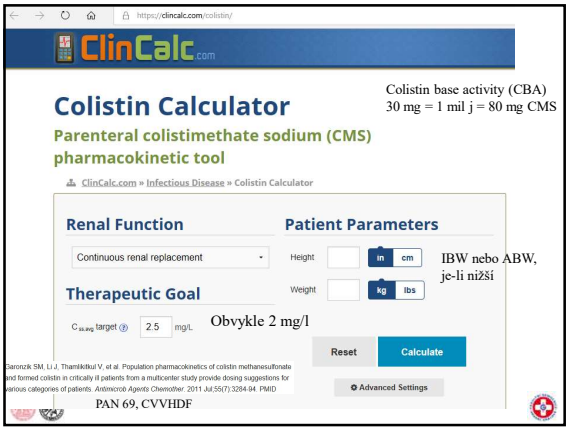


Colistin base activity (CBA)
30 mg = 1 mil j = 80 mg CMS

IBW nebo ABW, je-li nižší

Obvykle 2 mg/l

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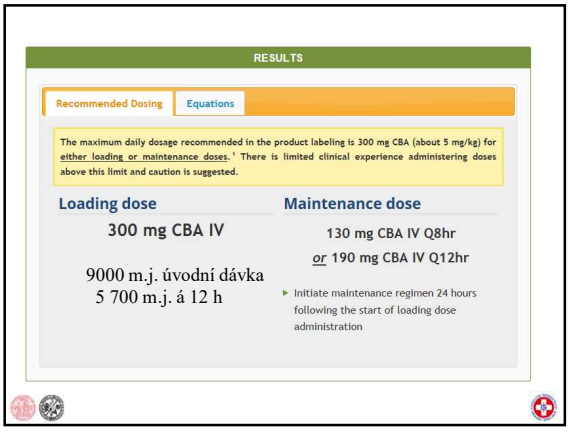


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## Literární zdroje (cave stáří)

**Table 3** | Dosing recommendations for selected intravenous antibiotics in patients on continuous RRT

| Drug | *Aronoff *et al.*[56] | ‡Trotman *et al.*[58] | §Heintz *et al.*[59] | ||Sanford Guide[4,60] |
|---|---|---|---|---|---|
| Amikacin | 7.5 mg/kg every 24–72 h | 10 mg/kg LD, then 7.5 mg/kg every 24–48 h | 10 mg/kg LD then 7.5 mg/kg every 24–48 h | 7.5 mg/kg every 24 h |
| Ciprofloxacin | 400 mg every 24 h | 200–400 mg every 12 h | 400 mg every 12–24 h | 200–400 mg every 24 h |
| Daptomycin | 8 mg/kg every 48 h | 4 mg/kg or 6 mg/kg every 48 h | 4 mg/kg or 6 mg/kg every 48 h | No recommendation |
| Levofloxacin | 500 mg every 48 h | 500 mg LD, then 250 mg every 24 h | 500–750 mg LD, then 250–500 mg every 24 h | 750 mg LD, then 500 mg every 48 h |
| Meropenem | 1–2 g every 12 h | 1 g every 12 h | 1 g LD then 0.5–1 g every 8–12 h | 1 g every 12 h |
| Piperacillin–tazobactam | 4.5 g every 8 h | 2.25–3.375 g every 6 h | 2.25–3.375 g every 6 h | 2.25 g every 6 h |
| Vancomycin | 1 g every 24–96 h | 15–20 mg/kg LD, then 1 g every 24 h | 15–25 mg/kg LD, then 10–15 mg/kg every 24 h | 500 mg every 24–48 h |

*Recommendations based on dialysate/ultrafiltrate/effluent rate of 2 l/h. ‡Recommendations for patients on continuous venovenous hemodialysis with a dialysate flow rate of 1 l/h. §Recommendations for patients on continuous venovenous hemodialysis with a dialysate flow rate of 1–2 l/h. ||Flow rates not specified. Abbreviations: LD, loading dose; RRT, renal replacement therapy.


Aronoff, G. R. *et al. Drug prescribing in renal failure: dosing guidelines for adults and children 5th edn (American College of Physicians, Philadelphia, 2007).*

Trotman, R. L., Williamson, J. C., Shoemaker, D. M. & Salzer, W. L. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. *Clin. Infect. Dis. 41, 1159–1166 (2005).*

Heintz, B. H., Matzke, G. R. & Dager, W. E. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy 29, 562–577 (2009).*

Gilbert, D. N. (Ed.) *The Sanford Guide to Antimicrobial Therapy 40th edn (Sanford, Sperryville, 2010).*


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## Recommended β-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy

Lucie Seyler[1], Frédéric Cotton[2], Fabio Silvio Taccone[3], Daniel De Backer[3], Pascale Macours[2], Jean-Louis Vincent[3] and Frédérique Jacobs[1*]

**Table 2 Pharmacokinetic parameters of the four antibiotics**

| Antibiotic (number of series) | $V_d$ (l/kg) | $C_{max}$ (μg/ml) | $C_{min}$ (μg/ml) | AUC (mg/hour/ml) | CL (ml/minute/kg) | $t_{1/2}$ (hours) |
|---|---|---|---|---|---|---|
| MEM 1 g twice daily ($n$ = 22) | 0.45 (0.20 to 3.03) | 26 (15 to 67) | 6 (2 to 11) | 134 (61 to 291) | 1.15 (0.54 to 3.37) | 4.39 (2.61 to 30.5) |
| TZP 4.0/0.5 g four times daily ($n$ = 21) | 0.44 (0.22 to 1.72) | 138 (36 to 262) | 60 (4 to 155) | 527 (62 to 1378) | 1.15 (0.27 to 6.26) | 4.16 (1.05 to 15.3) |
| FEP 2 g twice daily ($n$ = 11) | 0.55 (0.33 to 0.94) | 43 (28 to 83) | 11 (3 to 22) | 379 (148 to 483) | 1.04 (0.43 to 2.97) | 6.17 (3.30 to 22.9) |
| CAZ 2 g twice daily ($n$ = 15) | 0.37 (0.22 to 0.84) | 78 (54 to 118) | 24 (5 to 46) | 536 (258 to 906) | 0.52 (0.13 to 1.61) | 7.74 (2.52 to 33.5) |



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## Recommended β-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy

Seyler *et al. Critical Care* 2011, **15**:R137

Lucie Seyler[1], Frédéric Cotton[2], Fabio Silvio Taccone[3], Daniel De Backer[3], Pascale Macours[2], Jean-Louis Vincent[3] and Frédérique Jacobs[1*]

**Table 3 Probability of time the concentration is four times MIC attainment for *Pseudomonas* spp**

| Antibiotic, daily dose (number of patients) | Time period (number of series) | PK/PD target attainment (number of series (%)) |
|---|---|---|
| MEM 1 g twice daily ($n$ = 17) | All ($n$ = 22) | 18 (81%) |
| | Day < 48 hours ($n$ = 7) | 5 (71%) |
| | Days > 48 hours ($n$ = 15) | 13 (87%) |
| TZP 4 g four times daily ($n$ = 16) | All ($n$ = 21) | 15 (71%) |
| | Day < 48 hours ($n$ = 12) | 8 (66%) |
| | Days > 48 hours ($n$ = 9) | 7 (78%) |
| FEP 2 g twice daily ($n$ = 8) | All ($n$ = 11) | 0 (0%) |
| | Day < 48 hours ($n$ = 7) | 0 (0%) |
| | Days > 48 hours ($n$ = 4) | 0 (0%) |
| CAZ 2 g twice daily ($n$ = 12) | All ($n$ = 15) | 8 (53%) |
| | Day < 48 hours ($n$ = 8) | 3 (38%) |
| | Days > 48 hours ($n$ = 7) | 5 (71%) |

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## Individualizace

- Dostupnost měření hladin
- Komerční programy pro TMD
- Java PK for Desktop
- Android/iOS

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## Antibiotic Kinetics Lite


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## Děkuji za pozornost.

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