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**Implementation and validation of a Bayesian method for accurately forecasting duration of optimal pharmacodynamic target attainment with dalbavancin during long-term use for treating subacute and/or chronic staphylococcal infections**

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## Abstract

Dalbavancin is being increasingly used for long-term treatment of subacute and/or chronic staphylococcal infections. Here we implemented and validated a new Bayesian model by means of the MwPharm software for accurately forecasting duration of pharmacodynamic target attainment above the efficacy thresholds of 4.02 or 8.04 mg/L against staphylococci. Forecasting accuracy improved substantially with the *a posteriori* approach compared to the *a priori* approach, especially when two measured concentrations were used. This strategy may help clinicians in estimating proper duration of optimal exposure with dalbavancin during long-term treatment.

## Introduction

Dalbavancin is a new long-acting lipoglycopeptide with high effectiveness against the vast majority of Gram-positive bacteria [1, 2]. Currently, it is licensed for the treatment of acute bacterial skin and skin structure infections (aBSSSI) with a single 1500 mg dose or with two separate doses of 1000 mg and 500 mg one week apart in patients with preserved renal function. The favorable pharmacokinetic and safety profiles are important features of dalbavancin compared to other anti-Gram positive antimicrobials. In particular, the long elimination half-life of approximately 14 days may ensure potentially adequate exposure lasting for several weeks. Consequently, dalbavancin use has been progressively extended recently to several off-label indications requiring long-term treatment, such as bone and joint infections, infective endocarditis and/or endovascular prosthetic infections [3]. In this regard, two population pharmacokinetic studies, one carried out among patients undergoing orthopedic prosthetic surgery [4, 5] and the other in patients with osteoarticular infections [4, 5], showed that a regimen of two 1500 mg doses one week apart may provide optimal target attainment against staphylococci, defined as a free  $AUC_{24h}/MIC$  ratio  $> 111.1$ , for up to 5-6 weeks.

Therapeutic drug monitoring (TDM) may be a valuable tool for optimizing long-term treatment with antimicrobials. In this regard, our group recently showed that targeting dalbavancin total plasma concentration at  $\geq 4.02$  mg/L or  $\geq 8.04$  mg/L may ensure high likelihood of attaining this target against staphylococci with an MIC value up to the  $MIC_{90}$  (0.0625 mg/L) or to the EUCAST susceptibility breakpoint (0.125 mg/L), respectively [6].

Bayesian modelling may represent an effective way for predicting duration of time during which dalbavancin concentrations may persist above these predefined threshold, especially considering that renal function may affect drug exposure. This might allow clinicians to forecast duration of optimal treatment during long-term use, and to assess at which time point dalbavancin should be redosed in the clinical need for prolonging treatment.

The aim of this study was to assess the accuracy and precision of a new Bayesian method for forecasting duration of optimal target attainment, defined as maintaining target plasma concentrations  $\geq 4.02$  mg/L and/or  $\geq 8.04$  mg/L, during long-term use for treating subacute and chronic infections.

## Methods

### Study design

The study was articulated in two phases. In the first phase, a new Bayesian model for dalbavancin was implemented on the basis of data coming from a previously published population pharmacokinetic study [3]. In the second phase, the implemented Bayesian model was validated in a different cohort of patients who received long-term dalbavancin treatment for different types of subacute and chronic infections.

#### 1. Implementation of a new Bayesian model for dalbavancin

A new Bayesian model for dalbavancin was implemented by means of the EdSim++ platform in the MwPharm++ software [7]. The implemented model was based on a two-compartment population pharmacokinetic model carried out among 69 patients receiving dalbavancin for the treatment of different staphylococcal subacute and/or chronic infections, which included estimated glomerular filtration rate (eGFR) as a covariate on drug clearance (CL) [3]. This population pharmacokinetic model was selected because it was the largest based on real-world TDM data and included patients having different types of infection. The following population pharmacokinetic estimates (inter-individual variability, %CV) were included: CL of 0.041 L/h (31.76), V1 of 6.150 L (16.10), V2 of 10.510 L (37.19) and Q of 0.026 L/h (45.06). The relationship between dalbavancin CL and eGFR, which was calculated by means of the CKD-EPI formula [8], was parameterized as follows:  $CL = 0.029 \times e^{0.0043 \times eGFR}$ . The eGFR of the included patients ranged from 3 to 141 mL/min/1.73 m<sup>2</sup>. The developed model offered the opportunity of obtaining in each single patient different dalbavancin pharmacokinetic profiles, namely those obtained by means of the *a priori* approach based only on demographics and dosing data, and those obtained by means of the *a posteriori* or *Bayesian* approach based also on the measured drug concentrations other than on demographics and dosing data.

#### 2. Validation of the new Bayesian model for dalbavancin

Validation of the developed Bayesian model was performed in a new cohort of patients with similar demographic and clinical characteristics. The validation cohort included retrospectively patients who received, in the period between May 2022 and February 2023, long-term treatment with dalbavancin for different types of infections and underwent TDM of dalbavancin at the IRCCS, Azienda Ospedaliero-Universitaria di

Bologna, Italy. The local Ethics Committee approved the study (registration number 897/2021/Oss/AOUBo). Patient informed consent was waived due to the retrospective and observational nature of the study according to the hospital agreements. All of the patients received an initial treatment regimen based on two 1500 mg doses of dalbavancin one week apart. TDM of dalbavancin was performed for assessing duration of optimal treatment after completing the initial dosing regimen and according to a predefined scheme, [5]. The first TDM assessment was performed on day  $21 \pm 3$ ,  $28 \pm 3$  or  $35 \pm 3$  depending on the patient's eGFR classes of 90-120, 60-89 and 30-59 mL/min/1.73 m<sup>2</sup>, respectively [5].

Each patient TDM result along with demographic data (age, weight, height), eGFR, which was calculated by means of the CKD-EPI formula [8], and dosing history were fitted with the new Bayesian model for forecasting the duration of dalbavancin concentrations above the threshold of 4.02 or 8.04 mg/L. These values were previously identified to ensure high likelihood of optimal target attainment with dalbavancin against staphylococci, namely a free  $AUC_{24h}/MIC$  ratio  $> 111.1$  against pathogens with an MIC value up to the  $MIC_{90}$  (0.0625 mg/L) or to the EUCAST susceptibility breakpoint (0.125 mg/L), respectively] [6]. The free fraction of total dalbavancin concentration was estimated by considering a plasma protein binding of 93%, as reported in the literature [6]. On a case-by-case approach, whenever clinically needed (persistence of positive C-reactive protein and/or of clinical signs/symptoms of infection) and concentration dropped below these thresholds, additional dalbavancin doses were administered and additional TDM assessments were performed.

The goodness-of-fit of the prediction was evaluated by means of the coefficient of determination ( $r^2$ ) of the observed versus the population-predicted concentrations or of the observed versus the individual-predicted concentrations, of the weighted residuals (WRES) versus the predicted concentrations and of the WRES versus time. The residuals should not have any visual trend to be considered good enough. Bias and precision were estimated by calculating the mean percentage error (*mpe*) and the root mean squared percentage error (*rm spe*), respectively, as follows:

$$mpe(\%) = \frac{\sum_{i=1}^N pe}{N} \times 100$$

$$rm spe(\%) = \sqrt{\frac{\sum_{i=1}^N pe^2}{N}} \times 100$$

where N is the number of observed ( $C_{\text{obs}}$ ) and predicted concentration ( $C_{\text{pred}}$ ) pairs and  $pe$  is the prediction error calculated as  $pe = (C_{\text{obs}} - C_{\text{pred}})/C_{\text{obs}}$ .

The  $mpe$  is a measure of the estimate 's bias, namely the percentage errors by which forecasts of the model differ from actual values (over- and/or under- estimation). The  $rm spe$  is a measure of accuracy of prediction, namely the percentage of variation in the prediction.  $Mpe$  and/or  $rm spe$  values of  $\pm 15$ -20% were considered as acceptable [9].

Both in the *a priori* and in the *a posteriori* approach, each concentration-time profile estimate, together with the correspondent 95% confidence interval (CI) was automatically calculated at pre-defined time points by the MwPharm software. The distribution of the 95% CI widths of the dalbavancin plasma concentration estimates around the estimated values of 4.02 mg/L and 8.04 mg/L, namely the two efficacy thresholds, were considered as an indicator of the overall uncertainty of the *a priori* approach vs. the *a posteriori* approach.



## Results

A total of 67 patients were included in the validation cohort and contributed with 177 dalbavancin concentrations. Patient demographics and clinical characteristics are summarized in Table S1. Median (IQR) age and eGFR were 63.2 (48.5 - 75.9) years and 95.3 (66.2 – 107.6) mL/min/1.73 m<sup>2</sup>. Osteoarticular infections were the main indications for dalbavancin use (73.1%, 49/67 patients). Most of the patients (74.6%, 50/67) received two or three 1500 mg dalbavancin doses, and the median (IQR) number of TDM instances per patients was 2 (1 – 3.5). The demographic and clinical characteristics of the validation cohort were very similar to those of the development cohort (Table S1).

The predictive performances of the *a priori* and the *a posteriori* approaches are shown in Figures S1 and S2, and summarized in Table 1. Both approaches showed high correlation between the observed and the predicted concentrations ( $r^2$  of 0.88 and 0.95, respectively), and no trend emerged in the distribution of the WRES, neither versus the population predicted concentrations nor versus time. Notably, the *a posteriori* approach performed much better compared to the *a priori* approach in terms of both bias ( $mpe = -1.65\%$  vs.  $13.70\%$ ) and precision ( $rmse = 16.10\%$  vs.  $52.84\%$ ).

Figure 1 depicts the distributions of the widths of the 95% CI for the two efficacy thresholds estimated by means of the population prediction and of the individual prediction among patients receiving two or three 1500 mg doses of dalbavancin. When passing from the *a priori* approach to the *a posteriori* approach based on 1 or 2 concentration measurements, the width of the 95% CI decreased from 12.54 mg/L to 5.23 mg/L and to 1.16 mg/L, respectively, for the 8.04 mg/L threshold, and from 11.73 mg/L to 6.99 mg/L and to 1.84 mg/L, respectively, for the 4.02 mg/L threshold.

Figure 2 shows the dalbavancin pharmacokinetic profiles estimated by means of both the *a priori* and the *a posteriori* approaches in one typical patient (43 years old, weight 77 kg, eGFR 110 mL/min/1.73 m<sup>2</sup>) receiving two 1500 mg dalbavancin doses one week apart. It's worth noting that the width of the 95% CI progressively narrowed when passing from the *a priori* approach, to the *a posteriori* approach based on 1 measured concentration and to the *a posteriori* approach based on 2 measured concentrations, respectively. In particular, on day 21 the narrowing of the width was of 3.5-fold for the *a posteriori* approach based on 1 measured concentration vs. the *a priori* approach and of further 1.19-fold for the *a posteriori* approach based on 2 measured concentrations vs. that based on 1 measured concentration, respectively. Similarly, comparison

on day 35 the narrowing of the width was of 2.5-fold for the *a posteriori* approach based on 1 measured concentration vs. the *a priori* approach and of further 2.4-fold for the *a posteriori* approach based on 2 measured concentrations vs. that based on 1 measured concentration, respectively.

Figure S3 depicted the distribution of each patient individual CL. Median CL of the population was 0.029 L/h, and ranged from 0.018 to 0.051 L/h (inter-individual CV of 20.02 %). Illustrative examples of individual-predicted concentrations in patients receiving different dalbavancin dosing regimens for long-term treatment are depicted in Figure S4.

## Discussion

This study first developed and validated a Bayesian method for accurately estimating duration of optimal target attainment with dalbavancin during long-term use by means of the precision dosing software MwParm. Accuracy in forecasting duration of dalbavancin concentrations above the threshold of efficacy substantially improved when adopting the *a posteriori* approach compared to the *a priori* approach, especially when two measured concentrations were used.

Precision dosing programs are useful tools for optimizing antimicrobial dosing, as extensively reviewed elsewhere [10, 11]. Most of these programs implement Bayesian prediction, which is particularly convenient in routine clinical practice because of either the limited required number of samples or of the flexibility in sampling times. Clinical application of these softwares was successfully implemented both for drugs with high inter-individual pharmacokinetics variability, such as voriconazole [12] or piperacillin [13] and for those with narrow therapeutic indexes, such as the aminoglycosides [14] or vancomycin [15].

In regard to dalbavancin, the need for implementing a Bayesian approach arises mainly from the very-long elimination half-life, namely more than two weeks, which may render especially difficult to predict for how long drug levels may persist above a predefined threshold of efficacy during long-term use. Our findings showed that the *a posteriori* approach performed better than the *a priori* approach. This is in agreement with the findings of Chai et al. who showed a better accuracy of the *a posteriori* approach in predicting piperacillin and meropenem concentrations in critically ill patients with the ID-ODS program [16].

In regard to the number of sampling needed for obtaining an accurate prediction in the *a posteriori* approach, Felton et al. showed that the predictive performance of the *a posteriori* approach by means of the software BestDose was acceptable in predicting piperacillin concentrations among 7 out of 8 critically ill patients when the number of concentrations was at least of two [13]. This is in agreement with our findings and may be explained by the fact that in non-linear mixed-effects models, like the one used for developing this Bayesian model, a minimum of two samples is required for effectively separating residual variability from inter-individual variability. This supports our contention that including two samples 2-week apart after completing the initial treatment may provide reliable estimates of duration of concentrations above the efficacy thresholds.

The clinical usefulness of a reliable Bayesian method for dalbavancin could appear limited when considering the licensed indication with single dosing regimen in patients with aBSSSI. In this regard, we previously showed that a single 1500 mg dosing regimen may ensure high likelihood of optimal probability of target attainment for two weeks, namely the required duration of treatment [17, 18]. However, nowadays dalbavancin is being increasingly used for the long-term treatment of various staphylococcal subacute and/or chronic infections or even for suppressive therapy in case of inoperable staphylococcal prosthetic-related infections [17]. In this setting, our Bayesian method, by reliably forecasting the duration of dalbavancin concentrations above the efficacy thresholds, could reveal helpful for clinicians both in determining duration of optimal treatment or in guiding the time point for redosing in the clinical need of prolonging treatment once that dalbavancin concentration will drop below this threshold. In this regard, according to our previous population pharmacokinetic model, a valuable workflow for assessing TDM could be between day 21 and 35 depending on the patients' eGFR [3]. A recent expert opinion panel on dose regimen and therapeutic drug monitoring for long-term use of dalbavancin stated that the role of TDM could be especially valuable for treatment lasting more than 6 weeks and/or in cases of renal failure [18]. This could be especially the case when treating osteo-articular infections, endocarditis, or implant associated infections. The good fitness observed in the illustrative examples regarding patients receiving multiple dalbavancin dosing regimens may support the reliability of the model even in very long-term treatment. Additionally, the inclusion of eGFR in the model may provide forecasting accuracy in individualizing treatment even in patients with renal dysfunction.

We recognize that our study has some limits. The potential impact of hypoalbuminemia could not be ruled out in the model since none of the patient included in the aforementioned population pharmacokinetic model was severely hypoalbuminemic. Measuring unbound other than total drug moiety could be helpful to address this issue [19]. We cannot exclude that the sparse number of patient samples may have underestimated interpatient variability in dalbavancin CL. We cannot guarantee that our model could adequately perform even in critically ill patients with unstable clinical conditions.

In conclusion, our findings showed that the newly developed Bayesian model is accurate and precise and may allow reliable forecasting of duration of dalbavancin concentrations above the efficacy thresholds of

$\geq 4.02\text{mg/L}$  or  $\geq 8.04\text{mg/L}$ . Implementing this strategy may be beneficial for properly managing long-term treatment with dalbavancin. Prospective studies in real-life are warranted for confirming the reliability and clinical usefulness of this approach, especially in the context of targeted therapy when pathogen MIC is available.

## **Fundings**

No funding. This study was carried out as part of our routine work

## **Ethical approval**

The local Ethics Committee approved the study (registration number 897/2021/Oss/AOUBo).

## **Competing Interests**

PG. Cojutti and M. Gatti have received personal fees from Angelini and Shionogi. N. Punt is president of Medimatics, a company that provides consulting services on medical information systems located in Maastricht, The Netherlands. J. Douša is technical advisor at Mediware, the company that distributes Edsim++ and MwPharm++ located in Prague, Czech Republic. F. Pea participated in speaker bureau for Advanz Pharma, Angelini, BeiGene, Gilead, InfectoPharm, Menarini, Merck Sharp & Dohme, Pfizer, and Shionogi, and in advisory board for Advanz Pharma, bioMerieux, Merck Sharp & Dohme and Pfizer. P. Viale has served as a consultant for bioMerieux, Gilead, Merck Sharp & Dohme, Nabriva, Nordic Pharma, Pfizer, Thermo-Fisher, and Venatorx, and received payment for serving on the speaker's bureau for Correvio, Gilead, Merck Sharp & Dohme, Nordic Pharma and Pfizer. Other authors: none to declare.

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**Table 1.** Predictive performances of the developed method in the validation cohort (n = 177 concentrations)

Type of estimation	$r^2$	Bias		Precision	
		<i>mpe</i> (%)	95% CI	<i>rm spe</i> %	95% CI
<i>A priori</i> approach	0.88	-13.70	-21.3 – 6.09	52.84	34.49 – 66.26
<i>A posteriori</i> approach	0.95	-1.65	-4.04 – 0.74	16.10	13.82 – 18.08

*CI*, confidence interval; *mpe*, mean prediction error; *rm spe*, root mean squared prediction error



**Table S1.** Population characteristics of the development and validation cohorts

Parameter	Development cohort (n=69) [3]		Validation cohort (n=67)	
	Value	25-75 IQR or (%)	Value	25-75 IQR or (%)
Age (years)	62	51 - 73	63.2	48.5 - 75.9
Gender (male/female)	44/25		48/19	71.6/28.3
Weight (kg)	75	62 - 88	75	65 - 84.5
Height (m)	1.70	1.65 - 1.77	1.70	1.65 - 1.79
eGFR (mL/min/1.73m <sup>2</sup> )	93.0	72.0 - 104.0	95.3	66.2 - 107.6
Type of infections				
Prosthetic joint infection	26	37.7	26	38.8
Osteomyelitis	11	15.9	10	14.9
Spondylodiscitis	5	7.2	9	13.5
Endocarditis	7	10.1	9	13.5
Endovascular prosthetic infection	8	13.0	9	13.5
Infected pseudoarthrosis	4	5.8	2	2.9
Septic arthritis	1	1.5	2	2.9
Number of TDM instances per patient	3	2 - 5	2	1 - 4

Data are presented as median (IQR) for continuous variables, and as number (%) for dichotomous variables. eGFR, estimated glomerular filtration rate; TDM, therapeutic drug monitoring.

## Figure legend

### Figure 1

Comparison of the prediction performances of the *a priori* and *a posteriori* approaches. The plotted bars represent the widths of the 95% confidence intervals for the estimated concentration at the efficacy thresholds of 8.04 mg/L (squared) and 4.02 mg/L (circle) by means of the population predictions (red), the individual prediction based on 1 measured concentration (blue) and the individual prediction based on 2 measured concentrations (green) among the 56 patients of the validation cohort who received two or three 1500 mg doses of dalbavancin. This plot shows how the *a posteriori* approaches outperformed the *a priori* approach. The horizontal dotted lines identify concentrations at 8.04 and 4.02 mg/L.

### Figure 2

*A priori* population-predicted (A) and *a posteriori* individual-predicted based on 1 sample (B) and 2 samples (C) dalbavancin plasma concentrations with relative 95% confidence intervals, following administration of 1500 mg at day 1 and 1500 mg at day 8 in a male patient (43 years old, weight 77 kg, eGFR 110 mL/min/1.73 m<sup>2</sup>). Plasma concentration for individual predictions were assessed at day 21 and 35. The dashed and the dotted lines represent the threshold of efficacy of 8.04 and 4.02 mg/L for empirical therapy against *S. aureus*. Squared symbols identifies measured individual dalbavancin plasma concentrations.

### Figure S1

Diagnostic plots for the observed vs. population-predicted concentrations (A), weighted residuals vs. population-predicted concentrations (B) and weighted residuals vs. time (C). Solid line refers to linear regression between the observed and the predicted concentrations. Dashed lines refer to the identity lines.

### Figure S2

Diagnostic plots for the observed vs. individual-predicted concentrations (A), weighted residuals vs. individual-predicted concentrations (B) and weighted residuals vs. time (C). Solid line refers to linear regression between the observed and the predicted concentrations. Dashed lines refer to the identity lines.

### Figure S3

Distribution of the Bayesian-estimated individual values of clearance of each patient. Dashed line refers to the median population value (0.029 L/h).

### Figure S4

Individual-predicted dalbavancin plasma concentrations with relative 95% confidence intervals in four illustrative patients. Patient A (male, 59 years, 90 kg) receiving six dalbavancin doses for treating septic arthritis and undergoing five TDM assessments. Patient B (male, 76 years, 84 kg) receiving five dalbavancin doses for suppressive therapy of infected vascular aortic endoprosthesis and who had five TDM assessments. Patient C (male, 69 years, 77 kg) receiving seven dalbavancin doses for suppressive therapy of infected ventricular assist device and had eight TDM assessments. Patient D (male, age 66 years, 102 kg) with impaired renal function (mean eGFR of 26 mL/min/1.73 m<sup>2</sup>), receiving seven dalbavancin doses for suppressive therapy of infected endovascular prosthesis and had ten TDM assessments. The dashed and the dotted lines represent the threshold of efficacy of 4.02 and 8.04 mg/L for empirical therapy against *S. aureus*.













