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Age- and gender-related differences in teicoplanin levels in paediatric patients

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Objectives: Teicoplanin is a glycopeptide antibiotic active against Gram-positive bacteria, including methicillin-resistant staphylococci. While teicoplanin trough levels (TTLs) >10 mg/L are commonly considered appropriate, levels >20 mg/L are aimed for in the treatment of severe infections. Due to toxicity, it is recommended to avoid levels >60 mg/L.

Patients and methods: In our institution, the initial dosing schedule of teicoplanin (10–15 mg/kg every 12 h for three loading doses and every 24 h thereafter) is adapted according to TTLs analysed by a fluorescence polarization immunoassay on treatment days 2 to 4. Teicoplanin peak levels (TPLs) are analysed in selected cases 30 min after the end of infusion. In a retrospective analysis we evaluated 1357 TTLs and 333 TPLs from 410 treatment episodes from 2005 to 2011.

Results: Initial TTLs were <10 mg/L in 14.1% and <20 mg/L in 72.6% of episodes. Toddlers had significantly lower TTLs, with a 2-fold and 2.5-fold increased risk of having levels <10 mg/L (24.6%) and <20 mg/L (82.6%), respectively. For the entire cohort, follow-up TTLs were less likely to be <10 mg/L and more likely to be >20 mg/L when compared with initial TTLs ($P<0.001$, each). Adolescent girls had significantly higher initial TPLs ($P=0.001$) and significantly higher follow-up TTLs ($P=0.016$) than adolescent boys. In parallel, adolescent girls had initial TPLs >60 mg/L significantly more frequently ($P=0.012$) and follow-up TTLs <10 mg/L significantly less frequently ($P=0.005$).

Conclusions: More tailored dosing regimens with higher loading doses, especially for toddlers, should be considered. While further pharmacokinetic data in paediatric patients are pending, therapeutic drug monitoring is mandatory.

Keywords: glycopeptides, pharmacokinetics, therapeutic drug monitoring

Introduction

Teicoplanin is a glycopeptide antibiotic active against Gram-positive bacteria, including methicillin-resistant staphylococci.[1–4] In addition, it recently has also been described as synergistic with colistin in the treatment of multiresistant *Acinetobacter baumannii*.[5] Due to a long elimination $t_{\frac{1}{2}}$, once-daily dosing is feasible after achieving steady-state concentration.[1,6] Initial loading-dose regimens are recommended to ensure early achievement of effective concentrations,[7–9] which in adults has been shown to be crucial for a good prognosis in critically ill patients.[10] While teicoplanin trough levels (TTLs) >10 mg/L are commonly considered appropriate, levels >20 mg/L have been shown to be necessary for the treatment of severe and difficult-to-treat staphylococcal infections such as osteomyelitis and endocarditis.[10–12]

Side effects of teicoplanin include hypersensitivity, fever, rash, diarrhoea, thrombocytopenia, nephrotoxicity[2] and ototoxicity.[13] The occurrence of most of these side effects is dose dependent, and excessive levels should therefore be avoided.[1] Despite a lack of evidence, avoidance of levels >60 mg/L is commonly recommended.[1,2,11,14] Furthermore, considerable variability in the pharmacokinetic parameters of teicoplanin has been described.[15] To achieve optimal concentrations, therapeutic drug monitoring (TDM) is recommended and performed in many institutions.[7,9,11,16,17]

Pharmacokinetic data in paediatric patients of different age groups have been studied only in small numbers of individuals.[18–20] A higher clearance in younger children leads to lower levels than in adults. To overcome this, regimens with higher dosages are recommended for children.[1,2,19,20]

There are limited data on TDM in paediatric patients that evaluate the appropriateness of the recommended dosing regimen in the clinical setting,[20,21] and no data with regard to different age groups and gender.

The aim of this study was to evaluate teicoplanin levels in a real-life setting in a large paediatric cohort and the percentage of patients achieving adequate levels, and to examine the differences within this heterogeneous cohort.

Patients and methods

Clinical setting

The study retrospectively evaluated teicoplanin levels determined between 2005 and 2011 in a real-life setting at the Department of Paediatrics, Medical University of Graz, Austria. At our institution the recommended dose of teicoplanin is 10–15 mg/kg administered over 60 min every 12 h for three loading doses and every 24 h thereafter. TTLs are analysed on treatment days 2 to 4 and every 1–5 days during treatment at the discretion of the treating physician. Teicoplanin peak levels (TPLs) are analysed in selected cases 30 min after the end of infusion. In case of inadequate teicoplanin levels, doses are modified to achieve TTLs >10 mg/L (in case of severe infections >20 mg/L). Levels >60 mg/L should be avoided.

Laboratory methods

Teicoplanin levels were detected by means of a fluorescence polarization immunoassay using the Innofluor® Teicoplanin Test System (Seradyn, IN, USA) on a TDxFLx® Analyzer (Abbott Diagnostics, Vienna, Austria) according to the manufacturer's instructions. Serum samples were indicated as TTL or TPL by the assigning departments and were usually analysed within 2 h of blood sample collection; otherwise, samples were stored at 4°C and analysed within 24 h. The limit of quantification of the assay is 1.7 mg/L.

Analysis

Data were retrieved from the laboratory information management system. Statistical analyses were performed using SPSS Statistics Version 20 (IBM Corporation, 2011). Children were grouped by age into neonates/infants (<1.0 year), toddlers (1.0–5.9 years), school-age children (6.0–11.9 years) and adolescents (12.0–18.0 years). Teicoplanin levels were grouped into levels <10 mg/L (below target range), 10–19.9 mg/L (lower target range), 20–59.9 mg/L (upper target range) and >60 mg/L (above target range). Furthermore, for severe infections we defined TTLs <20 mg/L as below target range. ORs for having values below or above the target ranges were calculated. Proportions were compared using Fisher's exact test or the McNemar test, and medians were compared using the Mann–Whitney *U*-test or the Wilcoxon test. Correlations were analysed using Spearman's correlation coefficient, partial correlation or regression analysis. The study was approved by the Ethics Committee of the Medical University Graz.

Results

Trough levels

During the study period, a total of 1503 samples were obtained to determine TTLs. One hundred and forty-six TTLs were excluded because of detection error ($n=14$) or because they were obtained during dialysis ($n=132$). Thus, we analysed 1357 samples obtained during 410 episodes in 280 patients (median age of 7 years, range 0.0–18; 574 neonate/infant samples, 295 toddler samples, 213 school-age children samples and 275 adolescent samples). In 70 episodes the initial measurement was performed outside our institution and only follow-up measurements were available. A median of three TTLs (range 1–25) were obtained per episode. While specimens were recorded from nine paediatric divisions, the vast majority (94%) of TTL samples were from the division of paediatric haemato-oncology (PHO) and the paediatric intensive care unit (PICU).

Initial trough levels

We analysed the initial TTLs of 340 episodes (92 neonate/infant episodes, 69 toddler episodes, 62 school-age children episodes and 117 adolescent episodes). The initial TTL was <10 mg/L in 48 (14.1%) and <20 mg/L in 247 (72.6%) episodes, while initial TTLs ≥60 mg/L were not achieved. There was no linear correlation of initial TTL with children's age, but median initial TTLs were significantly lower ($P=0.001$) in toddlers when compared with neonates/infants and school-age children. As a consequence, when compared with the entire cohort, toddlers were at increased risk for having an initial TTL <10 mg/L (OR 2.5, $P=0.011$) and <20 mg/L (OR 2.0, $P=0.048$). For further details see Figure 1(a) and Table 1.

Follow-up trough levels

We analysed 1017 follow-up TTLs of 410 episodes. Median follow-up TTL was significantly higher than median initial TTL for all age groups except adolescents. Follow-up TTLs were <10 mg/L in 38 (3.7%) and <20 mg/L in 340 (33.4%) measurements and less likely to be <10 mg/L and more likely to be within the upper target range compared with initial TTL ($P<0.001$, each). Two (0.2%) follow-up TTLs were >60 mg/L. For further details see Figure 1(a) and Table 1.

There was an inverse linear correlation between follow-up TTL and children's age ($P<0.001$), with a median decrease of 0.26 mg/L per 1 year increase in age (95% CI 0.169–0.351 mg/L).

Peak levels

During the study period, 347 samples were obtained to determine TPLs. Twenty-two TPLs were excluded because of detection error ($n=17$) or because they were obtained during dialysis ($n=5$). Thus, we analysed 325 samples obtained during 203 episodes in 94 patients (median age of 11 years, range 0.0–18; 19/16 neonates/infant samples/episodes, 77/44 toddler samples/episodes, 77/49 school-age children samples/episodes and 152/94 adolescent samples/episodes). A median of 1 (range 1–14) TPL was obtained per episode. Specimens were recorded from five departments, with 94% from the PHO division.

Initial peak levels

We analysed 203 initial TPLs. There was a linear correlation between initial TPL and children's age ($P=0.006$), with a median increase of 1.1 mg/L per 1 year increase in age (95% CI 0.4–1.7 mg/L). Despite indicated as being TPL, 1.5% and 4.9% were <10 and <20 mg/L, respectively. Infants and toddlers had

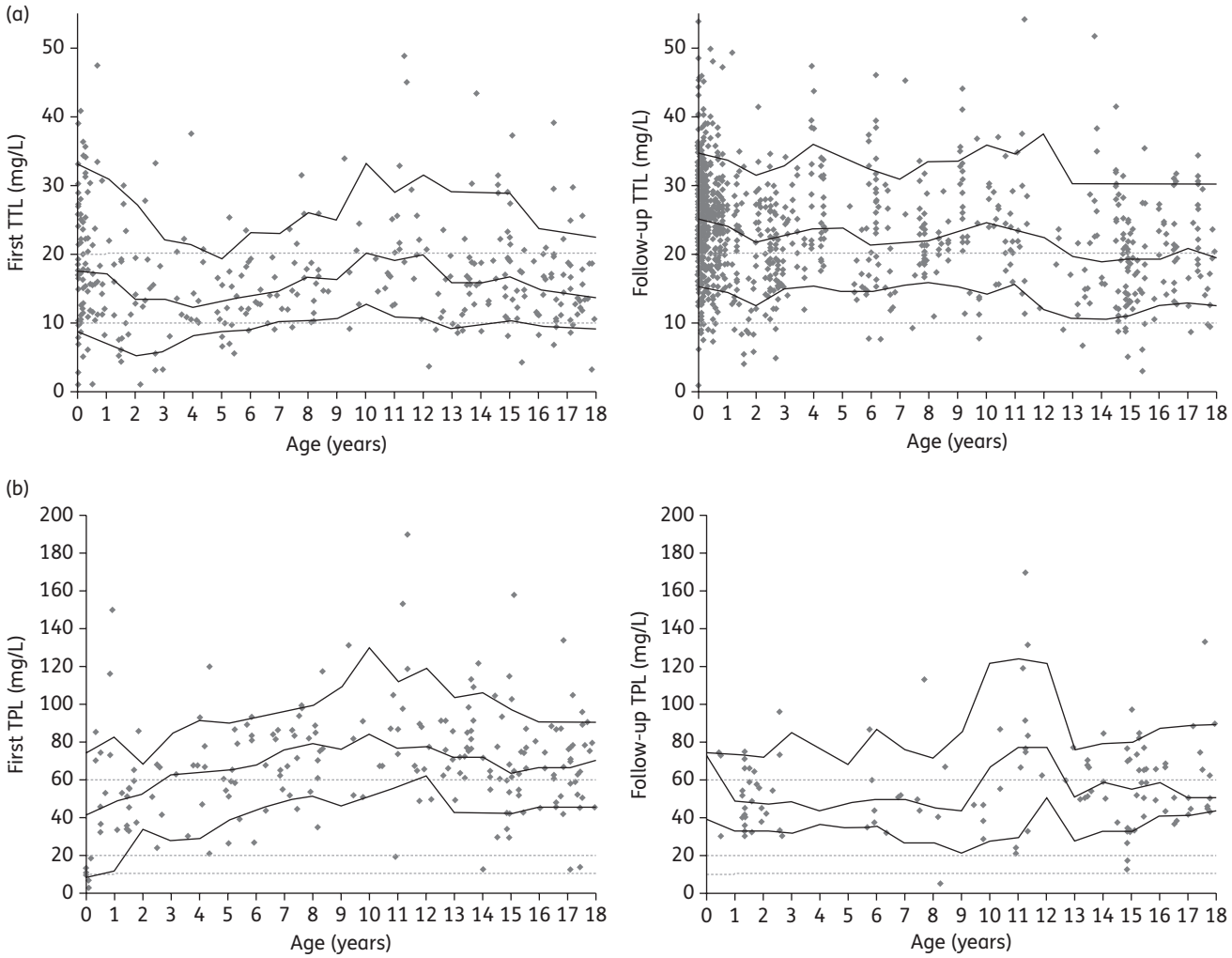

Figure 1. Initial (left) and follow-up (right) (a) TTLs and (b) TPLs plotted against children's age. Lines indicate median levels and 10th and 90th percentiles, and rhombuses indicate single data points.

significantly lower initial TPLs than school-age children and adolescents (see Table 2).

When compared with the entire cohort, neonates/infants had TPLs <10 mg/L significantly more often ($P<0.001$). For further details see Figure 1(b) and Table 2.

Follow-up peak levels

Follow-up TPLs were significantly lower than initial TPLs of the same episode ($P=0.001$), which was mainly attributable to lower values in patients aged >10 years (see Figure 1b and Table 2). The risk of TPLs >60 mg/L was significantly higher in initial TPLs (OR 2.8, $P<0.001$), but was not further associated with the number of samples taken per episode (data not shown).

Correlation between peak and trough levels

Three hundred pairs of TTL and TPL were available for analysis, of which 185 were pairs of initial levels. There was a linear correlation between initial TPL and TTL, with a median TPL increase of 2.44 mg/L for each 1 mg/L increase in TTL (95% CI 2.0–2.88, $P<0.001$). The median difference between initial TTL and TPL was 55.5 mg/L (range 17.1–141.1). Children with an initial TTL >20 mg/L were at increased risk for having TPL >60 mg/L (OR 4.6, $P<0.001$).

As seen for initial levels, there was a linear correlation between follow-up TPL and TTL, with a median TPL increase of 1.79 mg/L for each 1 mg/L increase in TTL (95% CI 1.29–2.29, $P<0.001$). The median difference between follow-up TTL and TPL was significantly lower compared with initial levels (41.2 versus 55.5 mg/L, $P<0.001$). Again, children with a follow-up TTL >20 mg/L were at increased risk for having TPL >60 mg/L (OR 6.8, $P<0.001$).

The differences between TTLs and TPLs were significantly higher in patients above than below 10 years of age for initial levels (median 57.4 mg/L, range 19.4–141.1 versus median 51.4 mg/L, range 17.1–137.9, $P=0.014$) as well as for follow-up levels (median 43.4 mg/L, range 14.2–143.4 versus median 39.2 mg/L, range 14.0–77.3, $P=0.049$).

Gender-related differences

Adolescent girls had significantly higher initial TPLs (median 76.0 versus 61.7 mg/L, $P=0.001$) and significantly higher follow-up

Table 1. Initial and follow-up TTLs (mg/L) for different age groups

	Initial measurement *n* (%)						Follow-up measurements *n* (%)						
	<10	10–19.9	<20	20–59.9	≥60	median (range)	<10	10–19.9	<20	20–59.9	≥60	median (range)	
All age groups	48 (14.1)	199 (58.5)	247 (72.6)	93 (27.4)	0 (0)	15.9 (1.7–48.9)	38 (3.7)	302 (29.7)	340 (33.4)	675 (66.4)	2 (0.2)	23.3 (1.7–81.5)[a]	
Neonates/infants, <1 year	12 (13.0)	42 (45.7)	54 (58.7)	38 (41.3)[c]	0 (0)	17.6 (1.7–47.5)	11 (2.3)	115 (23.9)	126 (26.1)	355 (73.7)[c]	1 (0.2)	25.1 (1.7–81.5)[a]	g
Toddlers, 1–5.9 years	17 (24.6)[d]	40 (58.0)	57 (82.6)[e]	12 (17.4)	0 (0)	13.2 (1.7–37.6)	11 (4.9)	76 (33.6)	87 (38.5)	138 (61.1)	1 (0.4)	22.1 (4.1–64)[a]	i
School-age children, 6–11.9 years	3 (4.8)	40 (64.5)	43 (69.4)	19 (30.6)	0 (0)	16.8 (9.1–48.9)	3 (2.0)	41 (27.2)[c]	44 (29.1)	107 (70.9)	0 (0)	23.1 (7.6–54.2)[b]	h
Adolescents, 12–18 years	16 (13.7)	77 (65.8)[c]	93 (79.5)[e]	24 (20.5)	0 (0)	15.5 (3.3–43.5)	13 (8.2)[f]	70 (44.3)[c]	83 (52.5)[g]	75 (47.5)	0 (0)	19.4 (3–51.8)	i, j

[a]$P<0.001$ when compared with the respective initial measurement of the age group.
[b]$P=0.024$ when compared with the respective initial measurement of the age group.
[c]Levels more frequently within the indicated range compared with the entire cohort ($P<0.05$).
[d]Increased risk of having initial TTLs <10 mg/L (OR 2.5, $P=0.011$).
[e]Increased risk of having initial TTLs <20 mg/L (OR 2.0 and 1.7, $P=0.048$ and 0.042 for toddlers and adolescents, respectively).
[f]Increased risk of having follow-up TTLs <10 mg/L (OR 3.0, $P=0.004$).
[g]Increased risk of having follow-up TTLs <20 mg/L (OR 2.6, $P<0.001$).
Age-related differences between median values: [h]$P<0.001$, [i]$P<0.01$ and [j]$P<0.05$.

Table 2. Initial and follow-up TPLs (mg/L) for different age groups

	Initial measurement *n* (%)						Follow-up measurement *n* (%)						
	<10	10–19.9	<20	20–59.9	≥60	median (range)	<10	10–19.9	<20	20–59.9	≥60	median (range)	
All age groups	3 (1.5)	7 (3.4)	10 (4.9)	62 (30.5)	131 (64.5)[c]	67.5 (2.8–190)	1 (0.8)	2 (1.6)	3 (2.5)	71 (58.2)	48 (39.3)	52 (5–170)[a]	
Neonates/infants, <1 year	3 (18.8)[e]	3 (18.8)[d]	6 (37.5)[f]	4 (25.0)	6 (37.5)	41.5 (2.8–150)	0 (0)	0 (0)	0 (0)	1 (33.3)	2 (66.7)	72.9 (30.5–74.6)	i
Toddlers, 1–5.9 years	0 (0)	0 (0)	0 (0)	25 (56.8)[d]	19 (43.2)	57.1 (21.3–120.2)	0 (0)	0 (0)	0 (0)	25 (75.8)[d]	8 (24.2)	45.2 (30.3–96.1)	i, j
School-age children, 6–11.9 years	0 (0)	1 (2.0)	1 (2.0)	9 (18.4)	39 (79.6)[g]	76.5 (19.2–190)	1 (3.6)	0 (0)	1 (3.6)	14 (50.0)	13 (46.4)	53.6 (5–170)[b]	h, i, j
Adolescents, 12–18 years	0 (0)	3 (3.2)	3 (3.2)	24 (25.5)	67 (71.3)	70.1 (12.5–157.9)	0 (0)	2 (3.4)	2 (3.4)	31 (53.4)	25 (43.1)	56.3 (12.8–133)[a]	

[a]$P<0.001$ when compared with the respective initial measurement of the age group.
[b]$P=0.002$ when compared with the respective initial measurement of the age group.
[c]Increased risk of having initial TPL >60 mg/L compared with follow-up TPLs (OR 2.8, $P<0.001$).
[d]Levels more frequently within the indicated range compared with the entire cohort ($P<0.05$).
[e]TPLs more frequently <10 mg/L (OR not calculable due to a low case number, $P<0.001$).
[f]Increased risk of having initial TPL <20 mg/L (OR 27.5, $P<0.001$).
[g]Increased risk of having initial TPL >60 mg/L compared with the entire cohort (OR 2.6, $P=0.016$).
Age-related differences between median values: [h]$P<0.001$, [i]$P<0.01$ and [j]$P<0.05$.

TTLs (20.8 versus 17.6 mg/L, $P=0.016$) than adolescent boys. In parallel, adolescent girls had initial TPLs >60 mg/L significantly more frequently (80.7% versus 56.8%, $P=0.012$) and follow-up TTLs <10 mg/L significantly less frequently (1.4% versus 13.8%, $P=0.005$).

There were no gender-related differences among other age groups.

Discussion

In this study we evaluated a large paediatric cohort for the appropriateness of the dosing regimen of teicoplanin in the clinical setting by analysing TDM data. While the package insert recommends three initial loading doses of 10 mg/kg, 12 h apart, followed by the same dose every 24 h, in our institution 10–15 mg/kg is recommended at the same intervals, allowing higher doses in selected patients. Despite this regimen, 14% of patients had TTLs below the target (10 mg/L) and more than 70% did not achieve levels considered as appropriate for treating severe infections. This is in line with previously published data.[11,20–22] A large study retrospectively evaluated more than 10000 teicoplanin levels, from adults as well as paediatric patients, obtained during a 13-year period from different hospitals in the UK. The study reported that the rate of patients having levels below target (10 mg/L) decreased from 23% to 13% during the study period. The paediatric patients included were, however, not evaluated separately in that study.[11] Dufort *et al*.[22] reported TTLs <10 mg/L in five of nine paediatric patients after standard loading doses (3×10 mg/kg every 12 h). Ito *et al*.[21] evaluated paediatric patients (187 patients, 0–18 years of age) and reported 7%–30% and 56%–86% of patients having TTLs <10 and <20 mg/L, respectively. However, in that study lower doses than recommended were administered in 39% of patients, and age-related differences were not evaluated.

This is the first time that age- and gender-related differences in teicoplanin levels have been analysed in a large paediatric cohort. Toddlers had significantly lower TTLs at the initial measurement as well as at follow-up measurements, which is in line with a pharmacokinetic study in a small PICU cohort.[18] As a consequence, toddlers in our study were at a 2.5-fold higher risk of having inappropriate initial levels of <10 and <20 mg/L, which were measured in 25% and 83%, respectively. Toddlers might therefore be at higher risk of treatment failure and development of resistance. By contrast, neonates and infants were more likely to have initial TTLs within the upper target range, without an increased risk of exceeding it. During treatment episodes, the rate of patients with TTLs below the target ranges decreased significantly for the entire cohort.

Evaluating TPLs, nearly two-thirds had levels >60 mg/L, with school-age children being at a 2.6-fold increased risk of having TPLs >60 mg/L at the initial measurement. However, it is not clear whether this is of clinical importance. It has been considered that teicoplanin side effects are rare if higher serum levels are avoided.[1] In the routine of different institutions it is recommended to avoid levels >60 mg/L.[1,2,11,14] This recommendation is based solely on one non-peer-reviewed study reporting that patients with TTLs >60 mg/L more often had elevated serum creatinine levels than those with TTLs between 20 and 40 mg/L [4/36 (11%) versus 14/43 (33%), $P<0.04$, Fisher's test]. The effects of nephrotoxic co-medication were not evaluated in that small, non-peer-reviewed study, and therefore limited evidence for this upper cut-off exists.[6] Further studies should clarify feasible upper cut-off levels for TTLs as well as for TPLs. According to our analysis, TPLs >60 mg/L have to be accepted when TTLs >20 mg/L are aimed for. Interestingly, differences between TPLs and TTLs were significantly higher in children >6 years of age than in younger children, which once more reflects age-related differences in the pharmacokinetics of teicoplanin.

This is the first report of gender-related differences in teicoplanin levels. Adolescent girls had higher levels, with a lower risk of having levels <10 mg/L and a higher risk of levels >60 mg/L, which was observed in >80% of TPLs in adolescent girls. Gender-related differences in protein binding, tissue distribution or renal excretion of teicoplanin are possible explanations. Further studies are needed to evaluate whether these gender-related differences in adolescents might be reproducible in adults or whether they reflect physiological differences in the transition to adulthood.

With respect to the described differences, more individualized dosing regimens with higher loading doses, especially for toddlers, should be considered. Optimal dosing regimens for adolescent girls should be clarified in future studies.

TDM is an important tool for more tailored dosing strategies.[7,9,11,16] This is also reflected by the observed differences between initial and follow-up measurements: while follow-up TTLs were significantly higher, follow-up TPLs were significantly lower and less likely to be >60 mg/L compared with initial measurements. Besides delayed achievement of a steady state, adequate dose modification guided by TDM might be an explanation for this observation. In our institution, we are used to increasing the dosage approximately proportionally according to the difference between the actual measured level and the target level. However, systematic analyses of how to modify dosage to rapidly achieve target levels do not exist. Due to the retrospective character of the study, neither the exact initial dosages, the exact time of first TTL (during or after the loading-dose phase) nor details on dose modifications were available for evaluation in each episode. Furthermore, different indications for teicoplanin administration (prophylactic, empirical, calculated) and the wide range of underlying diseases of the analysed patients (e.g. haemato-oncological, post-heart surgery, burns), and therefore different clinical conditions and co-medications, did not allow evaluation of the efficacy of treatment or of dose-dependent side effects.

In conclusion, a high rate of TTLs below the target was observed, together with significant age- and gender-specific differences. More tailored dosing regimens with higher loading doses, especially for toddlers, should be considered. While further pharmacokinetic data in paediatric patients are pending, TDM is mandatory.

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Transparency declarations

None to declare.

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