Dialyse hemodialyse: cefepim 7576

Clcr = creatinineklaring, CCVH = continue venoveneuze hemofiltratie, CCVHDF = continue venoveneuze hemodiafiltratie, GFR = glomerulaire filtratie snelheid, IHD = intermitterende hemodialyse, ke = eliminatiesnelheidsconstante, PTA = probability of target attainment, Scr = serumcreatinine, Sc = sieving coefficient

Onderbouwend	Bewijs	Effect	Opmerkingen
Seyler L ea. Recommended β-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. Crit Care. 2011;15:R137.	2	$T_{1/2}$: 6.17 uur (GIC: normale nierfunctie 2 uur): Cl: 1.04 ml/min/kg C_{max}: 43 µg/ml; C_{min}: 11 µg/ml Vd: 0.55 l/kg PK studie bij 8 IC patiënten die CVVHD(F) ondergingen. Regime: 2 g cefepim i.v. elke 12 uur Serum concentrations remained above four times the minimal inhibitory concentration for Pseudomonas spp. for ≥ 70% of the time interval between two doses in 0% of the patients treated with with cefepime (in the first 48 hours of treatment).	Auteurs: At the onset of sepsis in patients receiving CRRT, we suggest that similar β-lactam doses to those used in the absence of renal failure should be given during the first 48 hours of therapy: cefepime can be given at doses of 2 g three times daily. Dose reduction should be considered thereafter to avoid drug accumulation.
Malone RS ea. Pharmacokinetics of cefepime during continuous renal replacement therapy in critically ill patients. Antimicrob Agents Chemother. 2001;45:3148-55.	2	CVVH (n=5) $T_{1/2}$: 12.9 uur Cl_{tot}: 35.9 ml/min $Cl_{dialyse}$: 40% van Cl_{tot} CVVHDF (n=7) $T_{1/2}$: 8.6 uur Cl_{tot}: 46.8 ml/min $Cl_{dialyse}$: 59% van Cl_{tot} Regime: 1 of 2 gram cefepim elke 12 of 24 uur. (total 1-4 g per dag). Er werden geen bijwerkingen gezien. Zie ook tabel hieronder	Auteurs: Cefepime should be given in doses of 2 g/day for most infections caused by susceptible gram-negative pathogens, administered as either a single 2-g intravenous dose or in divided 1-g doses. However, 4 g of cefepime per day appears to be required for pathogens with potentially higher MICs such as P. aeruginosa or for empirical treatment of life threatening nosocomial infections, particularly in patients receiving treatment with CVVHDF.
Allaouchiche B ea. Pharmacokinetics of cefepime during continuous venovenous hemodiafiltration. Antimicrob Agents Chemother. 1997;41:2424-7.	2	$T_{1/2}$: 8.11 uur Sc: 0.72 C_{max}: 53 mg/l (0,5-1 uur na toediening) C_{min}: 17.7 mg/l (12 uur na toediening). V_d: 0.71 l/kg Cl_{DO} 66.6 ml/min Bij 6 anurische patiënten met acuut nierfalen die CVVHDF ondergingen. Regime: 2 g cefepim i.v. elke 12 uur	Auteurs: We conclude that there was no delay in the time to peak concentration for our patients compared to that of normal subjects and that the concentrations obtained with twice-daily 2-g infusions are greater than fivefold the cefepime MIC for the standard bacteria sensitive to cefepime. In intensive care patients under CVVHDF, we suggest the use of a 2-g twice-daily infusion of cefepime.

TABLE 5. Calculated pharmacodynamic parameters for cefepime with various dosage regimens during CRRT

Pharmacodynamic parameter	Parameter value by different dosage regimens and treatments							
	1 g every 24 h		1 g every 12 h		2 g every 24 h		2 g every 12 h	
	CVVH	CVVHDF (n = 2)	CVVH (n = 1)	CVVHDF (n = 1)	CVVH (n = 3)	CVVHDF (n = 4)	CVVH (n = 1)	CVVHDF
$T > MIC$	NA[a]							NA
MIC ≤ 4 µg/ml	NA	100%	100%	100%	100%	100%	100%	NA
MIC = 8 µg/ml	NA	74%	100%	100%	100%	100%	100%	NA
MIC = 16 µg/ml	NA	40%	100%	85%	100%	84%	100%	NA
AUC_{0-24}/MIC								
MIC ≤ 4 µg/ml	NA	118	209	145	263	262	419	NA
MIC = 8 µg/ml	NA	59	104	73	131	131	210	NA
MIC = 16 µg/ml	NA	30	52	36	66	65	105	NA

[a] NA, not available (dosage regimens not studied).

Barbhaiya RH ea. Pharmacokinetics of cefepime in subjects with renal insufficiency. Clin Pharmacol Ther. 1990;48:268-76.	2	68% van de toegediende dosis in dialysaat na 3 uur dialyse. Predialyse: t1/2 13h; Tijdens dialyse: t1/2 2.3h bij IHD-patiënten (n=5) die 1-malig 1000 mg i.v. cefipim toegediend kregen.	Auteurs: Cefepime is efficiently removed by hemodialysis, and thus an additional dose is needed to maintain therapeutic plasma concentrations subsequent to dialysis.

Overig	**Opmerkingen**
SPC Cefepim Fresenius Kabi 21-11-2018 Zelfde getallen als Barbhaiya (1990)	Hemodialyse (zowel bij ernstige als bij zeer ernstige infecties): oplaaddosis van 1 g, vervolgens 500 mg elke 24 uur, op dialysedagen toedienen na de dialyse Bij patiënten die hemodialyse ondergaan wordt ongeveer 68% van de totale hoeveelheid cefepim die bij aanvang van de dialyse in het lichaam aanwezig is tijdens een dialyseperiode van 3 uur uitgescheiden. De gemiddelde eliminatiehalfwaardetijd bij dialysepatiënten bedraagt 13 uur. ►GIC: predialyse (zie Barbhaiya 1990)
Al-Shaer MH ea. Applying cefepime population pharmacokinetics to critically ill patients receiving continuous renal replacement therapy. Antimicrob Agents Chemother. 2022;66:e0161121.	PK-model gemaakt op basis van verschillende datasets met in totaal 125 IC patiënten op continue dialyse (CVVH n=116; CVVHD n=2; Sustained Low Efficiency Dialysis=7) die werden behandeld met vancomycine 2 g elke 8 uur (n=14) of 2 g elke 12 uur (n=111). Auteurs: cefepime was well described using a five-compartment model and CRRT flow rates. The majority of patients achieved 100% $fT_{>MIC}$ while one third achieved 100% $fT_{>4xMIC}$. The mortality rate was 50%.
Chaijamorn W ea. Cefepime dosing regimens in critically ill patients receiving continuous renal replacement therapy: a Monte Carlo simulation study. J Intensive Care. 2018;6:6	1-compartiment PK-model gemaakt op basis van studiedata van kritisch zieke patiënten op continue dialyse die werden behandeld met cefepim. Deze studiedata zijn verkregen uit de literatuur. PTA 70% $fT_{>4MIC}$. Auteurs: This study revealed that the regimen of 2 g loading dose followed by 1.5–1.75 g every 8 h achieved the PTA target for P. aeruginosa (MIC of 8 mg/L) with two different modalities in ≥ 90% of virtual patients receiving CRRT with recommended effluent rate of 20–25 mL/kg/h, with a neurotoxicity risk of < 17%. All recommended dosing regimens for patients receiving CRRT from available clinical resources failed to achieve the PTA target.
Carlier M ea. Population pharmacokinetics and dosing simulations of cefepime in septic shock patients receiving continuous renal replacement therapy. Int J Antimicrob Agents. 2015;46:413-9.	PPK model gemaakt op basis van studiedata (oa Seyler 2011) van septische patiënten (n=13) op continue dialyse die werden behandeld met cefepim. The probability of target attainment was calculated against a conservative (60% T>MIC) and a higher PK/PD target (100%T>MIC) against an MIC of 8 mg/L, the clinical susceptibility breakpoint for Pseudomonas aeruginosa. A onecompartment model with between-subject variability (BSV) on clearance and volume of distribution (Vd) described the data adequately. **Table 3** Probability of target attainment (PTA in %) against a minimum inhibitory concentration (MIC) of 8 mg/L and probability of toxicity for different dosing strategies and different ultrafiltration flow rates (UFRs). Dose / UFR = 1000 mL/h: PTA 100% $T_{>MIC}$ / PTA 60% $T_{>MIC}$ / Probability of toxicity; UFR = 1500 mL/h: PTA 100% $T_{>MIC}$ / PTA 60% $T_{>MIC}$ / Probability of toxicity; UFR = 2000 mL/h: PTA 100% $T_{>MIC}$ / PTA 60% $T_{>MIC}$ / Probability of toxicity 1 g q12h: 64 / 95 / 0 / 31 / 80 / 0 / 9 / 51 / 0 2 g q12h: 89 / 99 / 5 / 82 / 98 / 0 / 73 / 95 / 0 1 g q8h: 95 / 100 / 3 / 87 / 99 / 0 / 79 / 95 / 0 2 g q8h: 99 / 100 / 30 / 96 / 100 / 9 / 92 / 100 / 3 1 g q6h: 100 / 100 / 10 / 97 / 100 / 2 / 93 / 100 / 0 q12h, every 12 h; q8h, every 8 h; q6h, every 6 h. Auteurs: Dosing simulations showed failure to achieve both a conservative and a higher PK/PD target using a dose of 1 g q12h for patients treated with a high UFR (≥1500 mL/h). The dose of 2 g q8h or 1 g q6h leads to optimal target attainment for high UFR. One gram q8h is optimal for low UFR (≤1000 mL/h).
Jang SM ea. Antibiotic Exposure Profiles in Trials Comparing Intensity of Continuous Renal Replacement Therapy. Crit Care Med. 2019 ;47:e863-e871.	Monte Carlo Simulatie (MCS) op basis van studiedata van patiënten die CCVHDF ondergingen. Deze data was verkregen in eerdere studies. Auteurs: Lower target attainment was especially prominent for cefepime, where 2g doses every 12 hours yielded no patients achieving a fT greater than 4 × MIC target. In contrast, our MCS suggests that 74.9–89.2% of modeled patients would have met that target. The intensity of effluent flow rates (less intensive vs intensive) did not substantially

	influence the probability of target attainment of antibiotic dosing regimens regardless of pharmacodynamic target.
Descombes E ea. Three-times-weekly, post-dialysis cefepime therapy in patients on maintenance hemodialysis: a retrospective study. BMC Pharmacol Toxicol 2016;17:4	Dosis: 775 mg (12.7 mg/kg) resp. 1125 mg (17.2 mg/kg) na de dialyse Predialyse dalspiegel: 10.7 resp. 11.3 mg/l Bij patiënten met een dialysevrij interval van 48 resp. 72 uur na de dialyse. Retrospectieve studie naar 12 infecties bij 9 patiënten op high-flux IHD 3x per week 4 uur, die werden behandeld met cefepim. Initiële post-dialysedosis was 15 mg/kg, daarna gedoseerd o.b.v. dalspiegels vlak voor de volgende dialyse. These levels always largely exceeded the EUCAST susceptibility breakpoints for all the targeted bacteria (> 1 mg/l) with the exception of Pseudomonas aeruginosa (> 8 mg/l). Cefepime concentrations were higher in anuric patients compared to those with preserved diuresis (15.6 vs 9.3 mg/l) and decreased on average by 81 % during dialysis (from 10.5 to 2 mg/l). The clinical outcome of all patients was good. Auteurs: geef cefepim 1 g na de dialyse (bij interval van 48 uur) en 1.5 g na de dialyse (bij interval van 72 uur) zonder routinematige spiegelcontrole bij infecties met gevoelige bacteriën, Bij minder gevoelige bacteriën en significante restfunctie zijn hogere initiële doses nodig (1.5 g bij 48 uurs-interval en 2 g bij 72-uurs interval) op geleide van de dalspiegel.

Risicogroep	

Opmerkingen:

- Werkgroep 13-6-2022: ook bij dialyse rekening houden met ernst infectie. Voor CVVH advies Malone 2001, Allaouchiche 1997 en simulatie Jang 2019 volgen met op de eerste dag 100% van de normale dosering.
  In de studie van Lau 2021 is gevonden dat de Cmin goed correleert met het optreden van neurotoxiciteit met een hogere drempelwaarde (49 mg/l) dan in eerdere studies is gevonden. Dit geeft meer ruimte, omdat de behandeling werd beperkt door de gedachte dat cefepim heel toxisch is.
  Bij betalactam antibiotica heeft continu doseren de voorkeur.

	Wijziging kinetiek	**Effect dialyse**	**Actie**	**Datum**
Beslissing werkgroep	Ja	Ja	Ja	13 juni 2022