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Comparison of gentamicin dose estimates derived from manual calculations, the Australian 'Therapeutic Guidelines: Antibiotic' nomogram and the SeBA-GEN and DoseCalc software programs

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Aim
To compare gentamicin dose estimates from four predictive methods.

Methods
A retrospective study was conducted, comprising patients at Fremantle Hospital who received gentamicin therapy and had at least one gentamicin serum concentration reported. A manual calculation method, the Australian 'Therapeutic Guidelines: Antibiotic' (TGA) nomogram and the SeBA-GEN and DoseCalc software packages were compared. SeBA-GEN dose estimates were regarded as the reference standard.

Results
There were 64 males and 30 females with mean age of 58 ± 16 years. In patients with moderate renal impairment (CL_{Cr} = 30–60 ml min^{-1}; n = 21), mean dose estimates using DoseCalc and the manual calculation method were comparable to SeBA-GEN but the mean TGA nomogram dose (230 mg; 95% confidence interval 179, 281) was significantly lower than SeBA-GEN (286 mg; 261, 311; P = 0.002; one-way RM ANOVA). In patients with mild renal impairment (CL_{Cr} = 60–90 ml min^{-1}; n = 48), DoseCalc (392 mg; 367, 427) was comparable to SeBA-GEN (377 mg; 362, 392). Although the manual method (341 mg; 306, 376; P = 0.007) and the TGA nomogram (335 mg; 302, 368; P < 0.001) estimates were significantly lower than SeBA-GEN, the practical difference was modest.

Conclusions
SeBA-GEN and DoseCalc are generally comparable for estimation of gentamicin doses in patients with renal impairment. The 'Therapeutic Guidelines: Antibiotic' nomogram is a valid approach to dosage estimation, but only when used in patients with normal renal function. Simple manual calculations are a suitable alternative in patients with renal impairment.

Introduction

Once-daily gentamicin dosing has proven to be at least as effective as, and apparently less nephrotoxic than, traditional multiple-daily dose regimens [1–3]. Since 1995, several approaches to therapeutic drug monitoring for gentamicin have been proposed, including nomograms [4–7], a two-point manual calculation method [4] and a computer-based Bayesian method (SeBA-GEN)

that has been well validated [8, 9]. In Western Australia, the locally authored DoseCalc software program has been promoted in tertiary and secondary hospitals, but there has been limited external assessment of its performance [10].

SeBA-GEN can be used to predict a starting dose and then to determine daily doses on the basis of one or more serum drug concentrations (SDCs), with a nominal target area under the serum concentration–time curve (AUC) of 101 mg l^{-1} h [8]. DoseCalc can predict a starting dose or utilize one SDC to estimate a new dose of gentamicin, with a nominal target AUC of 85 mg l^{-1} h [10]. The target AUC for SeBA-GEN and DoseCalc can be user-defined.

The use of one SDC to estimate a new gentamicin dose is also the basis of nomograms used in Australia [7, 11], which are essentially identical and have been developed from the report by Begg and colleagues [4]. The initial dose of gentamicin is based on the patient's calculated creatinine clearance (CL_{Cr}) and subsequent doses are adjusted according to the SDC determined between 6 and 14 h after the dose. However, we have been concerned that the caveat to the nomograms – 'to be used in patients with normal renal function' – is overlooked by practitioners, especially those with limited access to more sophisticated computer-based methods.

Given that many patients in tertiary hospitals are elderly and often will have impaired renal function, doses in the range of 3–5 mg kg^{-1} day^{-1} may be more appropriate than the recommended doses of 6–7 mg kg^{-1} day^{-1} in patients with normal renal function [7, 9]. The smaller doses will produce lower peak SDCs and higher trough concentrations, but a similar AUC, compared with conventional doses in patients with normal renal function. Therefore, in patients with creatinine clearance <50 ml min^{-1} and one reported SDC, the use of nomograms intended for patients with normal renal function will invariably lead to predicted doses that are lower than estimates obtained from a method that is based on achieving a target AUC, but the shape of the concentration–time curve is less desirable.

In a preliminary study of 31 patients, comparing SeBA-GEN, DoseCalc and the Australian 'Therapeutic Guidelines: Antibiotic' (TGA) nomogram, we have previously shown that DoseCalc predicts approximately 20% lower doses of gentamicin for a given target AUC than SeBA-GEN [12]. As expected, the TGA nomogram predicted lower doses of gentamicin for all patients with impaired renal function. Results of the preliminary study prompted us to consider alternative methods of gentamicin dose prediction in patients with renal impairment. We concluded that a simple manual calculation method would be a useful tool in clinical settings where computer-based methods are not available. Hence, the aim of the present study was to conduct a more detailed comparison of estimates from SeBA-GEN, DoseCalc, the TGA nomogram and a manual method of calculating gentamicin doses. Our hypotheses were that: (i) doses of gentamicin that were prescribed according to the TGA nomogram in patients with renal impairment would be inadequate when compared with computer-based methods, and (ii) gentamicin dose estimates using a manual calculation method would be superior to nomograms in patients with renal impairment and an acceptable alternative to computer-based methods.

Methods

This study was approved by the Human Research Ethics Committee at Curtin University of Technology. Ethics approval and patient consent was not required at Fremantle Hospital and Health Services as this was a retrospective audit of data routinely collected by pharmacists in the hospital. All patients who were admitted to Fremantle Hospital from January to June 2000 and received gentamicin were considered for inclusion in this study. Each patient was assigned a unique identification code to preserve patient confidentiality. Exclusion criteria included patients less than 18 years of age (due to low patient numbers and variable dosage regimens used); patients receiving multiple daily doses of gentamicin; patients without measured weight and height; patients with no biochemistry data; and patients with no gentamicin SDC reported or where the SDC was <0.5 mg l^{-1} (reported as '< 0.5 mg l^{-1}' by the pathology laboratory at Fremantle Hospital). Patients were classified according to renal function [11] as severe renal impairment (CL_{Cr} < 30 ml min^{-1}), moderate renal impairment (CL_{Cr} = 30–60 ml min^{-1}), mild renal impairment (CL_{Cr} = 60–90 ml min^{-1}) and normal renal function (CL_{Cr} > 90 ml min^{-1}).

Four methods of dosage prediction were compared: SeBA-GEN; DoseCalc; the TGA nomogram [7], which also appears in the Australian Medicines Handbook [11]; and a manual calculation method based on established principles (Appendix 1). The first dose predictions were determined using SeBA-GEN, DoseCalc, and the First Dose Table (Table 1). Subsequent dose estimates were determined using SeBA-GEN, DoseCalc, the TGA nomegram and the manual calculation method. Predicted doses from SeBA-GEN were regarded as the reference standard because this method has been comprehensively validated [8, 9].

For prediction of the first dose of gentamicin, SeBA-

Table 1
Table for the determination of initial dose of gentamicin ('First Dose Table'); adapted from Begg and colleagues [4, 7, 11]

CL_{Cr} (ml min^{-1})	Initial dose (mg kg^{-1})	Target AUC (mg l^{-1} h)	Maximum daily dose (mg)
>66	5–7	70–100	560
54–66	5–6	85–100	480
42–54	5	100	400
30–42	4	100	320
21–30	3	100	240
<21	Seek specialist advice		

GEN and DoseCalc require baseline information such as gender, height, weight, age and serum creatinine. Several hospitals in Western Australia, including Fremantle Hospital, recommend a 'starting dose' table that was developed at the QEII Medical Centre in 1996 (Table 1). The 'First Dose Table' is based on the report by Begg *et al.* [4] and is similar to the 'starting dose' table in the TGA (Table 19 in reference [7]). A feature of the locally used First Dose Table (Table 1), which was employed in the present study, is the provision of a maximum recommended dose, to guard against excessive doses caused by arithmetic errors such as using the patient's actual body weight rather than ideal body weight. For the First Dose Table, creatinine clearance (CL_{Cr}) must be determined (Equations 1 and 2, Appendix 1) and the dose is calculated from the patient's ideal body weight. The manual calculation method for estimation of a subsequent dose based on a gentamicin SDC is shown in Appendix 1.

Statistical analyses were performed using SigmaStat® Version 2.03 (SPSS Inc., Chicago, IL, USA; 1997). Data are summarized as mean ± SD or mean and 95% confidence interval (95% CI), as indicated. Data were analysed using one-way RM ANOVA with the All Pairwise Multiple Comparison Procedure (Tukey's Test) for *post-hoc* analysis. A significance level of $P < 0.05$ was used.

Results

A total of 117 patients met the selection criteria and 27 patients were excluded according to the exclusion criteria. From the eligible patients, gentamicin SDCs for 23 patients could not be used in the study due to inconsistent or inaccurate data in medical records, such as uncertainty of dose given or disparity between times recorded in medical records and the pathology report forms. Hence, data from 94 patients were available for the study. The patient group comprised 64 males and 30 females with mean age of 58 ± 16 years (male = 59 ± 15 years; female = 57 ± 18 years), actual body weight of 79 ± 19 kg (male 84 ± 17 kg; female 67 ± 17 kg) and mean ideal body weight of 67 ± 11 kg (male 73 ± 7 kg; female 54 ± 6 kg). Six patients were classified as having severe renal impairment (CL_{Cr} < 30 ml min^{-1}) and were excluded from detailed analysis because appropriate interpretation of SDCs would have required an individual clinical assessment. Hence, gentamicin SDCs from 26 patients with moderate renal impairment, 44 patients with mild renal impairment and 18 patients with normal renal function have been evaluated.

First dose predictions using SeBA-GEN, DoseCalc, and the First Dose Table are presented in Table 2, along with the dose that was prescribed. DoseCalc underestimated the predicted dose in patients with moderate renal impairment but was comparable to SeBA-GEN in mild renal impairment and normal renal function. The First Dose Table was comparable to SeBA-GEN in patients with moderate renal impairment but underpredicted the gentamicin dose in mild renal impairment and normal renal function (Table 2). By comparison, the mean prescribed dose in moderate renal impairment (272 mg) was not significantly different from that obtained from SeBA-GEN (240 mg; $P = 0.14$; power = 0.4) or that obtained from the First Dose Table (241 mg; $P = 0.12$; power = 0.28). It was notable that the prescribed dose, which should have been determined using the First Dose Table, was significantly higher than the First Dose Table predictions in mild renal impairment and normal renal function. Due to the retrospective nature of the study, it was not feasible to determine the reason(s) for this observation.

Second and third dose estimates using SeBA-GEN, DoseCalc, the manual dose calculation method and the TGA nomogram are presented in Table 3. Although there were no differences of practical significance between DoseCalc and SeBA-GEN, the findings of principal interest were related to the manual calculation method and the TGA nomogram. Estimates from the manual calculation method in patients with moderate renal impairment were comparable to those obtained from SeBA-GEN but the manual method underestimated the gentamicin dose in mild renal impairment and normal renal function (Table 3). By contrast, the TGA nomogram estimates were significantly lower than SeBA-GEN (and the manual method) in moderate renal impairment. In mild renal impairment, the nomogram also underestimated the gentamicin dose (compared with SeBA-GEN) but mean estimates from the nomo-

Table 2
First dose predictions of gentamicin using SeBA-GEN, DoseCalc and the First Dose Table (**Table 1**). The prescribed dose is provided for comparison

Method	Dose (mg)*	P-value for method† SeBA-GEN	DoseCalc	First Dose Table	Prescribed dose
CL_{Cr} = 30–60 ml min^{-1}; *n* = 25 (moderate renal impairment)					
SeBA-GEN	240 (224, 256)	–	<0.001	NS	NS
DoseCalc	144 (116, 172)	<0.001	–	<0.001	<0.001
First Dose Table	241 (223, 259)	NS	<0.001	–	NS
Prescribed dose	272 (240, 304)	NS	<0.001	NS	–
CL_{Cr} = 60–90 ml min^{-1}; *n* = 44 (mild renal impairment)					
SeBA-GEN	352 (339, 365)	–	NS	0.048	0.006
DoseCalc	358 (329, 387)	NS	–	0.007	0.048
First Dose Table	327 (313, 341)	0.048	0.007	–	<0.001
Prescribed dose	383 (367, 399)	0.006	0.048	<0.001	–
CL_{Cr} >90 ml min^{-1}; *n* = 15 (normal renal function)					
SeBA-GEN	497 (460, 534)	–	NS	<0.001	NS
DoseCalc	512 (484, 540)	NS	–	<0.001	NS
First Dose Table	382 (366, 398)	<0.001	<0.001	–	<0.001
Prescribed dose	501 (475, 527)	NS	NS	<0.001	–

**Data are mean (95% CI);* n = *84 complete sets of data. †One-way RM ANOVA; Tukey test. To compare the methods, read down the column (or across the row) to the desired comparator row (or column).*

gram and the manual calculation method were comparable. In normal renal function, the TGA nomogram was comparable to SeBA-GEN.

Discussion

We have shown that the performance of SeBA-GEN and DoseCalc software packages in the prediction of gentamicin doses is comparable, except in first dose predictions for patients with moderate renal impairment, where DoseCalc routinely estimated lower doses than SeBA-GEN. This was most likely a function of the *a priori* parameters and the lower target AUC for DoseCalc (85 mg l^{-1} h *vs.* 101 mg l^{-1} h). Our study confirms the validity of printed nomograms, when used in patients with normal renal function, and we have demonstrated that a relatively simple method of manual calculation could be useful when nomograms are inappropriate and software applications are not available.

The foundation of current approaches to gentamicin dosage predictions in Australia was the report by Begg and colleagues in 1995 [4]. First dose predictions were based on the premise that 5–7 mg kg^{-1} was a suitable dose in patients with normal renal function, an approach that was consistent with other reported methods [5, 6]. The starting dose recommendations of Begg *et al.* [4] were adopted in the Australian 'Therapeutic Guidelines: Antibiotic' (9th Edition, 1996/1997) and by hospitals, often with minor modification to suit local practice (Table 1). The TGA [7] now has a series of tables that, depending on the interpretation, can lead to dose estimates which are approximately half those derived from conventional guidelines [4]. It is acknowledged in the TGA that aspects of the recommendations remain to be formally validated [7].

In the present study, we were able to confirm preliminary findings [12] that first dose DoseCalc predictions were similar to those from SeBA-GEN in patients with normal renal function or mild renal impairment, but significantly lower in patients with moderate renal impairment (Table 2). We were not able to determine the cause of this discrepancy but this finding may have clinical relevance, given the importance of the first dose of gentamicin, particularly in regard to concentration-dependent bactericidal effect [1, 2].

The First Dose Table compared favourably with SeBA-GEN in moderate renal impairment. In patients with mild renal impairment, it is reasonable to conclude that the 7% difference between the two methods (327 mg *vs.* 352 mg) is of little practical difference.

Table 3
Second or third dose estimates of gentamicin using SeBA-GEN, DoseCalc, TGA nomogram and Manual Calculation

Method	Dose (mg)*	P-value for method† SeBA-GEN	DoseCalc	Manual calculation	TGA Nomogram
CL_{Cr} = 30–60 ml min^{-1}; *n* = 21 (moderate renal impairment)					
SeBA-GEN	286 (261, 311)	–	NS	NS	0.002
DoseCalc	301 (259, 350)	NS	–	NS	<0.001
Manual calculation	296 (244, 348)	NS	NS	–	<0.001
TGA Nomogram	230 (179, 281)	0.002	<0.001	<0.001	–
CL_{Cr} = 60–90 ml min^{-1}; *n* = 48 (mild renal impairment)					
SeBA-GEN	377 (362, 392)	–	NS	0.007	<0.001
DoseCalc	392 (367, 427)	NS	–	<0.001	<0.001
Manual calculation	341 (306, 376)	0.007	<0.001	–	NS
TGA Nomogram	335 (302, 368)	<0.001	<0.001	NS	–
CL_{Cr} >90 ml min^{-1}; *n* = 14 (normal renal function)					
SeBA-GEN	501 (461, 541)	–	0.04	<0.001	NS
DoseCalc	434 (378, 490)	0.04	–	<0.001	NS
Manual calculation	314 (250, 378)	<0.001	<0.001	–	<0.001
TGA Nomogram	466 (403, 529)	NS	NS	<0.001	–

**Data are mean (95% CI);* n = *83 complete sets of data. †One-way RM ANOVA; Tukey test. To compare the methods, read down the column (or across the row) to the desired comparator row (or column).*

However, the underestimation by the First Dose Table (Table 2) in patients with normal renal function may have clinical relevance and was probably due to the maximum daily dose restriction (Table 1).

For estimation of second or subsequent doses of gentamicin, the method of Begg *et al.* [4] was based on classical pharmacokinetic principles and required two SDCs during the dosage interval. The SeBA-GEN package was subsequently developed and validated [8, 9] and has proved to be a valuable tool in the clinical environment, with a requirement for only one SDC per day. As SeBA-GEN, DoseCalc and the TGA nomogram require only one SDC during the 24-h dosage interval to predict the next dose, these are the principal methods employed in Western Australian hospitals. Hence, it has become routine practice to obtain only one blood sample per day when patients are receiving gentamicin therapy. In general, the blood sample is obtained between 6 and 14 h after the single-daily dose of gentamicin. Depending on the renal function status, interpretation of the SDC could be based on the nomogram or may be completed by a clinical pharmacologist or pharmacist with access to the software.

In patients with mild or moderate renal impairment, our data show that doses predicted from the TGA nomogram will be underestimates (Table 3). This is more likely if SDCs are determined late in the 6–14-h post-dose period because the dosage underestimation is associated with the lower initial dose and longer elimination half-life of gentamicin in these patients. As the peak serum concentration will be lower, due to the smaller dose compared with patients with normal renal function, the concentration approximately 6 h after the dose may be within the accepted range of the nomogram, indicating that no change (or an increase [10]) of dose is required. However, due to the longer half-life, the serum concentration 12–14 h after the dose could be considerably higher than the accepted range of the nomogram, thus predicting a reduction in dose.

The manual method of dosage estimation was evaluated in this study, because of its potential value as an alternative (or back-up) to software packages and as an educational tool for practitioners who will routinely use nomograms or software applications. This method was adapted from Begg *et al.* [4] and was based on the premise that clearance of gentamicin is related to creatinine clearance [13, 14]. The manual calculation method compared favourably with SeBA-GEN dose estimates in patients with moderate renal impairment (Table 3) but it underestimated the gentamicin dose in

patients with mild or no renal impairment. A contributing factor to the underestimation may have been the method of determining gentamicin clearance (CL_{Gm}). Equation 3 (Appendix 1) produced a CL_{Gm} value close to the CL_{Cr} in patients with moderate renal impairment, but the estimated gentamicin clearance in patients with mild or no renal impairment was approximately 90% of CL_{Cr}. Thus, in the patients where gentamicin clearance was underestimated (usually those with mild or no renal impairment), the calculated AUC would have been overestimated, leading to prediction of a lower dose. Hence, alternatives to our equation 3 could be used (for example, CL_{Gm} [ml min^{-1}] = $2 + 77 \times CL_{Cr}/100$ [14]), and the volume of distribution could be varied for specific patient groups [5, 14, 15]. Although the predicted dose from the manual calculation method was almost 40% lower than the SeBA-GEN estimate in normal renal function, in patients with mild renal impairment the manual method underestimated the dose by only 10% (Table 3). This is not likely to be a clinically relevant difference for the majority of patients. Furthermore, the manual method and the TGA nomogram were not significantly different in mild renal impairment, suggesting that either method could be used as a practical alternative to SeBA-GEN.

We conclude that there are no clinically significant differences between the gentamicin doses predicted by SeBA-GEN and DoseCalc software packages, although the apparent underestimation of first dose predictions from DoseCalc in patients with moderately impaired renal function requires further investigation. The TGA nomogram is a valid method for dosage estimates, provided that the caveat – 'to be used in patients with normal renal function' – is observed by practitioners and alternative methods are used in patients with impaired renal function. Overall, our simple manual calculation method was shown to be a suitable method of gentamicin dose estimation in patients with mild to moderate renal impairment, when one SDC is available and use of the TGA nomogram is not appropriate. In a practice setting where computer applications are not available, relatively simple manual calculation methods are suitable for gentamicin dosage estimates in patients with impaired renal function.

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References

1 Barclay ML, Kirkpatrick CM, Begg EJ. Once daily aminoglycoside therapy: is it less toxic than multiple daily doses and how should it be monitored? Clin Pharmacokinet 1999; 36: 89–98.
2 Freeman CD, Nicolau DP, Belliveau PP, Nightingale CH. Once-daily dosing of aminoglycosides: review and recommendations for clinical practice. J Antimicrob Chemother 1997; 39: 677–86.
3 Barza M, Ioannidis JP, Cappelleri JC, Lau J. Single or multiple daily doses of aminoglycosides: a meta-analysis. Br Med J 1996; 312: 338–45.
4 Begg EJ, Barclay ML, Duffull SB. A suggested approach to once-daily aminoglycoside dosing. Br J Clin Pharmacol 1995; 39: 605–9.
5 Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2184 adult patients. Antimicrob Agents Chemother 1995; 39: 650–5.
6 Morris RG, Sallustio BC, Vinks AT, LeGatt DF, Verjee ZH, Desoky EE. Some international approaches to aminoglycoside monitoring in the extended dosing interval era. Ther Drug Monit 1999; 21: 379–88.
7 Therapeutic Guidelines: Antibiotic, 11th edn. North Melbourne: Therapeutic Guidelines Limited, 2000; 229–33.
8 Duffull SB, Kirkpatrick CM, Begg EJ. Comparison of two Bayesian approaches to dose-individualization for once-daily aminoglycoside regimens. Br J Clin Pharmacol 1997; 43: 125–35.
9 Kirkpatrick CM, Duffull SB, Begg EJ. Pharmacokinetics of gentamicin in 957 patients with varying renal function dosed once daily. Br J Clin Pharmacol 1999; 47: 637–43.
10 Paterson DL, Robson JM, Wagener MM, Peters M. Monitoring of serum aminoglycoside levels with once-daily dosing. Pathology 1998; 30: 289–94.
11 Australian Medicines Handbook, 3rd edn. Adelaide: Australian Medicines Handbook, 2002; 95–6.
12 Cooper JA, Batty KT, Ilett KF. Comparison of once-daily gentamicin dosage predictions by DOSECALC, Seba-Gen and the Australian Antibiotic Guidelines Nomogram. Proceedings 24th Federal Conference of the Society of Hospital Pharmacists of Australia, 1999; 1: 41.
13 Australian Pharmaceutical Formulary and Handbook, 15th edn. Deakin: Pharmaceutical Society of Australia, 1992; 208–9.
14 Czock D, Giehl M, Keller F. A concept for pharmacokinetic-pharmacodynamic dosage adjustment in renal impairment: the case of aminoglycosides. Clin Pharmacokinet 2000; 38: 367–75.
15 Bearden DT, Rodvold KA. Dosage adjustments for antibacterials in obese patients. Clin Pharmacokinet 2000; 38: 415–26.
16 Australian Pharmaceutical Formulary and Handbook, 17th edn. Curtin: Pharmaceutical Society of Australia, 2000; 268–71.
17 Triggs E, Charles B. Pharmacokinetics and therapeutic drug monitoring of gentamicin in the elderly. Clin Pharmacokinet 1999; 37: 331–41.

Appendix 1

Manual calculation method for estimation of a gentamicin dose from one serum drug concentration

Equation 1: Ideal body weight (IBW; kg; [15])

$$IBW(Male) = 50 + [0.92 \times (Ht - 150)]$$

$$IBW(Female) = 45.5 + [0.92 \times (Ht - 150)]$$

where: Ht is height (cm).

Equation 2: Creatinine clearance (CL_{Cr}; ml min^{-1}; [16])

$$CL_{Cr} = [(140 - Age) \times Wt \times CF]/S_{Cr}$$

where: Age is in years; Wt is IBW (kg); CF is correction factor (Male: 1.23; Female: 1.04); S_{Cr} is serum creatinine (μmol l^{-1}).

Equation 3: Gentamicin clearance (CL_{Gm}; ml min^{-1} kg^{-1}; [13])

$$CL_{Gm} = (0.82 \times CL_{Cr}) + 0.11$$

where: CL_{Cr} is in ml min^{-1} kg^{-1}.

Equation 4: Gentamicin elimination rate constant (k; h^{-1})

$$k = CL_{Gm}/V$$

where: CL_{Gm} is in l h^{-1} kg^{-1}; V is volume of distribution (0.25 l kg^{-1} of IBW; [8, 14, 15, 17]).

Equation 5: Peak concentration at end of infusion (C_{end}; mg l^{-1}; [4])

$$C_{end} = C_{measured}/e^{-k \times (t - t[end])}$$

where: $C_{measured}$ is the measured SDC of gentamicin (mg l^{-1}); t is time of SDC after the start of the gentamicin infusion (h); t_{end} is time for gentamicin infusion (0.5 h according to standard protocol in hospital).

Equation 6: Trough concentration at end of dosage interval (C_{24}; mg l^{-1}; [4])

$$C_{24} = C_{measured} \times e^{-k \times (24 - t)}$$

Equation 7: Area under the curve (AUC; mg l^{-1} h; [4])

$$AUC = 1.065 \times [(C_{end} - C_{24})/k]$$

Equation 8: New dose (mg; [4])

$$Dose = (Target\ AUC \times Previous\ dose)/AUC\ for\ previous\ dose$$

where: Target AUC was set at 100 mg l^{-1} h; AUC for previous dose was from equation 7.