Dissertation

The Role of Age and Sex on Teicoplanin Serum Levels in Children and Adults - Analysis of Teicoplanin Therapeutic Drug Monitoring

submitted by

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Statutory Declaration

Declaration

I hereby declare that this dissertation is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this dissertation. Due acknowledgement has been made in the text to all other material used. Throughout this dissertation and in all related publications I followed the guidelines of “Good Scientific Practice”.

Graz, May 5th, 2015

Foreword and Acknowledgement

Thanks to my supervisors PD Dr. Volker Strenger, Dr. Jasmin Pansy, and PD Dr. Ines Zollner-Schwetz, whose assistance in the completion of this project has been very helpful.

Thanks to my family and friends who supported me!

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Abbreviations and Definitions

BMI – body mass index

CI – confidence interval

CONS - coagulase-negative staphylococci

CSF – cerebrospinal fluid

EMA – European Medicines Agency

ESCMID - European Society for Clinical Microbiology and Infectious Diseases

EUCAST - European Committee on Antimicrobial Susceptibility Testing

FDA - Food and Drug Administration

HPLC - High performance liquid chromatography

IV – intravenous

MARS - Molecular Adsorbent Recirculating System

MIC – minimum inhibitory concentration

MRSA – methicillin-resistant *Staphylococcus aureus*

MSSA – methicillin-susceptible *Staphylococcus aureus*

OR – odds ratio

RR –risk ratio

RRT – renal replacement therapy

TDM – therapeutic drug monitoring

TPL – teicoplanin peak level

TTL – teicoplanin through level

VISA – vancomycin intermediate *Staphylococcus aureus*

VRE – vancomycin resistant enterococci

VRSA – vancomycin resistant *Staphylococcus aureus*

VWD – von Willebrand Disease

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Abstract (German)

Hintergrund: Ziel dieser Arbeit war es Teicoplaninspiegel von pädiatrischen sowie auch erwachsenen Patienten und Patientinnen insbesondere im Hinblick auf geschlechts-und altersspezifische Unterschiede zu untersuchen.

Methoden: Am Univ.-Klinikum Graz sind Teicoplanin-Dosierungen von 6-15 mg/kg einmal täglich empfohlen, meist mit einer zusätzliche Gabe am ersten Therapietag (loading dose). Der erste Teicoplanin Talspiegel (teicoplanin trough level – TTL) wird am Therapietag 3 oder 4 gemessen und die Dosierung entsprechend angepasst mit dem Ziel, Spiegel >10 µg/mL zu erreichen (>20 µg/mL bei schweren Infektionen). In einer retrospektiven Studie haben wir 4413 Teicoplaninspiegel von 1380 Patienten analysiert, die von 2005 bis 2014 bestimmt wurden.

Ergebnisse. Die ersten Spiegel pro Episode lagen in 32,2% <10 µg/mL, in 73,3% <20 µg/mL. Erwachsene (15,0-64,9 Jahre) und ältere Patienten (≥65,0 Jahre) hatten signifikant niedrigere TTLs im Vergleich zu Kindern (0-14,9 Jahre) und folglich ein 3,7 bzw. 3,5-fach erhöhtes Risiko für subtherapeutische Spiegel <10 µg/mL (41.3% und 40.0% vs. 15.9%, p<0.001 für beide).

Insgesamt stiegen die Spiegel im Verlauf der Behandlungsepisoden rasch an, die Rate an subtherapeutischen follow-up Spiegeln war signifikant niedriger als bei den Erst-Spiegeln (32,2% der Erst- und 13,2% der follow-up Spiegel lagen <10 µg/mL, 73,3% und 58.7% <20 µg/mL, p jeweils <0.001). Während es bei Kindern keine geschlechtsspezifischen Unterschiede gab, hatten erwachsene Männer niedrigere Spiegel als Frauen und konsekutiv auch ein doppelt so hohes Risiko für Spiegel im subtherapeutischen Bereich (p<0.001).

Schlussfolgerung. Die Teicoplanin Pharmakokinetik ist abhängig von Alter und Geschlecht, mit höheren Serumspiegeln bei jüngeren und weiblichen Patienten. Ein Drittel der Patienten hat erste Talspiegel im subtherapeutischen Bereich.

Abstract (English)

Background. The aim of the study was to evaluate teicoplanin levels in real-life setting in a large cohort of paediatric and adult patients with special respect to sex- and age-related differences.

Methods.

At our hospital, different dosing recommendations comprise dosages ranging from 6 to 15 mg/kg per once daily single dose. Most recommendations include an additional second dose within the first 24 h ("loading dose"). Initial TTLs are analysed on treatment day 3 or 4 and dosing is adapted according to trough teicoplanin levels (TTLs) to achieve levels in the target range >10 µg/mL, >20 µg/mL for severe infections. In a retrospective analysis we evaluated 4413 TTLs obtained during 1380 treatment episodes from 2005 to 2014.

Results. Initial TTLs were <10µg/mL in 32.2% and <20µg/mL in 73.3% of patients. Adults (15.0-64.9 years) and elderly patients (≥65 years) had significantly lower TTLs when compared to children (0-14.9 years) and a consecutively 3.7- and 3.5-fold increased risk of having levels <10µg/mL (41.3% and 40.0% vs. 15.9%, respectively, $p<0.001$, each). For the entire cohort, follow-up TTLs were less likely to be <10 µg/mL (13.2%) and <20µg/mL (58.7%) when compared to initial TTLs ($p<0.001$, each). Initial and follow up TTL courses were different in females and males (initial: $p<0.001$; follow up: $p=0.013$). In adults, males were at an increased risk for having initial TTLs <10 ($p<0.001$). There were no sex-related differences in children.

Conclusion. Teicoplanin pharmacokinetics depends on age and sex with higher levels in younger patients and females. A significant proportion of patients, especially adults, has initial TTLs below the target range; thus, more tailored dosing regimens with higher loading doses should be considered in these patient groups. Therapeutic drug monitoring is mandatory to achieve therapeutic concentrations.

1 Introduction

1.1 Glycopeptide antibiotics

1.1.1 History

1.1.1.1 Vancomycin

The discovery and clinical development of antibiotic substances was one of the major medical achievements of the 20th century. (1) The first antimicrobial substances which were discovered and used in clinical practice were penicillin and sulphonamides in the 1930s. This heralded the so-called “Golden Age of Antibiotics”, a term used to describe the following 30 years, during which most of the antibiotic classes which are used in the clinical everyday practice today were discovered. (1)

The first description of a glycopeptide molecule involved ristocetin (2), but it was the discovery of vancomycin in the 1950s, which generated great interest in this new class of antimicrobial agents. Dr. E.C. Kornfield, an organic chemist at the company Eli Lilly (Indianapolis, USA), who had begun a major program to discover new antimicrobial agents with activity against staphylococci analysed a soil sample obtained from the interior jungle of Borneo. (3) Though it was only 20 years ago since the initial deployment of penicillin and later macrolides and tetracyclines, there was an increasing rate of staphylococcal strains with resistance to these agents. (4)

E.C. Kornfield isolated a microorganism from the soil sample from Borneo, which was subsequently named "*Streptomyces orientalis*". In broth fermentation this microorganism yielded a compound with a high degree of antimicrobial activity against staphylococci. (5) The compound was then named 05865.
Further studies were done on this compound and they revealed that after 20 serial passages of staphylococci in culture media containing either penicillin or compound 05865, resistance to penicillin increased 100,000-fold, compared with only a 4–8-fold for compound 05865. (4) The burden of drug-resistant staphylococci in US hospitals led the US Food and Drug Administration (FDA) to approve the compound 05865 in a "fast-track" procedure. The compound was then named "Vancomycin", a term derived from the word "vanquish". However, some scientists at Eli Lilly preferred to call it "Mississippi mud", because of its brown colour when it was won from fermentation. (3)

Though vancomycin as a glycopeptide antibiotic agent seemed to have a promising career by then, it was not widely used during the first decades after its discovery. In fact, other agents such as methicillin and other anti-staphylococcal penicillins were discovered and were the drugs of choice for the therapy of staphylococcal infections.
Vancomycin was thought to be ototoxic and nephrotoxic based on study results from the mid-1950s. (3, 6-10) For these reasons, it was not intensively marketed during the next decades. It was more than 20 years later that it was found, that impurities in earlier preparations were most likely responsible for the ototoxic and nephrotoxic effect. Newer and purer preparations were retested in the 1970s and were then found to produce no ototoxicity and little nephrotoxicity in animal models. (11-14) From the 1980s onwards vancomycin was widely used in clinical practice. (5)

1.1.1.2 Other naturally occurring glycopeptides

Ristocetin was the first glycopeptide antibiotic agent to be described in the early 1950s by Abbott Laboratories (Chicago, USA) (2) isolated from *Amycolatopsis lurida* collected in 1951 from Colorado Springs, USA. However, during its use as an antibiotic in humans, several patients developed thrombocytopenia and platelet agglutination as an adverse event and it had to be withdrawn from the market. (15, 16)

In fact, further studies revealed that platelet agglutination caused by ristocetin can occur only in the presence of von Willebrand factor multimers, so if ristocetin is added to blood lacking this factor (or its receptor), the platelet agglutination will not occur. (17-19) Therefore, ristocetin is now used *in vitro* in the diagnosis of conditions such as von Willebrand disease (vWD) and Bernard-Soulier syndrome. (20)

Other naturally occurring glycopeptides such as avoparcin (21) and actaplanin (22) have been used in veterinary practice.

The burden of methicillin resistant *Staphylococcus aureus* (MRSA) infections in the 1980s led to new interest in the search for novel antimicrobial agents including glycopeptides. Due to innovative methods to identify new strains, the ability to produce glycopeptides and to identify their structure more quickly, several naturally occurring new glycopeptides were identified from 1982 to 1996, though none of them found their way to a widespread use in clinical practice. (1, 23) Since 1996, no further naturally occurring glycopeptides were identified. (1)

1.1.1.3 Next generation semisynthetic glycopeptides

Telavancin, dalbavancin, and oritavancin are semisynthetic lipoglycopeptides with promising results for the treatment of patients with infections caused by multi-drug-resistant gram-positive pathogens. (1, 24)
As the naturally occurring glycopeptides, each of the new agents acts by inhibition of cell wall synthesis. Modifications to the molecular structure result in different *in vitro* activities for the three semisynthetic glycopeptides. All three lipoglycopeptides contain lipophilic side chains, which prolong their half-life, help to anchor the agents to the cell membrane and increase their activity against gram-positive cocci. (24) In addition to the inhibition of cell wall synthesis, telavancin and oritavancin are also able to disrupt bacterial membrane integrity and increase membrane permeability; oritavancin is also able to inhibit RNA synthesis.(25-27)

Telavancin

Telavancin was the first next generation glycopeptide antibiotic with approval in Europe in 2011. (28) It is a semisynthetic derivate of vancomycin. (29)

Telavancin possesses multiple modes of action including – next to inhibition of cell wall synthesis - the depolarization and permeabilization of the bacterial membrane, as for the other new glycopeptide oritavancin. (25) However, telavancin has a markedly shorter half-life than oritavancin, even though is highly protein-bound and largely distributes in the organism. (25, 30)

The antimicrobial spectrum of telavancin includes gram-positive strains and is very similar to that of teicoplanin and vancomycin. *Staphylococcus aureus* and *Staphylococcus epidermidis*, whether methicillin susceptible or resistant show a lower minimum inhibitory concentration (MIC) to Telavancin than to vancomycin and teicoplanin (2-4 dilutions). (30-32) Telavancin is active against vancomycin-intermediate *Staphylococcus aureus* (VISA) but displays poor activity versus

vancomycin-resistant *Staphylococcus aureus* (VRSA). Telavancin also demonstrates potent activity against various species of streptococci, enterococci, against a broad range of anaerobic gram-positive bacteria and *Corynebacterium* spp. (24)

Oritavancin

Oritavancin is a derivative of the natural glycopeptide chloroeremomycin. (33) It was the first clinical candidate of this new generation of glycopeptides. As vancomycin, oritavancin was discovered by the company Eli Lilly (Indianapolis, USA) in the late 1990's. After the preclinical development and the first clinical trials, it was then successively taken over first by Intermune (Brisbane, USA) in 2001, then by Targanta Therapeutics (St-Laurent, Canada) in 2005 and finally Targanta and, thus, oritavancin, was acquired by The Medicines Company (Parsippany, USA) in 2009.
The FDA approved oritavancin for acute bacterial skin and skin structure infections on April 2014 (34), the European Medicines Agency (EMA) approved oritavancin in March 2015. (28)

As compared to vancomycin, oritavancin has a prolonged half-life and a higher bactericidal character, the latter by allowing anchoring and subsequent destabilization of the membrane. (26, 27) It has a stronger ability to form dimers, which cooperatively bind to peptidoglycan and may explain residual activity on vancomycin-resistance strains. (35)

Oritavancin is highly active against common gram-positive pathogens including MRSA, VISA, VRSA, and vancomycin-resistant enterococci (VRE). (36) The drug is administered as a single intravenous dose of 1200 mg over 3 hours in adult patients, and because of its terminal half-life of 393 hours, repeat dosing is not required in the treatment of bacterial skin and skin structure infections. (37-39)

Adverse events are similar to those described for vancomycin. Additionally, increased liver enzymes and osteomyelitis have been reported. (36, 40, 41)

Dalbavancin

Dalbavancin is a semi-synthetic derivative of a teicoplanin analogue. (42) It was discovered by Biosearch Italia (Gerenzano. Italy) and is now licenced by Durata Therapeutics International (Chicago, USA).
Dalbavancin was approved by the FDA for acute bacterial skin and skin structure infections in May 2014 and EMA approval was achieved in February 2015. (28, 34)
Dalbavancin displays a prolonged half-life 147 to 258 hours, which allows for once-weekly dosing. (24, 43, 44)

Dalbavancin provides a superior antimicrobial activity compared to vancomycin and teicoplanin against staphylococci including coagulase-negative species, which are usually less susceptible to teicoplanin, and against *Streptococcus pyogenes* and *Streptococcus pneumoniae*. (45, 46). Dalbavancin is active against vancomycin-susceptible enterococci, but not against vancomycin-resistant strains (24).

1.1.2 Structure and function of glycopeptides

Glycopeptide antibiotics are a class of drugs of microbial origin produced in actinomycetes. They have in common a basic structure consisting of seven peptides, each peptide with an amino acid residue. Five of these seven amino acid residues are common to all glycopeptides. (47, 48) This basic structure is termed aglycone and is biologically active.

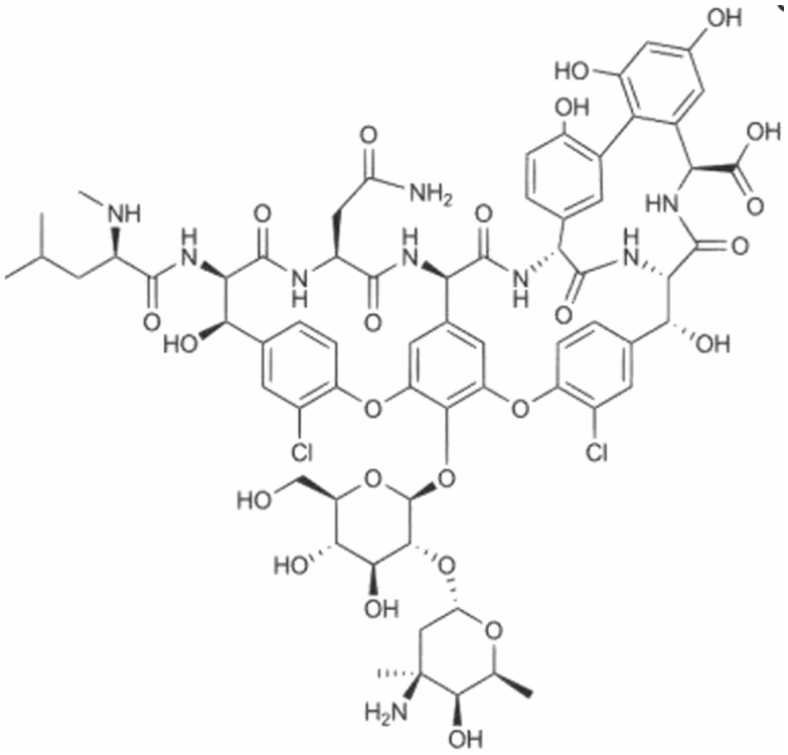

Figure 1: Molecular structure of vancomycin (49)

Sugars and aminosugars are mainly located on the outside of the molecule and do not affect antimicrobial activity *in vitro*. (48) However, they do affect pharmacokinetic properties of the single glycopeptides. For example, in ristocetin, the sugars are presumed to be responsible for causing platelet aggregation, which prevents its use as an antibiotic agent. (50) In the teicoplanins, an aminosugar is substituted by a fatty acid chain, which confers increased hydrophobicity and, thus, better tissue penetration. (48, 51)

The structure of some glycopeptides allows them to adopt a bracelet-like configuration with a cleft in the molecule into which the bacterial target site binds (see Figure 2).

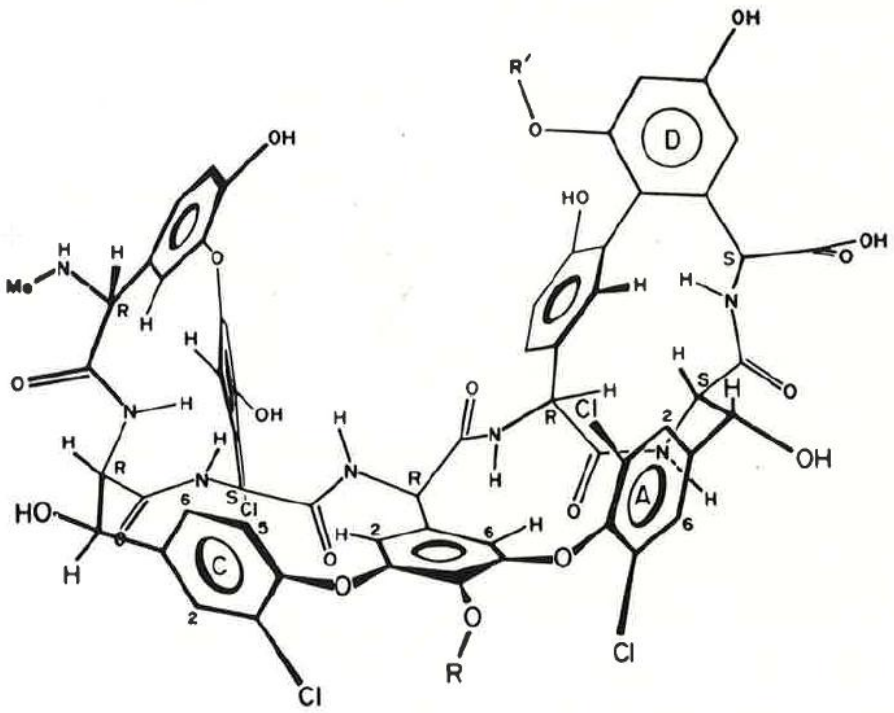

Figure 2: Three-dimensional model of the structure of a glycopeptide forming a bracelet-like structure (48)

The molecular mechanism of action has been best described for vancomycin. The D-Alanyl-D-Alanine terminus of pentapeptidic precursors represents the primary target of vancomycin. (48, 52, 53) Vancomycin forms a stoechiometric complex with the D-Ala D-Ala dipeptide via the formation of five hydrogen bounds. The formation of this complex prevents the transpeptidation reactions. (54-56).

In vitro, vancomycin also alters the permeability of cytoplasmic membranes and may impair RNA synthesis, (57, 58) but these mechanisms are probably not relevant *in vivo*, as the drug does not have access to membrane or intracellular compartments of the bacteria.

1.1.3 Trade names

Vancomycin is available as Vancocin® and Vancomycin®, as well as Vancomycin in combination with the different company names in Austria and Europe, and as Vancocin® and Lyphocin® in the USA.

Telavancin is available under the trade name Vibativ® in Europe and under Arbelic® in the USA.

Oritavancin is available in the USA under the trade name Orbactiv®, in Europe, oritavancin is approved under the same trade name, but not yet available for purchase.

Dalbavancin is available under the trade name Xydalba® in Europe and Dalvance® in the USA.

1.2 Teicoplanin

1.2.1 History

In the course of a screening program at the Lepetit Research Center (Gerenzano, Italy) for antibiotic-producing strains of Actinomycetes in 1978, Parenti and colleagues were able to isolate a strain named *Actinoplanes teichomyceticus* from a soil sample from India. This strain produced two antibacterial agents, which had not been described before. They named the two antibacterial agents teichomycin A1 and teichomycin A2. While teichomycin A1 was not considered worthy of further development, teichomycin A2 was described to be highly active against gram-positive pathogenic bacteria, both *in vitro* and *in vivo*. (59)
Teicoplanin was first approved in Europe in 1988 and it is now used in many other countries around the world with the noticeable exception of the United States.

1.2.2 Structure of Teicoplanin

The structure of glycopeptides is based on a central heptapeptide domain in which five of the seven amino acid residues are common to all glycopeptides. (1, 47, 48) This basic structure containing seven amino acid rests is labelled aglycone and considered biologically active.
Compared to other glycopeptides, teicoplanin has the amino group of an aminosugar replaced by a fatty acid chain. (51) This provides teicoplanin with an increased hydrophobicity compared to vancomycin. (48)

The structure of teicoplanin and its components was further elucidated in 1984 (60) while it was already under evaluation for the use in humans. New methods with a higher purification of the agents allowed a further analysis of the

components. By the use of paper chromatography, thin-layer chromatography procedures, which were then usually employed for the identification of new antibiotics, as well as reverse phase high performance liquid chromatography (HPLC), Borghi *et al.* (60) were able to show that Teichomycin-A2 was composed of five major components of very similar polarity, designated A2-1, A2-2, A2-3, A2-4 and A2-5 together forming Teichomycin A2, and smaller components, which were later labelled RS-1 to RS-4.

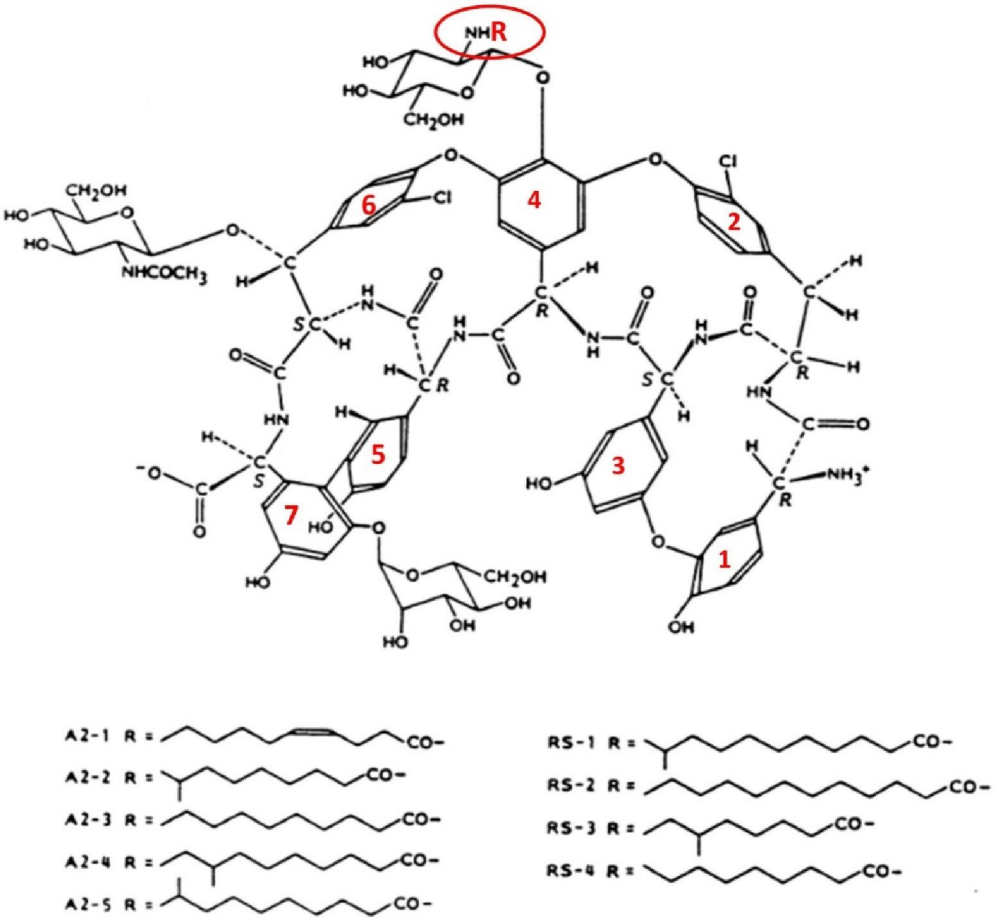

Figure 3: Molecular structure of the teicoplanin components. (61) Teicoplanin's structure is a heptapeptid (the seven amino acids of the peptide are numbered 1-7). 'R' marks the position of the fatty acid chain residues.

1.2.3 Mode of action

Glycopeptide antibiotics act on the late stage of cell wall synthesis in dividing bacterial organisms. The bacteria produce peptidoglycan, which is the major structural polymer forming the bacterial cell wall. During cell division the cell wall is elongated and peptidoglycan is needed for the biosynthesis of the bacterial cell wall. Glycopeptides interfere with the formation of this peptidoglycan by inhibiting the transpeptidation reaction. (47, 48, 62) Figure 4 shows the peptidoglycan structure and mechanism of action of glycopeptides antibiotics.

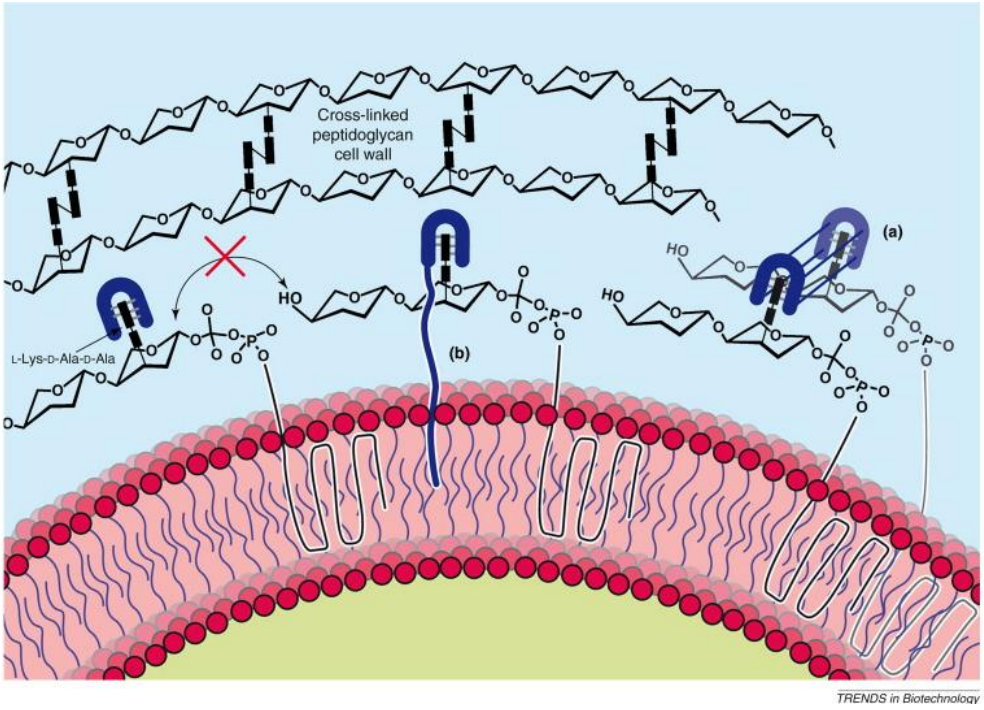

Figure 4: Peptidoglycan structure and mechanism of action of glycopeptides antibiotics

Glycopeptides inhibit transglycosylation and transpeptidation by binding to the C-terminal D-Ala-D-Ala of the late peptidoglycan precursor. (a) Vancomycin-type glycopeptide activity is based on dimerization, which enhances binding to the target peptide through both cooperative and allosteric effects. (b) Lipoglycopeptides (e.g. teicoplanin and its derivatives) have fatty acyl chains anchored in the phospholipid bilayer that enhance the binding affinity. (63)

Similar to vancomycin, teicoplanin inhibits cell wall synthesis in susceptible bacteria. It inhibits polymerisation of peptidoglycan in bacterial cell walls by binding non-specifically to saturate the outer layers of the bacterial peptidoglycan. It then binds to the terminal amino acyl- D-Ala-D-Ala precursor, which fits into a cleft in the teicoplanin molecule (as shown in Figure 5). (48, 63-65)

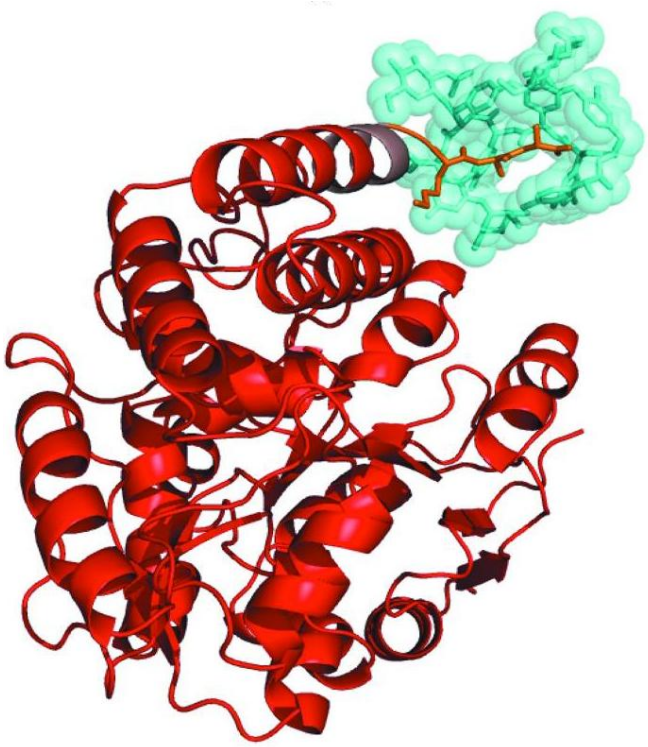

Figure 5: Teicoplanin with its ligand
Teicoplanin (cyan) binds to the Lys-D-Ala-D-Ala target protein (orange), which is covalently fused to a carrier protein (red). (65)

1.2.4 Pharmakokinetic profile

1.2.4.1 Absorption

Teicoplanin cannot be absorbed after oral administration, though oral administration has been used in the treatment of patients with pseudomembranous colitis. (66, 67).
Beside intravenous administration, intramuscular injection is another way of administration. This is well tolerated and provides a rapid absorption with serum concentrations reaching 12 µg/mL at 4 hours after administration of 6 mg/kg intramuscularly. In comparison the intravenous (IV) administration of the same dose resulted in serum concentrations of 43 µg/mL at 30 minutes after the administration. (68) After intramuscular administration systemic availability approaches 100% and clearance is similar to the IV administration route. (69)

1.2.4.2 Distribution

After IV administration, teicoplanin was shown to have a long serum half-life. (69) After one single administration the pharmacokinetics of teicoplanin follow a tri-exponential decay: Peak concentrations immediately after the end of the infusion vary with the infusion rate and are described to range from 30 to 250 µg/mL. (70-72) The initial alpha (α) half-life was shown to range between 0.4 and 1 hour, thereafter beta (β) half-life was shown to range between 4.7 and 15.4 hours and the last gamma (γ) half-life was shown to be 83 to 168 hours, respectively. (70-73).

Figure 6 shows the serum concentrations of teicoplanin after one single IV administration of 15 mg/kg in five healthy subjects. In this model half-lives were described with α=0.5, β=9.7, and γ=88.1 hours. (70)

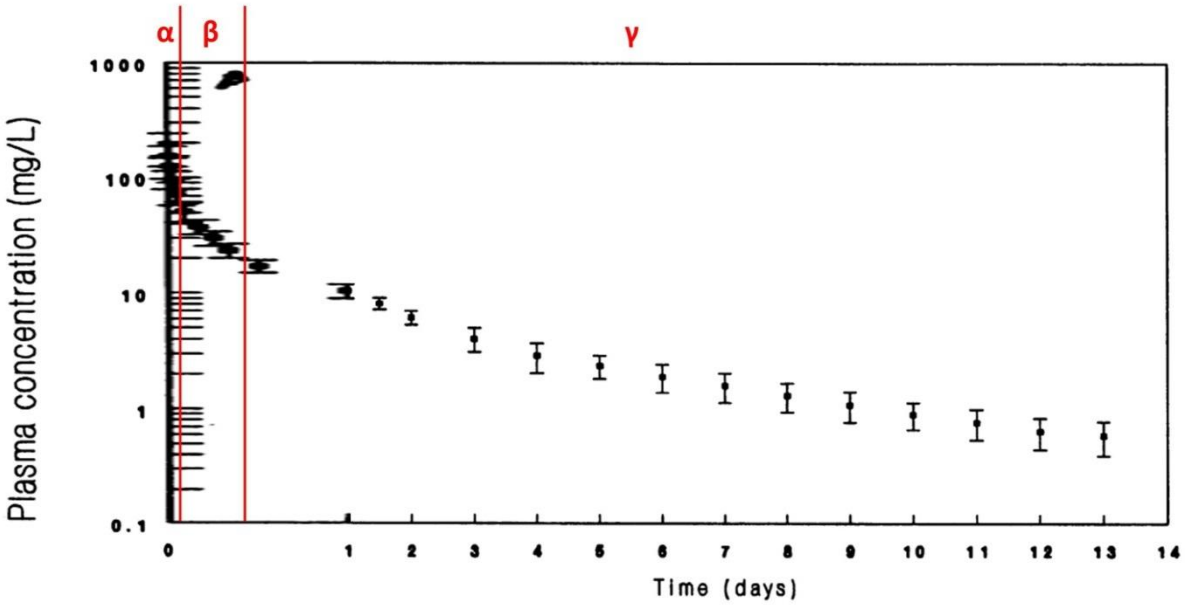

Figure 6: Teicoplanin pharmacokinetics: Half-life and plasma elimination Mean plasma concentration of teicoplanin (±standard deviation) after IV administration of 15 mg/kg. (70) Initial (α) half-life is 0.5 hours, β half-life is 9.7 hours, and γ half-life is 88.1 hours, respectively.

The volume of distribution is used in pharmacokinetic studies to describe to which extent a pharmacologic agent distributes from the blood to the extravasal space and tissues. In other words, it is the theoretical volume that the total amount of administered drug would have to occupy (if it was uniformly distributed), to provide the same concentration as it currently is in blood plasma. Lipophilic substances tend to have a higher volume of distribution, while polar substances and those with a high rate of protein binding tend to have a lower volume of distribution.

For teicoplanin the initial volume of distribution is low with values from 0.07 to 0.11 L/kg, increasing then to 1.32 to 1.50 L/kg during the distribution phase and decreasing thereafter to 0.8 to 0.87 L/kg during the steady state phase. (69, 70)

Teicoplanin is highly bound to serum proteins – mainly albumin. The free fraction of teicoplanin is known to range from 6 to 12%. (69)

1.2.4.3 Tissue distribution

Teicoplanin concentration in various tissues has been found to be highly variable. Several different types of tissue concentrations have been studied. However, different dosing regimens, patient characteristics and time of specimen collection make it difficult to directly compare this data.

Bone

After a single dose of 6 mg/kg, concentration of teicoplanin in the bone was 7 µg/mL at 12 hours and 1 to 2 µg/mL at 24 hours. The concentration in cartilage was described to be lower than in bone (3.5 and 2 µg/mL at 12 and 24 hours). (74)

For total hip replacement surgery, a single IV dose of 10 mg/kg was demonstrated to result in a mean intraoperative concentration in bone over 6 mg/kg. (75) However, in some patients the concentration was as low as 2.6 mg/kg.

For the surgery of more distal joints such as the knee, some authors have reported on the method of local administration of teicoplanin. Teicoplanin was given locally into a vein under tourniquet. If a dose 400 mg is given IV below the inflated tourniquet, the concentrations in the skin, subcutaneous tissue, bone and synovia at 1 hour reached 7.4 to 14.6 µg/mL, which is considered higher than the MIC of susceptible staphylococci. (76) When a higher dose of 800 mg was given IV before inflation of the tourniquet concentrations in these tissues were found to be low with 2.0 to 2.8 mg/kg at 1 hour). (76)

Cerebrospinal fluid

When administered as an IV infusion teicoplanin does not reach the cerebrospinal fluid (CSF). However, intraventricular administration can be used. Of 4 patients

who received IV doses of 400 mg once daily for neurosurgical shunt infections, CSF concentrations were <1 µg/mL in all cases. In one patient who received IV doses of 1200 mg once daily for four days subsequent CSF concentrations were also low and ranged from 1.5 to 2 µg/mL.

Single reports on intraventricular administration of teicoplanin describe CSF concentrations of 18 to 38 µg/mL in infants (after intraventricular administration of 5 mg/day) and adults (after intraventricular administration of 20 mg/day). (77)

Intraocular concentration

Briggs *et al*. (78) studied 20 patients who were administered teicoplanin and then had a vitrectomy. Only eight patients had detectable concentrations of teicoplanin in the vitreous body, including 4 out of 5 patients who received a higher loading dose regimen with 600 mg administered 24 and 48 hours prior to surgery. Vitreal teicoplanin concentration ranged from 0.5 to 1.8 µg/mL. (78)
Teicoplanin concentration in aqueous humour was studied in two cohorts consisting of 19 and 52 subjects, respectively. (79, 80) De Lalla *et al*. (80) reported on low mean teicoplanin concentration in aqueous humour of 0.5 µg/mL (±0.26 µg/mL) after IV administration of 400 to 600 mg teicoplanin 1 to 12 hours prior to surgery. Antoniadou *et al*. (79) administered either 600 mg as an IV infusion 1 to 20 hours prior to surgery or 25 mg as a subconjunctival injection 1 to 24 hours prior to surgery. None of the patients had any detectable teicoplanin concentration in the aqueous humour.

Fat

Teicoplanin concentrations in fat were described to be low after a single dose of 400 mg IV. In patients after breast surgery with serum teicoplanin concentrations

of 14.7 to 36.3 µg/mL, teicoplanin concentrations in fat tissue varied from 0.5 to 5.9 µg/mL and in one patient no teicoplanin was detectable.

In patients undergoing coronary artery surgery or valve replacement concentration in mediastinal fat reached mean concentrations of 5.9 mg/kg at 1 hour, 3.2 mg/kg at 4 hours, and 1.2 mg/kg at 16 hours, respectively. (81)

Wound exudate

Steer *et al*. [34] administered 12 mg/kg of teicoplanin to seven patients with burns and analysed teicoplanin concentrations in burn wound exudates at 24 hours. The mean concentration in the wound fluid was 7.4 µg/mL (±2.5 µg/mL), and, thus, reached 60% of the teicoplanin concentration in serum. [34]

Others

Lenders *et al*. (74) analysed teicoplanin concentration in tonsil tissue: After a single IV injection of teicoplanin 400 mg, the concentration in tonsil tissue was 8 µg/mL after 12 hours and 3 µg/mL after 48 hours.
Teicoplanin was reported to reach breast milk in small concentrations; however, it is then not absorbed after oral intake. (69)
Teicoplanin is known to pass the placenta. However, up to date the clinical significance of this is not clear. (69)

Teicoplanin as prophylactic agent in cardiac surgery

Due to teicoplanin's antimicrobial characteristics including its activity against most staphylococci and the long half-life, it has been suggested as an ideal prophylactic

agent for patients undergoing cardiac surgery. Several authors have investigated teicoplanin tissue penetration in the context of cardiac surgery.

Isringhaus *et al*. (81) analysed teicoplanin concentration in serum, pericardium, myocardium, muscle, and mediastinal fat in patients undergoing coronary artery surgery or valve replacement. After a single dose of 800 mg IV concentrations in myocardium at 1, 4, and 8 hours after the administration were 34 mg/kg, 43 mg/kg, and 12 mg/kg, respectively. The lowest concentration was reached in fat tissue, which is in line with other reports (see above).
Other studies (82, 83) reported on similar high concentrations in myocardium and pericardium and similar low concentrations in sternal bone and fat.

Table 1: Distribution of teicoplanin in tissues

Patients: Age (years)	Dosage	Number of patients	Tissue	Concentration (µg/mL or mg/kg) at 1h	4h	16h	Ref.
24.9 (mean)	400 mg SD	41	Serum		12	5	(74)
		41	Tonsil		9	5	
		41	Bone		6	3.2	
		41	Cartilage		8	3.2	
58 ±24	6 mg/kg 12 h 10 mg/kg SD	5	Sinus fluid	0.7			(75)
		16	Cancellous bone	6.2 (3.8-10.9)			
		16	Cortical bone	7.1 (2.6-12.1)			
69 ±6	800 mg before inflating tourniquet	11	Serum	8.5 ±3.9			(76)
		6	Skin	2.0 ±2.8			
		8	Subcutaneous tissue	2.3 ±1.1			
		3	Bone	2.2 ±0.8			
		8	synovia	2.8 ±1.0			
65 (54-83)	800 mg SD	3	Serum before bypass	36.2 ±13,4	11,3 ±3,5	6,7 ±2,3	(81)
		3	Serum after bypass	11,2 ±2,0	6,9 ±0,07	3,9 ±0,8	
		3	Pericardium	26,2 ±12,4	26,0 ±4,1	12,6 ±3,6	

		3	Myocardium	34,3 ±9,5	43,4 ±42,9	12,0 ±6,2	
		3	Skeletal muscle	15,9 ±4,8	27,5 ±30,0	3,1 ±1,4	
		3	Mediastinal fat	5,9 ±2,7	3,2 ±0,2	1,2 ±0,3	
60 (52-69)	12 mg/kg SD	16	Serum	70	20		(83)
		16	Thoracic wall fat	3	4		
		16	Pericardium	22	16		
NR	6 mg/kg		Thoracic wall fat	10,5 ±3,6	7,6 ±2,2 1,1 ±1,1 35,7 ±9,4		(71)
		13	Sternal bone	0,8 ±0,8			
		13	Pericardium	12,1 ±3,3			
		13	Myocardium	46,9-47,1			
		13		±4,2-7,5			
		13	Valve	10,8 ±7,5			
	12 mg/kg	10	Thoracic wall fat	18,5 ±7,5	16,2 ±4,4 1,9 ±1,3 47,4 ±5,4		
		10	Sternal bone	0,0			
		10	Pericardium	37,8 ±5,7			
		10	Myocardium	69,5-80,3			
		10		±12,2-14,2			
			Valve	24,8 ±4,8			
60.1-65.8	12 mg/kg	22	Valve	2,8 ±1,4	2,7 ±1,9		(82)

(means)		22	Muscle	6,7 ±3,6	3,8 ±1,8		
		22	Fat	8,8 ±6,7	4,8 ±2,5		
43 (23-74)	400 mg SD	21	Serum	25,4 ±6,2			(84)
		21	Breast	2,8 ±2,6			
		21	Fat	1,9 ±1,4			
0.25-54	5-20 mg intrathecal	7	CSF	>40 (3h)		14.8-26.8 mean (24 h)	(77)
18-92	600 mg 1 or 12 h preop	5	Vitreous sample	0.5 (ND in 4/5)			(78)
	600 mg 24 h preop	5		0.5-0.9 (ND in 3/5)			
	600 mg 24 and 48 h preop	5		0.5-1.8 (ND in 1/5)			
70 (mean)	400-600 mg 1-24 h preop	19	Aqueous humour	0.54 ±0.26		0.16 ± 0.53 (24h)	(80)
74 (mean)	600 mg 1-20 h preop	12	Aqueous humour	0.0			(79)
	25 mg subconjunctival 1-24 h preop	40		0.0			
44 (21-82)	12 mg/kg SD	7	Burn wound fluid		10.8-12.4 (5-6h)	7.0 (14 h)	(85)

Abbreviations: ND – not detectable; NR – not reported; preop – preoperatively; SD – single dose

Adapted from Wilson (69)

1.2.4.4 Elimination

Drug elimination is described via its clearance. Clearance (expressed as volume/time) describes the removal of the drug from a volume of blood in a given unit of time. Clearance does not describe the amount of removed drug, but the volume of blood, from which the drug is completely removed. Drugs can be cleared from the body by different mechanisms, pathways, or organs, including hepatic metabolism, renal and biliary excretion, and clearance by other organ systems (gastrointestinal, pulmonary, etc.). Total body clearance of a drug is the sum of all the clearances by these different mechanisms.

Teicoplanin is almost exclusively eliminated renally after IV administration and can be recovered in the urine for as long as 25 days. (86) Total body clearance and renal clearance of teicoplanin are very similar. (70) Faecal excretion accounts for a further small amount of the total drug clearance (<5%). (87) Teicoplanin is not hepatically metabolised and does not undergo any other biotransformation pathway. (88)
Even though the unbound clearance of vancomycin is similar to that of teicoplanin, tissue binding of teicoplanin is higher compared to vancomycin accounting for the longer half-life. In fact, equilibrium is reached only slowly and the majority of the drug is eliminated in the terminal phase. (69)

For teicoplanin total body clearance is rather low with around 11 ml/h/kg and is not dose dependent. (69) After administration of doses 6, 12, 15, 20, and 25 mg/kg different authors have reported very similar clearance rates of 10.0 to 11.3 ml/h/kg. (68, 70, 72)
Renal clearance is described to range from 8.1 to 10 ml/h/kg in the various studies. (68-70) Teicoplanin is excreted almost entirely by glomerular filtration and both tubular reabsorption and renal secretion are only minimal. (69)

1.2.5 Teicoplanin in renal failure and in patients on renal replacement therapy

Teicoplanin elimination half-life is prolonged in patients with renal insufficiency. The clearance of teicoplanin is correlated linearly with creatinine clearance. (69, 89-91) Lam and colleagues designed a dosage normogram based on the relationship between teicoplanin clearance and creatinine clearance and an average desired steady-state concentration of 20µg/mL. (92)

In patients on haemodialysis as renal replacement therapy (RRT), teicoplanin levels were shown to decrease during the procedure, though teicoplanin could not be recovered in the dialysate. (91) These findings lead authors to suggest the existence of non-renal pathways of metabolism and of excretion of teicoplanin in patients on haemodialysis. (93)

In several analyses, varying degrees of elimination through different filter membranes have been documented for teicoplanin. Teicoplanin is characterised by its high protein binding and teicoplanin is, together with the protein, bound to the surface of membranes in general, and especially to the surface of membranes with a high adhesion capacity (e.g. polysulfone membranes). Teicoplanin concentration during dialysis is time dependent: After start of the external circulation, the effect of protein absorption of the filter membrane is higher than at the end. This is due to a saturation effect and results in lower teicoplanin serum concentrations at the beginning of a dialysis session and a steady increase after saturation of the membrane. (94-101)
Similarly, depending on the RRT technique and the membrane material chosen there is also a considerable impact on drug plasma levels of vancomycin. (102-105)

In any case of RRT, measurement of serum concentration is crucial in order to achieve teicoplanin concentrations within the target ranges. (99, 101)

1.2.6 Teicoplanin in hepatic failure and in patients on liver replacement therapy

In patients with hepatic function impairment no dose adjustment is needed.

Molecular Adsorbent Recirculating System (MARS) represents a mode of albumin dialysis and is used for the removal of albumin bound toxins as a liver replacement therapy in patients with liver failure. Teicoplanin, which is highly protein bound, can be removed very efficiently with MARS. Majcher-Peszynska and colleagues reported that the concentration of teicoplanin decreased by 90% during a six-hour session of MARS from 47.1 µg/mL to 4.9 µg/mL. (106) Weiler and colleagues reported on teicoplanin clearance rates during albumin dialysis of 75% over eight hours. (107)

1.2.7 Antimicrobial susceptibility

1.2.7.1 Gram-positive organisms

The specific mode of action of teicoplanin (interference with the formation of peptidoglycan, inhibition the transpeptidation reaction with finally the inhibition of gram-positive cell wall synthesis) makes this agent exclusively active against gram-positive organisms.
The antimicrobial activity against both methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA) is comparable to that of vancomycin, with a MIC90 (mean minimum inhibitory concentration which is able to inhibit 90% of bacterial isolates) of 0.2 to 1.5 µg/mL. The susceptibility of coagulase-negative Staphylococci (CONS) is more variable with MICs of 2 to 4 µg/mL. (108)
There are also reports on teicoplanin resistant CONS: In the United Kingdom and Ireland teicoplanin is widely used in clinical practice. A recent analysis from these

regions on non-susceptibility trends among staphylococci using BSAC breakpoint tables for the interpretation of MICs show that 3.1% of oxacillin resistant CONS and 1.5% of oxacillin susceptible CONS isolated from blood were resistant to teicoplanin (MIC >8 µg/mL) and 23.4 % of oxacillin resistant CONS and 7.6% of oxacillin susceptible CONS were intermediate to teicoplanin (MIC = 8 µg/mL). (109)

In vitro, teicoplanin has a superior antimicrobial activity than vancomycin against most streptococcal species, including *Streptococcus pneumoniae*, with a MIC50 of 0.06 to 0.12 µg/mL and a MIC90 of 0.12 to 0.25 µg/mL, respectively, compared with values of 0.25-0.5 µg/mL and 0.5-1.0 µg/mL for vancomycin. (110) A higher antimicrobial activity is also described against enterococci with MIC90 values for teicoplanin from 0.2 to 3.1 µg/mL, versus 1.6 to 4.0 µg/mL for vancomycin. (108, 111)

Other gram-positive bacteria susceptible to teicoplanin include Corynebacteria, *Clostridium* spp including *Clostridium difficile*, *Bacillus* spp, *Listeria monocytogenes*, and *Propionibacterium acnes*. For most of them, the MIC90 values are low ranging from 0.3 to 0.8 µg/mL. (111-114).

1.2.7.2 Gram-negative organisms

Teicoplanin is not active against gram-negative bacteria, *Mycobacterium* spp and fungi.

1.2.7.3 EUCAST breakpoint tables

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) was formed in 1997 and is convened by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the National Breakpoint Committees of Europe (France: CA-SFM; Germany: DIN; Netherlands: CRG; Norway: NWGA; Sweden: SRGA; UK: BSAC WP).

The EUCAST objectives include setting common European antimicrobial breakpoints for surveillance, harmonising breakpoints for existing and new drugs, and promoting standardisation of methodologies. The latest EUCAST breakpoint tables for interpretation of MICs list the following breakpoints for teicoplanin and vancomycin:

Table 2: EUCAST breakpoint tables for the interpretation of teicoplanin and vancomycin MICs

Bacterial species	MIC breakpoint (µg/mL)			
	Teicoplanin		Vancomycin	
	S ≤	R >	S ≤	R >
Staphylococcus aureus	2	2	2	2
Coagulase negative staphylococci	4	4	4	4
Enterococcus sp	2	2	4	4
Streptococcus group A	2	2	2	2
Streptococcus group B	2	2	2	2
Streptococcus group C	2	2	2	2
Streptococcus group G	2	2	2	2
Streptococcus pneumonia	2	2	2	2
Viridans group streptococci	2	2	2	2
Haemophilus influenzae	--	--	--	--
Moraxella catarrhalis	--	--	--	--
Neisseria gonorrhoeae	--	--	--	--
Neisseria meningitidis	--	--	--	--

Gram-positive anaerobes except *Clostridium difficile*	IE	IE	2	2
Clostridium difficile	--	--	2	2
Gram-negative anaerobes	--	--	--	--
PK/PD (Non-species related) breakpoints	IE	IE	IE	IE
Enterobacteriaceae	--	--	--	--
Pseudomonas spp.	--	--	--	--
Acinetobacter spp.	--	--	--	--

Abbreviations: S – susceptible; R – resistant; IE - insufficient evidence that the species is a good target for therapy with the agent

Table version 5.0, valid from 2015-01-01 (115)

1.2.8 Adverse events

Teicoplanin is generally well tolerated after both intramuscular and intravenous administration. One or more adverse events as discovered in clinical trials or via postmarketing surveillance were experienced by 10.3% of 3,377 patients treated with teicoplanin. (116) The most frequently experienced adverse events were hypersensitivity (2.6%), abnormal liver function (1.7%), fever (0.8%), local intolerance (1.6%), abnormal renal function (0.7%) and ototoxicity (0.3%). Pain with intramuscular injection is described to be only minimal.

In a recent meta-analysis (117) including 24 clinical trials and a total of 2,332 patients that compared teicoplanin with vancomycin, there were significantly fewer total adverse events for teicoplanin than for vancomycin (risk ratio (RR) 0.57 (95% confidence interval (CI) 0.45 - 0.72)). There were significantly fewer adverse events requiring the discontinuation of treatment with teicoplanin (RR 0.54 (95% CI 0.33 - 0.87). There was significantly less nephrotoxicity reported for teicoplanin (RR 0.44 (95% CI 0.32 - 0.61). (117) Similar RRs for any adverse event, for adverse events requiring discontinuation, and for nephrotoxicity were observed in studies that recruited children. However, among children alone, none of the

differences were statistically significant. Severe nephrotoxicity, defined as the need for haemodialysis or other RRT, was reported only with vancomycin and only among adults. (117)

The incidence of ototoxicity associated with teicoplanin is extremely low. Greenberg and colleagues reported a few patients who developed tinnitus or a mild loss of high-frequency hearing. However, the mean trough serum levels of teicoplanin of these patients were rather high with 41µg/mL. (118)

Red man syndrome is a well-known adverse event in patients receiving vancomycin. This syndrome usually appears within 4–10 minutes after start of an infusion or soon after the completion of an infusion and it is characterized by flushing and/or an erythematous rash that affects the face, neck, and upper torso. The symptoms are caused by a nonspecific mast cell degranulation and do not represent an IgE-mediated allergic reaction. A previous red man syndrome after vancomycin represents no contraindication for the administration of teicoplanin, as most of these patients tolerate teicoplanin well. (119-121)

Allergic cross-reactivity may occur between vancomycin and teicoplanin. (122) Since uncertainty exists about cross-reactivity and because of its long half-life, teicoplanin should probably not be administered to patients with serious hypersensitivity reactions to vancomycin.

Thrombocytopenia during teicoplanin use have been reported (123, 124) which is more likely with high prolonged doses. A number of other adverse events have been reported in clinical trials, the most common being rash, diarrhoea, nausea and vomiting.

1.2.9 Trade names

Teicoplanin is available under the trade name Targocid® in Austria and in all other European countries, except for Greece (Talinac®) and Italy (Targosid®).
Teicoplanin is not approved and, thus, not available in the USA.

1.3 Background and aim of the study

As a glycopeptide antibiotic, Teicoplanin is active against gram-positive bacteria including methicillin-resistant Staphylococci. (125-128) Initial loading dose regimens are recommended to ensure rapid achievement of effective concentrations, (129-131) which has been shown to be important to improve prognosis in critically ill patients. (132) After achieving steady-state concentration, once daily dosing is feasible. (69, 125) While teicoplanin trough levels (TTL) >10 µg/mL are commonly considered appropriate, levels >20 µg/mL have been considered to be necessary to treat deep seated staphylococcal infections (osteomyelitis and endocarditis). (132-134). It is generally recommended to avoid levels >60 µg/mL, despite lacking data supporting this cut off level. (125, 126, 133, 135)

Wide variability of pharmacokinetic parameters of teicoplanin has been shown. (136) Therefore, therapeutic drug monitoring (TDM – the measurement of the serum concentration of the agent and subsequent dosage adjustment in order to keep the concentration in the therapeutic range) is performed in many institutions. (129, 131, 133, 137, 138)

By evaluating preliminary data of this thesis including exclusively paediatric patients, we were able to show significant age and sex-related differences in teicoplanin levels in this age group with young children having significant lower levels and adolescent girls having significant higher levels compared to the entire cohort. (139)
There are no data on pharmacological differences between adults of different age groups and it is unclear, whether the sex-related differences observed in adolescent girls can also be observed adults.

The aim of the study was to evaluate teicoplanin levels in real-life setting in a large cohort of paediatric and adult patients with special respect to sex-and age-related differences.

2 Material and Methods

2.1 Study design

This is a retrospective cross-sectional study evaluating teicoplanin levels determined between 2005 and 2014 in paediatric and adult male and female patients in a real-life setting at the University Hospital, Medical University of Graz, Austria.

2.2 Clinical Setting

This study was conducted at our university affiliated hospital with a capacity of 1539 beds (including 152 intensive care unit beds) and a staff of 7828 people (including 1351 physicians). The hospital comprises all sub disciplines including cardiac surgery, haemato-oncological departments, organ transplantation and stem cell transplantation units, paediatric, neonatal, and several surgical and internal medical intensive care units.

At our hospital, different dosing recommendations comprise dosages ranging from 6 to 15 mg/kg per once daily single dose. Most recommendations include an additional second dose within the first 24 h ("loading dose"). Initial TTLs are analysed on treatment day 3 or 4 by discretion of the treating physician and every 1 to 5 days during treatment thereafter. In selected cases specimens are collected 30 minutes after the end of the infusion to determine teicoplanin peak levels (TPLs). Dosages are modified allowing also higher doses in case of inadequate teicoplanin levels to achieve TTLs >10µg/mL (in case of severe infections >20µg/mL). It is recommended to avoid levels >60µg/mL.

2.3 Data collection

We retrieved all teicoplanin levels done at the University Hospital from 2005 to 2014. Teicoplanin levels were either labelled as trough or peak levels by the assigning departments.
TTLs and TPLs were then classified as initial or follow-up levels according to the interval to the last determination. For each patient we recorded age at sampling, sex, number of teicoplanin treatment episodes, number of TTLs and TPLs obtained during each treatment episode, the interval between the single determinations during the single treatment episodes, and the assigning deparments.

2.4 Inclusion criteria

All patients who had at least one treatment episode with teicoplanin with at least one determination of TTL were included.
TPLs were only included if a corresponding TTL from the same day was recorded.

2.5 Exclusion criteria

Exclusion criteria were detection error as well as repeated episodes in the same patients.
All TTLs with detection error were excluded: If the TTL with the detection error was the initial TTL, the entire treatment episode including all corresponding follow-up TTLs was excluded. If the TTL with the detection error was a follow-up level, the other TTLs of the same treatment episode were not excluded.
Some patients had repeated treatment episodes with teicoplanin. In these patients only levels obtained during the first treatment episode were included; all other levels obtained during later treatment episodes were excluded.

TPLs were excluded if no corresponding TTL from the same day was recorded, in case of detection error, and of repeated treatment episodes in the same patients.
As for TTLs, if the TPL with the detection error was the initial TPL, the entire treatment episode including all corresponding follow-up TPLs was excluded. If the TPL with the detection error was a follow-up level, the other TPLs of the same treatment episode were not excluded. All TPLs corresponding to TTLs from repeated treatment episodes were excluded.
In some treatment episodes TPLs were not determined together with the initial TTL, but only later during the treatment episode together with a follow-up TTL. All follow-up TPLs, with no available corresponding initial TPL were excluded.

2.6 Laboratory Methods

Measuring of teicoplanin TLs were performed fully automated using the particle enhanced turbidemetric QMS(®) Teicoplanin immunoassay (Thermo Fisher Scientific, Indianapolis, IN) on a Cobas 311Analyzer (Roche Diagnostics, Vienna, Austria) according to the manufacturer's instructions. Samples were analysed within 2 hours after blood sample collection in most cases or stored at 4°C and analysed within 24 hours. The limit of quantification of the immunoassay is <3.0 µg/mL with a dynamic measuring range of 3 – 100 µg/mL.

2.7 Analysis

After approval by the ethics committee of the Medical University Graz (EK-Nr: 24-337 ex 11/12), data were retrieved from the laboratory information management system.

Patients were grouped into children (0-14.9 years), adults (15.0-64.9 years), and elderly patients (≥65.0 years).
TTLs were grouped into levels below target, within the lower and upper target range, and above target range as defined in Table 3. TPLs were grouped into levels within the target range and above the target range as defined in Table 3.

Table 3: Classifcation of TTLs and TPLs according to the target ranges

	TTLs
Lower target range	10.0-19.9 µg/mL
Upper target range /target range for severe infections	20.0.-59.9 µg/mL
Below the target range	<10.0 µg/mL
Below the target range for severe infections	<20 µg/mL
Above the target range	≥60 µg/mL
	TPLs
Target range	<60.0 µg/mL
Above the target range	≥60 µg/mL

Descriptive analysis was used to characterize the study population and the rates of patients with TTLs and TPLs below, within, or above the target ranges. We calculated odds ratios (OR) of having values below or above the target ranges separately for children, adults, and elderly patients, as well as for males and females in these age groups.
TTLs and TPLs were both not normally distributed, thus, nonparametric testing was used.
Proportions between groups were compared by means of Fisher´s Exact test, TTLs and TPLs between independent groups were compared by means of Mann-Whitney-U Test or Kruskal Wallis Test, TTLs and TPLs between dependent groups were compared by using the Wilcoxon Test.

For the graphical illustration of the association between age and the teicoplanin levels, moving medians of initial and follow-up TTLs and TPLs over a period of

seven years with 10th and 90th percentiles were plotted against patients' age. Spearman correlation coefficient was used to assess the univariate association between age and TTLs and TPLs.

For TTLs, multivariate regression analysis was additionally performed to assess the association of age, sex, and TTLs and to create smoothed percentile curves of age-dependent TTLs. Therefore models using age, age^2, age^3 and age^4, sex and interaction terms of age and sex were tested. Due to the skewed distribution TTL scores were logarithmised. White test and Breusch-Pagan Test were used to test for heteroscedasticity. When significant heteroscedasticity was detected, weighted least square methods were used. To test for normal distribution of Z scores Anderson-Darling test and Kolmogorov Smirnov test were used. Finally, correlations between residuals and the independent were analysed. For the final model predicted mean values, 10% and 90% percentiles were calculated.

For data analysis Microsoft Excel 2013 (Microsoft Corporation, Redmont, WA, USA), SPSS 22 (IBM SPSS Statistics, Chicago, IL, USA), and SAS 9.2 (SAS Institute Inc., Cary, NC, USA; REG and MODEL procedure) were used. A p-value of <0.05 was considered statistically significant.

3 Results

3.1 Teicoplanin trough levels

3.1.1 Patients and samples

Over the study period, a total of 5084 samples were obtained to determine TTLs. After exclusion of 59 TTL samples because of detection error, 5025 TTLs were available obtained during 1794 treatment episodes in 1380 patients. A total of 414 initial TTLs and 412 follow-up TTLs were excluded because they were obtained during repeated treatment episodes in the same patients. Thus, 1380 initial TTLs and 2819 follow-up TTLs were eligible for the final analysis (see figure 7).

We analysed the initial TTLs of 1380 patients. Age distribution of the patients is shown in Table 4 and figure 8.

Table 4: Age distribution of the study population

Age group	Number of patients		
	Total	**Males**	**Females**
Children	473	266	207
Adults	477	322	155
Elderly patients	430	235	195

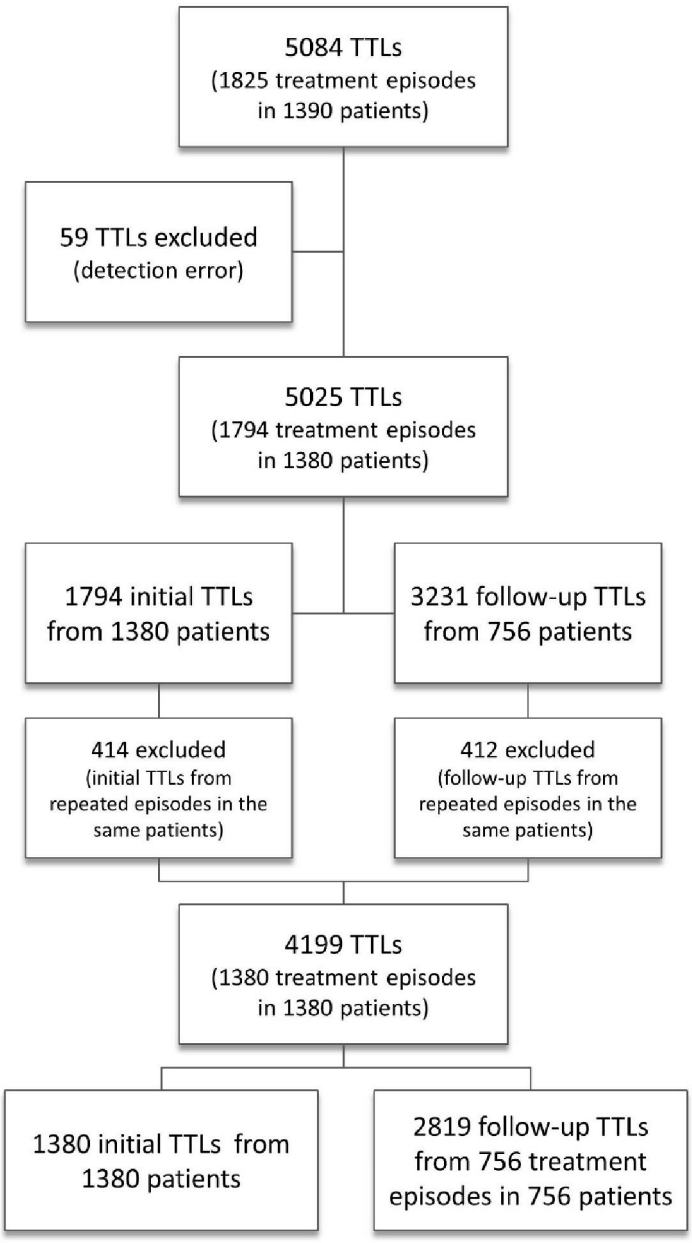

Figure 7: Sample and patient flow chart

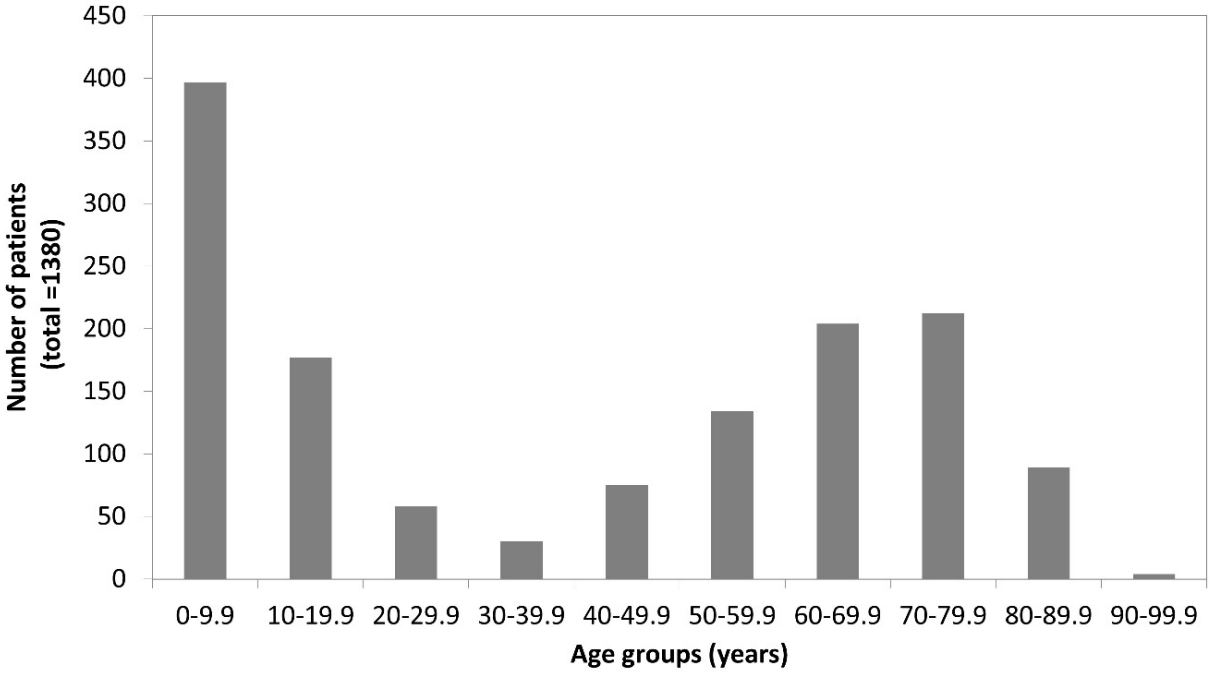

Figure 8: Age distribution of the study population

3.1.2 Initial TTLs

The initial TTL was <10 µg/mL in 444 (32.2%) and <20µg/mL in 1011 patients (73.3%), initial TTLs were ≥60mg/ L in 9 (0.7%) patients.

Median initial TTLs decreased gradually from infants (median TTL 16.9 µg/mL) to young adults with the nadir of the TTLs at the age of 30 to 39.9 years (median TTL 9.9 µg/mL), then a slight increase until the age of 60 to 69.9 (median TTL 13.6 µg/mL) and again a decrease thereafter (see table 5).

Figure 9 shows the age-dependent course of the initial TTLs as moving medians with 10th and 90th percentiles calculated from the raw data, Figure 10 shows the predicted smoothed percentile curves.

Table 5 : Median initial TTLs (with 10th and 90th percentiles) according to the patients' age

Age (years)	Number of patients	Median initial TTLs (µg/mL)	10^{th} percentile (µg/mL)	90^{th} percentile (µg/mL)
0-0.9	197	18.3	8.2	31.2
1-1.9	43	18.5	9.0	25.8
2-2.9	32	17.8	6.7	25.3
3-3.9	30	14.7	8.1	26.1
4-4.9	18	14.9	8.8	29.2
5-9.9	77	15.6	9.1	24.8
10-19.9	177	14.0	7.5	25.1
20-29.9	58	11.1	5.9	22.2
30-39.9	30	9.9	3.4	22.2
40-49.9	75	11.9	6.4	25.8
50-59.9	134	11.1	5.0	28.4
60-69.9	204	13.6	4.0	28.4
70-79.9	212	12.4	4.1	26.0
80-89.9	89	12.1	2.9	41.3

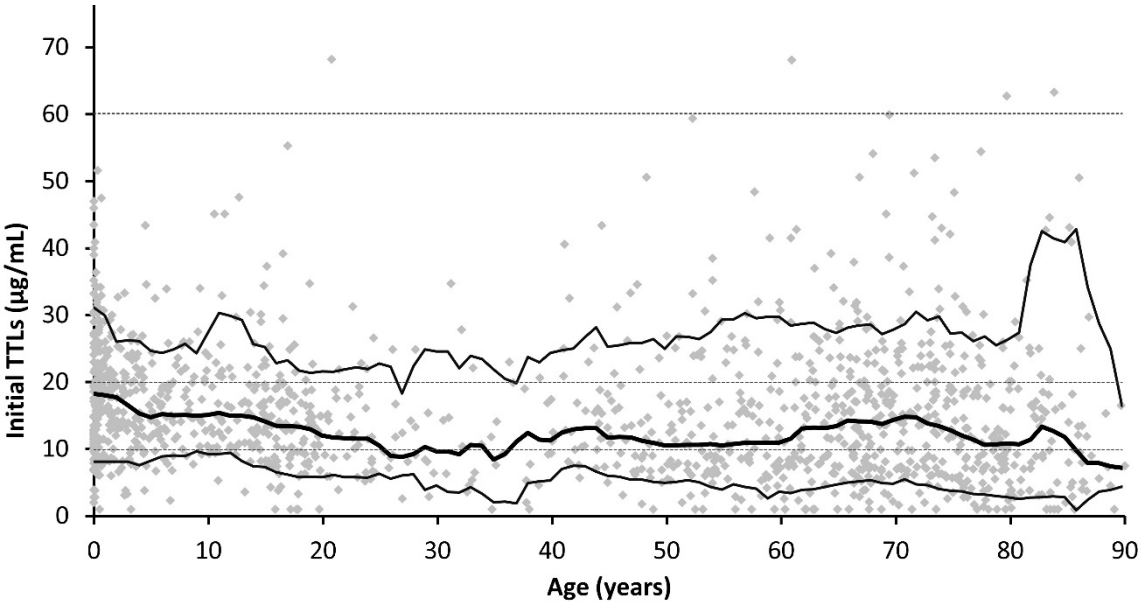

Figure 9: Percentile charts of initial TTLs over patients' age (raw data)

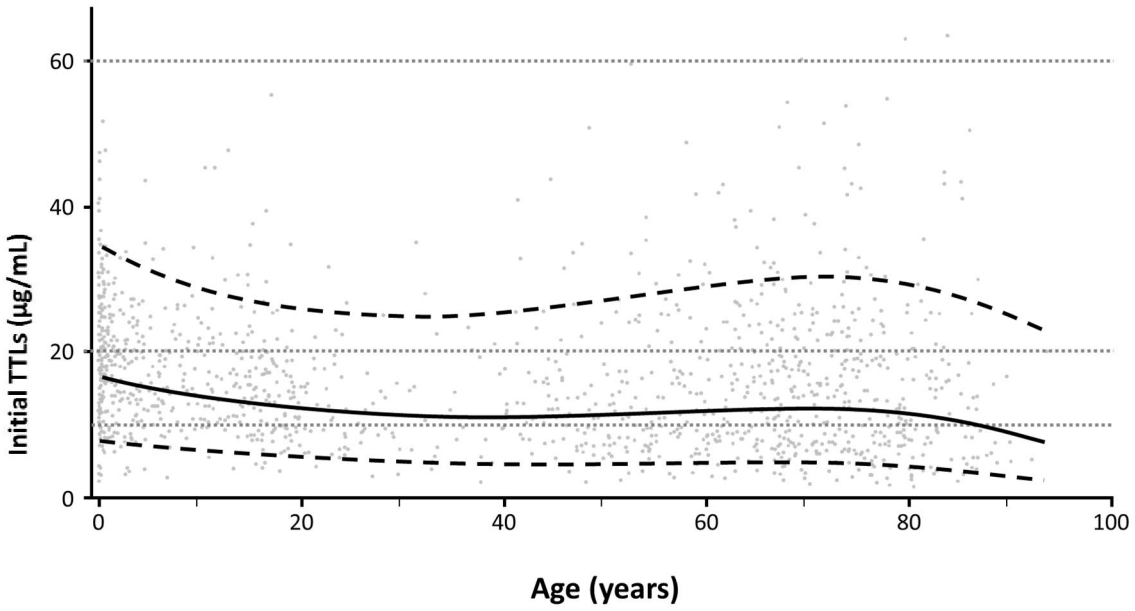

Figure 10: Percentile charts of initial TTLs over patients' age (predicted data) Lines indicate median levels and 10th and 90th percentiles and rhombuses indicate single data points.

Up to the age of 10 years approximately 90% of the patients had values within the target range (10.0-59.9 µg/mL). While the rate of patients with TTLs above the target range (≥60 µg/mL) did not change with age, the rate of patients with values below the target range (<10 µg/mL) increased significantly with age with approximately 40% of adults and elderly patients having values <10 µg/mL (see Figure 11).

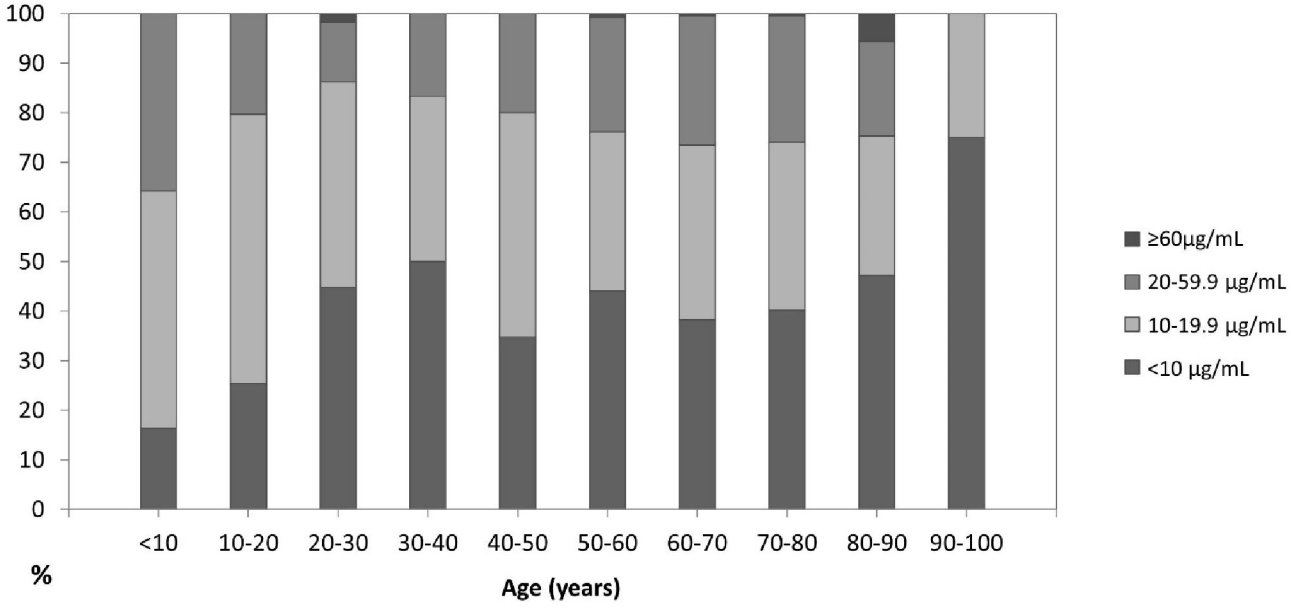

Figure 11 : Rates of initial TTLs within and beyond the target ranges and the target ranges for severe infections by age

Adults and the elderly patients had significantly lower TTLs when compared to children (median 11.7 and 13.0 vs. 16.8 µg/mL, p<0.001, each). As a consequence, when compared to children, there was a higher risk for adults and for the elderly for having an initial TTL <10 µg/mL and <20 µg/mL (adults: OR 3.7 (2.7-5.1) and 2.1 (1.6-2.9), p<0.001 each; the elderly OR 3.5 (2.6-4.8), p<0.001 and 1.5 (1.2-2.1), p=0.004).

Table 6 Initial TTLs for different age groups

	Initial TTLs				
TTLs	**<10 µg/mL n (%)**	**10-19.9 µg/mL n (%)**	**<20* µg/mL n (%)**	**20-59.9 µg/mL n (%)**	**≥60 µg/mL n (%)**
All age groups	444 (32.2)	567 (41.1)	1011 (73.3)	360 (26.1)	9 (0.7)
Children	75 (15.9)	234 (49.5) [b]	309 (65.3)	164 (34.7) [d]	0 (0)
Adults	197 (41.3) [a]	185 (38.8)	382 (80.1) [c]	92 (19.3)	3 (0.6)
Elderly patients	172 (40.0) [a]	148 (34.4)	320 (74.4) [c]	104 (24.2)	6 (1.4)

*Sum of TTLs <10 µg/mL and 10-19.9 µg/mL

[a]Increased risk of having initial TTLs <10 µg/mL compared to children for adults (OR 3.7 (2.7-5.1)) and for the elderly (OR 3.5 (2.6-4.8), both p<0.001)

[b]Levels more frequently within the indicated range in children compared to adults (p=0.001) and the elderly (p<0.001)

[c]Increased risk of having initial TTLs<20 µg/mL compared to children for adults (OR 2.1(1.6-2.9), p<0.001) and for the elderly (OR 1.5 (1.2-2.1), p=0.004)

[d]Levels more frequently within the indicated range in children compared to adults (p<0.001) and the elderly (p=0.001)

3.1.3 Follow-up TTLs

We analysed 2819 follow-up TTLs obtained from 756 patients.

Again, there was a nonlinear decrease from infants (median TTL 20.8 µg/mL) to children and young adults until the age of 32 (median TTL 15.0µg/mL) years and a slight increase until the age of 70 (median TTL 16.5µg/mL) and again a decrease thereafter (see table 7 and figure 12).

Table 7: Median follow-up TTLs (with 10th and 90th percentiles) according to the patients' age

Age (years)	Number of patients	Median follow-up TTLs (µg/mL)	10th percentile (µg/mL)	90th percentile (µg/mL)
0-0.9	106	24.1	11.8	30.8
1-1.9	11	22.0	9.9	27.1
2-2.9	22	19.2	13.1	26.4
3-3.9	7	24.3	13.0	26.4
4-4.9	9	22.3	9.3	25.1
5-9.9	43	18.5	8.9	29.3
10-19.9	80	18.4	9.4	27.2
20-29.9	35	15.2	9.9	26.7
30-39.9	20	15.0	8.2	26.1
40-49.9	41	15.6	10.1	27.6
50-59.9	83	16.3	7.4	35.1
60-69.9	133	17.2	8.2	29.5
70-79.9	116	16.6	8.7	28.6
80-89.9	49	15.9	6.1	34.3

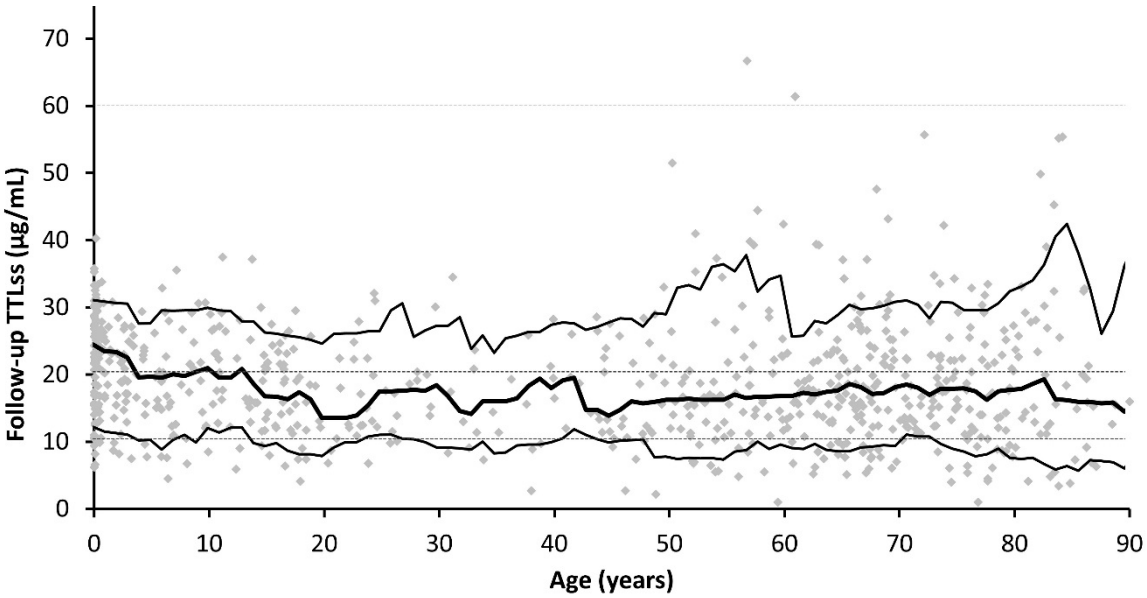

Figure 12: Percentile charts of follow-up TTLs over patients' age (raw data)

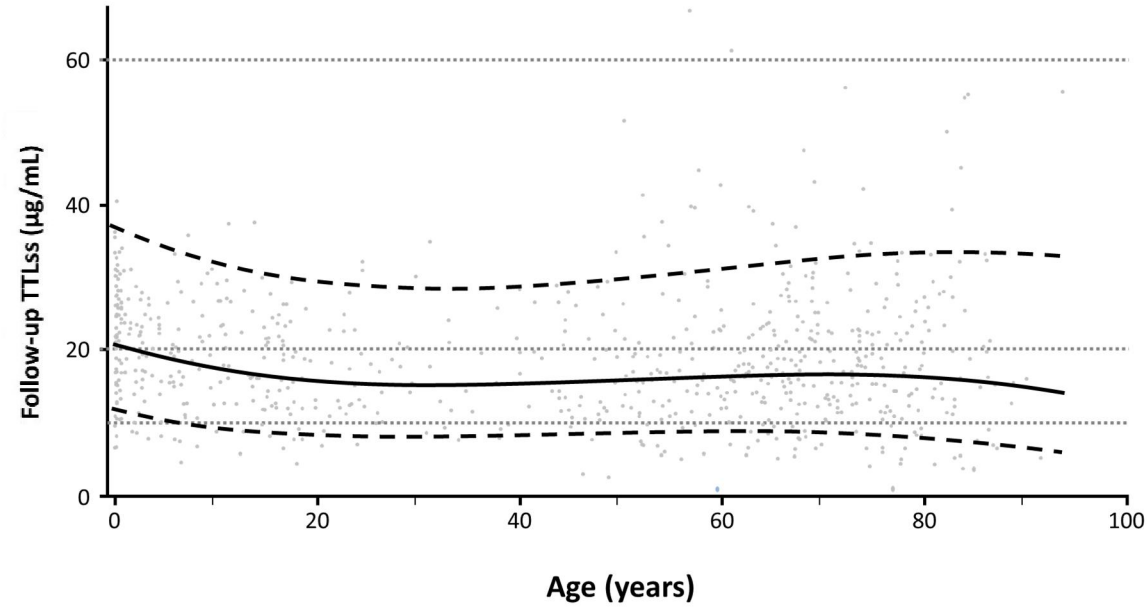

Figure 13: Percentile charts of follow-up TTLs over patients' age (predicted data) Lines indicate median levels and 10th and 90th percentiles and rhombuses indicate single data points.

Follow-up TTLs were <10 µg/mL in 100 (13.2%) patients, <20 µg/mL in 444 (58.7%) and ≥60 µg/mL in 2 (0.3%).

Again, adults and elderly people had significantly lower TTLs when compared to children (16.1 and 17.4 vs. 21.6 µg/mL, p<0.001 and p=0.001). As a consequence, when compared to children, there was a higher risk for adults and for the elderly for having a follow-up TTL <10 µg/mL and <20 µg/mL (adults: OR 2.0 (1.1-3.5), p=0.019 and 2.9 (2.0-4.1), p<0.001; the elderly OR 2.2 (1.3-4.0), p=0.005), and 2.0 (1.4-2.9), p<0.001, see table 8).

Table 8: Initial and follow-up TTLs for different age groups

			Initial TTLs		
TTLs	**<10 µg/mL n (%)**	**10-19.9 µg/mL n (%)**	**<20* µg/mL n (%)**	**20-59.9 µg/mL n (%)**	**≥60 µg/mL n (%)**
All age groups	444 (32.2)	567 (41.1)	1011 (73.3)	360 (26.1)	9 (0.7)
Children	75 (15.9)	234 (49.5) [b]	309 (65.3)	164 (34.7) [d]	0 (0)
Adults	197 (41.3) [a]	185 (38.8)	382 (80.1) [c]	92 (19.3)	3 (0.6)
Elderly patients	172 (40.0) [a]	148 (34.4)	320 (74.4) [c]	104 (24.2)	6 (1.4)
			Follow-up TTLs		
TTLs	**<10 µg/mL n (%)**	**10-19.9 µg/mL n (%)**	**<20* µg/mL n (%)**	**20-59.9 µg/mL n (%)**	**≥60 µg/mL n (%)**
All age groups	100 (13.2)	344 (45.5)	444 (58.7)	310 (41)	2 (0.3)
Children	19 (8.1)	85 (36)	104 (44.1)	132 (55.9) [h]	0 (0)
Adults	41 (14.9) [e]	150 (54.3) [f]	191 (69.2) [g]	83 (30.1)	2 (0.7)
Elderly patients	40 (16.4) [e]	109 (44.7)	149 (61.1) [g]	95 (38.9)	0 (0)

*Sum of TTLs <10 µg/mL and 10-19.9 µg/mL

[a]Increased risk of having initial TTLs <10 µg/mL compared to children for adults (OR 3.7 (2.7-5.1)) and for the elderly (OR 3.5 (2.6-4.8), both p<0.001)

[b]Levels more frequently within the indicated range in children compared to adults (p=0.001) and the elderly (p<0.001)

[c]Increased risk of having initial TTLs<20 µg/mL compared to children for adults (OR 2.1(1.6-2.9), p<0.001) and for the elderly (OR 1.5 (1.2-2.1), p=0.004)

[d]Levels more frequently within the indicated range in children compared to adults (p<0.001) and the elderly (p=0.001)

[e]Increased risk of having follow-up TTLs <10 µg/mL compared to children for adults (OR 2.0(1.1-3.5), p=0.019) and for the elderly (2.2 (1.3-4.0), p=0.005)

[f]Levels more frequently within the indicated range in adults compared to children (p<0.001) and the elderly (p=0.028)

[g]Increased risk of having follow-up TTLs<20 µg/mL compared to children for adults (OR 2.9 (2.0-4.1) and for the elderly (OR 2.0 (1.4-2.9), both p<0.001)

[h]Levels more frequently within the indicated range in children compared to adults and to the elderly (both p<0.001)

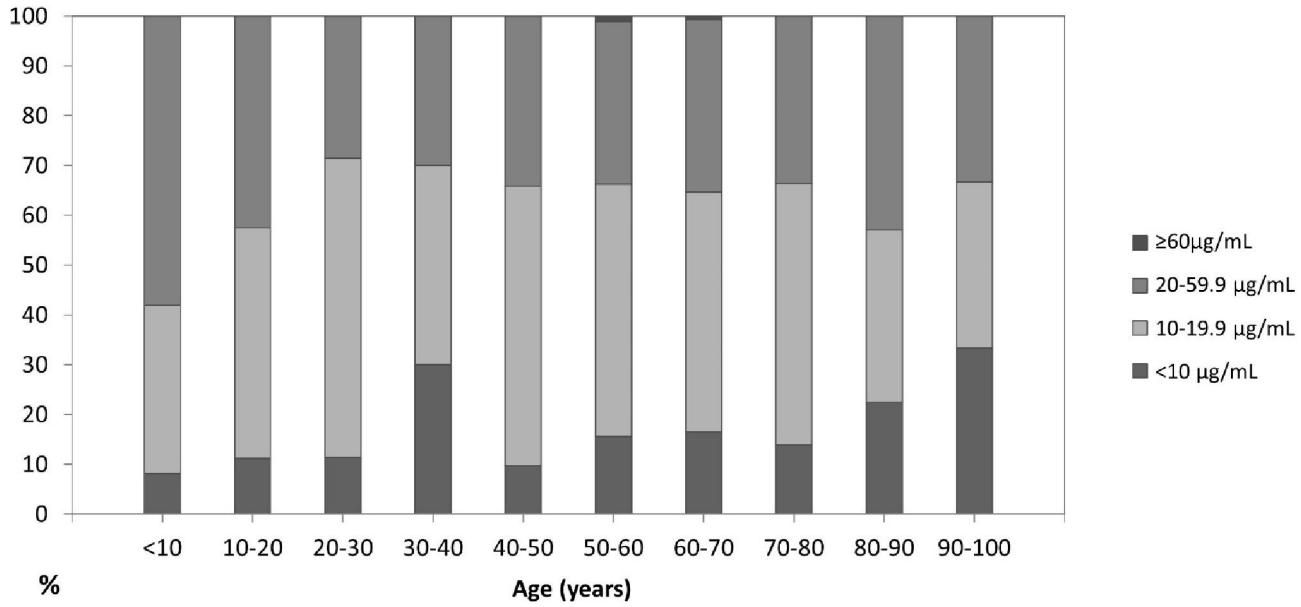

Figure 14: Rates of follow-up TTLs within and beyond the target ranges and the target ranges for severe infections by age

3.1.4 Initial vs. follow-up TTLs

Median follow-up TTL was significantly higher than initial TTL in all age groups (children 21.6 vs. 16.8 µg/mL, adults 16.1 vs. 11.7 µg/mL, the elderly 17.4 vs. 13.0 µg/mL, p<0.001 for all).

Table 9: Differences between median initial and follow-up TTLs

Age (years)	Number of patients	Initial TTLs (µg/mL)	Follow-up TTLs (µg/mL)	Difference between initial and follow-up TTLs (µg/mL)	p-value
0-0.9	106	18.3 (8.2-31.2)	24.1 (11.8-30.8)	5.8	0.002
1-1.9	11	18.5 (9-25.8)	22 (9.9-27.1)	3.5	0.050
2-2.9	22	17.8 (6.7-25.3)	19.2 (13.1-26.4)	1.4	0.242
3-3.9	7	14.7 (8.1-26.1)	24.3 (13-26.4)	9.6	0.398
4-4.9	9	14.9 (8.8-29.2)	22.3 (9.3-25.1)	7.5	0.401
5-9.9	43	15.6 (9.1-24.8)	18.5 (8.9-29.3)	2.9	0.043
10-19.9	80	14 (7.5-25.1)	18.4 (9.4-27.2)	4.4	0.200
20-29.9	35	11.1 (5.9-22.2)	15.2 (9.9-26.7)	4.2	0.033
30-39.9	20	9.9 (3.4-22.2)	15 (8.2-26.1)	5.1	0.062
40-49.9	41	11.9 (6.4-25.8)	15.6 (10.1-27.6)	3.7	0.354
50-59.9	83	11.1 (5-28.4)	16.3 (7.4-35.1)	5.3	0.002
60-69.9	133	13.6 (4-28.4)	17.2 (8.2-29.5)	3.6	<0.001
70-79.9	116	12.4 (4.1-26)	16.6 (8.7-28.6)	4.2	<0.001
80-89.9	49	12.1 (2.9-41.3)	15.9 (6.1-34.3)	3.8	0.008

Compared to initial TTLs, follow-up TTLs were less likely to be <10 µg/mL and <20 µg/mL (13.2 vs. 32.2% and 58.7 vs. 73.3%, p<0.001, each) and more likely to be

within the overall target range of 10.0-59.9 µg/mL (86.5 vs. 67.2%, p<0.001) and to be within target range for severe infections (20.0-59.9 µg/mL: 41.0 vs. 26.1%, p<0.001). There was no difference between rates of initial vs. follow-up TTLs within the lower target range (10.0-19.9 µg/mL) and above the target range (≥60 µg/mL).

We evaluated the course of TTLs during the single treatment episodes: The initial determination is mainly done on treatment day 3, but is occasionally done also before or afterwards. However, the study design did not allow the specific determination of the interval from the first administration to the first blood sampling. The following tables and figures therefore describe patterns of TTLs not starting from the first administration of teicoplanin but starting from the first determination of the TTL (initial TTL) which is labelled day 0. After the first determination (day 0) teicoplanin concentrations are determined in intervals according to the treating physician. Table 10 shows the number of samples taken on each treatment day starting from the day of the initial determination (day 0).

Table 10: Number of TTL samples obtained during the treatment episodes

Treatment day (day 0=initial TTL)	Number of samples
0	1380
1	307
2	320
3	282
4	260
5	206
6	157
7	172
8	115
9	106
10	87

11	86
12	70
13	63
14	71

When evaluating TTLs over the duration of the single treatment episodes, the TTLs increased from median values of 14.1 µg/mL at the initial determination to 18.2 µg/mL on day 1 after the initial determination to a maximum of 20.1 µg/mL on day 2 after the initial determination and remained stable thereafter with levels between 17 and 20 µg/mL (see figure 15).

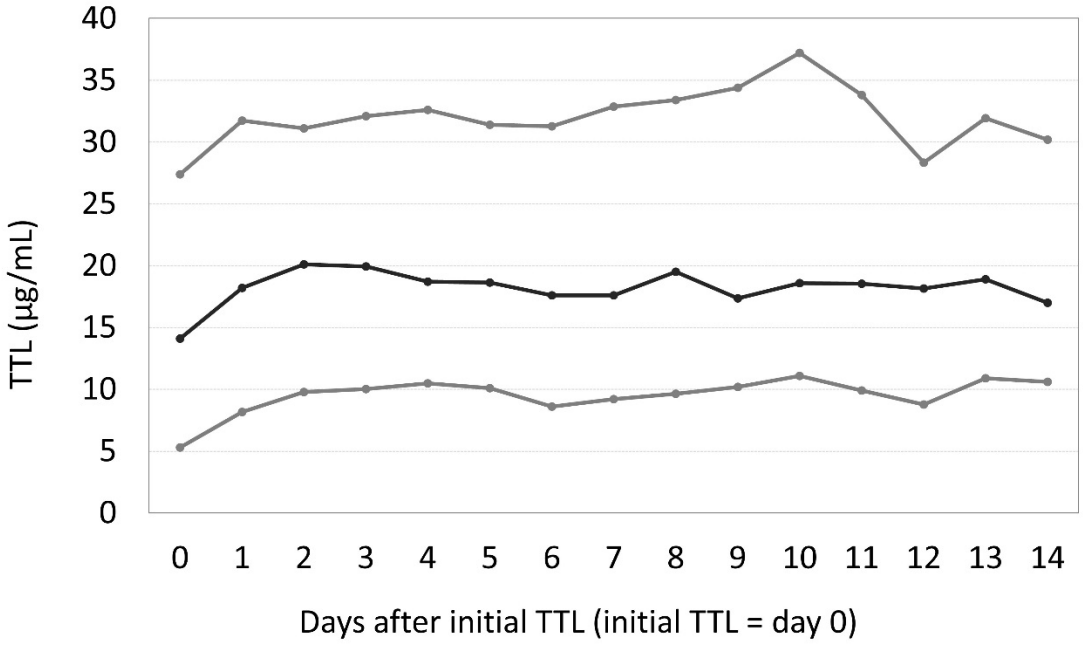

Figure 15 : Median TTLs over the duration of the single treatment episodes
The course of median TTLs is shown as black line, grey lines indicate 10th and 90th percentiles of the TTLs over the single days of the treatment episode

The patterns of TTLs over the duration of the single treatment episodes were similar in all age groups (see figure 16).

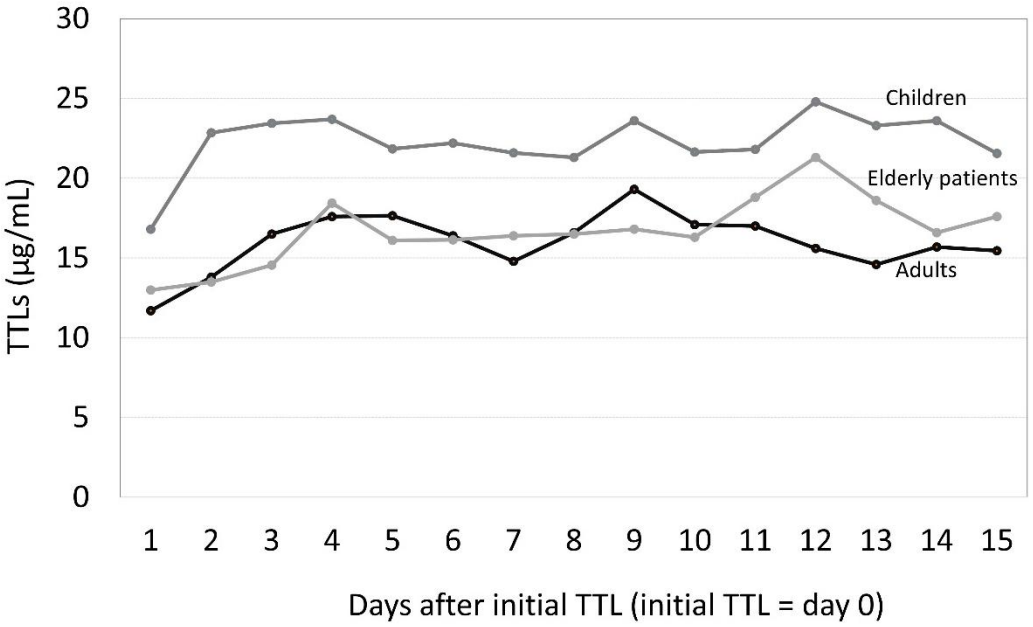

Figure 16: Median TTLs over the duration of the single treatment episodes displayed separately for children, adults, and elderly patients

3.2 Teicoplanin peak levels

Over the study period, a total of 648 samples were obtained to determine TPLs. After exclusion of 44 TPL samples because no corresponding TTL was determined and of 39 TPL samples because of detection error, 565 TPLs were available obtained during 334 treatment episodes in 151 patients. A total of 183 initial TPLs and 96 follow-up TPLs were excluded because they were obtained during repeated treatment episodes in the same patients. Thus, 151 initial TPLs and 138 follow-up TPLs were eligible for the final analysis (see figure 17).

We analysed the initial TPLs of 151 patients (93 children, 54 adults, 4 elderly patients). Age distribution of the patients having TPLs determined is shown in Table 11 and Figure 18.

Table 11: Age distribution of the study population (TPLs)

Age group	Number of patients		
	Total	**Males**	**Females**
Children	93	50	43
Adults	54	33	21
Elderly patients	4	2	2

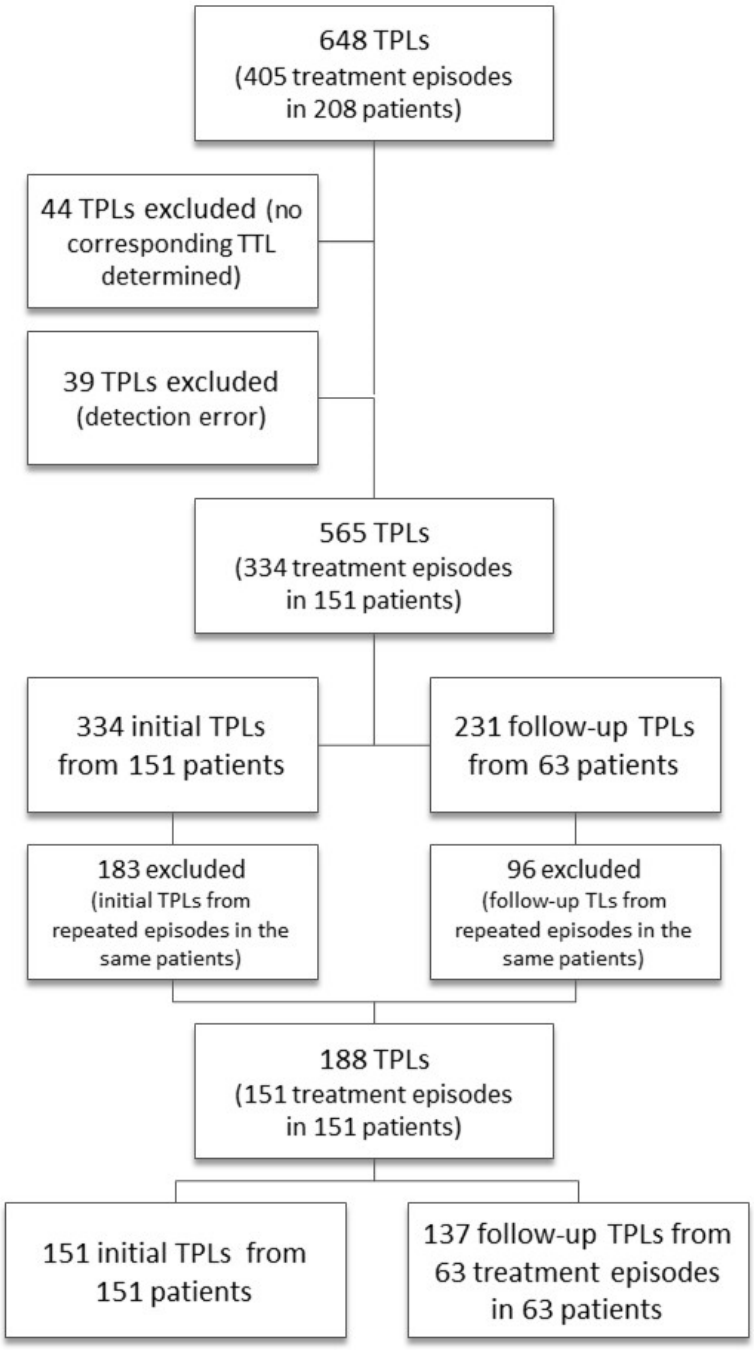

Figure 17: Sample and patient flow chart for TPLs

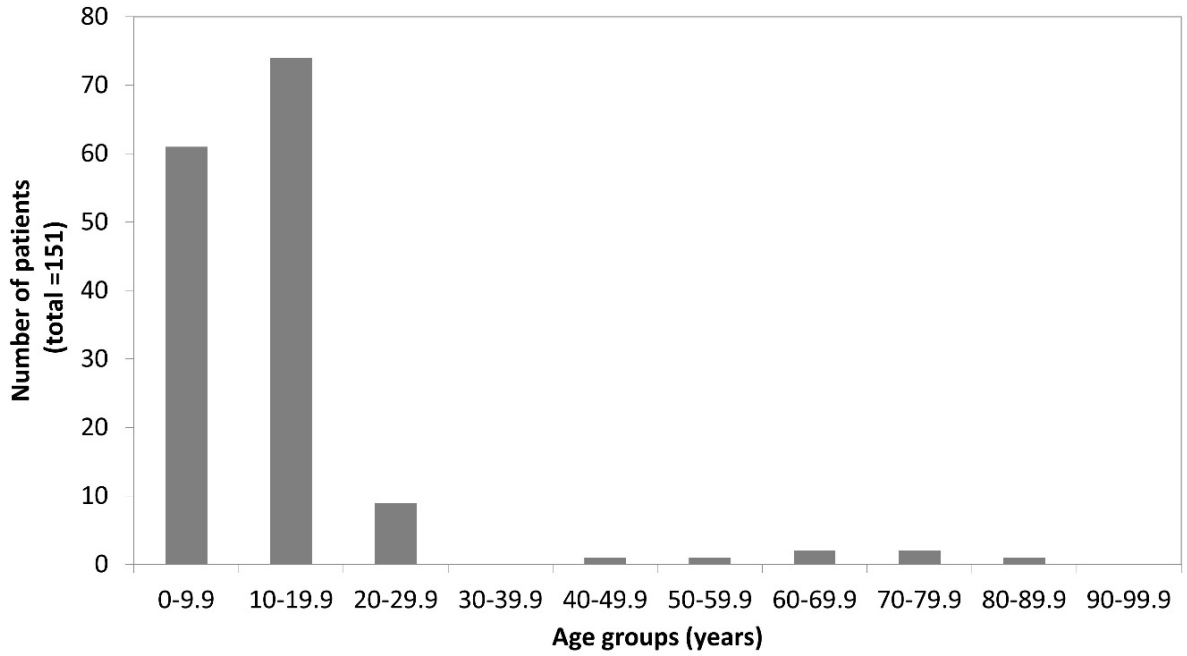

Figure 18: Age distribution of the study patients with TPLs

The majority patients having TPLs determined were children and young adults up to the age of 30 years. In patients aged ≥30 years only seven had TPLs done.

3.2.1 Initial TPLs

Initial TPLs did not follow an age-dependent distribution. Median values ranged from 48.6 µg/mL to 66.9 µg/mL in infants and young children up to the age of five years, increased then to median values of 78.9 µg/mL up to the age of 10 years and decreased thereafter. However, there was no significant correlation of initial TPLs with age.

Table 12 : Median initial TPLs (with 10th and 90th percentiles) according to the patients' age

Age (years)	Number of patients	Median initial TPLs (µg/mL)	10th percentile (µg/mL)	90th percentile (µg/mL)
0-0.9	4	64.4	31.2	120.9
1-1.9	6	48.6	37.8	60.6
2-2.9	3	66.9	54.0	67.9
3-3.9	7	62.8	34.2	72.3
4-4.9	8	63.9	36.9	101.3
5-9.9	33	78.9	51.3	99.4
10-19.9	74	66.6	45.7	101.5
20-29.9	9	46.7	33.5	70.9
30-39.9	0	--	--	--
40-49.9	1	24.7	24.7	24.7
50-59.9	1	44.2	44.2	44.2
60-69.9	2	58.6	43.5	73.7
70-79.9	2	20.2	9.4	30.9
80-89.9	1	23.6	23.6	23.6

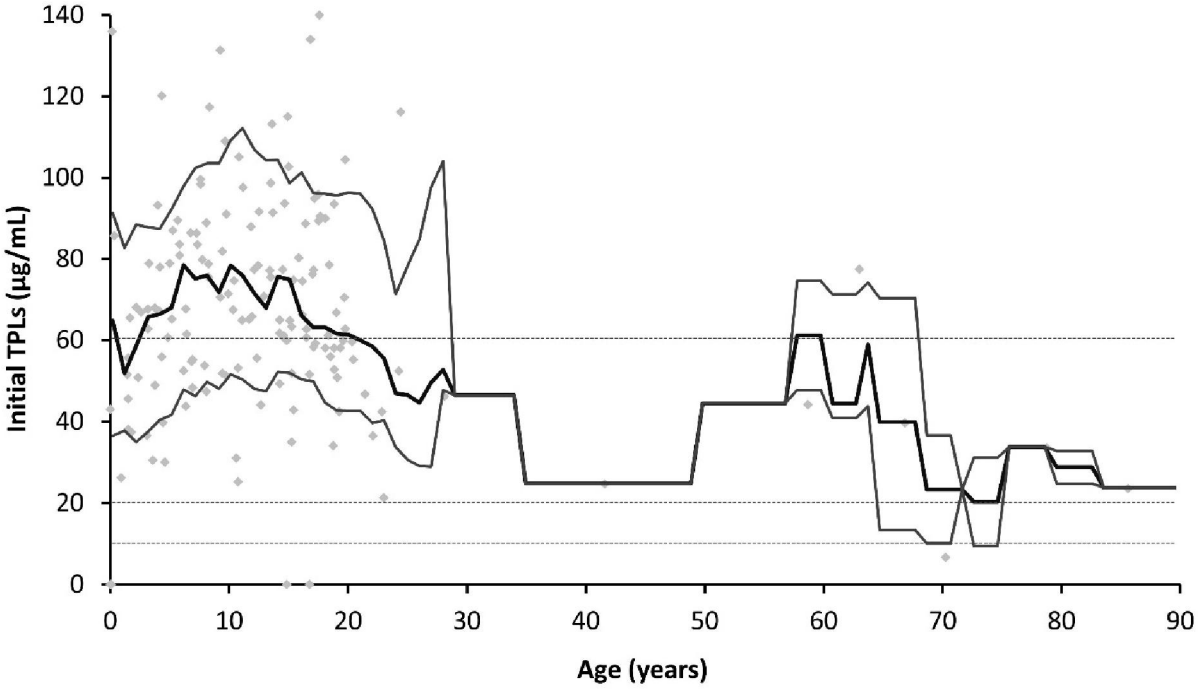

Figure 19: Percentile charts of initial TPLs over patients' age
Lines indicate median levels and 10th and 90th percentiles, and rhombuses indicate single data points.

The initial TPL was ≥60 µg/mL in 91 of 151 patients (60.3%). While children and adults had initial TPLs ≥60 µg/mL in 67.7% and 51.8%, there were no cases of initial TPLs ≥60 µg/mL in elderly patients. However, only four elderly patients had any initial TPLs determined.

The risk for having initial TPLs beyond the target range of 60 µg/mL did not significantly differ between the single age groups.

Table 13 Initial TPLs for different age groups

	Initial TPLs		
	Number of patients n (%)	**TPL <60 µg/mL: n (%)**	**TPL ≥60 µg/mL: n (%)**
All age groups	151 (100%)	60 (39.7%)	91 (60.3%)
Children	93 (61.6%)	30 (32.3%)	63 (67.7%)
Adults	54 (35.8%)	26 (48.2%)	28 (51.8%)
Elderly patients	4 (2.6%)	4 (100%)	0 (0%)
No increased risk for having TPLs ≥60 µg/mL for any age group.			

3.2.2 Follow-up TPLs

We analysed 137 follow-up TTLs obtained from 63 patients.

As seen for initial TPLs, follow-up TPLs did not follow any age dependent distribution. Except for the 3 infants <1 year of age and the 2 elderly patients who had lower values, the follow-up TPLs ranged from 48.9 µg/mL to 61.1 µg/mL (see Table 14).

Table 14: Median follow-up TPLs (with 10th and 90th percentiles) according to the patients' age

Age (years)	Number of patients	Median follow-up TPLs (µg/mL)	10th percentile (µg/mL)	90th percentile (µg/mL)
0-0.9	3	26.2	24.4	64.9
1-1.9	3	61.1	52.5	65.2
2-2.9	3	54.4	51.2	69.6
3-3.9	1	53.5	53.5	53.5
4-4.9	2	48.9	43.9	53.9
5-9.9	16	52.5	37.9	81.1
10-19.9	29	59.4	41.5	82.9
20-29.9	4	58.6	43.9	102.4
30-39.9	0	--	--	--
40-49.9	0	--	--	--
50-59.9	0	--	--	--
60-69.9	0	--	--	--
70-79.9	2	29.0	22.9	35.0
80-89.9	0	--	--	--

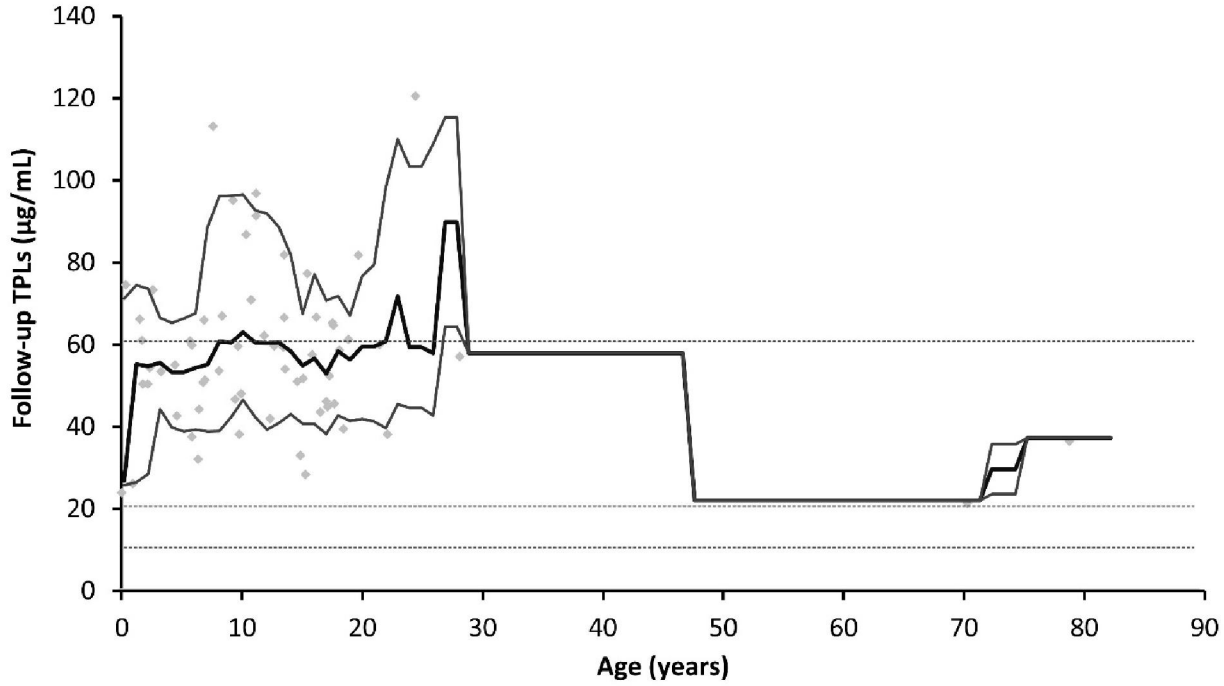

Figure 20: Percentile charts of follow-up TPLs over patients' age
Lines indicate median levels and 10th and 90th percentiles (blue for males, red for females), and rhombuses indicate single data points.

Follow-up TPLs were ≥60 µg/mL in 24 of 63 patients (38.1%). While children and adults had initial TPLs ≥60 µg/mL in 39.0% and 40.0% of patients, there were no cases of follow-up TPLs≥60 µg/mL in elderly patients. However, only two elderly patients had any follow-up TPLs determined. The risk for having follow-up TPLs beyond the target range of 60 µg/mL did not significantly differ between the single age groups.

Table 15: Initial and follow-up TPLs for different age groups

	Initial TPLs		
	Number of patients n (%)	**TPL <60 µg/mL: n (%)**	**TPL ≥60 µg/mL: n (%)**
All age groups	151 (100%)	60 (39.7%)	91 (60.3%)
Children	93 (61.6%)	30 (32.3%)	63 (67.7%)
Adults	54 (35.8%)	26 (48.2%)	28 (51.8%)
Elderly patients	4 (2.6%)	4 (100%)	0 (0%)
	Follow-up TPLs		
	Number of patients n (%)	**TPL <60 µg/mL: n (%)**	**TPL ≥60 µg/mL: n (%)**
All age groups	63 (100%)	39 (61.9%)	24 (38.1%)
Children	41 (65.1%)	25 (61.0%)	16 (39%)
Adults	20 (31.7%)	12 (60.0%)	8 (40.0%)
Elderly patients	2 (3.2%)	2 (100%)	0 (0%)

No increased risk for having TPLs ≥60 µg/mL for any age group.

3.2.3 Initial vs. follow-up TPLs

Median follow-up TPLs were significantly lower than initial TPLs children and in adults (children 67.5 vs. 55.1 µg/mL, p=0.006, adults 72.5 vs. 57.3 µg/mL, p=0.012, respectively).

Table 16: Differences between median initial and follow-up TPLs

Age (years)	Number of patients	Initial TPLs (µg/mL)	Follow-up TPLs (µg/mL)	Difference between initial and follow-up TPLs (µg/mL)
0-0.9	3	64.4 (31.2-120.9)	26.2 (24.4-64.9)	-38.2
1-1.9	0	48.6 (37.8-60.6)	--	--
2-2.9	3	66.9 (54-67.9)	54.4 (51.2-69.6)	-12.5
3-3.9	1	62.8 (34.2-72.3)	53.5 (53.5-53.5)	-9.3
4-4.9	2	63.9 (36.9-101.3)	48.9 (43.9-53.9)	-15.0
5-9.9	16	78.9 (51.3-99.4)	52.5 (37.9-81.1)	-26.4
10-19.9	29	66.6 (45.7-101.5)	59.4 (41.5-82.9)	-7.1
20-29.9	4	46.7 (33.5-70.9)	58.6 (43.9-102.4)	11.9
30-39.9	0	--	--	--
40-49.9	0	24.7 (24.7-24.7)	--	--
50-59.9	0	44.2 (44.2-44.2)	--	--
60-69.9	0	58.6 (43.5-73.7)	--	--
70-79.9	2	20.2 (9.4-30.9)	29 (22.9-35)	8.8
80-89.9	0	23.6 (23.6-23.6)	--	--

Consecutively, overall initial TPLs were more likely to be beyond the target range of 60 µg/mL (OR 2.6 (95% CI 1.6-4.3), p<0.001). When analysing the single age groups, only in children but not in adults and elderly patients initial TPLs were more likely to be ≥ 60 µg/mL than follow-up TPLs (OR 3.7 (95% CI 2.0-6.9), p<0.001).

3.3 Sex-related differences

3.3.1 Sex-related differences for initial and follow-up TTLs

From 1380 patients included, 823 were males (59.6%) and 557 were females (40.4%). Age and sex distribution of the study patients is shown in figure 21.

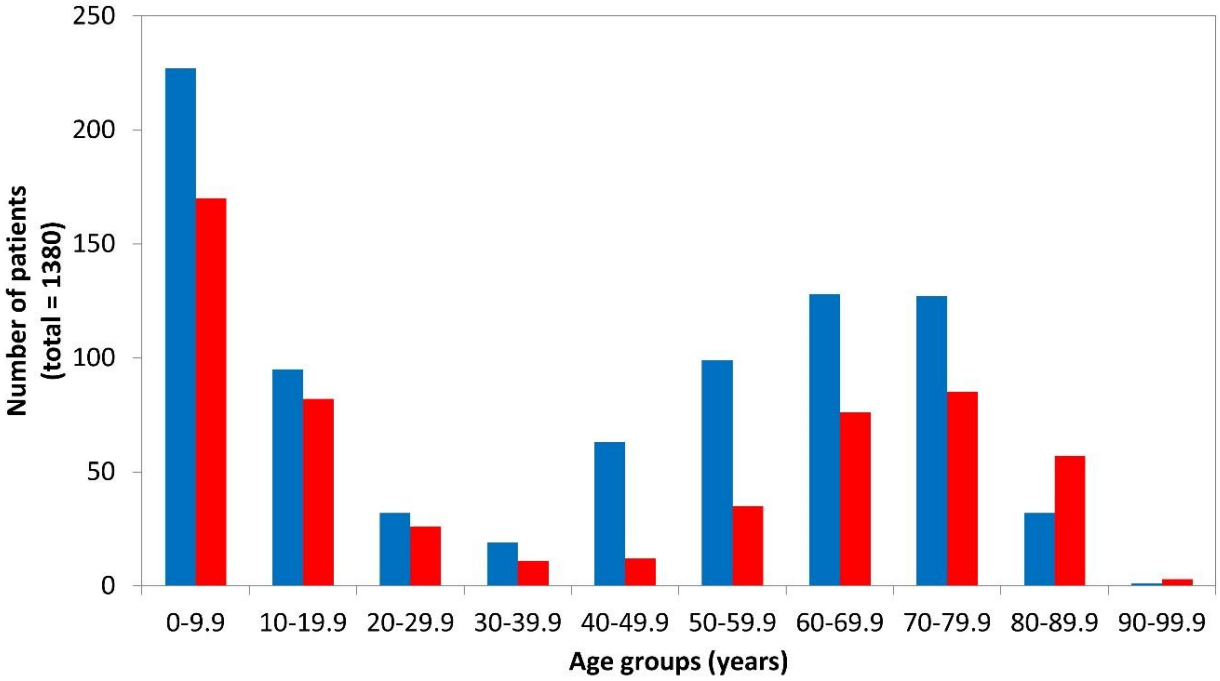

Figure 21: Age and sex distribution of the study population
Red bars represent female patients, blue bars represent male patients

In the univariate analysis females had higher initial and follow-up TTLs compared to males (median initial TTLs 15.5 vs. 13.2 µg/mL, median follow-up TTLs 19.4 vs. 17.2 µg/mL, $p<0.001$, each). These sex-related differences were related to age:

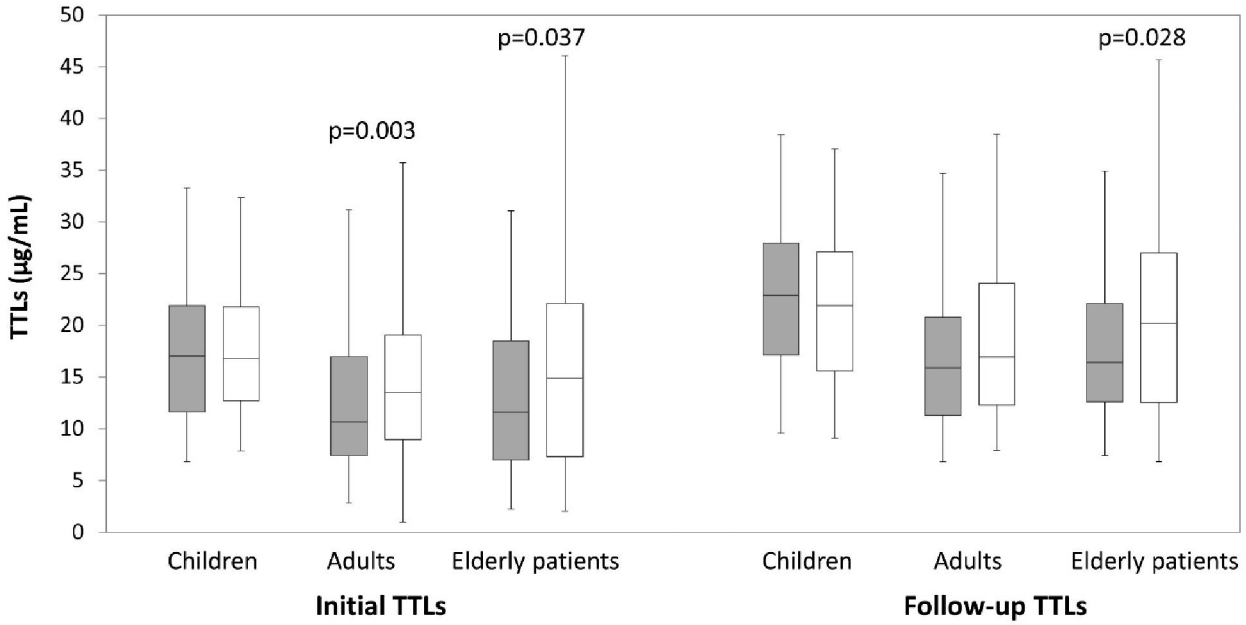

Figure 22: Boxplots of initial and follow-up TTLs in male (grey boxes) and female (white boxes) children, adults, and elderly patients.
Boxes indicate median values and the interquartile ranges, whiskers indicate the 95% confidence intervals. p-values are given for significant differences.

In children initial and follow-up TTLs did not differ between females and males.
In adults females had significantly higher initial TTLs compared to males (13.5 vs. 10.7 µg/mL, p=0.003). In elderly patients, females had higher initial and follow-up TTLs compared to males (median initial TTLs 14.9 vs. 11.6 µg/mL, p=0.037; median follow-up TTLs 19.9 vs. 15.9 µg/mL, p=0.028).
Table 17 and Table 18 show the median initial and follow-up TTLs in males and females for different age groups.

Table 17: Median initial TTLs for males and females in different age groups

Age (years)	Initial TTLs (µg/mL)		Difference of median TTLs between males and females (µg/mL)
	Males	Females	
0.0-9.9	17.5 (7.9-27.3)	17.7 (8.4-28.4)	0.1
10.0-19.9	13.2 (7.4-22.4)	15.9 (8.4-29.1)	2.7
20.0-29.9	10.1 (5.2-19.3)	11.8 (6.4-23.9)	1.7
30.0-39.9	9.3 (4.4-22.3)	10.4 (2-19)	1.1
40.0-49.9	11.9 (5.9-26)	12.3 (9.1-22.9)	0.4
50.0-59.9	10.6 (4.4-26.8)	13.5 (6.2-31.4)	2.9
60.0-69.9	10.9 (3.7-26.3)	16.5 (5.7-30.6)	5.6
70.0-79.9	10.9 (3.9-25)	14.6 (4.8-30.7)	3.7
80.0-89.9	13.5 (3.7-26.5)	11.9 (2.5-43.7)	-1.6

Table 18: Median follow-up TTLs for males and females in different age groups

Age (years)	Follow-up TTLs (µg/mL)		Difference of median TTLs between males and females (µg/mL)
	Males	Females	
0.0-9.9	21.7 (10.6-30.4)	22.2 (10.6-30.1)	0.5
10.0-19.9	16.2 (9.3-26.7)	19.2 (11-27.3)	3.1
20.0-29.9	15.1 (9.7-22.3)	17.2 (10.6-30.6)	2.1
30.0-39.9	17.5 (7.5-23.2)	14.4 (10.7-26.8)	-3.1
40.0-49.9	18.6 (9.4-28.2)	13.8 (11-21.9)	-4.8
50.0-59.9	16.2 (6.9-38.7)	16.9 (11-26.7)	0.8
60.0-69.9	16.5 (8.4-26.6)	20.6 (7.7-34.6)	4.1
70.0-79.9	15.2 (8.6-26.2)	18 (8.9-29.2)	2.8
80.0-89.9	15.9 (4.8-32.8)	17.7 (6.7-36.8)	1.8

There were no sex-related differences in risk for having initial and follow-up TTLs <10 µg/mL in children (see fFigure 23). In adults, males were at an increased risk for having initial and follow-up TTLs <10 µg/mL (OR 2.0 (95% CI 1.4-3.1), p<0.001 and 2.6 (1.1-6.0), p=0.029) and in elderly patients, males were at an increased risk of having follow-up TTLs <20 µg/mL (OR 1.9 (1.1-3.3), p=0.017). Consecutively, adult males were at an increased risk of having initial and follow-up TTLs outside the target range of 10.0-59.9 µg/mL (OR 2.1, 95% CI 1.4-3.1 and 2.3, 95%CI 1.0-5.2, p<0.001 and 0.050, respectively).

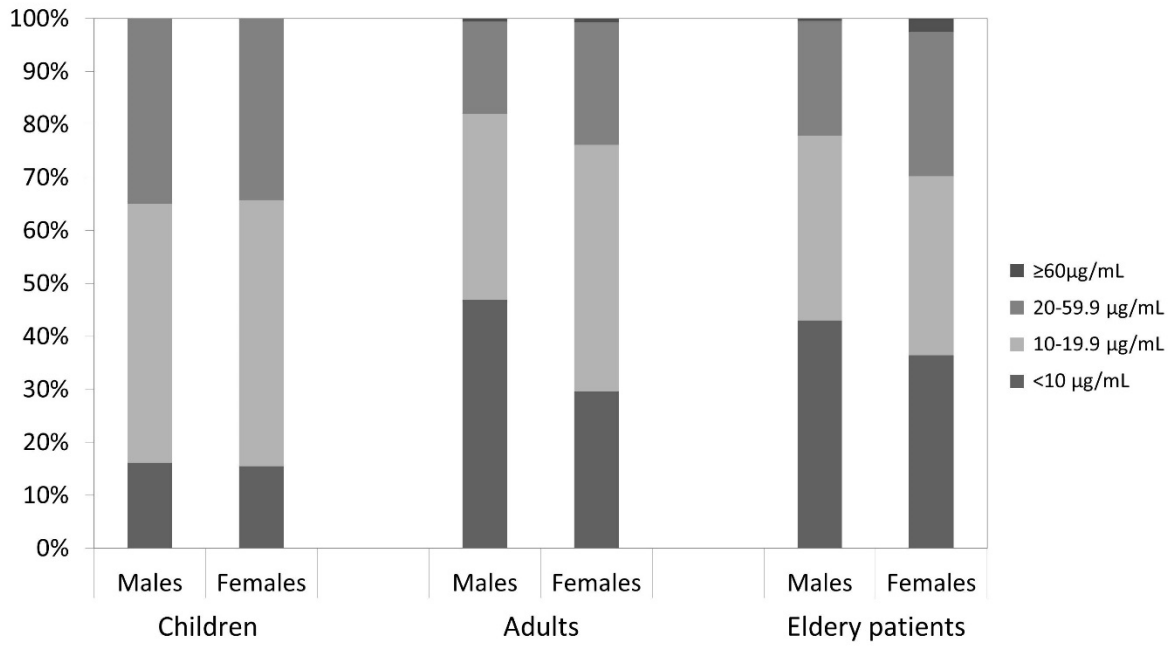

Figure 23: Rates of initial TTLs within and beyond the target ranges and the target ranges for severe infections for males and females by age

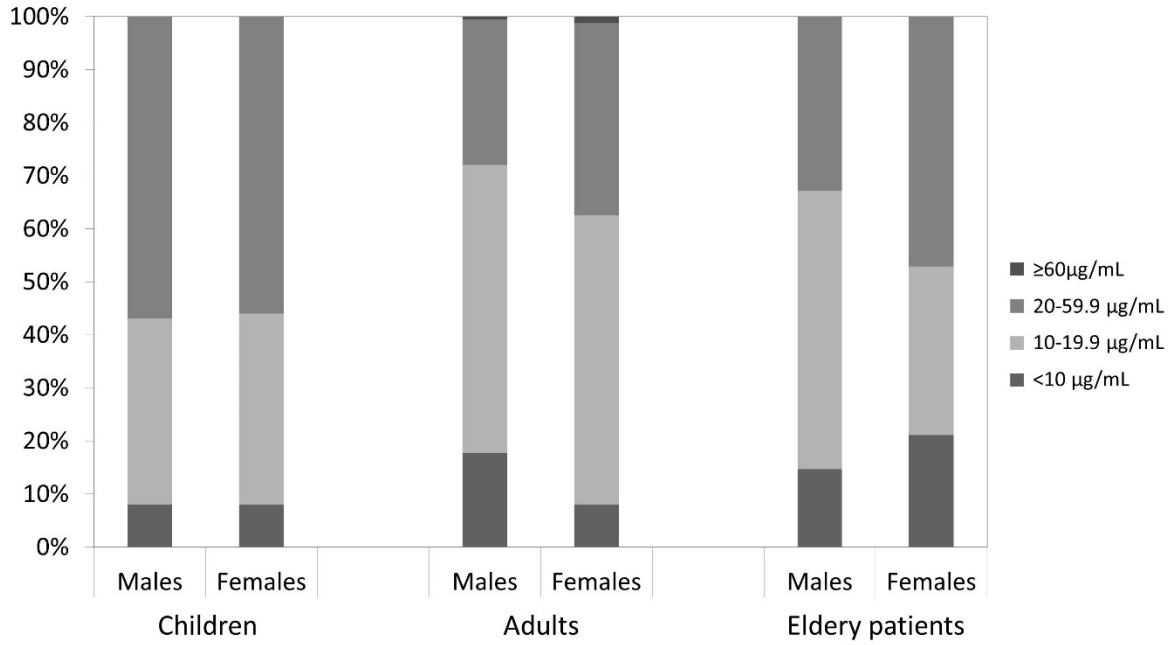

Figure 24: Rates of follow-up TTLs within and beyond the target ranges and the target ranges for severe infections for males and females by age

In the multivariate analysis with the inclusion of age and sex as independent variables, sex alone was no independent predictor of TTL, neither for initial nor for follow-up levels. However, the interaction term between age and sex was an independent and significant predictor. Thus, initial and follow up TTLs according to the patients' age differed significantly between females and males (initial TTLs: $p < 0.001$; follow up TTLs: $p = 0.013$). The age-dependent distribution with higher levels in younger patients, a nadir of TTLs at the age of 30 to 40 years and the slight increase thereafter as seen in the total study population was true for both groups, females and males and in both initial and follow-up TTLs.

Median initial and follow-up TTLs with 10^{th} and 90^{th} percentiles in males and females are displayed in figure 25 Figure 28 (raw data and predicted data by using multivariate regression analysis).

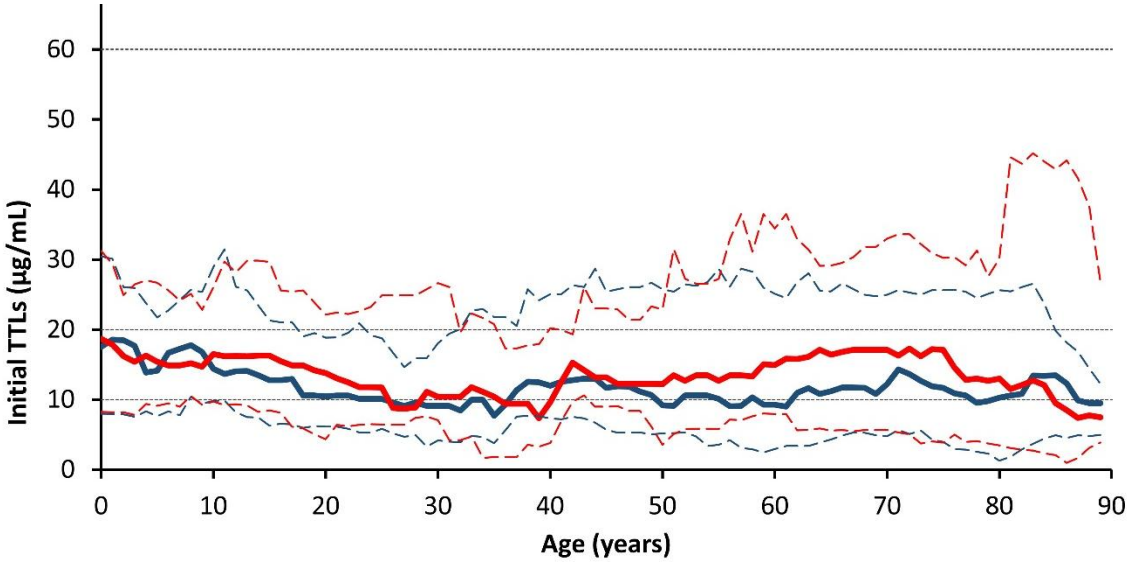

Figure 25: Percentile charts of initial TTLs over age for males and females (raw data)

Lines indicate median levels, dashed lines the 10th and 90th percentiles (blue for males, red for females)

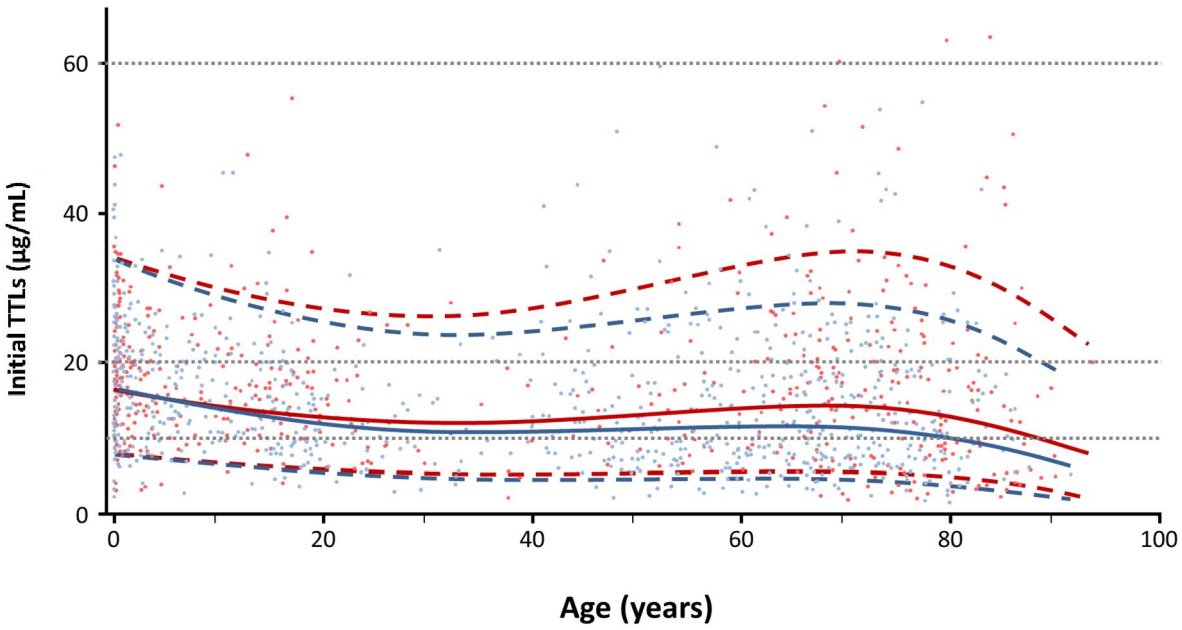

Figure 26: Percentile charts of initial TTLs over age for males and females (predicted data)

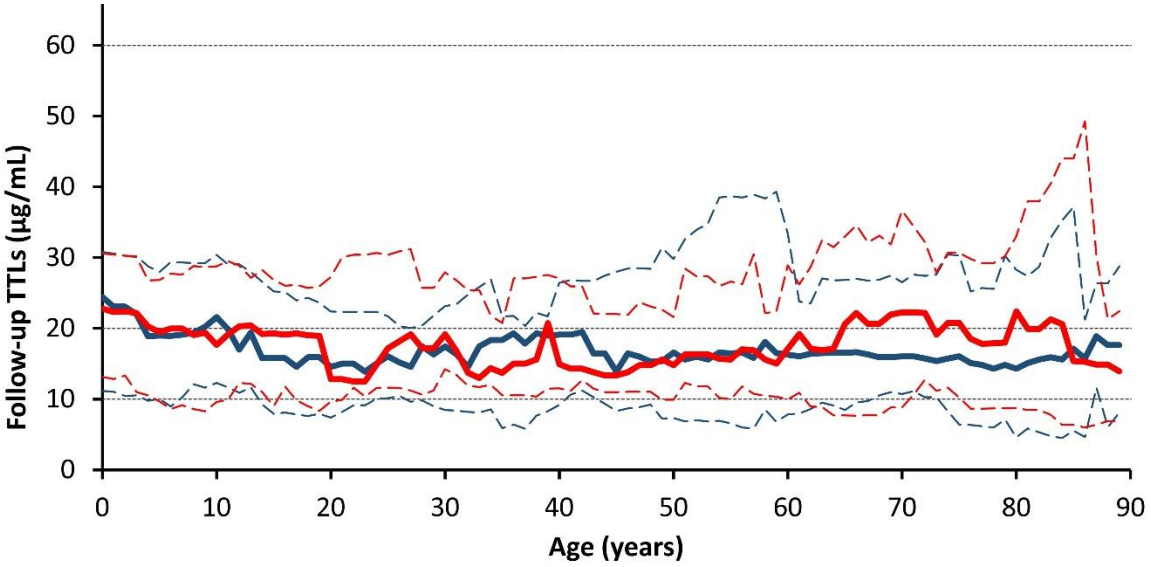

Figure 27 : Percentile charts of follow-up TTLs over age for males and females (raw data)

Lines indicate median levels, dashed lines the 10th and 90th percentiles (blue for males, red for females)

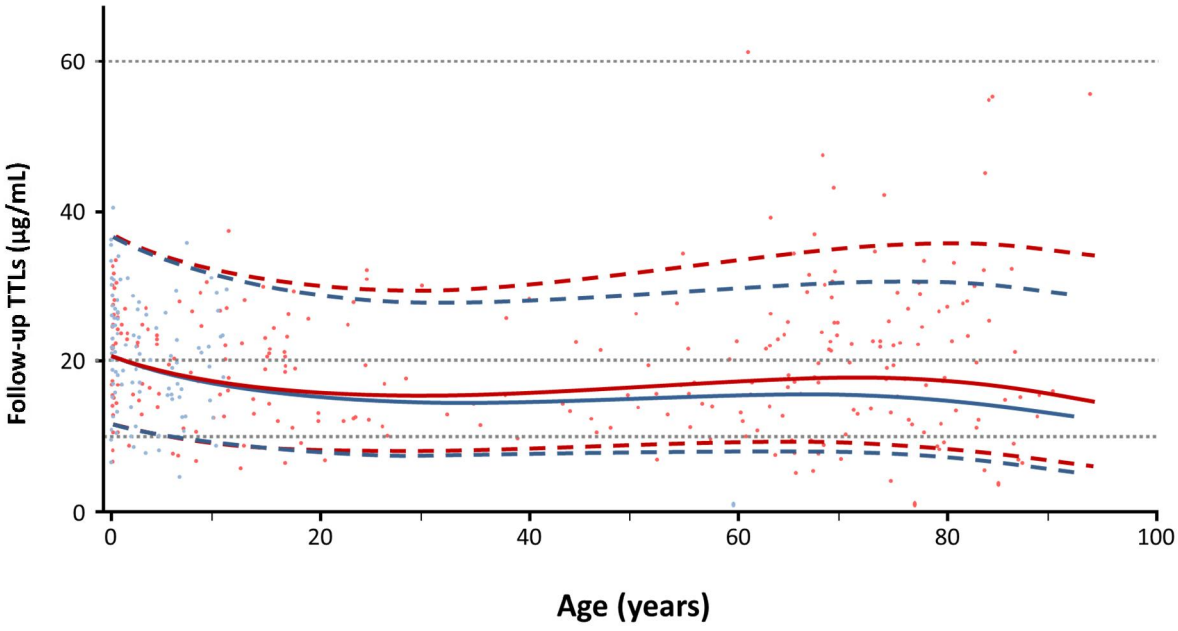

Figure 28 : Percentile charts of follow-up TTLs over age for males and females (predicted data).

3.3.2 Sex-related differences for initial and follow-up TPLs

From 151 patients who had TPLs determined, 85 were males (56.3%) and 66 were females (43.7%). Age and sex distribution of the study patients is shown in figure 29.

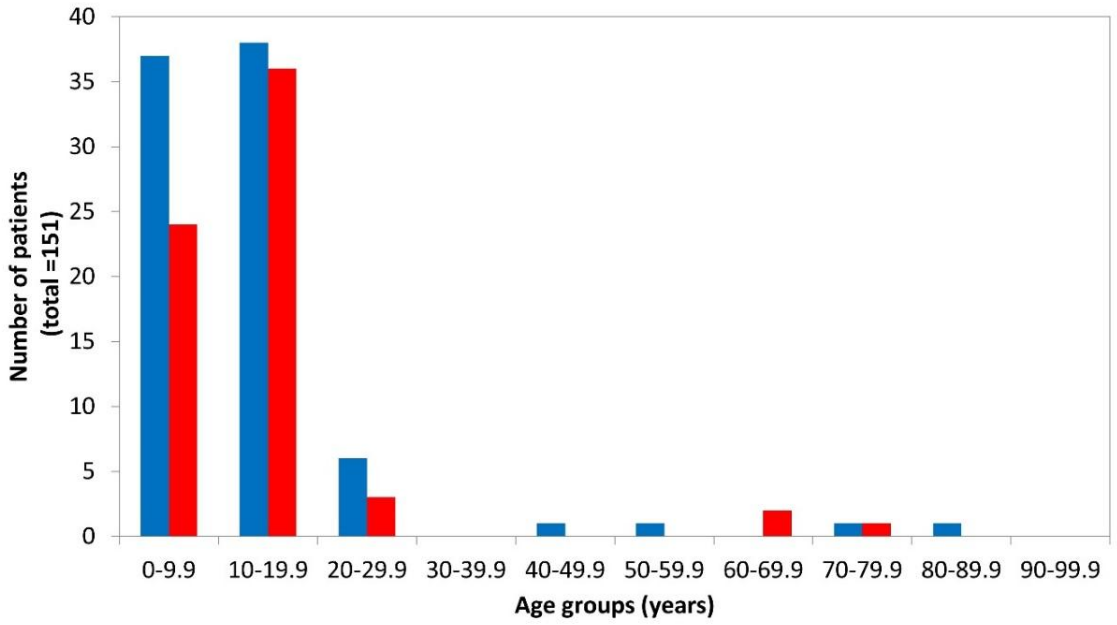

Figure 29: Age and sex distribution of study patients with TPLs
Red bars represent female patients, blue bars represent male patients

In children and elderly patients initial TPLs did not differ between males and females. In adults, females had higher initial TPLs compared to adults (median TPLs 66.3 vs. 58.1 µg/mL, p=0.032):

Table 19: Initial TPLs in males and females of different age groups

Age groups	Number of patients		Median TPLs (µg/mL)		p-value
	Males	Females	Males	Females	
Children	50	43	68.0	67.6	0.835
Adults	33	21	58.1	66.3	**0.032**
Elderly patients	2	2	28.6	23.2	1.000

A detailed list of age-dependent initial TPLs for male and female patients is given in table 20.

Table 20: Median initial TPLs for males and females in different age groups

Age (years)	Initial TPLs (µg/mL)		Difference between males and females (µg/mL)
	Males	Females	
0.0-9.9	70.6	66.2	-4.4
10.0-19.9	63.1	73.2	10.1
20.0-29.9	46.5	59.6	13.2
30.0-39.9	--	--	--
40.0-49.9	24.7	--	--
50.0-59.9	44.2	--	--
60.0-69.9	--	58.6	--
70.0-79.9	33.6	6.7	-26.9
80.0-89.9	23.6	--	--

In children, 68.0% of the male patients and 67.4% of the female patients had TPLs ≥60 µg/mL, in adults 42.4% of the male compared to 66.7% of the female patients had TPLs ≥60 µg/mL, however, this difference was not significant (p=0.101). No elderly patient had an initial TPL ≥60 µg/mL.

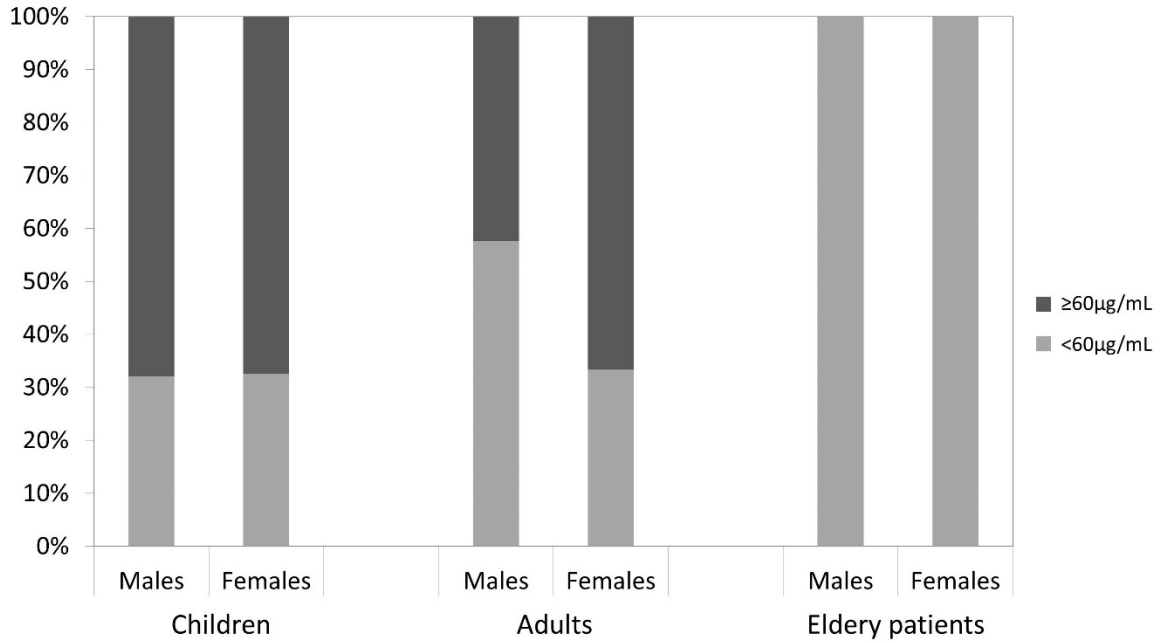

Figure 30: Rates of initial TPLs within and beyond the target for males and females by age

While in the total study population females had significantly higher follow-up TPLs compared to males (median levels 61.1 vs. 50.9 µg/mL, p=0.028), the differences in the single age groups did not reach statistical significance.

Table 21 : Follow-up TPLs in males and females of different age groups

Age groups	Number of patients		Median TPLs (µg/mL)		p-value
	Males	Females	Males	Females	
Children	23	18	53.5	63.7	0.078
Adults	10	10	45.9	60.0	0.082
Elderly patients	1	1	36.6	21.4	1.000

In children, 26.1% of the male patients and 55.6% of the female patients had TPLs ≥60 µg/mL, in adults 30.0% of the male and 50.0% of the female patients. No elderly patient had a follow-up TPL ≥60 µg/mL. The differences between males and females were not statistically significant.

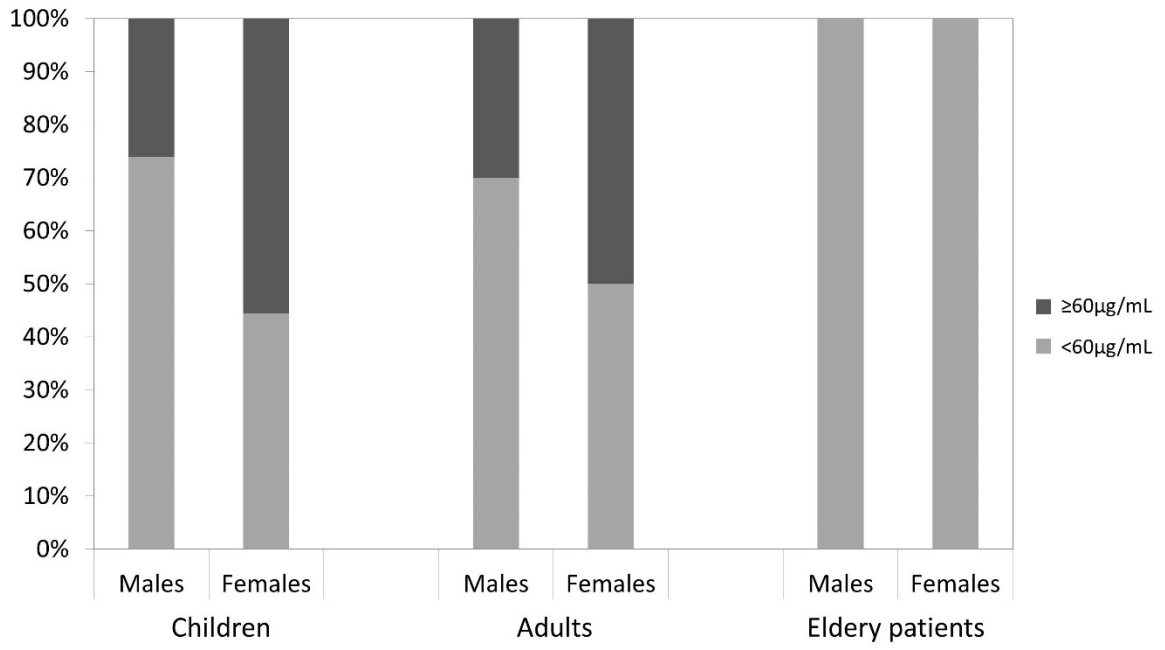

Figure 31: Rates of follow-up TPLs within and beyond the target for males and females by age

4 Discussion

4.1 Target ranges

4.1.1 Risk for subtherapeutic concentrations

We evaluated the appropriateness of teicoplanin dosing regimen in clinical setting by analysing TDM data of 1380 adult and paediatric patients. In our cohort, nearly one third of patients had initial TTLs below the target (<10µg/mL) and more than 70% did not achieve levels >20µg/mL, which are considered appropriate for treating severe infections.

Underdosing with teicoplanin has been highlighted as a significant concern also in previous analyses (131, 133, 139-144): Dufort *et al*. (142) studied teicoplanin concentrations in 21 febrile neutropenic paediatric patients. They revealed that 55.6% of the patients who received three loading doses of 10 mg/kg at 12-h intervals and a maintenance dosage of 10 mg/kg thereafter had low concentrations (<10 µg/mL).
Similarly, Sanchez *et al*. (141) evaluated teicoplanin pharmacokinetics in 21 critically ill children aged 7 days to 12 years. They reported that following the administration of the same loading and maintenance dosing regimen (3x 10 mg/kg every 12 hours, then 10 mg/kg once daily) 89% of critically ill infants and children did not achieve TTLs >10 µg/mL.
Ramos-Martin *et al*. (145) evaluated teicoplanin in a pharmacokinetics hospital-based study including 39 children mainly recruited from oncological wards or from the intensive care unit after cardiac surgery and 33 adults recruited from oncological wards (all adults had acute lymphocytic or acute non-lymphocytic

leukaemia and febrile neutropenia). Based on 306 serum samples of these patients the authors present a population pharmacokinetic model with predicted teicoplanin serum concentrations <10 µg/mL by day 4 of treatment in 39% to 70% of children and in 75% of adults.
Tobin *et al*. (133) analysed retrospectively more than 10,000 teicoplanin levels obtained from different hospitals in the UK over a 13 year period. While the authors reported a decreasing rate of patients having levels below target (<10µg/mL) from 23% to 13% during the 13-year study period, they neither evaluated differences between initial and follow-up levels nor influences of age or sex.

Targocid® data sheet recommends loading doses of 400 mg corresponding to at least 6 mg/kg 12-hourly for three dosages and 6 mg/kg thereafter for most infections and higher doses of 800 mg corresponding to at least 12 mg/kg for infections of the bones and joints and endocarditis.
In our cohort, the rate of patients with TTLs below the target ranges decreased significantly during the course of the treatment episode with only 13% of the follow-up TTLs being <10 µg/mL. This might the consequence of dose adjustments according to TDM or of a delayed achievement of a steady state. However, the study design did not allow a further discrimination.

Underdosing has been generally assumed to result from a failure to follow data sheet recommendations on loading doses based on concerns on adverse events, foremost nephrotoxicity. (133)
However, more recent studies showed that doses considerably higher than those recommended in the data sheet are required to efficiently achieve therapeutic concentrations. (146-148)
Combined with the findings of this study that a significant proportion of patients – especially male adults and elderly patients – do not achieve therapeutic concentrations, this would suggest that a further re-evaluation of current teicoplanin dosing guidelines is needed so as to ensure that more patients reach more rapidly optimal concentrations.

4.1.2 Risk for toxic concentrations

To minimize the risk of side effects caused by higher teicoplanin serum levels, levels >60µg/mL are recommended to be avoided in different institutions. (125, 126, 133, 135)

However, there is limited evidence for this recommendation, which is solely based on a non-peer-reviewed study with a small patient number and without evaluating additional nephrotoxic co-medication. (69, 139)

In a more recent analysis of 549 outpatient treatment episodes in adults Matthews and colleges (149) found no association of TTLs >60 µg/mL and baseline serum creatinine and no correlation between pre-treatment and post-treatment creatinine and teicoplanin levels, nor for teicoplanin dosing regimens and side effects (renal injury, neutropenia, thrombocytopenia, eosinophilia, rash, fever, nausea, vomiting,etc.).

In our cohort, very few patients had TTLs >60µg/mL – in both initial and follow-up levels - and even in the groups with the highest median values – namely children, and females the rates of patients with TTLs >60 µg/mL were <1%. Here, we were not able to investigate possible other spurious reasons for such high teicoplanin levels >60 µg/mL in these patients. Such high values might also result from incorrect specimen collection by means of technique and timing or incorrect administration time.

Though further research on the upper cut-off value for the target range of teicoplanin levels is needed, meanwhile it seems reasonable avoiding through levels >60 µg/mL. However, while it is unclear how to interpret this upper cut-off value in the context of trough levels, there is even more uncertainty on how to interpret it in the context of teicoplanin peak levels. As shown in our analysis the difference between trough and peak levels is around 50 µg/mL. (139) Thus, avoiding levels >60 µg/mL is hardly possible when TTLs are aimed to be within the target range. In fact, despite 32% of the initial trough levels were <10 µg/mL, 60% of the initial TPLs were ≥ 60 µg/mL.

4.2 Age-related differences

In an evaluation of preliminary data of this theses only including paediatric patients we found age and sex-related differences of teicoplanin levels with toddlers (1-6 years of age) having significantly lower TTLs when compared to neonates and infants and to older children and a further decrease of median teicoplanin concentrations in adolescents (12-18 years of age). (139) In the entire cohort including adults and elderly patients, raw data and smoothed centile curves showed a more continuous decline of the TTLs from infants over adolescents to adults with the nadir in patients between 30 and 40 years of age and consecutively with the highest rate of inappropriate TTLs in this age group (except of the age group >90 years of age with only 9 patients included).
Some authors have described similar pharmacokinetic data in children: Lukas *et al*. (150) conducted a population pharmacokinetics analysis including 20 infants and children aged 4 months to 10 years. They revealed that 8% of younger children aged <12 months had TTLs <10 µg/mL compared to 35% of children aged ≥12 months.

In another analysis, Ramos-Martin and colleagues (145) created a pharmacokinetics model of teicoplanin based on data from 39 children and 33 adults. They reported that the rate of predicted subtherapeutic concentrations <10 µg/mL increased with increasing weight/age from 39% in children with a presumed body weight of 10 kg to 55% in children with a presumed body weight of 25 kg to 70% in children with a presumed body weight of 50 kg and 75% in adults. (145)

Other authors failed to demonstrate a significant association between teicoplanin pharmacokinetics and age (13 children aged 2 to 12 years) (151) or showed a not statistically significant trend towards a decreasing clearance with increasing age (12 children aged 2.4 to 11 years). (152)

Finally, Tarral *et al*. (153) compared 6 children with a mean age of 7 years with 4 neonates with a mean age of 8.5 days and found that clearance was higher in neonates.

In the current study, we investigated the role of age on teicoplanin pharmacokinetics in a considerably larger cohort of unselected paediatric and adult patients. The rate of patients with inappropriate levels increased with age from infancy to childhood and adulthood with the highest rates of subtherapeutic levels in young adults

4.3 Sex-related differences

In the analysis of preliminary data only including paediatric patients, we noticed sex-related differences for teicoplanin levels, but only in adolescents: Adolescent girls had higher median levels and consecutively a lower risk of having levels <10µg/mL and higher risk of levels >60µg/mL. (139) One aim of the extended analysis was to investigate whether these sex-related differences can also be observed in adults.

The current literature provides very sparse information on sex-related differences of teicoplanin pharmacokinetics. The only report on this topic by Matthews *et al*. (154) who evaluated teicoplanin levels in 141 adults with bone and joint infections showed that male sex was associated with lower TTLs compared to females.

In our considerably larger cohort, differences between males and females start around 15 to 20 years of age. And despite the rather small difference of median levels between males and females of up to 5.6 µg/mL, the overall high rate of low or borderline levels around 10 µg/mL makes this difference clinically relevant: In fact, male adults and male elderly patients had a more then 3.5-fold higher risk of having inappropriate initial levels with the used dosing regimens compared to females.

Teicoplanin distribution varies significantly between different tissues with high concentrations in skeletal muscles and especially low concentrations in fat tissue.

(69, 71, 81-84) Thus, body composition might account for the observed differences between males and females. (155, 156) Body composition and body fat differ between males and females: While young (25 years) males with a body mass index (BMI) of 19 to 25 have body fat rates of 9 to 19%, females with the same BMI have higher body fat rates of 22 to 33% and the difference between males and females remains stable over age (13 to 23% body fat in 60-year old males with a BMI of 19 to 25 compared to 25 to 35% in females). (155) Following the administration of weight-adapted doses of teicoplanin, low fat penetration might account for higher values in the other body compartments and higher serum concentrations in females.

Both the differences of teicoplanin levels between males and females as well as sex-related differences in body composition and body fat rates start with puberty (157, 158) which further supports this hypothesis.

Differences in protein binding or renal excretion of teicoplanin might further explain these sex-related differences. Other factors (volume status of the patients, diuretic co-medication, volume overload etc.) might have potentially influenced teicoplanin pharmacokinetics via the same mechanisms, but should not have been affected by sex, yet the study design did not allow assessing these factors separately.

4.4 Therapeutic drug monitoring

TDM is an important tool for more tailored dosing strategies. (129, 131, 133, 137) This is also reflected by the observed differences between initial and follow-up measurements: While follow-up TTLs were significantly higher and more likely to be in the therapeutic range >10 µg/mL, follow-up TPLs were significantly lower and less likely to be >60µg/mL compared to 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 approximately increase dosage proportionally according to the difference between

actual measured level and target level. However, systematic analyses how to modify dosage to rapidly achieve target levels do not exist.

4.5 Limitations

The main limitations of the current study are due to the retrospective character. In a very large cohort with different underlying diseases (e.g. medical, surgical, paediatric, haemato-oncologic) and therefore different clinical conditions and co-medications and different indications for teicoplanin administration (prophylactic, empiric, calculated), we were not able to evaluate exact initial dosages, exact sampling time of the initial TTL (during or after loading dose phase) as well as details on dose modifications. Furthermore, our data does not allow any conclusions about efficacy of treatment or dose dependent side effects. However, the current analysis comprises the largest cohort to be evaluated for appropriateness of teicoplanin levels as well as for sex-and age-related differences in a real life setting.

4.6 Conclusion

In conclusion, a high rate of TLs below the target range and significant age- and sex-specific differences with low levels in adult and elderly males were observed. More tailored dosing regimens with higher loading doses especially in adults should be considered. As long as further pharmacokinetic data are pending TDM is mandatory.

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6 Appendix

Publications:

Strenger, V*; Hofer, N*; Rödl, S; Hönigl, M; Raggam, R; Seidel, MG; Dornbusch, HJ; Sperl, D; Lackner, H; Schwinger, W; Sovinz, P; Benesch, M; Urlesberger, B; Urban, C. Age- and gender-related differences in teicoplanin levels in paediatric patients. J Antimicrob Chemother. 2013; 68(10):2318-2323
*equal contribution

Hofer N, Zollner-Schwetz I, Pansy J, Hoenigl M, Raggam R, Krause R, Roedl S, Avian A, Lackner H, Urban C, Strenger V. Age- and sex-related differences of teicoplanin serum levels in pediatric and adult patients - An analysis of teicoplanin therapeutic drug monitoring. *Under review*.