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CKJ Review

CKJ REVIEW

Optimization of anti-infective dosing regimens during online haemodiafiltration

Nynke G. L. Jager[1,2], Anthe S. Zandvliet[3], Daniel J. Touw[4] and Erik L. Penne[5]

[1]Department of Clinical Pharmacy, Northwest Clinics, Alkmaar, The Netherlands, [2]Department of Clinical Pharmacology and Pharmacy, Academic Medical Centre, Amsterdam, The Netherlands, [3]Department of Clinical Pharmacology and Pharmacy, VU Medical Centre, Amsterdam, The Netherlands, [4]Department of Clinical Pharmacy and Pharmacology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands and [5]Department of Internal Medicine, Northwest Clinics, Alkmaar, The Netherlands

Correspondence and offprint requests to: Nynke G.L. Jager; E-mail: ngljager@gmail.com

Abstract

Online haemodiafiltration (HDF) is increasingly used in clinical practice as a routine intermittent dialysis modality. It is well known that renal impairment and renal replacement therapy can substantially affect the pharmacokinetic behaviour of several drugs. However, surprisingly few data are available on the need for specific dose adjustments during HDF. Due to convection, drug clearance may be increased during HDF as compared with standard haemodialysis. This may be of particular interest in patients undergoing anti-infective therapy, since under-dosing may compromise patient outcomes and promote the emergence of bacterial resistance. Drug clearance during HDF is determined by (i) dialysis characteristics, (ii) drug characteristics and (iii) patient characteristics. In this review, we will discuss these different determinants of drug clearance during HDF and advise on how to adjust the dose of antibacterial, antimycotic and antiviral agents in patients undergoing HDF. In addition, the possible added value of therapeutic drug monitoring is discussed. The review provides guidance for optimization of anti-infective dosing regimens in HDF patients.

Key words: antibiotics, antifungals, anti-infective, antivirals, haemodiafiltration

Introduction

Online haemodiafiltration (HDF) is increasingly used in clinical practice as a routine intermittent dialysis modality. During HDF, diffusion—the working principle of haemodialysis (HD)—and convection—the working principle of haemofiltration—are combined to optimize clearance of uraemic toxins. Diffusion is very efficacious for removal of components with low molecular weight (MW). Convective transport is based on a pressure gradient between the blood and dialysate compartment in the dialyser, resulting in a flux [or ultrafiltration (UF)] across the membrane. Clearance by convection is directly related to the magnitude of the convection volume and is less affected by MW up to the range of 30–40 kDa. Hence, due to the convection component, clearance of relatively large molecules is typically improved in HDF as compared with standard HD. Three large randomized controlled trials have suggested improved clinical outcomes after long-term HDF as compared with low- or high-flux HD, when large convection volumes are applied [1–3].

It is well recognized that renal impairment and renal replacement therapy (RRT) can substantially affect the pharmacokinetics

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of a drug. Several studies investigating drug concentrations during HD are available in the literature. However, practical dosing advice for dialysis patients as mentioned in text books often originates from studies in which traditional low-flux dialysers were used. Such advice may lead to under-dosing when patients are treated with high-flux HD or HDF. Switching patients from low-flux HD to high-flux HD or HDF should trigger a reassessment of dosing regimens, especially for drugs with a narrow therapeutic range.

Limited data are available regarding the need for additional dose adjustments when solute removal is increased during HDF as compared with HD, probably due to the fact that HDF is a rather new development in dialysis practice. Dosing regimens suitable for patients with normal renal function may result in drug accumulation in HDF patients. Conversely, dosing regimens suitable for patients treated with standard HD may result in subtherapeutic drug levels due to enhanced clearance by HDF, possibly leading to undertreatment. In addition, the emergence of bacterial resistance could be promoted.

A solid understanding of the various determinants affecting drug clearance by dialysis may help to judge the risk of under- and overtreatment in order to optimize patient outcome. Drug clearance during RRT is determined by (i) dialysis characteristics, (ii) drug characteristics and (iii) patient characteristics. In this review, we will discuss the different determinants of drug clearance and provide recommendations for drug dosing in HDF patients, in particular to optimize antibacterial, antimycotic and antiviral therapy.

Determinants of drug clearance during intermittent chronic dialysis

Dialysis characteristics

Dialysis characteristics that may affect drug clearance during HDF include dialysis efficiency, treatment time and treatment frequency (Table 1). Dialysis efficiency is dependent on both diffusion and convection [4]. Drug removal by diffusion mainly depends on the applied blood and dialysate flow rates and the dialyser specifications. Drug removal by convection depends on the convection volume, which is determined by several factors that are described elsewhere [5] and include blood flow rate and dialyser specifications. Major dialyser specifications that affect drug clearance include the dialyser surface area, the dialyser UF coefficient (KUF) and the membrane composition, as described below.

Table 1. Determinants of drug clearance during HDF

Dialysis characteristics	Convection volume
	Dialyser specifications (KUF, membrane surface area, membrane composition)
	Blood flow rate
	Dialysate flow rate
	Treatment time
	Treatment frequency
Drug characteristics	Molecular weight
	Protein binding
	Volume of distribution
	Route of elimination
Patient characteristics	Disease state (e.g. sepsis)
	Hypoalbuminaemia
	Residual kidney function
	Body size

Dialyser surface area

The surface area of the dialyser is the maximal area available for blood contact and is directly related to the clearance of low MW solutes [6].

Ultrafiltration coefficient

The KUF is defined as the amount of fluid per hour transferred through the membrane per mmHg pressure gradient across the membrane [7]. High-flux dialysers (KUF >20 mL/h/mmHg) are more permeable resulting in improved drug clearance of relatively high MW [8] as compared with low-flux dialysers (KUF ≤20 mL/h/mmHg). The addition of a convection component results in a further improvement of drug clearance. High-flux dialysers can be used for high-flux HD or online HDF; low-flux dialysers can only be used for low-flux HD. Dialyser flux has increased over the years due to technical advances. Most dialysis centres now routinely perform high-flux HD.

Dialyser membrane composition

During dialysis treatment, typically with high UF rates as during HDF, a protein layer is formed on the dialyser membrane [4, 9]. The extent to which this occurs depends on the dialyser membrane composition. Generally, this will negatively affect solute removal since the permeability of the membrane will decrease. Conversely, adsorption may contribute to increased drug clearance, especially if the drug is highly protein bound. For example, in an *in vitro* HDF experiment it was shown that teicoplanin could be eliminated by adsorption to the membrane [10]. The relevance of this observation for clinical practice is not clear.

Increasing the dialysis treatment time—as in nocturnal dialysis—or increasing dialysis frequency—as in short daily dialysis—may have a substantial effect on removal of a drug. Generally, drug removal is increased by increasing treatment time and/or frequency. Drug dosing considerations for nocturnal and short daily dialysis are discussed extensively elsewhere [11]. Very few studies have investigated solute clearances during nocturnal HDF. None of these studies addressed drug clearance.

Drug characteristics

The extent to which a drug is affected by dialysis is determined primarily by several physicochemical characteristics of the drug, including MW, protein binding, volume of distribution (Vd) and plasma clearance.

Molecular weight

The movement of drugs or other solutes through the membrane is largely determined by the size of the molecules in relation to the pore size of the dialysis membrane. Larger molecules (arbitrarily defined at >500 Da) can only be removed with high-flux dialysers. HDF is exclusively performed with high-flux dialysers. Moreover, the addition of convection (as opposed to low- or high-flux HD) may lead to more efficient removal of larger molecules.

Protein binding

Only the unbound fraction of a drug is cleared by dialysis. Hence, drugs with a high degree of protein binding are not efficiently eliminated by dialysis. Convective as well as diffusive transport of solutes across artificial kidney membranes is limited by protein binding.

Volume of distribution

A drug with a large Vd is distributed widely throughout tissues and is present in relatively small amounts in the blood. Thus, a larger Vd is related to less-efficient drug removal during intermittent RRT.

Route of elimination

Removal of a drug from the systemic circulation can occur by renal and nonrenal clearance. Renal clearance includes glomerular filtration, active secretion and absorption. Impairment of renal clearance may for some drugs be limited to reduced glomerular filtration, but for other drugs, also disruption of active tubular secretion (e.g. piperacillin, flucloxacillin) or tubular absorption may be comprised. In general, if for a particular drug, nonrenal clearance is large compared with renal clearance, the impact of RRT on drug removal is limited. However, when a drug is excreted by glomerular filtration but actively reabsorbed by the tubule, this drug is not renally cleared, but RRT will induce enhanced removal of this drug from the systemic circulation.

Besides pharmacokinetic characteristics, the pharmacodynamic characteristics of a drug also play a role when deciding how the dose should be adjusted when HDF is performed. Anti-infective activity of a drug can depend on: (i) the time during which the antimicrobial agent concentration is maintained above the minimum inhibitory concentration of the pathogen ($T > \text{MIC}$, e.g. β-lactam antibiotics) also known as time-dependent; (ii) the ratio between the peak plasma concentration and the MIC (C_{max}/MIC, e.g. aminoglycosides) also known as concentration-dependent; or on (iii) the ratio between the area under the concentration-time curve (AUC) and the MIC (AUC/MIC, e.g. vancomycin).

Notably, not only the parent drug but also active or toxic metabolites should be taken into consideration. For instance, only trace amounts of oseltamivir are eliminated in the urine, but since its active metabolite oseltamivir carboxylate (OC) is renally eliminated, oseltamivir dose adjustments are indicated in patients with renal impairment and on dialysis [12].

Patient characteristics

Besides a reduction of glomerular filtration, renal impairment may also affect other pharmacokinetic processes including absorption, distribution, metabolism and elimination.

Absorption may be decreased due to uraemic neuropathy, an interaction with concomitant medication or intestinal oedema.

Distribution, indicated by Vd, may be increased in case of sepsis, due to fluid shifts from the intravascular compartment to the interstitial space. Also, reduced protein binding, for instance due to hypoalbuminaemia, may result in a larger amount of free drug that may distribute into the tissues, leading to a higher Vd and enhanced clearance.

Oxidative metabolic pathways for certain drugs may be accelerated; other metabolic functions such as acetylation, hydrolysis and reduction may be reduced. These concepts are elucidated into more detail by Swan and Bennett [13].

Residual kidney function can be an important contributor to drug clearance [14]. The presence of residual kidney function may especially affect drugs that are actively secreted or reabsorbed by the tubule.

Next to renal impairment, RRT can also affect patient characteristics, such as albumin loss during dialysis. Although it has been reported that albumin loss in the dialysate is significantly greater during HDF compared with HD [15], albumin levels are shown to be similar in HDF and HD patients [2, 16].

Pharmacokinetics and pharmacodynamics of anti-infective agents during HDF

The various categories of anti-infective drugs (antibacterial, antimycotic and antiviral drugs) include a wide variety of drug characteristics. While data on conventional HD are available for a selection of anti-infective drugs, removal by HDF has typically not been investigated. An additional effect on drug clearance due to convection during HDF (as opposed to low- or high-flux HD) can be anticipated for compounds with a relatively high MW, provided that protein binding is low and Vd is small. In contrast, for low MW drugs HDF will not result in increased clearance, since their removal during RRT is not typically impacted by convection but mostly driven by diffusion. In Figure 1, a systematic evaluation of drug characteristics is presented that can help identify with which drugs to anticipate increased clearance by HDF.

Following careful selection of a dosing regimen to initiate anti-infective therapy during HDF, treatment may be further optimized by therapeutic drug monitoring (TDM). TDM aims at improving clinical outcome by individual dose-adjustments based on measured drug concentrations in biological fluids. TDM can be of high value for drugs with a small therapeutic window and large inter-individual differences in pharmacokinetics. Furthermore, the amount of drug removal during an HDF session can be calculated, based on drug concentrations of samples collected pre- and post-filter at several time points. This concept is elucidated in more detail by Zandvliet *et al.* [17].

The most relevant drug characteristics, the anticipated additional effect of convection, dosing suggestions and advice on whether to apply TDM are listed in Table 2.

Aminoglycosides

Aminoglycosides are hydrophilic agents characterized by low Vd, low protein binding and almost complete renal clearance. These characteristics explain their rapid and consistent extracorporeal clearance during RRT. Netilmicin was studied by Basile *et al.* in 1985, where clearance based on low-volume HDF was compared with standard low-flux HD. From this study, it appeared that a markedly increased clearance was observed by the implementation of a high-flux filter and a high UF flow rate [19]. Sombolos *et al.* [18] observed increased removal of gentamicin in a small study comparing online HDF with low-flux HD. Given their relatively high MW, similar effects of convective transport can be anticipated for the other aminoglycosides, especially for amikacin and streptomycin.

Aminoglycosides are characterized by concentration-dependent bacterial killing; their effectiveness improves with higher peak drug concentrations. The risk of aminoglycoside toxicity (nephro- and oto-), has been associated with elevated trough concentrations (C_{min}), where C_{min} for gentamicin and

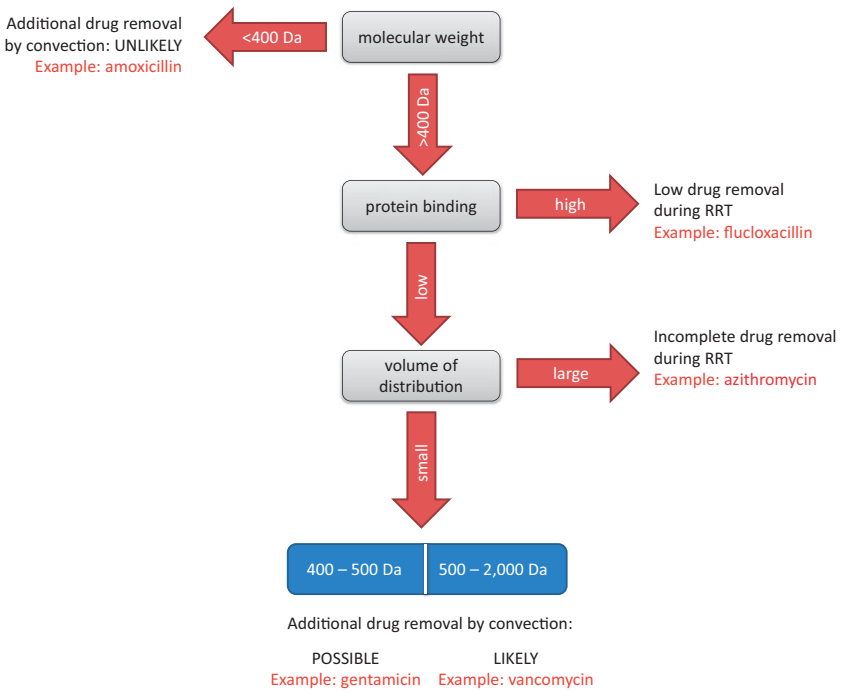

Fig. 1. Systematic evaluation of drug characteristics to assess the potential increment of drug clearance by convection.

tobramycin should be <1 mg/L and for amikacin <5 mg/L. Therefore, administering an aminoglycoside prior to dialysis should theoretically allow the achievement of a high peak concentration (thereby enhancing bacterial killing), while subsequent early dialytic clearance should help to minimize the AUC and trough concentrations (thereby limiting toxicity) [32]. However, this point is controversial in the literature, where the *Renal Drug Handbook* [30] and the Kidney Disease Program [31] advise to administer aminoglycosides after dialysis, presumably based on older studies [33], and more recent studies indicate that aminoglycosides should be administered prior to dialysis [34, 35]. Unfortunately, for most patients with renal impairment, also with RRT, attaining both adequate peak and trough concentrations is unlikely. Therefore, treatment with aminoglycosides is discouraged. When there is no other treatment option, the authors advise to administer aminoglycosides prior to dialysis, where peak and trough concentrations should be measured to optimize the patients' dosing regimen.

Glycopeptides

Glycopeptides are hydrophilic antimicrobials with a very high MW, which prevents removal during low-flux HD. However, glycopeptides are reported to be partly removed by high-flux HD [20, 21]. Sombolos *et al.* [22] observed subtherapeutic vancomycin concentrations in online HDF patients, even when anuric, after treatment with 15 mg/kg during the last hour of a 4-h dialysis session. In coherence with the drug characteristics, these findings suggest that teicoplanin and vancomycin may be efficiently removed by online HDF.

The effectiveness of glycopeptides improves with a higher AUC. Therefore, glycopeptides should be administered at the end of dialysis or during the last hour of the dialysis, avoiding early dialytic clearance. TDM, in the form of AUC estimation (target AUC/MIC ≥400 [36, 37]) with the aid of Bayesian feedback [38] starting from the first dose, is strongly advocated for patients undergoing HDF.

β-lactams

β-lactam antibiotics (penicillins, cephalosporins and carbapenems) are hydrophilic compounds, with a low Vd and a predominant renal clearance. Most β-lactam antibiotics have a MW below 500 Da. The degree of protein binding differs between the different compounds, ranging from below 10% to above 90%. Consequently, not all β-lactam antibiotics are efficiently removed by RRT.

As opposed to the other penicillins, piperacillin has a relatively high MW of 517.6 Da and low protein binding. Therefore, the addition of convection to diffusion might increase its clearance. Indeed, piperacillin clearance was larger during online HDF as compared with historical data from patients who were treated with conventional HD [23].

Ceftazidime and ceftriaxone both have a MW >500 Da. For ceftazidime, increased drug removal during HDF is anticipated. For ceftriaxone, due to its high protein binding (85–95%), extracorporeal clearance by HDF is less likely.

From a pharmacokinetic study on doripenem (MW 420.5 Da, carbapenem group) in patients with sepsis who were treated with high-volume HDF, it appeared that a substantial amount of doripenem was eliminated [26].

The effectiveness of β-lactam antibiotics in clinical studies is suggested to be time-dependent: it depends mainly on the duration of the presence of the agent at a concentration superior to the target pathogen's MIC, $T > MIC$ [39–41]. Therefore, intravenously administered β-lactam antibiotics should be administered post-dialysis, avoiding early dialytic clearance. When an analytical assay is available, TDM can be applied to guide dosing optimization in case of difficult to treat infections where high doses, and thus high drug concentrations, are applied.

Sulfonamides and trimethoprim

Trimethoprim is lipophilic and has a large Vd. Sulfamethoxazole and sulfadiazine, however, are hydrophilic and have a smaller Vd.

Table 2. Drug characteristics and anticipated impact of HDF on a selection of anti-infective agents (adapted, with adjustments, from Zandvliet *et al.* [17] with permission)

Category	Drug	MW (Da)	Vd (L/kg)	Protein binding (%)	Renal clearance (%)	Removal by low-flux iHD	Removal by high-flux iHD	Anticipated additional effect of convection	Dose recommendation
Antibiotics									
Aminoglycosides	Tobramycin	467.5	0.22–0.33	<5	90–95	+	+	Possibly	Full dose pre-dialysis + TDM
	Gentamicin	477.6	0.23–0.30	0–30	90–95	+	+	Possibly [18]	Full dose pre-dialysis + TDM
	Amikacin	585.6	0.22–0.29	<20	94–98	+/–	+	Likely	Full dose pre-dialysis + TDM
	Streptomycin	581.6	0.26	34–35	29–89	+/–	+	Likely	Full dose pre-dialysis + TDM
	Netilmicin	475.6	0.16–0.3	<5	80	+	+	Possibly [19]	Full dose pre-dialysis + TDM
Glycopeptides	Teicoplanin	1875–1891	0.94–1.4	90–95	>97	–	+/– [20]	Likely	Post-dialysis, as high-flux HD + TDM
	Vancomycin	1449.3	0.47–1.1	10–60	>80	–	+/– [21]	Likely [22]	Post-dialysis, as high-flux HD + TDM
Penicillins	Amoxicillin	365.4	0.3	15–25	50–70	+	+	Unlikely	Post-dialysis, as high-flux HD (+TDM)
	Clavulanic acid	199.2	0.3	25	40	+	+	Unlikely	Post-dialysis, as high-flux HD (+TDM)
	Benzylpenicillin	334.4	0.3–0.42	60–85	60–90	+	+	Unlikely	Post-dialysis, as high-flux HD (+TDM)
	Flucloxacillin	453.9	0.13	95	66–76 active secretion	–	+	Unlikely	Post-dialysis, as high-flux HD (+TDM)
	Piperacillin	517.6	0.18–0.3	20–30	60–80 active secretion	+ (30–40%)	+	Likely [23, 24]	Post-dialysis, as eGFR 10–20 mL/min (+TDM)
	Tazobactam	300.3	0.18–0.33	20–30	80 active secretion	+ (30–40%)	+	Unlikely	Post-dialysis, as high-flux HD (+TDM)
Cephalosporins	Ceftazidime	546.6	0.18–0.4	5–24	60–90	+	+	Likely	Post-dialysis, as eGFR 10–20 mL/min (+TDM)
	Cefuroxime	424.4	0.13–1.8	33–50	85–90	+	+	Possibly	Post-dialysis, as high-flux HD (+TDM)
	Cefotaxime	455.5	0.15–0.55	40	40–60	+	+	Possibly	Post-dialysis, as high-flux HD (+TDM)
	Ceftriaxone	554.6	0.12–0.18	85–95	30–65	–	+/–	Possibly	Post-dialysis, as high-flux HD (+TDM)
	Cefazolin	454.5	0.13–0.22	80	75–95	+	+	Possibly	Post-dialysis, as high-flux HD (+TDM)
Carbapenems	Imipenem	317.4	0.17–0.3	13–21	20–70	+ (55%) [25]	+	Unlikely	Post-dialysis, as high-flux HD (+TDM)
	Cilastatin	380.4	0.22	40	75	+ (63%) [25]	+	Unlikely	Post-dialysis, as high-flux HD (+TDM)
	Meropenem	383.5	0.35	2	65–70	+	+	Unlikely	Post-dialysis, as high-flux HD (+TDM)
	Doripenem	420.5	0.24	8	70	+	+	Possibly [26]	Post-dialysis, as high-flux HD (+TDM)
	Ertapenem	475.5	0.1	85–95	38	+/–	+/–	Unlikely	Post-dialysis, as high-flux HD (+TDM)
Sulfonamides and trimethoprim	Trimethoprim	290.3	1.0–2.2	30–70	40–80	+	+	Unlikely	As high-flux HD
	Sulfamethoxazole	253.3	0.28–0.38	50–70	15–30	+	+	Unlikely	As high-flux HD
	Sulfadiazine	250.3	0.29	20–55	80	+	+	Unlikely	As high flux HD
Macrolides	Azithromycin	785.0	18–31	12–52	6–12	–	–	Unlikely	As high-flux HD
	Clarithromycin	748.0	2–4	70–80	15–40	+/–	+/–	Possibly	As high-flux HD
	Clindamycin	425.0	0.6–1.2	60–95	10	–	+/–	Unlikely	As high-flux HD
	Erythromycin	733.9	0.6–1.2	60–95	2–15	–	–	Unlikely	As high-flux HD

(continued)

Table 2. Continued

Category	Drug	MW (Da)	Vd (L/kg)	Protein binding (%)	Renal clearance (%)	Removal by low-flux iHD	Removal by high-flux iHD	Anticipated additional effect of convection	Dose recommendation
Quinolones	Ciprofloxacin	331.3	2.5	20–40	40–70	−	−	Unlikely	As high-flux HD
	Levofloxacin	361.4	1.1–1.5	24–40	>85	−	−	Unlikely	As high-flux HD
	Moxifloxacin	401.4	2	30–50	20	−	−	Unlikely	As high-flux HD
	Norfloxacin	319.3	2.5–3.1	14	30	−	−	Unlikely	As high-flux HD
	Ofloxacin	361.4	1.5–2.5	25	65–80	−	−	Unlikely	As high-flux HD
Other antibiotics	Colistimethate sodium (colistin)	∼1748	0.09–0.85	55	80	−	+/− [27]	Likely	Loading dose: 9 million IU, followed by 2 million IU twice daily [28]
	Daptomycin	1620.7	0.09–0.10	90–92	50–78	−	−	Possibly	As high-flux HD
	Metronidazole	171.2	0.7–1.5	10–20	20	+	+	Unlikely	As high-flux HD
	Linezolid	337.3	0.6	30	30	+ (30%)	+	Unlikely	As high flux HD (+TDM)
Antimycotics									
Triazoles	Fluconazole	306.3	0.65–0.7	11–12	80	+ (50%)	+	Unlikely	As high-flux HD
	Itraconazole	705.6	10	99.8	<0.03	−	−	Unlikely	As high-flux HD
	Voriconazole	349.3	4.6	58	<2	+/− (13%)	+/−	Unlikely [29]	As high-flux HD + TDM
	Posaconazole	700.8	25	>98	<0.2	−	−	Unlikely	As high flux HD
Other antimycotics	Flucytosine	129.1	0.65–0.91	2–4	90	+	+	Unlikely	Post-dialysis, as high flux HD + TDM
	Caspofungin	1093.3	0.15	97	1.4	−	−	Unlikely	As high-flux HD
	Anidulafungin	1140.2	0.43–0.71	>99	<1	−	−	Unlikely	As high-flux HD
Antivirals									
	Aciclovir	225.2	0.7	9–33	40–70	+	+	Unlikely	Post-dialysis, as high-flux HD
	Ganciclovir	255.2	0.47–0.87	1–2	85–100	+	+	Unlikely	Post-dialysis, as high-flux HD
	Oseltamivir	312.4 (284.4 active metabolite)	0.3–0.4	42 (3 active metabolite)	>5 (99 active metabolite)	+	+	Unlikely	As high-flux HD

This table is based on data from the *Renal Drug Handbook* [30] and the Kidney Disease Program [31].
iHD, intermittent haemodialysis; eGFR, estimated glomerular filtration rate.

All three compounds are moderately protein bound, mainly renally cleared and have a MW ~250 Da. These compounds will be substantially cleared by HD, but no additional clearance by HDF is expected. The major metabolite of sulfamethoxazole, N-4-acetyl sulfamethoxazole, is primarily renally cleared and has been demonstrated to accumulate in patients with renal failure [42]. Sulfonamides and trimethoprim display concentration dependent killing (AUC/MIC) and should be administered after dialysis, when administered intravenously. TDM of sulfamethoxazole and its main metabolite may be considered, especially in dialysis patients who are treated for *Pneumocystis jiroveci* pneumonia (PJP) with high doses of co-trimoxazole [43].

Macrolides

Macrolides are lipophilic agents, with a large Vd (due to accumulation in neutrophils), moderate to high degree of protein binding and low to moderate renal clearance. Therefore, both HD and HDF are not expected to efficiently remove macrolides from the plasma. Toxicity of these agents in patients with renal failure has been observed. The dose should be reduced based on renal function [44].

Quinolones

Fluoroquinolones are lipophilic agents, with large Vd and a relatively low MW. Therefore, these agents will only be marginally cleared by HD, and no additional clearance by HDF is expected.

Other antibiotics

Colistin is administered as an inactive prodrug, colistin methanesulfonate (CMS), which is mostly excreted unchanged in the urine (70%) and partly converted to the active colistin. Renal excretion of colistin is negligible. As a result, in patients with renal impairment, a greater fraction of the administered CMS dose may be converted into colistin, leading to increased plasma concentrations of colistin. Both CMS and colistin exhibit a small Vd and moderate protein binding. Due to the high MW of CMS, additional clearance from HDF is to be expected. Since CMS is a mixture of approximately 30 different components, bioanalytical analysis of this drug is complicated and there is no readily available assay for TDM purposes [45]. For severely ill patients with infections caused by multi-resistant Gram-negative bacteria, a loading dose of 9 million IU followed by 2 million IU twice daily is recommended in HDF patients [28].

Metronidazole is a lipophilic compound with a moderate Vd. It exhibits a low degree of protein binding and is about 20% renally cleared. Metronidazole is to some extent removed by dialysis and based on its low MW (171.2 Da), no additional removal by HDF compared with HD is anticipated.

Linezolid is a rather hydrophilic compound, with a relatively small Vd, moderate protein binding and approximately 30% is renally cleared. Linezolid is to some extent removed by dialysis, although based on its low MW (337.3 Da), no additional removal by HDF compared with HD is anticipated.

Successful treatment outcome is associated with AUC/MIC and $T > \text{MIC}$ [46]; linezolid should, therefore, be administered after dialysis. When TDM is available, trough concentrations (target C_{min} 2–6 mg/L [47, 48]) can be measured to guide dosing.

Daptomycin is a hydrophilic compound, with a very high MW (1620.7 Da) and high protein binding, and is predominantly cleared by the kidneys. Due to its high MW, daptomycin is not removed when low-flux HD is applied. When using HDF, some extra clearance is to be anticipated. TDM assays are not widely available and there is no clear target concentration defined, diminishing the value of TDM in these patients.

Triazole antimycotics

Fluconazole is a hydrophilic compound with a small Vd, low degree of protein binding and predominant renal clearance. Fluconazole is substantially cleared by HD; due to its MW of 306.3 Da no additional clearance by HDF is to be anticipated. The pharmacokinetic/pharmacodynamic index related to efficacy is AUC/MIC, therefore fluconazole should be administered after dialysis.

Itraconazole, voriconazole and posaconazole are lipophilic compounds with a high degree of protein binding and are only very marginally cleared by the kidneys. Therefore, HD and also HDF will have no large effect on clearance of these drugs. Hafner *et al.* [29] conducted a clinical trial and indeed demonstrated that only a limited proportion of the administered voriconazole dose was removed during a 6-h treatment with HD (12.7%) or online HDF (13.1%). Since pharmacokinetics of voriconazole are shown to be unpredictable and the added value of TDM-guided dosing of voriconazole is demonstrated in a prospective clinical trial [49], TDM is advised during treatment and prophylaxis. Trough samples should be taken 2 days after onset of treatment and a range of 2–6 mg/L should be taken as a reference [50, 51].

Other antimycotics

Caspofungin exhibits a small Vd, but also a high degree of protein binding and very limited renal clearance; removal by HD or HDF will be negligible.

Flucytosine exhibits a low Vd, low degree of protein binding, is mainly renally cleared and will, therefore, be removed by HD. Due to its limited MW (129.1 Da), no additional removal by HDF is anticipated. The effectiveness of flucytosine is suggested to be time-dependent. Therefore, flucytosine should be administered post-dialysis, avoiding early dialytic clearance. TDM, in the form of peak levels to reduce toxicity (<100 mg/L) and trough levels to avoid resistance (>25 mg/L, before dialysis) starting from the first dose, is strongly advocated for patients undergoing HDF [52].

Anidulafungin exhibits a large Vd, high degree of protein binding and very limited renal clearance; removal by HD or HDF will be negligible.

Antiviral agents

Aciclovir and ganciclovir both have a low MW, low Vd and low degree of protein binding, and are predominantly renally cleared. Consequently, these agents are substantially cleared by HD and HDF, where no additional clearance of HDF compared with HD is to be anticipated. Aciclovir and ganciclovir should be administered post-dialysis, to avoid early dialytic clearance.

Oseltamivir is considered to be a prodrug, which is converted to the active metabolite OC. Oseltamivir itself is not renally cleared; OC, on the contrary, is approximately 99% renally cleared. It also exhibits a low Vd and a low degree of protein binding and is, therefore, substantially cleared by HD and HDF, where no additional clearance of HDF compared with HD is to be anticipated. Oseltamivir should be administered post-dialysis, to avoid early dialytic clearance.

Conclusions

Intermittent HDF is increasingly used in routine dialysis practice. Only a few clinical pharmacokinetic studies in HDF

patients treated with anti-infective agents have been published. Especially for patients with severe infections adequate dosing regimens are essential and should be individualized based on residual clearance and mode of dialysis. Incremented drug clearance during HDF as compared with HD, due to convective transport, can be anticipated for substances with a high MW, low to moderate protein binding, small Vd and moderate to high degree of renal clearance.

For drugs with a narrow therapeutic range, concentration measurements may result in further individualization of the dosing regimen. Particularly for the aminoglycosides and glycopeptides, with established therapeutic ranges and widely available analytical assays, TDM is strongly recommended for treatment optimization.

Conflict of interest statement

None declared.

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