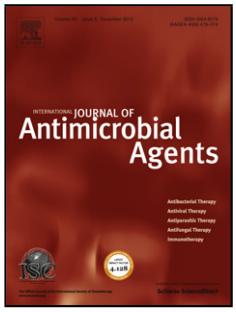

Title: First-dose pharmacokinetics of aminoglycosides in critically ill haematological malignancy patients

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Highlights

- An increased volume of distribution was found in a sample of critically ill hematologic malignancy patients
- The body weight that yielded the most precise estimation of volume of distribution was actual body weight
- Current aminoglycoside doses resulted in suboptimal peak concentrations in the majority of the study sample
- Further examination of dose optimization via comprehensive population pharmacokinetic analyses are needed in the critically ill hematologic malignancy population

First-dose pharmacokinetics of aminoglycosides in critically ill haematological malignancy patients

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ABSTRACT

The primary objective of this study was to determine the volume of distribution (V_d) (L/kg) of intravenous aminoglycosides (AGs) in critically ill haematological malignancy patients. Secondary objectives were to determine the body weight (actual, ideal, adjusted or lean) that yields the most precise estimate of V_d when normalised in L/kg as well as the frequency that current first-dose strategies result in post-distributional peak concentrations (C_{peak}) within the target range (tobramycin 16–24 mg/L; amikacin 32–48 mg/L). In total, 58 AG doses were included (tobramycin, n = 34; amikacin, n = 24). Median V_d was 0.38 L/kg normalised per the most precise dose weight, which was actual body weight (ABW). The median dose was 445 mg (5.8 mg/kg ABW) for tobramycin and 1200 mg (13.8 mg/kg ABW) for amikacin. Target C_{peak} (tobramycin 20 mg/L; amikacin 40 mg/L) was achieved in only 25% of all AG episodes, with 4% exceeding the target and 71% falling below the target. Twenty-four organisms were isolated in the study sample; target C_{peak} achievement (tobramycin 20 mg/L; amikacin 40 mg/L) would yield a peak:minimum inhibitory concentration of 10 in 75% and 52% of organisms, respectively. In conclusion, an increased V_d of AGs was identified in this critically ill haematological malignancy patient sample, and current dosing yielded a suboptimal C_{peak} in the majority of patients.

1. Introduction

Gram-negative infections pose a significant danger to patients. Aminoglycosides (AGs) are commonly utilised in combination with β-lactams to treat Gram-negative infections in critically ill patients. They remain key agents in the treatment of infections caused by multi-drug resistant organisms [1]. AGs exhibit concentration-dependent activity with optimal efficacy achieved when the peak serum concentration to minimum inhibitory concentration (MIC) ratio is ≥10 [2]. Extended-interval AG dosing (EIAD) was developed to help achieve this pharmacokinetic/pharmacodynamic (PK/PD) target and to minimise trough-dependent toxicity [3].

Concerns exist that current doses used in EIAD regimens may not reliably result in achievement of the target peak serum concentration/MIC ratio in critically ill patients, due in part to an increased volume of distribution (V_d) [4]. Literature evaluating the V_d of AGs in critically ill patients is limited by a minimal number of trials, small sample sizes, varying populations and methodological differences [5–7]. Regardless, these studies have demonstrated an overall increase in AG V_d in the critically ill. The aetiology for the increased V_d has been proposed to include aggressive fluid resuscitation, capillary leak and altered protein binding [8,9].

Cancer patients also exhibit an increased V_d compared with the general population although the aetiology is unknown [10]. The impact of an increased V_d on antimicrobial dosing is of great concern in cancer patients owing to the diminished innate immune

response, particularly in those with haematological malignancy. In a previous study, severe sepsis patients with malignancy had a 52% higher mortality rate compared with those without malignancy [11]. As such, the purpose of this study was to evaluate the first-dose kinetics of intravenous (i.v.) AGs in a critically ill haematological malignancy population.

The primary objective was to determine the V_d (L/kg) of i.v. AGs in critically ill haematological malignancy patients. Secondary objectives were to determine the body weight [actual (ABW), ideal (IBW), adjusted (AdjBW) or lean (LBW)] that yields the most precise estimate of V_d when normalized on a L/kg basis as well as the frequency that current first doses result in post-distributional peak concentrations (C_{peak}) within the target range.

2. Methods

2.1. Study design and sample

This was a single-centre, retrospective cohort study performed at The University of Texas MD Anderson Cancer Center (MDACC) in Houston, TX. MDACC is a National Cancer Institute-recognised comprehensive cancer centre with a 26-bed medical intensive care unit (MICU) managed by full-time intensivists and multidisciplinary personnel. The study was approved by the Investigational Review Board of MDACC. A waiver of informed consent was granted.

Patients were included if they were aged ≥19 years, diagnosed with haematological malignancy, admitted to the MICU between 1 August 2009 and 31 August 2011, received a dose of i.v. AG in the emergency centre (while awaiting MICU transfer) or in the MICU, and had two serum levels obtained within 24 h of the first AG dose. The first AG serum level must have been obtained between 3–9 h after the dose, and the second level ≥3 h after the first level. This was done to ensure post-distributional levels and at least one typical half-life of 3 h between the two levels [12,13]. Patients were excluded if they received more than one dose of the current AG within 48 h prior to the dose being evaluated, were receiving renal replacement therapy or plasmapheresis, or were pregnant.

2.2. Current aminoglycoside practice and pharmacokinetic analysis

Within the MICU of MDACC, AGs are typically dosed via an EIAD strategy. This consists of 7 mg/kg tobramycin or gentamicin and 15–20 mg/kg amikacin using IBW (or AdjBW if >120% IBW), with each dose infused over 1 h. According to MDACC clinical pharmacy practice, AG serum levels are obtained in most patients 4 h and 10 h following completion of the infusion for pharmacokinetic analysis. Tobramycin and amikacin are the predominant AGs prescribed for the treatment of Gram-negative infections.

The elimination rate constant (k_e), half-life ($t_{1/2}$), C_{max}, V_d, C_{peak} and C_{trough} were calculated using a one-compartment, i.v. infusion model based on the Sawchuk–Zaske method (equations shown in Table 1) [14,15]. C_{max} corresponds to the concentration at

the end of a 1-h infusion and was used to calculate V_d in Equation 6. C_{peak} was the concentration determined utilising Equation 4 and a t = 1.7 h, corresponding to the time after the end of infusion when the distribution phase is expected to be complete following large-dose AG administration [12]. C_{trough} was the concentration calculated at 24 h (Fig. 1).

The target C_{peak} for tobramycin and amikacin were 20 mg/L and 40 mg/L, respectively [3]. Given variability in peak concentrations with EIAD reported previously [3], a 20% variability was incorporated, resulting in a target C_{peak} range of 16–24 mg/L for tobramycin and 32–48 mg/L for amikacin. These concentrations were established to target a peak:MIC of 10 for organisms with a MIC of 2 mg/L for tobramycin and 4 mg/L for amikacin.

2.3. Weight analysis

In addition to ABW, three other definitions of weight (kg) were utilised according to the following equations:

AdjBW = IBW + 0.4(ABW–IBW), if ABW is >20% IBW (Eq. 1)

IBW male = 50 + (2.3 × inches > 60) (Eq. 2)

IBW female = 45.5 + (2.3 × inches > 60)

LBW male = (9270 × ABW)/(6680 + 216 × BMI)(Eq. 3)

LBW female = (9270 × ABW)/(8780 + 244 × BMI)

where BMI is the body mass index.

The V_d (L/kg) for each patient was normalised to L/kg by dividing the calculated V_d (L) by each specific definition of weight (kg).

2.4. Statistical analysis

Descriptive statistics were used to summarise patient demographic and clinical characteristics. Age and sex were analysed using $N = 55$, as three patients contributed more than one dose of AG, leaving these two variables unchanged. Clinical measurements were analysed using total $N = 58$. Mean, standard deviation, median and range were provided for continuous variables. Frequencies and percentages were provided for categorical variables. Comparisons between tobramycin and amikacin were made using *t*-test when variables were continuous. A χ^2 test or Fisher's exact test, if more appropriate, were used for categorical variables.

To identify which dose weight best normalised V_d in a L/kg fashion, the distributions of dose weights were summarised and the variances were compared with each other using ratios in a pair-wise manner. Ratios of variance estimates were ranked to identify, on a relative basis, the most precise weight to normalise V_d on a L/kg basis. An *F*-

statistic was computed for each ratio producing *P*-values that could be used to assess the ratio of estimated variances statistically. Then, a linear model regressing V_d (L/kg) on BMI was used to determine which of the weight definitions would provide the most precise estimate of V_d (L/kg) across varying values of BMI. The smallest residual sum of squares (RSS), based on the fitted linear model, was used to determine the most precise weight definition. Subsequently, the estimated slope coefficient nearest to 0 in absolute value, associated with the fitted linear model, was used to identify the weight definition that remained most stable over BMI.

The frequency for which each prescribed dose yielded a C_{peak} within the target range was reported. In addition, the observed C_{peak} was evaluated with regard to attainment of an optimal concentration (10× MIC) for a series of MIC values (tobramycin, 0.5, 1, 2 and 4 mg/L; amikacin, 1, 2, 4 and 8 mg/L). Lastly, for the subset of patients in which a Gram-negative organism was isolated, the frequency for which the dose prescribed yielded a concentration of ≥10× the actual MIC was reported. All analyses were conducted using Stata v.12 (StataCorp LP, College Station, TX).

3. Results

3.1. Patients

During the study period, 1350 i.v. AG doses were dispensed, of which 1292 were excluded. Predominant exclusion criteria were previous AG administration within the prior 48 h and absence of two serum drug levels for pharmacokinetic analysis. Thus, 58

doses of AG (tobramycin, *n* = 34; amikacin, *n* = 24), in 55 patients, were included in the study owing to 3 patients having had a second episode of AG administration (Fig. 2). Baseline characteristics are shown in Table 2. The study sample had a median BMI of 26.3 kg/m^2, a median Acute Physiology and Chronic Health Evaluation (APACHE) II score of 24 and was admitted to the ICU predominantly for respiratory distress.

3.2. Volume of distribution

As shown in Table 3, the median V_d for amikacin and tobramycin was 34.80 L and 28.95 L, respectively. No statistically significant difference was found between the V_d (L) of tobramycin and amikacin; therefore, the two groups were merged for subsequent analysis. Numerous parameters were included in a linear regression analysis investigating factors associated with V_d (L) (Table 4). Of these, ABW, BMI, creatinine clearance [16] and albumin were found to be independently associated with V_d. The median V_d values, normalised per body weight parameter, were: ABW 0.38 L/kg; IBW 0.46 L/kg; AdjBW 0.42 L/kg; and LBW 0.53 L/kg. A pair-wise comparison of body weights revealed that ABW yielded the most precise estimate of V_d when normalised on a L/kg basis (Table 5). The distribution of the individual V_d (L/kg) values for each body weight and the relationship with BMI are depicted in Fig. 3. Three BMI outliers were identified leading to fitted lines with and without the presence of outliers, and all parameter estimates from the linear regression were obtained with outliers excluded. Similar to that identified through pair-wise comparison, the body weight that yielded the most precise estimation of V_d was ABW as it was least variable across BMI (β = 0.001) and had the lowest RSS (1.575).

3.3. Target peak attainment

The median prescribed doses of tobramycin and amikacin were 445 mg (5.8 mg/kg ABW) and 1200 mg (13.8 mg/kg ABW), respectively, with a median C_{peak} of 11.1 mg/L and 27.1 mg/L, respectively (Table 3). Target C_{peak} was attained in only 25% of episodes, with an additional 4% of episodes exceeding the target. The median 24-h C_{trough} was 1.99 mg/L and 2.12 mg/L for tobramycin and amikacin, respectively.

3.4. Organisms present in the study sample

In total, 24 organisms were isolated from the study sample. *Pseudomonas aeruginosa* and *Escherichia coli* isolated from blood cultures were most common (Table 2). The MIC_{50} and MIC_{90} values (MIC that inhibits 50% and 90% of the isolates, respectively) for tobramycin were 1 mg/L and 8 mg/L, respectively; for amikacin, the MIC_{50} and MIC_{90} values were 4 mg/L and 24 mg/L, respectively. A C_{peak} of 20 mg/L for tobramycin would attain a peak:MIC ratio of ≥10 in 75% of isolates (18/24), whilst a lower C_{peak} of 10 mg/L would attain this ratio in 50% (12/24). For amikacin, MIC analysis was assessed on 23 organisms owing to missing data for 1 organism. A C_{peak} of 40 mg/L for amikacin would yield a peak:MIC ratio of ≥10 in 52% of isolates (12/23), whilst a peak of 20 mg/L would attain this ratio in 43% (10/23).

4. Discussion

The V_d of AG in critically ill haematological malignancy patients was found to be 0.38 L/kg with respect to ABW. An increased V_d is consistent with previous studies including critically ill surgical, medical, burn and trauma patients in which the V_d was found to be 0.36 L/kg [17], 0.43 L/kg [18], 0.42 L/kg [6] and 0.3 L/kg [5], respectively. Utilisation of current doses for AGs in critically ill haematological malignancy patients resulted in suboptimal C_{peak} concentrations based on first-dose kinetics in the majority of patients in the present study. Such findings necessitate consideration of the increased V_d in order to avoid suboptimal AG dosing.

A number of factors may affect AG V_d in the critically ill. A predominant theory involves aggressive fluid resuscitation [8,17,18]. With early goal-directed therapy, hypotensive septic patients receive substantial i.v. fluid boluses to optimise central venous pressure, mean arterial pressure and central venous oxygenation [19]. Cumulative fluid balance (CFB) and its effect on V_d in the critically ill has been evaluated previously, with conflicting results [17,18]. Similar to Triginer et al. [18], in the current study a positive correlation between CFB and V_d was observed although this did not reach statistical significance. This may be attributable to the small sample size and relatively large portion of patients with CFB between 0 and +5.99 L (n = 36). CFB may not always impact V_d, as a positive fluid balance may only indicate fluid resuscitation versus a volume overloaded state. Aside from CFB, patients with sepsis may have an increased V_d secondary to capillary leak and decreased vascular tone. Although highly probable, we were unable to quantify these variables; however, in support of this theory, a

significant inverse relationship was found between albumin and V_d. Creatinine clearance was found to be positively correlated with V_d. This may be due to the fact that the creatinine clearance estimation takes into account patient weight. V_d was significantly influenced by body weight, supporting our decision to normalise V_d on a L/kg basis. Furthermore, the association with BMI and V_d supported assessment of this parameter in the evaluation of initial AG dosing.

Clinical studies have demonstrated a positive correlation between AG peak:MIC and improved efficacy, specifically efficacy rates of 80–90% with peak:MIC ≥10 compared with 70% with a peak:MIC of 5 [2,20]. Moore et al. evaluated optimal AG peak:MIC concentrations, with C_{peak} determined 1 h after the end of a 30-min infusion using traditional doses of AG [2]. In a small crossover study involving 11 healthy volunteers, Demczar et al. evaluated the distribution phase of AG following traditional (2 mg/kg) and large-dose (7 mg/kg) administration. Completion of the AG distribution phase was found to occur 30 min following a 1-h infusion for the traditional dose, but 1.7 h following a 1-h infusion for the high dose [12]. Whilst the EIAD regimen described by Nicolau et al. targeted similar peak:MIC ratios, peak levels were obtained immediately following the end of a 1-h infusion [3]. Controversy exists in that this may have overestimated AG peak levels by ignoring the longer distribution phase associated with larger AG doses. Some experts suggest that with larger doses, the AG peak level should be evaluated at the end of the distribution phase as it represents the maximum concentration of the drug at the site of activity [12]. In line with this rationale, we calculated the AG C_{peak} as occurring 1.7 h following the end of a 1-h infusion. Attainment of the target peak:MIC

was relatively poor, although this may be a more realistic assessment of drug level at the site of infection. For purposes of completeness, an analysis was conducted comparing target concentration attainment using C_{max} (i.e. end of infusion) versus C_{peak} (i.e. 1.7 h following completion of the infusion). Although slightly improved, the majority of patients (53%) still did not achieve AG concentrations that crossed the lower threshold of the target (similar to the 71% identified with C_{peak}). Therefore, irrespective of the timing selected to determine PK/PD goal attainment in this patient sample, suboptimal AG serum concentrations were noted, highlighting an opportunity for dosage optimisation. It is important to note that the magnitude of this discordance would be greater and perhaps clinically relevant if the half-life of the patient is shorter.

An additional factor involved in the poor attainment of target peak:MIC in this study may be that current EIAD mg/kg dosing was validated in a different patient population [3]. Originally proposed EIAD was not developed or validated in the critically ill, who have been shown to have an increased V_d [5,6,17,18]. A larger V_d will necessitate higher AG doses than those proposed in the study by Nicolau et al. in order to attain similar levels [3,6,18]. As shown in this study utilising high-dose AG therapy, <30% of patients attained a post-distributional target C_{peak}. This is consistent with previous studies in critically ill patients [4,21]. Previous studies have also proposed dose increases based on suboptimal levels attained. Taccone et al. evaluated EIAD with amikacin doses of 25 mg/kg (ABW or AdjBW) targeting a peak >64 mg/L with an expected V_d of 0.4 L/kg. Even with this regimen, target levels were only achieved in 64% of patients. A dose of

28 mg/kg would be needed for 70% of patients to achieve a peak concentration of 64 mg/L [7].

In accordance with this suggestion for use of higher AG doses and for completeness, we examined whether a dosage increase alone could optimise C_{peak} target attainment in this study sample. For example, use of Equation 7 (Table 1) and the sample-derived median k_e and V_d (L/kg ABW) resulted in a dose of ca.10 mg/kg ABW for tobramycin and 20 mg/kg ABW for amikacin needed to achieve a C_{peak} of 20 mg/L and 40 mg/L, respectively. Evaluation of this new dose in conjunction with each individual patient's pharmacokinetic values yielded a predicted C_{peak} target attainment in ca. 50% of the study patients. However, ca. 25% of study patients would achieve a C_{peak} above the target and the remaining 25% below. A C_{peak} above (in contrast to below) the target is likely of less concern to the bedside clinician given the concentration-dependent efficacy of AG agents and available data that does not demonstrate peak-dependent toxicity [22,23]. However, the large variability observed in attained C_{peak} is reflective of the large variability observed in k_e and V_d within this sample, irrespective of dose. This exercise highlights that C_{peak} attainment is not simply optimised by dose alone, but rather influenced by a number of factors that we could not control or account for retrospectively and likely other factors whose influence was not examined. Admittedly, it may be impossible to truly capture all of the influencing factors in a highly dynamic critically ill patient sample, particularly with haematological malignancy. It should be emphasised that in order to appropriately determine a more optimal first-dose AG

regimen, a population analysis and comprehensive evaluation of confounding variables would be required, which was outside the scope of this research.

It should also be noted that in this study an empirical serum C_{peak} of 20 mg/L tobramycin and 40 mg/L amikacin was considered optimal to account for Gram-negative pathogens with MICs of 2 mg/L and 4 mg/L, respectively. However, higher doses may not be warranted if institution-specific organisms exhibit lower MICs. Interestingly, the peak:MIC target against the 24 organisms isolated in this study is more clinically feasible and likely attained with tobramycin versus amikacin. Furthermore, although the C_{peak} target was not commonly met in the study sample with current doses, there was attainment of optimal peak to MIC ratio in a substantial number of patients. This serves to confound clinical results associated with higher AG dosing when current practice is only suboptimal for a subset of patients. Therefore, it is recommended that higher AG targets may only be warranted for empirical therapy (i.e. unknown pathogen MIC) and for infections caused by organisms with higher MICs. Consequently, it is important to consider a reduction in dose if the organism's MIC is lower than expected.

Lastly, studies vary in the use of ABW, IBW or AdjBW for dosing purposes [2,3,12,22] and may differ from reference recommendations for the optimal dose weight [24,25]. In this study, the least amount of variability (i.e. most precise) in V_d when normalised to L/kg was identified with ABW. This study predominantly consisted of patients considered normal to overweight, with a median weight of 79.9 kg and BMI of 26.3 kg/m^2. Therefore, ABW may not be the most appropriate (or precise) weight in the

obese population (i.e. BMI > 30 kg/m^2). Pai et al. demonstrated that tobramycin had a decreased V_d/total body weight in obese compared with normal weight patients (0.3 ± 0.11 vs. 0.35 ± 0.11; $P \leq 0.008$) [26]. LBW has been proposed as a body size descriptor to improve drug dosing across a larger weight spectrum. LBW was not found to provide the most precise estimation of V_d for AG dosing in the current study, which could be a reflection of the BMI range in this analysis. In our patient sample, ABW was found to be the most precise weight to normalise V_d in L/kg, and thus use of ABW-based dosing should improve reliability of pharmacokinetic target attainment with first-dose AGs in clinical practice. Further investigation is needed in the obese population.

There are several limitations to this study that deserve mention, including a relatively small sample size and limited patient population. Furthermore, all patients had a haematological malignancy. Although this limits generalisability, this information contributes to optimising AG dosing strategies in one of the most vulnerable critically ill populations. There is also the possibility of selection bias as analysis was limited to those patients in which serum AG levels were obtained. One may assume that practitioners were more likely to order AG levels in patients with a suspected altered V_d; however, our practice is to perform pharmacokinetic analysis with EIAD in most patients. In addition, the pharmacokinetic analysis was comprised of only one set of data points after a single dose. As alluded to earlier, given the dynamic nature of critically ill patients, multiple factors affecting drug clearance that were not accounted or controlled for could lead to substantial pharmacokinetic variability. Given this was a retrospective evaluation of current clinical practice, additional serum AG levels were not

available. This study was also limited to a pharmacokinetic evaluation with no correlation to clinical outcomes. Similarly, while the aminoglycoside post-antibiotic effect in neutropenic populations is speculated to be decreased, the clinical implications of a prolonged drug-free interval in neutropenic patients have not been determined [27,28]. Lastly, although a suboptimal C_{peak} was demonstrated in the majority of the sample, we were unable to utilise the pharmacokinetic evaluation to confidently determine a more optimal first-dose AG regimen in lieu of a formal population analysis.

5. Conclusion

Critically ill haematological malignancy patients have an increased V_d in comparison with previous reports of non-critically ill patients. Current AG doses resulted in suboptimal peak concentrations in the majority of the study sample. This was especially true when considering organisms with higher MICs. These findings necessitate further examination of dose optimisation via comprehensive population pharmacokinetic analyses. Lastly, further clinical studies are needed to assess safety and efficacy outcomes with higher AG doses as well as to evaluate pharmacokinetic parameters in the obese.

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Fig. 1. Pharmacokinetic analysis of aminoglycoside (AG) dosing. C_{max}, ; C_{peak}, ; C_{trough}, .

Fig. 2. Aminoglycoside (AG) dose screening. i.v., intravenous.

Fig. 3. Association between volume of distribution (V_{ss}) in L/kg and body mass index (BMI) by weight definition. Beta is the estimated slope coefficient for the fitted regression line, and RSS is the residual sum of squares. The solid line (——) represents the fitted line without three BMI outliers, and the dashed line (- - -) represents the fitted line with the BMI outliers present.

Table 1

Pharmacokinetic equations (one-compartment model)

Eq. 1	$k_e = (\ln C_1 - \ln C_2)/(t_{interval})$
	k_e = elimination rate constant (h^{-1})
	C_1 = first level obtained (mg/L)
	C_2 = second level obtained (mg/L)
	$t_{interval}$ = time between levels (h)
Eq. 2	$t_{1/2} = 0.693/k_e$
Eq. 3	$C_{max} = C_0/e^{-ke * t}$
	$C_0 = C_1$
	t = time from the end of infusion to C_0
Eq. 4	$C_{peak} = C_{max} * e^{-ke * t}$
	t = time from C_{max} to C_{peak} (1.7 h)
Eq. 5	$C_{trough} = C_{peak} * e^{-ke * t}$
	t = time from C_{peak} to 24 h (21.3 h)
Eq. 6	$V_d = (D/t')*(1/k_e) * (1-e^{-ke * t'})/(C_{max} - C_0e^{-ke * t'})$
	D = dose in mg
	t' = length of infusion (i.e. 1 h)
Eq. 7	$D/X = (V_d/X)*t'*k_e*(C_{max} - C_0e^{-ke * t'})*[1/(1 - e^{-ke * t'})]$
	X = patient weight in kg
	D/X = dose in mg/kg
	V_d/X = volume of distribution in L/kg

Table 2

Summary of patient characteristics

Characteristic	Total	Aminoglycoside		*P*-value
		Tobramycin	Amikacin	
Demographics	*N* = 55	*n* = 33	*n* = 22	
Age (years)				
Mean ± S.D.	51.4 ± 14.3	52.6 ± 14.5	49.6 ± 14.2	0.445
Median (range)	53 (22–83)	55 (22–83)	50.5 (23–77)	
Sex [*n* (%)]				
Female	20 (36.4)	14 (42.4)	6 (27.3)	0.252
Male	35 (63.6)	19 (57.6)	16 (72.7)	
Primary malignancy [*n* (%)]				
Leukaemia	30 (54.5)	18 (54.5)	12 (54.5)	0.983 [a]
Lymphoma	11 (20.0)	6 (18.2)	5 (22.7)	
Multiple myeloma	9 (16.4)	5 (15.2)	4 (18.2)	
Myelodysplastic syndrome	4 (7.3)	3 (9.1)	1 (4.5)	
Aplastic anaemia	1 (1.8)	1 (3.0)	0 (0.0)	
Clinical measurements [b]	*N* = 58	*n* = 34	*n* = 24	
Actual weight (kg)				
Mean ± S.D.	83.5 ± 19.4	81.7 ± 21.2	86.2 ± 16.7	0.391
Median (range)	79.9 (51.8–126.7)	76.0 (51.8–126.7)	87.6 (58.0–117.5)	
Ideal body weight				
Mean ± S.D.	67.2 ± 12.1	65.3 ± 12.7	70.0 ± 10.8	0.140
Median (range)	68.3 (45.5–98.3)	65.9 (45.5–98.3)	73.1 (45.5–84.0)	
Adjusted body weight				
Mean ± S.D.	74.8 ± 12.5	72.8 ± 12.2	77.7 ± 12.6	0.141

Median (range)	77.6 (50.5–96.0)	75.5 (51.8–94.3)	80.6 (50.5–96.0)	
Lean body weight				
Mean ± S.D.	57.1 ± 12.6	54.9 ± 12.6	60.2 ± 12.1	0.117
Median (range)	58.5 (34.4–76.9)	56.5 (34.4–76.9)	64.8 (36.1–76.3)	
BMI (kg/m^2)				
Mean ± S.D.	27.8 ± 6.6	28.0 ± 7.9	27.7 ± 4.2	0.901
Median (range)	26.3 (19.1–56.2)	26.1 (19.1–56.2)	27.4 (21.5–36.5)	
Reason for ICU admission [*n* (%)]				
Respiratory distress	29 (50.0)	14 (41.2)	15 (62.5)	0.314 [a]
Haemodynamic instability	14 (24.1)	8 (23.5)	6 (25.0)	
Neutropenic fever	7 (12.1)	5 (14.7)	2 (8.3)	
Septic shock	4 (6.9)	4 (11.8)	0 (0.0)	
Other [c]	4 (6.9)	3 (8.8)	1 (4.2)	
APACHE II score [d]				
Mean ± S.D.	24.3 ± 5.8	24.1 ± 6.3	24.5 ± 5.1	0.784
Median (range)	24 (14–39)	24 (14–39)	25 (14–33)	
Neutropenic [*n* (%)]				
No	23 (39.7)	14 (41.2)	9 (37.5)	0.778
Yes	35 (60.3)	20 (58.8)	15 (62.5)	
Serum creatinine (mg/dL)				
Mean ± S.D.	1.2 ± 0.8	1.4 ± 1.0	1.0 ± 0.4	0.106
Median (range)	1.0 (0.4–6.1)	1.1 (0.5–6.1)	0.9 (0.4–2.4)	
Creatinine clearance (mL/min)				
Mean ± S.D.	78.2 ± 45.1	67.1 ± 33.8	93.9 ± 54.4	0.025
Median (range)	68.9 (15.0–283.5)	60.4 (15.0–155.1)	86.5 (28.1–283.5)	
No. of vasopressors used [*n* (%)]				

0	25 (43.1)	15 (44.1)	10 (41.7)	0.266 [a]
1	25 (43.1)	14 (41.2)	11 (45.8)	
2	6 (10.3)	5 (14.7)	1 (4.2)	
3	2 (3.4)	0 (0.0)	2 (8.3)	
Culture positive	*N* = 24 [e]	*n* = 18	*n* = 6	
Blood	16 (66.7)	11 (61.1)	5 (83.3)	0.797 [a]
Pulmonary	5 (20.8)	4 (22.2)	1 (16.7)	
Urine	3 (12.5)	3 (16.7)	0 (0.0)	
Organism/susceptibility	MIC_{50}	MIC_{90}	MIC ≤ 2 mg/L	MIC ≤ 4 mg/L
Tobramycin	1 mg/L	8 mg/L	18 (75%)	–
Amikacin [f]	4 mg/L	24 mg/L	–	12 (52%)

S.D., standard deviation; BMI, body mass index; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC that inhibits 50% and 90% of the isolates, respectively.

[a] *P*-value from Fisher's exact test; all other *P*-values are from a *t*-test (continuous values) or χ^2 test (categorical values).

[b] Three patients were administered aminoglycoside doses on two separate occasions, resulting in 58 clinical observations.

[c] Includes acute coronary syndrome, altered mental status, gastrointestinal bleeding and sepsis.

[d] Due to missing data, total *N* = 53 (amikacin, *n* = 22; tobramycin, *n* = 31).

[e] Total organisms (*N* = 24): *Pseudomonas aeruginosa* (11); *Escherichia coli* (7); *Acinetobacter baumannii* (3); *Klebsiella pneumoniae* (1); *Serratia marcescens* (1); *Enterobacter cancerogenus* (1).

[f] Due to missing data, for amikacin MIC, *n* = 23.

Table 3

Summary of population kinetics

	Amikacin (*N* = 24)	Tobramycin (*N* = 31)
Kinetic variables		
Population k_e		
Mean ± S.D.	0.11 ± 0.08	0.10 ± 0.06
Median (range)	0.10 (0.02–0.3)	0.09 (0.01–0.26)
$t_{1/2}$ (h)		
Mean ± S.D.	8.76 ± 7.33	11.12 ± 12.12
Median (range)	6.53 (2.29–31.45)	7.51 (2.68–70.15)
Population V_d (L)		
Mean ± S.D.	39.85 ± 18.30	30.80 ± 15.18
Median (range)	34.80 (13.03–72.10)	28.95 (7.90–80.44)
Population V_d (L/kg ABW)		
Mean ± S.D.	0.46 ± 0.19	0.40 ± 0.16
Median (range)	0.37 (0.22–0.84)	0.39 (0.12–0.78)
Levels		
C_{peak} (mg/L)		
Mean ± S.D.	26.44 ± 10.65	14.11 ± 7.54
Median (range)	27.07 (8.28–47.95)	11.12 (4.88–40.49)
C_{max} (mg/L)		
Mean ± S.D.	33.48 ± 15.84	16.97 ± 9.80
Median (range)	32.89 (9.88–74.38)	13.11 (5.38–52.74)
C_{trough} (mg/L)		
Mean ± S.D.	4.41 ± 5.80	2.63 ± 2.77
Median (range)	2.12 (0.06–23.65)	1.99 (0.06–13.69)

k_e, elimination rate constant; S.D., standard deviation; $t_{1/2}$, half-life; V_d, volume of distribution; ABW, actual body weight; C_{peak}, post-distributional peak concentration; C_{max}, concentration at the end of a 1-h infusion; C_{trough}, concentration calculated at 24 h.

Table 4

Linear regression analysis with response variable: volume of distribution (L)

	b (SE)	*P*-value
APACHE II score		
1 unit increase	0.34 (0.42)	0.422
CFB		
100 unit increase	–0.18 (3.57)	0.961
ABW		
10 kg increase	5.65 (1.13)	<0.001
BMI		
5 kg/m^2 increase	7.78 (2.66)	0.005
Serum creatinine		
1 unit increase	–2.52 (2.52)	0.322
Creatinine clearance		
5 unit increase	0.84 (0.23)	0.001
Albumin		
1 unit change	–9.11 (3.42)	0.010
Total protein		
1 unit change	–5.10 (2.50)	0.052

APACHE, Acute Physiology and Chronic Health Evaluation; CFB, cumulative fluid balance; ABW, actual body weight; BMI, body mass index.

N = 55 due to removal of three outliers with BMI > 40 kg/m^2, with the exception of APACHE II score (*N* = 51), CFB (*N* = 53), albumin (*N* = 52) and total protein (*N* = 28).

Table 5

Pair-wise comparisons of body weights

	Ratio [a] (*P*-value [b])			
	ABW	AdjBW	IBW	LBW
ABW	1.00 (—)	1.19 (0.506)	1.49 (0.129)	1.86 (0.019)
AdjBW	—	1.00 (—)	1.25 (0.392)	1.56 (0.092)
IBW	—	—	1.00 (—)	1.24 (0.406)
LBW	—	—	—	1.00 (—)

ABW, actual body weight; AdjBW, adjusted body weight; IBW, ideal body weight; LBW, lean body weight.

[a] Ratio = estimated variance of column variable/ estimated variance of row variable.

[b] *P*-value is based on an *F*-test with degrees of freedom = 57 both for numerator and denominator.

Table 6

Number (%) of patients attaining C_{peak}:MIC of 10 (±20%) with the current first-dose strategy

Tobramycin/amikacin MIC (mg/L)		*N* (%)
0.5/1	Attain	4 (7)
	Over	51 (93)
	Under	0 (0)
1/2	Attain	16 (29)
	Over	29 (53)
	Under	10 (18)
2/4 [a]	Attain	14 (25)
	Over	2 (4)
	Under	39 (71)
4/8	Attain	1 (2)
	Over	0 (0)
	Under	54 (98)

C_{peak}, post-distributional peak concentration; MIC, minimum inhibitory concentration.

[a] MIC values for which study target C_{peak} values were derived.

Figure 1. Pharmacokinetic Analysis ***(intended for color reproduction)***

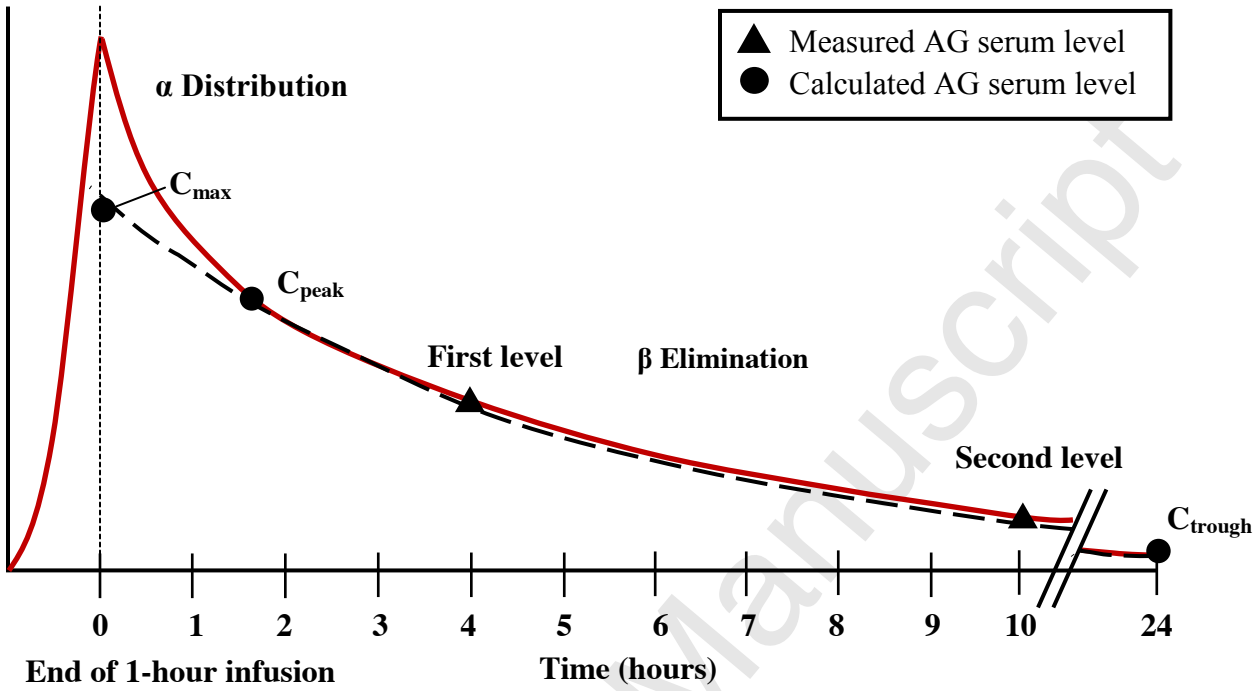


Figure 2. Aminoglycoside Dose Screening

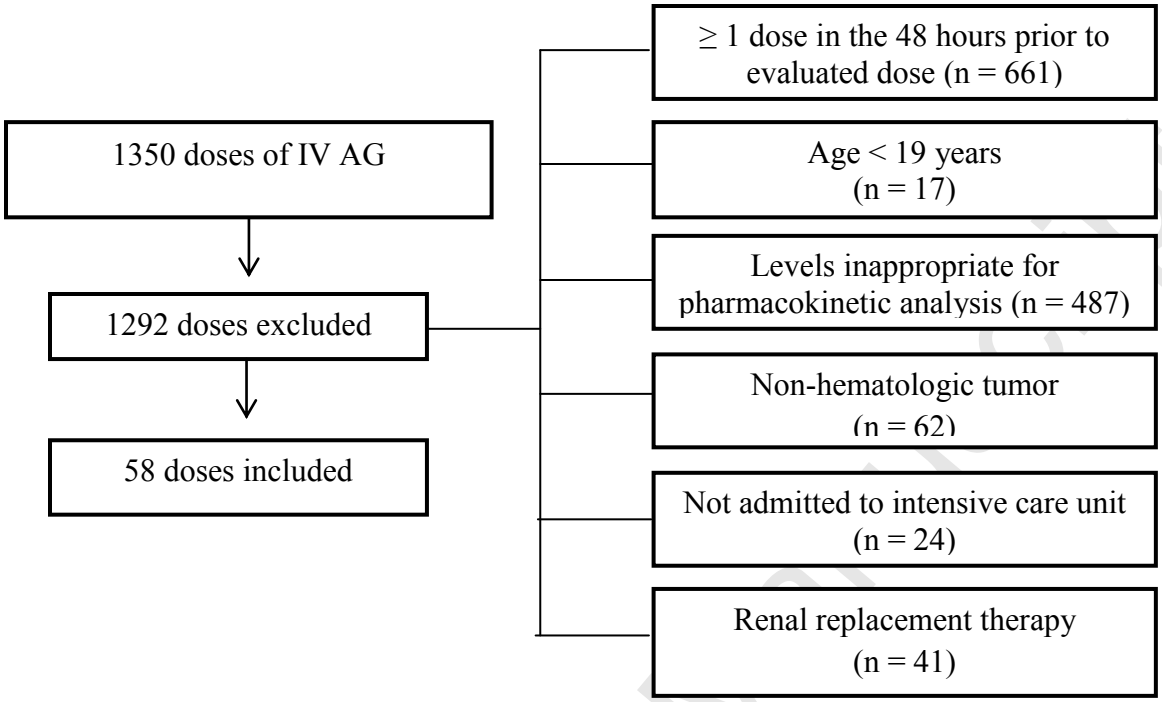
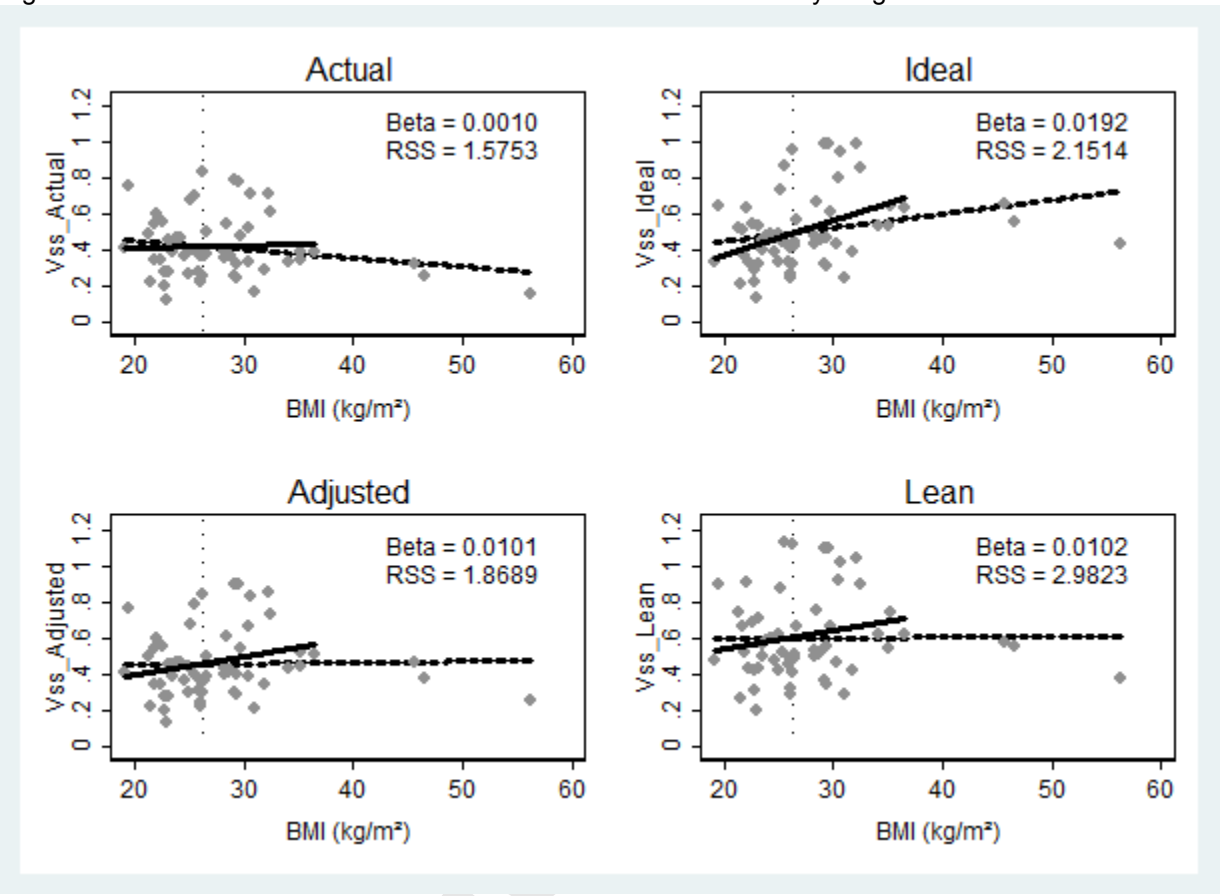


Figure 3. The association between Volume of Distribution and BMI by weight definition



* Beta is the estimated slope coefficient for the fitted regression line and RSS is the Residual Sum of Squares. The solid line (──) represents the fitted line without bmi outliers, and the dashed line (- - -) represents the fitted line with bmi outliers present.