



Pharmacodynamics and dosing of aminoglycosides

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Despite their toxicity, aminoglycosides continue to play a pivotal role in the management of serious infections. Indeed, their toxicity has led to comparatively restrained usage, and as a result resistance, although widespread, has usually remained at low levels for many pathogens. Aminoglycosides are valuable drugs for empirical treatment of gram-negative sepsis, for the management of serious *Pseudomonas aeruginosa* infections, and as supportive agents in the definitive treatment of endocarditis.

The discovery and analysis of their pharmacodynamic (PD) properties has led to a significant shift in dosing practices in the last decade. Extended-interval dosing has now become the standard in most clinical settings, based on the theory and clinical evidence of efficacy and toxicity. This article examines the PD properties of aminoglycosides *in vitro* and *in vivo*, and shows how this has been applied to dosing strategies. Inevitably, changes in dosing have required changes in monitoring practice. A critique of these changes is also included.

Pharmacokinetic properties

Aminoglycosides are very poorly absorbed when administered orally, and must be given parenterally for the treatment of systemic infections. The agents demonstrate remarkably similar kinetics, with similar elimination half-lives of generally 2 to 3 hours in normal subjects, and similar volumes of distribution (Table 1). When given by intravenous injection they demonstrate three-compartment first-order elimination, although two- and one-compartment models fit the time-concentration profiles reasonably well [1]. For gentamicin at least, the higher doses used with once-daily dosing

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Table 1
Pharmacokinetics of aminoglycosides used systematically

Agent	Volume of distribution	Elimination half-life	
		Normal	CrCl < 10 mL/min
Amikacin	0.3	2.5–3	30
Arbekacin		2.3	
Dibekacin	0.16	2.1	5
Gentamicin	0.22–0.3	2.5–3	30–50
Isepamicin	0.11	2.3	47
Kanamycin	0.27	2–5	72–96
Netilmycin	0.26	2–2.3	40
Sisomicin	0.22	2–3	35–80
Streptomycin		2.5	100
Tobramycin	0.33	2.5–3	56

Data from references [6,138,139,141,143,146].

demonstrate pharmacokinetic (PK) differences to the lower traditional doses, including a longer distribution half-life and reduced clearance [2]. The distribution phase becomes prominent with the high dose, and can lead to distortions in the application of peak levels to monitoring.

Volumes of distribution are low, consistent with the distribution of drug into extracellular water. Penetration to several body fluids including synovial fluid, peritoneal, ascitic, and pleural fluids is good, but poor into the central nervous system and the vitreous. Aminoglycosides distribute quite slowly into bile, feces, the prostate, and amniotic fluid [1]. Volumes of distribution are higher, and peak levels are lower in patients with sepsis [3], fever including febrile neutropenia [1,4], severe burns, congestive cardiac failure, peritonitis, in the immediate postpartum period, and on parenteral nutrition [1]. They are much higher on a liter per kilogram basis in neonates, of the order of 50% to 100% compared with children and adults [5]. Protein binding of almost all aminoglycosides is less than 10%.

Clearance is predominantly renal by glomerular filtration and is substantially reduced in the setting of poor renal function. Hence, clearance is also reduced in the elderly and in the neonate [1]. Elimination half-lives are increased about 10-fold in end-stage renal disease, where nonrenal clearance becomes most important, accounting for about three quarters of total clearance [6]. Clearance is more rapid in children than in adults, as it is in pregnancy and the immediate postpartum period, and in cystic fibrosis patients.

There are significant intersubject variations in PK parameters, both in normal subjects and even more so in the clinical setting, even in patients with so-called “normal renal function.” The most noticeable parameters affected are the volume of distribution and the elimination half-life [1]. These variations are reduced by once-daily dosing. For instance, in healthy volunteers given 2 and 7 mg/kg doses of gentamicin, the coefficients of variation of the steady-state volume of distribution and the elimination

half-life were 48% and 42%, respectively, for the low dose and 21% and 17%, respectively, for the high dose [2].

Pharmacodynamics

Pharmacodynamics refers to the dynamics of drug action (ie, inhibition and killing). More precisely it is the relationship between the fluctuating concentrations seen with dosing and the killing of bacteria. It is often referred to as “pharmacokinetics-pharmacodynamics.” In this article it is referred to as “pharmacodynamics.” Readers are directed to some more detailed reviews for further elaboration of aminoglycoside PD concepts and findings [7,8].

In vitro pharmacodynamics

Aminoglycosides are rapidly bactericidal *in vitro*, and demonstrate concentration-dependent killing (ie, killing is more rapid and profound with increasing concentrations to many multiples of the minimum inhibitory concentration [MIC]) [9]. The upper limits of concentration-dependent killing have not been defined, but are well above peak concentrations seen in clinical practice, even with extended interval dosing. *In vitro*, aminoglycosides also induce moderate postantibiotic effects, namely a period of delayed regrowth after brief exposure [10]. The postantibiotic effect has been confirmed to occur *in vivo* [11,12]. At clinically achievable concentrations, the postantibiotic effect for aminoglycosides is usually of the order of 2 to 4 hours. An additional property is the phenomenon of adaptive resistance, which is a period of resistance to killing lasting several hours after initial exposure [13]. The combination of concentration-dependent killing, postantibiotic resistance, and adaptive resistance provides the theoretical basis for exploring higher doses given less frequently.

Subpopulations with reduced susceptibility to aminoglycosides are a normal feature of some bacterial species, especially *P aeruginosa* [14] and *Staphylococcus aureus* [15]. The presence of these subpopulations is readily detected in population analysis profiles, and they are manifest as small and diminishing proportions of the natural population that are inhibited at 2, 4, 8, and sometimes 16 times the MIC as measured by conventional methods [14]. The importance of these resistant subpopulations was emphasized in an *in vitro* PK model, which found that peak to MIC ratios of at least 10 were required to prevent their emergence over 24 hours [16,140]. Preventing the selection of resistant subpopulations for some species lends further weight to the concept of giving higher doses.

Pharmacodynamics in animal and in vitro models

A range of animal models has been used to examine the PD of aminoglycosides. The first model that clearly defined the PD predictors of efficacy

was the neutropenic mouse thigh model [147]. Regression analysis showed that the PD parameter that best predicted bacterial killing in vivo was the area-under-the-curve (AUC) to MIC ratio. The 24-hour AUC:MIC ratios (AUC₂₄:MIC) of 80 to 100 produced maximum effects against a strain of *Escherichia coli* with an MIC of 1 mg/L. The investigators also noted that at dosing intervals of 12 to 24 hours (equivalent to once every several days in a human with normal renal function) the time that the levels exceeded the MIC ($T > MIC$) was more predictive of killing. It was hypothesized that this was caused by regrowth after the postantibiotic effect had abated during the very long dosing intervals. In this and other animal models, the third PD predictive parameter, peak concentration to MIC ratio (C_{max} :MIC), is also correlated, but with lower statistical probability, to bacterial killing. Ratios of 8 to 10 predict maximum effect.

Human pharmacodynamic studies

The earliest indicator of a PD relationship for aminoglycosides was recognized in the late 1980s when Moore et al [18] related efficacy to the ratio of peak to MIC. Human PD studies designed to define the PD parameters that predict efficacy are limited, however, and have largely been conducted after most of the once-daily dosing studies. The most important of these found that the C_{max} :MIC ratio of gentamicin and tobramycin was the best predictor of efficacy, using defervescence and normalization of white cell count as end points [19]. Logistic regression analysis showed that a ratio of greater than or equal to 10 within 48 hours of commencing therapy was associated with a greater than or equal to 90% probability of fever resolution by day 7.

Aminoglycosides seem to have two PD predictors of efficacy: AUC₂₄:MIC and the C_{max} :MIC ratio. The AUC₂₄:MIC ratio makes more sense because, in theory at least, extremely rapid clearance could reduce the AUC substantially while C_{max} remains unaffected. It seems unlikely that very low AUCs with high C_{max} values would be effective. In clinical studies it is rarely possible to separate the two parameters with a limited range of dosing schedules, which may explain why the C_{max} :MIC ratio was selected in the key human study. C_{max} :MIC may also be a useful additional parameter reducing the risk of selecting resistant subpopulations of some bacterial species as noted previously.

In clinical practice either or both of these parameters could be used, even though they are influenced differently by host factors. C_{max} :MIC ratio is related almost exclusively to volume of distribution, whereas the AUC₂₄:MIC ratio is influenced by both volume of distribution and clearance. Target values of 80 to 100 and 8 to 10, respectively, are reasonable based on animal and human PD studies. It has been argued that getting high peaks to achieve satisfactory C_{max} :MIC ratios against *P aeruginosa* should be the

main aim of therapy, because susceptible members of this species have median MIC values of 2 µg/mL [20].

Toxicodynamics

Nephrotoxicity

Aminoglycosides are obligate nephrotoxins, and renal impairment is eventually detected in all patients if treated for long enough [21]. The toxicity occurs because of the accumulation of aminoglycosides within the proximal tubular epithelial cell in lysosomal phospholipid complexes, which eventually rupture and initiate cell death [22]. As a consequence, the local renin-angiotensin system is activated, leading to local vasoconstriction and a decrease in the glomerular filtration rate, so-called “tubuloglomerular feedback” [22]. Reductions in glomerular filtration rate and increase in plasma creatinine values are the standard measure of nephrotoxicity.

Uptake into the tubular epithelium is saturable and the increasing luminal concentrations that occur with higher doses do not result in greater rates of uptake [23]. Gilbert [24] hypothesized that once-daily dosing takes advantage of this fact and in addition provides a period where aminoglycosides could leach back into the lumen and reduce the rate of accumulation. In support of this, studies in rabbits and dogs have shown that aminoglycosides are more nephrotoxic when the same total daily dose is given in divided doses or by continuous infusion [23]. In humans, Verpoorten et al [25] have shown that a single daily dose of gentamicin or netilmicin reduces renal cortical accumulation by 30% to 50% compared with continuous infusion. Furthermore, prospective clinical studies have shown that continuous infusion leads to more rapid onset of nephrotoxicity than intermittent dosing [26,27].

Definitions of nephrotoxicity vary in clinical studies and in practice. The most commonly chosen is a 50% increase over baseline in plasma creatinine or an increment of 0.5 mg per 100mL (50 µmol/L) [72]. Although it is recognized that this is a fairly insensitive measure, it has been selected to be clinically meaningful and less susceptible to day-to-day fluctuation. Reductions in creatinine clearance of this magnitude take 5 to 12 days of treatment to become manifest [28]. Sensitive measures of renal tubular damage, such as the detection of *N*-acetylglucosaminase, β₂-microglobulin, phospholipids, or alanine aminotransferase in urine, suggest that nephrotoxicity is common [29]. Routine monitoring for these is not recommended.

The exact relationship between circulating drug concentrations and nephrotoxicity has not been defined precisely, although nephrotoxicity is more common when trough levels are elevated. This is not surprising because the determinant of nephrotoxicity is related to the level and duration of concentrations in the proximal tubular lumen, and this varies with dosing

schedule, to a lesser extent dose, and the individual's renal function. The importance of duration was delineated in a comparative study of once-versus twice- or thrice-daily dosing of netilmicin [30]. These investigators showed that comparable nephrotoxicity rates were observed about 3 days later in the once-daily group. The relationship to dosing schedule plus duration of treatment has been reinforced recently by simulations on patients who had become nephrotoxic with prolonged amikacin use [29]. In the elderly, the presence of diabetes mellitus and the duration of treatment seem to be more important predictors of nephrotoxicity than the dosing frequency [31].

Another recent study has shown the daily AUC and the dosing schedule (once- versus twice-daily dosing) to be one of the significant predictors of time to onset of nephrotoxicity [32]. For twice-daily dosing, nephrotoxicity was observed if daily AUC was over 100 mg*h/L, whereas for once-daily dosing it was not observed at all, but was predicted to occur if AUC exceeded 700 mg*h/L, a value substantially above that achievable with any current dosing schedule. This study also confirmed the role of concomitant vancomycin, but not amphotericin B, in reducing the time to onset of nephrotoxicity.

Surprisingly, nephrotoxicity varies according to the time of day of administration [33]. It has been shown in animal models and humans that nephrotoxicity is more likely when the drug is administered at times of rest compared with times of activity. This has led to a recommendation for once-daily doses to be given at 1:30 PM [29]. On current evidence, the best way to minimize nephrotoxicity is to administer the drug at extended dosing intervals (mostly once-daily); in the early afternoon; and for the shortest period that is clinically feasible [22].

Nephrotoxicity is exacerbated by any condition that reduces renal blood flow, and by co-administration of some drugs including loop diuretics, cyclosporin, cisplatin, and vancomycin, but not teicoplanin [31,32]. Clinical studies suggesting that cephalosporins worsen the nephrotoxicity of aminoglycosides have been refuted [34]. The data on amphotericin B are conflicting [32,35], and the risk is lower than that seen with vancomycin. Hepatic insufficiency seems to be an important risk factor for nephrotoxicity [21]. It is assumed that the increased risk results from intrarenal vasoconstriction secondary to stimulation of the renin-angiotensin system [24].

Considerable uncertainty persists about the relative toxicity of different aminoglycosides [1]. When dose-response curves are examined against dose or serum concentration, the order of nephrotoxicity seems to be gentamicin greater than tobramycin, greater than amikacin, greater than netilmicin. By contrast, head-to-head studies have tended to show comparable nephrotoxicity. This has been attributed to the fact that these studies involved the control of serum levels, shifting the risk to the lower end of the dose-response curve and reducing the likelihood of detecting true differences [1].

Fortunately, nephrotoxicity is reversible. Renal function returns to normal after a period of 3 to 6 weeks [28].

Ototoxicity

Ototoxicity is manifest as auditory (cochlear) and vestibular toxicity, although they do not necessarily occur together. The mechanism is similar, namely damage to the sensory hair cells in the cochlea and the labyrinth [36]. Unlike nephrotoxicity, once auditory or vestibular toxicity develops clinically it is frequently irreversible. The frequency of clinically reported ototoxicity is much lower than nephrotoxicity, but in contrast cannot practically be monitored for early detection before the onset of symptoms. The ototoxicity of aminoglycosides and the differences between agents have been exploited in the management of Meniere's disease, where these drugs have been injected intratympanically [37].

Auditory toxicity

Hearing loss is an important complication of aminoglycoside therapy, but uncommonly reported by patients. Tinnitus is reported more frequently, but is more often transient. When audiometry is used to assess hearing loss, toxicity is documented more frequently [36]. Most commonly, hearing loss is documented as a 15-dB reduction in at least the frequencies tested in the range 0.25 to 8 MHz. Prospective studies have shown that if testing is also performed in the high-frequency range (10 to 18 MHz), toxicity is even more frequent [36]. Auditory toxicity is common, but usually subclinical. Brummett and Fox [36] have pointed out that auditory toxicity rates are confounded by illness or surgery, which by themselves have been documented to induce hearing loss [38].

The relationship between aminoglycoside PD parameters and auditory toxicity is unclear. Animal models suggest that ototoxicity is related with AUC of concentrations in cochlear perilymph, which in turn are proportional to the area under the plasma AUC [39]. If this is so, then aminoglycoside regimens that use the same total daily dose have the same incidence of ototoxicity. To support this, in the combined studies from one meta-analysis of once-daily versus multiple-daily dosing, rates of clinically reported hearing loss were 0.4% for once-daily dosing and 0% for multiple-daily dosing [40], whereas hearing loss rates determined audiometrically were 5.1% and 7.8%, respectively. These differences are not statistically significant. There may be differences in ototoxicity between aminoglycosides administered systemically, but this has not been convincingly demonstrated by any study or meta-analysis. Certainly, differences have been seen in animal models, and can be shown when the drugs are administered by direct intratympanic injection [37].

A rare form of auditory toxicity, often occurring after a single dose, has been described associated with two different mutations in the mitochondrial

12S ribosomal RNA gene [41]. A family (perhaps maternal) history of this type of toxicity is a contraindication to the use of aminoglycosides. Whether the more common form of ototoxicity observed after several days of therapy has a genetic basis is unknown.

Vestibular toxicity

Like auditory symptoms, vestibular symptoms after aminoglycoside therapy are rarely reported. More sensitive methods for detecting vestibular toxicity are available, particularly electronystagmography, and toxicity rates are generally higher when this method is used. In prospective dosing studies, electronystagmography has been used infrequently because of the practical difficulties of conducting this test before and after treatment. From the same meta-analysis noted previously, clinically reported vestibular toxicity rates of 0.3% and 0.2% were found for once-daily and multiple-daily dosing, respectively, whereas rates detected by electronystagmography were 2.1% and 4.8% [40]. Again, these rates are not statistically significant, consistent with the hypothesis that toxicity may be related to AUC of drug exposure.

Neuromuscular blockade

Neuromuscular blockade is a rarely reported adverse effect of aminoglycoside use, although it may be more common than is reported [1]. It is more likely to occur when given intravenously and co-administered with neuromuscular blocking drugs or anesthetic agents.

The move to once-daily (extended-interval) dosing

Once-daily dosing of aminoglycosides was initially introduced for the treatment of urinary tract infection [42–45]. The high and prolonged urinary levels justified this move. It was less obvious initially that this approach might be useful for the treatment of systemic infection, and there was considerable concern that giving the total daily dose as a single dose once-daily increases toxicity because of the high peaks. Nevertheless, the cumulative in vitro and animal data noted previously provided the rationale, and clinical studies were conducted from the late 1980s for the next decade.

Published data on once-daily dosing where identical or very similar total daily doses given once-daily have been compared with multiple-daily doses include 45 studies to date, mostly prospective, in over 6500 patients or patient episodes. An additional 20 published studies involving more than 900 patients have examined once-daily dosing, either with unequal total daily doses or in an uncontrolled fashion, or in one case by comparing multiple daily doses with continuous infusion. Aminoglycosides studied include netilmicin, gentamicin, amikacin, tobramycin, and sisomicin. Studies have examined comparative efficacy and safety in a wide range of

infections, such as serious infections, febrile neutropenia, pelvic inflammatory disease, intra-abdominal infection, gram-negative infections, urinary tract infections, acute exacerbations of cystic fibrosis, postpartum endometritis, and surgical prophylaxis. Children or neonates have been the subjects of or been included in at least 17 studies.

Many of these studies have been subjected to 10 formal meta-analyses (Table 2) [40,46–54], and at least six systematic reviews [3,55–59]. A summary of the findings of the meta-analyses is included in Table 2. Depending on study selection and the choice of meta-analysis method, these meta-analyses have shown either equivalence or superiority for once-daily dosing in clinical efficacy, bacteriologic efficacy, and nephrotoxicity. None have shown differences in auditory, vestibular, or mortality rates.

Although there has been variation in the methodology and conclusions, the meta-analyses and reviews have concluded that once-daily dosing is at least as efficacious as, and no more nephrotoxic than, multiple-daily dosing. Auditory and vestibular toxicity rates are not different, although vestibular toxicity has been sufficiently infrequent to preclude meaningful comparison. The interpretation of these meta-analyses has been open to criticism over such issues as the wide variation in definition of nephrotoxicity used in the prospective studies [60]. The cumulative evidence has been enough, however, to convince experts [61] and the prescribers about the advantages of moving to once-daily dosing.

Eleven of the 45 studies noted previously [62–72] were published after the completion of the last two meta-analyses by Ali and Goetz [46] and Kale-Pradhan et al [54], and an additional two were published in full [32,73], having previously been included in some analyses in abstract form. None of these subsequent studies demonstrated differences between once-daily and multiple-daily doses in terms of clinical or bacteriologic efficacy, or toxicity. Overall, publications on more than 3500 patients who have received once-daily high doses of aminoglycosides provide powerful evidence that toxicity is not increased, and may be decreased compared with traditional multiple-daily dosing.

Dosing in conventional infections

Dosing by age

Because renal function varies with age, recommendations for starting doses should vary with age if the AUC_{24}/MIC ratio is the PD target. Although once-daily dosing is now used widely for standard therapeutic situations, there is no consensus on doses. Doses used in prospective once-daily comparative studies outside the urinary tract have ranged from 3 to 5 mg/kg daily for gentamicin, 4 mg/kg for tobramycin, 3.8 to 6.6 mg/kg for netilmicin, and 11 to 20 mg/kg for amikacin. Only one of these studies aimed

Table 2
Meta-analyses of single versus multiple daily doses of aminoglycosides

First author and reference	No. studies ^a included (excluded)	Patient numbers	Meta-analysis method ^b	Outcomes					
				Clinical efficacy	Bacteriologic efficacy	Nephro- toxicity	Auditory toxicity	Vestibular toxicity	Mortality
Galloe et al [51]	16	1200	Confidence profile	ns	—	ns	ns	—	—
Barza et al [48]	21 (4)	3091	Fixed-RR	S	—	S (<i>P</i> = .05)	ns	ns	—
			Random-RR	ns	—	ns	ns	ns	—
Munckhof et al [40]	19 (9)	2881	Random-RD	S	ns	ns	ns	ns	—
Ferriols-Lisart and Alminana [49]	18 (49)	2317	Fixed-OR	S	—	S	ns	—	—
Hatala et al ^c [52]	13 (29)	1610	Random-RR	— ^d	ns	ns	ns	—	ns
Freeman and Strayer [50]	15 (20)	2733	Fixed-OR	ns	—	S	—	—	—
			Fisher's combined	S	—	S	—	—	—
			Mean-p	S	—	S	—	—	—
Bailey et al [47]	20 (101)	2849	Random-RD	S	ns	ns	ns	—	—
Ali and Goetz [46]	26 (14)	3552	Random-RD	S	ns	ns	ns	ns	—
Hatala et al ^e [53]	4 (2)	422	Random-RD	ns	ns	ns	—	—	ns
Kale-Pradhan et al [54]	14 (31)	2498	Fixed-OR	ns	S	ns	ns	ns	—

Abbreviations: ns, not statistically significant for once-versus multiple-daily dosing; OR, odds ratio; RD, rate difference, RR, relative risk; S, statistically significant, favoring once-daily dosing.

^a Includes studies with two comparative regimes or agents that were usually analyzed as separate studies.

^b Confidence profile method, Mantel-Haenzel Fixed effects or Der Simonian and Laird Random effects model.

^c Studies on immunocompetent patients only.

^d Could not be analyzed as statistically too heterogenous.

^e Studies on immunocompromised patients only.

to adjust starting doses according to age, and that study was only in children [62]. One clinical program has routinely used 7 mg/kg daily for gentamicin and tobramycin [20].

The author's clinical experience using a combination of peak and AUC estimates and targets of 12 and 80, respectively, shows that starting doses of gentamicin and tobramycin need to be age adjusted because of differences in clearance at different ages [74,75]. Mean once-daily doses for these drugs and targets are: less than 30 weeks gestation neonates: 3 mg/kg; 31 weeks gestation to 4 weeks corrected age: 3.5 mg/kg; greater than 4 weeks and less than 10 years: 7.5 mg/kg; 10 to 29 years: 6 mg/kg; 30 to 60 years: 5 mg/kg; and greater than 60 years: 4 mg/kg. Given the similar kinetics and potency of netilmicin, it is likely that identical age-stratified doses apply. The potency of amikacin is fourfold lower than the other three drugs, whereas the PK is similar; targets and doses should be fourfold higher. This would result in children and young adults receiving greater than 20 mg/kg of amikacin daily, higher than has been used in most clinical studies. The safety of such doses has not yet been confirmed.

Because of considerable intersubject variation in kinetics, it is wise to adjust doses according to levels taken early in the course of treatment. Some of the methods for monitoring, discussed in detail later, only suggest dosing adjustments if levels suggest reduced clearance. Other methods allow upward adjustment of doses to avoid underdosing. Based on the currently accepted PD targets, underdosing is common with conventional doses of 4 to 5 mg/kg daily for gentamicin and tobramycin [74]. The clinical program that recommends starting doses of 7 mg/kg reduces the likelihood of underdosing [20].

Dosing by weight

Besides age-related differences in glomerular filtration rate, once-dosing is also affected by body weight because of the milligram per kilogram basis for dosage selection. Although aminoglycosides distribute into adipose tissue, it is much less than into extracellular water and hence ideal body weight has been recommended as the basis for dosing to avoid overdosing obese patients [1]. Related concerns have been expressed about underdosing underweight patients. Using a simple parameter, the ratio of total body weight to ideal body weight (TBW:IBW), Traynor et al [76] were able to show in a sample of over 1700 patients that dosage adjustment is required for underweight and overweight patients. They recommended increasing the dose by a factor of 1.13 for underweight patients (TBW:IBW ratio < 0.75) and reducing the dose by adjusting the weight with the formula: $0.43 \times \text{TBW} + 0.57 \times \text{IBW}$. Ideal body weight is calculated by the method of Devine [77].

Male IBW \pm 50 kg + 2.3 kg/each inch over 5 feet

Female IBW \pm 45.5 kg + 2.3 kg/each inch over 5 feet

An alternative strategy is to choose the lower of the two weights: TBW and IBW [78].

Administration rate

The initial standard method of aminoglycoside administration was to infuse the drug over 30 to 60 minutes. Bolus administration of multiple daily doses has become common practice in many countries [79,80], but with the move to once-daily dosing there has been some hesitancy in using bolus administration. Only one study, performed in children, has examined the use of higher (approximately 5 mg/kg) once-daily doses by bolus (2 to 3 minute) administration [81]. The investigators were unable to demonstrate any alteration in toxicity in 123 infants, children, and adolescents using this mode of administration.

Dosing in special situations

In certain clinical situations the kinetics of aminoglycosides may differ from those seen in children and adults, the doses may be different or there may be special toxicity issues. These clinical situations are discussed later, with an emphasis on selection of starting doses. It is recommended that doses thereafter be based on monitoring, using one of the methods described later.

Dosing schedules in special situations

Renal impairment

The introduction of third- and fourth-generation cephalosporins, carbapenems, and monobactams has significantly reduced reliance on aminoglycosides in patients with significant renal impairment. Nevertheless, there are circumstances in these types of patients when aminoglycosides are considered a necessary part of the treatment, and hence it is important to have a safe approach to their use. Choices of approach are influenced in part by the need or otherwise to preserve residual renal function. More latitude for dosing error exists in patients with end-stage renal disease, including those on dialysis.

Patients with renal failure have reduced volumes of distribution and reduced clearance of aminoglycosides [82]. Hence, dosage reduction should be greater at the lowest levels of glomerular filtration rate than is predicted by the creatinine clearance alone. This has been factored into the usual recommendations for starting doses.

Most authorities recommend selecting starting doses based on the patient's calculated creatinine clearance, even though it is understood that relationship between aminoglycoside clearance and creatinine clearance is

far from complete [1]. The Cockcroft-Gault formula is usually used to calculate the creatinine clearance [83], and can be modified using the ideal rather than the actual body weight [84]. An adaptation in SI units was developed by Bjornsson [85], and other modifications have been proposed more recently, including adaptation to lean body weight [35], and adjustment for abnormally low plus changing creatinine values [78]. The last of these is recommended. The Cockcroft-Gault formula does not work well in children, and alternative strategies for estimating clearance in pediatric patients, using age and body length, have been proposed [86]. Because of transplacental transfer of creatinine, plasma creatinine values cannot be used to estimate renal function in neonates. Details of all these estimators of creatinine clearance are given in Table 3.

Dosage adjustment for renal impairment can be achieved by reducing the dose, increasing the dosing interval, or both. The PD importance of peak

Table 3
Estimation of creatinine clearance in milliliter per minute from serum creatinine values

Method	Ages	Formulae
Cockcroft-Gault [83]	18 y	$\frac{(140 - \text{age}) \times \text{total} \cdot \text{body} \cdot \text{weight in kg}}{72 \times \text{creatinine in mg/dL}}$ $\frac{(140 - \text{age}) \times \text{total} \cdot \text{body} \cdot \text{weight in kg}}{814 \times \text{creatinine in mmol/L}}$ Females = above value \times 0.85
Pesola adjustment to Cockcroft-Gault [144]	18 y	Use Devine [77] lean body weight (LBW) in formula Males LBW = $0.9 \times (\text{height [cm]} - 150) + 50$ Females LBW = $0.9 \times (\text{height [cm]} - 150) + 45$
Kirkpatrick adjustment to Cockcroft-Gault [78]	18 y	Use dosing weight (DWT) = the lower of lean body weight (Devine) and total body weight Use a correction factor (CF) if baseline serum creatinine before the commencement of therapy (S_{Cr1}) is below 0.06 mmol/L: $CF = \frac{0.06}{S_{Cr1}} \text{ if } >1 \text{ else } CF = 1$ Hence: estimated creatinine clearance = $\frac{(140 - \text{age}) \times DWT \text{ in Kg}}{814 \times S_{Cr1} \text{ in mmol/L}}$
Bjornsson [85]	18 y	$\frac{(160 - \text{age})}{250 \times \text{creatinine in mmol/L}} \times \frac{\text{Weight in Kg}}{70}$ Females = above value \times 0.9
Schwartz [86]	1 mo to 18 y	Low birth weight infants ≤ 1 y $0.33 \times \text{L/creatinine}$ Full-term infants ≤ 1 y $0.45 \times \text{L/creatinine}$ Children 2–12 y $0.55 \times \text{L/creatinine}$ Adolescents girls 12–18 y $0.55 \times \text{L/creatinine}$ Adolescents boys 12–18 y $0.70 \times \text{L/creatinine}$ where L = length (height) in cm, and creatinine is in mg/dL

levels suggests that interval adjustment is preferred, although in significant renal impairment the intervals can become quite long and lead to prolonged periods without effective drug, a situation where time above MIC becomes an important determinant of efficacy [17]. In all instances, it is essential to monitor levels and adjust doses when necessary.

The following methods have been used for choosing initial doses in patients with impaired renal function: scaled reduction of dose [87,88], scaled increase in dosing interval [47], and adjustment of both dose and interval [84,89]. All perform satisfactorily and ultimately the choice of method is up to the user. Methods that attempt to maintain higher peak levels balanced against dosing intervals of no longer than 48 hours are preferred. The method proposed by Gilbert and Bennett [84] comes closest to achieving these aims, and is presented here in tabular format (Table 4). Recommendations for isepamicin are based primarily on interval adjustment [90]. None of these methods has been applied to pediatric patients with renal impairment, although application of adult dosing regimens is unlikely to cause problems.

Dialysis

The differences in aminoglycoside kinetics in patients undergoing intermittent hemodialysis, continuous ambulatory peritoneal dialysis, and continuous arteriovenous or venous-venous hemodiafiltration require specialized dosing. In complete renal shutdown, the elimination half-life is substantially

Table 4
Recommended dosing schedules for adult patients with impaired renal function

Estimated Cr Cl (mL/min) ^a	Dose (mg/kg)			Dosing interval (h)	Dose (mg/kg)	Dosing interval (h)
	Gentamycin Tobramycin	Netilmicin	Amikacin Kanamycin Streptomycin		Isepamicin	
90	5	6.5	15	24	8	24
80	5	6.5	15	24	8	24
70	4	5	12	24	8	24
60	4	5	12	24	8	24
50	3.5	4	7.5	24	8	24
40	2.5	4	7.5	24	8	48
30	2.5	2	4	24	8	48
20	4	3	7.5	48	8	72
10	3	2.5	4	48	8	72
<10 ^b	2	2	5	48	8	96

^a See Table 3 for estimation methods.

^b As in patients on hemodialysis.

prolonged (see Table 1). Standard texts provide dosing guidance for the three types of dialysis [89], but monitoring is essential, and dosing guidelines should be considered indicative only for the initial dose. Area-based monitoring methods give better control than single-dose methods.

The commonest recommendation for hemodialysis is to give half the dose given to an adult with normal renal function after each dialysis [89]. The intriguing concept of giving a higher dose just before the hemodialysis session to get a high peak but the same AUC needs further work to determine its value [91]. For patients on continuous ambulatory peritoneal dialysis, the recommended dose is 3 to 4 mg/L of dialysate per day for gentamicin, tobramycin, and netilmicin, and 15 to 20 mg/kg for amikacin, kanamycin, and streptomycin. Kinetics in hemodiafiltration is highly variable. A dose equivalent to that given for a patient with a creatinine clearance of 10 to 20 mL/min is recommended.

Neonates

Aminoglycosides are a standard part of the regimen for the management of neonatal sepsis. Reduced renal clearance in neonates compared with infants has been recognized for many years, and twice daily regimens have consequently become the standard. More recently, the PKs of once-daily gentamicin in neonates has been studied extensively [5,17,75,92–101]. Single studies have been conducted on netilmicin [102] and amikacin [103]. Once-daily doses have ranged from 3 to 5 mg/kg. Most of these studies have compared once-daily with twice-daily dosing, and often at different total daily doses, and examined only peak and trough levels, providing only limited PK information. Those that have provided more detailed PK data have shown that volumes of distribution are larger and elimination half-lives are longer the earlier the gestational age [5,17,75,94]. Because half-lives are normally around 8 hours, there is a trade-off between peaks and AUCs even with once-daily dosing. Starting doses of 3 to 3.5 mg/kg generate AUC values in the target range, whereas peaks of 8 to 10 µg/mL can be expected [17,75]. A recent critical analysis of published studies concluded that the starting dose in neonates up to 7 days old should be 3.5 mg/kg [104]. Alternatively, a formula has been developed that can be used to select starting doses based on gestational age and birth weight [94]. None of the prospective studies has shown differences in efficacy or toxicity with once-daily dosing.

Pregnancy

Gentamicin and presumably other aminoglycosides cross the placenta in significant amounts [105,106]. When administered at the time of delivery, modest levels can be found in the newborn [107]. In view of their known toxicity, aminoglycosides are categorized by the Food and Drug Administration as category C drugs. They are not teratogenic, and reports of

neonatal nephro- or ototoxicity are lacking. Although they are not recommended for any common conditions in pregnancy, the lack of fetal toxicity reports, and the widespread use of aminoglycosides, especially gentamicin, in early onset neonatal sepsis suggest that they could be used for maternal infective conditions where delivery is imminent (eg, chorioamnionitis).

Doses need to be higher in pregnancy because of the increased volume of distribution and high clearance, as noted in studies on the treatment of pyelonephritis [142] and other conditions [109]. Once-daily dosing has not been studied formally, and uncertainty remains about the fetal safety of administering once-daily doses. There is only a small amount of published experience [107]. Hence, traditional twice- or thrice-daily dosing is still recommended by many authorities.

Cystic fibrosis

Aminoglycosides are a standard part of the treatment of acute exacerbations of *P aeruginosa* lung infection in patients with cystic fibrosis and other forms of bronchiectasis. Cystic fibrosis patients usually have more rapid clearance and higher volumes of distribution of antibiotics, including aminoglycosides, than age-matched controls [110]. Hence, higher doses are frequently recommended [111–113]. A Cochrane systematic review of once-daily dosing identified 10 studies, of which only three satisfied the criterion of a randomized controlled trial [114]. The review concluded that whereas no difference in outcome measures was detected between once- and multiple daily dosing, the number of patients was small and power to detect a difference was low. Others have expressed concern about once-daily dosing because of the long periods in which levels are below the MIC because of more rapid clearance [112]. Nevertheless, once-daily dosing for cystic fibrosis exacerbations has become popular in some countries [115]. Although inhaled aminoglycosides are regaining importance in the management of cystic fibrosis *Pseudomonas* infection [116], their PDs with this method of dosing have not been studied, and doses have been derived empirically.

Endocarditis

The aminoglycosides gentamicin and streptomycin have an established role as adjunctive agents to cell wall-active antibiotics in the treatment streptococcal, enterococcal, and staphylococcal endocarditis [108]. Use of these agents requires that the isolate not have high-level resistance, because the synergistic effect is lost, and specific laboratory testing for these resistances should be performed to rule out this possibility. Doses traditionally used are lower than those used for conventional infections. Typically, gentamicin doses of 1 mg/kg 8-hourly have been used, although twice daily dosing (of 80 mg) and higher doses (1.5 mg/kg) have been recommended by

some authorities [108]. The usual dose of streptomycin is 7.5 mg/kg up to 500 mg 12-hourly. Conventional PD parameters cannot be applied to the choice of dose in endocarditis.

Once-daily dosing of aminoglycosides has been explored in animal models of endocarditis and to a limited extent in human cases of endocarditis [117]. Early animal studies on *Enterococcus faecalis* endocarditis were discouraging [118], but in subsequent studies viridans streptococcal, *E coli*, and *Serratia marcescens* endocarditis have shown equivalence of daily and thrice-daily dosing [117]. Two human studies have examined the effects of once-daily netilmicin or gentamicin in the treatment of mainly penicillin-susceptible viridans streptococcal endocarditis [119,145].

Other conditions

The PKs of aminoglycosides in patients with febrile neutropenia do not differ significantly from the normal population [4,120]. The same is not true for critically ill patients, such as those in intensive care. In this setting it is common to see patients with significantly larger volumes of distribution, especially those on parenteral nutrition [121,122]. Higher starting doses with early monitoring are recommended [3]. Severe burns also increase volumes of distribution significantly [123] and higher initial doses are required as a result [124].

Monitoring

Conventionally, aminoglycosides have been monitored during therapy to reduce the likelihood of toxicity. The collection of peak and trough levels with 8-hourly dosing became standard practice worldwide, and laboratory assays became universally available and inexpensive as a result. This method of monitoring has a number of problems. It focuses on somewhat arbitrary targets for peak and trough based on values seen in adults with normal renal function and there is no real accounting for the intersubject variation in kinetics. The relative weighting of peaks and troughs is unclear, even though it became widely accepted that troughs should be less than 2 mg/L. Difficulty could be experienced with achieving targets in patients with impaired renal function. The development of nomograms [125] and computer programs to calculate individual PK values [126,127] resulted in some slight improvements, but therapeutic targets remained somewhat arbitrary.

With the emergence of once-daily dosing, it soon became clear that the use of conventional monitoring methods and targets was inappropriate. For instance, a trough near 2 mg/L with once-daily dosing implies significantly reduced clearance. In patients with normal renal function, troughs are substantially below the lower limit of the assay (generally around 0.5 mg/L for gentamicin and tobramycin). Three groups of monitoring methods have now been developed for monitoring once-daily aminoglycosides. Further,

there is prospective evidence for the value of monitoring and dosage adjustment with once-daily dosing in reducing toxicity, strengthening the case for routine monitoring [128].

Single-level methods

One type of monitoring involves the collection of a single level in the elimination phase, usually between 6 and 14 hours after completion of dosing. The first of the single-level methods to be developed was the Hartford method, based on 7 mg/kg daily dose and a level collected between 6 and 14 hours [129]. A simple nomogram was constructed and the level compared with the nomogram to decide whether to continue with the same schedule, or increase the dosing interval to 36 or 48 hours. If the level was sufficiently high, the recommendation was that the aminoglycoside should be stopped. Prospective evaluation in over 2000 adult patients showed this to be an effective and safe method of dosing and dosing adjustment [20].

A variation on this method was developed at the Barnes-Jewish Hospital in St Louis, MO. Based on a 5 mg/kg daily dose they constructed a similar nomogram, with a similar recommendation to lengthen the dosing interval based on a level measured between 6 and 14 hours postdosing [47]. A third single-level method has been promulgated in Australia through the so-called “Antibiotic Guidelines” [88]. Based on a varying dose depending on age (the ones noted previously), a level taken at 6 to 14 hours after dosing is compared with a graph that defines a target band over the sampling interval. If the level falls above or below this band, the dose is adjusted by simple algebra to achieve a level with the next dose in the middle of the target band.

All of the single-dose methods assume that the patient has a normal volume of distribution. In more severely ill patients, volumes of distribution are often elevated, reducing peak levels. Because peaks are not measured in these methods, reduced peaks are not recognized [130]. Further, the first two methods do not recognize underdosing because they recommend continuing with the same daily dose if the 6- to 14-hour level is low. Nevertheless, these methods are simple to apply and less costly.

Area-under-the curve methods

Two methods have been developed in which two levels are measured and the AUC estimated using a simplified monoexponential model. The Christchurch method is based on a starting dose 5 to 7 mg/kg once-daily and the collection of two levels at approximately 1 hour and 6 to 14 hours postdosing [131]. The AUC is calculated from a series of equations using the two data points, and doses adjusted to achieve target AUCs of 72, 86, and 101 for doses of 5, 6, or 7 mg/kg once-daily. Prospective evaluation of this method has shown it to be practical and useful [132].

A similar method, the peak-AUC or Aladdin method, which uses the same monoexponential PK model, uses both AUC and peak to calculate

potential dosage adjustments [74]. AUCs are calculated from the two levels collected about 0.5 to 1 hour and 6 to 14 hours postdosing using the Aladdin computer program, and doses and dosing intervals iteratively adjusted to achieve a target AUC of 80 mg*h/L and a virtual peak of 12 mg/L. The program also adjusts doses according to AUC alone, allowing the clinician to choose the dosing interval, and continue with 8- or 12-hourly dosing if they so choose, or continue with once-daily dosing should the program recommend longer dosing intervals. Prospective evaluation has shown this to be an effective method [74,133].

Bayesian methods

Bayesian methods applied to aminoglycoside monitoring have a long history [134,135]. Bayesian methods usually use population PK values to generate prior probabilities, and then recommend dosage adjustment based on one or two measured levels. Two computer programs have been developed, ABBOTTBASE and SeBA-GEN, and have been compared for their predictive value in dosage adjustment in once-daily dosing [136]. SeBA-GEN includes analysis of individual sequential data and also factors in the error associated with measurement of levels. These programs have the advantage of increasing the likelihood of dosage changes resulting in predicted levels and targets, although the added benefits of this level of sophistication over the simpler methods noted previously have yet to be demonstrated [137].

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