

TDM monograph Gentamicin

Synonyms: Cidomycin, Genticyn, Garamyci

Summary

Indication:	<p><u>Minimise risk of toxicity</u></p> <p><u>Adults and children</u></p> <p>To minimise the risk of toxicity, C_{trough} monitoring is recommended in all patients that receive iv gentamicin for >3 days. When there are doubts regarding drug clearance (i.e. special populations, such as premature neonates, or a renal function <60 mL/min) it is recommended to monitor the C_{trough} before the second dose.</p> <p><u>Maximise chance of efficacy</u></p> <p><u>Adults</u></p> <p>Routine TDM to maximise the chance of efficacy is not recommended. This can however be considered locally or in individual cases, especially when gentamicin is dosed $\leq 6\text{mg/kg}$ and in case of special populations, such as (but not limited to) critically ill, patients with abnormal fluid balance, obese or underweight patients, cystic fibrosis patients or patients who receive renal replacement therapy.</p> <p><u>Children, including neonates</u></p> <p>Routine exposure monitoring for efficacy purposes is recommended when gentamicin treatment lasts >3 days</p>
Sample material:	plasma or serum - depending on the validated matrix of the used assay
Time of sampling:	<p><u>Definitions</u></p> <p>AUC_{0-24h}: the exposure over an interval of 24 hours</p> <p>C_{trough}: just before the next administration</p> <p>C_{max}: 30 minutes after the end of a 30-minutes infusion</p> <p>C_{mid}: 6-14 hours after end of administration</p> <p><u>Minimise risk of toxicity: C_{trough} monitoring</u></p> <p>C_{trough} monitoring is performed at least before the third dose. When there are doubts regarding drug clearance (i.e. special populations, such as premature neonates or a renal function <60 mL/min) it is recommended to monitor the C_{trough} before the second dose. If feasible (i.e. not causing a dosing delay $>\sim 24\text{h}$), it should be considered to postpone the second dose until the C_{trough} is known, to determine the best dosing interval. See <i>MIPD-based TDM</i> for the time of sampling in case C_{trough} is not directly measured but to be estimated using pharmacokinetic (PK) modelling (e.g. model-informed precision dosing (MIPD)).</p> <p><u>Maximise the chance of efficacy: AUC_{0-24h} or C_{max} monitoring</u></p> <p>Preferably, PK modelling is employed where a limited sampling strategy is combined with Bayesian fitting to simulate individual drug exposure. See <i>PK</i></p>

	<i>modelling-based TDM and Traditional TDM</i> for sampling times to estimate AUC _{0-24h} .
Storage conditions:	2-8 °C
Interpretation:	<p>Target to minimise the risk of toxicity: C_{trough} < 1 mg/L. A stricter target C_{trough} of <0.5 mg/L can be justified in some cases, for example in patients with a high risk of nephrotoxicity.</p> <p>Target to maximise the chance of efficacy: <u>Adult and pediatric patients:</u> (1) AUC_{0-24h} > 80 mg*h/L or (2) C_{max} > 15 mg/L.</p> <p>Target to maximise the chance of efficacy: <u>Neonates (0-1months):</u> (1) AUC_{0-24h} > 80 mg*h/L or (2) C_{max} > 8 mg/L.</p>
Evidence level:	<p>Toxicity - C_{trough} monitoring: 1 Efficacy - AUC_{0-24h} or C_{max} monitoring: 3</p>

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Introduction

Gentamicin is an aminoglycoside antibiotic with a small therapeutic window that is currently used primarily as part of short-term empirical combination therapy. The most clinically relevant micro-organisms are gram-negative rods, especially Enterobacterales, with an ECOFF of 2 mg/L (1). In particular, aminoglycosides are used as add on therapy to beta-lactams to cover the Enterobacterales less sensitive to beta-lactams, such as those that contain an ESBL. Furthermore, low dose gentamicin is used in the treatment of endocarditis as adjunctive therapy to enhance the killing of gram-positive bacteria. For the treatment of infections due to *P. aeruginosa*, gentamicin is considered inferior to other aminoglycosides and not advised. Aminoglycosides exhibit concentration-dependent microbiologic activity in both *in vivo* and *in vitro* models. Aminoglycosides can cause nephro- and ototoxicity. Once-daily dosing (or extended-interval dosing) of aminoglycosides has nowadays been (almost) universally implemented (2,3). There is consensus that this dosing scheme makes optimal use of the pharmacological characteristics of aminoglycosides, increasing the probability that the concentration drops below the threshold for nephrotoxicity when the next dose is administered (4). TDM is shown to improve target attainment and may result in decreased nephrotoxicity, thereby improving the safety of aminoglycosides (5,6). The role of TDM in improving aminoglycoside efficacy is less certain; limited evidence shows no effect of TDM on mortality in one trial (6), while a second trial showed that intensive TDM did improve efficacy, with regard to length of hospital stay, albeit targeting lower (peak) target concentrations than what is nowadays recommended (5).

Dosing guidelines

See [gentamicine](#) | [SwabID \(antibiotica.app\)](#)

Indications/Criteria for TDM

General

TDM for aminoglycosides has two aims: to minimise the risk of toxicity and to maximise the chance of effective treatment. Since toxicity is related to the trough concentration, i.e. the concentration just before administering the next dose, C_{trough} monitoring is performed for the first aim. The second aim can be reached by either exposure (AUC)- or peak concentration-based monitoring.

Adults

To minimise the risk of toxicity, C_{trough} should be monitored for all patients treated with iv gentamicin for more than 3 days. When there are doubts regarding drug clearance (i.e. special populations or a renal function <60 mL/min) it is recommended to monitor the C_{trough} after the first dose. In these cases, it can be considered to postpone the second dose until the C_{trough} is known.

In Appendix I, dose-exposure simulations are presented, showing that target attainment is reached in 90% of adult patients when a dose of 7 mg/kg is administered. Consequently, routine TDM for efficacy purposes is not recommended when gentamicin is dosed in line with EUCAST recommendations (i.e. 7 mg/kg).

TDM for efficacy purposes can be considered when treatment lasts >3 days in patient populations where high variability has been demonstrated in population pharmacokinetic studies, especially when gentamicin is dosed ≤ 6 mg/kg. Patient populations with high pharmacokinetic variability include (but are not limited to) critically ill patients, patients with abnormal fluid balance, obese or underweight patients or patients who

receive renal replacement therapy or extracorporeal membrane oxygenation (8). For more details we refer to dose-exposure simulations presented in Appendix I.

Children

To minimise the risk of toxicity, C_{trough} should be monitored for all pediatric patients treated with iv gentamicin in the same way as recommended for adults.

Locally or in individual cases where an impaired clearance might be expected, for example in premature neonates, an earlier sample before the second dose is recommended. If feasible (i.e. not causing a dosing delay $> \sim 24\text{h}$), it should be considered to postpone the second dose until the C_{trough} is known, to determine the best dosing interval.

In the paediatric population, routine TDM for efficacy purposes is not recommended when gentamicin therapy lasts < 3 days. For longer treatment, TDM for efficacy purposes is recommended, since there is a large variability in PK (Appendix 1). In neonates, gentamicin is typically administered as standard empirical therapy in neonatal sepsis and often discontinued within 36 hours due to a negative blood culture or the absence of gram-negative bacteria. This means that for the majority of these patients, exposure monitoring will not be necessary.

Reference values

Efficacy

Adults

Over the years there has been much debate on the most predictive PK-PD index for efficacy of treatment with aminoglycosides; C_{max} /Minimal inhibitory Concentration (MIC) or $\text{AUC}_{0-24\text{h}}/\text{MIC}$. Most data has been derived from preclinical neutropenic rodent thigh infection models that generally show $\text{AUC}_{0-24\text{h}}/\text{MIC}$ as the best predictor for efficacy (9,10). Clinical studies point either towards $C_{\text{max}}/\text{MIC}$ (11,12), $\text{AUC}_{24\text{h}}/\text{MIC}$ (13,14) or both (15). These clinical studies have significant limitations. For instance, these studies investigated nowadays outdated dose regimens with multiple daily doses, often as monotherapy. This practice has nowadays been abandoned where extended interval dosing or once-daily dosing in combination with other classes of antibiotics is common practice. In a study in 236 patients with a gram-negative bacterial infection receiving aminoglycosides, a paper from 1987 that is often cited as evidence for the importance of the peak concentration, no comparison was made with $\text{AUC}_{0-24\text{h}}/\text{MIC}$ as predictor (11). Kashuba and colleagues found $C_{\text{max}}/\text{MIC}$ to be a (slightly) better predictor than $\text{AUC}_{0-24\text{h}}/\text{MIC}$ for defervescence in 78 patients with pneumonia caused by gram-negative bacteria, although $\text{AUC}_{0-24\text{h}}/\text{MIC}$ also was shown to be predictive and $\text{AUC}_{0-72\text{h}}/\text{MIC}$ was found to be a better predictor for the leukocyte response (15).

In light of the available preclinical data and the limitations of published clinical studies, multiple reviews, expert opinions and guidelines nowadays advocate $\text{AUC}_{0-24\text{h}}$ to be used as the primary efficacy target for aminoglycoside dosing (10,16–18). An additional - but from a quality of evidence perspective less convincing - argument pointing towards the $\text{AUC}_{0-24\text{h}}$ as primary driver for efficacy could be found in the fact that no major differences in effectiveness have been demonstrated since the transition from multiple-daily dosing regimens towards once-daily regimens in the early 1990's - where peak concentrations were much lower with the multiple-daily dosing regimens with similar $\text{AUC}_{0-24\text{h}}$ (16).

Although firm evidence for the minimal AUC_{0-24h} target for efficacy of aminoglycosides is lacking, an AUC_{0-24h}/MIC of >30 for *Enterobacteriaceae* or >60 $mg/L \cdot h$ for *P. aeruginosa* and *S. aureus* is correlated with bacterial stasis in preclinical rodent infection models (10). In clinical practice, gentamicin is mainly used to target Enterobacterales, and is not used (anymore) to target *P. aeruginosa* and *S. aureus* (the latter in infections other than endocarditis). For TDM, an AUC_{0-24h} of at least 80 $mg/L \cdot h$ is proposed in recent guidelines (10,18). This target AUC_{0-24h} is sufficient for bacterial stasis for wild type Enterobacterales, but does not always assure bacterial *kill*, especially for isolates with high MIC's of 1 or 2 mg/L . The proposed target is assumed to be sufficient based on the fact that aminoglycosides are primarily used in combination therapy regimens and the achievement of high exposure of aminoglycosides at the effect site such as the urinary tract (10). Nevertheless, clinicians should take this rationale into account, especially when treating a patient with an impaired immune system in combination with bacterial infections caused by a less susceptible pathogen (i.e. high MIC). Moreover, when gentamicin is used as the sole active antimicrobial agent, higher AUC_{0-24h}/MIC ratios may be required to actively treat the infection. In particular when the focus of infection is different from the urinary tract or when the patient is immunocompromised. Such treatments may need to be guided by more extensive TDM.

When the dosing interval exceeds 24h, it is recommended to target an $AUC >80$ $mg \cdot h/l$ for the first 24h. In these cases, it is accepted that the second part of the dosing interval may result in a lower AUC - this will be necessary to ensure a trough concentration below 1 or 0.5 mg/L .

As a target for C_{max} based TDM, a C_{max}/MIC ratio of at least 8 should be pursued. This target was identified in one prospective study that investigated the relationship between C_{max} and efficacy (11). Considering an MIC of 2 mg/L as the epidemiological cut-off value (ECOFF) for Enterobacterales (1) this commonly translates to a target peak concentration of at least 15 mg/L .

Children

Since no specific reference values for the pediatric population are available, the guidelines described above will be applied; For AUC-based TDM and C_{max} based TDM, an $AUC_{0-24h} >80$ $mg/L \cdot h$ or a C_{max} of >15 mg/L , respectively, are recommended to ensure optimal therapeutic effectiveness.

Neonates (0-1 month)

In line with with general recommendations, an efficacy target of $AUC_{0-24h} >80$ $mg/L \cdot h$ is recommended. Practical experience shows that in this population, a $C_{max} >8$ mg/L usually corresponds to an $AUC >80$ $mg/L \cdot h$ (unpublished data Erasmus MC). Additionally, a retrospective survey on the measured MIC values of pathogens obtained from neonates treated with gentamicin (the vast majority being gram-negative rods) in the Radboudumc, ErasmusMC, and Amsterdam UMC, demonstrate that over 95% of these MICs are ≤ 1 mg/L (data not published).

Relationship with occurrence of side effects & toxicity

Aminoglycosides can exert several toxic effects, most notably nephro- and ototoxicity.

Nephrotoxicity

Renal toxicity is caused by three general mechanisms, namely direct tubular toxicity, reduction in glomerular filtration and reduction in renal blood flow (19). Direct toxicity is mediated through accumulation in tubular cells and can be decreased by extended interval dosing and ensuring trough levels below a threshold value (19). Although many factors, including duration of treatment, age and baseline renal

function, play a role, most data on aminoglycoside-induced nephrotoxicity point towards the trough concentration (i.e. concentration at the end of the dosing interval) as the primary predictor (8). Recently, a comprehensive overview was published on the relationship between gentamicin concentrations and nephrotoxicity (20). No randomized controlled trials were found, but five observational studies including 615 patients and 1 observational study including 187 patients evaluated a C_{trough} of 2 mg/L and 1 mg/L, respectively. This meta-analysis showed that patients with $C_{trough} < 2$ mg/L had significantly less risk of nephrotoxicity (odds ratio [OR] 0.22, 95% confidence interval [CI] 0.12–0.40) compared with patients with $C_{trough} \geq 2$ mg/L (20). One study using a $C_{trough} < 1$ mg/L target showed significantly less risk of nephrotoxicity compared with patients with $C_{trough} \geq 1.1$ mg/L (OR 0.07, 95% CI 0.02–0.24) (21). One prospective study comparing routine clinical practice with active TDM showed a lower risk of nephrotoxicity in the active TDM group with a median gentamicin C_{trough} of 0.7 mg/L (+/- 0.6mg/L) versus routine clinical practice with a median C_{trough} of 1.4 (+/- 1.4 mg/L) (5).

Based on these findings, a maximum C_{trough} of 1 mg/L is advised. There is no evidence for targeting C_{trough} levels lower than 1 mg/L. Nevertheless, some experts advocate a lower C_{trough} target of 0.5 mg/L to further minimise the risk of nephrotoxicity in the most vulnerable patients, for example patients with a high risk of nephrotoxicity or neonates. The rationale behind this being that a $C_{trough} < 0.5$ mg/L could further reduce toxicity.

There is no clear relationship between AUC_{0-24h} and toxicity, although an higher AUC_{0-24h} was identified as a predictor for nephrotoxicity in some studies (8). No upper limit for AUC_{0-24h} is defined (yet), although higher doses can of course result in high, toxic trough concentrations (8). The literature also lacks a specified upper limit for peak gentamicin concentrations, indicating a level of flexibility in managing these peaks. However, encountering exceptionally high peak concentrations (>20-30 mg/L) necessitates caution, as this may signal the occurrence of errors in dosing, sampling or measurement. In such scenarios, it is crucial to thoroughly investigate and rectify any potential mistakes to ensure patient safety and treatment.

Regarding children en neonates, there are no studies specifically on the relation between exposure and nephrotoxicity. Hence, it is advised to use trough levels as described for the adult population. Some clinics use a lower target for the C_{trough} (<0.5mg/L).

Ototoxicity

Gentamicin treatment is also associated with a risk of ototoxicity and/or vestibulotoxicity. This is irreversible in most cases. Recent studies have demonstrated an important role for 1555A>G variant in the mitochondrial 12S rRNA gene, MT-RNR1, in the risk of developing ototoxicity (22). Although the number of doses, the duration of therapy and the cumulative dose are shown to be weak predictors of aminoglycoside ototoxicity (23), there are no studies that have evaluated different PK/PD indices with ototoxicity (24). One study investigating a population pharmacokinetic model with tobramycin in cystic fibrosis patients demonstrated a correlation between the tobramycin concentration in the peripheral compartment and the risk of ototoxicity (23). Yet, no reference plasma concentrations for minimising the risk of ototoxicity are currently available.

Children and especially neonates, are considered more vulnerable to the ototoxic effects of aminoglycosides. A retrospective uncontrolled study in 528 critically ill neonates during the first week of life showed that ototoxicity occurred in 13.1% of these patients, especially in those with lower birth weight (25). In addition, neonates with gentamicin C_{max} above 10 mg/L were at an increased risk for otoacoustic emission screen failure. No relationship with C_{trough} was found, although the study only considered a relatively high cut-off for C_{trough} of >2 mg/L (25).

Reference values in special populations

Endocarditis

For patients with endocarditis, gentamicin is always used in combination with beta-lactam antibiotics. This combination is believed to be synergistic due to fact that the beta-lactam antibiotic facilitates intracellular uptake of the aminoglycoside (26). This synergy was observed *in vitro* in streptomycin sensitive- and resistant enterococci with gentamicin concentrations of 3 - 5 mg/L. The synergistic effect did not increase with increasing gentamicin concentrations (27). The SWAB guideline advises a dose of 3 mg/kg for specific cases of endocarditis (28), which is expected to result in an AUC_{0-24h} of around ~35-45 mg*h/L and peak concentrations of 8 - 12 mg/L. There is no literature on the added value of routine TDM of gentamicin in endocarditis for efficacy purposes. Considering the above, it is not useful to perform TDM for efficacy purposes. To minimise the risk of toxicity, we recommend the same approach to C_{trough} monitoring in endocarditis patients as in other infections.

Intermittent hemodialysis

Published data for patients on intermittent hemodialysis treated with aminoglycosides are limited. Studies assessing the PK/PD target of gentamicin have not been conducted in the hemodialysis population. Nonetheless, since there seems no reason to assume that the target for efficacy in hemodialysis patients treated with gentamicin is different from that in patients without hemodialysis, the same target for AUC_{0-24h} can be adopted for this patient population. Predialysis dosing ensures a higher probability of target attainment of the AUC_{0-24h} target as well as peak concentrations compared to postdialysis dosing (29,30). For patients receiving intermittent hemodialysis, it is recommended to target AUC_{0-24h}, and not C_{max}, since it is in most cases not possible to reach both the target C_{max} and the target C_{through} within 1 dose interval (30). Aiming for a C_{trough} <1 mg/L is recommended.

Intraperitoneal administration

When gentamicin is administered intraperitoneally (IP), this is done to obtain a high concentration locally. In peritoneal dialysis (PD) patients with peritonitis median gentamicin serum levels between 1.9 and 3.1 mg/L were reported (31). Two published studies investigating outcomes between patients with different gentamicin levels have not demonstrated any difference in gram-negative or culture-negative peritonitis cure rate (32,33) Although firm evidence is unavailable, routine measurement of through concentrations is recommended to prevent nephrotoxicity and conserve existing renal function. Aiming for a C_{trough} <1 mg/L is recommended.

MIC

The advised reference values are based on treatment of infections caused by a pathogen with an MIC =<2 mg/L (1). A retrospective survey on the measured MIC values of pathogens obtained from neonates treated with gentamicin in the Radboudumc, ErasmusMC, and Amsterdam UMC, demonstrate that over 95% of these MICs are ≤1 mg/L (data not published).

Summary

Toxicity:

C_{trough} < 1 mg/L. In patients with high risk of nephrotoxicity a C_{trough} of <0.5 mg/L could be considered, in specific vulnerable patient groups such as neonates or patients with pre-existing renal impairment.

Efficacy:

- General (adults and children): $AUC_{0-24h} \geq 80 \text{ mg/L} \cdot \text{h}$
 - Alternative: $C_{max} \geq 15 \text{ mg/L}$
- Neonates (<1 month): General: $AUC_{0-24h} \geq 80 \text{ mg/L} \cdot \text{h}$
 - Alternative: $C_{max} \geq 8 \text{ mg/L}$

Sampling & storage conditions

Definitions

AUC_{0-24h} : the exposure over an interval of 24 hours

C_{trough} : just before the next administration

C_{max} : 30 minutes after the end of a 30-minutes infusion

C_{mid} : 6-14 hours after end of administration

Minimise risk of toxicity: C_{trough} monitoring

C_{trough} monitoring is performed at least before the third dose. When there are doubts regarding drug clearance (i.e. special populations such as premature neonates, or a renal function <60 mL/min) it is recommended to monitor the C_{trough} before the second dose. If feasible (i.e. not causing a dosing delay >~24h), it should be considered to postpone the second dose until the C_{trough} is known, to determine the best dosing interval.

See *MIPD-based TDM* for the time of sampling in case C_{trough} is not directly measured but to be estimated using pharmacokinetic (PK) modelling (e.g. model-informed precision dosing (MIPD))

Maximise the chance of efficacy: AUC_{0-24h} or C_{max} monitoring

Preferably, PK modelling is employed where a limited sampling strategy is combined with Bayesian fitting to simulate individual drug exposure. See *PK modelling-based TDM* and *Traditional TDM* for sampling times to estimate AUC_{0-24h} .

PK modelling-based TDM

Obtain 1-2 PK samples (at least a C_{mid} , preferably two concentrations such as a C_{max} and C_{mid} or C_{mid} and C_{trough}). This information can be used in a PK model / MIPD software tool to estimate AUC_{0-24h} and C_{trough} . In patients undergoing hemodialysis, assuming gentamicin is administered prior to hemodialysis, a peak level, pre-dialysis trough level and a post dialysis trough level should be drawn. The AUC_{0-24h} can be estimated using PK modelling.

Traditional TDM

Obtain at least a C_{max} and C_{trough} . AUC can be manually calculated using first order pharmacokinetic equations.

Storage

Samples should be stored at 2-8 °C

Additional information concerning the interpretation of results

When AUC-guided monitoring is not feasible, for instance due to limited resources, peak concentrations can be measured as an alternative approach. In normal patients without comorbidities, there is a strong correlation between exposure (AUC_{0-24h}) and C_{max} . Caution is advised for patients where this correlation is different or absent, for instance renally impaired patients, neonates, augmented renal clearance, obese or

underweight individuals. Interpretation of gentamicin concentrations collected in hemodialysis patients is more complex than interpretation of gentamicin levels from patients without hemodialysis. Therefore, we recommend that these levels are interpreted by a clinical pharmacist with experience in TDM in this patient population.

When the dosing interval exceeds 24h, it is recommended to target an AUC >80 mg*h/l for the first 24h. In these cases, it is accepted that the second part of the dosing interval may result in a lower AUC - this will be necessary to ensure a trough concentration below 1 or 0.5 mg/L.

Bio-analytical assay

In general, immuno-assays are used to measure total gentamicin concentrations in serum or plasma. Considering a plasma protein binding of <10%, total concentrations can be used for TDM purposes.

Background information [extended]

Pharmacodynamics

See 'Reference values'.

Pharmacokinetics

See KNMP Kennisbank: <https://kennisbank.knmp.nl/>. In short, aminoglycosides have a distribution volume of 0,25 L/kg in adults and are predominantly cleared unchanged renally. Plasma protein binding is <10%.

Interactions

For drug-drug interactions with gentamicin, see KNMP Kennisbank: <https://kennisbank.knmp.nl/> or the Lexicomp® Drug Interactions checker: <https://www.uptodate.com/drug-interactions/>

PK parameters

See *Population models*.

Population models

It is necessary to take notice of the specific patient under treatment and to select an appropriate population PK model that was developed with data from a population with characteristics as similar as possible to the local patient or population under treatment as various models for different patient populations are available within MIPD software tools.

The review by Hodiamont et al. provides an overview of published gentamicin population PK parameters for several patient populations(8).

Ideally, clinicians validate the selected population PK model with local data from the population under treatment as differences in PK behaviour of gentamicin may exist.

Literature

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Colophon

The first version of this guideline has been constituted by S. Coenradie, pharmacist and dr. D.J. Touw, hospital pharmacist-clinical pharmacologist in May 2005 under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA)

Appendices

Appendix I. Expected variability in AUC_{0-24h} for common special population

Revision

The latest version of this guideline has been constituted by dr. Nynke Jager, hospital pharmacist-clinical pharmacologist Radboudumc Nijmegen, dr. Cornelis Smit, hospital pharmacist Antonius hospital, Sneek, dr. Reinier van Hest, hospital pharmacist Amsterdam UMC, Mirjam Slijkhuis, hospital pharmacist Amsterdam UMC, dr. Alan Abdulla, hospital pharmacist Erasmus MC, Rotterdam, Robert Flint, hospital pharmacist Erasmus MC, Rotterdam and prof. dr. Daan Touw, hospital pharmacist-clinical pharmacologist UMCG, Groningen.

The guideline was reviewed by dr. Caspar Hodiament, medical microbiologist Amsterdam UMC, Prof. Karel Allegaert, pediatrician-neonatologist, Leuven, prof. dr. Catherijne Knibbe, hospital pharmacist-clinical pharmacologist, Antonius Hospital Nieuwegein/Utrecht and dr. Miquel Ekkelenkamp, medical microbiologist UMCU, Utrecht.

Under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA) and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)

Appendix 1 TDM monografie gentamicine: variabiliteit AUC subpopulaties (in Dutch)

Tabel 1: Berekeningen variatie CL gentamicine o.b.v. [Hodiamont 2022]

Subpopulatie	Gemiddelde CL/70 kg (spreiding)
Volwassenen	4,72 (3,06-6,36)
Obese patiënten	4,45 (3,46-5,44)
Kritiek zieke patiënten (variabele nierfunctie)	3,43 (0,95– 5,91)
Kinderen	7,35 (4,76-9,94)
Neonaten	3,40 (1,77 – 5,03)
Ouderen	3,0 (2,21 – 3,79)
Patiënten met IHD	5,82 (5,80 – 5,84)
Patiënten met PD	Nvt

De variatie in klaring is gebaseerd op de ranges van farmacokinetische parameters in verschillende populaties zoals vermeld in tabel 1 in van Hodiamont et al. 2022.

De spreiding in klaring is als volgt berekend: eerst is de standaarddeviatie berekend door de gemiddelde klaring te vermenigvuldigen met de gemiddelde interindividuele variabiliteit in klaring, die in de tabel van Hodiamont et al 2022 gerapporteerd is als een variatiecoëfficiënt (CV). Kortom: standaarddeviatie = gemiddelde CL * (CV(%)/100). Vervolgens zijn de boven- en ondergrenzen van de spreiding in klaring berekend m.b.v. de standaarddeviatie te vermenigvuldigen met de z-waarde die hoort bij een 80% betrouwbaarheidsinterval, eenzijdig. Het resulterende getal is vervolgens opgeteld bij de gemiddelde CL om de bovengrens te verkrijgen en afgetrokken van de gemiddelde CL om de ondergrens van de spreiding te verkrijgen. Er is gekozen voor een eenzijdig 80% betrouwbaarheidsinterval, omdat dan de bovengrens van de spreiding in de CL het getal betreft waar 90% van de populatie onder zit. Hierbij wordt dus aangenomen dat een inadequate blootstelling (door hoge CL) tot maximaal 10% van de populatie acceptabel is.

Tabel 2: Berekening gentamicine blootstelling (AUC) op basis van de populatie PK gegevens uit tabel 1

Subpopulatie	Dosering	Spreiding AUC ₀₋₂₄ (mg*h/L)#
Volwassenen	5 mg/kg bij 70 kg = 350 mg	55-114
	6 mg/kg bij 70 kg = 420 mg	66-137
	7 mg/kg bij 70 kg = 490 mg	77-160
Obese patiënten **	5 mg/kg bij 125 kg (CL=5.3-8.4 L/h)^ bij eGFR 90-120 mL/min/1.73m ² : 80% van de standaarddosering: 5 * 125 * 0.8 = 500 mg	60-94
	6 mg/kg bij 125 kg (CL=5.3-8.4 L/h)^ bij eGFR 90-120 mL/min/1.73m ² : 80% van de standaarddosering: 6 * 125 * 0.8 = 600 mg	71-113
	7 mg/kg bij 125 kg (CL=5.3-8.4 L/h)^ bij eGFR 90-120 mL/min/1.73m ² : 80% van de standaarddosering: 7 * 125 * 0.8 = 700 mg	83-132
Kritiek zieke patiënten (variabele nierfunctie)	5 mg/kg bij 70 kg = 350 mg	59-368
	6 mg/kg bij 70 kg = 420 mg	71-442
	7 mg/kg bij 70 kg = 490 mg	83-516

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Kinderen 1 mnd-12 jaar	5 mg/kg bij 20 kg. (CL=1.9-3.9 L/h) [^] Dosis= 100 mg	25-52
	6 mg/kg bij 20 kg. (CL=1.9-3.9 L/h) [^] Dosis= 120 mg	31-63
	7 mg/kg bij 20 kg. (CL=1.9-3.9 L/h) [^] Dosis= 140 mg	36-73
Neonaten	<i>Prematuur postnatale leeftijd 0-7 dagen</i> 5 mg/kg bij 2 kg. (CL=0.12-0.35 L/h) [^] Dosis= 10 mg	29-83
	<i>Prematuur postnatale leeftijd 1-4 weken</i> 4 mg/kg bij 2 kg. (CL=0.12-0.35 L/h) [^] Dosis=8 mg	23-67
	<i>A-term</i> 4 mg/kg bij 3,5 kg (CL=0.19-0.53 L/h) [^] Dosis= 14 mg	26-74
Ouderen	5 mg/kg bij 70 kg = 350 mg	92-158
	6 mg/kg bij 70 kg = 420 mg	111-190
	7 mg/kg bij 70 kg = 490 mg	129-222
Patiënten met IHD	5 mg/kg bij 70 kg = 350 mg	60
	6 mg/kg bij 70 kg = 420 mg	72
	7 mg/kg bij 70 kg = 490 mg	84
Patiënten met PD	nvt	nvt

Berekening variatie AUC gentamicine o.b.v. variatie klaring in tabel 1.

$AUC_{0-24} = \text{Dosis per 24 uur} / CL$ [in L/h]

Analooq aan de legenda van tabel 1 betreft het de spreiding in AUC_{0-24} voor 80% van de populatie, omdat dan de ondergrens van de spreiding in de AUC_{0-24} het getal betreft waar 90% van de populatie boven zit. Hierbij wordt dus aangenomen dat een inadequate blootstelling tot maximaal 10% van de populatie acceptabel is

*dose weight o.b.v. $70 \cdot (TBW/70)^{0.73}$.

** doseeradvies gentamicine bij obesitas conform KNMP Kennisbank oktober 2023

[^] range van CL is bij lichaamsgewichten anders dan 70 kg herberekend tov tabel 1, omdat die tabel de CL/70 kg opgeeft. CL is allometrisch geëxtrapoleerd $CL = CL \text{ bij } 70 \text{ kg} \cdot (TBW/70)^{0.75}$

References

Hodiamont et al. Clinical Pharmacokinetics of Gentamicin in Various Patient Populations and Consequences for Optimal Dosing for Gram-Negative Infections: An Updated Review. Clinical Pharmacokinetics 2022;61:1075-94.