Predictive performance of gentamicin dosing nomograms

Jieon Lee¹
Seonghae Yoon¹
Donghoon Shin¹
HyeKyung Han¹
Hyungmi An¹,²
Jongtae Lee¹
Kyoung Soo Lim³
Kyung-Sang Yu¹
Howard Lee¹

¹Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Korea; ²Department of Statistics, College of Natural Sciences, Seoul National University, Seoul, Korea; ³Department of Clinical Pharmacology and Therapeutics, CHA University School of Medicine and CHA Bundang Medical Center, Seongnam, Korea

Background: Several nomograms have been proposed to facilitate the determination of initial gentamicin dosing regimens in clinical settings. This study aimed to assess the predictive performance of these nomograms in Korean patients.

Methods: Gentamicin concentrations were determined in 84 patients with infective endocarditis (IE) and in 95 patients with other infections. All patients underwent therapeutic drug monitoring in Seoul National University Hospital from 2006 to 2012. Individual pharmacokinetic parameters were estimated using a Bayesian method, which predicted steady state peak and trough serum concentrations. Six nomograms were evaluated in patients with “other” infections: the Thomson guidelines, Hull-Sarubbi table, and Rule of Eights, for multiple daily dosing; and the Hartford nomogram, Barnes-Jewish Hospital nomogram, and Sanford Guide, for extended-interval dosing. In IE patients, synergistic combination dosing nomograms, based on the American Heart Association dosing interval guidelines, were evaluated.

Results: Gentamicin dosing nomograms performed poorly in attaining the target peak serum concentrations. Multiple-daily dosing nomograms predicted peak serum gentamicin concentrations better than did the extended-interval dosing nomograms (31.9%–72.3% vs 4.3%–45.7%, respectively). Similarly, in patients with IE, the once-daily dosing nomogram resulted in a significantly lower percentage of patients achieving target peak gentamicin concentrations than that associated with the thrice-daily dosing nomogram (P=0.0015). All of the multiple-daily dosing, extended-interval dosing, and synergistic combination dosing nomograms predicted the nontoxic target trough concentrations in >80% of patients.

Conclusion: Gentamicin dosing nomograms performed poorly in achieving the target peak serum concentrations. New gentamicin nomograms may be required in patients with IE, particularly for once-daily dosing. Therapeutic drug monitoring is highly recommended for gentamicin to ensure that the target concentrations are achieved.

Keywords: antibiotics, infectious endocarditis, therapeutic drug monitoring, Bayesian method

Introduction

Gentamicin is an aminoglycoside antibiotic with bactericidal activity against aerobic gram-negative organisms. Although gentamicin has been widely used, it is potentially toxic to the kidney (nephrotoxicity) and the inner ear (ototoxicity).¹ Therefore, it is essential to use an appropriate initial dose and dosing interval for gentamicin to minimize its toxicity, while maintaining its efficacy. When determining the appropriate gentamicin dose, many factors need to be considered, eg, infection site, patient age, sex, body weight, serum creatinine, and creatinine clearance.²–⁴

Several nomograms and dosing guidelines have been developed to optimize the initial dosage regimen for gentamicin. These can be categorized into three groups:
multiple-daily dosing (MDD), extended-interval dosing (EID), and gram-positive synergistic combination dosing (SCD). MDD regimens administer gentamicin intermittently, twice- or thrice-daily. Although MDD has been conventionally used, once-daily administration of gentamicin in EID regimens may be preferable because of the increased convenience. In fact, several studies in various clinical settings demonstrated that EID was as safe as or safer than MDD, with equal efficacy.\(^5\)–\(^8\) SCD is generally reserved for patients with serious infections, such as infective endocarditis (IE), in which \(\beta\)-lactams or vancomycin is frequently coadministered.\(^9\),\(^10\)

One study in Kuwait revealed that up to 63% of patients were outside the target ranges when an initial gentamicin dose regimen was chosen based on six MDD nomograms.\(^11\) Similarly, another study in the USA reported that EID nomograms, including the Hartford nomogram, did not achieve the target peak concentration of 20 \(\mu\)g/mL in most patients.\(^12\) To the best of our knowledge, no study has ever reported the predictive performance of SCD nomograms. Moreover, although the MDD, EID, and SCD nomograms mentioned above have been widely used for the determination of gentamicin dose in Korea, their performances have not yet been systematically reviewed.

Based on this understanding, the objective of the present study was to evaluate the predictive performance of several gentamicin nomograms and dosing guidelines, in Korean patients. To this end, various gentamicin nomograms were retrospectively evaluated, by comparing the percentage of patients whose predicted peak and trough concentrations achieved the target therapeutic and nontoxic ranges, respectively.

**Materials and methods**

**Subjects**

Gentamicin concentrations were determined in patients \(>19\) years of age, who underwent therapeutic drug monitoring (TDM) at Seoul National University Hospital from January 2006 to December 2012. Subjects with one or more sets of paired steady state peak and trough serum gentamicin concentrations, with documented actual sample collection times, were included. Subjects with incomplete demographic data relating to age, serum creatinine, or body weight were excluded. Subjects were also excluded if they were on dialysis or pregnant. Eligible subjects were classified into two infection groups; IE, and infections other than IE (OI). The study protocol was reviewed and approved by the Institutional Review Board at Seoul National University Hospital (approval number 1309-016-518). This study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki (sixth revised), Good Clinical Practices,\(^13\) and other regulatory laws and requirements.

**Determination of gentamicin concentrations**

Serum gentamicin concentrations were determined by chemiluminescent immunoassay using the Architect i2000SR (Abbott Laboratories, Abbott Park, IL, USA).\(^14\) The precision for the gentamicin assay was 3.6%–8.2%. The lower limit of quantitation was 0.2 \(\mu\)g/mL.

**Dosing nomograms**

Table 1 shows the MDD and EID nomograms evaluated in OI patients and the SCD nomograms evaluated in IE patients. The following three MDD nomograms were evaluated: the Thomson guidelines, Hull-Sarubbi table, and the Rule of Eights. The Thomson guidelines (Table S1) recommend a dose ranging from 80 to 160 mg, with a dosing interval of 8 hours, 12 hours, or 24 hours, depending on the patient’s creatinine clearance and body weight.\(^15\) In the Hull-Sarubbi table, a loading dose is administered, followed by a maintenance dose, at a dosing interval determined by the patient’s creatinine clearance and body weight;\(^16\) the dosing chart shown in Table S2 was used to determine a maintenance dose for each patient in the present study. Lastly, the Rule of

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**Table 1** Target serum concentrations of gentamicin by nomogram

| Classification          | Nomogram                                      | Dosing interval (h) | Peak (\(\mu\)g/mL) | Trough (\(\mu\)g/mL) | Target infections                          | References |
|------------------------|-----------------------------------------------|---------------------|---------------------|-----------------------|--------------------------------------------|------------|
| Multiple-daily dosing (MDD) | Thomson guidelines, Hull-Sarubbi table, Rule of Eights | 8, 12               | 5–10               | <2                   | Infections other than IE                   | 11,15,28   |
| Extended-interval dosing (EID) | Hartford nomogram, Barnes-Jewish Hospital nomogram, Sandford Guide | 24, 36, 48         | >20                | <2                   | Infections other than IE                   | 19,29,30   |
| Synergistic combination dosing (SCD) | American Heart Association guideline | 8, 12               | 3–4                | <1                   | IE                                          | 20,31,32   |
Eights assigns doses of 1.0 to 1.66 mg/kg to be administered at variable intervals, depending on the patient’s serum creatinine. In this study, a median dose of 1.33 mg per patient’s ideal body weight was chosen. The dosing interval in the Rule of Eights is 8 hours for patients with normal serum creatinine (ie, <1.24 mg/dL); for those with elevated serum creatinine, dosing is repeated every 8 hours, 12 hours, or 24 hours, selecting whichever is closest to eight times the patient’s serum creatinine level (mg/dL). The typical target peak and trough concentrations for MDD are 5–10 µg/mL and <2 µg/mL, respectively.

For EID, the Hartford nomogram, the Barnes-Jewish Hospital nomogram, and the Sanford Guide were evaluated. The Hartford nomogram and the Barnes-Jewish Hospital nomogram recommend gentamicin at 7.0 mg/kg and 5.0 mg/kg, respectively, with dosing intervals of 24 hours, 36 hours, or 48 hours, depending on the patient’s creatinine clearance (Table S3). Similarly, the Sanford Guide recommends a dose ranging from 4.0 to 5.1 mg/kg, with a dosing interval of 24 hours or 48 hours, based on the patient’s creatinine clearance (Table S4). The target peak concentration for EID is >20 µg/mL, higher than that of MDD, while its target trough concentration is the same, <2 µg/mL.

Gentamicin remains an important therapy, in both the European and American guidelines, for SCD treatment of patients with IE. For example, the American Heart Association guideline recommended a dose of 3 mg/kg/day, based on the patient’s actual body weight. Although MDD has been widely used for the treatment of IE, recent reports have indicated that once-daily regimens can also be employed. In the present study, we chose clinically practical dosing intervals of 8 hours, 12 hours, or 24 hours for the evaluation of SCD nomograms. Because other antibiotics are concomitantly used with gentamicin in SCD, its target peak and trough concentrations are typically lower than those of MDD and EID, at 3–4 µg/mL (peak) and <1 µg/mL (trough) for 8-hour dosing, and >10 µg/mL and <1 µg/mL for 24 hours dosing, respectively. The present study evaluated nomograms for initial dosing only. Additional details of the nomograms and guidelines are provided in Tables S1–S4.

**Calculation of individual pharmacokinetic (PK) parameters and steady state peak and trough concentrations**

The Abbottbase® Pharmacokinetic System program (version 1.10; Abbott Laboratories) was used to derive individual PK parameters and steady state peak and trough concentrations throughout the study. The Pharmacokinetic System program is based on the Bayesian maximum a posteriori method, using a one-compartment linear model. Like other Bayesian dose individualization methods, the prior model estimates the population PK parameters of gentamicin as follows:

\[
V_d (L) = 0.27 \times WT (kg), \text{CV } = 30%, \quad \quad (1)
\]

\[
CL_{TB} (L/h) = CL_R + CL_{NR}, \quad \quad (2)
\]

\[
CL_R (L/h) = 0.815 \times CL, \text{CV } = 40%, \text{ and } \quad (3)
\]

\[
CL_{NR} (L/h) = 0.0025 \times LBW (kg), \text{CV } = 25%, \quad \quad (4)
\]

where \(V_d\) represents the volume of distribution; \(CL_{TB}\) is total body clearance; \(CL_R\) and \(CL_{NR}\) are renal and nonrenal clearance, respectively; \(CL\) is creatinine clearance, calculated using the Cockcroft–Gault equation; \(WT\) is actual body weight; \(LBW\) is lean body weight, calculated for females, as

\[
LBW = (\text{height} - 150 \text{ cm}) \times 0.9 + 45 \text{ kg}, \quad \quad (5)
\]

or for males, as

\[
LBW = (\text{height} - 150 \text{ cm}) \times 0.9 + 50 \text{ kg}; \quad \quad (6)
\]

and CV is the interindividual coefficient of variation. Based on equations 1–4, individual PK parameters were estimated, taking into account gentamicin concentrations and covariates for each patient.

After individual PK parameters had been estimated, steady state peak and trough concentrations were predicted using the dose-estimator section of the PKS program as follows:

\[
C_{ss} = \frac{K_v}{k_e \times V_d} \times \left( \frac{1 - e^{-k_v \cdot t_{inf}}} {(1 - e^{-k_v \cdot t})} \right) \times e^{-k_v \cdot t}, \quad \quad (7)
\]

where \(C_{ss}\) represents predicted steady state concentration, \(t_{inf}\) is the duration of intravenous infusion (30 minutes), \(K_v\) is the dosing rate, \(t\) is the time of concentration measurement after termination of drug infusion, \(K_s\) is the elimination rate constant, and \(\tau\) is the dosing interval. The steady state peak and trough gentamicin concentrations were the values predicted using equation 7, at the end of intravenous infusion and immediately before the next scheduled administration, respectively.

**Statistical analysis**

SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA) was used for statistical analysis in the present study.
Demographic data and individual PK parameters were summarized using descriptive statistics, such as mean and standard deviation. All of the continuous data were first evaluated for normality of distribution by plotting a histogram followed by the Shapiro–Wilk test for normality. The mean values were compared between infection groups (OI vs IE), using the Student’s t-test or the Mann–Whitney U test for normally or nonnormally distributed variables, respectively.

The predicted peak and trough concentrations were assessed against the target therapeutic and nontoxic ranges for gentamicin, respectively. Predictive performance was then defined as the percentage of subjects whose peak and trough concentrations achieved the target therapeutic and nontoxic goals, respectively. Using the GLIMMIX procedure in SAS, generalized linear mixed models were developed to compare the predictive performance of MDD and EID nomograms in OI patients, and SCD nomograms in IE patients. Furthermore, pair-wise post hoc comparisons were made based on the models, with multiplicity adjusted. A two-sided P≤0.05 was considered to be statistically significant.

Results

Subjects

Of 703 patients who underwent gentamicin TDM, 524 patients were excluded because: their peak or trough gentamicin concentrations were not available or were obtained at nonsteady state (n=352); they were <19 years old (n=64); demographic data were missing (n=65); or they were on dialysis or pregnant (n=43) (Figure 1). As a result, the final analysis population included a total of 179 patients, who were classified into two infection groups: IE (n=84) and OI (n=95). Of these 179 patients, 110 were male and 69 were female. Baseline characteristics, including individual PK parameters, were comparable between the OI and IE patient groups, except that patients with OI were significantly older than those with IE (49 vs 56 years) (P=0.0005) (Table 2).

Predictive performance of nomograms

In the OI group, MDD nomograms generally resulted in a higher percentage of patients achieving the target therapeutic peak concentrations than did EID nomograms (31.9%–72.3% vs 4.3%–45.7%) (Table 3); fewer patients attained the therapeutic target using the Rule of Eight compared with the Hartford nomogram. On the other hand, nontoxic target trough concentrations were reached in a relatively large proportion of patients (>80%) by all of the MDD and EID nomograms, although more patients achieved the nontoxic target using EID nomograms than using MDD nomograms (94.7%–97.9% vs 83.0%–90.4%) (Table 3). Collectively, when assessed against both the peak and trough targets, the Thomson guidelines performed significantly better than did the other nomograms, while the predictive performances of the Barnes-Jewish Hospital nomogram and the Sanford Guide were lowest, at 6.4% and 4.3%, respectively (Figure 2).

Similar performance findings were noted for the SCD nomograms in patients with IE. For example, the once-daily dosing nomogram resulted in a significantly lower percentage of patients achieving the target therapeutic peak concentrations than did the thrice-daily dosing nomogram (21.2% vs 38.8%) (P=0.0146) (Table 4). A high percentage of patients attained the target nontoxic trough concentration (80.0%–100.0%) (Table 4), and no significant difference was observed between the nomograms in this respect. Together, these data indicated that thrice-daily dosing was associated with the best predictive performance in SCD nomograms, for both peak and trough concentration targets (Figure 2).

Discussion

This study indicated that gentamicin dosing nomograms performed poorly in attaining the intended target peak (therapeutic) concentrations, irrespective of the dosing frequency and the type of infection. For example, the percentage of patients who failed to attain the target peak concentrations was >50% for most nomograms, which even increased to >95% for some EID nomograms, such as the Barnes-Jewish Hospital nomogram and the Sanford Guide. However, the target trough concentrations were achieved relatively well by all of the nomograms (80%–100%) (Tables 3 and 4). Furthermore, the percentage of patients whose predicted peak and trough concentrations achieved both the therapeutic and the nontoxic targets, respectively, was <50% for all of the nomograms, with the exception of the Thompson guidelines, which performed slightly better (67.0%) (Figure 2).

The poor predictive performance of these gentamicin dosing nomograms, particularly in achieving the target peak concentrations, may reflect large interindividual variability in the PK parameters for gentamicin, leading to different tissue accumulation and dispositional characteristics between subjects.21,22 Furthermore, the typical population gentamicin PK parameters can vary depending on the clinical setting. For example, they may be altered in seriously ill patients receiving a great deal of hydration.5,6,23,24 Because the use of nomograms oversimplifies these differences, poor predictive performance may result, as clearly exemplified in this study. Moreover, given that the peak gentamicin concentrations are likely to be overestimated due to the longer distributional half-life,22 the predictive...
703 patients, who underwent Therapeutic Drug Monitoring (TDM) in Seoul National University Hospital between January 2006 and December 2012

352 patients were excluded because their gentamicin concentrations were obtained at nonsteady state or <1 set of peak and trough

50 patients aged <19 years were excluded

351 patients

35 patients with missing demographic data were excluded

287 patients

65 patients with missing demographic data were excluded

222 patients

43 patients on dialysis or pregnant were excluded

179 patients

84 patients with infective endocarditis

95 patients with other infections than infective endocarditis

Figure 1 Flow chart of subject inclusion and exclusion criteria.

Table 2 Baseline characteristics of the subjects (n=179)

| Characteristics | Patients with infective endocarditis (n=85) | Patients with infections other than infective endocarditis (n=94) | Total patients (n=179) |
|-----------------|-------------------------------------------|---------------------------------------------------------------|-----------------------|
| Age (yr)        | 49±17                                     | 56±15                                                         | 53±17                 |
| Sex (male/female) | 48/37                                      | 62/32                                                         | 110/69                |
| Body weight (kg)| 59.0±11.0                                  | 62.0±11.0                                                     | 60.7±11.0             |
| Height (cm)     | 165.4±9.0                                  | 165.4±8.4                                                     | 165.4±8.7             |
| Serum creatinine (mg/dL) | 1.0±0.4                                   | 1.0±0.5                                                       | 1.0±0.4               |
| Creatinine clearanceb (mL/min) | 80.9±31.0                                   | 79.6±31.5                                                     | 80.1±29.5             |

Individual pharmacokinetic parameters for gentamicin

| Total clearance (L/h) | 4.2±1.7 | 4.3±1.6 | 4.2±1.7 |
| Total volume of distribution (L) | 19.6±5.1 | 17.7±4.1 | 18.6±4.7 |
| Elimination rate constant (h⁻¹) | 0.2±0.1 | 0.3±0.1 | 0.2±0.1 |
| Half-life (h) | 4.0±2.9 | 3.4±1.9 | 3.7±2.4 |

Notes: All data are presented as mean ± standard deviation, except for sex. *No significant difference was found between patients with infective endocarditis and those with other infections, except for age (P<0.012); bestimated by the Cockcroft–Gault equation.
Table 3 Predictive performance of multiple-daily dosing and extended-interval dosing nomograms in patients with infections other than infective endocarditis (n=94)

| Classification | Nomogram                        | $C_{\text{peak}}^*$ (μg/mL) | $C_{\text{trough}}^*$ (μg/mL) | Patients achieving the target concentration range$^a$ |
|----------------|---------------------------------|-----------------------------|------------------------------|---------------------------------|
|                |                                 |                             |                              | Peak $^e$ n (%)                  | Trough n (%)                   |
| Multiple-daily dosing | Thomson guidelines               | 7.9±2.3                     | 1.0±1.5                      | 68 (72.3%)                      | 85 (90.4%)                     |
|                  | Hull-Sarubbi table              | 5.5±1.3                     | 1.1±0.9                      | 55 (58.5%)                      | 85 (90.4%)                     |
|                  | Rule of Eights                  | 5.0±1.7                     | 1.3±1.4                      | 30 (31.9%)                      | 78 (83.0%)                     |
| Extended-interval dosing | Hartford nomogram               | 20.4±4.8                    | 0.4±0.9                      | 43 (45.7%)                      | 89 (94.7%)                     |
|                  | Barnes-Jewish Hospital nomogram | 14.5±3.6                    | 0.3±0.7                      | 6 (6.4%)                        | 86 (95.7%)                     |
|                  | The Sanford Guide               | 13.1±3.8                    | 0.4±0.8                      | 4 (4.3%)                        | 86 (97.9%)                     |

Notes: $^a$Mean ± standard deviation is presented; $^b$the target ranges of peak (therapeutic) and trough (nontoxic) gentamicin concentrations were 5–10 μg/mL and <2 μg/mL, respectively, for multiple daily dosing; and >20 μg/mL and <2 μg/mL, respectively, for extended-interval dosing; $^c$all pair-wise comparisons, based on a generalized linear mixed model, were statistically significant, except for the Hull-Sarubbi table vs the Hartford nomogram; and the Barnes-Jewish Hospital nomogram vs the Sanford Guide; $^d$significantly lower vs all the extended-interval dosing nomograms; $^e$significantly higher vs all the multiple daily dosing nomograms.

The present study had several limitations. Because of its retrospective nature, the predicted performance of nomograms was not assessed against clinical outcomes, such as treatment success, disappearance of target infections, or development of toxicity. Moreover, a one-compartment model was used in the present study (because blood samples were sparsely collected at trough and peak), although gentamicin may behave...
following a two-compartment model. Another limitation was that subjects were relatively young, with normal or moderately-altered renal function, which cautions against the generalization of the study results to elderly subjects or to patients with chronic kidney disease. Therefore, future prospective studies employing more frequent PK samplings and various clinical settings are warranted to address all of these limitations.

**Conclusion**

Most gentamicin dosing nomograms failed to achieve the target peak concentrations, although the Thomson guidelines performed slightly better than the other methods. New nomograms are needed in IE patients because the current AHA guideline did not predict the therapeutic peak concentration effectively, particularly for once-daily dosing. TDM of gentamicin is highly recommended.

**Disclosure**

The authors report no conflicts of interest in this work.

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**Table S1** Thomson guidelines

| \(\text{CL}_{\text{cr}} (\text{mL/min})\) | Weight (kg) | 40–49 | 50–59 | 60–69 | 70–79 | >80 |
|---|---|---|---|---|---|---|
| 20–29 | 80 (24) | 100 (24) | 100 (24) | 120 (24) | 120 (24) |
| 30–39 | 100 (24) | 100 (24) | 120 (24) | 120 (24) | 140 (24) |
| 40–49 | 80 (12) | 100 (12) | 140 (24) | 140 (24) | 160 (24) |
| 50–59 | 100 (12) | 100 (12) | 120 (12) | 120 (12) | 160 (24) |
| 60–69 | 100 (12) | 120 (12) | 140 (12) | 140 (12) | 160 (12) |
| 70–79 | 120 (12) | 140 (12) | 140 (12) | 160 (12) | 160 (12) |
| 80–89 | 140 (8) | 140 (12) | 140 (12) | 160 (12) | 160 (12) |
| 90–99 | 140 (8) | 140 (8) | 160 (8) | 160 (8) | 180 (12) |
| >100 | 140 (8) | 160 (8) | 160 (8) | 180 (8) | 180 (12) |

*Notes:* The table shows dose (mg) and dosing interval (8, 12, or 24 h) determined from the patient’s weight and creatinine clearance (\(\text{CL}_{\text{cr}}\)). *Estimated by the Cockcroft–Gault equation.*

**Table S2** Hull-Sarubbi table

| \(\text{CL}_{\text{cr}} (\text{mL/min})\) | Percentage of LD\(^b\) to use for MD | Dosing interval (h) |
|---|---|---|
| >90 | 84 | 8 |
| 80 | 80 | 8 |
| 70 | 76 | 8 |
| 60 | 84 | 12 |
| 50 | 79 | 12 |
| 40 | 72 | 12 |
| 30 | 86 | 24 |
| 20 | 75 | 24–36 |
| <20 | Give LD x1, then check random level(s) |

*Notes:* *Estimated by the Cockcroft–Gault equation; \(^b\)loading dose (LD) (=2 mg/kg of dosing weight) is first determined, and maintenance dose (MD) and dosing interval is consequently selected based on patient’s creatinine clearance (\(\text{CL}_{\text{cr}}\)).*

**Table S3** Hartford and Barnes-Jewish Hospital nomograms.

| Nomogram | Gentamicin dose (mg/kg) | Dosing interval (h) |
|---|---|---|
| | \(\text{CL}_{\text{cr}} \geq 60 \text{ mL/min}\) | \(\text{CL}_{\text{cr}} 40–59 \text{ mL/min}\) | \(\text{CL}_{\text{cr}} 20–39 \text{ mL/min}\) |
| Hartford nomogram | 7 | 24 | 36 | 48 |
| Barnes-Jewish Hospital nomogram | 5 | 24 | 36 | 48 |

*Note:* *Estimated by the Cockcroft–Gault equation.*

Abbreviation: \(\text{CL}_{\text{cr}}\), creatinine clearance.

**Table S4** The Sandford Guide nomogram

| \(\text{CL}_{\text{cr}} (\text{mL/min}{^a})\) | Dosing regimen | Dosing interval (h) |
|---|---|---|
| \(\geq 80\) | 5.1 | 24 |
| 60–79 | 4.0 | 24 |
| 40–59 | 3.5 | 24 |
| 30–39 | 2.5 | 24 |
| 20–29 | 4.0 | 48 |

*Note:* *Estimated by the Cockcroft–Gault equation.*

Abbreviation: \(\text{CL}_{\text{cr}}\), creatinine clearance.
