Dialyse hemodialyse: cefiderocol

CVVHD = continu venoveneuze hemodialyse, CVVHDF = continue venoveneuze hemodiafiltratie, HD = hemodialyse

	Wijziging kinetiek	Effect dialyse	Actie	Datum
Beslissing werkgroep	Ja	Ja	Ja	20 maart 2025

Literatuur

Onderbouwend	Bewijs	Effect	Opmerkingen
Katsube T ea. Cefiderocol, a siderophore cephalosporin for gram-negative bacterial infections: pharmacokinetics and safety in subjects with renal impairment. J Clin Pharmacol. 2017;57:584-91.	3	De AUC van cefiderocol was 4.1x hoger en de t1/2 was 3.4x hoger bij ESRD patiënten zonder HD (n = 8) in vergelijking met patiënten met een normale nierfunctie (n = 8) (CLcr ≥ 90 mL/min, AUC = 213, t1/2 = 3 uur) na een eenmalige intraveneuze toediening van 1000 mg cefiderocol gedurende 1 uur. De AUC van cefiderocol was 1.5x hoger en de t1/2 was 3.4x hoger bij ESRD patiënten met HD (n = 8) in vergelijking met patiënten met een normale nierfunctie (n = 8) na een eenmalige intraveneuze toediening van 1000 mg cefiderocol gedurende 1 uur. Ongeveer 60% van cefiderocol werd verwijderd door hemodialyse gedurende 3 tot 4 uur. Verminderde nierfunctie had geen significante invloed op de Cmax.	Bij de hemodialysegroep werd cefiderocol tweemaal toegediend: de eerste dosis ongeveer 1 uur na afloop van de HD (periode 1, zonder HD) en de tweede dosis (na een uitwasperiode van 72 uur) ongeveer 2 uur vóór de HD (periode 2, met HD). De aanzienlijke verwijdering van cefiderocol door hemodialyse suggereert dat een aanvullende dosis na intermitterende HD nodig is.
Mornese Pinna S ea. Pharmacokinetic of cefiderocol in critically ill patients receiving renal replacement therapy: a case series. Antibiotics (Basel). 2022;11:1830.	2	Case-serie over IC-patiënten (n=3) met acuut nierfalen die CVVH kregen i.v. 2 g cefiderocol elke 8 uur voor een ernstige infectie. - Patiënt 1 (56 jr): t1/2 7.6 uur, AUC0–8h 644 ng/ml.h. fCthrough 12.2x hoger dan MIC - Patiënt 2 (71 jr): t1/2 2 uur, AUC0–8h 272 ng/ml.h en herstel nierfunctie. fCthrough 3x hoger dan MIC - Patiënt 3 (45 jr): t1/2 9.6 uur en AUC0–8h 773 ng/ml.h . fCthrough 15x hoger dan MIC.	Exacte fCthrough niet berekend maar uitgegaan van eiwitbinding van 58%. Auteurs: even in critically ill patients with severe infections and AKI, the cefiderocol dosing of 2 g q8 h led to very high plasma exposure. Given the few therapeutic options against DTR-AB and the reduced cefiderocol penetration into ELF, TDM results may be the option to enhance the dosing interval and achieve clinical cure.
Gatti M ea. Pharmacokinetics/pharmacodynamics of cefiderocol administered by continuous infusion in	2	Case-serie over patiënten (n=5) die CVVHDF (effluent flow: 2.7-3.7 l/h)kregen. Cefiderocol 6g/24h per continu infuus. Cltot: 4.8 l/h; Css (vrije fractie): 26.5 mg/l.	Auteurs: continuous infusion of full doses of cefiderocol could be a useful strategy to attain aggressive PK/PD targets for the treatment of severe CRAB infections in critically ill patients undergoing high-intensity

a case series of critically ill patients with carbapenem-resistant Acinetobacter baumannii infections undergoing continuous venovenous haemodiafiltration (CVVHDF). Int J Antimicrob Agents. 2023;62:106852.		In alle gevallen werd een optimale PK/PD-target behaald; mediane fCss/MIC-ratio was 14.9. 4 patienten hadden renale restklaring. Er werden geen cefiderocol-gerelateerde bijwerkingen gezien.	CVVHDF and who have residual diuresis
Kobic E ea. Cefiderocol pharmacokinetics in a patient receiving continuous venovenous hemodiafiltration. Open Forum Infect Dis. 2021;8:ofab252.	1	Case-report over patiënt met ESRD die CVVHDF kreeg. Klinische verbetering na toevoegen van 2 g cefiderocol i.v. elke 8 uur aan polymyxine B en tobramycine ter behandeling van infectie met multi-drug resistent P. aeruginosa. De t1/2 was 6.2 uur en klaring 2.3 l/h. CLcvvhdf was 2.2 l/h. Na klinische verbetering werd cefiderocol na 2 weken gestopt. Table 2: resultaat simulatie met adviesdoseringen fabrikant. 	Auteurs: the pharmacokinetic data revealed that this cefiderocol dose produced sufficiently high exposures (ie, 98% fT > MIC 8 μg/ mL) and a positive clinical response was observed. Similarly, the selected cefiderocol dose was well tolerated, which is reinforced as the total cefiderocol exposure seen in this patient was similar to those in the clinical trials of infected patients
Möhlmann JE ea. Continuous infusion of cefiderocol in a critically ill patient with continuous venovenous haemofiltration. Br J Clin Pharmacol. 2023;89:3753-3757.	1	Case-report over IC-patiënt die CVVH (effluent flow: 2.1-3 l/h) kreeg vanwege acuut nierfalen. Eerst 2 g cefiderocol 3dd, vervolgens continue infusie 4 g/24h . Totale blootstelling was 915 mg uur/l. Ongebonden plasmaconcentratie was gemiddeld 8x hoger dan MIC 2 mg/l, waarmee 100% fT > MIC werd gehaald.	Auteurs: continue infusie van 4 g cefiderocol per 24 uur resulteert in adequate plasmaconcentraties bij een ernstig zieke patiënt met CVVH.
SmPC Fetcroja 19-07-2024 + EPAR Zelfde getallen als Katsube 2016 en Katsube 2017		De AUC was 1.5x hoger en t1/2 was 3.4x hoger bij ESRD patiënten met HD t.o.v. patiënten met een normale nierfunctie na 1-malig 1 g cefiderocol i.v. Ongeveer 60% van Fetcroja werd verwijderd met een hemodialysesessie van 3 tot 4 uur. Based on plasma PTA simulations using relevant PDTs, the doses of cefiderocol in different renal function categories are predicted to be sufficient for the treatment of infections caused by pathogens having MICs up to 2 mg/L.	Clcr < 15 ml/min (met of zonder intermitterende hemodialyse): 0.75g elke 12 uur. Aangezien cefiderocol met hemodialyse wordt verwijderd, moet cefiderocol op dagen van hemodialyse zo snel mogelijk na voltooiing van de hemodialyse worden toegediend. The results of the dedicated renal impairment study showed a significant effect of renal function on the pharmacokinetics of cefiderocol, which is expected for a substance that is predominantly renally excreted. The proposed dosage adjustment for renally impaired patients is not based directly on the

			results of the RI study but on population-PK models and Monte Carlo simulations of PTA. During model development, different renal function markers were tested (CrCL, adjusted eGFR and absolute eGFR) and were found to simulate similar PTA. The proposed posology in section 4.2. of the SPC is based on Cockcroft-Gault CrCL which is supported. Regarding safety in renally impaired patients, the prosed doses lead to similar AUC across the different renal impairment groups which is adequate from a PK perspective. Regarding efficacy in renally impaired patients, the reader is referred to the PD section where the PTA analyses are presented and assessed.

Overig	**Opmerkingen**
Amerikaanse productinformatie (label) Fetroja 12-11-2021.	CLcr less than 15 mL/min, with or without intermittent HD: 0.75 grams every 12 hours. Cefiderocol is removed by HD; administer Fetfoja immediately after HD for patients receiving intermittent HD. The effluent flow rate-based dosing recommendations in Table 2 are predicted to provide cefiderocol exposures similar to those achieved with a dose of 2 grams given every 8 hours in patients not receiving CRRT. These recommendations are intended to provide initial dosing in patients receiving CRRTG. Dosing regimens may need to be tailored based on residual renal function and patient's clinical status.

Table 2 Recommended Dosage of FETROJA for Patients Receiving CRRT

Effluent Flow Rate[a]	Recommended Dosage of FETROJA
2 L/hr or less	1.5 grams every 12 hours
2.1 to 3 L/hr	2 grams every 12 hours
3.1 to 4 L/hr	1.5 grams every 8 hours
4.1 L/hr or greater	2 grams every 8 hours

CRRT = continuous renal replacement therapy.

[a] Ultrafiltrate flow rate for CVVH, dialysis flow rate for CVVHD, ultrafiltrate flow rate plus dialysis flow rate for CVVHDF.

<table>
<tr>
<td>Katsube T et al. Pharmacokinetic/pharmacodynamic modeling and simulation of cefiderocol, a parenteral siderophore cephalosporin, for dose adjustment based on renal function. Antimicrob Agents Chemother. 2016;61:e01381-16.</td>
<td>Population PK model was developed for cefiderocol and dose adjustments were determined based on renal function. Plasma, urine, and dialysate concentration data were collected from two phase 1 studies involving healthy subjects and subjects with varying degrees of renal impairment. Monte Carlo simulations were conducted to calculate the probability of target attainment (PTA) for different dosing regimens. The PTA was based on the fraction of time during the dosing interval where the free drug concentration in plasma exceeds the minimum inhibitory concentration (MIC). Proposed dose regimens:

TABLE 6 Dose regimens based on renal function to provide similar cefiderocol exposure among renal function groups and >90% of PTA for 75% $T_{f>MIC}$ against an MIC of ≤4 μg/ml
<table>
<tr><th>Renal function</th><th>Dose regimen</th></tr>
<tr><td>Augmented (CG-CL_{CR}, ≥120 ml/min)</td><td>2 g q6h, 3-h infusion</td></tr>
<tr><td>Normal (MDRD-eGFR, ≥90 ml/min/1.73 m^2)</td><td>2 g q8h, 3-h infusion</td></tr>
<tr><td>Mild impairment (MDRD-eGFR, 60 to <90 ml/min/1.73 m^2)</td><td>2 g q8h, 3-h infusion</td></tr>
<tr><td>Moderate impairment (MDRD-eGFR, 30 to <60 ml/min/1.73 m^2)</td><td>1.5 g q8h, 3-h infusion</td></tr>
<tr><td>Severe impairment (MDRD-eGFR, 15 to <30 ml/min/1.73 m^2)</td><td>1 g q8h, 3-h infusion</td></tr>
<tr><td>ESRD (MDRD-eGFR, <15 ml/min/1.73 m^2)</td><td>0.75 g q12h, 3-h infusion</td></tr>
<tr><td>Requiring intermittent HD</td><td>0.75 g q12h, 3-h infusion[a]</td></tr>
</table>
[a]A supplemental (third) dose of 0.75 g with a 3-h infusion is administered after the completion of intermittent HD on dialysis days.</td>
</tr>
<tr>
<td>Wei X ea. Cefiderocol dosing for patients receiving continuous renal replacement therapy. Clin Pharmacol Ther. 2022;112:1004-7.</td>
<td>This report describes a scientific approach for including effluent flow rate (QE)–based dosing recommendations for patients receiving CRRT in the product labeling. Effluent flow rate (Q_E)–based dosing recommendations of cefiderocol for patients receiving CRRT (CVVH, CVVHD, and CVVHDF). Using the clearance estimated by CL = 1.14 + 0.422 × QE and a target daily AUC, cefiderocol dosing regimens for patients receiving CRRT in relevant ranges of QE were determined. Cefiderocol CRRT dosing was determined with the goal of achieving an observed average value of daily area under the concentration-time curve (daily AUC = 1,560 μghour/mL) in HABP/VABP patients, across a clinically relevant QE range (0.5–5L/hour).
Table 1 Determination of Q_E–based dosing recommendations of cefiderocol for patients receiving CRRT[4,6]
<table>
<tr><th colspan="7">Prediction of cefiderocol daily doses for patients receiving CRRT according to effluent flow rate (Q_E)</th></tr>
<tr><td>Q_E (L/hour)</td><td>0.5</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
<tr><td>CL_{CRRT} (L/hour)[a]</td><td>0.211</td><td>0.422</td><td>0.844</td><td>1.27</td><td>1.69</td><td>2.11</td></tr>
<tr><td>CL (L/hour)[b]</td><td>1.35</td><td>1.56</td><td>1.98</td><td>2.41</td><td>2.83</td><td>3.25</td></tr>
<tr><td>Daily dose (g)[c]</td><td>2.11</td><td>2.44</td><td>3.10</td><td>3.75</td><td>4.41</td><td>5.07</td></tr>
</table>
<table>
<tr><th colspan="2">Recommended dosage of cefiderocol for patients receiving CRRT in the US product labeling</th></tr>
<tr><td>Q_E[d]</td><td>Recommended dosage of cefiderocol</td></tr>
<tr><td>2 L/hour or less</td><td>1.5 g every 12 hours</td></tr>
<tr><td>2.1 to 3 L/hour</td><td>2 g every 12 hours</td></tr>
<tr><td>3.1 to 4 L/hour</td><td>1.5 g every 8 hours</td></tr>
<tr><td>4.1 L/hour or greater</td><td>2 g every 8 hours</td></tr>
</table>
AUC, area under the curve of concentration vs. time; CL, total clearance; CL_{CRRT}, extracorporeal clearance by CRRT; $CL_{nonrenal}$, nonrenal clearance; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; f_u, unbound (free) fraction of plasma drug concentration.
[a]$CL_{CRRT} = Q_E \times f_u$ (f_u of cefiderocol = 0.422). [b]$CL = CL_{CRRT} + CL_{nonrenal}$ ($CL_{nonrenal}$ of cefiderocol = 1.14 L/hour). [c]Daily dose = target daily AUC × CL (target daily AUC = 1,560 μghour/mL). [d]Ultrafiltrate flow rate for CVVH, dialysis flow rate for CVVHD, ultrafiltrate flow rate plus dialysis flow rate for CVVHDF.

The predicted PK profiles from CRRT patients (with Qe records from phase III trials, n=9) were similar to those in patients not receiving CRRT. The predicted geometric means of Cmax and daily AUC in patients receiving CRRT were 107 μg/mL and 1,553 μghour/mL, respectively, which are comparable to those from patients with HABP/VABP in phase III trials (geometric mean Cmax and daily AUC of 99.7 μg/mL and 1,560 μghour/mL, respectively), indicating that the recommended Q_E–based dose regimens would provide adequate plasma exposure to cefiderocol in patients receiving CRRT.</td>
</tr>
</table>

Fouad A ea. Validation of cefiderocol package insert dosing recommendation for patients receiving continuous renal replacement therapy: a prospective multicenter pharmacokinetic study. Open Forum Infect Dis. 2024;11:ofae451.	Prospectief, multicenter, open-label, PK-studie met IC-patiënten (n=14) op CVVHDF die cefiderocol (2g elke 6u – 1.5g elke 12u) toegediend kregen. Gemiddelde klaring was 3.5 l/h, AUC 1444 mg.h/l (vergelijkbaar met blootstelling in fase 3 studies). O.b.v. simulaties (gebaseerd op de doseeradviezen van de fabrikant), lijken alle patiënten 100% fT > MIC (tot 8 mg/l) te bereiken (doel: ≥75% fT > MIC). Cefiderocol werd goed verdragen. Five patients were dosed as per product label, and 9 patiënts had additional dose adjustments due to obesity, residual renal function, or effluent flow rates that fluctuated between dosing cutoffs. Auteurs: The FDA-recommended dosing regimen for cefiderocol in patients receiving CRRT resulted in appropriate drug exposures, with concentrations exceeding relevant MIC susceptible breakpoints in all patients at each effluent flow rate. The CRRT study population AUCdaily was also within range of the AUC observed in phase 3 clinical trials for patients not requiring CRRT, suggestive of a safe and therapeutic profile. Cefiderocol concentrations best fitted a 2-compartment model.

Zoektermen

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Search #	Zoektermen
#1	(cefiderocol[MeSH Terms] OR cefiderocol) AND (renal replacement therapy[MeSH Terms] OR dialysis OR heamofiltration OR renal replacement therapy)