Drugs (2021) 81:555–574
https://doi.org/10.1007/s40265-021-01469-2

REVIEW ARTICLE

Post-Dialysis Parenteral Antimicrobial Therapy in Patients Receiving Intermittent High-Flux Hemodialysis

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Accepted: 16 January 2021 / Published online: 16 February 2021

Abstract
Patients with end-stage renal disease (ESRD) requiring intermittent hemodialysis (IHD) are at increased risk of infection, which represents a leading cause of mortality in this population. The use of additional vascular access devices such as peripherally inserted central catheters to treat such infections should be minimized in patients with ESRD requiring IHD in order to mitigate complications such as infection and thrombosis and to maintain venous patency for hemodialysis access. Intravenous antimicrobial dosing following IHD has the advantages of avoiding additional access devices and providing convenience for patients and providers. Vancomycin, cefazolin, and aminoglycosides have historically been regarded as the primary intravenous antimicrobials administered with IHD given their relatively low cost, convenient dosing, and longevity of clinical use. Despite this, a growing body of literature is evaluating the use of an expanded list of antimicrobials that may be employed using post-dialysis dosing for patients requiring IHD; however, the available data are largely limited to pharmacokinetic studies and small cohorts of infected patients or uninfected subjects. Post-dialytic dosing of intravenous antimicrobials may be considered on a patient-by-patient basis after careful consideration of clinical, microbiological, and logistical factors that may influence the probability of treatment success. This document reviews and evaluates currently available information on the post-dialytic administration of an expanded list of intravenous antimicrobials in the setting of thrice-weekly, high-flux IHD.

1 Introduction

Patients with end-stage renal disease (ESRD) requiring intermittent hemodialysis (IHD) are at an exquisitely high risk of infection compared with the general population, representing one of the leading causes of mortality in this patient cohort. Over the last two decades, admissions due to infections in patients receiving IHD have increased by over 40% [1]. In addition, comparatively worse clinical outcomes for systemic infections have been described in patients requiring IHD compared with those not requiring renal replacement [2], possibly owing to alterations in immune function in patients with ESRD [3]. Methicillin-resistant *Staphylococcus aureus* (MRSA) in particular is a prominent pathogen among patients receiving IHD. A recent meta-analysis including 38 studies and 5596 patients worldwide found a 6.2% prevalence of MRSA colonization among patients receiving dialysis and an association between colonization and risk of MRSA infection [4]. In the US, the risk of MRSA infection is approximately 100-fold higher for dialysis patients compared with the general population. This is particularly noteworthy given the 30% mortality rate associated with invasive MRSA infections [4].

In the setting of outpatient parenteral antimicrobial therapy (OPAT), peripherally inserted central catheters (PICC) are commonly used when prolonged durations of therapy are prescribed. However, the Kidney Disease Outcomes

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Key Points

Infected patients with end-stage renal disease requiring hemodialysis may benefit from antimicrobial dosing following dialysis in order to decrease the risk of complications from the use of additional catheters.

Data on many of these intravenous agents administered following dialysis are generally limited to pharmacokinetic studies and small cohorts of patients.

The use of off-label intravenous antimicrobial dosing following dialysis may be considered for select patients after carefully weighing numerous patient-specific, infection-specific, and logistical factors

Quality Initiative (KDOQI) guidelines for vascular access recommend avoidance of PICC lines in patients with chronic kidney disease due to the risk of vein occlusion, stenosis, and thrombosis, which may compromise vascular access for IHD [5]. In fact, it can take less than 1 month for PICC placement to compromise a vein for dialysis access [6]. In the clinical setting, it is common practice to place a tunneled central venous catheter (CVC) for these patients to allow for OPAT with agents that are not administered following IHD; however, this strategy is resource- and labor-intensive, and not without risk of complications.

Currently, vancomycin, cefazolin, and aminoglycosides are the only parenteral antimicrobials for which there is widespread clinical use and experience for administration following IHD. Given the clinical burden of invasive infections such as MRSA and the critical importance of preserving venous access in patients with ESRD, published data on the use of parenteral antimicrobials that may be administered following hemodialysis is undoubtedly necessary. The increasing incidence of infections caused by multidrug-resistant (MDR) organisms [7] represents an additional incentive to evaluate antimicrobial dosing strategies for an expanded list of agents in special populations such as ESRD.

Potential benefits of antimicrobial dosing with IHD using existing dialysis vascular access include decreased risks of infectious and thrombotic complications and improved convenience for the patient and provider team, since additional intravenous access is avoided in this setting. Even short-term use of small caliber central catheters (such as PICC) may contribute to risk. In a cohort of 150 patients undergoing placement of a PICC, 7% of patients with no baseline stenosis developed venographic evidence of central venous stenosis or occlusion [8].

Fortunately, several pharmacokinetic (PK) studies have been published over the past decade describing the potential for post-IHD administration of various antimicrobials, although the quality of evidence is heterogenous and additional high-quality data are urgently needed. Aside from limitations with the available data, a number of clinical, microbiological, and logistical factors must be considered prior to applying these data to clinical practice. Antimicrobial cost and scheduling limitations represent only a few potential barriers to implementation in clinical practice.

In addition, the presence of ESRD and the use of IHD have a significant potential to alter the PK of antimicrobials from changes in distribution to alterations in drug metabolism [9]. Antimicrobial clearance may be considerably reduced in patients with ESRD, and decreased protein binding in these patients will decrease fractional drug concentrations in the vasculature, potentially increasing volume of distribution (Vd). The resulting increase in drug concentrations into the tissue could lead to enhanced pharmacologic effect. Increases in Vd in the setting of ESRD have been documented for several antibiotics, including vancomycin, cephalosporins, and aminoglycosides. The presence of ESRD has also been associated with reductions in non-renal drug metabolism, with impairment of cytochrome P450 enzymes secondary to accumulation of endogenous inhibitory toxins described [9]. Filter type, flux membrane, ultrafiltration rate, dialysate flow rate, diffusion efficiency, and duration of IHD may all influence dialyzability, along with antimicrobial characteristics such as Vd, protein binding, and molecular size [9–11].

High-efficiency IHD refers to the use of membranes with increased surface area and rate of urea clearance, whereas high-flux IHD refers to membranes with increased ultrafiltration capacity, originally defined as coefficient of ultrafiltration (Kuf) > 15 mL/mmHg/h and redefined as β2 microglobulin clearance > 20 mL/min [9, 12]. Given the apparent clinical benefit and the narrowing cost margin compared with low-flux dialyzers, high-flux dialyzers have become standard of care for clinical practice in the US and many other developed countries [12].

The aim of this review is to describe and evaluate the available literature on the post-dialytic administration of parenteral antimicrobials in patients with ESRD requiring IHD, and to summarize the proposed dosing strategies for these agents based on the existing data. This review will focus primarily on studies evaluating thrice-weekly high-flux IHD, the most common mode currently utilized in clinical practice. Precise filter membrane types will not be discussed in detail as they are not consistently reported in the published literature and their specific impact on removal efficiency of antimicrobials is largely unknown.

2 Methods of Literature Review

A literature review was performed using the PubMed and Ovid search engines. Search terms included antibiotics, antifungals, hemodialysis, ESRD, and pharmacokinetics. Conference archives were also searched for relevant abstracts. The search included only studies in English and the years of publication ranged from 1978 to 2020. Publications were assessed for relevancy prior to inclusion, with emphasis on those evaluating high-flux IHD. Studies utilizing low-flux IHD were only included in select clinical contexts lacking data on high-flux IHD. Studies assessing antimicrobial dosing in the settings of continuous renal replacement therapy (CRRT), peritoneal dialysis, home dialysis, and extended IHD were excluded. Antimicrobials included in this review were limited exclusively to those currently commercially available and with supporting literature evaluating thrice-weekly intra-dialytic or post-dialytic dosing with IHD.

3 Results

3.1 Vancomycin

Vancomycin is a glycopeptide antibiotic with a spectrum of activity limited to Gram-positive bacteria, including MRSA, that has been in clinical use since the late 1950s. The currently accepted pharmacodynamic (PD) index associated with efficacy against *S. aureus* for vancomycin is an area under the curve to minimum inhibitory concentration (AUC/MIC) ratio ≥ 400 [13]. It must be noted that this PK/PD target is largely based on retrospective observational data and remains unproven in the setting of ESRD requiring IHD [13]. Vancomycin is primarily cleared renally, with renal clearance accounting for ~70% of total clearance in patients with normal renal function and as high as 95% of total clearance in patients with ESRD [10]. The increased proportion of renal clearance in ESRD may be due to metabolic changes from the presence of uremic toxins [10]. The dialyzability of vancomycin using high-flux membranes is 25–50% [11, 14, 15]. Owing to its high degree of renal clearance, low cost, clinical longevity, feasibility of therapeutic drug monitoring (TDM), and the increased incidence of MRSA infections among patients with ESRD requiring IHD, there is a wide breadth of experience with administering vancomycin with or following IHD.

Vancomycin dosing in the setting of high-flux IHD is well described and the general approach to therapy is summarized in Table 1 [9–11, 13]. In patients requiring IHD, a loading dose of 15–25 mg/kg is recommended in order to rapidly achieve therapeutic concentrations [13, 16]. TDM is recommended to be utilized for determination of maintenance doses, which are typically 5–10 mg/kg [9, 13]. It should be noted that dose requirements are generally higher if vancomycin is administered intradialytically (during the last 1–2 h of IHD depending on dose) as this practice has been shown to decrease vancomycin serum levels by 25–35% [13, 17, 18]. Following high-flux IHD, vancomycin plasma concentrations rebound over 3–6 h due to redistribution of the drug from protein binding sites. Therefore, it is recommended to monitor serum vancomycin levels prior to IHD [10]. Typically, for a pre-IHD serum level < 25 µg/mL, vancomycin will be administered following IHD, with dose selection depending on the following factors: vancomycin serum concentration, patient weight, site and severity of infection, and probability of target attainment. It is recommended to hold vancomycin redosing in the setting of a pre-IHD serum level > 25 µg/mL [9]. Frequency of TDM may be shifted to weekly once multiple consecutive therapeutic pre-IHD serum levels are recorded [19].

Although frequent TDM for vancomycin is commonly performed in the clinical setting for patients with ESRD requiring IHD, multiple algorithms have been proposed to simplify dosing and decrease the number of concentration determinations. Older algorithms have demonstrated an economic benefit by reducing quantity of serum vancomycin levels obtained. Although the investigators were able to achieve the desired pre-IHD serum levels $> 95\%$ of the time, outdated PK/PD targets were utilized in these studies [11, 13, 15]. The targeted pre-IHD serum concentration ranges were 5–15 µg/mL or 5–20 µg/mL in two of these studies, lower than the currently recommended pre-IHD target range of 15–20 µg/mL as a surrogate to achieve AUC of 400–600 µg*h/mL [11, 13, 15]. A more recent study evaluating the performance of algorithmic vancomycin dosing administered following IHD utilized Monte Carlo simulations to predict the proportion of patients who would achieve serum level targets using an existing protocol. The results demonstrated that only 15.6% of patients were predicted to achieve a pre-IHD concentration of 15–20 µg/mL with a dosing strategy of 1 g load, followed by 500 mg maintenance doses administered intradialytically during the last hour. A new protocol, using a tailored dosing strategy based on weight ranges, was developed and prospectively validated in 29 patients. Using this updated protocol, 65.5% of maintenance pre-IHD troughs fell between 10 and 20 µg/mL, and 37.9% fell between 15 and 20 µg/mL [20]. A recent systematic review evaluating vancomycin dosing strategies in the setting of high-flux IHD found that individualized weight-based dosing (WBD) appeared to outperform non-WBD, such as algorithmic dosing, in achieving the PK/PD target. A pre-IHD concentration of 15–20 µg/mL was achieved in 50–67% of the studies using WBD compared with 37–38% of non-WBD studies for the maintenance dose. The authors

Table 1 Proposed post-dialytic dosing regimens for intravenous antimicrobials administered following thrice-weekly high-flux hemodialysis in patients with chronic ESRD

Agent	Loading dose	Proposed dose after each IHD session	Dialyzability (% dialyzed), high-flux[a]	Molecular weight (Daltons)	Protein binding (%)	Comments
Amikacin [9, 57]	–	5–7.5 mg/kg	20%	586	4–11	TDM recommended to individualize maintenance dose
Cefazolin [9, 52, 53, 55–57, 60, 61]	–	2 g	60–62%	455	85	Consider 3 g dose for 72-h interdialytic period
Cefepime [9, 78, 80, 85]	–	1–2 g	68–81%	480	16–20	Consider 2 g dose for invasive infections and infections caused by *Pseudomonas* spp. Available evidence limited; additional data required to inform optimal dosing with IHD
Ceftazidime [9, 62, 65, 71, 72]	–	2 g	Unknown (45% low-flux)	547	17–21	Consider 3 g dose for 72-h interdialytic period for resistant organisms and deep-seated infections. Available evidence limited; additional data required to inform optimal dosing with IHD
Daptomycin [9, 32–36, 38]	–	6–12 mg/kg (dose depending on indication)	39–50%	1620	92	Consider 50% higher dose for 72-h interdialytic period; lack of clinical, safety data for doses > 12 mg/kg
Ertapenem [86, 99, 100]	–	1 g	70%	497.5	85–95	Available evidence limited; additional data required to inform optimal dosing with IHD
Fluconazole [9, 116–119]	800 mg	400–800 mg	40–50%	306	11–12	Dosing assumes invasive candidiasis Higher end of dosing suggested for *Candida glabrata* infections when susceptible
Gentamicin [9, 57, 104, 106]	2–3 mg/kg	1–2 mg/kg	54%	478	0–30	TDM recommended to individualize maintenance dose
Telavancin [23, 25, 26, 28]	–	10 mg/kg	Unknown (6% low-flux)	1755.6	90	Dialyzer type not specified in single case series evaluating telavancin dosing with IHD Comparatively worse clinical outcomes reported in patients with CrCl < 50 mL/min and treated with telavancin in phase III studies. Use with caution Available evidence limited; additional data required to inform optimal dosing with IHD
Tobramycin [9, 57, 104]	2–3 mg/kg	1–2 mg/kg	25–70%	467	< 30	TDM recommended to individualize maintenance dose
Vancomycin [9–11, 13, 16]	15–25 mg/kg	5–10 mg/kg	25–50%	1485	20–55	TDM recommended to individualize maintenance dose to achieve pre-IHD level of 15–20 µg/mL as a surrogate for AUC 400–600 µg*h/mL Higher doses of vancomycin likely required if administered intradialytically

AUC area under the curve, *CrCl* creatinine clearance, *ESRD* end-stage renal disease, *IHD* intermittent hemodialysis, *TDM* therapeutic drug monitoring

[a]Dependent on multiple factors including duration, dialysis membrane, and flow rates

concluded that further research evaluating the achievement of AUC/MIC ≥ 400 and assessment of clinical outcomes in this patient population is necessary [21].

Although algorithms for vancomycin dosing in IHD have shown limited potential in achieving the target levels studied, reported performance is mixed and more data are certainly needed on the use of algorithms that reliably achieve pre-IHD levels of 15–20 μg/mL as a surrogate for the contemporary PK/PD target attainment of AUC/MIC 400–600 μg*h/mL[13] for severe, invasive MRSA infections. Several other limitations exist with the available data, including small sample sizes, differences in vancomycin administration times, monitoring protocol inconsistencies, and the variability of PK in this patient population [19]. Therefore, it is advisable to utilize individualized TDM in order to determine an appropriate vancomycin maintenance dosing schedule for patients with ESRD requiring IHD [19].

3.2 Telavancin

Telavancin is a lipoglycopeptide and derivative of vancomycin with a spectrum of activity encompassing Gram-positive organisms, including species with increasing resistance such as vancomycin-intermediate *S. aureus* (VISA) [22]. Similar to vancomycin, telavancin's antimicrobial activity against *S. aureus* appears to correlate best with AUC_{24}/MIC [23]. A minimum free (unbound) AUC_{24}/MIC ratio ($fAUC_{24}$/MIC) of approximately 50 is required for bacteriostatic activity against vancomycin-susceptible *S. aureus* isolates, whereas an $fAUC_{24}$/MIC > 150 is necessary for maximum bactericidal activity [24]. Using existing single-dose PK data, a 10 mg/kg dose of telavancin based on actual body weight has been calculated to provide an $fAUC_{24}/MIC_{90}$ of ~ 800 against clinical isolates of *S. aureus* [24]. The US FDA-approved indications of telavancin include complicated skin and skin structure infections (cSSSI) and hospital-acquired (HABP) and ventilator-associated bacterial pneumonia (VABP) [23]. Telavancin's enhanced potency against *S. aureus* relative to vancomycin has supported its role as an alternative agent for difficult-to-treat Gram-positive infections, which constitute a significant burden for many patients with ESRD receiving IHD. The FDA prescribing information for telavancin does not provide a recommended dosing strategy for telavancin in the setting of IHD, noting insufficient data. However, in recent years several studies have sought to describe potential dosing strategies for this patient population and provide preliminary support for the use of telavancin in thrice-weekly post-IHD dosing [25–27].

A study of 44 uninfected adults was performed to determine PK parameters of telavancin in the setting of varying degrees of renal dysfunction. Subjects were divided into three groups, consisting of normal renal function (creatinine clearance [CrCl] > 80 mL/min, $n = 15$), severe renal impairment (CrCl < 30 mL/min, $n = 15$), and ESRD on IHD ($n = 14$). All subjects received one dose of telavancin 7.5 mg/kg over a 1-h infusion. The mean AUC_{48} based on total drug concentrations for the ESRD patients was 1336 μg*h/mL, approximately 2.5-fold higher than patients with normal renal function (539 μg*h/mL) [25].

A separate compilation of two phase I PK studies evaluated medically stable adults with varying degrees of renal function, from normal (CrCl > 80 mL/min) to ESRD (requiring IHD). A total of 72 subjects were enrolled between the two studies ($n = 29$ for study A and $n = 43$ for study B), including 6 with ESRD receiving IHD, all of whom were enrolled in study A. Subjects in study A received a single dose of telavancin 7.5 mg/kg over a 1-h infusion and subjects in study B received a single dose of telavancin 10 mg/kg over a 1-h infusion. ESRD subjects received a 4-h low-flux hemodialysis session that was started 2–4 h after telavancin administration. The mean AUC_{∞} for the ESRD subjects in study A was 1010 μg*h/mL, almost double that of the subjects with normal renal function (560 μg*h/mL). In addition, clearance of telavancin was decreased in ESRD patients at 8.18 mL/h/kg, compared with 13.7 mL/h/kg (study A) and 17.0 mL/h/kg (study B) in patients with normal renal function. In the ESRD patients, the 4-h low-flux IHD session eliminated ~ 6% of the telavancin dose. Treatment-emergent adverse events were similar for ESRD patients, occurring in 2/6 (33%), compared with 24/72 (33%) of all patients enrolled [26].

Most recently, a retrospective, two-center case-series of eight hospitalized patients with baseline ESRD requiring IHD who were treated with telavancin monotherapy for refractory MRSA bacteremia was conducted to quantify clinical outcomes associated with the use of off-label dosing of telavancin in this patient population. Dialyzer type was not mentioned in this study. The dosing strategy utilized for telavancin was 10 mg/kg thrice-weekly following IHD in five patients and 10 mg/kg every 48 h for the remaining three patients. Durations of therapy were not reported. All patients included had either recurrent or persistent (≥ 3 days) MRSA bacteremia, with vancomycin MIC of ≥ 2 mg/L in seven of eight cases (87.5%). The source of infection was deemed to include arteriovenous (AV) graft or fistula in seven of eight cases (87.5%) and mitral valve endocarditis in the remaining case. Microbiological cure and 30-day survival were noted in seven of eight patients (87.5%). Median duration of bacteremia was significantly shorter following switch to telavancin therapy (1 day) compared with antibiotic therapy preceding telavancin (16 days). No adverse events were noted in this study [27].

Based on the exposure profile of telavancin in ESRD, the available PK data appear to support the feasibility of thrice-weekly post-IHD telavancin dosing. However, clinical data are extremely limited and dialyzer types were either low-flux

or unreported [25–27]. The optimal dosing of telavancin following high-flux IHD remains unknown and the safety profile of telavancin dosing with IHD is poorly characterized. In addition, the available PK data in patients requiring IHD are limited to single-dose analyses, and the potential for drug accumulation after repeated doses following IHD certainly exists. This is relevant from a toxicology perspective when considering the possible adverse effects of telavancin, which include prolongation of the QTc interval [23].

In addition, it must be noted that patients with pre-existing moderate–severe renal dysfunction experienced lower rates of treatment success in a subgroup analysis of phase III trials evaluating telavancin for cSSSI, and also experienced increased mortality in phase III trials evaluating telavancin for HABP/VABP [27, 28]. These findings seem to dispute data showing that mean telavancin serum inhibitory titers (SIT) against a reference strain of *S. aureus* correlated with mean telavancin plasma concentrations for patients with varying degrees of renal insufficiency, suggesting no compromise in antimicrobial activity related to ESRD [27]. Nonetheless, a careful risk/benefit assessment should be conducted prior to considering telavancin in this setting.

3.3 Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic with a broad spectrum of activity against Gram-positive bacteria, including MRSA and vancomycin-resistant enterococci (VRE). Daptomycin is highly protein bound, has a relatively low Vd, and is eliminated primarily by the kidneys [29]. One report suggested that the PD parameter $AUC_{24}/MIC > 666$ based on total drug concentrations correlates with improved outcomes in patients treated with daptomycin, but this requires further validation and a definitive threshold has yet to be defined [30]. In patients with ESRD requiring IHD, the FDA-approved dosing strategy is 4 or 6 mg/kg every 48 h, regardless of the dialysis schedule [29]. In clinical practice, high off-label daptomycin doses of 8–12 mg/kg every 24 h for normal renal function and 8–12 mg/kg every 48 h for CrCl < 30 mL/min and ESRD are occasionally utilized for severe infections caused by *Staphylococcus spp*. and *Enterococcus spp*. The prescribing information notes a mean AUC_{∞} of 1193 µg*h/mL in patients receiving hemodialysis following a single administration of 4 mg/kg, compared with an AUC_{∞} of 417 µg*h/mL in patients with CrCl > 80 mL/min [29]. A concerning adverse event associated with daptomycin is elevation of creatine phosphokinase (CPK), with sequelae of myopathy and even rhabdomyolysis in rare instances. Limited data suggest that elevations in CPK are associated with prolonged trough levels of daptomycin > 25 µg/mL [31]. Given the dearth of vancomycin alternatives that may be administered thrice-weekly following IHD for invasive Gram-positive infections, several studies over the past 10 years have evaluated the potential for daptomycin to fit this niche.

The potential for thrice-weekly dosing was initially suggested by a PK pilot study of six uninfected patients requiring chronic IHD which demonstrated trough concentrations out to 68 h that exceeded the MIC_{90} for *S. aureus* following a 6 mg/kg dose of daptomycin administered following IHD [32]. The mean simulated concentration at 68 h was 10.9 ± 3.3 µg/mL, and mean AUC_{∞} assuming no IHD was 2168 µg*h/mL. The percentage removal of daptomycin following a 4-h high-flux hemodialysis session was noted to be 52% in this study [32]. This figure is markedly higher than the prescribing information quoted value of 15% using an unspecified dialyzer membrane type [29]. The authors noted that prospective PK validation is required for daptomycin administered post-hemodialysis.

A separate PK study of 16 uninfected patients on chronic IHD receiving daptomycin 6 mg/kg thrice-weekly following IHD was performed. The proportion of daptomycin removed by high-flux HD (HFHD) was found to be 39%. The mean total drug steady-state C_{min} at 72 h, drawn prior to IHD, was 15.3 µg/mL [33]. Although well above the steady state C_{min} of 6.7 µg/mL, with a 6 mg/kg dose in healthy volunteers, it remains below the suggested toxicity threshold of trough > 25 µg/mL [29, 31]. The data also suggest that concentrations would remain above the *S. aureus* susceptibility breakpoint for daptomycin (1 µg/mL) during the 72-h interdialytic period without exceeding the 6 mg/kg dose, based on an estimated free drug trough concentration of 1.5 µg/mL [33].

A Monte Carlo analysis sought to determine an optimal post-dialysis dosing scheme for daptomycin by targeting AUC values found in the *S. aureus* bacteremia-infective endocarditis (SAB-IE) study. Patients received a 3.5-h HD session using high-flux membranes thrice weekly and several blood samples were collected over a 3-day time period. Based on the results, the authors recommended consideration of a 50% higher dose be administered for the 72-h interdialytic period [34]. Although this strategy could result in one daptomycin dose per week of 9 mg/kg or higher, potentially resultant high C_{max} concentrations have not been linked to an increased risk of toxicity [34, 35].

Daptomycin PK following IHD were further elucidated in a separate 5000-subject Monte Carlo PK/PD analysis that modeled data from 26 patients receiving high-flux thrice-weekly IHD from three previous publications [33, 35–37]. The goal of this analysis was to identify a dosing scheme that would provide comparable AUC profiles to the values seen in the SAB-IE study to achieve similar efficacy and toxicity. The mean AUC_{48} and AUC_{72} values for the 6 mg/kg dose following IHD were 1236.9 and 1497.6, respectively. These values exceeded the SAB-IE study values of AUC_{48} and AUC_{72} of 860.0 and 1374.7, respectively. However, AUC values tended to be lower for the 48- to 72-h interval

with post-dialysis dosing. The $AUC_{48–72}$ for the 6 mg/kg dose administered following IHD was 260.7, almost half that of the $AUC_{48–72}$ value of 514.7 for the SAB-IE study. Using a 9 mg/kg dose administered following IHD, the $AUC_{48–72}$ value increased to 391.1. The collective results of this pooled analysis support the previous conclusions that a 4–6 mg/kg dose may be administered following IHD for the 48-h interdialytic period, and a 50% higher dose should be considered for the 72-h interdialytic period for infections caused by *S. aureus*. Based on the findings, this strategy is expected to achieve adequate antibiotic exposure throughout the dosing interval while maintaining a very low probability of trough concentrations exceeding the suggested threshold [36]. The authors of this analysis also suggest considering more frequent CPK monitoring in this patient population, given the elevated baseline risk of myopathies and a higher probability of C_{min} concentrations exceeding the evaluated threshold—72-h C_{min} of ~25 µg/mL—in one of the studies [36].

Although multiple PK studies have proposed daptomycin dosing strategies following IHD, parenteral antibiotics may be administered during the last hour of a dialysis session in the community, which may compromise activity of a concentration-dependent antibiotic such as daptomycin. Indeed, a PK study of seven uninfected subjects receiving thrice-weekly IHD for ESRD evaluated the administration of daptomycin 6 mg/kg over 30 min at the end of a dialysis session. A 35% reduction in both C_{max} and AUC was described using high-permeability membranes. To offset this, the authors suggested increasing the dose from 6 to 9 mg/kg if administered intradyalitically [37]. A recent review of antimicrobial dosing with different forms of renal replacement therapy offers a similar strategy, and recommends a 15–20% dose increase of daptomycin when administered intradyalitically [33, 35, 37–39]. Although intradialytic dosing of daptomycin has been described, it is less preferable to post-IHD dosing as it adds further complexity to already highly variable PK in this patient population.

A recent prospective pilot study evaluated the PK of daptomycin administered at 10 mg/kg over a 2-min infusion thrice weekly following 4-h high-permeability IHD. Eleven patients with Gram-positive infections and either a long-term indwelling catheter or retained prosthesis were included. All patients achieved clinical resolution and no patients experienced elevated creatine kinase values. The median AUC/MIC ratio was 11,516 and ranged from 2248–36,908. AUC values were based on either 48 or 72 h depending on the interdialytic window. Considering the reported MIC_{90} of 0.5 µg/mL and the susceptibility breakpoint of 1 µg/mL for daptomycin against *S. aureus* isolates, the authors concluded that the high-dose strategy achieved the PK/PD target of AUC_{24}/MIC > 666 for optimal bactericidal activity more effectively than standard doses and appeared to be well-tolerated [32, 40].

Although available PK data appear to support a thrice-weekly post-HD daptomycin dosing scheme, study populations are generally limited to small cohorts of uninfected patients receiving high-flux hemodialysis for a relatively short duration, with few exceptions. Although dosing with IHD appears to be well tolerated [39], clinical outcome data of infected patients using this dosing strategy are limited. If dialysis-based daptomycin dosing is employed, it is important to ensure that it is administered following IHD and consideration is given to increasing the dose (50%) for the 72-h interdialytic period to optimize AUC for the 48- to 72-h window.

3.4 Cefazolin

Cefazolin is a first-generation cephalosporin that is used to treat many infections associated with Gram-positive organisms, including methicillin-susceptible *Staphylococcus aureus* (MSSA) and some highly susceptible Enterobacterales. Similar to other cephalosporins, the PK/PD driver of efficacy for cefazolin is the proportion of time that free-drug concentrations remain above the MIC during the dosing interval, also referred to as *f*T > MIC. A target of > 50% *f*T > MIC for cefazolin is often referenced [41–44], although the maximal bactericidal effect of cephalosporins may require > 60–70% *f*T > MIC [45, 46]. These studies did not evaluate cefazolin dosing following IHD and it is unknown whether these targets, along with those suggested for other β-lactams in this review, are adequate for special populations, including those with ESRD. Critically ill patients may require a higher target, as evidenced by one PK/PD study demonstrating improved rates of clinical cure and bacteriological eradication with 100% T > MIC for ceftazidime and cefepime [47]. Other studies have advocated for free trough (minimum) β-lactam concentrations of at least two- to fivefold the MIC (fC_{min}/MIC > 2–5), which have been associated with improved outcomes in patients treated for lower respiratory tract infections caused by Gram-negative pathogens [48–51].

The FDA makes no clear recommendation on dosing of cefazolin in patients undergoing IHD, however does comment on patients with CrCl ≤ 10 mL/min, recommending half of the usual dose every 18–24 h [52]. Cefazolin is widely distributed into most body tissues with high protein binding (80%), and up to 80% is cleared unchanged through the kidneys. Given that cefazolin is a commonly prescribed antibiotic for invasive Gram-positive infections in both inpatient and outpatient settings, several studies over the past couple of decades have evaluated various dosing strategies in patients undergoing IHD [53–56]. Antimicrobial dosing references currently recognize thrice-weekly post-dialytic cefazolin dosing, as multiple studies have demonstrated favorable clinical outcomes with this strategy [53, 56, 57].

Early data supporting post-dialytic cefazolin dosing includes a prospective PK analysis of anuric patients with chronic ESRD requiring IHD at an outpatient dialysis center who were treated with cefazolin 1 g ($n = 11$) or 2 g ($n = 4$) post-dialysis thrice-weekly for a variety of positive blood and wound cultures [58]. No duration of therapy was specified. High-flux polysulfone dialyzers were used in this study. The mean peak cefazolin level was 193 µg/mL, below the threshold of > 470 µg/mL that has been associated with cefazolin-induced encephalopathy and seizures [59]. After extrapolation to 48 and 72 h, all pre-dialysis total serum levels remained well above 8 µg/mL, the MIC breakpoint used in this study. All infected patients treated with cefazolin experienced clinical resolution, with one discontinuation due to rash. No toxic effects of cefazolin were observed among study patients [58]. The authors concluded that cefazolin 1 g (~ 15 mg/kg) post-dialysis is well-tolerated and effective against susceptible isolates in anuric patients with chronic ESRD requiring IHD.

Additional early evidence supporting post-dialytic cefazolin dosing includes a PK study of 15 patients with ESRD and suspected or documented infection receiving either conventional IHD ($n = 5$), high-efficiency IHD ($n = 5$), or high-flux IHD ($n = 5$) over ~ 4 h. Safety and efficacy endpoints were also assessed. Patients received cefazolin administered at 20 mg/kg based on actual body weight (range 1–2 g dose) post-IHD for at least three doses. Pre-dialysis and post-dialysis cefazolin concentrations were obtained. The mean pre-dialysis total cefazolin concentration was 41.6 (± 23.9) µg/mL for those receiving high-flux IHD over the three dialysis sessions, corresponding to approximately ≥ 2.5-fold the MIC breakpoint of 16 µg/mL for susceptible bacteria used in this study. Dialyzability of cefazolin was ~ 60% for those receiving high-flux IHD. All patients showed clinical resolution of infection with cefazolin treatment without any adverse reactions. The authors concluded that 20 mg/kg cefazolin administered thrice-weekly post-IHD appears to be a well-tolerated and effective dosing strategy and achieves adequate serum levels [60]. The optimal dosing weight adjustment in obese patients with ESRD requiring IHD was not determined.

Subsequently, a PK study evaluated a fixed cefazolin dose of 2 g thrice-weekly in 15 uninfected patients with chronic ESRD requiring IHD. All patients received high-flux IHD, with one exception of medium-flux IHD. Approximately half of the patients were anuric. The mean dose based on actual body weight was 28.7 ± 5.22 mg/kg, and the mean cefazolin total trough concentration on day 7 was 61 ± 22 µg/mL. All included patients achieved predialysis total serum concentrations of 3- to 18-fold the MIC for susceptible organisms, defined as ≤ 8 µg/mL in this study. Of note, there were an increased number of adverse reactions compared with the above cited study by Marx et al., which could be due to the use of fixed doses leading to higher concentrations [60]. Of the 15 patients studied, reported reactions included mouth ulcers ($n = 1$), urticaria ($n = 1$), and *Clostridioides difficile* infection ($n = 1$) [54].

A separate study evaluated the PK of cefazolin in patients undergoing IHD with high-efficiency HD (HEHD, $n = 15$) or HFHD ($n = 10$), with a focus on dialytic clearance. Patients received a cefazolin dose of 15 mg/kg after each IHD session. Approximately 60% of included patients were anuric. Mean dialytic clearance values and reduction ratios for cefazolin were significantly greater in the high-flux group compared with the high-efficiency group. Mean cefazolin reduction ratios were 0.62 ± 0.08 versus 0.50 ± 0.07, respectively. These patient data were then used to devise a PK model to simulate cefazolin serum concentrations for both types of dialyzers, using post-dialytic cefazolin doses of 15 mg/kg and 20 mg/kg. Based on the results of this model, the authors concluded that doses of 15–20 mg/kg after each IHD session maintained therapeutic serum concentrations, defined as > 8 µg/mL, throughout a 48- or 72-h interdialytic period, regardless of dialyzer type or presence of residual renal function [61].

An additional report describes a prospective investigation of a thrice-weekly cefazolin dosing regimen, as part of a newly developed dosing protocol, in infected patients receiving long-term IHD with susceptible organisms. Low- and high-flux dialyzers were used at the study site, with ultrafiltration coefficients ranging from 4.9 to 55 mL/mmHg/h. The presence of residual renal function was not measured. Cefazolin serum concentrations were collected at the end of a 72-h interdialytic interval. Patients on IHD received thrice-weekly doses of 20 mg/kg (maximum dose of 2 g) based on actual body weight. All 72-h serum cefazolin concentrations remained above the susceptibility breakpoint of 8 µg/mL, with a mean concentration of 42.9 ± 25.8 µg/mL. No adverse reactions were reported with this dosing strategy. The authors suggested thrice-weekly 20 mg/kg dosing of cefazolin is adequate for patients undergoing chronic IHD [55].

Further clinical data supporting the post-dialytic dosing strategy include a prospective study conducted over 84 months in patients infected with MSSA bacteremia and undergoing chronic high-flux hemodialysis. Vancomycin ($n = 77$) and cefazolin ($n = 46$) therapies were compared, with treatment failure determined at 12 weeks after the initial blood culture result. Patients in the vancomycin group received a loading dose of 15 mg/kg and 500 mg dose after each IHD session, targeting a serum concentration of 10–15 µg/mL. Cefazolin was administered at 2 g dose post-dialysis for the 48-h interdialytic intervals and 3 g for the 72-h interdialytic interval as per standard practice at this institution. Treatment failure was significantly more common for the vancomycin group (31.2% vs. 13%). Overall, patients with MSSA bacteremia who received cefazolin had a lower

length of stay (6.5 vs. 13 days), mortality (4.4% vs. 10.4%), and infection recrudescence (8.7% vs. 20.8%) compared with those receiving vancomycin. The authors of this study concluded that cefazolin dosing following IHD using the 2g/2g/3g regimen is well tolerated and effective for the treatment of MSSA infections in patients with ESRD requiring IHD [53].

Additional clinical data are captured by a retrospective study of patients with confirmed MSSA bacteremia who received thrice-weekly post-dialytic cefazolin of 2–3 g, as per dosing protocol, compared with those receiving cloxacillin 500–2000 mg four times daily to complete 2 weeks of therapy. Outcomes assessed included death or readmission within 30 days of MSSA bacteremia, presence of metastatic complications, recrudescence, adverse reactions, and hospital costs. A total of 27 patients were included, of whom 14 received cefazolin therapy. Two patients in the cloxacillin group and one patient in the cefazolin group suffered mortality. All of the infection recurrences occurred in the cloxacillin group and 7/8 metastatic complications were associated with cloxacillin treatment. The cefazolin group had lower mean length of stay (10 days vs. 20 days) and hospitalization cost. The authors acknowledged that using cefazolin doses of 3 g thrice-weekly leads to excessive serum levels and may increase the risk of toxicity. Three patients receiving cefazolin experienced idiosyncratic reactions, namely Stevens–Johnson syndrome ($n = 2$) and leukopenia ($n = 1$), all occurring with the 3 g thrice-weekly dose. Given the idiosyncratic nature, these reactions were unlikely to be dose-related. The authors concluded that cefazolin administered following IHD, using a 2 g dose thrice-weekly, was justifiable based on clinical and economic endpoints [56].

Based on review of the available literature, a cefazolin dosing strategy of 2 g thrice-weekly following IHD may be utilized for most infections, regardless of the presence of residual renal function. A 3 g dose should be considered for the 72-h interdialytic window, particularly for severe and/or deep-seated infections, to improve attainment of trough concentrations above the MIC. Although positive clinical outcomes have been demonstrated with cefazolin administered following IHD, larger studies are still necessary to validate this dosing. In addition, total cefazolin concentrations were collected in these studies. Therefore, the proportion of the dosing interval that free concentrations exceeded the MIC breakpoint cannot be completely evaluated. Despite the availability of limited data evaluating a WBD strategy of 20 mg/kg following IHD, the authors place preference on the standardized dosing strategy recommended previously, given simplicity of dosing, improved convenience, favorable safety profile of cefazolin, and comparatively higher mean total trough concentrations [54, 60].

3.5 Ceftazidime

Ceftazidime is an inexpensive and oft-utilized third-generation cephalosporin with potent bactericidal activity against a wide range of Gram-negative pathogens, such as Enterobacterales, *Burkholderia pseudomallei*, and *Pseudomonas aeruginosa*. It displays protein binding of approximately 20% and a Vd of 0.23 L/kg. Approximately 80–90% of ceftazidime is eliminated unchanged in the urine, with a half-life of 1–2 h in patients with normal renal function [62]. This is increased to 28–45 h in patients with ESRD as elimination is almost entirely dependent upon renal excretion [63]. Ceftazidime is significantly removed by various dialysis methods. Using low-flux filters, a 6- to 8-h IHD session removed approximately 88% of ceftazidime in the plasma in one study and 55% of ceftazidime during a 4-h IHD session in another [64, 65]. Dialyzability using high-flux filters is unknown. The parameter corresponding to effective PD activity for ceftazidime is the attainment of free-drug concentrations exceeding the MIC for > 45% of the steady-state dosing or interdialytic interval (fT > MIC) [66, 67], with maximal bactericidal activity requiring > 60–70% fT > MIC [45, 46]. One PK/PD study of critically ill patients demonstrated improved rates of clinical cure and bacteriological eradication with the attainment of 100% T > MIC for ceftazidime and cefepime [47]. In other studies evaluating cefepime or meropenem, free trough (minimum) β-lactam concentrations of at least two- to five-fold the MIC (fC_{min}/MIC > 2–5) have been associated with improved outcomes in patients treated for lower respiratory tract infections caused by Gram-negative pathogens [48–50]. In vitro PK models specifically evaluating continuous infusions of ceftazidime against *P. aeruginosa* have demonstrated efficacy with concentrations of at least fourfold the MIC (C_{min}/MIC > 4) [68, 69].

Several PK studies were conducted in the early 1980s that sought to describe ceftazidime elimination in the setting of varying degrees of renal function. However, the dialyzers used in these studies, namely cuprophan membrane capillary flow or coil, would be considered 'low-flux' by contemporary standards, thus limiting extrapolation of these data to current practice. An early PK study of nine anuric patients with ESRD requiring IHD demonstrated a ceftazidime elimination half-life of approximately 34 h following administration of 1 g of ceftazidime [65]. Post-dialytic drug concentrations were reduced by 55%, resulting in a ceftazidime elimination half-life of 3 h during hemodialysis. The results set the stage for the study of ceftazidime dosing following thrice-weekly IHD. A subsequent study inferring PK data extrapolated from 14 patients with ESRD, of whom 2 were non-dialysis requiring, suggested that a ceftazidime dose of 0.5–2 g every 36–48 h, adjusted by indication, would

constitute appropriate dosing in patients with creatinine clearance < 15 mL/min [63]. A third study, conducted by Hoffler et al. involved a PK analysis of a single 2 g ceftazidime dose in 29 subjects with varying degrees of renal function, from normal to ESRD requiring IHD. Based on the delineated dose adjustment factors, ceftazidime could be downtitrated to 0.5 g daily in patients with ESRD who would normally receive a ceftazidime daily dose of 6 g [70].

These recommendations persisted for approximately 30 years until recently, when Loo et al. utilized raw data of six anephric adults from the Hoffler et al. study, which used low-flux membranes, in order to simulate dosing efficacy from the perspective of more contemporary and efficient high-flux hemodialysis methods [71]. The modeling was based on known non-renal elimination rates and dialysis drug removal of 55–88%. By re-estimating the probabilities of target attainment (PTA) of various ceftazidime dosing recommendations using Monte Carlo simulations, the authors were able to predict that PTA of 70% T > MIC for MIC of ≤ 8 µg/mL could be attained throughout a 48-h interdialytic period with both 1 and 2 g doses of ceftazidime. However, the authors concluded a similar PTA was only possible with the 2 g dose during the longer 72-h interdialytic period for MIC > 4 µg/mL. Dosing of 1 g daily achieved 100% PTA, even for resistant organisms with MIC of 32 mg/L, and may be preferred when MIC is unknown or for critically ill patients who may benefit from a higher %T > MIC [47, 71].

Clinical reports on the administration of ceftazidime thrice-weekly following IHD are scarce. Recently, a case of *P. aeruginosa* infective endocarditis with previous treatment failure in an anuric patient with ESRD requiring high-flux IHD was presented [72]. The ceftazidime MIC was 2 µg/mL for the isolate. Serum ceftazidime concentrations were collected at various intervals out to 72 h. The authors noticed a dip in pre-IHD concentrations below 8 µg/mL at 70 h using a ceftazidime dosing strategy of 2g/2g/2g thrice-weekly following IHD. With previous studies documenting optimal bactericidal activity of cephalosporins at trough concentrations greater than fourfold the MIC (corresponding to 8 µg/mL in this case), the dose was subsequently adjusted to 2g/2g/3g to maximize PTA for the 72-h interdialytic interval [48–51, 68, 69, 72]. The adjustment resulted in an improved trough of 15 µg/mL for the 72-h interdialytic window. This regimen, combined with oral ciprofloxacin, was used for a total of 6 weeks and was well-tolerated, with a positive clinical outcome [72].

Currently, there is very limited published literature evaluating ceftazidime dosing following IHD. There is also a paucity of data available on the clearance of ceftazidime using high-flux compared with low-flux dialysis and the clinical impact of varying dosing strategies. Additional studies evaluating the achievement of more aggressive PK/PD targets such as fC_{min}/MIC > 2–5 would be highly valuable. Based on what is available, a thrice-weekly ceftazidime dose of 2 g following IHD may be reasonable for most non-critically ill patients with susceptible infections caused by Enterobacterales. A ceftazidime dosing strategy of 2g/2g/3g thrice-weekly following IHD, using a higher dose for the 72-h interdialytic window, could be considered for patients with resistant organisms such as *P. aeruginosa* or deep-seated infections, although sufficient data are lacking to justify widespread adoption of these dosing strategies.

3.6 Cefepime

Cefepime is a fourth-generation cephalosporin developed in the early 1990s with a broad spectrum of activity against both Gram-positive and Gram-negative bacteria, including *Enterobacter spp*., *Citrobacter spp.,* and *P. aeruginosa*, but lacking an effect on strictly anaerobic bacteria or MRSA [73, 74]. A suggested PK/PD target for optimal bactericidal activity of cefepime is the attainment of free-drug concentrations above the MIC (fT > MIC) for ≥ 60% of the dosing interval [45, 46, 75]. However, a target of 100% T > MIC for cefepime and ceftazidime demonstrated improved rates of clinical cure in one study of critically ill patients, suggesting achievement of this target may be necessary to optimize outcomes in this population [47]. In other PK/PD studies evaluating cefepime for Gram-negative infections, free trough concentrations of at least twofold the MIC (fC_{min}/MIC > 2) and total trough concentrations of at least fourfold the MIC (C_{min}/MIC > 4) have been associated with reduced risk of treatment failure and improved microbiological success, respectively [48, 49].

Cefepime is primarily eliminated by the kidney in unchanged form (85%), with a half-life of approximately 2 h in subjects with normal renal function. In anuric patients on IHD, the half-life is extended at up to 22 h [76]. Cefepime has been shown to demonstrate flow-dependent clearance in patients receiving high-flux IHD, with a dialytic clearance of 120 mL/min and 179 mL/min at dialysis flow rates of 300 mL/min and 400 mL/min, respectively [77]. Cefepime is slightly bound to plasma proteins (16–19%) and is effectively cleared by dialysis [76]. The prescribing information contains varying dosing recommendations for patients on IHD, with 1 g on day 1 and 500 mg daily thereafter suggested for most patients, and 1 g daily for those with severe infections [78]. Moreover, a separate dosing guideline suggests a dose reduction of 50–75% administered once daily [79].

Multiple PK studies have evaluated cefepime PK/PD in patients with ESRD requiring IHD, introducing the potential for thrice-weekly dosing following IHD. A multidose PK study was conducted and included six infected patients on chronic IHD with no residual renal function receiving 2 g of cefepime at the end of thrice-weekly IHD using a

high-flux polysulfone dialyzer. Trough and peak level serum concentrations were obtained as well as the percentage of drug eliminated and intradialytic half-life. In these patients, the mean peak and trough total serum concentrations were 166 ± 49 μg/mL and 23 ± 7 μg/mL, respectively. The mean removal of cefepime was approximately 70% following a 3.5-h dialysis session. The authors concluded that 2 g of cefepime after each IHD session achieved drug levels well above the MIC_{90} of 8 μg/mL for most target pathogens and serves as an efficient and cost saving strategy for chronic, anuric IHD patients with severe infections [80]. Given the absence of clinical correlation to patients with active infection, 5 years later researchers from the same group reported on their clinical experience treating 11 anuric patients on IHD with cefepime according to the suggested dosing protocol and reported a success rate of 82% [81].

Despite the generally well-tolerated treatment experience to date, some concern of cefepime-induced neurotoxicity with elevated plasma trough concentrations using this dosing strategy remains. Cefepime-induced neurotoxicity using higher doses in the setting of ESRD has been previously reported, including one case of an anuric patient requiring IHD with septicemia who experienced a tonic-clonic seizure after 5 days of cefepime administered at 1 g every 12 h, which is considered higher than the recommended dose in the setting of IHD. Pre-IHD serum cefepime levels for three urgent, daily dialysis sessions following the onset of toxicity and discontinuation of cefepime were 105 μg/mL, 66 μg/mL, and 9.7 μg/mL, respectively. The dialyzer type was not reported [82]. A study of patients with febrile neutropenia and mildly impaired renal function reported that the probability of cefepime-associated neurological toxicity, manifested as altered mental status, confusion, or myoclonia, increases steadily with trough plasma levels exceeding 22 μg/mL [83]. However, a research letter reported the clinical experience and safety of 33 patients receiving a cefepime dosing strategy of 2 g thrice-weekly following IHD compared with alternative regimens, including 13 patients receiving cefepime 1 g daily, in patients with Gram-negative bacteremia. Overall, no difference in clinical success was seen in patients receiving cefepime 2 g post IHD versus the comparator group (94% vs. 87%; $p = 0.4$). Furthermore, cefepime was well-tolerated and no differences were reported in the safety outcomes between the groups [84].

Most recently, a PK study of nine patients undergoing high-flux thrice-weekly IHD evaluated cefepime dosing using TDM [85]. The initial dose utilized was 15 mg/kg (ranging from 750–1500 mg), and subsequent doses administered thrice-weekly following IHD were based on trough serum levels obtained prior to the next dialysis session. The mean cefepime doses prior to the 48 and 72-h interdialytic intervals were 775 ± 210 mg and 1125 ± 225 mg, respectively. Five patients in the study had residual diuresis of > 400 mg/day and the remaining four were anuric. Despite this, the prescribed cefepime doses achieved trough concentrations well above EUCAST breakpoints and MIC_{90} for all reference organisms with the exception of *P. aeruginosa*. The reference laboratory (Clinical Pharmacology Laboratory, CHUV University Hospital, Switzerland)-recommended trough range was 2–15 μg/mL, and only one anuric patient with a trough of ~ 23 μg/mL reached the previously suggested trough threshold of 22 μg/mL for toxicity [83]. It is worth noting that the cefepime doses that were used in these patients were, on average, ~ 50% lower than the fixed post-dialytic dose of 2 g proposed by Schmaldienst et al. [80]. Another pertinent finding was ~ 80% of the drug was eliminated during a 4-h high-flux dialysis session, implying a potential treatment option for patients suffering from accumulation and toxicities. Mean cefepime concentrations were much lower in non-anuric patients. In patients with residual diuresis, higher doses of cefepime should be considered. The authors concluded that in patients with highly-susceptible pathogens, a thrice-weekly 1g/1g/1.5g cefepime dosing strategy may be well-tolerated and efficacious. However, in patients with infections caused by less-susceptible organisms such as *P. aeruginosa*, a 1.5g/1.5g/2g dosing strategy should be implemented along with serum trough monitoring to avoid toxicities. It is pertinent to highlight that the average doses utilized in this study were lower than those recommended by the authors at 775 ± 210 mg and 1125 ± 225 mg during the 48 and 72-h interdialytic intervals, respectively [85]. Although TDM of cefepime may be a useful tool in this special population, it is not readily available at most institutions and additional data are needed on the cost effectiveness of this intervention prior to widespread implementation.

Similar to ceftazidime, the available data supporting cefepime dosing following IHD are sparse. Although apparently feasible from a PK/PD standpoint and well-tolerated in the small cohorts evaluated, larger studies are required to validate cefepime doses administered thrice-weekly following IHD prior to widespread adoption in current practice. Based on the available literature, a cefepime dose of 1 g thrice-weekly following IHD with an increased dose of 1.5 g for the 72-h interdialytic interval may be considered for non-severe, highly susceptible infections in anuric patients. However, clinicians should consider an increased cefepime dose of 2 g following IHD thrice-weekly for severe infections and/or those caused by less susceptible pathogens such as *P. aeruginosa*, particularly in those with residual renal function. Additional safety data using this increased dose are urgently needed as the mean cefepime trough concentration demonstrated in one study (23 μg/mL) slightly exceeded the suggested trough threshold of 22 μg/mL for toxicity [81].

3.7 Ertapenem

Ertapenem is a long-acting, once daily parenteral carbapenem with a broad spectrum of activity against Gram-negative bacteria, including extended-spectrum β-lactamase (ESβL) producers, Gram-positive bacteria, and anaerobes, but lacking activity against *P. aeruginosa, Acinetobacter baumannii, and Enterococcus* spp. Ertapenem's broad spectrum of activity makes it a preferred agent for the treatment of chronic, complicated, mixed infections requiring long durations of therapy [86–89]. Ertapenem has a relatively low Vd (Vd at steady state = 0.12 L/kg in adults) and 80% is eliminated via the kidneys [86]. Ertapenem exhibits nonlinear PK due to concentration-dependent plasma protein binding, which ranges from 90 to 95% at therapeutic concentrations. Following the administration of a 1 g dose, the plasma concentration of total drug is approximately 150 µg/mL and about 92% is protein bound. In early PK studies, higher doses of 2–3 g were administered, resulting in higher total concentrations (> 150 µg/mL) and higher free drug concentrations due to only 85% of drug being protein bound [88]. In patients with normal renal function, the plasma half-life is approximately 4 h [86]. For carbapenems, free drug concentrations greater than the organism's MIC ($fT > MIC$) should be maintained for ≥ 40% of the dosing interval for optimal bactericidal effect, a lower target than required for penicillins and cephalosporins [45, 46, 89–92]. In studies evaluating β-lactam PK/PD in the setting of invasive infections caused by Gram-negative pathogens, free drug trough concentrations of ≥ 4–5 times the MIC (fC_{min}/MIC > 4–5) for β-lactams have been suggested to maximize bacterial killing and limit the emergence of resistance [49, 50, 93, 94]. Additional data are required to confirm whether these targets are applicable for ertapenem, specifically. MIC susceptibility breakpoints for ertapenem for clinically relevant organisms include 0.5 µg/mL for Enterobacterales, 4 µg/mL for anaerobes, and 1 µg/mL for streptococcus [95]. It should be noted that for many of the studies below, total drug concentrations are provided.

In patients with severe renal impairment (CrCl < 30 mL/min/1.73m^2) and ESRD requiring IHD, the FDA-approved dosing strategy is 500 mg daily, compared with standard dosing of 1 g daily [86]. This dosing strategy was based on an initial open-label PK study of 26 otherwise healthy volunteers with varying degrees of renal function (7 of whom had ESRD), who were administered a single 1 g dose of ertapenem and were compared with an historical control of healthy young and elderly adults [87]. The AUC_{∞} for ESRD patients was increased by 192% versus healthy controls, and half-life extended to 14.1 h. Based on an AUC_{∞} ratio (pooled control/ESRD) for total drug, an estimated adjusted dose of 500 mg daily was recommended to achieve therapeutic benefit without compromising safety and achieve total drug exposure in slight excess of that observed with the 1 g daily dose in the pooled control group. Free drug concentrations were measured at the midpoint of the dosing interval (12 h) to ensure PD parameters were met, and resulted at 6.7 µg/mL for ESRD patients, above the MIC breakpoints for targeted pathogens. The authors also demonstrated that approximately 30% of ertapenem was removed via a 4-h low-flux hemodialysis session. As such, a supplemental 150 mg dose is recommended if the initial 500 mg dose was administered prior to dialysis [87]. As this study only evaluated single-dose administration, accumulation with daily dosing was not assessed.

From a safety perspective, there have been reports of neurotoxicity with ertapenem, potentially linked to accumulation in patients with severe renal impairment and ESRD receiving 500 mg of ertapenem daily [96–98]. Neurotoxicity may manifest in varying degrees, including seizures, hallucinations, and cognitive dysfunction. It is possible that the prolonged half-life and decreased renal clearance, in the setting of repeated daily doses, may result in drug accumulation [76]. The mechanism for neurotoxicity is not completely understood, but ertapenem's lipophilicity and affinity for γ-aminobutyric acid neurotransmitter, combined with increased permeability of the blood–brain barrier to β-lactams in impaired renal function may play a role [98]. In addition, among the 13 patients cited in a review of the literature, neurotoxicity presented after administration of 3–7 consecutive daily doses and resolved within 7–14 days [96]. These patients received low-flux dialysis, which, as mentioned previously, removes ~ 30% of ertapenem plasma concentrations compared with high-flux dialysis, which can remove up to 70% [97]. However, neurotoxicity has also been reported with ertapenem dosing following high-flux IHD. A recent review of 99 patients receiving hemodialysis reported 10 patients (10%) who developed neurotoxicity, defined as seizure or laryngospasm. Of these 10 patients, 6 received 500 mg daily and 2 received 1 g followed by 500 mg daily. The remaining 2 patients required continuous venovenous hemofiltration (CVVH) and received a dose of 1 g daily [98]. Alternate ertapenem dosing strategies in the setting of IHD have been suggested, ranging from 500 mg to 1 g thrice-weekly following IHD, introducing a more convenient dosing regimen that would reduce the number of infusions, improve adherence, and possibly minimize the potential for toxic accumulation [99–101].

Thrice-weekly dosing of 1g following IHD was first evaluated in a 10-patient pilot study [99]. The dialyzer type was not specified. Total ertapenem trough concentrations were measured at 44 and 68 h and resulted at 3.4–22.6 µg/mL and 0.5–9.6 µg/mL, respectively. The authors noted that all trough levels were maintained above the MIC for each pathogen during the intradialytic periods. The mean elimination half-life was longer than first identified by Mistry et al.

[87], at 19.9 ± 5.5 h. No adverse effects were observed and clinical success was achieved in 8 of the 10 patients.

A PK investigation of optimal ertapenem dosing in IHD patients was subsequently evaluated using a single dose of 1 g ertapenem administered to seven hospitalized non-infected patients undergoing high-flux hemodialysis [100]. The mean elimination half-life was similar to that seen previously with 1 g administered post-hemodialysis at 19.3 ± 6.6 h. Total ertapenem concentrations evaluated at 48 h (mean 42 µg/mL) exceeded the MIC for *Streptococcus,* Enterobacterales, and anaerobic bacteria. Six patients experienced an adverse event during the study but these were determined to be possibly unrelated to the study drug in all cases. The authors concluded that a thrice-weekly regimen would likely produce pharmacodynamically sufficient exposure for antimicrobial efficacy and reduce the potential for drug accumulated adverse events with less frequent dosing. The authors also identified additional patient-related factors that may require attention when considering different dosing regimens in ESRD, including protein binding, non-renal clearance of ertapenem, and factors affecting distribution such as fluid status [100]. As with the initial PK study, only single doses were administered, therefore the potential for accumulation cannot truly be assessed. Troughs at 72 h were also not measured. As previously noted, plasma concentrations at 48 h, two-thirds of the 72-h dosing interval, were maintained above the MIC for targeted pathogens.

A more conservative dosing schedule—500 mg thrice-weekly following IHD—has been suggested based on a Taiwanese prospective study that evaluated intradialytic plasma concentrations [101]. Twenty-two hospitalized, infected patients with ESRD were assigned to either receive 500 mg daily, the reference group, or 500 mg thrice-weekly after each dialysis session. When compared, the mean total and free ertapenem plasma levels were significantly higher in the reference group versus the experimental group, and approximately 50% of ertapenem was cleared with each hemodialysis session. The dialyzer type was not reported in this study. Data from the reference group were collected and used to simulate three different dosing regimens—500 mg daily, 250 mg daily, and 500 mg every other day—which were compared with the observed data in the experimental group. Free plasma ertapenem trough concentrations, at both 48 and 72 h, for the experimental group were above 2 µg/mL and correlated well with the simulated results. Additionally, in the reference group, concentrations well exceeded these minimums. It should be noted that 2 µg/mL was the MIC breakpoint for Enterobacterales until 2012, when It was changed to its current value of 0.5 µg/mL [95]. Clinical efficacy and safety data were not reported, except for two cases of neurotoxicity seen in the reference group on days 7 and 9. The authors concluded that the dosing regimen of 500 mg thrice-weekly following IHD is adequate to maintain minimum concentrations for efficacy and reduce the potential for toxic accumulation [101].

Available PK data suggest that the current ESRD dosing regimen of 500 mg daily exceeds the necessary concentrations for efficacy and has the potential for toxic accumulation. While the available studies are limited, a simplified thrice-weekly post-IHD dosing scheme offers more convenient dosing while maintaining plasma levels necessary for antimicrobial activity. Ertapenem 500 mg administered following IHD demonstrated trough concentrations adequate for most organisms, but these data cannot be extrapolated to all types of dialyzers [101]. Trough levels observed with single-dose administration of 1 g following IHD also exceed necessary concentrations for efficacy [99, 100]. An additional strategy of a 1 g loading dose following IHD succeeded by 500 mg after subsequent IHD sessions has also been suggested based on a report that utilized this dosing scheme for the treatment of urinary tract infections in anuric patients requiring IHD [102]. At this time, additional studies evaluating consecutive dosing of both the 500 mg and 1 g post-HD in regard to PK/PD and clinical endpoints are warranted prior to widespread adoption of these alternative dosing strategies.

3.8 Aminoglycosides

Aminoglycosides are broad spectrum, bactericidal antibiotics that have been in clinical use since the 1940s. This review will limit discussion to gentamicin, tobramycin, and amikacin, the most commonly used aminoglycosides in practice. Due largely to their narrow therapeutic index and boxed warnings of nephrotoxicity and ototoxicity, their current place in therapy is generally reserved to MDR aerobic Gram-negative bacilli and synergistic therapy for Gram-positive infectious endocarditis. Owing to a high degree of glomerular clearance, low cost, decades of clinical use, and feasibility of TDM, there is a wealth of clinical experience with dialysis-based dosing of aminoglycosides, particularly gentamicin [103, 104]. However, safety is a palpable concern, with reported ototoxicity incidence as high as 60% for patients receiving hemodialysis [105]. Reported dialyzability of aminoglycosides ranges widely from 20 to 75%, depending on dialysis method, filter type, flow rates, and duration [8, 104, 106]. Aminoglycoside PK characteristics are also highly variable in the setting of ESRD due to inter-patient differences in Vd, residual renal function, and dialysis modalities [104]. A delay in tissue distribution in the range of 2 h has also been described in patients with renal failure receiving aminoglycosides [104]. Dosing of aminoglycosides has been described both following IHD (summarized in Table 1) and pre-IHD, where aminoglycosides have been shown to achieve a higher probability of attaining PK/PD targets, such as $C_{max} > 8$ µg/mL, and limit exposure

(AUC) in some PK models [9, 104, 107–109]. However, the safety profile of pre-IHD aminoglycoside dosing is unclear and has recently come into question [110]. In addition, an evolving body of evidence suggests that the AUC/MIC ratio may be the most reliable PK/PD index associated with the antibacterial activity of aminoglycosides [111]. Although preserving peak concentrations, pre-IHD aminoglycoside dosing would naturally limit AUC values given the dialyzability of these agents.

Logistics with pre-IHD dosing also limit practicality due to potential scheduling issues and associated risks with short or interrupted dialysis sessions [112]. To optimize the probability of treatment success and limit toxicity, TDM is recommended for aminoglycoside therapy. Peak concentrations of 7–10 μg/mL and pre-IHD concentrations of 3.5–5 μg/mL have been suggested for gentamicin and tobramycin in the setting of ESRD requiring IHD when treating serious infections caused by Gram-negative bacilli [104]. The corresponding recommended amikacin peak and pre-IHD concentrations are 20 μg/mL and < 10 μg/mL, respectively. The performance of TDM immediately following IHD should be avoided due to a pronounced rebound in aminoglycoside concentrations [104].

Aminoglycoside PK characteristics were elucidated in a prospective observational study of 167 patients treated with 216 total courses of aminoglycosides and requiring IHD for either stage 5 CKD or acute renal failure. For the patients with ESRD, the mean Vd using ideal body weight (IBW) and half-life off-IHD were 0.37 L/kg and 45.7 h, respectively. Due to a prolonged distribution phase in this patient population, concentrations to determine elimination rates were collected at least 18 h after the initial dose. Clinical outcome data were also collected and included 110 patients treated with a total of 117 courses lasting at least 5 treatment days. The overall treatment success rate was 91%, with pneumonia and *Pseudomonas* spp. representing the most common site of infection and isolated organisms, respectively. The mean serum peak concentration for gentamicin and tobramycin was 7.7 μg/mL and the mean serum pre-IHD concentration was 3.9 μg/mL. The authors concluded that careful attention was warranted when utilizing aminoglycosides in this patient population due to the abundance of unpredictable variables at play, including variability in interpatient PK, type of renal failure, and dialyzer characteristics [104].

The PK parameters for gentamicin using high-flux dialyzers have been characterized in several PK studies [104, 106–108, 110]. A study of eight patients with ESRD requiring IHD and treated with aminoglycosides for suspected or known infection caused by Gram-negative bacilli was conducted utilizing high-flux polysulfone membrane dialyzers. The mean intra-dialytic half-life was found to be 2.24 h and gentamicin concentrations rebounded approximately 28% at 1.5 h following completion of IHD. Gentamicin dialyzability was 54% [106]. A separate study of 8 uninfected subjects with ESRD requiring IHD was conducted to assess gentamicin PK using high-performance cellulose acetate dialyzers. The median steady-state Vd was found to be 13.5 L and the terminal half-life was 39.4 h [108]. Clinical and PK data on the use of tobramycin and amikacin in the setting of IHD are much more limited and will not be discussed in detail [9, 109, 113, 114].

Although aminoglycoside dosing in the setting of ESRD requiring IHD is well-referenced, the optimal dosing strategy for the treatment of invasive, life-threatening infections caused by Gram-negative bacilli is unknown and is influenced by several patient-specific and microbiological factors. In addition, the clinical outcomes of ESRD patients requiring aminoglycoside therapy may be suboptimal, with mortality exceeding 40% in one cohort of dialysis patients receiving aminoglycoside therapy for systemic infections [2, 115]. In this study, patients who died had significantly lower, and often subtherapeutic, serum concentrations compared with those who survived [2]. Therefore, individualized post-dialytic dosing with TDM is strongly recommended to improve the probability of treatment success.

3.9 Fluconazole

Fluconazole is a widely utilized and well-tolerated azole antifungal with activity against *Cryptococcus* spp. and several species of *Candida*, notably excluding *C. krusei* [116, 117]. Plasma protein binding of fluconazole is relatively low (< 15%) and it exhibits great tissue penetration at all studied body sites, including the cerebrospinal fluid. Renal excretion accounts for approximately 80% of fluconazole clearance, and a 3-h IHD session reduces fluconazole exposure by ~ 50%, although the prescribing information does not list the dialyzer characteristics related to this metric [116]. Fluconazole's dialyzability is owed to its high degree of renal clearance and low molecular weight. In the setting of ESRD requiring IHD, the prescribing information for fluconazole injection recommends administering 100% of the recommended dose after each IHD session. Given its excellent bioavailability of > 90%, fluconazole should be administered enterally whenever clinically feasible.

Initially, a study of five patients with ESRD and suspected fungal infection was performed in order to describe the PK of fluconazole in the setting of IHD. A variety of dialysis membranes were used, with ethylenevinylalcohol (EVAL) and polymethylmethacrylate (PMMA) each being used in two patients, and polyacrylnitryl (PAN) being used in the remaining patient. Fluconazole doses of 100–200 mg were administered following each IHD session. On average, a 4-h dialysis session decreased fluconazole exposure by 39%. The single-pass extraction ratio was 59% using a dialyzer blood flow rate of 180 mL/min. After weeks of

therapy, fluconazole reached concentrations fourfold higher than the C_{max} after the initial dose. Based on the PK profile, the achievement of proposed effective concentrations against candidiasis, and the changes in fluconazole serum concentrations following repeated dosing, the authors concluded that usual doses of fluconazole injection may be administered after each IHD session [118].

A subsequent study of 40 volunteers, 10 with ESRD requiring IHD, was undertaken to evaluate the multiple-dose PK of oral fluconazole in four cohorts separated by degree of renal function. Patients receiving thrice-weekly IHD received a fluconazole loading dose of 200 mg, followed by 100 mg after each IHD session. Blood samples were collected at several intervals following multiple doses and included pre-IHD and post-IHD fluconazole concentrations. Fluconazole concentrations decreased ~40–50% during dialysis and the concentration 24 h after each dose was ~4 µg/mL, notably lower than suggested levels of at least 7–8 µg/mL for treating invasive candidiasis [117–119]. The mean AUC_{24} at day 10 for subjects with ESRD and receiving a fluconazole 100 mg maintenance dose with each IHD session was 107.5 µg*h/mL. Notably, this value is approximately half of the mean day 10 AUC_{24} of 217.7 µg*h/mL for patients with normal renal function (CrCl > 50 mL/min) receiving fluconazole 200 mg daily. Based on these findings, the authors concluded that patients with ESRD receiving IHD and requiring fluconazole should be administered the full recommended maintenance dose for the indication every 48–72 h following each IHD session [119].

Fluconazole's PK and safety profile support the appropriateness of intravenous dosing thrice-weekly following IHD in patients with ESRD unable to receive enteral administration. The full recommended dose for the indication (generally 400–800 mg for invasive infections) should be utilized and administered only after each IHD session for this patient population.

4 Discussion

Patients with ESRD are at a significantly increased risk of invasive infections, with particular attention to *S. aureus*, implicated in up to 39% of dialysis-related infections, given the associated morbidity and mortality [112]. Furthermore, a high proportion of these infections are related to vascular access. Therefore, strategies to reduce the risk of catheter-related complications are essential in this patient population [120]. The administration of intravenous antimicrobials following IHD has several advantages, including convenience, guaranteed adherence, and, most importantly, the avoidance of placing a temporary catheter. The placement of a PICC or small-bore central catheter (SBCC) is costly, resource- and labor-intensive, and introduces the very tangible risk of thrombotic and infectious complications. Indeed, to preserve hemodialysis vascular access options, the placement of a PICC in patients with ESRD is considered contraindicated in the KDOQI guidelines [5]. Unfortunately, the selection of antimicrobials that may be administered following IHD has been historically limited to vancomycin, cefazolin, and aminoglycosides. Despite experience with these agents, published dosing recommendations in the setting of IHD are often contradictory and may not reference specific dialyzer type [108]. The utilization of other intravenous antimicrobials has been hampered by cost, scarcity or complete lack of supporting evidence, as well as inexperience in this clinical setting.

This review provides a comprehensive summary of the available data for the administration of an expanded list of intravenous antimicrobials following thrice-weekly high-flux IHD in patients with chronic ESRD. It must be noted that the dosing strategies proposed are based on PK studies and the clinical outcomes of small cohorts of patients. Thus, many limitations exist with the application of these data to current clinical practice, particularly the intensive care setting, given the known alterations of PK in this patient population. Critically ill patients often experience increased Vd secondary to inflammatory response, fluid resuscitation, capillary leak, and alterations in protein binding [9, 121]. Changes in metabolism secondary to decreased non-renal clearance have also been well-described in patients with ESRD [9].

The evolution of hemodialysis technology over the last few decades further limits the relevance of the findings from older studies [19]. This is clearly evident with the modification of vancomycin dosing recommendations, from once-weekly to thrice-weekly dosing, in patients requiring hemodialysis [112]. Major developments in dialysis therapy, with an increased focus on optimizing removal of uremic toxins, have changed the landscape of this clinical service, improving outcomes, and allowing personalization of treatment plans along the way [12]. Indeed, standards for urea clearance are higher than those used 20 years ago. Dialysis membrane composition plays a clear role, as evidenced by increased vancomycin clearance using polysulfone dialyzers compared with cuprophan [122], representing just one of multiple known examples. Given these factors, knowledge of dialyzer permeability and ultrafiltration capacity is of critical importance given the high potential for alteration of antimicrobial PK during IHD.

As previously implied, several of the studies evaluated in this review include small cohorts of uninfected patients treated for short durations. Studies including patients with ESRD and invasive infections are scarce [26, 40, 53, 56, 106]. Thus, numerous gaps continue to exist in the literature. A careful evaluation of the potential risks and benefits of utilizing intravenous antimicrobials administered following IHD is certainly warranted. The use of such off-label and

largely investigational dosing strategies discussed for the majority of antimicrobials in this review should be limited to situations where intravenous therapy is required based on clinical and microbiological factors, the antimicrobial chosen is expected to adequately distribute to the site of infection based on its known PK properties in other populations, and/or the risks of placing an additional vascular access device for traditional dosing of OPAT clearly outweigh the benefits. Nonetheless, additional PK/PD and clinical data are urgently needed to define optimal dosing and to evaluate clinical outcomes for severe infections for several of the agents described in this review. Potential areas of interest and future research include evaluation of the influence of residual renal function, data in obese patients requiring IHD, and cohort studies evaluating outcomes in infected patients with varying severities of illness and in those with high-burden disease. Indeed, limited data suggest that the degree of residual renal function may have relevant implications on dosing selection for agents that are primarily renally cleared [85]. For example, vancomycin concentrations have been shown to be up to 40% lower in patients with residual renal function compared with anuric patients [123]. For this reason, the dosing strategies listed in Table 1 are suggested by the authors specifically for anuric patients with chronic ESRD, unless otherwise specified in the text.

Clinical pharmacists are uniquely positioned to assist providers in selecting antimicrobials that could be administered following IHD, identifying appropriate candidates for therapy, and ensuring transitions of care between the Infectious Diseases team, nephrology physician, and nursing staff to ensure that antimicrobials administered at the dialysis site are properly administered in order to optimize PK parameters [6, 19]. If the decision is made to proceed with therapy employing an intravenous agent administered following IHD, the clinician could be faced with barriers to optimal implementation of the plan in clinical practice.

Unsurprisingly, the most significant barrier to the use of several of the agents described is cost, which has influenced the practicality and unrivaled experience of cefazolin, vancomycin, and aminoglycoside use in ESRD patients requiring IHD. Dialysis centers may be unwilling to incur the cost of relatively more expensive antimicrobials such as daptomycin and ertapenem. Therefore, coordination, feasibility, and coverage must be assessed on a patient-by-patient basis when considering the use of such agents. In addition, dialysis centers may be unwilling to administer the intravenous antimicrobial after IHD, and instead may infuse the agent during the last 1–2 h of dialysis due to scheduling and/or cost repercussions to extending the dialysis session. It is clear that this practice has the potential to significantly alter PK parameters such as AUC and C_{max} [38], given that many of the agents described are efficiently removed by high-flux IHD filters [11, 32, 76]. In order to position the patient for the best chance of clinical success, thorough coordination with the nephrologist and dialysis center staff is essential and may allow for an exception to this practice. If infusion time is a factor, the option of rapid administration should be investigated for the antimicrobial of choice. Daptomycin, for example, is FDA-approved to be administered by injection over 2 min, which is significantly shorter than the traditional 30-min infusion [9].

Post-dialytic dosing suggestions for the intravenous antimicrobials discussed are summarized in Table 1, and assume the use of thrice-weekly, high-flux IHD over 3- to 4-h sessions, with interdialytic periods of 48, 48, and 72 h, respectively, in anuric patients with chronic ESRD. These dosing strategies do not apply to other types of renal replacement therapy, such as CRRT or peritoneal dialysis. Dosing ranges are used in several circumstances as numerous clinical and microbiological factors should be considered when establishing a regimen, such as patient weight, degree of intrinsic renal function, immunologic status, site and severity of infection, MIC of organism, and characteristics of the dialysis modality [9].

5 Conclusion

Despite the availability of published strategies supporting post-IHD dosing of several parenteral antimicrobials, clear limitations to widespread clinical application exist with many of these agents. Therefore, post-dialytic dosing of intravenous antimicrobials may be considered on a patient-by-patient basis after careful consideration of all clinical, microbiological, and logistical factors that may influence the probability of treatment success.

Declarations

Conflict of interest Christo Cimino, Yvonne Burnett, Nikunj Vyas, and Anne H. Norris have no conflicts of interest to disclose.

Funding No funding was used in the preparation of this manuscript.

Author contributions All authors contributed to the literature review and preparation of this manuscript.

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