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MAJOR ARTICLE

# Attainment of Target Antibiotic Levels by Oral Treatment of Left-Sided Infective Endocarditis: A POET Substudy

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***Background.*** In the POET (Partial Oral Endocarditis Treatment) trial, oral step-down therapy was noninferior to full-length intravenous antibiotic administration. The aim of the present study was to perform pharmacokinetic/pharmacodynamic analyses for oral treatments of infective endocarditis to assess the probabilities of target attainment (PTAs).

***Methods.*** Plasma concentrations of oral antibiotics were measured at day 1 and 5. Minimal inhibitory concentrations (MICs) were determined for the bacteria causing infective endocarditis (streptococci, staphylococci, or enterococci). Pharmacokinetic/pharmacodynamic targets were predefined according to literature using time above MIC or the ratio of area under the curve to MIC. Population pharmacokinetic modeling and pharmacokinetic/pharmacodynamic analyses were done for amoxicillin, dicloxacillin, linezolid, moxifloxacin, and rifampicin, and PTAs were calculated.

***Results.*** A total of 236 patients participated in this POET substudy. For amoxicillin and linezolid, the PTAs were 88%–100%. For moxifloxacin and rifampicin, the PTAs were 71%–100%. Using a clinical breakpoint for staphylococci, the PTAs for dicloxacillin were 9%–17%.

Seventy-four patients at day 1 and 65 patients at day 5 had available pharmacokinetic and MIC data for 2 oral antibiotics. Of those, 13 patients at day 1 and 14 patients at day 5 did only reach the target for 1 antibiotic. One patient did not reach target for any of the 2 antibiotics.

***Conclusions.*** For the individual orally administered antibiotic, the majority reached the target level. Patients with sub-target levels were compensated by the administration of 2 different antibiotics. The findings support the efficacy of oral step-down antibiotic treatment in patients with infective endocarditis.

**Keywords.** infective endocarditis; pharmacokinetics; pharmacodynamics; oral antibiotics; target attainment.

Infective endocarditis (IE) carries 6-months mortality rates between 24% and 29% [1, 2] and 5-years mortality of up to 50% [3]. The majority of IE cases are caused by *Staphylococcus* spp. (especially *Staphylococcus aureus*), *Streptococcus* spp., and *Enterococcus* spp. (particularly *Enterococcus faecalis*) [4].

Recommended antibiotic treatments of IE are based on observational studies using varying antibiotic dosing and duration [5–9]. Long-term and high-dose treatments are necessary for successful outcome of IE [10–12]. This is especially due to the serious consequences of insufficient treatments and the inoculum effect resulting from the high bacterial concentrations in the heart valves [13]. Furthermore, bacteria growing in the vegetations during IE fulfill the definition of a biofilm infection supporting the need of high-dose and long-term antibiotic therapy and, in several cases, combining 2 antibiotics with different killing mechanisms [14, 15]. However, recommendations are not based on thorough pharmacokinetic (PK) analyses of antibiotic treatments.

The dogma that antibiotic therapy of left-sided IE must be administered intravenously during the entire treatment period was

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challenged in the POET (Partial Oral Endocarditis Treatment) trial [16]. After clinical stabilization with intravenous antibiotics, patients with left-sided IE (N = 400) caused by *S. aureus*, Coagulase-negative staphylococci (CoNS), *Streptococcus* spp. or *E. faecalis* were randomized to either oral therapy with 2 antibiotics using regimens designed for the study or conventional full-length intravenous therapy [16, 17]. The switch to oral therapy was noninferior to conventional intravenous administration after 6 months, and the number of relapses of positive blood cultures were similar in the 2 groups. The orally treated patients had a significantly reduced mortality rate after a median follow-up of 3.5 years and after 5.4 years [18, 19].

Clinical and systematic pharmacokinetic/pharmacodynamic (PK/PD) antibiotic analyses after changing from intravenous to oral therapy, in a randomized context, have not yet been reported. In general, attainment of target antibiotic levels is important for optimal bacterial killing and clinical outcome [20]. Although the POET trial was not designed or powered to evaluate outcome in subgroups of patients, and the collected PK/PD data are not sufficient to analyze the correlation to outcome, the data allow for general analyses of target attainment with prespecified PK/PD targets.

The aim of the present study was to perform the first PK/PD analyses of oral IE treatments by performing population PK modeling and determining the probabilities of target attainment (PTAs) for the oral antibiotics used in the POET trial.

## METHODS

### Study Design

The POET trial and the protocol have been published elsewhere [16, 17]. In brief, clinically stable adult patients with left-sided IE on native or prosthetic valves, who fulfilled the modified Duke criteria, were eligible (Supplementary Appendix 1).

### Ethics

The trial was approved by the scientific ethics committee of the Capital Region of Denmark (H-R-2011-40) and by the Danish Data Protection Agency (30-0598). It was performed in accordance with the Declaration of Helsinki. All participants provided written, informed consent.

### Clinical Microbiology

Patients with blood cultures positive for *Streptococcus* spp., *E. faecalis, S. aureus*, or CoNS were included in the study. Disk diffusion susceptibility testing was performed in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [21]. Minimal inhibitory concentrations (MICs) were determined with the use of a gradient strip method (Etest®; bioMérieux, Marcy-l'Étoile, France) or VITEK2® (bioMérieux).

### Antibiotic Regimens

Intravenous antibiotic treatment was administered in accordance with European Society of Cardiology guidelines, with modifications endorsed by the Danish Society of Cardiology [9, 22]. The trial investigators developed oral treatment regimens as part of the trial [16, 17]. Antibiotics for which published data showed moderate to high bioavailability were favored. The oral regimens were based on PK calculations and MICs for each bacterial species published by EUCAST [21]. In all cases, the oral regimens consisted of 2 antibiotics from different drug classes with different antimicrobial mechanisms of action and different metabolism to reduce the risk of de facto monotherapy, for example, due to reduced absorption, fast metabolism, or fast elimination of one drug.

In the oral treatment group, both antibiotics were administered orally. Patients in the intravenous group received at least 1 antibiotic intravenously, but adjunctive oral treatment was allowed. Some patients were changed to alternative antibiotic drugs at randomization, and others were maintained on the same antibiotics. Thus, the study population for each particular antibiotic at day 1 comprised both patients who were already receiving the antibiotic and patients who received the first dose of that antibiotic.

Antibiotic oral regimens are provided in Table 1.

### Pharmacokinetic Measurements

To ensure that patients obtained sufficient antibiotic levels, plasma concentrations of orally administered antibiotics were to be measured at the day of randomization (day 1) at 30 minutes, 1 hour, 2 hours, 4 hours, and 6 hours after dose administration and repeated on day 5, assuming achievement of steady state at this time. For the intravenously treated patients, a similar PK analysis was performed at day 1. Samples were analyzed by high-pressure liquid chromatography using Agilent 1290 Infinity (Agilent Technologies, Santa Clara, California, USA) providing the total concentration in plasma. The plasma samples were analysed at an accredited hospital laboratory at the Department of Clinical Biochemistry at Aarhus University Hospital, Denmark (DS/EN/ISO/IEC 15189), by existing methods validated according to standard laboratory procedures, essentially as described in [23].

### Pharmacokinetic Analyses

PK data from orally administered amoxicillin, dicloxacillin, linezolid, moxifloxacin, and rifampicin treatments, and PK data from intravenously administered dicloxacillin, linezolid, and moxifloxacin treatments were included. Some patients had available PK data for a single drug and/or from a single assessment day only, and we defined a *treatment* as a PK data series for *1* antibiotic at *1* assessment day. Treatments with large fluctuations (irregular deviations of more than 10% and at least 0.5 mg/L) were presumed related to sampling or measurement

**Table 1. Clinical Breakpoints and Pharmacokinetic/Pharmacodynamic Targets**

| Drug | Dose | Approximate Unbound Fraction (%) | Bacterial Species | Clinical Breakpoint (mg/L) | Pharmacokinetic/ Pharmacodynamic Target |
|---|---|---|---|---|---|
| Amoxicillin | PO: 1000 mg q6 h | 80 | Enterococci | 4 | $fT > BP$ or $fT > MIC$ more than 50% of dosing interval[b] |
| | | | Staphylococci Streptococci | 0.5[a] | |
| Dicloxacillin | PO: 1000 mg q6 h | 3 | Staphylococci | 0.5[c] | $fT > BP$ more than 50% of dosing interval[b] |
| | IV: 3000 mg q6 h | | | | |
| Linezolid | PO or IV: 600 mg q12 h | Not used | Enterococci Staphylococci | 4 | $AUC_{12}/BP > 50$ or $AUC_{12}/MIC > 50$ |
| | | | Streptococci | 2[d] | |
| Moxifloxacin | PO or IV: 400 mg q24 h | 50 | Enterococci Streptococci | 0.5[e] | $fAUC_{24}/BP > 30$ or $fAUC_{24}/MIC > 30$[b] |
| | | | Staphylococci | 0.25 | |
| Rifampicin[f] | PO: 600 mg q12 h | Not used | Staphylococci Streptococci | 0.064 | $AUC_{12}/BP > 500$ or $AUC_{12}/MIC > 500$ |

Abbreviations: AUC, area under concentration-time curve; BP, clinical breakpoint; IV, intravenous; MIC, minimal inhibitory concentration; PO, oral; T, time.

[a]For amoxicillin we defined a BP of 0.5 mg/L for staphylococci and streptococci as determined for viridans streptococci.

[b]The letter *f* indicates the free unbound concentration; eg, $fT > MIC$ means the time above MIC of the unbound concentration.

[c]For dicloxacillin, for which there are no BPs determined by EUCAST, we defined a BP of 0.5 mg/L for staphylococci [40].

[d]For linezolid we defined a BP of 2 mg/L for streptococci as determined for *Streptococcus pneumoniae* and hemolytic streptococci groups A, B, C, and G.

[e]For moxifloxacin we defined a BP of 0.5 mg/L for enterococci and streptococci as determined for *S. pneumoniae* and hemolytic streptococci groups A, B, C, and G.

[f]For rifampicin, no BP for enterococci was defined.

errors and excluded. Treatments with extreme (more than 5 standard deviations from the mean of the remaining concentrations) or unrealistic concentrations (eg, a concentration rise not possible with the administered dose) were presumed related to measurement errors and excluded. Detailed exclusion criteria are provided in Supplementary Appendix 2. We developed a population PK model for each antibiotic, using non-linear mixed effects modelling in Matlab Simbiology (Version 9.11 (R2021b), The MathWorks Inc., Natick, Massachusetts, USA). The population PK analyses are described in Supplementary Appendix 3. Loglikelihood profiles used for selection of absorption parameters, due to limited data in the absorption phase, are shown in Supplementary Figure 1. We used the individual estimates from the population PK models to compute the individual concentration-time curves for estimation of time above MIC (T > MIC) or area under the concentration-time curve (AUC).

#### Clinical Pharmacokinetic/Pharmacodynamic Targets and Breakpoints

For amoxicillin, dicloxacillin, and moxifloxacin, the PK/PD targets are defined according to the free fraction only, whereas the total amount (protein bound and unbound) is considered for linezolid and rifampicin (Table 1), because the published PK/PD papers for these drugs evaluated the total AUC [20, 24].

β-Lactams display time-dependent killing with T > MIC correlating to efficacy. For amoxicillin and dicloxacillin, we defined the target as the time above MIC of the unbound fraction ($fT > MIC$) exceeding 50% of the dosing interval [20, 25]. Unbound concentrations were estimated assuming unbound fractions of 80% for amoxicillin and 3% for dicloxacillin [26, 27].

For linezolid, moxifloxacin, and rifampicin, the ratio of AUC to MIC correlates best to efficacy. For linezolid, we defined the target as $AUC_{12}/MIC > 50$ (12-hour AUC) due to a reported target of $AUC_{24}/MIC > 100$ [20]. For moxifloxacin, we defined the target as $fAUC_{24}/MIC > 30$ and assumed an unbound fraction of 50% [28, 29]. For rifampicin, the clinical PK/PD target for non-mycobacterial infections is uncertain, but an $AUC_{24}/MIC$ ratio of 952 was associated with a 1-log-kill for a *S. aureus* strain in a neutropenic murine thigh model [24]. Based on this, we defined the target as $AUC_{12}/MIC > 500$.

Clinical breakpoints (BPs) were defined in accordance with EUCAST (Table 1) [30]. When there were no available BPs, we defined the BPs as those determined for closely related pathogens.

#### Data Presentation

The graphic processing was performed with GraphPad Prism 9 (Version 9.0.0, GraphPad Software Inc., San Diego, California, USA). For each antibiotic, we provided (i) a figure showing the average concentration-time curve, using the measured concentrations and the protocol timepoints and (ii) a figure relating the individual PK measures to BPs for staphylococci, streptococci, and enterococci, using all the PK data for each antibiotic regardless of the individual patients' infecting bacterial species. This enabled analyses with larger sample sizes than restricted by the number of individual pathogens and the related MICs. Finally, we created (iii) a figure relating the individual PK

measures to the individual MICs (except for dicloxacillin due to a lack of MIC data).

### Outcomes

The primary outcome, the probabilities of target attainment (PTAs), was calculated as the percentage of patients reaching the target in relation to MICs. Secondary outcome was PTAs in relation to BPs.

## RESULTS

### Patients and Treatments

A total of 236 patients were included in this substudy, of whom 175 patients had 2 oral antibiotics, 35 patients received an oral antibiotic adjunctive to intravenous treatment, and 26 patients received intravenous antibiotics alone. PK data from patients treated with amoxicillin, dicloxacillin, linezolid, moxifloxacin, or rifampicin were available for 392/261 treatments at day 1/day 5 (Figure 1). In total, 50 treatments were excluded due to irregular PK data (N = 38), extreme or biologically unrealistic concentrations (N = 7), insufficient PK data (N = 4), or unclear route of administration (N = 1). Thus, 355/248 treatments at day 1/day 5 were included in the concentration-time curves and subsequent analyses of PK related to BP, and 251/189 treatments at day 1/day 5 with available MICs were included in analyses of PK related to MIC.

Detailed inclusions and exclusions for subgroups are visualized in Figure 1.

### Pharmacokinetic Profiles

The concentration-time curves show that PK data followed similar profiles at day 1 and 5 for amoxicillin (Figure 2*A*), moxifloxacin (Figure 2*C*), and rifampicin (Figure 2*D*), although with substantial inter-individual variation. For linezolid, the plasma concentrations were significantly higher at day 5 (Figure 2*B*). PK data for dicloxacillin at day 1 and 5 followed different profiles with higher concentrations at day 5 (Figure 2*E*). The concentration-time curves for intravenously administered antibiotics are provided in Supplementary Figure 9.

### Population Pharmacokinetic Analyses

The estimated population PK parameters are listed in Supplementary Table 1. The estimated initial linezolid concentrations are presented in Supplementary Figure 2. Goodness-of-fit plots confirmed an adequate fit of the individual PK data and showed no model misspecifications (Supplementary Figures 3–8).

### Amoxicillin

For amoxicillin, the PTAs in relation to BP were 75%/85% (at day 1/day 5) for enterococci and 100%/100% for staphylococci and streptococci (Figure 3*A*). For MICs, the PTAs were 97%/100% for enterococci (N = 31/25) and 100%/100% for streptococci (N = 45/39) (Figure 4*A*).

### Linezolid

For linezolid, the PTAs in relation to BP for the orally treated patients were 27%/54% for enterococci and staphylococci and 67%/84% for streptococci (Figure 3*B*). Correspondingly, the PTAs for the intravenously treated patients were 11% for enterococci and staphylococci and 56% for streptococci (Supplementary Figure 10*A*). For MICs, the PTAs were 88%/90% for enterococci (N = 16/10), 90%/100% for staphylococci (N = 10/8), and 100%/92% for streptococci (N = 15/13) (Figure 4*B*). Correspondingly, the PTAs for the intravenously treated patients were 100% for enterococci (N = 4), 33% for staphylococci (N = 3), and 100% for streptococci (N = 2) (Supplementary Figure 11*A*).

### Moxifloxacin

For moxifloxacin, the PTAs in relation to BP for the orally treated patients were 34%/49% for enterococci and streptococci and 83%/83% for staphylococci (Figure 3*C*). Correspondingly, the PTAs for the intravenously treated patients were 20% for enterococci and streptococci and 40% for staphylococci (Supplementary Figure 10*B*). For MICs, the PTAs were 81%/79% for enterococci (N = 21/19), 100%/100% for staphylococci (N = 3/4), and 75%/81% for streptococci (N = 16/16) (Figure 4*C*). Correspondingly, the PTAs for the intravenously treated patients were 75% for enterococci (N = 4), 100% for staphylococci (N = 6), and 50% for streptococci (N = 2) (Supplementary Figure 11*B*).

### Rifampicin

For rifampicin, the PTAs in relation to BP were 81%/66% for staphylococci and streptococci (Figure 3*D*). For MICs, the PTAs were 100%/100% for staphylococci (N = 28/17) and 78%/71% for streptococci (N = 45/38) (Figure 4*D*).

### Dicloxacillin

For dicloxacillin, the PTAs in relation to BP for the orally treated patients were 9%/17% for staphylococci (Figure 3*E*), whereas it was 56% for the intravenously treated patients (Supplementary Figure 10*C*).

### Target Attainment of Oral Antibiotics in Combinations

A total of 74 patients at day 1 and 65 patients at day 5 had available PK and MIC data for both oral antibiotics. At day 1, 61 (82%) patients reached the target for both antibiotics, and 13 (18%) patients reached the target for one antibiotic only. At day 5, 50 (77%) patients reached the target for both antibiotics, 14 (22%) patients reached the target for one antibiotic only, and 1 (2%) patient failed to reach the target for any of the 2 antibiotics.

## DISCUSSION

The present study analyzed the individual PK data in relation to the individual MICs of the IE causing pathogens, which is unique compared to other studies [31, 32]. For the individual

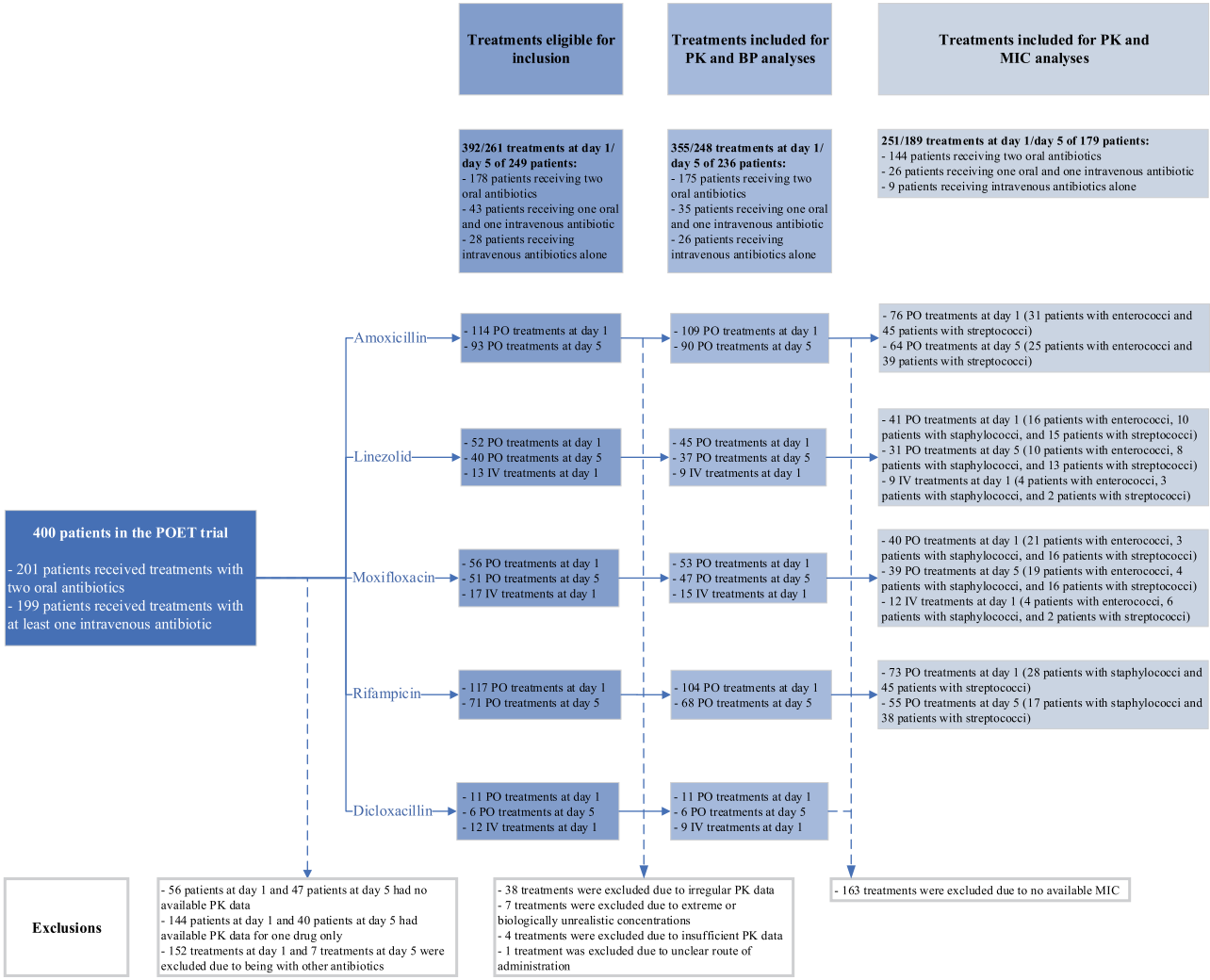


**Figure 1.** Participant flow. A *treatment* is defined as a PK data series for 1 antibiotic at 1 assessment day. Abbreviations: BP, clinical breakpoint; IV, intravenous; MIC, minimal inhibitory concentration; PK, pharmacokinetic; PO, oral; POET, Partial Oral Endocarditis Treatment.

orally administered antibiotic, the majority of patients reached the target levels. Patients with sub-target levels were compensated by the administration of 2 different antibiotics. Hence, the PK/PD analyses of the POET study support the efficacy in changing to oral step-down antibiotic therapy of IE in stabilized patients. In addition, substantial variations in PKs were observed, confirming previous observations [20, 33]. The pragmatic trial design, with a menu of oral options, does not allow for the selection of a single preferred regimen [31]. An array of antibiotic combinations worked in oral step-down therapy of IE.

Long-term intravenous antibiotic administration has been a medical dogma of IE therapy. This view has been challenged in a few smaller studies and retrospective evaluations and recently in the randomized, controlled POET study [16, 31, 32]. Studies on the change to oral antibiotic therapy for other infections have also been published. In the OVIVA (Oral versus Intravenous Antibiotics for Bone and Joint Infection) trial, 1054 patients were randomly assigned within 7 days after surgery to receive intravenous or oral antibiotics [34]. Oral therapy was noninferior to intravenous treatment assessed by treatment failure after 1 year. Still, the OVIVA study did not include PK/PD analyses.

Our analyses of PTAs in relation to BPs at day 1 were as low as 27% for enterococci and staphylococci for linezolid and 34% for enterococci and streptococci for moxifloxacin. Rifampicin and amoxicillin showed more satisfying PTAs in relation to BP. More importantly, PK/PD analyses using the MICs revealed substantially higher PTAs for most antibiotics. Enterococci were, as expected, the species with the lowest PTAs. Still, the PTAs using MICs were higher, which presumably would be further improved by the antibiotic combinations.

The low PTAs for oral dicloxacillin in relation to BP were primarily caused by the high degree of protein binding. The applied unbound fraction was based on data from healthy

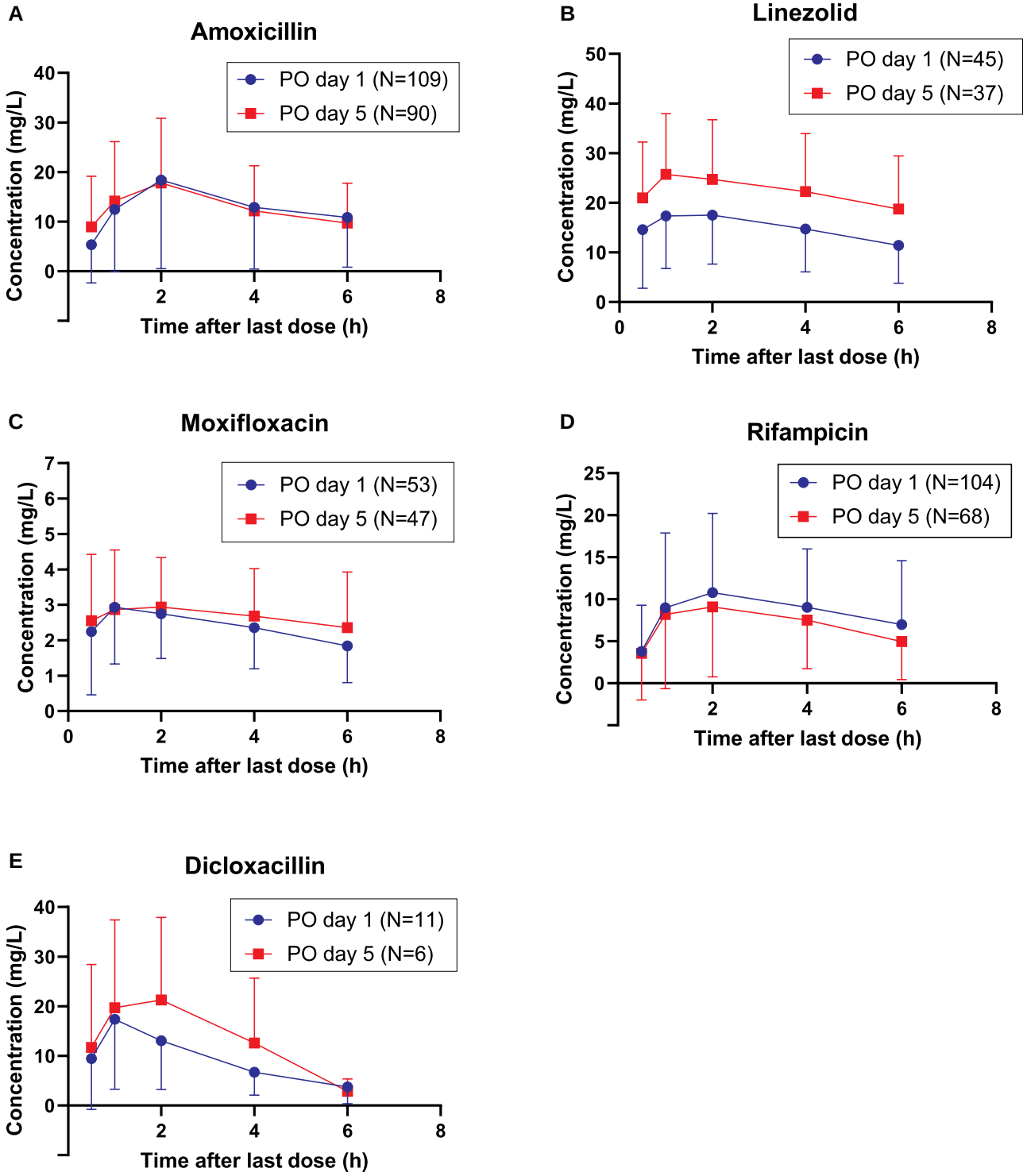


**Figure 2.** Concentration-time curves of oral antibiotics. Presented as mean ± SD. Abbreviation: PO, oral.

individuals [27], and protein binding can be significantly lower in critically ill patients with hypoalbuminemia [35, 36], which may significantly impact the PTAs. We also assumed that protein binding was immediate, constant over time, and of equal magnitude, but non-linear protein binding and/or inter-individual variation may have influenced the analyses. Furthermore, individual MICs for dicloxacillin would likely have increased the PTAs, because values of 0.25 mg/L or 0.125 mg/L would have resulted in PTAs of 27%/50% or 82%/83% at day 1/day 5, respectively.

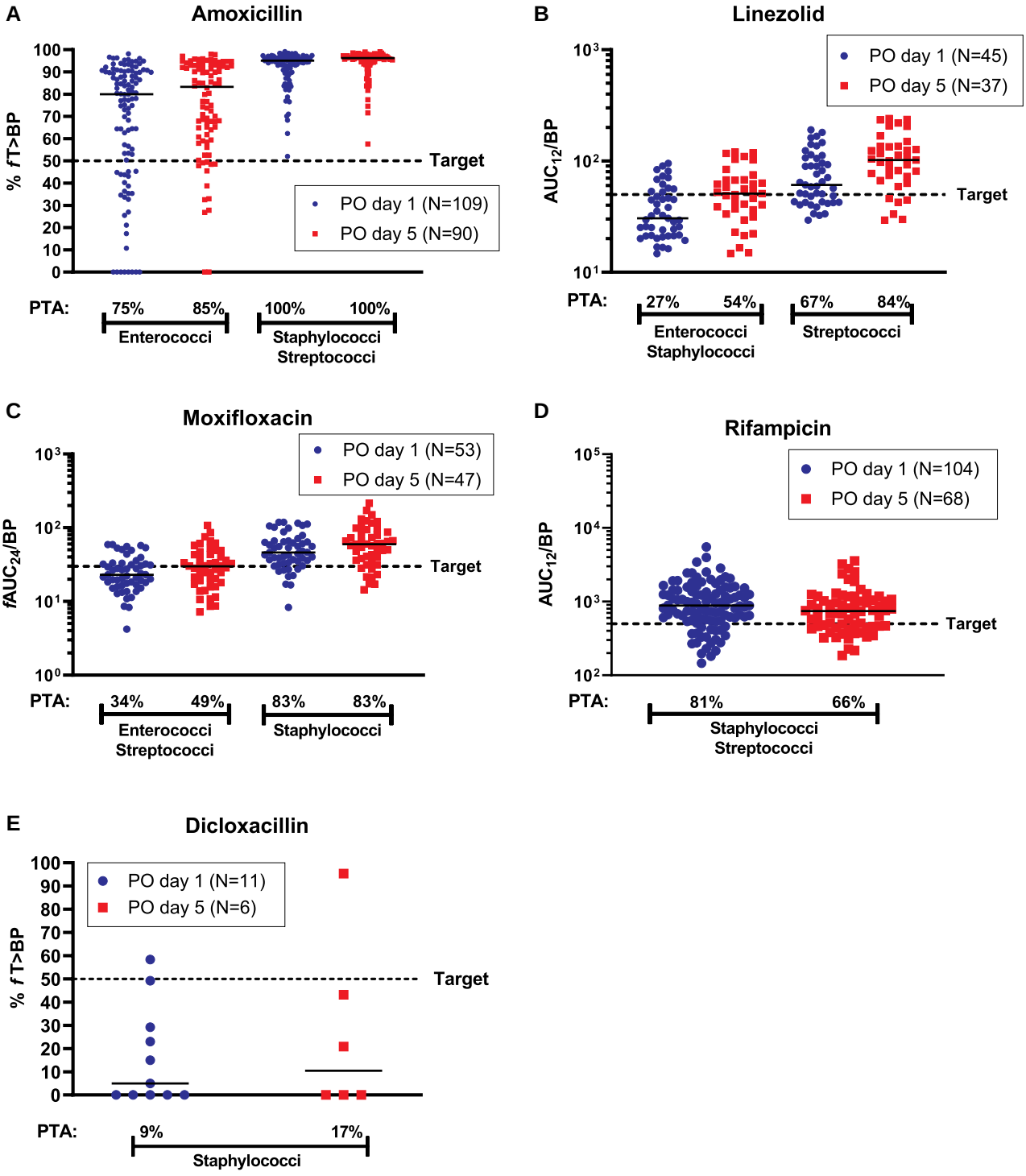


**Figure 3.** Target attainment of oral antibiotics in relation to clinical breakpoints. Solid black bars are median values. The letter *f* indicates the free unbound concentration; eg, *f*T > BP means the time above BP of the unbound concentration. Abbreviations: AUC, area under concentration-time curve; BP, clinical breakpoint; PO, oral; PTA, probability of target attainment; T, time.

Reduced PTAs may be managed by different strategies. One option is to determine drug concentrations and conduct individual PK/PD analyses. This method is not clinically feasible, and the study does not support a general recommendation for PK measurements in all patients shifted to oral treatment of IE, although it can be necessary in specific cases. Another option is to increase the antibiotic dose in monotherapy. This can be preferable for some patients but is not always possible and

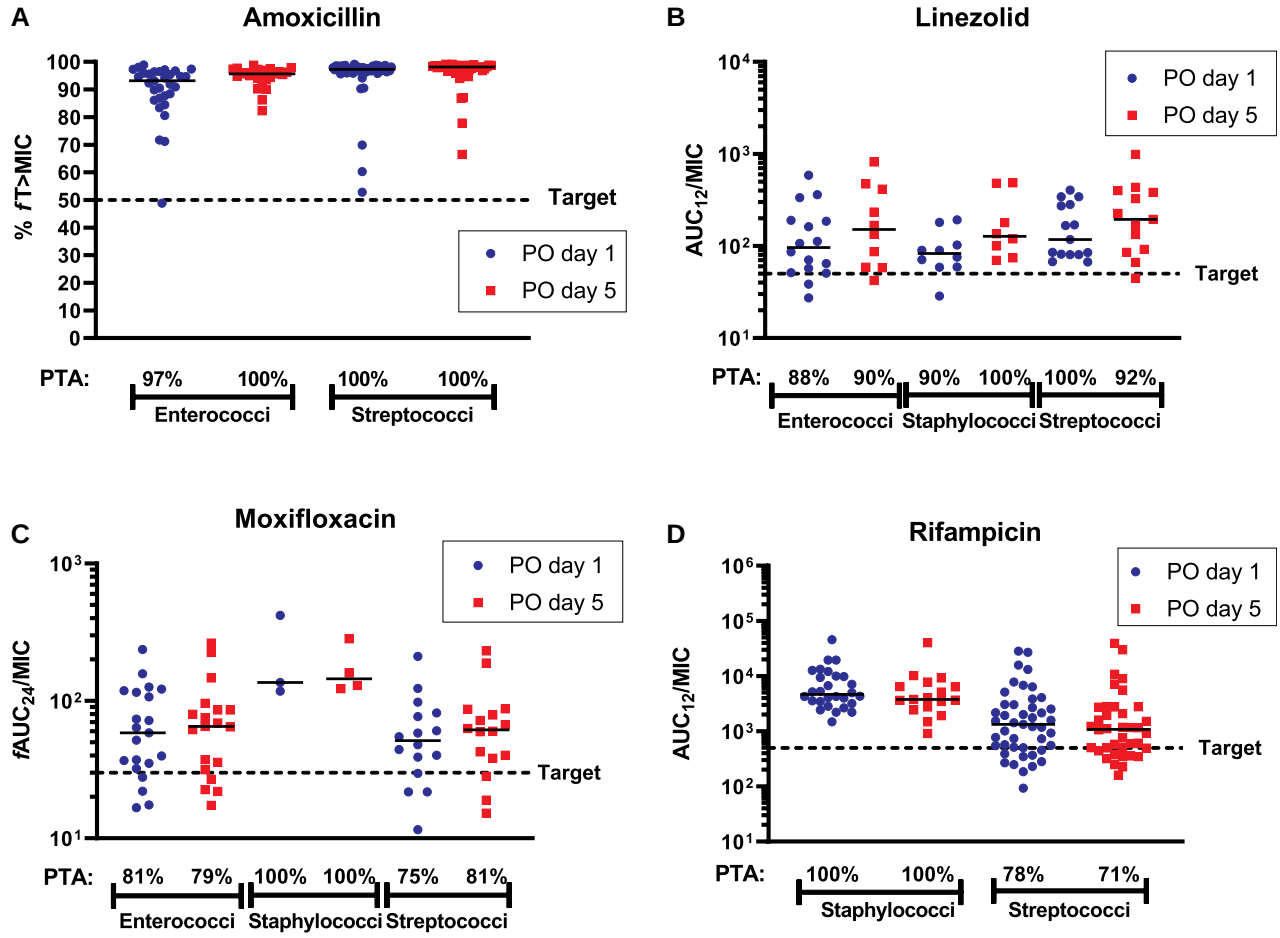


**Figure 4.** Target attainment of oral antibiotics in relation to minimal inhibitory concentrations. Solid black bars are median values. The letter *f* indicates the free unbound concentration; eg, *f*T > MIC means the time above MIC of the unbound concentration. Abbreviations: AUC, area under concentration-time curve; MIC, minimal inhibitory concentration; PO, oral; PTA, probability of target attainment; T, time.

can increase adverse effects. We argue that the optimal choice is combining two antibiotics from different drug classes with different mechanisms of action and metabolism. A failure to reach the clinical PK/PD target for 1 drug is likely compensated by the other.

The pattern of antimicrobial activity differs for antibiotic classes implying the need for different types of PK/PD targets (eg, T > MIC or AUC/MIC) [37]. We defined the PK/PD targets according to existing literature, but the specific quantities of exposures needed for successful outcomes remain debatable. The optimal clinical PK/PD target for antibiotic plasma concentration can depend on the specific pathogen, the type of infection and organ affected, and patient characteristics, further complicating the generalization of PK/PD targets [20, 38].

The present study has some limitations. First, the PK measurements of the POET study were a safety parameter and not designed for subgroup analyses. Therefore, some sample sizes were small. Second, a substantial number of treatments were excluded due to a lack of PK data, a lack of MICs, or poor data quality. Third, comparisons between orally treated patients at day 1 and 5 have limited value, because potential differences may have been diminished by the patients receiving the antibiotics prior to day 1. However, substantial differences (as for linezolid) would likely have been detected, and the steady state concentrations are clinically of equal (or greater) importance than the PK of the first dose, especially because patients were already stabilized with intravenous treatment. In addition, PK data were limited to 1 day only for some patients, potentially making a comparison between day 1 and 5 imbalanced. However, a systematic factor influencing the inclusion of patients at day 1 and/or 5 seems unlikely. Fourth, a potential limitation could be the use of E-test instead of broth microdilution for MIC determination. However, for the involved antibiotics, no substantial differences have been reported [39]. Fifth, antibiotic doses were given independent of body weight, and loading doses may be preferable when changing to a new antibiotic.

In conclusion, by performing the first PK/PD analyses for oral treatments of IE, we found that for the individual orally

administered antibiotic, the majority of patients obtained sufficient drug exposures. Patients with sub-target levels were compensated by the administration of 2 different antibiotics. The findings support the efficacy of oral step-down antibiotic therapy after clinical stabilization in patients with infective endocarditis.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

***Author contributions.*** K. I., N. I., J. H. L., C. M., and H. B. designed the POET trial and wrote the protocol. K. I. and H. B. lead the POET trial. The PK/PD substudy was planned by C. M., K. I., N. I., S. G., U. C., H. E., J. P., N. E. B., D. H., E. F., L. K., M. S., M. P., J. K., C. T. P., N. T., C. L., H. L. N., L. L., J. J. C., F. R., K. F., and H. B. C. L., H. L. N., L. L., J. J. C., F. R., and C. M. contributed with microbiological data. PK/PD analyses were conducted by M. B., J. C. H., H. W., A. M T., K. F., N. H., K. I., H. B., and C. M. M. B. and C. M. did first manuscript writing. All co-authors contributed to the manuscript and approved the final version. All authors had access to data.

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