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# Expert Opinion on Dose Regimen and Therapeutic Drug Monitoring for Long-Term Use of Dalbavancin: Expert Review Panel

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ABSTRACT

*Background:* Dalbavancin is a lipoglycopeptide with a long elimination half-life and is currently licensed for the treatment of acute bacterial skin and skin structure infections in adults. Dalbavancin's potential in treating off-label complex Gram-positive infections is promising and real-world experience in treating such infections is growing. However, clear guidance on extended dosing regimens is lacking.
*Objectives:* This study aimed to provide clear expert opinion based on recent pharmacokinetic literature and expert and real-world experience in infection areas that require > 2 weeks of treatment.
*Methods:* A single face-to-face meeting was held in September 2022 to collate expert opinion and present safety data of dalbavancin use in these clinical indications. A survey was completed by all authors on their individual experience with dalbavancin, which highlighted the heterogeneity in the regimens that were used.
*Results:* After review of the survey data and recent literature, this study presents expert panel proposals that accommodate different healthcare settings and resource availability, and centre around the length of treatment duration including up to or exceeding 6 weeks. To achieve adequate dalbavancin concentrations for up to 6 weeks, 3000 mg of dalbavancin should be given over 4 weeks for the agreed complex infections requiring > 2 weeks of treatment. Therapeutic drug monitoring (TDM) is advised for longer treatment durations and in cases of renal failure. Specific dosing recommendations for other special populations require further investigation.
*Conclusions:* These proposals based on expert opinion have been defined to encourage best practice with dalbavancin, to optimise its administration beyond the current approved licenced dose across different healthcare settings.



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## 1. Introduction

Dalbavancin was approved by the Food and Drug Administration (FDA) in 2014 and European Medicines Agency (EMA) in 2015. Dalbavancin is a semisynthetic lipoglycopeptide derived from a teicoplanin-like antibiotic [1]. Dalbavancin exerts antimicrobial activity mainly through interaction with terminal D-alanyl-D-alanine residues of peptidoglycan precursors [2], which prevent both transpeptidase and transglycosylase enzyme activity [3,4]. The blockade of the catalysing peptidoglycan cross-linking process results in alterations in the bacterial cell wall integrity and cell death [5]. The addition of a lipophilic side chain enables dimerisation of the molecule and enhances dalbavancin anchoring to lipid II in the cellular membrane and adherence to the target site, prolonging its half-life and significantly increasing dosing intervals [5,6]. In addition, dalbavancin lipophilic side chains reduce the risk of cross-sensitivity to vancomycin [7]. Dalbavancin also has an amidated carboxyl side group responsible for enhanced anti-staphylococcal activity.

Dalbavancin is only approved for treating acute bacterial skin and skin structure infections in adults and is administered intravenously (IV) either as a 1500 mg single infusion or 1000 mg dose followed by 500 mg one week later [3,8]. Dalbavancin demonstrates a long terminal elimination half-life of approximately 14.4 days, extensive plasma-protein binding, good tissue penetration and a favourable safety profile [8–11]. Dalbavancin does not require dose adjustments for mild to moderate renal dysfunction and patients on chronic haemodialysis. The recommended dose is reduced by 25% for patients with severe renal dysfunction (creatine clearance $< 30$ mL/min/1.73m$^2$) [3,9].

Dalbavancin demonstrates activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate *Staphylococcus aureus* (*S. aureus*), multidrug-resistant (MDR) coagulase-negative staphylococci and VanB-producing vancomycin-resistant enterococci [9,12,13]. Staphylococcal and streptococcal species, particularly *S. aureus*, are the most common Gram-positive species implicated in bone and joint infections (BJIs), prosthetic joint infections (PJIs) and infective endocarditis (IE) [14,15]; these are complex infections that are not covered by the current dalbavancin license.

Considering its activity against Gram-positive cocci, including MDR strains, the long half-life and favourable safety profile, dalbavancin represents a potential alternative to daily IV antibiotic administration and prolonged hospitalisation for patients with BJIs, IE, PJIs and vascular graft infections (VGIs) [8,16]. This is of particular interest in the context of centres with limited inpatient resources and where there is a need to improve patient flow through acute care hospitals [17]. Dalbavancin could therefore be a useful addition to outpatient parenteral antimicrobial therapy (OPAT) services in these settings [18].

Experience of the prolonged use of dalbavancin in these complex infections is growing, with published case series providing favourable clinical results [8,14,19–24]. While the first administered dose is almost constantly 1500 mg and the second 1500 mg or 1000 mg, the use of lower doses (e.g. 500 mg) as weekly additional doses tends to be replaced over time by higher doses with larger intervals (Table 1). However, it is notable that the dosing strategies used in these reports vary and there are no clear recommendations or published guidance on extended dosing regimens to date.

To address this unmet need, the current authors reviewed recent pharmacokinetic (PK) literature, including a study focusing on pharmacokinetic-pharmacodynamic (PK-PD) targets validated against MRSA only, to propose potential regimens to prolong the treatment beyond the approved licensed dosing regimen [25]. The scope of this guidance refers to dalbavancin treatment lasting $> 2$ weeks.

## 2. Materials and methods

A group of invited experts participated in a single face-to-face meeting in September 2022. The invited experts were identified by the highest scores, according to the ADVANZ PHARMA internal healthcare professional tiering calculator, with excellent professional reputations as key opinion leaders with significant experience with dalbavancin. The purpose of this meeting was to collate expert opinion on the use of dalbavancin in clinical practice. The meeting included a review of the safety profile and PK-PD profile of dalbavancin, and feedback from an online survey completed by all authors (Appendix A) on individual experience using prolonged dosages of dalbavancin for the complex infections listed in Box 1. No follow-up meetings were required.

**Box 1**. Type of complex infections eligible for off-label dalbavancin use.

- Infective endocarditis (IE)
- Bone and joint infections (BJIs)
- Prosthetic joint infections (PJIs)
- Vascular graft infections (VGIs)
- Catheter-related bacteraemia and other Gram-positive biofilm-related infections

## 3. Results

The authors aimed to identify clinical indications where dalbavancin treatment can be prolonged beyond the approved licenced dose and to optimise its administration. All 11 authors (representing six European countries) completed the survey. The presentation of preliminary questionnaire results and existing literature confirmed the heterogeneity of dalbavancin dosing regimens (Figure 1), and therapeutic drug monitoring (TDM) use across countries and clinical settings, highlighting the need for clear guidance [20]. Despite heterogeneity in specific dosing schedules among authors, the total administered dose (3000 mg) within 4 weeks (Days 1–29) was unanimous amongst all authors' preliminary questionnaire results across all considered infection types.

The authors identified the off-label indications (Box 1) where dalbavancin is most frequently reported in the literature and used in clinical practice. Advisors agreed that the proposed recommendations would be appropriate in these clinical indications.

### 3.1. Dosing

The authors acknowledge previously described dosing regimens for the prolonged use of dalbavancin (Table 1) and appreciate the need for flexibility in a recommended dalbavancin dosing schedule for special populations and healthcare infrastructure [8,26]. There is recognised variability across Europe in the availability of OPAT services and resource availability for specialist follow-up and monitoring.

The results of the Phase 2b study by Rappo et al. of dalbavancin in osteomyelitis (PJIs were excluded from this study) against standard of care found that 1500 mg on Day 1 and Day 8 provided antibiotic coverage for 6 weeks and was well tolerated [21]. However, this study was open label with a small and potentially underpowered standard of care comparator group. All patients underwent surgical debridement, biopsy and culture, regardless of the presence of necrotic bone, which was found in 60% of patients.

**Table 1**
Examination of existing case studies and off-label uses of dalbavancin.

| Reference, year | Patient population (*n*) | 1st dose (*n* cases) | 2nd dose and interval (*n* days) | Pathogen(s) (%) | Withdrawal for adverse event | Success rate (%) |
|---|---|---|---|---|---|---|
| [21], 2018 | Osteoarticular infection (40) | 1500 mg<br>*N* doses: 2 | 1500 mg (7) | Staphylococci (68.6%)<br>Enterococci (11.4%) | None | 94% |
| [17], 2019 | Endocarditis and/or blood stream infections (83) | 1500 mg (38)<br>1000 mg (42)<br>*N* doses: 2–10 | 1000 or 1500 mg<br>Additional doses:<br>1000 mg (14)<br>500 mg (8) | Staphylococci (> 70%) | None | 100% |
| [14], 2021 | Implant-associated infection (64, including 19 osteomyelitis) | 1500 mg (12)<br>1000 mg (50)<br>*N* doses: 3–7 | 500 mg (7) | Staphylococci (68.8%) Methicillin resistance in 93.3% | None | 73.6%<br>Improvement: 15.7% |
| [23], 2021 | Prosthetic joint infections (17) | 1500 mg (15)<br>1000 mg (2)<br>*N* doses: 2–10 | 1000 mg (7)<br>500 mg (14) | Staphylococci (16/17) | None | 73.1% |
| [23], 2021 | Bone and joint infections (15) | 1500 mg<br>*N* doses: 2 | 1500 mg (7) | Staphylococci (12/15) | None | 87% |
| [30], 2022 | Osteomyelitis (42) | 1500 mg<br>*N* doses: 2 | 1500 mg (7) | Staphylococci (78.6%) | None | 78.6% |
| [31], 2022 | Prosthetic joint infections (89) | 1500 mg (89)<br>*N* doses: 2 | 1500 or 1000 mg (?) | Staphylococci (46.1%)<br>*Cutibacterium* spp. (11.3%) | None | 77.5% |
| [8], 2023 | Osteoarticular infections (17) | 1500 mg<br>*N* doses: 2 | 1500 mg (7)<br>Additional doses:<br>1500 mg (28–54) | Staphylococci (all) | None | 100% |
| [32], 2023 | Infective endocarditis (124) | 500 mg (1)<br>750 mg (2)<br>1000 mg (55)<br>1500 mg (66)<br>*N* doses: 1–2 | 500 mg (8) or 1500 mg (15) | Staphylococci (62.1%), *Enterococcus faecalis* (19.4%), *Streptococcus* spp. (9.7%), *Enterococcus faecium* (2.4%), *Abiotrophia defectiva* (0.8%) and *Enterococcus casseliflavus* (0.8%) | None | 95.9% |

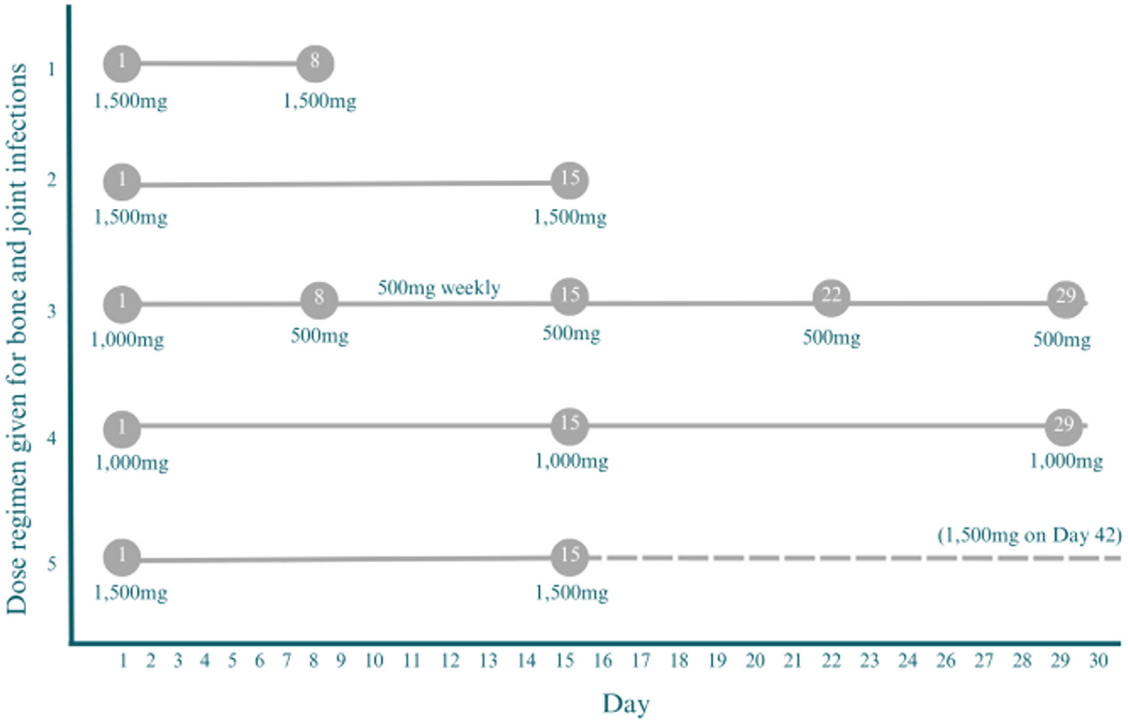


**Figure 1.** Example of the preliminary questionnaire results of the given dose regimens used by authors in bone and joint infections only. This example highlights the heterogeneity of the dose regimens in use.

Dunne et al. described the PK-PD for two dosage regimens of dalbavancin in osteomyelitis. The authors postulated that the efficacy of drugs with a long half-life, such as dalbavancin, are enhanced by providing higher doses earlier in the course of therapy and concluded that a regimen of 1500 mg on Day 1 and 1500 mg on Day 8 may be associated with better clinical outcomes than a regimen of 1000 mg on Day 1 and weekly dosing of 500 mg [26].

Cojutti et al. reported in their population PK analysis of dalbavancin that a two-dose regimen of 1500 mg on Day 1 and Day 8 produced efficacy against *S. aureus* for up to 5 weeks in BJIs, dependent on the patients' renal function, which also supported findings from Dunne et al. [25,26].

Data from systematic literature reviews corroborate the studies highlighted with efficacy shown in complex infections using a 3000 mg regimen over a 4-week period [27,28].

**Table 2**
*f*AUC 0-24/MIC ratios for different MIC values (target value for 2-log kill = 110) [33].

| Weeks after the 2nd or subsequent 1500 mg injection | *f*AUC/MIC MIC = 0.03 | *f*AUC/MIC MIC = 0.06 (i.e. *S. aureus* $MIC_{90}$) | *f*AUC/MIC MIC = 0.125 (i.e. *S. aureus* breakpoint) | *f*AUC/MIC MIC = 0.250 (i.e. PK/PD breakpoint) |
|---|---|---|---|---|
| 2 | 1232 | 615 | 296 | **148** |
| 3 | 1064 | 532 | **256** | **128** |
| 6 | 728 | **364** | **175** | **88** |

Data in bold indicate circumstances where dalbavancin concentration could be useful. *f*AUC0-24h were derived from concentrations assuming a plasma protein binding of 93% (cf. product information).

The authors agreed that dosing can be modified according to the healthcare setting, need for regular clinical review and predicted duration of therapy. This may be useful for some patient groups if weekly monitoring of progress/review opportunities for IV to oral switch therapy is required, for example in the supervised OPAT setting [29].

### 3.2. Expert Panel Proposals on Dosing Regimen

The best PD predictor of the bactericidal activity of dalbavancin is the $fAUC_{24}$/MIC ratio, and data from animal models show that the mean *f*AUC/MICs for net stasis, 1-log kill and 2-log kill are 27.1, 53.3 and 111.1, respectively [33]. Thus, TDM of dalbavancin can be considered alongside calculation of the $fAUC_{24}$/MIC ratio. Determination of dalbavancin MIC of *S. aureus* or other isolated microorganisms should be performed by broth microdilution. The so called "trough" concentration measured at Day 28, or Day 35 or more can be used to evaluate the 24-hour AUC according to the very extended half-life exhibited by dalbavancin. Thus, the calculated *f*AUC/MIC ratio may be compared with the 2-log kill target value of 110 [34], which correlates with a 2-log reduction of inoculum in animal infection models.

In a French real-life experience (Hervochon C, 2023 [unpublished data, submitted for publication]), measured concentration values were obtained at various times after the second or subsequent 1500 mg dose of dalbavancin at Day 0 and Day 15 (Table 2) [35]. The data show the importance of the dalbavancin MIC for a given strain when deciding on whether or not to measure dalbavancin concentration. Not all healthcare sites are able to perform TDM, but most sites have suitable facilities to measure dalbavancin.

As can be seen in Table 2, the "safety margin" obtained by comparison with the PK/PD target is directly related to the MIC. Where the MIC value is up to 0.06 mg/L ($MIC_{90}$) and up to the sixth week after the second or subsequent 1500 mg injection, the value of *f*AUC/MIC (364–532) is far above the target value and thus it could be decided that TDM could be unnecessary according the "safety margin". When MIC = 0.125 mg/L, at the third week after the second or subsequent 1500 mg injection, TDM could be necessary according to the usual variability of dalbavancin PK and uncertainty of drug and MIC measurement, even with an *f*AUC/MIC value of 256 (2.5 times the target value). With an MIC of 0.03 mg/L, the target value is reached up to the sixth week and TDM could be unnecessary. Finally, if strains are without specific breakpoints and can be evaluated by the PK/PD breakpoint (MIC of 0.250 mg/L) as specified by EUCAST recommendations, the TDM seems to be unavoidable.

It has been suggested that a trough serum concentration of dalbavancin > 8.04 mg/L is associated with a high probability of this target attainment against *S. aureus* with an MIC up to the EUCAST clinical breakpoint of susceptibility for dalbavancin (0.125 mg/L) [36]. Considering this data and the real-world experience with dalbavancin in complex infections—including BJIs, PJIs, IE, VGIs and catheter-related bacteraemia—the authors propose the following scenarios and potential regimens to guarantee the most adequate exposure beyond the first 2 weeks:

1. **If treatment with dalbavancin is expected to last a maximum of 6 weeks**

In therapy areas that would only require a maximum of 6 weeks treatment, 3000 mg of dalbavancin over 4 weeks is recommended to provide cover for 4–6 weeks. This includes medically treated infections such as infectious endocarditis, acute osteomyelitis and diabetic foot osteomyelitis. The authors would consider administering a theoretically equivalent one of the following regimens (Figure 2):

a. 1500 mg on Day 1 and 1500 mg on Day 15.
b. 1500 mg on Day 1 and 1500 mg on Day 8.
c. If the healthcare setting allows and encourages weekly monitoring, 1000–1500 mg on Day 1 and 500 mg weekly from Day 8 up to 6 weeks.

2. **If treatment with dalbavancin is expected to last more than 6 weeks**

If available, TDM is advised for treatment lasting beyond 6 weeks, to accommodate for the high variability in the serum concentration of dalbavancin [37]. For therapy areas such as PJIs, VGIs and BJIs, where treatment with dalbavancin is often expected to exceed 6 weeks, the authors would consider administering a theoretically equivalent one of the following initial regimens:

a. 1500 mg on Day 1 and 1500 mg on Day 15.
b. 1500 mg on Day 1 and 1500 mg on Day 8.
c. If the healthcare setting allows and encourages weekly monitoring, 1000–1500 mg on Day 1 and 500 mg weekly from Day 8 up to 6 weeks.

In this clinical scenario, TDM should guide the timing of the subsequent dose of dalbavancin (beyond 3000 mg), detect underdosing and consequently also reduce cost to healthcare systems. The literature supports initiation of TDM between Day 28 and Day 35, dependent on renal function and also likely on weight (Figure 3) [25]. The authors suggest that if the blood serum concentration of dalbavancin is > 8 mg/L, TDM should be repeated in 1 weeks. If the blood serum concentrations of dalbavancin is < 8 mg/L, the next dose of dalbavancin should be given.

3. **If treatment with dalbavancin is expected to last more than 6 weeks and TDM is unavailable within the healthcare setting**

Therapeutic drug monitoring availability significantly varies across different healthcare settings. However, the authors are unaware of any study reporting dalbavancin intolerance related to overexposure (Table 1), including in vancomycin allergic patients [38]. Therefore, for therapy areas where treatment is predicted to exceed a duration of 6 weeks, the authors suggest the following dose regimens in the absence of TDM (Figure 4):

a. 1500 mg on Day 1, 1500 mg on Day 15 and 1500 mg on Day 43 to provide treatment coverage for 12 weeks.
b. 1500 mg on Day 1, 1500 mg on Day 8 and 1500 mg on Day 43 to provide treatment coverage for 12 weeks.

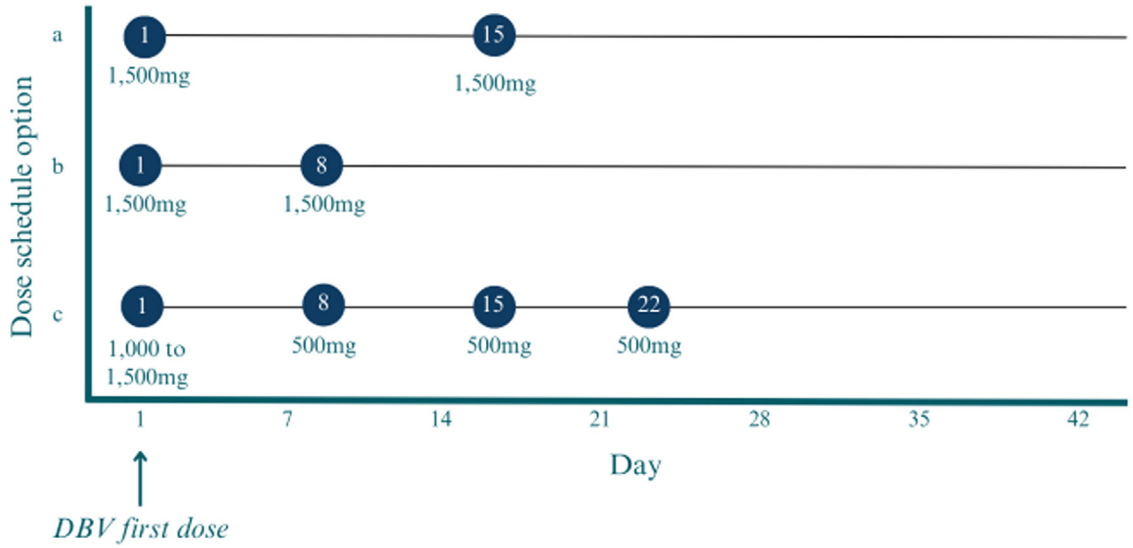


**Figure 2.** Dose regimens for clinical scenarios where the expected duration of dalbavancin (DBV) treatment is a maximum of 6 weeks. Day 1 is the first day of treatment with dalbavancin. A total of 3000 mg dalbavancin should be administered by week 4 to provide treatment cover for 4–6 weeks, with flexibility in the choice of dose regimen to meet the needs of the healthcare setting.

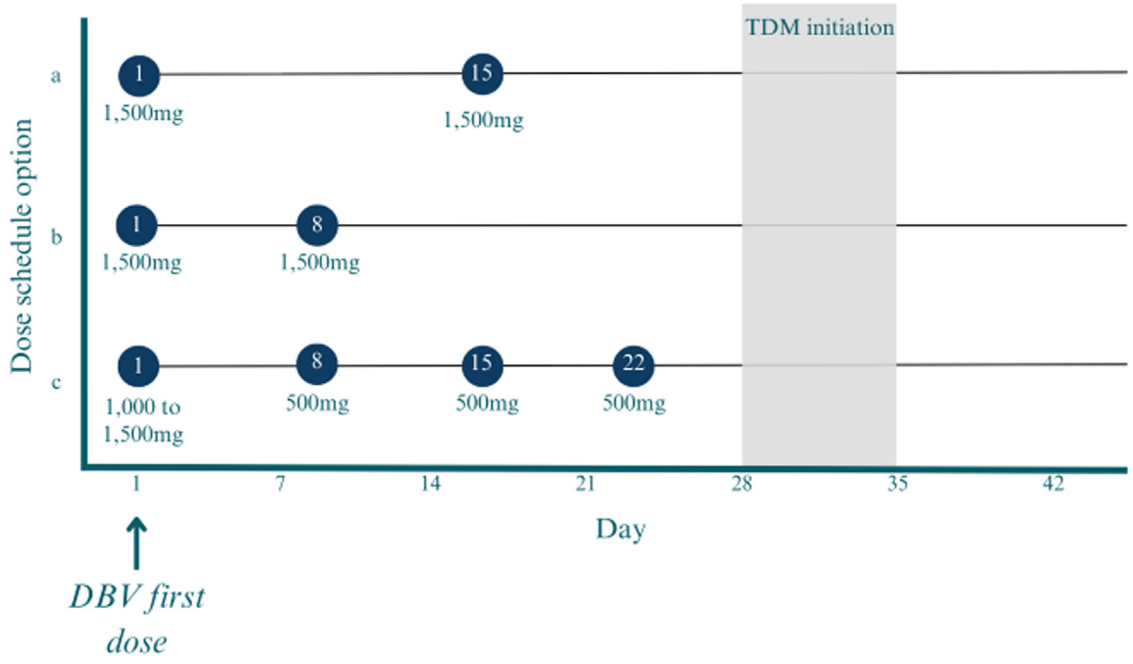


**Figure 3.** Dose regimens for clinical scenarios where the expected duration of dalbavancin (DBV) treatment is more than 6 weeks and therapeutic drug monitoring (TDM) is available for use. Day 1 is the first day of treatment with dalbavancin. A total of 3000 mg dalbavancin should be administered over 4 weeks to provide treatment cover for 4–6 weeks, with flexibility in the choice of dose regimen to meet the needs of the healthcare setting. Therapeutic drug monitoring should guide the timing of the subsequent dalbavancin dose and be initiated between Day 28 and Day 35 (Cojutti, 2022).

c. 1000–1500 mg on Day 1 and 500 mg weekly from Day 8 administered at the discretion of the physician.

Efficacy of treatment should be measured in accordance with local guidelines to assess the clinical and microbiological outcome.

In any of the selected regimens listed above, it is mandatory to clinically follow-up the patient to document the correct outcome, avoid potential underexposure and minimise selection of resistance as well as the potential emergence of adverse events.

Determination of glycopeptide MICs are method dependent and should be determined by broth microdilution (ISO standard 20776-1) [39]. The MICs must be determined in the presence of polysorbate-80 (0.002% in the medium for broth dilution methods; agar dilution methods have not been validated) [40]. Manufacturers' instructions for commercial systems should be followed to ensure accuracy.

## 4. Discussion

The authors represent expertise across Europe and aim to provide expert panel proposals for dalbavancin use. Expert discussion and experience with dalbavancin highlighted common off-

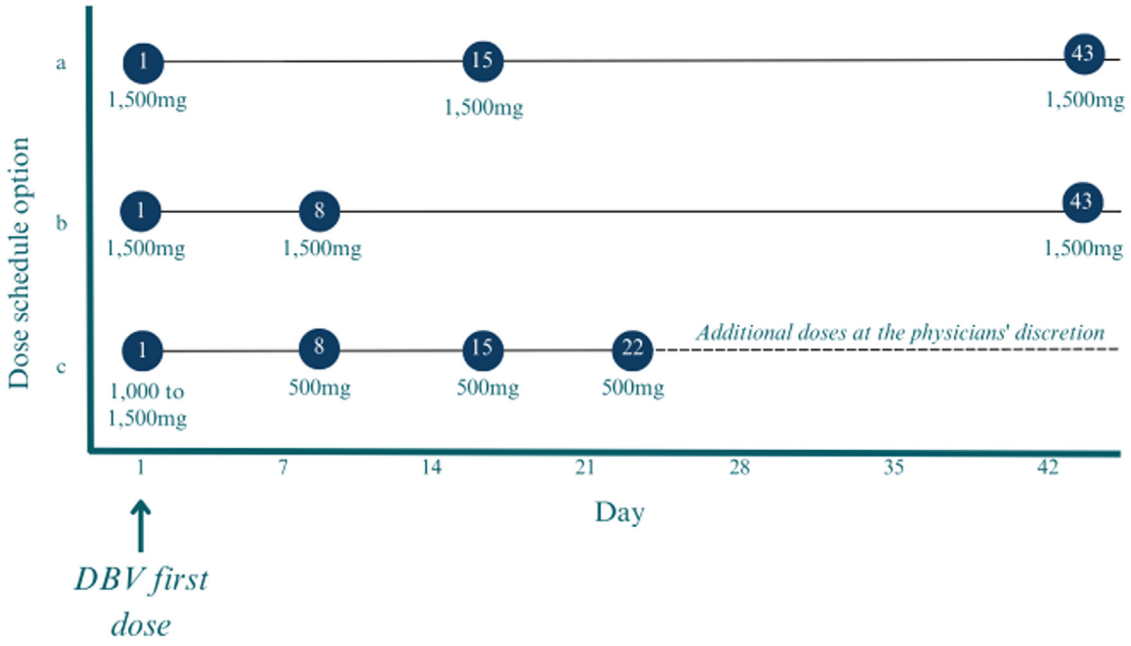


**Figure 4.** Dose regimens for clinical scenarios where the expected duration of dalbavancin (DBV) treatment is more than 6 weeks and therapeutic drug monitoring (TDM) is unavailable for use. Day 1 is the first day of treatment with dalbavancin. A total of 3000 mg dalbavancin should be administered over 4 weeks to provide treatment cover for 4–6 weeks, with flexibility in the choice of dose regimen to meet the needs of the healthcare setting. Physician discretion should be used if administering 500 mg weekly doses of dalbavancin.

label therapeutic areas where it is prescribed without fixed regulatory guidance (Box 1) and for an extended duration. Literature studies call for clarification in these areas where dalbavancin could act as a promising opportunity for treating complex Gram-positive infections [8].

Heterogeneity in survey results and presented data on dosing regimens confirmed that expert guidance is needed to assist healthcare professionals on dalbavancin use requiring > 2 weeks of treatment in off-license special populations. It was recognised that there was wide variability in availability of dalbavancin TDM. The authors suggest that a total of 3000 mg dalbavancin over 4 weeks should be administered for special populations requiring extended dalbavancin treatment (usually following initial inpatient antibiotic treatment) to give antibiotic coverage for 4–6 weeks. Whilst extended-duration dalbavancin offers an attractive definitive treatment option and enables early hospital discharge, the authors stress that antimicrobial stewardship dictates that every opportunity should be taken to consider IV to oral switch therapy when antimicrobial sensitivities and lack of drug interactions allow.

The authors are unaware of any study reporting dalbavancin intolerance related to overexposure (Table 1), including in vancomycin allergic patients [38]. Within these expert panel proposals, TDM aims to detect underexposure of dalbavancin and guide the timing of the subsequent dose. In this way, TDM could be useful in optimising treatment, reducing underexposure to dalbavancin and monitoring interindividual variability [37].

Dalbavancin is useful in the OPAT setting for those patient groups where extended daily IV therapy (e.g. with teicoplanin or daptomycin) indicated for treatment of complex and MDR Gram-positive infections is not possible, especially for staphylococci. This includes deep-seated infections in patients with reduced mobility or advanced care needs, and in people who inject drugs where home treatment with an indwelling IV device is undesirable. Other important groups where extended-interval dalbavancin is useful is in those patients in whom drug interactions preclude the use of extended-spectrum agents such as linezolid and where adherence to therapy is of concern (e.g. in people who inject drugs) [18].

Dalbavancin may facilitate the discharge of patients treated for complex deep-seated infections with first-line parenteral anti-MRSA agents such as vancomycin, teicoplanin or daptomycin. Besides real-world data, dalbavancin has demonstrated use as a consolidation therapy after prior antibiotic treatment in patients with IE and/or bloodstream infections produced by Gram-positive cocci [17,41].

Dalbavancin has no requirement for dose adjustment according to renal function, except in cases of severe renal dysfunction [3]. Studies for *S. aureus* have shown that the probability of target attainment of total dalbavancin concentration is strongly related to renal function, with a double 1-week apart 1500 mg dose in patients with preserved renal function relating to optimal antibiotic coverage for 4–6 weeks [19,25].

To the authors' knowledge no decrease in dalbavancin concentration or drug interaction has been observed when dalbavancin has been used in combination with rifampicin, but this should be confirmed with real-world pharmacokinetic data. The authors agree that in the absence of contrary data, whenever possible, dalbavancin should be combined with rifampicin in Staphylococcal PJIs. In vitro studies support the combination of dalbavancin and rifampicin when anti-biofilm treatment is required with the aim of preventing the selection of rifampicin-resistant mutants [42,43]. Further research is needed regarding its use as a single agent against biofilm-associated PJIs in patients where rifampicin is not a suitable option, also to improve treatment compliance and dalbavancin tolerance including the risks of drug-drug interactions.

Dalbavancin use can reduce overall healthcare costs by facilitating earlier discharge of patients when compared with other antibiotic regimens. Of note, the benefit of using dalbavancin is greatest when used before the end of the first week of admission [44]. Reduction of inpatient stay offsets dalbavancin acquisition costs estimated at €3324–11038, depending on the scenario [45]. Therapeutic drug monitoring may result in additional costs, especially in situations where multi-dosing dalbavancin is required. Of note,

by following these proposals, most patients treated for prolonged dalbavancin treatment may not require TDM.

These expert panel proposals do not include reference to the risk of emergence of dalbavancin-resistant mutants during extended dosing interval dalbavancin. However, in vitro selection of mutants with reduced susceptibility to dalbavancin following exposure and case reports have been described where mutations in the *Walk* gene of staphylococci altering the cell wall metabolism have been detected [46–48]. The high doses (i.e. 1500 mg) of administered dalbavancin theoretically reduce the risk of emergence of resistance, and this is supported by published studies to date, which have reported a low rate of resistance [8]. Eventually, it may be possible to personalise dosing regimens to optimise exposure and reduce the risk of resistance. Therapeutic drug monitoring may have a role in keeping within the therapeutically effective concentration range to prevent resistance [25].

The authors acknowledge calls for guidance and further research on dalbavancin use as long-term suppressive therapy, where there are no oral antibiotic alternatives and particularly for inoperable prosthetic valve or VGIs [8,49]. This guidance does not consider this area due to a lack of published data. However, the authors note reports of successful dalbavancin use as a suppressive therapy managed on a case-by-case basis in bacteraemia, PJI and cardiac device-related endocarditis, with few reported side effects [8,20,23,31,49]. Further research in this area is required to investigate the long-term effects of dalbavancin use as a suppressive antibiotic therapy.

The authors acknowledge some limitations of this guidance due to the paucity of data. Further investigation is required to make definitive recommendations on dalbavancin use according to subcategories of the special populations (e.g. native/prosthetic/cardiac implantable electronic devices IE) for which 2-log killing AUC/MIC targets rather than stasis or 1-log kill are indicated and to a wider microorganism range especially staphylococci with vancomycin MIC $>$ 1, *Corynebacterium* spp. and *Enterococcus faecium*. The authors acknowledge that this guidance does not include reference to microbiological analysis and its routine use; data on probability of target concentration attainment at various MICs would further justify the use of TDM. Additionally, most data discussed for these expert panel proposals were obtained from real-world examples rather than clinical trials.

The authors also acknowledge that there is evolving real-world dalbavancin prescribing practice reflecting changing healthcare needs and hospital admission/discharge dynamics. For instance, patients may be switched to a single dose of dalbavancin to complete the final 1–2 weeks of an already established course of inpatient antibiotic treatment (e.g. with vancomycin) in order to support early discharge or to bridge across to definitive (potentially) oral therapy pending microbiological results following an orthopaedic intervention [16,50]. Dalbavancin may also be used as an alternative therapy for staphylococcal infections if vancomycin MIC $>$ 1 mg/L and alternative agents are unsuitable. Further real-world experience describing the extent and experience of these new therapeutical opportunities would be welcome.

## 5. Conclusions

To achieve adequate dalbavancin concentrations for up to 6 weeks, 3000 mg of dalbavancin should be given over 4 weeks for defined complex infections requiring $>$ 2 weeks of treatment. There is no requirement for TDM if treatment is expected to last up to 6 weeks. If more than 6 weeks of treatment is predicted and it is available, TDM should be initiated between Day 28 and Day 35, depending on renal function, to guide the timing of the next dose of dalbavancin and detect underdosing. The specific dosing schedule can be modified to meet clinical need and the described regimens aim to accommodate different healthcare settings. Specific dosing recommendations for other special populations require further investigation.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.106960.

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