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Therapeutic drug monitoring of glycopeptide antimicrobials: An overview of liquid chromatography-tandem mass spectrometry methods

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ABSTRACT

Therapeutic drug monitoring (TDM) is a critical clinical tool used to optimize the safety and effectiveness of drugs by measuring their concentration in biological fluids. These fluids are primarily plasma or blood. TDM, together with real-time dosage adjustment, contributes highly to the successful management of glycopeptide antimicrobial therapies. Understanding pharmacokinetic/pharmacodynamic (PK/PD) properties is vital for optimizing antimicrobial therapies, as the efficacy of these therapies depends on both the exposure of the patient to the drug (PK) and pharmacodynamic (PD) parameters such as the in vitro estimated minimum drug concentration that inhibits bacterial growth (MIC). Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) is widely recognized as the gold standard for measuring small molecules, such as antibiotics. This review provides a comprehensive overview of LC-MS/MS methods available for TDM of glycopeptide antibiotics, including vancomycin, teicoplanin, dalbavancin, oritavancin, and telavancin.

1. Introduction

Therapeutic drug monitoring (TDM) is a clinical tool employed to optimize both the effectiveness and safety of drugs through dose tailoring which involves measuring drug concentration in biological fluids, primarily plasma or blood [1]. The rising incidence of infections in both adults and children due to antibiotic-resistant Gram-positive and Gram-negative bacteria is becoming a global health concern. TDM has proven to aid effective management of antimicrobial therapies and is strongly recommended for specific hydrophilic antibiotics like glycopeptides [2–4]. The efficacy of antibiotic therapy hinges both on the patient's exposure to the drug (pharmacokinetic parameters, PK), including the maximum plasma concentration (C_{max}), the area under the 24-hour plasma concentration curve as a function of time (AUC_{24}), the minimum pre-dose plasma concentration (C_{trough}), and pharmacodynamic (PD) properties such as the level of susceptibility of the microorganisms which is assessed in vitro by the minimum drug concentration that inhibits bacterial growth (MIC) [5,6]. Understanding the PK/PD relationship is crucial for optimizing antibiotic use [7]. Antimicrobials can be classified as either time-dependent, concentration-dependent, or mixed concentration-dependent drugs with time-dependency [5,8–11]. Time-dependent antibiotics have in vivo activity related to the percentage of persistence of the drug's (free) plasma concentration above the MIC during the administration interval [(%) t > MIC], therefore the evaluated PK parameter is C_{trough} [5,6,8–10]. For concentration-dependent antibiotics, the evaluated PK parameter is the C_{max}/MIC ratio [5,7,8,10], and for mixed-dependent antimicrobials with time-dependency, the ratio of steady-state AUC_{24} to MIC (AUC/MIC ratio) significantly describes drug exposure [8]. TDM is vital in managing antibiotic therapy. It assesses patient exposure to the drug,

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; AUC_{24}, area under the 24-hour plasma concentration curve; C_{max}, maximum plasma concentration; CSF, cerebrospinal fluid; C_{trough}, minimum pre-dose plasma concentration; EMA, European Medicines Agency; LC-MS/MS, Liquid chromatography coupled to MS/MS; LLOQ, lower limit of quantification; *m/z*, ratios of mass-to-charge; ME, matrix effect; MIC, minimum drug concentration that inhibits bacterial growth; MRSA, methicillin-resistant Staphylococcus aureus; MS/MS, Tandem mass spectrometry; NP, nosocomial pneumonia; PD, pharmacodynamic; PIP, pediatric investigation plan PK, Pharmacokinetics; TAT, turnaround times; TDM, Therapeutic Drug Monitoring; VAMS, Volumetric Absorptive Microsampling.

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Table 1
Characteristics of the evaluated LC-MS/MS methods for determination of vancomycin in human samples.

Authors (Year)	Analytes	Samples	Run Time	Calibration range	Stability studies
Ringeling (2022) [46]	Vancomycin;Clindamycin	Plasma; synovial fluid	5.2 min	0.5–50 mg/L	− 80 °C for 72 and 168 h
Fan (2020) [47]	Vancomycin;Crystalline degradation products	Serum	5 min	1.057–105.7 μg/mL	25 °C for 24 h; −80 °C for 518 days
Fan (2019) [48]	Vancomycin	Serum	4.5 min	10–100 mg/L	−80 °C for 279 and 497 days
Jin (2023)[55]	Vancomycin; Meropenem;Valproate	Serum; CSF	8 min	0.1–10 μg/mL and 1–100 μg/mL	25 °C for 6 h; −20 °C for 30 days; three freeze–thaw cycles (-20 °C to 25°)
Barco (2016) [20]	Vancomycin	Plasma	3 min	0.1–128 μg/mL	4 °C for 7 days; −20 °C for 30 days; three freeze–thaw cycles (-20 °C to 25 °C)
Liu (2018) [49]	Vancomycin	Serum	8 min	1–2000 ng/mL	25 °C for 6 h; −80 °C for 30 days;three freeze–thaw cycles (-20 °C to 25 °C)
Silva (2019) [50]	Amikacin VancomycinCreatinine	Plasma	5.5 min	0.5–100 mg/L	three freeze–thaw cycles (-20 °C to 25 °C)
Hana Brozmanová [51]	Vancomycin	Serum	5 min	0.1–100 mg/L	–
Andriguetti (2019) [53]	VancomycinCreatinine	Plasma; VAMS	8.5 min	1–100 mg/L	22 °C and 45 °C for 1; 7 and 14 days
Bijleveld (2014)[33]	Amikacin GentamicinVancomycin	Plasma	7.5 min	1–100 mg/L	25 °C and −80 °C for 96 h and 100 days:three freeze–thaw cycles (−80 ∘C to 25 °C)
Barco (2020) [52]	Amikacin Amoxicillin Ceftazidime Ciprofloxacin Colistin Daptomycin Gentamicin Linezolid Meropenem Piperacillin Teicoplanin Tigecycline Tobramycin Vancomycin	Plasma	5 min	1–100 mg/L	storage on ice and at 25 °C for 2, 4 and 6 h; −20 °C and −80 °C for 1, 2, 4 weeks;three freeze–thaw cycles (-20 °C to 25 °C)

preventing sub-therapeutic levels and ensuring efficacy levels.

Tandem mass spectrometry (MS/MS) is an analytical technique based on the ionization of a molecule and its subsequent fragmentation into ions of different ratios of mass-to-charge (m/z) [12]. Liquid chromatography coupled to MS/MS (LC-MS/MS) is widely employed in clinical laboratories [1,12–16] and is considered the gold standard for small molecule measurement, like antibiotics [1,15–17]. Meanwhile, LC-MS/MS allows the quantification of a panel of analytes from very small volumes, crucial in special contexts like pediatrics [1,18,19]. However, this technique's limitations include being expensive and thus only available in a few specialized centers, requiring skilled personnel, and having long turnaround times (TAT) due to the necessity of sample preparation [8]. Analysis times usually vary between 5 and 10 min per sample depending on several factors. These include the physical and chemical properties of the analytes, the number of analyses to be simultaneously monitored, the chosen chromatographic conditions, and the MS analyzer's characteristics [8]. In cases requiring rapid assessment of drug concentration or where LC-MS/MS isn't available, using an automated immunoassay may play a significant role [20]. Ensuring proper accuracy may be achieved by cross-validating the results obtained by immunoassay against those obtained by LC-MS/MS during method validation. However, immunoassays are only available for a few antimicrobial drugs [8].

2. Background

Glycopeptide antimicrobials are a group of glycosylated peptides including both naturally occurring compounds and semi-synthetic derivatives, the progenitor of which is vancomycin [21–23]. These drugs exhibit antibacterial activity against Gram-positive organisms and are commonly used for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) or ampicillin-resistant *Enterococcus* strains [24].

Glycopeptides work by inhibiting cell wall synthesis in bacteria. They attach to the D-alanine dimer terminus of the lipid precursor II of the bacterial cell wall, which blocks the cross-linking of the peptidoglycan layer [25]. This group of antimicrobials includes vancomycin, teicoplanin, and newer glycopeptides like dalbavancin, oritavancin, and telavancin [5,26–30].

Measurement of glycopeptides can be complex due to the "matrix effect" (ME). This occurs in mass spectrometry when molecules that co-elute with the target compound alter the ionization efficiency of the electrospray interface, which can affect the accuracy of measurements [20]. The matrix effect has been found to be an issue in LC-MS/MS methods for vancomycin quantification [31–33].

Daptomycin, a cyclic lipopeptide antibiotic, consists of a cyclic polypeptide core of 13 amino acids. The 10C-terminal residues of this core form a ring closed by an ester bond, and a three-amino-acid exocyclic side chain capped with a terminal tryptophan linked to a fatty acyl residue (decanoic acid) [34]. Despite therapeutic indications of daptomycin overlapping with certain glycopeptides, it is not considered in this review due to its distinct structural class.

3. Vancomycin

Vancomycin, discovered in the 1950 s, is the progenitor of the glycopeptide class [35]. Its chemical structure comprises a glycosylated hexapeptide chain abundant in rare amino acids, many of which contain aromatic rings linked by ether bonds, creating a rigid structure [36,37]. Vancomycin falls under the category of time-dependent antimicrobials. An AUC-based TDM approach has recently been recommended as opposed to solely monitoring C_{trough} levels to ensure the achievement of a PK/PD target of $AUC_{0\text{-}24h}/MIC > 400–600$ and reduce acute kidney injury rates [6,38–45].

It is understood that nephrotoxicity and/or ototoxicity associated with vancomycin can occur due to excessive drug exposure [8,39] The adoption of TDM is hence strongly recommended for managing vancomycin therapy [8]. Vancomycin is commonly measured in routine clinical laboratories using immunoassays [20], which generally possess lower specificity, accuracy, and precision than chromatography-based

Table 2
Characteristics of the evaluated LC-MS/MS methods for determination of teicoplanin in human samples.

Authors (Year)	Analytes	Samples	Run Time	Calibration range	Stability studies
Fung (2012) [65]	Teicoplanin	Serum	–	12.6–200 μg/mL	–
Chae (2018) [66]	Teicoplanin A2-2/A2-3	Plasma	6.5 min	3.3–50 mg/L	–
Barco (2020) [52]	Amikacin Amoxicillin Ceftazidime Ciprofloxacin; Colistin Daptomycin Gentamicin Linezolid Meropenem Piperacillin Teicoplanin A2 − 2 A2 − 3 Teicoplanin A2 − 4 A2 − 5 Tigecycline TobramycinVancomycin	Plasma	5 min	1–100 mg/L	storage on ice and at 25 °C for 2, 4 and 6 h; −20 °C and −80 °C for 1, 2, 4 weeks;three freeze–thaw cycles (−20 °C to 25 °C)
Begou (2017) [56]	Teicoplanin A2-1 Teicoplanin A2-2,3 Teicoplanin A2,4-5Teicoplanin A3-1	Plasma	8.5 min	25–6400 ng/mL	−20 °C for 6 months;three freeze–thaw cycles (−20 °C to 25 °C)

assays. However, immunoassays allow for shorter TAT, which are crucial for emergency management.

In their 2016 study, Barco et al. [20] compared the performance of a UHPLC-MS/MS method developed and validated according to international guidelines on bioanalytical method validation with a commercially available immunoassay by analyzing 138 real samples. The immunoassay displayed unsatisfactory accuracy with samples showing toxic vancomycin levels, leading to a clinical discordance in the classification of the samples as sub-therapeutic, therapeutic, or toxic ranges in approximately 10 % of the analyzed samples.

In total, 11 studies, outlined in Table 1, described the development of an LC-MS/MS method for quantifying vancomycin and its application to human samples for TDM. All these studies aimed at quantifying vancomycin in serum/plasma [20,46–52]; one also included cerebrospinal fluid (CSF) [46], and another integrated Volumetric Absorptive Microsampling (VAMS) [53]. Chromatographic run times ranged from 4.5 to 8.5 min. Fast run times are highly desirable to optimize equipment use and ensure appropriate TAT. Most studies investigated vancomycin's stability in their respective matrices. Vancomycin was stable in serum/plasma stored at −20 °C or −80 °C for up to 518 days [47]. It also remained stable on ice and at room temperature (25 °C) in whole blood (for up to 2 h) and plasma (for up to 6 h) [52]. Vancomycin's stability was also investigated in VAMS stored at 22 °C and 45 °C for up to 14 days, with results falling within acceptable ranges [53]. Andriguetti et al. (2019) [53] developed and validated a successful LC-MS/MS method for quantifying vancomycin from VAMS, which were extracted by adding 250 μL of extraction solution, consisting of a mixture of methanol and water (1:1, v/v), containing 0.1 % of formic acid and creatinine-D3 at a concentration of 0.25 g/mL, to a polypropylene microtube. This method was applied to 60 patient samples, with the results compared with plasma concentrations. Vancomycin concentrations ranged 4.02–70.48 mg/L in plasma and 3.96–79.67 mg/L in VAMS, with an average increase in VAMS of 9.5 percent. To estimate plasma concentrations, vancomycin levels in VAMS must be multiplied by a correction factor of 0.934. Differences between plasma and alternative matrices such as capillary blood in drug concentrations are indeed possible due to interactions of analytes with filtration or absorption materials. This must be evaluated during method development [1,54]. Hence, a comparison between plasma and microsampling devices' levels is always needed for application in a clinical setting [1,54].

4. Teicoplanin

Teicoplanin is a mixture of five major components (A2-1 through A2-5), one hydrolysis component (A3-1), and four minor components (RS-1 through RS-4), produced by the actinomycete Actinoplanes teichomyceticus [25]. All major components contain an N-acyl-beta-D-glucosamine, but vary in terms of the acyl-aliphatic chains (R) [56]. Teicoplanin can be administered intravenously or intramuscularly and shares similar properties with vancomycin, yet exhibits a longer duration of action [5]. Like vancomycin, teicoplanin displays time-dependent antimicrobial activity, and the PK/PD relationship most indicative of its efficacy is the duration of maintenance of plasma concentrations above MIC (t > MIC) [3,6,42,57–60]. The therapeutic target range for teicoplanin is 10–20 mg/L (15–30 mg/L for severe infections) for C_{trough} and 30–40 mg/L for C_{max} [3,6,42,61]. Toxicity is expected at C_{max} > 80 mg/L [3,6,42]. Recently, the AUC_{24}/MIC ratio has also emerged as a PK/PD parameter linked to clinical efficacy [3,62,63]. In a 2016 study, Matsumoto and colleagues [64] suggested the AUC_{24}/MIC ratio at day 3 as an optimal target for monitoring response to teicoplanin in patients with MRSA infections [64].

To the best of our knowledge, four LC-MS/MS methods, summarized in Table 2, developed for quantifying teicoplanin have been developed and applied to human samples [52,56,65,66]. All of these methods quantified teicoplanin in serum or plasma samples. The total chromatographic run time ranged from 5 to 8.5 min, but one study did not report this information. Teicoplanin stability has been examined in two studies [52,56]. Barco et al. (2020) assessed the stability of teicoplanin isoforms (A2-2 A2-3 and A2-4 A2-5) across various conditions. They report that these isoforms are stable in plasma samples stored at −20 °C and −80 °C for four weeks, or stored at room temperature (25 °C) or on ice for up to 6 h. They are also found that these isoforms are stable in whole blood samples stored at 25 °C or on ice for up to 2 h before centrifugation.

Begou et al. (2017) considered teicoplanin stability in plasma samples stored at −20 °C for up to six months and determined concentrations were within acceptable ranges.

To date, no method has been published for quantifying teicoplanin in biological fluids using microsampling devices.

5. Dalbavancin

Dalbavancin, a semisynthetic lipoglycopeptide, boasts faster and more potent bactericidal activity than vancomycin and teicoplanin, as well as a long terminal half-life ranging from 149 to 250 h in human subjects [67]. It has time-dependent bactericidal activity, with the PK/PD parameter most closely correlating with its antibacterial activity being the ratio AUC/MIC [68]. Dalbavancin has been approved in Europe to treat acute bacterial skin and skin structure infections (ABSSSI) in adults and pediatric patients aged three months and older. Additionally, off-label schemes have been proposed for various indications [68,69]. TDM for dalbavancin exposure is considered essential

Table 3
Characteristics of the evaluated LC-MS/MS methods for determination of dalbavancin in human samples.

Authors (Year)	Analytes	Samples	Run Time	Calibration range	Stability studies
Seraissol (2022) [73]	Ceftriaxone Dalbavancin	Serum	4 min	1–50 mg/L	25 °C for 6 h; 4 °C for 72 h; −20 °C and −80 °C for 6 months; three freeze–thaw cycles (-20 °C to 25 °C)
Barone (2023) [76]	Dalbavancin	Plasma	4 min	2–77 mg/L	Three freeze–thaw cycles (−80 °C to 25 °C)
Alebic-Kolbah (2011) [74]	Dalbavancin	PlasmaUrine	3.5 min	0.5–500 μg/mL (plasma) 5–50 μg/mL (urine)	Four freeze–thaw cycles (-20 °C to 25 °C); 25 °C for 24 h;-20 °C for 256 days
Nicolau (2007) [77]	DalbavancinOH-Dalbavancin	Plasma Skin blister fluid	–	1.0–128 mg/mL	–
Mula (2023) [75]	Dalbavancin Daptomycin Linezolid Tedizolid Moxifloxacin Levofloxacin Ertapenem Meropenem	Plasma	10 min	6.25–200 μg/mL	−20 °C and −80 °C for 90 days; three freeze–thaw cycles (−80 °C to 25 °C)

to guide the timing of the next dosage, detect underdosing, and subsequently reduce costs for health systems [70–72]. So far, five papers have been published concerning dalbavancin measurement in human samples (Table 3); four of these described analytical method development and validation [73–76], while the fifth was a PK study [77], which provided a brief summary of the method in use. These papers reported dalbavancin levels in serum or plasma, one of them also in urine [74], and another in skin blister fluid [77]. The total reported chromatographic run time ranged from 4.5 to 10 min. Four out of five papers have assessed dalbavancin stability.

Seraissol and colleagues (2022) [73] presented a method for extracting, separating and quantifying a wide range of analytes, including amoxicillin, piperacillin, cefazolin, cefepime, cefotaxime, ceftazidime, ceftolozane, ceftriaxone, ertapenem, meropenem, ciprofloxacin, moxifloxacin, levofloxacin, daptomycin, dalbavancin, linezolid and tazobactam. Given the differences in physicochemical properties of such a large panel of analytes, in order to optimize the chromatographic conditions in terms of separation and peak characteristics (shape, asymmetry), they divided the analytes in four groups and developed three different LC-MS/MS methods. Dalbavancin was analyzed simultaneously with ceftriaxone. Stability studies revealed that dalbavancin is stable in plasma samples stored for up to six hours at room temperature and up to three days at + 4 °C, and was stable in whole blood for up to 24 h stored at + 4 °C. Plasma samples spiked with dalbavancin were stable when stored at −20 °C and −80 °C for three months, but longer times were not evaluated. Long-term stability (256 days) was demonstrated by Alebic-Kolbah et al. (2011) [74]. Mula et al. (2023) [75] demonstrated that dalbavancin is stable in plasma up to 15 days and three months when stored, respectively, at −20 °C and −80 °C.

Barone et al. (2023) [76] developed a microsampling-based LC-MS/MS method which allows dalbavancin quantitation from only 3 μL of human plasma.

6. Oritavancin

Oritavancin, a novel lipoglycopeptide, exhibits bactericidal activity and a spectrum similar to that of vancomycin, making it a viable therapeutic alternative for the treatment of Gram-positive skin infections [78,79]. Moreover, multidose regimens of oritavancin are also used in clinical practice [80–82]. The bactericidal activity of oritavancin is concentration-dependent [80,83].The efficacy of oritavancin treatment is related to the C_{max}/MIC ratio that correlates well with efficacy [79]. A C_{max}/MIC ratio of 4 is recommended for the standard MRSA inoculum (5 x 105 cfu/mL), and a ratio of 16 for higher size inoculum (10^8 cfu/mL) [79]. Bhavnani and colleagues [84] first analyzed the PK/PD relationships describing the efficacy of oritavancin in patients with bacteremia in 2006, finding a relationship between drug exposure and microbiological response. The pooled analysis of the SOLO-I and SOLO-II trials suggests that the PK of oritavancin is not significantly affected by variations in patient age, renal function, weight, gender, or diabetes status [78,85], hence dose adjustment isn't required for patients affected by mild-to-moderate hepatic and/or renal impairment [78,79]. However, only one PK study mentioned an LC-MS/MS method for measuring oritavancin in plasma and skin blister fluid [86]. The reported lower limit of quantification (LLOQ) for skin blister fluid and plasma was 1.25 and 0.075 g/ml, respectively. Unfortunately, information on the extraction procedure, chromatographic and MS conditions, and method validation was not reported because of the clinical focus of the paper.

The scarcity of LC-MS/MS methods for oritavancin reported in the literature could be explained by the lack of indications for its TDM. Importantly, changes in oritavancin exposure in patients with severe hepatic and/or renal impairment have not been studied [78]. Moreover, since oritavancin is a relatively new drug, clinical practice may greatly vary from randomized clinical trials in terms of intra- and inter-individual pharmacokinetic variability. As such, monitoring levels under real-world conditions could be beneficial in determining the actual needlessness of TDM, especially in special populations and/or when multidose regimens of oritavancin are administered.

7. Telavancin

Telavancin, a semisynthetic derivative of vancomycin, exhibits concentration-dependent bactericidal activity against aerobic and anaerobic Gram-positive bacteria [5]. It was indicated for treating adults with nosocomial pneumonia (NP) caused or thought to be caused by MRSA, but marketing authorization has been withdrawn in Europe in 2018 [87]. This antibiotic works through two mechanisms: the inhibition of bacterial cell wall synthesis and inducing depolarization and permeabilization of the bacterial membrane [88]. Its bactericidal activity is concentration-dependent and correlates well with AUC_{24}/MIC [87–89]. Notably, telavancin has been found to increase serum creatinine levels and may potentially cause nephrotoxicity [88]. The recommended dose was 10 mg/kg/day for 7–21 days, with dose adjustments necessary special populations such as the elderly, those with renal impairment, or obese individuals [87,88,90,91]. Dose adjustment was not required for patients with mild or moderate hepatic impairment. However, there is no information available regarding patients with severe hepatic impairment [87]. A pediatric investigation plan (PIP) was approved by the European Medicines Agency (EMA) in 2017 [92] for treating complicated skin and soft tissue infections in patients under 18 years old. It should be noted that no LC-MS/MS method for assessing telavancin in human samples has been found in the literature.

8. Conclusion

In this manuscript, we have provided an overview of the LC-MS/MS methods available in the literature for TDM of glycopeptide antimicrobials. While several methods have been described for vancomycin, teicoplanin, and dalbavancin, there are currently no methods available for oritavancin and telavancin. Considering its PK and PD characteristics, TDM could prove useful for oritavancin clinical management.

CRediT authorship contribution statement

Alessia Cafaro: Conceptualization, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Sebastiano Barco:** Writing – review & editing. **Federica Pigliasco:** Writing – review & editing. **Chiara Russo:** Writing – review & editing. **Marcello Mariani:** Writing – review & editing. **Alessio Mesini:** Writing – review & editing. **Carolina Saffioti:** Writing – review & editing. **Elio Castagnola:** Conceptualization, Writing – review & editing. **Giuliana Cangemi:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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