Dosing of Aminoglycosides in Chronic Kidney Disease and End-Stage Renal Disease Patients Treated with Intermittent Hemodialysis

Barbora Agatha Halouzková, Jan Miroslav Hartinger, Vojtěch Krátký, Vladimír Tesař, Ondřej Slanař

Department of Clinical Pharmacology and Pharmacy, Institute of Pharmacology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; Department of Nephrology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

Received: November 19, 2021
Accepted: February 25, 2022
Published online: April 20, 2022

Keywords
Gentamicin · Amikacin · Tobramycin · Renal insufficiency · Dialysis membranes · Pulse dosing · Conventional dosing · Renal dialysis

Abstract
Background: The dosing of aminoglycosides (AGs) in patients with kidney disease is challenging due to their markedly prolonged half-life, which renders pulse dosing schedules unsuitable. We performed a review of the literature that describes the pharmacokinetics of, and dosing recommendations for, AG for patients with abnormal renal functions and various renal replacement therapy modalities, focusing on patients treated with intermittent hemodialysis (iHD).

Summary: During one iHD session, dialysis removes a remarkable amount of the drug regardless of the dialyzer type. In patients with severely reduced kidney functions, the distribution phase is prolonged, which needs to be taken into account when drawing samples shortly after drug administration or following an iHD session.

Key Messages: The doses recommended for the pulse dosing of patients without kidney disease leads to unacceptably high overall systemic exposure for patients with severely reduced kidney functions even with dosing intervals extended up to 48 h. Therefore, lower doses accompanied by extended dosing intervals must be applied for this patient group. The clinical evidence and current recommendations support the dosing of AG following, rather than before, HD sessions. In patients with end-stage kidney disease, the samples for TDM of AGs should not be drawn earlier than 2 h after end of the infusion and 4 h after the end of iHD session to allow full (re)distribution of the drug.

Introduction
Aminoglycosides (AGs) comprise crucial agents in the treatment of Gram-negative infections, where they exert a rapid killing effect, and the prolonged suppression of bacterial growth after plasmatic levels has declined to their subinhibitory concentrations. This “post-antibiotic effect” allows for the once-daily or “pulse” dosing of patients with normal or mildly reduced kidney functions even though AGs evince short half-lives and are virtually completely eliminated from the body during one dosing interval [1–5]. In cases of G+ infections, the
post-antibiotic effect of AGs is less pronounced; however, they act to exert synergism with beta-lactams due to the latter’s ability to facilitate the penetration of AG into cells [6]. In the 1980s, AGs were gradually replaced by newer antibiotics such as cephalosporins, carbapenems, and fluoroquinolones due to their lower toxicity.

Owing to the limited clinical use of AGs in recent decades, the prevalence of AG resistance has declined, and today, they comprise a valuable component in the treatment of multidrug-resistant severe Gram-negative infections [6–8].

The effect of AGs is concentration-dependent with respect to the application of a once-daily dosing regimen, i.e., their activity increases with higher peak concentrations [9, 10]. In this dosing strategy, their efficacy correlates with the ratio of the serum peak drug concentration to the minimal inhibitory concentration ($C_{\text{max}}$/MIC) or the ratio of the area under the concentration curve to the minimal inhibitory concentration (AUC/MIC) [11, 12].

Due to the short half-life ($T_{1/2}$), the most significant part of the exposure of the drug represented by the AUC occurs immediately following the administration of the drug, and the AUC correlates strongly with the peak concentration in patients with normal kidney functions. This renders the $C_{\text{max}}$/MIC something of a questionable target since it may only represent a surrogate marker for AUC/MIC [13].

AGs evince a rather low therapeutic index due to potential nephro- and ototoxicity. Since the uptake of AGs by the kidneys and inner ear tissue is saturable, the same amount of drug is absorbed by the cells during the drug exposure regardless of the AG concentration. Therefore, the key parameter that correlates with toxicity is probably neither the concentration nor the total exposure, but the time the sensitive tissues are exposed to the drug [14, 15].

Bacterial infections comprise the second leading cause of death for chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients; the primary overall cause of death remains cardiovascular diseases [16]. In particular, catheter-associated bacterial infections make up one of the main causes of morbidity in this patient group [17, 18], and even though AGs are used frequently in this clinical setting, the determination of the appropriate dosage regimen remains controversial, particularly due to disease-affected pharmacokinetics [19, 20]. The diligent optimization of the dosing is essential in terms of preventing AG toxicity while maintaining the maximal therapeutic effect [6, 10, 11, 21–23]. The aim of this review was to provide a summary of the evidence available on the pharmacokinetics and dosing strategies of AGs in patients with abnormal kidney functions, with particular reference to patients treated with intermittent hemodialysis (iHD).

**AG Dosing Strategies**

Generally, two dosing strategies have been developed for AGs. The pulse dosing strategy aims at obtaining peak levels of 8–10 times above the MIC and allows the drug to be eliminated completely during one dosing interval before the administration of the next dose. The second, so-called conventional dosing strategy is aimed at attaining lower peaks and does not allow for the drug to be completely eliminated before the administration of the next dose (see Table 1 for conventional dosing target levels). Even though the pulse dosing strategy is popular due to the associated low time and personnel requirements, the preferability of this dosing approach remains a matter of debate [24–26].

Two meta-analyses published by Barza et al. [25] and Ali and Goetz [24] are of particular interest in this respect. Both analyses concluded that single daily pulse dosing and conventional multiple daily dosing regimens are comparable with respect to both efficacy and toxicity. Barza et al. [25] warns that patients with febrile neutropenia (which may reduce the post-antibiotic effect) and abnormal kidney functions and pediatric patients may not benefit from the pulse dosing approach, concerning with which Ali and Goetz [24] is in agreement. However, they do not deny that the single daily dosing regimen exerts a beneficial effect on reducing the accumulation of AG in the kidneys. The meta-analysis conducted by Ali and Goetz [24] concludes that although the better overall clinical efficacy of pulse dosing was evident for an analyzed group of patients (+3.06%, 95% CI: 0.17–5.95%), there were no significant differences in terms of the clinical and microbiological response rates when studies that included adjunctive antibiotic therapy were excluded. However, it should be noted that only 3 studies that considered patients on AG monotherapy were included in the meta-analysis. Therefore, no data are currently available that convincingly indicate the superiority of either of the dosing strategies for patients on AG monotherapy, which is a common therapeutic regimen particularly with respect to urinary tract infections (UTIs). According to Ali’s meta-analysis, kidney, auditory, and vestibular toxicity incidence rates did not differ between the two regimens. Interestingly, according to an extensive Cochrane meta-analysis on the possible synergy of AGs with beta-
lactams in the treatment of sepsis, the most extensive increase in nephrotoxicity when AGs were added to beta-lactams was observed for the once-daily rather than the twice- and three-times-daily regimens [26]. Thus, these studies demonstrate that the general condition of the patient, the indication, and the combination of antibiotics must be considered carefully when selecting a tailored dosing schedule [24, 25].

**AG Pharmacokinetics and Dosing in Patients with Normal Kidney Functions and Mild-To-Moderately Reduced Kidney Functions**

AGs comprise hydrophilic compounds with a small volume of distribution that are eliminated almost entirely by glomerular filtration. Approximately 5% of the filtered drug is reabsorbed by proximal renal tubules [27, 28]. Their clearance (CL) is directly proportional to the glomerular filtration rate (GFR) [23], and for patients with normal kidney functions, the elimination T 1/2 is 2–4 h [29].

The aforementioned pharmacokinetic and pharmacodynamic properties determine the ratio for the AG once-daily pulse dosing strategy for patients with normal or mild-to-moderately reduced kidney functions. The aim of this dosing strategy is to achieve a peak level of in excess of 8–10 times the MIC and to allow for the complete elimination of the drug before the administration of the subsequent dose. If deemed necessary, the dosing interval can be prolonged to up to 48 h according to the recorded plasmatic levels so as to allow for this washout period for patients with reduced kidney functions [14, 15]. Therapeutic drug monitoring (TDM) should always be performed when determining individual dosing strategies, and nomograms (if available) can be used to accurately estimate the dosing interval [23]. Nevertheless, with respect to patients with more severely reduced kidney functions, the reduced degree of elimination capacity and the prolonged T 1/2 would result in a dosing interval of over 48 h. However, the significantly higher drug exposure over a prolonged period without a washout period would render such a dosing schedule questionable. Therefore, the most recently published clinical recommendations and articles recommend the conventional dosing regimen for this group of patients [30, 31].

**AG Pharmacokinetics and the Dosing of Patients with Severely Reduced Kidney Functions and Receiving Renal Replacement Therapy**

In patients with severely reduced kidney functions, T 1/2 is significantly prolonged, and with concern to ESRD patients treated via iHD, the T 1/2 is as long as 2–3 days during the inter-dialytic period with HD providing the only significant CL mechanism. Due to these profound PK changes, target peak plasmatic levels of 8 times higher than the MIC would lead to an unacceptably long elimination phase, as well as extreme drug exposure without the occurrence of a washout period [30–32], unless the patient was being treated with CRRT [33–35]. Therefore, AG target plasmatic levels used for pulse dosing strategy are unsuitable for this group of patients, thus necessitating the application of the conventional dosing approach with a lower target C max and a higher C troughs [14]. The target levels during conventional dosing depend on the severity of infection; the C max must exceed the MIC, but

### Table 1. Target levels for the conventional dosing of AGs

| Antibiotic         | Indication                        | C max (mg/L) | C trough (mg/L) |
|--------------------|-----------------------------------|--------------|-----------------|
| Amikacin           | Life-threatening infections*       | 25–30        | <4–8            |
|                    | Serious infections†               | 20–25        |                 |
|                    | UTIs                              | 15–20        |                 |
| Gentamicin/tobramycin | Life-threatening infections*   | 8–10         | <1–2            |
|                    | Serious infections†               | 6–8          |                 |
|                    | UTIs                              | 4–6          |                 |

The values are based on commonly used data taken from clinical guidelines (i.e., not fully validated EBM information) [14, 72]. * Examples of life-threatening infections: sepsis, neutropenia, burns, pneumonia, non-urinary infections due to pseudomonas, bone and joint infections. † Examples of serious infections: pelvic inflammatory disease, pyelonephritis, peritonitis, soft-tissue infections.
Aminoglycoside Dosing in CKD and ESRD

Kidney Blood Press Res 2022;47:448–458
DOI: 10.1159/000523892

not to 8–10 times, and the trough levels may be measurable (see Table 1). This dosing strategy, if applied to patients with preserved kidney functions, would lead to twice- or three-times-daily dosing. Nevertheless, with respect to CKD and ESRD patients, the dosing interval has to be prolonged even for conventional dosing so as to attain the desired target trough concentrations [14]. Therefore, the dose must be lowered for patients with severe renal insufficiency and the dosing interval prolonged and individualized according to the TDM.

The amount of the drug removed by one HD session depends on the type of dialysis membrane, the blood and dialysate flow rates, the length of the dialysis session, and other factors [36–38]. Moreover, the effectivity of the dialysis removal of AG may be negatively influenced by potential technical issues such as recirculation due to fistula stenosis [39] or clinical complications such as hemodynamic instability requiring the earlier than planned termination of the HD session [40]. This occasionally leads to variations in the extent of the drug removed during HD sessions. At least with respect to gentamicin, the dialysis CL correlates with the creatinine CL, whereas the dialysis setting is usually adjusted to the urea CL, thus providing a further reason for variability in the amount of gentamicin eliminated [37]. The Mayo Clinic Antimicrobial Therapy Quick Guide recommends the assumption that one HD session removes 50% of the amount of the drug in the body [41]. The results of studies that measured HD efficacy in the CL of AG have commonly been influenced by various methodological issues, as summarized in Table 2.

With regard to the AG distribution phase in CKD patients, the Mayo Clinic Antimicrobial Therapy Quick Guide recommends waiting for 2 h following infusion so to allow for the completion of the distribution phase [41]. It is worth noting that some published clinical studies have failed to take into account the longer AG distribution period in ESRD patients when taking peak level samples and may therefore have recorded inappropriately high peak levels [34]. The same applies to sampling after an HD session since the drug is redistributed from the tissues into the bloodstream for a certain period following HD; in this case, false low concentrations are recorded if samples are taken prematurely [4, 37, 42]. This so-called rebound phenomenon is also variable. With respect to gentamicin, Sowinski et al. [37] described a median plasmatic concentration...
The extent of rebound concentrations also depends on the setting of the dialysis process, i.e., it is set at only 3.1 ± 8.8% during a slow 8-h daily home hemodialysis session [43]. It is clear that during the significantly slower extended daily dialysis process, equilibration between the tissues and the bloodstream concentrations occurs as early as during the prolonged HD session itself.

The $T_{1/2}$ of AGs in patients treated via peritoneal dialysis (PD) is prolonged to a similar extent as during the inter-dialysis period for patients treated via iHD [44, 45]. PD patients usually evince an AG elimination capacity similar to that of patients in pre-dialysis. Elimination via PD amounts to around 4.33 mL/min (for gentamicin) with additional nonrenal CL of 5.16 mL/min [46]. It is worth noting that most studies to date have described the PK of AGs in PD patients during the treatment of peritonitis, and CL via PD is even more reduced when the peritoneum is not inflamed [47, 48]. If PD patients with a systemic infection other than peritonitis are treated with i.v. AGs, the same approach should be taken to that applied to patients with CKD stage 5.

Treatment of peritonitis for PD patients represents one of the most specific cases of the AG dosing of patients with ESRD. When treating peritonitis, the AG should be diluted in the PD fluid and administered directly to the peritoneal cavity via a PD catheter. With respect to gentamicin, the currently valid 2016 International Society of Peritoneal Dialysis guidelines for peritonitis treatment recommend either the once-daily i.p. administration of 0.6 mg/kg or administration in the form of all daily exchanges (an 8 mg/L loading dose and 4 mg/L maintenance doses) [49]. Even though the doses applied in recently reported clinical studies varied, most of the studies applied the once-daily dosing approach [46, 50, 51], and only one small-scale study compared the once-daily (40 mg during a night dwell) and the continuous (10 mg four times daily) intraperitoneal administration of gentamicin and determined no difference in terms of the efficacy of the treatment [51].

PK studies of i.p. gentamicin dosing for patients without peritonitis provide inaccurate estimations since the absorbed amount that reaches the systemic circulation is increased in the presence of peritoneal inflammation [52]. A further factor that influences gentamicin absorption comprises the dwell length; 50% of the administered gentamicin dose is absorbed during a 3-h dwell and 75% during a 6-h dwell during the treatment of peritonitis [46]. This factor plays an important role concerning especially automated PD programs involving series of several short exchanges. Even though this suggests that short dwells are theoretically ideal in terms of the administration of AG since they allow for attaining high local concentrations without excessive systemic absorption and toxicity, this approach has not been validated, and the ISPD continues to recommend a minimum 6-h dwell for the intraperitoneal administration of all antibiotics [49]. When gentamicin is absorbed from the peritoneal cavity during once-daily dosing, it forms a “plasmatic reservoir” and penetrates back to the peritoneal cavity during subsequent exchanges so that low concentrations of gentamicin are present in the PD fluid at the end of each dwell period until the drug is fully eliminated [46, 50].

While the pulse dosing strategy can be used during continuous renal replacement therapy (CRRT), it must be applied over prolonged dosing intervals [33, 34]. Boyer et al. [34] demonstrated that most patients should not be re-dosed sooner than after 30 h, which suggests that the 36-h dosing interval is ideal for clinical praxis. Nevertheless, some patients in their study evinced shorter elimination half-lives that allowed for re-dosing as soon as after 24 h, which stresses the importance of TDM and the individualization of the dosing regimen in this particular clinical setting [34]. Roger et al. [33] studied the influence of various CRRT modalities on the AG PK and determined no significant difference in the AG CL between continuous veno-venous hemofiltration and continuous veno-venous hemodiafiltration, even though the CL value of the latter technique was numerically lower (1.8 ± 1.3 L/h and 1.3 ± 1.0 L/h, respectively). Since patients treated via CRRT often have an AKI, possibly accompanied by the repair of kidney functions, the determination of the most suitable dosing interval is particularly important in terms of obtaining a washout period that reduces the risk of nephrotoxicity. Nevertheless, since patients in intensive care units who are on CRRT therapy may be fluid-overloaded, the administration of relatively high doses (25 mg/kg of amikacin) may be required so as to attain an adequate $C_{\text{max}}$ in the pulse dosing setting [33].

Timing of Administration of AG in Patients Treated with iHD with Respect to the HD Session

The dosing of AG in ESRD patients treated via chronic iHD involves a number of uncertainties in terms of, e.g., how to plan the administration of AG with respect to the planned HD session, what to do when the HD session has to be interrupted earlier than planned due to compli-
Aminoglycoside Dosing in CKD and ESRD

An FDA-approved (currently the only officially recommended) scheme advises post-dialysis dosing according to which a half of the usual dose is administered in the final hour of hemodialysis, without the administration of the drug during the inter-dialysis period. This dosage regimen was introduced before the PK, and pharmacodynamic properties of AGs were known in detail. The CL of AGs during dialysis resembles the renal CL of patients with normal renal functions [53], and in a similar way to other antibiotics [54], a part of the administered dose is eliminated before it is distributed into the tissues when administered during dialysis. The elimination of AG is very slow during the inter-dialysis period and varies considerably. If one considers standard triweekly 4-h-long HD sessions, it would not be possible for most ESRD patients to eliminate the whole of the administered dose and attain an unmeasurable trough concentration before the initiation of the subsequent dialysis session, even if a reduced dose was administered following HD. Therefore, the same target levels as applied in the conventional dosing regimen are usually applied for dialysis patients; nevertheless, the AG exposure of patients will inevitably be higher than for those with normal kidney functioning [6, 55].

The disadvantage of this dosage regimen concerns the potential development of a reversible adaptive resistance period, which occurs mainly, but not exclusively, in *Pseudomonas aeruginosa* several hours following the initial exposure of the bacteria to the AG. The AG absorption into the bacterial cells during this period is reduced, which may act to hamper the efficacy of the treatment [6]. Since adaptive resistance lasts only several hours following the disappearance of the drug from the bacterial environment, in the case of pulse dosing, it fades away during the washout period [56]. Nevertheless, adaptive resistance is usually expressed as a multiple of the drug’s T$_{1/2}$, an indication that would result in meaninglessly long dosing intervals for ESRD patients [57, 58]. On the other hand, some authors have proved that the exposure of sub-MIC concentrations is able to increase the duration of the post-antibiotic effect [59].

A further dosing strategy, which has been significantly less substantiated by the clinical data to date, concerns so-called pre-dialysis dosing, according to which the whole of the AG dose is administered prior to dialysis [11, 60–62]. In silico semi-mechanistic simulation models have demonstrated that this regimen may be as effective as post-dialysis dosing and less toxic. Pre-dialysis administration allows for targeting toward a higher C$_{\text{max}}$ due to the effective CL of the drug during subsequent hemodialysis, which imitates the pulse dosing regimen in patients with normal kidney functions. Thus, the patient would not be exposed to high levels of AGs over long periods of time even though a high C$_{\text{max}}$ is attained via which the bactericidal activity may be enhanced [11, 61].

Although this hypothesis appears promising, Eyler [57] and others have suggested that the lack of clinical data precludes the recommendation of pre-dialysis dosing for routine praxis and that practical difficulties may arise such as increased AG exposure when the patient is unable to complete the whole of the planned dialysis session. Therefore, pre-dialysis dosing must still be regarded as experimental [57] since all the studies concerned, with the exception of 1 case report on the pre-dialysis administration of gentamicin, comprise single-dose pharmacokinetic studies in uninfected patients or in silico simulations [10, 11, 19, 53, 60–62].

Hiraki et al. [53] described the application of this experimental therapy for a patient with MRSA infectious endocarditis. The patient (an 87-year-old woman) received hemodialysis for 3 h 3 times weekly. Gentamicin was administered prior to the hemodialysis via a 30-min intravenous infusion. The doses varied between 10 mg and 120 mg, and the dialysis was initiated 90 min following the completion of the infusion. Since the therapy was targeted at the G+ synergy, the target peak levels were set at lower values, which meant that the effect of the gentamicin itself could not be evaluated. Very low doses (even 10 mg) had to be administered so as to attain levels of below 2 mg/L before the next dose could be administered, and the gentamicin concentration remained virtually the same during the whole of the inter-dialysis period due to the very low CL. This resulted in low overall exposure (AUC), thus rendering this dosing approach somewhat questionable [63].

Kamel Mohamed et al. [10] performed a single-dose study involving 5 patients receiving HD in a 3-times-weekly schedule aimed at determining the PK parameters of tobramycin administered at the beginning or at the end of a dialysis session. The patients received 1–1.5 mg/kg of tobramycin either during the first or the final 30 min of hemodialysis. Due to the administration of the same dose, the two dosing schemes resulted in comparable peak tobramycin levels; however, dosing in the first 30 min of the HD session led to significantly lower overall exposure, with a 90% reduction in the AUC and a concentration level prior to the subsequent HD session of 0.16 ± 0.09 mg/L. The authors assumed that the toxicity, but not the efficacy, was closely related to the AUC, thus indicating that the efficacy of the treatment was preserved with a reduction in the toxicity [10]. It is however uncertain wheth-
er such a large reduction in the AUC would not result in the higher frequency of treatment failures, especially since a number of studies have proved that the AUC parameter best correlates with the treatment efficacy [11–13].

Teigen et al. [19] performed a NONMEM population PK study based on levels measured in 46 HD patients. The authors suggested, based on the model, that gentamicin should be dosed during the initial dialysis phase aimed at reducing waiting times; they proposed 300 mg as the first dose, 240 mg as the second dose, and 220 mg as the third dose for patients treated triweekly with HD. This dosing regimen led to the achievement of predefined peaks over 8 mg/L and a sufficiently low AUC in a substantial number of patients in the study, and the authors are inclined toward the pre-dialysis dosing of AGs [19].

On the other hand, Zhuang et al. [55] mention that the benefits of pre-dialysis dosing are based mainly on the assumption that the $C_{\text{max}}$/MIC comprises the treatment target. Based on their in vitro study of the efficacy of gentamicin concerning MSSA, MRSA, and *Pseudomonas aeruginosa*, they concluded that the post-dialysis model should be the preferred option. Indeed, the pre-dialysis dosing PK profile revealed that sufficient gentamicin concentrations were maintained for only very short time periods and decreased rapidly to low post-hemodialysis values after 4 h. Thus, the efficacy of the temporary high concentration resulting from pre-dialysis dosing is dubious and may not be able to provide for a sustained bactericidal effect for sufficiently long time periods [55]. This observation is supported especially by the fact that the post-antibiotic effect is not maintained for the whole of the inter-dialysis period (usually 2 or 3 days) [55, 59].

Zhuang et al. [55] further support the hypothesis that the $C_{\text{max}}$/MIC is not the only possible PK target. They concluded that the slow elimination of gentamicin in patients with ESRD could allow for the complete elimination of bacteria within 24 h following the administration of a single 1.7 mg/kg dose of gentamicin, although such a regimen would not attain a $C_{\text{max}}$/MIC ratio of eight. This process occurs since the gentamicin concentration in ESRD patients decreases only slightly over time during the inter-dialysis period; thus, the bactericidal efficacy of the drug is maintained for a longer period of time [55]. Moreover a further clinical study demonstrated that if the ratio of the pre-dialysis (i.e., $C_{\text{trough}}$) levels of gentamicin or tobramycin to the MIC was >6 in HD patients with a G– rod bloodstream infection treated via post-dialysis dosing, the 30-day all-cause mortality rate was lower than for patients with lower $C_{\text{trough}}$/MIC ratios [63]. This evidence appears to counter the theory of adaptive resistance, which may require washout period for long enough time. These findings most probably mirror the fact that adaptive resistance has, to date, been best described with respect to *Pseudomonas aeruginosa* [58], whereas it may play a less important role for other bacterial strains.

With regard to toxicity, Decker et al. [42] conducted a study on 6 uninfected anuric patients receiving short daily hemodialysis sessions on a regular basis six times per week. The mean length of dialysis was 2.5 h, the patients were administered one gentamicin dose following HD, and a series of blood samples were drawn over 4 days. Based on population PK model simulations, the authors concluded that the daily AG dosing of short daily hemodialysis patients allows for persistently high trough concentrations that are able to induce AG toxicity. Dosing every second day would better allow for the sufficient CL of gentamicin before the administration of the subsequent dose [42].

The tree-times-weekly application of iHD is considered the standard and most predictable approach to therapy, whereas the situation is more complicated in cases where the patient is dialyzed less frequently, i.e., once or twice per week. No clear recommendations have been defined for such patients; the less frequent dialysis sessions of whom has a number of reasons, e.g., residual kidney functions or the intentional under-dialyzing of patients in palliative care aimed at improving their quality of life by reducing the number of visits to the dialysis center. It would appear advisable that such patients should be dosed in a similar way as other iHD patients with doses recommended for conventional dosing after every HD session and the measurement of at least two plasmatic levels during the inter-dialysis period so as to determine whether the patient needs an additional dose between the two dialysis sessions. The drug $T_{1/2}$ can be calculated from any two levels drawn within the inter-dialysis period (e.g., in the mornings of 2 subsequent days) according to the following formulas: $Ke = \frac{\ln(C1) - \ln(C2)}{\Delta t}$, where $Ke$ is the elimination constant, $C1$ and $C2$ are the drawn levels during the inter-dialysis period so as to determine the interval between the levels, and $T_{1/2} = \frac{\ln(2)}{Ke}$. If the $T_{1/2}$ is known, the approximate time required to attain the target concentrations can be calculated and the dosing interval adjusted accordingly.

### Current Dosing Schemes for Patients with Abnormal Kidney Functions

As previously mentioned, the determination of the optimal dosing regimen for patients with CKD is demanding due to a number of variables such as the severity and
Aminoglycoside Dosing in CKD and ESRD

Kidney Blood Press Res 2022;47:448–458
DOI: 10.1159/000523892

Site of infection, differences in the volume of distribution, and the residual GFR. In the case of acute kidney injury, the dynamics of the deterioration/repair of kidney function also comprises an important factor when planning dosing schedules. In the case of ESRD treated via chronic iHD, the efficacy of the dialysis may also vary according to the type of dialysis membrane, the length of the dialysis session, the dialysate and blood flows, and other technical and clinical issues [37, 64], although in the case of AGs, the role of the type of dialysis membrane is less important than for larger molecules [19].

As previously stated, AGs are administered preferably in accordance with the pulse dosing strategy whenever possible, i.e., for patients with normal and mild-to-moderately reduced renal functions. This dosing schedule has been observed to be broadly as effective as the conventional dosing approach, and various meta-analyses have demonstrated that the risks are essentially balanced between these two dosing regimens [6, 24, 25, 57, 65]. In order to avoid AG toxicity in patients with severely reduced kidney functions, the dose should be reduced and the dosing interval extended. While recommendations vary regarding the critical GFR value that is low enough for switching the patient from pulse to conventional dosing, the value usually lies between 20 and 40 mL/min [30, 31]. Moreover, due to the uncertainty inherent in the estimation of the GFR value, TDM should always be performed in cases where AGs are administered to CKD patients, and the dose should be adjusted according to the recorded levels. This approach also facilitates the switch

Table 3. Dosing scheme for gentamicin and tobramycin for the treatment of Gram-negative infections in patients with ESRD

|                  | IHD                          | AKI not on CRRT | CRRT [34]          |
|------------------|------------------------------|-----------------|---------------------|
| Initial dosing   | 2 mg/kg after HD             | 2 mg/kg         | 5–10 mg/kg          |
| Monitoring peaks | After 2nd dose*              | After 2nd dose* | After 2nd dose*     |
| Monitoring troughs | Before every HD              | Re-dose when level <1 mg/L | 24 h after 1st dose (than adjust the dosing interval) |
| Target goal (peak) | Life-threatening infections: 8–10 mg/L | Serious infections: 6–8 mg/L | UTIs: 4–6 mg/L | 8× over the MIC |
| Target goal (trough) | <1–2 mg/L                      | <2 mg/L         |                      |

The values are based on commonly used data taken from clinical guidelines (i.e., not fully validated EBM information) [14, 30, 34, 71, 72, 74]. HD, hemodialysis; AKI, acute kidney injury; CRRT, continuous renal replacement therapy; MIC, minimal inhibitory concentration. * Due to the longer distribution phase, it is advisable to take the peak levels 2 h after the end of infusion [41].

Table 4. Dosing scheme for amikacin for the treatment of Gram-negative infections

|                  | IHD                          | AKI not on CRRT | CRRT [33, 34]       |
|------------------|------------------------------|-----------------|----------------------|
| Initial dosing   | 5–7.5 mg/kg after HD         | 5 mg/kg         | 15–30 mg/kg Q24–48 h |
| Monitoring peaks | After 2nd dose*              | After 2nd dose* | After 2nd dose*      |
| Monitoring troughs | Before every HD              | Re-dose when level <1 mg/L | 24 h after 1st dose (than adjust the dosing interval) |
| Target peak levels | Life-threatening infections: 25–30 mg/L | Serious infections: 20–25 mg/L | UTIs: 15–20 mg/L | 8× over the MIC |
| Target trough levels | <4–8 mg/L                     | <5 mg/L         |                      |

The values are based on commonly used data taken from clinical guidelines (i.e., not fully validated EBM information) [14, 33, 34, 72]. HD, hemodialysis; AKI, acute kidney injury; CRRT, continuous renal replacement therapy; MIC, minimal inhibitory concentration. * Due to the longer distribution phase, it is advisable to take the peak levels 2 h after the end of the infusion [41].
between the dosing regimens and the individualization of the dose in cases of unstable kidney functions.

AGs are administered today as a monotherapy only in the case of Gram-negative UTIs. Amikacin is administered primarily as a reserve antibiotic for gentamicin and tobramycin-resistant infections. In the case of Gram-positive and most Gram-negative infections other than UTIs, AGs are usually administered in combination with cell wall-targeting agents such as beta-lactam antibiotics or vancomycin rather than as a monotherapy. They are used synergistically to treat endovascular infections caused by Enterococcus spp., Staphylococcus aureus, Streptococcus spp., and Listeria [14, 30, 66–76]. An overview of the dosing regimens of AGs for patients with abnormal kidney functions is provided in Tables 3–5. Table 5 (gentamicin dosing for Gram-positive synergy) considers gentamicin only since cited recommendations do not provide any information on other AGs. Due to similarities in terms of the PK and pharmacodynamics with gentamicin, the target levels for tobramycin should be the same as for gentamicin. No clear recommendation is provided in the literature for amikacin; therefore, conventional dosing targets (non-CRRT dosing in Table 4) should be applied when Gram-positive synergy is required.

When calculating the dose of AGs for obese patients, it must be considered that these hydrophilic antibiotics are distributed to a lesser extent to adipose tissue; therefore, the total body weight (TBW) should not be used for the calculation of the dose. This also applies to obese patients with reduced kidney functions. Most authors recommend the use of the adjusted body weight (ABW), calculated as ABW = IBW + 0.4(TBW – IBW), where IBW stands for the ideal body weight for a patient with a given weight [2].

**Conclusion**

The aim of this paper was to provide a review of the PK and the evidence available for current AG dosing recommendations for patients with abnormal kidney functions, especially for ESRD patients treated via iHD. AGs evince a T1/2 of approximately 2–3 days in these patients, and during HD sessions, approximately 50% of the drug is removed from the body [4, 36]. Samples for the determination of AG levels should be taken no sooner than 2 h following the completion of the infusion [41] or 4 h after the end of an HD session [4, 37] in order to prevent the determination of false high or false low levels due to the drawing of samples during the (re)distribution phase. Reduced post-dialysis dosing is currently the only approved dosing regimen for patients treated via iHD. While several experimental publications have discussed pre-dialysis administration [10, 11, 19, 53, 60–62], this concept is not yet supported by a sufficient amount of clinical evidence [55].

Furthermore, it is necessary to expand current knowledge of the use of AG antibiotics as a monotherapy (e.g., in UTIs) for patients with impaired renal functioning, especially since high serum or plasma levels need not necessarily correlate with high urine levels when the GFR is reduced. Moreover, pulse dosing has not been demonstrated to be more effective than conventional dosing when AG was used as a single antimicrobial agent [24]. With the increasing incidence of microbial resistance to first-line antibiotics, the use of AGs is increasing, and since treatment using AGs can lead to significant toxicity levels, the correct determination of the dosing regimen is crucial.
Aminoglycoside Dosing in CKD and ESRD

Acknowledgments

We would like to thank Darren Ireland for thorough language correction of the text.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

References

1. Pesola GR, Akhavan I, Madu A, Shah NK, Carlon GC. Prediction equation estimates of creatinine clearance in the intensive care unit. Intensive Care Med. 1993;19:39–43.
2. Velissaris D, Karamouzos V, Marangos M, Piriakos C, Karamikolas M. Pharmacokinetic changes and dosing modification of aminoglycosides in critically ill obese patients: a literature review. J Clin Med. 2014;6:227–33.
3. Blaser J, Stone BB, Groner MC, Zinner SH. Comparative study with enoxacin and netilmicin in a pharmacodynamic model to determine importance of ratio of antibiotic peak concentration to MIC for bactericidal activity and emergence of resistance. Antimicrob Agents Chemother. 1987;31:1054–60.
4. Dunfee TP, Anandan JV. Characterization of gentamicin pharmacokinetics in patients hemodialyzed with high-flux polysulfone membranes. Am J Kidney Dis. 1999;34:222–7.
5. Florczykowski B, Storer A. Gentamicin dosing and monitoring challenges in end-stage renal disease. Adv Pharmacoepidemiol Drug Saf. 2013;2:3.
6. Hanberger H, Edlund C, Furebring M, Giske C, Melhus A, Nilsson LE, et al. Rational use of aminoglycosides: review and recommendations by the Swedish Reference Group for Antibiotics (SRGA). Scand J Infect Dis. 2013;45:161–75.
7. Drusano GL, Ambrose PG, Bhavnani SM, Bertino JS, Naftzger AN, Louk A. Back to the future: using aminoglycosides again and how to dose them optimally. Clin Infect Dis. 2007;45:753–60.
8. Krause KM, Serio AW, Kane TR, Connolly LE. Aminoglycosides: an overview. Cold Spring Harb Perspect Med. 2016;6(6):a027029.
9. Fisman DN, Kaye KM. Once-daily dosing of aminoglycoside antibiotics. Infect Dis Clin North Am. 2000;14:475–87.
10. Kamel Mohamed OH, Wahba IM, Watnick S, Earle SB, Bennett WM, Ayres JW, et al. Administration of tobramycin in the beginning of the hemodialysis session: a novel intradialytic dosing regimen. Clin J Am Soc Nephrol. 2007;2:694–9.
11. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis. 1998;26:1–2; quiz 11–2.
12. Begg EF, Barclay ML, Kirkpatrick CM. The therapeutic monitoring of antimicrobial agents. Br J Clin Pharmacol. 2001;52(Suppl 1):355–435.
13. Bland CM, Pai MP, Lodise TP. Reappraisal of contemporary pharmacokinetic and pharmacodynamic principles for informing aminoglycoside dosing. Pharmacotherapy. 2018;38:1229–38.
14. Mui E. Stanford health care aminoglycoside dosing guideline. 2017; 8. BCPS: 05/2012.
15. Lacy M, Nicolau D, Nightingale CH, Quintiliani R. The pharmacodynamics of aminoglycosides. Clin Infect Dis. 1998;27:23–7.
16. Collins AJ, Foley RN, Gilbertson DT, Chen SC, United States Renal Data System public health surveillance of chronic kidney disease and end-stage renal disease. Kidney Int Suppl. 2015;5(1):2–7.
17. Johnson DW, Dent H, Hawley CM, McDonald SP, Rosman JB, Brown FG, et al. Association of dialysis modality and infectious mortality in incident dialysis patients in Australia and New Zealand. Am J Kid Dis. 2009;53:290–7.
18. Polkinghorne KR, McDonald SP, Atkins RC, Kerr PG. Vascular access and all-cause mortality: a propensity score analysis. J Am Soc Nephrol. 2004;15(2):477–86.
19. Teigen MM, Duffull S, Dang L, Johnson DW. Dosing of gentamicin in patients with end-stage renal disease receiving hemodialysis. J Clin Pharmacol. 2006;46:1259–67.
20. Mac-Kay MV, de Liger JPF, Bursón JS, Carraña JH. A graphical approach to aminoglycoside dosage regimens in end-stage renal disease patients undergoing haemodialysis. Drug Invest. 1994;8:294–308.
21. Feldman L, Sherman R, Weissgarten J. N-acetylcysteine use for amelioration of aminoglycoside-induced ototoxicity in dialysis patients. Semin Dial. 2012;25(5):491–4.
22. Mingedo-Leclercq MP, Tulkens PM. Aminoglycosides: nephrotoxicity. Antimicrob Agents Chemother. 1999;43(5):1003.
23. Sima M, Hartinger J, Cikankova T, SlanaøF. Estimation of once-daily amikacin dose in critically ill adults. J Chemother. 2018 Feb;30(1):37–43.
24. Ali MZ, Goetz MB. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. Clin Infect Dis. 1997;24:796–809.
25. Barza M, Ioannidis JP, Cappelleri JC, Lau J. Single or multiple daily doses of aminoglycosides: a meta-analysis. BMJ. 1996;312:338–45.
26. Paul M, Lador A, Grozinsky-Glasberg S, Leibovici L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. Cochrane Database Syst Rev. 2014 Jan 7;2014(1):CD003344.
27. Gilbert DN. Urinary tract infections in patients with chronic renal insufficiency. Clin J Am Soc Nephrol. 2006;1:327–31.
28. Adis Medical Writers. Aminoglycoside use in critically ill patients requires careful regimen planning and drug monitoring to avoid nephrotoxicity. Drugs Ther Perspect. 2013 Sep;29(9):282–86.
29. Mathews A, Bailie GR. Clinical pharmacokinetics, toxicity and cost effectiveness analysis of aminoglycosides and aminoglycoside dosing services. J Clin Pharm Ther. 1987;12:273–91.
30. Monteforte M. Aminoglycoside dosing and monitoring guidelines for adult patients at stony brook university hospital. 2015;14.
31. Stankowicz MS, Ibrahím J, Brown DL. Once-daily aminoglycoside dosing: an update on current literature. Am J Health Syst Pharm. 2015;72:1357–64.
32 Vogelman B, Gudmundsson S, Leggett J, Tumridge J, Ebert S, Craig WA. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. J Infect Dis, 1988;158:831–47.
33 Roger C, Wallis SC, Muller L, Saissi G, Lipman J, Lefrant JY, et al. Influence of renal replacement modalities on amikacin population pharmacokinetics in critically ill patients on continuous renal replacement therapy. Antimicrob Agents Chemother. 2016;60(8): 4903–11.
34 Boyer A, Timsit JF, Klouche K, Canet E, Phan TN, Bohé J, et al. Aminoglycosides in critically ill septic patients with acute kidney injury receiving continuous renal replacement therapy: a multicenter, observational study. Clin Ther. 2021;43(6):1116–24.
35 Brasseur A, Hites M, Roisin S, Cotton F, Vincent JL, De Backer D, et al. A high-dose aminoglycoside regimen combined with renal replacement therapy for the treatment of MDR pathogens: a proof-of-concept study. J Antimicrob Chemother. 2016;71(5):1386–94.
36 Dager WE, King JH. Aminoglycosides in intermittent hemodialysis: pharmacokinetics with individual dosing. Ann Pharmacother. 2006;40(9):1–14.
37 Sowinski KM, Magner SJ, Luckiri A, Scott MK, Hamburger RJ, Mueller BA, et al. Influence of hemodialysis on gentamicin pharmacokinetics, removal during hemodialysis, and recommended dosing. Clin J Am Soc Nephrol. 2008;3(2):355–61.
38 Vercaigne LM, Ariano RE, Zacharias JM. Bayesian pharmacokinetics of gentamicin in a haemodialysis population. Clin Pharmacokinet. 2004;43:205–10.
39 Zerbaa A, Beladi Mousavi SS, Beladi Mousavi M. A review article: access recirculation among end stage renal disease patients undergoing maintenance hemodialysis. Nephrol Dial Transplant. 2013;5:728–32.
40 McGuire S, Horton EJ, Renshaw D, Jimenez MJM, et al. Short-course adjunctive gentamicin in patients with peritonitis (GIPD study). Clin J Am Soc Nephrol. 2012;7(8):1249–56.
41 Wilson JW, Estes LL. Mayo clinic antimicrobial therapy quick guide. 2nd ed. Oxford university press; 2012. p. 390.
42 Decker BS, Mohamed AN, Chambers M, Kraus MA, Moe SM, Sowinski KM. Gentamicin pharmacokinetics and pharmacodynamics during short-daily hemodialysis. Am J Kidney Dis. 2012;60:144–50.
43 Manley HJ, Baillie GR, McClaran ML, Bender WL. Gentamicin pharmacokinetics during slow daily home hemodialysis. Kidney Int. 2003;63:1072–8.
44 Low CL, Baillie GR, Evans A, Eisele G, Venezia RA. Pharmacokinetics of once-daily IP gentamicin in CAPD patients. Perit Dial Int. 1996;16(4):759–84.
45 Regeur L, Colding H, Jensen H, Kampmann JP. Pharmacokinetics of amikacin during hemodialysis and peritoneal dialysis. Antimicrob Agents Chemother. 1977;11(2):214–8.
46 Varghese JM, Roberts JA, Wallis SC, Boots RJ, Healy H, Fasset RG, et al. Pharmacokinetics of intraperitoneal gentamicin in peritoneal dialysis patients with peritonitis (GIPD study). Clin J Am Soc Nephrol. 2012;7(8):1249–56.
47 Somani P, Shapiro RS, Stockard H, Higgins JT. Unidirectional absorption of gentamicin from the peritoneum during continuous ambulatory peritoneal dialysis. Clin Pharmacol Ther. 1982;32(1):113–21.
48 Richey GD, Schleupner CJ. Peritoneal fluid concentrations of gentamicin in patients with spontaneous bacterial peritonitis. Antimicrob Agents Chemother. 1981;19:312–5.
49 Li PK, Szeto CC, Piraino B, de Arteaga J, Fan S, Figueredo AE, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. Perit Dial Int. 2016;36(5):481–508.
50 Tosukhowong T, Eiam-Ong S, Thamutok K, Wittayalertpanya S, Na Ayudhya DP. Pharmacokinetics of intraperitoneal ceftazolin and gentamicin in empiric therapy of peritonitis in continuous ambulatory peritoneal dialysis patients. Perit Dial Int. 2001;21(6):587–94.
51 Lye WC, Wong PL, van der Straaten JC, Leong SO, Lee EF. A prospective randomized comparison of single versus multidose gentamicin in the treatment of CAPD peritonitis. Adv Perit Dial. 1995;11:179–81.
52 de Paep M, Lameire N, Belpaire F, Bogart M. Peritoneal pharmacokinetics of gentamicin in man. Clin Nephrol. 1983;19:107–9.
53 Hiraki Y, Hiraïke M, Nagano M, Ozono Y, Manabe K, Misumi N, et al. Pharmacokinetics and administration method of gentamicin in a patient on haemodialysis. Scand J Infect Dis. 2012;44:630–4.
54 Hartinger JM, Šima M, Hronová K, Halouzková BA, Szonowska B, Polakovic V, et al. Vancomycin pharmacokinetics in patients treated with intermittent haemodialysis based on therapeutic drug monitoring. J Chemother. 2021;34:1–8.
55 Zhuang L, He Y, Xia H, Liu Y, Sy SK, Derendorf H. Gentamicin dosing strategy in patients with end-stage renal disease receiving haemodialysis: evaluation using a semi-mechanistic pharmacokinetic/pharmacodynamic model. J Antimicrob Chemother. 2016;71:1012–21.
56 Karlowsky JA, Zelenitsky SA, Zhanel GG. Aminoglycoside resistance. Pharmacotherapy, 1997;17:549–55.
57 Eyer R. We give aminoglycoside antibiotics at the end of hemodialysis. Semin Dial. 2016;29(12):746–54.
58 Barclay ML, Begg EJ. Aminoglycoside adaptive resistance: importance for effective dosing regimens. Drugs. 2001;61:713–21.
59 Lowdin E, Odenholm I, Cars O. In vitro studies of pharmacodynamic properties of vancomycin against Staphylococcus aureus and Staphylococcus epidermidis. Antimicrob Agents Chemother. 1998;42:2739–44.
60 Brater DC. Drug dosing in patients with impaired renal function. Clin Pharmacol Ther. 2009;86:843–5.
61 Deng L, Duffull S. Development of a semi-mechanistic model to describe the pharmacokinetics of gentamicin in patients receiving haemodialysis. J Clin Pharmacol. 2006;46:662–73.
62 Heintz BH, Matzke GR, Dager WE. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. Pharmacotherapy, 2009;29:562–77.
63 Heintz BH, Thompson GR 3rd, Dager WE. Clinical experience with aminoglycosides in dialysis-dependent patients: risk factors for mortality and reassessment of current dosing practices. Ann Pharmacother. 2011;45:1338–45.
64 Decker BS, Mueller BA, Sowinski KM. Drug dosing considerations in alternative hemodialysis. Adv Chronic Kidney Dis. 2007;14:18–26.
65 Matsuo H, Hayashi J, Ono K, Andoh K, Andoh Y, Sano Y, et al. Administration of aminoglycosides to hemodialysis patients immediately before dialysis: a new dosing modality. Antimicrob Agents Chemother. 1997;41:2597–601.
66 Watanakunakorn C, Bakie C. Synergism of vancomycin-gentamicin and vancomycin-streptomycin against enterococci. Antimicrob Agents Chemother. 1973;4:120–4.
67 Lee J, Yoon S, Shin D, Han H, An H, Lee J, et al. Predictive performance of gentamicin dosing nomograms. Drug Des Devel Ther. 2014;8:1097–106.
68 Veinstein A, Venisse N, Badin J, Pinsard M, Robert R, Dupuis A. Gentamicin in hemiolyzed critical care patients: early dialysis after administration of a high dose should be considered. Antimicrob Agents Chemother. 2013;57:977–82.
69 Picard W, Bazin F, Clouzeau B, Bui HN, Soulat M, Guilhon E, et al. Propensity-based study of aminoglycoside nephrotoxicity in patients with severe sepsis or septic shock. Antimicrob Agents Chemother. 2014;58:746–74.
70 Ong DSY, Frencken JF, Klein Klouwenberg PMC, Juermanns N, van der Poll T, Bonten MMJ, et al. Short-course adjunctive gentamicin as empirical therapy in patients with severe sepsis and septic shock: a prospective observational cohort study. Clin Infect Dis. 2017;64:1731–6.
71 Davis GA. Clinical pharmacokinetics service and anticoagulation guidelines. 2017;128.
72 Committee NPHAA-IS. Aminoglycosides dosing and monitoring guidelines. 2017;18.
73 State of Queensland (Queensland Health). Aminoglycoside dosing in adults. 2018;29.
74 Clarkson A. Gentamicin prescribing guideline for adult patients. 2017 Nov. SCPAaIC.
75 Liverpool Hospital. Drug guideline: gentamicin. 2019 Feb 7.
76 Stony Brook Medicine. SBUH aminoglycoside dosing protocol. 2017 Oct 7.