The pharmacokinetics of teicoplanin in infants and children

Michael D. Reed, Toyoko S. Yamashita, Carolyn M. Myers and Jeffrey L. Blumer

Introduction

Teicoplanin is a glycopeptide antibiotic chemically related to the vancomycin–ristocetin group of antibiotics. Its in-vitro spectrum of antibacterial activity is equal to or superior to that of vancomycin and it is active against aminoglycoside and vancomycin-resistant strains of Entercoccus faecalis.

A number of controlled and uncontrolled clinical studies have demonstrated the drug’s efficacy in the treatment of bacterial infections involving the skin and skin structure, bone and joints, septicaemia, heart valves and infections associated with intravenous catheters.

The pharmacokinetics of teicoplanin have been extensively evaluated in adults and reveal a very different disposition profile from vancomycin. The elimination half-life of teicoplanin in adult volunteers has been described to range between 50 and 168 h depending on the length of sample collection supporting its once-daily dosage recommendations.

The pharmacokinetics of teicoplanin were assessed after a single dose and under multidose conditions in 12 infants and children. Study patients ranged in age from 2.4 to 11 years. Each patient received teicoplanin 6 mg/kg body weight given intravenously over 20–30 min, once daily for five consecutive days. Multiple timed blood and urine samples were obtained over the 6 day sampling period and were analysed for teicoplanin by both microbiological assay and HPLC. Three-compartment pharmacokinetic analysis was used to describe the drug’s disposition characteristics. Peak and 24 h trough serum teicoplanin concentrations averaged 39.3 and 1.8 mg/L after the first dose with little accumulation observed after 5 days of therapy. Teicoplanin disposition was variable; \( V_{ss} \) ranged from 0.31 to 0.68 L/kg, \( t_{1/2} \) from 6.5 to 18.1 h and \( Cl \) from 29 to 51 mL/h/kg. A substantial amount of the administered drug distributed rapidly to the largest, third compartment, with egress approximately four-fold slower than ingress. The majority of the drug was excreted unchanged in the urine. Teicoplanin administration was well tolerated by all study subjects. Using the teicoplanin pharmacokinetic data derived in our study, a dose of teicoplanin 8 mg/kg body weight administered every 12 h should achieve target serum trough concentrations averaging 11 mg/L in children. Higher doses, e.g. 15 mg teicoplanin/kg administered every 12 h, may be needed for the treatment of deep-seated staphylococcal infections and/or endocarditis.

Materials and methods

Infants and children between the ages of 2 and 12 years admitted to the Paediatric Intensive Care Unit of Rainbow Babies and Children’s Hospital following an elective surgical procedure were eligible for enrolment into this study. Patients were permitted to receive any form of prophylactic or therapeutic drug therapy, including antibiotics (with the exception of vancomycin), before, during or after

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Teicoplanin administration. Patients were excluded from this study if they had a known allergy to vancomycin, were acutely ill, haemodynamically unstable, had received vancomycin within the previous 24 h or an investigational new drug within 14 days of study enrollment, were morbidly obese (>200% ideal body weight), or had renal (serum creatinine > 1.4 mg/dL) or hepatic (serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than twice normal for age) dysfunction. This study was approved by the Institutional Review Board for Human Subjects Investigation of the University Hospitals of Cleveland, and written consent was obtained from a parent or guardian of each study object.

Prior to teicoplanin administration, each patient gave a complete history and underwent physical examination and blood was obtained for the determination of serum electrolytes, creatinine, urea nitrogen, calcium, phosphorus, alkaline phosphatase, AST, ALT, total and direct bilirubin, total protein, albumin and complete blood count with differential, platelet count, prothrombin time and partial thromboplastin time. A microscopic and macroscopic urinalysis was performed. These laboratory determinations were performed in the clinical laboratories of the University Hospitals of Cleveland. Each subject was examined daily and laboratory parameters were repeated on study days 3 and 5 and just before hospital discharge.

Drug administration and sample collection
Teicoplanin was provided as a sterile crystalline powder equivalent to 200 mg (Marion Merrell Dow Research Institute, Cincinnati, OH, USA). The drug was reconstituted with sterile water. Each study subject received teicoplanin 6 mg/kg body weight admixed in either normal saline or 5% dextrose in water, administered intravenously over 20–30 min once-daily for a total of 5 days. Immediately following drug administration, the intravenous infusion tubing was flushed with 3–10 mL normal saline to ensure administration of the total dose. Each dose of teicoplanin was administered by a research nurse using an autosyringe.

Venous blood samples (1.5–2.0 mL) were obtained for the determination of teicoplanin at time 0, immediately upon completion of the infusion (approximately 20–30 min) and at 45 min and 1, 2, 6, 12 and 24 h after the beginning of the first teicoplanin infusion; 1, 4 and 8 h after the start of the second dose infusion; 1, 8 and 24 h after the start of the third dose infusion; 1 and 12 h after the start of the fourth dose infusion; and 0, 30 and 45 min and 1, 2, 6, 12 and 24 h after the start of the fifth dose infusion. A didtional blood samples were obtained 36, 60, 84, 108 and 132 h after the start of this fifth and last dose infusion, for as long as the study subject remained hospitalized. Blood was collected in sterile glass tubes, allowed to clot and centrifuged immediately. Before administration of the first dose, a urine sample was obtained and all urine excreted thereafter over the first 24 h study period was collected as timed samples. All samples were stored at −80°C until analysed.

Quantification of teicoplanin in serum and urine
The concentration of teicoplanin was quantified in serum and urine. All serum and urine samples obtained from study patients were subdivided into two aliquots before storage allowing quantification by two different methods. The concentration of teicoplanin in one set of serum and urine samples was determined using a previously described agar diffusion microbiological assay16 in the research laboratories of Marion Merrell Dow. The lower limit of detection for serum and urine using this method were 0.19 mg/L and 3.0 mg/L teicoplanin, respectively.

The concentration of teicoplanin in the second aliquot of serum and urine samples was analysed by HPLC in the Paediatric Pharmacology Laboratory, Rainbow Babies and Children’s Hospital. Analyses were performed on a Varian Instruments model 5560 liquid chromatograph equipped with a variable-wavelength UV 200 detector set at 214 nm and 9090 A autosampler with a V alco model C6W injection valve fitted with a 50 μL loop. Peaks were integrated on a DS 604 computer and printed on a Hewlett-Packard Thinkjet printer.

Chromatography was performed using a modification of the method described by Borghi and colleagues.17 A guard column (4 cm × 4 mm) filled with Vydac 40 μm pellicular reversed-phase packing was placed between the injector and the column. Samples were analysed using a 25 cm × 4.6 mm ODS 5 μm Biophase column kept at a constant temperature of 30°C using a heater block. The mobile phase consisted of 0.025 M potassium phosphate, pH 6.0, stored in reservoir A and acetonitrile stored in reservoir B. The rate of flow was set at 1 mL/min. A gradient from 20% to 35% from reservoir B (80–65% reservoir A) was programmed between 0 and 15 min after which the mobile phase was maintained at 35% reservoir B for the next 5 min. The mobile phase was then returned to starting conditions of no gradient and after 10 min a new sample could be injected.

Teicoplanin was extracted from samples using a modification of the method for moxalactam by Bawdon et al.18 In a 12 × 75 mm glass tube, 0.4 mL serum was combined with 0.4 mL water and left for 15 min, after which 0.01 mL phosphoric acid (85%) and 2 mL acetonitrile were added. This mixture was vortexed for 20 s and then centrifuged for 2 min at 2500 g. The entire supernatant solution was added to 4 mL methylene chloride in a 12 mL heavy-walled conical tube, vortexed for 2 s and centrifuged for 1 min at 2500 g. The majority of the bottom organic layer was discarded and the remaining mixture centrifuged briefly at 2500 g. The upper aqueous layer was transferred to an autosample vial for analysis.

Well mixed urine (0.2 mL) was added to 0.6 mL water.
and 0.005 mL phosphoric acid in a 12 mL heavy-walled conical tube and mixed briefly. After the addition of 2 mL acetonitrile and 4 mL methylene chloride, the entire mixture was vortexed for 20 s and then processed as described above for serum.

Serum standard curves were analysed in triplicate on two separate occasions. Six concentrations between 0.4 and 50 mg/L yielded correlation coefficients of >0.999, a mean coefficient of variation (CV) of all triplicates of 7.6% and a mean CV of the individual slopes in the two experiments of 3.8%. The assay’s lower limit of detection was 0.2 mg/L; recovery of teicoplanin from serum was 90%. Triplicate urine standard concentrations between 4 and 100 mg/L yielded correlation coefficients of 0.999, a mean CV of the triplicates of 4.4% and a mean CV of the individual slopes of 3.3%. Teicoplanin recovery from urine was 94%. The CV of the slopes of the regression lines used to calculate patient samples was 2.8% for serum and 4% for urine.

**Pharmacokinetic analysis**

The disposition of teicoplanin was characterized using standard three-compartment pharmacokinetic methods. Teicoplanin pharmacokinetic disposition characteristics obtained after administration of the first dose and after incorporating each patient’s complete dosing/serum teicoplanin concentration history for co-modelling of all serum teicoplanin concentrations obtained during the entire study period (five or more days) was determined using PCNONLIN. This analysis permitted estimation of the important teicoplanin pharmacokinetic parameters: distribution half-life \( t_{1/2,d} \), elimination half-lives \( t_{1/2,b} \) and \( t_{1/2,y} \); mean residence time (MRT); volumes of distribution of the central compartment \( V_c \) and the peripheral compartments \( V_1 \) and \( V_2 \), steady-state volume of distribution \( V_{ss} \); corresponding rate constants \( K_{1,0} \) and the intercompartmental rate constants \( K_{1,2}, K_{2,1}, K_{1,3} \) and \( K_{3,1} \), and clearance values, including total body clearance \( Cl \) and renal clearance \( Cl_{r} \). Renal clearance was determined from the ratio of the total amount of teicoplanin recovered in urine to the area under the predicted serum concentration–time profile determined over the same time interval.

**Statistical analysis**

Statistical analysis was performed using multiple analysis of variance (MANOVA), multiple analysis of covariance (MANCOVA), paired Student’s t-test, Pearson correlation and linear regression analysis. All statistical analyses were performed using standard methods with an accepted level of significance of \( P < 0.05 \). Data are presented as the mean, standard error of the mean (±S.E.M.), standard deviation around the mean (±S.D.) and range.

**Results**

Twelve infants and children were enrolled and completed the first dose and multi-dose evaluation. The characteristics of these study subjects including type of surgical procedure performed are shown in Table I. All cardiac surgery patients had a cardiac index of \( \geq 3.5 \text{L/min/m}^2 \) throughout the study. One study subject inadvertently received two doses of vancomycin beginning 12 h after the first teicoplanin infusion. Vancomycin administration was discontinued and the study subject completed five doses of teicoplanin. The first 48 h of teicoplanin concentration-time data obtained in this patient were excluded from analysis. No biochemical, functional or clinical toxicity was associated with the administration of teicoplanin in any study subject.

The absolute values of teicoplanin concentrations in serum and urine were different for the two assay methodologies employed. Microbiological determinations of serum teicoplanin concentrations were always higher than those determined by HPLC (Figure 1; slope of line = 1.15). This difference in quantified value probably reflects the antibacterial activity of the drug’s minor metabolites. Nevertheless, the close relationship between these two methods of analysis is reflected by the highly significant correlation between measured values \( (r = 0.97; P < 0.0001) \) (Figure 1). Similar, but larger discrepancies were observed between HPLC and microbiological analysis of teicoplanin concentrations in urine (Figure 2), probably reflecting the accumulation of teicoplanin metabolites in

**Table I. Patients’ characteristics**

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<tr>
<td>Male:female ratio</td>
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<tr>
<td>Age (years)a</td>
<td>6 ± 3.1 (2.4–11.4)</td>
</tr>
<tr>
<td>Weight (kg)a</td>
<td>21.4 ± 11 (9.3–42.5)</td>
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<td>Surface area (m²)a</td>
<td>0.8 ± 0.3 (0.45–1.35)</td>
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<td>Serum creatinine (µmol/L)a</td>
<td>53 ± 18 (35–88.4)</td>
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<tr>
<td>Serum albumin (g/L)a</td>
<td>35 ± 7 (17–45)</td>
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<tr>
<td>A ST (U/L)a</td>
<td>20 ± 12 (10–49)</td>
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<tr>
<td>Total bilirubin (µmol/L)a</td>
<td>15.4 ± 12 (1.7–42.8)</td>
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<tr>
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<td>1</td>
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<tr>
<td>subaortic valve repair</td>
<td>1</td>
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<td>head surgery</td>
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a Abbreviations: A ST, alanine aminotransferase; ASD, atrial septal defect; VSD, ventricular septal defect.

b D ata are presented as mean ± s.e.m., with range in parentheses.

c N umber of patients undergoing each procedure.
Based on this high degree of concordance and the desire to describe the disposition characteristics of parent teicoplanin, we have elected to present the remainder of our data using HPLC methodology, unless otherwise stated for comparative purposes.

The overall mean ($\pm$S.D.) serum teicoplanin concentration–time curve over the whole study period is shown in Figure 3. Peak serum teicoplanin concentrations obtained at the end of the infusion averaged 39.3 (7.6) mg/L after the first dose and 40.8 (7.4) mg/L after the fifth dose; 24 h trough teicoplanin concentrations averaged 1.8 (0.6) mg/L after the first dose and 3.1 (1.2) mg/L 24 h after administration of the fifth dose. The teicoplanin serum concentration–time curve constructed from samples quantified by microbiological analysis is also shown in Figure 1 and is nearly superimposable.

The teicoplanin pharmacokinetic parameters estimated in our study subjects after first dose administration and under multidose conditions are shown in Table II; analyses were performed using teicoplanin serum concentration–time data obtained from both HPLC and microbiological techniques. Data from one subject after first dose administration were insufficient for three-compartment pharmacokinetic analysis and thus, are not included in the first dose summary data (Table II).

Teicoplanin disposition was variable across the age range of subjects studied. Teicoplanin steady-state volume of distribution ($V_{ss}$) ranged from 0.31 to 0.68 L/kg after the first dose and from 0.23 to 1.2 L/kg with multiple dosing. Similarly, teicoplanin terminal elimination, $t_{1/2}$ and body Cl were also variable, ranging from 6.5 to 18.1 h and from 29 to 51 mL/h/kg after the first dose, and being 4.5–39.3 h and 14.2–42.1 mL/h/kg with multiple dosing, respectively (HPLC; Table II).

To assess any influence of age on the disposition characteristics of teicoplanin, the primary pharmacokinetic parameter estimates $MRT$, $V_1$, $V_2$, $V_3$, $V_{ss}$, Cl and Cl, were plotted against age (data not shown). In this small group of patients representing a broad age range, no statistically significant relationships were identified between these teicoplanin pharmacokinetic parameter estimates and patient age. Nevertheless, a trend was observed between teicoplanin body Cl (decreasing) with increasing age, $r = -0.47$. 

**Figure 1.** Linear relationship between serum teicoplanin concentrations determined by HPLC and microbiological assay (‘micro’) ($r = 0.97$; $P < 0.0001$).

**Figure 2.** Quantification of urinary teicoplanin concentrations in urine using HPLC (■) and microbiological assay (▲). Each bar represents the mean ± s.d. for the percentage of dose excreted over the time shown.

**Figure 3.** Overall mean serum teicoplanin concentration–time curve after multidose administration (5 days) when concentrations are quantified by HPLC (▲), and microbiological assay (○). Open symbols denoting peak teicoplanin concentrations on study days 2, 3 and 4 are simulated values from the individual data.
Teicoplanin pharmacokinetics in children

The 24 h urinary recovery of teicoplanin after first dose administration averaged 44% and 65% when urine concentration data were analysed using HPLC and microbiological methodology, respectively (Table II). The majority of the drug was excreted in the urine during the first 6 h sampling period (Figure 2). Urine teicoplanin concentrations declined and then increased slightly over the next two sampling periods (Figure 2). The dependence of teicoplanin $Cl$ on renal excretion is reflected in the $Cl_r$ : $Cl_0$ ratio, this was 0.51 and 0.8 when urine teicoplanin concentrations were determined using HPLC and microbiological methodology respectively (Table II).

Discussion

Teicoplanin is a glycopeptide antibiotic that exhibits bactericidal activity in vitro against a range of aerobic and anaerobic Gram-positive bacteria.1–5 Like vancomycin, it inhibits cell wall synthesis of susceptible bacteria by binding to the terminal acyl-$\alpha$-alanyl-$\alpha$-alanine residue of cell wall peptidoglycan.2,5–7 These glycopeptides are inactive against Gram-negative bacteria as they are unable to penetrate the cells' outer lipopolysaccharide membrane and bind to their peptidoglycan receptors.2,5

Teicoplanin pharmacokinetics have been studied in both animals2,7,12 and humans.2,5–15 Like vancomycin, the drug is poorly absorbed into systemic circulation from the gastrointestinal tract;2,5,12 this characteristic permits the oral administration of either agent for the treatment of Clostridium difficile-associated pseudomembranous colitis.2,11 In contrast to vancomycin, teicoplanin is not associated with the frequent development of ‘red man syndrome’, renal dysfunction,5,22 or severe pain following intramuscular injection.2,5,7,12 Teicoplanin absorption from intramuscular injection sites appears to be rapid and complete,2,9,12 supporting this route for drug administration.7 Furthermore, teicoplanin is extensively bound to plasma protein (>90%)
and is only slowly eliminated from the body. Terminal teicoplanin elimination half-lives in adult subjects range from 50 to 168 h compared with 3–9 h for vancomycin. Buniva and colleagues reported 80% recovery of the teicoplanin dose excreted unchanged by the kidney over their 16 day sampling period. A prolonged sampling strategy, as performed in this study and others, is necessary to describe accurately the polyexponential character of teicoplanin disposition. Sampling strategies of shorter duration may not permit sufficient characterization of the drug’s terminal elimination half-life leading to quantitative discrepancies in important pharmacokinetic parameters. Studies incorporating a very prolonged sampling strategy (e.g., sample collection for 2-3 weeks after prolonged teicoplanin dosing) have described the very prolonged elimination characteristics for the drug. The variation in the duration of blood and urine sampling between studies probably accounts for the differences reported in teicoplanin pharmacokinetic data.

Teicoplanin is a complex of five major components (A 2-1 to A 2-5) and some minor components, all of which are glycopeptide analogues. Recovery studies of radiolabelled teicoplanin administered to rats and humans reveal a very limited extent of metabolism. Two metabolites have been identified but account for only 2–3% of the total drug recovered. These two metabolites appear to have a similar spectrum of antibacterial activity to the parent compound, but their antibacterial potency is much lower, ranging from 1.5 to 12% of that observed for teicoplanin. HPLC is a very specific means of determining the concentration of an individual compound, distinct from metabolites and other substrates. In contrast, microbiological methods used to determine drug concentrations are far less specific, extrapolating drug concentration from the antibacterial activity of the drug against a standard bacterial strain.

A cumulation of the two antibacterially active teicoplanin metabolites probably accounts for the observed differences in drug quantification between HPLC and microbiological methodology (Figures 1 and 2) and the differences observed in teicoplanin MRT, t1/2, and CI calculations (Table II).

The teicoplanin pharmacokinetic data obtained in children in the present study are consistent with single-dose paediatric data reported by Tarral et al. and differ from the single-dose paediatric data of Terragna et al. and from multi-dose data reported for adults. Teicoplanin pharmacokinetic data in the present study (Table II) and the study by Tarral et al. reveal a smaller teicoplanin Vdss and a more rapid teicoplanin CI; both parameter estimates are approximately two- to three-fold different in paediatric patients compared with adults (Table III). Furthermore, considerable variation is observed in the reported teicoplanin disposition characteristics in the majority of studies performed in paediatric and adult subjects. This variability is independent of the method of sample analysis, i.e., either microbiological or HPLC analysis, or the pharmacokinetic model employed. Despite the apparent differences observed among the reported paediatric studies and the present study, the disposition of teicoplanin in paediatric patients appears to reflect a more rapid CI and a smaller Vd than observed in adults (Tables II and III). The reason(s) for these observed differences in teicoplanin disposition characteristics between paediatric and adult subjects is unclear, but appears similar to differences observed between these two patient populations and other antimicrobial agents including vancomycin and β-lactam antibiotics.

The kidney is the primary route for elimination of teicoplanin and its minor metabolites. In the present study, CI, accounted for only 51% of total body CI (Table II). In contrast, when urine teicoplanin concentrations were determined using microbiological methodology, CI, accounted for 80% of body CI (Table II), reflecting the antibacterial activity of teicoplanin and its two active metabolites concentrated in the urine (Figure 2). This renal excretion rate of parent teicoplanin (51%; Table II) is consistent with values described by other investigators and would appear to reflect the relatively short duration of drug administration (i.e., first dose) and the sampling strategy. Further, a substantial amount of teicoplanin distributes to the third peripheral compartment as reflected by the large volume of Vd compared with the much smaller volumes observed for V1 and V2 (Table II). Distribution into this large compartment is much more rapid than egress (ingress is approximately four-fold greater than egress; Table II), accounting for the slow elimination able to be defined by studies which incorporate extended sampling periods (e.g. of weeks). Thus, it is most likely that

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urinary recovery of teicoplanin would have also exceeded 80–90% in the present study if we had continued our urine sampling for 10–14 days after the last teicoplanin dose.2,10,24

Considerable debate persists regarding the appropriate dose and dosing interval for teicoplanin, mainly because several different teicoplanin dosing regimens have been used in clinical trials, leading to different rates of bacterial and/or clinical efficacy.7,30,31 Early clinical studies in adults incorporating preliminary pharmacokinetic and in-vitro microbiological data used a loading dose of teicoplanin/6 mg followed by 3 mg/kg administered once daily. This regimen proved inadequate for severe S. aureus infections,7,30–33 prompting a dosage revision to a 12 mg/kg load followed by 6 mg/kg administered once daily.7,30,34 Unfortunately, although all infections involving indwelling vascular catheters were treated successfully with this higher teicoplanin dose and catheter removal, bacterial failures were again described for patients with S. aureus endocarditis or mycotic aneurysms. These results prompted investigators to discontinue their study prematurely.34 The exact reasons for these failures are unknown but they clearly raise doubt as to the appropriateness of these dosage regimens for the treatment of deep-seated staphylococcal infections.2,7,30 Based upon these reported experiences, most investigators suggest that higher teicoplanin doses are necessary to achieve therapeutic success. For most infections, teicoplanin dosing regimens that result in trough serum teicoplanin concentrations of approximately 10 mg/L appear adequate.7 In contrast, higher serum trough concentrations of 20 mg/L are recommended for the treatment of endocarditis caused by S. aureus.7 Further work is necessary to assess the clinical and bacterial efficacy of teicoplanin dose regimens which are designed to achieve these suggested target trough concentrations.

The teicoplanin pharmacokinetic data obtained in the present study provide some insight into the design of appropriate dosing regimens for the use of this drug in pediatrics. Our data and those of Tarral et al.14 support the need for higher doses, administered more frequently to children as compared with adults. The preliminary pharmacodynamic data in adults suggest that trough teicoplanin serum concentrations between 10 and 20 mg/L should be effective in the treatment of most systemic infections; for most patients, these concentrations should be achieved by day 2 or 3 of therapy. Using the teicoplanin pharmacokinetic data derived in our present study, a dose of teicoplanin 8 mg/kg administered every 12 h should be effective in achieving target trough serum teicoplanin concentrations averaging 11 mg/L within 48 h, and represent an appropriate regimen to initiate carefully controlled clinical efficacy evaluations in infected paediatric patients. Higher doses may be needed, e.g., 15 mg/kg teicoplanin administered every 12 h for the treatment of bacterial endocarditis.

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References


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