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Bock, M.; Hasselt, J.G.C. van; Fuursted, K.; Ihlemann, N.; Gill, S.; Christiansen, U.; ... ; Moser, C.

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Original article

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Magnus Bock [1,*], Johan G.C. Van Hasselt [2], Kurt Fuursted [3], Nikolaj Ihlemann [4], Sabine Gill [5], Ulrik Christiansen [6], Niels Eske Bruun [7,8,9], Hanne Elming [8], Jonas A. Povlsen [10], Lars Køber [9,11], Dan E. Høfsten [11], Emil L. Fosbøl [11], Mia M. Pries-Heje [11], Jens Jørgen Christensen [9,12], Flemming S. Rosenvinge [13,14], Christian Torp Pedersen [15,16], Jannik Helweg-Larsen [17], Niels Tønder [15], Kasper Iversen [9,18], Henning Bundgaard [9,11], Claus Moser [1,19]

[1] *Department of Clinical Microbiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark*
[2] *Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands*
[3] *Department of Bacteria, Parasites and Fungi, Statens Serum Institut, Copenhagen, Denmark*
[4] *Department of Cardiology, Bispebjerg Hospital, Copenhagen, Denmark*
[5] *Department of Cardiology, Odense University Hospital, Odense, Denmark*
[6] *Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark*
[7] *Department of Clinical Medicine, Aalborg University, Aalborg, Denmark*
[8] *Department of Cardiology, Zealand University Hospital, Roskilde, Denmark*
[9] *Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark*
[10] *Department of Cardiology, Aarhus University Hospital, Aarhus N, Denmark*
[11] *Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark*
[12] *The Regional Department of Clinical Microbiology, Region Zealand, Denmark*
[13] *Department of Clinical Microbiology, Odense University Hospital, Odense, Denmark*
[14] *Research Unit of Clinical Microbiology, Department of Clinical Research, University of Southern Denmark, Odense, Denmark*
[15] *Department of Cardiology, Nordsjællands Hospital, Hillerød, Denmark*
[16] *Department of Public Health, University of Copenhagen, Copenhagen, Denmark*
[17] *Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark*
[18] *Department of Emergency Medicine, Copenhagen University Hospital, Herlev-Gentofte, Copenhagen, Denmark*
[19] *Department of Immunology and Microbiology, University of Copenhagen, Copenhagen, Denmark*

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ABSTRACT

Objectives: Benzylpenicillin is commonly used to treat infective endocarditis, particularly for streptococcal infections. This study aimed to perform pharmacokinetic/pharmacodynamic analyses of benzylpenicillin to assess the probability of target attainment (PTA) across different pathogens, MIC values, pharmacokinetic/pharmacodynamic targets, and renal function levels.

Methods: In the Partial Oral Endocarditis Treatment trial, patients with left-sided infective endocarditis were randomly assigned to either conventional intravenous or partial oral antibiotic treatment. This substudy included patients receiving intravenous benzylpenicillin (3000 mg q6h). Pharmacokinetic measurements were conducted, and a population pharmacokinetic model was developed to estimate PTAs through model-based simulations. Pharmacokinetic/pharmacodynamic targets were based on time above MIC (or 4 × MIC) of the free concentration (fT > MIC or fT > 4 × MIC).

Results: A total of 75 patients were included, and 291 plasma concentrations were obtained. MIC values were available for 68 patients. Individual target attainment for 50% fT > MIC and 50% fT > 4 × MIC targets was 100% (56/56) and 94.6% (53/56) for streptococci, 100% (3/3) for staphylococci, but only 66.7% (6/9) and 33.3% (3/9) for *Enterococcus faecalis*. For more stringent targets of 100% fT > MIC and 100% fT > 4 × MIC, individual target attainment was 89.3% (50/56) and 75.0% (42/56) for streptococci, 100.0% (3/3) and 66.7% (2/3) for staphylococci, but 33.3% (3/9) and 11.1% (1/9) for *E. faecalis*. Simulations showed PTAs above 90% for MIC values ≤ 0.5 mg/L at the 50% fT > MIC target, and for MIC values ≤ 0.063 mg/L at

* Corresponding author. Magnus Bock, Department of Clinical Microbiology, Copenhagen University Hospital, Rigshospitalet, Henrik Harpestrengs Vej 4a, Copenhagen DK-2100. Denmark.
E-mail address: magnus.nikolaj.bock@regionh.dk (M. Bock).

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50% fT > 4 × MIC or 100% fT > MIC targets. Higher renal clearance was associated with substantially lower PTAs.

Discussion: Intravenous benzylpenicillin achieved target levels in most patients with infective endocarditis, particularly for those infected with streptococci or susceptible staphylococci. However, low individual target attainment in patients with *E. faecalis* suggests limitations in treating enterococcal endocarditis, especially in patients with preserved renal function. **Magnus Bock, Clin Microbiol Infect 2025;31:1350**

Introduction

Benzylpenicillin, an intravenously administered β-lactam, primarily targets gram-positive pathogens such as *Streptococcus spp*. Its central role in the treatment of infective endocarditis (IE) caused by streptococci is emphasized by international guidelines [1]. Furthermore, some centres use benzylpenicillin in IE caused by susceptible strains of staphylococci or enterococci. However, for β-lactam susceptible enterococci, ampicillin (or amoxicillin) is generally recommended over benzylpenicillin because of lower MIC, in combination with ceftriaxone or gentamicin [1].

IE is considered a biofilm infection on the endocardium, commonly featuring bacterial vegetations on native or prosthetic heart valves [2,3]. The 6-month mortality rates range from 24% to 29% [4]. Prolonged and high-dose antibiotic treatment is necessary for the successful outcome of IE [1,2]. The Partial Oral Endocarditis Treatment (POET) trial demonstrated the non-inferiority of oral step-down treatment compared with traditional full-length intravenous therapy [5,6]. Nonetheless, it is generally believed that both initial stabilization and patients ineligible for partial oral therapy still require intravenous antibiotics.

Achieving sufficient plasma levels of antibiotics is important for bacterial killing and clinical outcomes [7,8]. The mechanism of action of β-lactams relies on the acylation of penicillin-binding proteins, thereby inhibiting peptidoglycan synthesis [9]. When maximal acylation is reached, the bacterial killing cannot increase further. Thus, β-lactams exhibit time-dependent bacterial killing, where efficacy is determined by the duration that the antibiotic concentration remains above a certain threshold [10,11]. This is typically measured as the percentage of time the free, unbound plasma concentration exceeds the MIC (fT > MIC). For penicillins, the standard clinical pharmacokinetic/pharmacodynamic (PK/PD) target is achieving 50% fT > MIC [7]. However, in biofilm infections, increased tolerance to antibiotics may necessitate higher plasma levels over an extended duration [12], and the optimal clinical PK/PD target in IE remains debated [13]. Increasing the target antibiotic concentrations to 4 × MIC over the entire dosing interval has been suggested [8,14], based on previous clinical studies [15,16]. Hence, evaluating the target attainment of benzylpenicillin in IE using higher targets is important for optimizing treatment strategies based on antibiotic susceptibility and patient characteristics such as renal function, because penicillins are primarily eliminated in the kidneys.

Thus, in the present study, we performed PK/PD analyses of benzylpenicillin in patients with IE to determine the probabilities of target attainment (PTAs) by evaluating various bacterial species, MIC values, PK/PD targets, and levels of renal function.

Methods

Ethics

The POET trial (ClinicalTrials.gov: NCT01375257) received approval from the regional scientific ethics committee for the Capital Region of Denmark (H-R-2011-40) and the Danish Data Protection Agency (30-0598). The original approval included the collection and use of the plasma samples described in this study. It was conducted in compliance with the principles outlined in the Declaration of Helsinki, and all participants provided written informed consent.

Study design

The results of the POET trial and the protocol have been published previously [5,17]. In summary, eligible participants were adult patients diagnosed with left-sided IE and blood cultures positive for *Staphylococcus aureus*, coagulase-negative staphylococci, *Streptococcus spp*., or *Enterococcus faecalis*. At randomization, all patients had undergone a minimum of 10 days (7 days after heart valve surgery) of intravenous antibiotic therapy with a satisfactory clinical response according to prespecified stabilization criteria (afebrile for at least 2 days, C-reactive protein reduced to <25% of its peak level or <20 mg/L, and leukocyte counts below 15×10^9/L). The patients were randomly assigned to partial oral therapy with two oral antibiotics or conventional full-length intravenous therapy. The primary endpoint was a composite outcome including all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteraemia with the primary pathogen.

For the present analysis, all participants in the POET trial who received benzylpenicillin were screened for eligibility. Demographic information, clinical characteristics, and patient outcomes were gathered. Creatinine clearance was determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [18].

Drug administration, PK measurements, and clinical microbiology

Eligible patients received 3000 mg benzylpenicillin (5 million IU) q6h by short intravenous infusions over approximately 30 minutes. Patients had plasma concentrations determined at the day of randomization (day 1) in the intravenously treated group. For each patient, blood samples were collected at approximately 0.5, 1, 2, 4, and 6 hours after administration. The 6-hour sample timing varied between patients, occurring before, during, or after the next benzylpenicillin infusion. Unfortunately, the exact timepoint of the second dose was not recorded. Consequently, we chose to exclude the 6-hour measurement for all patients to prevent bias. For three patients, notable irregularities were detected in the PK curves, suggesting an exchange of sample times for two samples, resulting in fluctuating concentrations (Fig. S1). We decided to exchange the sample times before subsequent analysis.

Samples were analysed by high-pressure liquid chromatography using Agilent 1290 Infinity (Agilent Technologies, Santa Clara, CA, USA) providing the total concentration in plasma.

MICs of benzylpenicillin were evaluated by a gradient strip method (Etest; bioMérieux, Marcy-l'Étoile, France) or VITEK2 (bioMérieux).

Population PK analysis

The population PK analysis was performed in Monolix (Version 2023R1, Lixoft, Antony, France) using the Stochastic Approximation Expectation-Maximization algorithm. The graphic processing of the obtained results was partially carried out in GraphPad Prism 10 (Version 10.1.2, GraphPad Software Inc., San Diego, CA, USA).

During structural model building (Supplementary Methods), PK models with one or two compartments and first-order elimination were evaluated. The dose was modelled as a constant infusion over 30 min in the central compartment.

Because previous studies have found an effect of body weight and creatinine clearance on the PK of benzylpenicillin [19–22], they were selected as potential PK covariates. Body weight and creatinine clearance were normalized to observed median values of 78 kg and 74.8 mL/min, respectively, and introduced as power functions (Supplementary Methods).

The evaluation of the PK model was conducted according to conventional methods [23]. Goodness-of-fit plots were generated to evaluate the adequacy of the final model, and a visual predictive check was conducted by simulating the final model 500 times.

Individual target attainment and PK/PD analyses

We used the individual estimates from the population PK model to compute the individual concentration–time curves for estimation of time above MIC (fT > MIC) assuming a free unbound fraction of 45% [19]. We performed the analyses using four different PK/PD targets, namely 50% fT > MIC, 50% fT > 4 × MIC, 100% fT > MIC, and 100% fT > 4 × MIC [8].

To further explore the PTA relative to individual MIC, we conducted a simulation of the final model in Simulx (Version 2023R1, Lixoft). First, PK parameters were sampled for 10 000 patients with a median creatinine clearance of 74.8 mL/min. Second, we simulated the model using the standard dose of 3000 mg q6h and computed individual estimates of concentration–time curves at day 5 assuming steady-state conditions at this point. Third, the PTA using the specified PK/PD targets and varying MIC values (0.016 -16 mg/L) was calculated. Finally, 90% CIs were derived from 500 simulations, each based on 1000 parameter sets sampled from the final model's variance–covariance matrix [24]. Using these 500 PTA estimates, we determined the 5th and 95th percentiles for each target and MIC.

Similar simulations were conducted assuming a creatinine clearance of 40.8 mL/min, representing the 10th percentile, and 103.2 mL/min, representing the 90th percentile of estimated creatinine clearance.

Results

Patient characteristics

A total of 75 patients treated with benzylpenicillin in the POET trial were included. The demographic and clinical data are summarized in Table 1. Most patients were infected by streptococci (79%, 59/75), and 10 (13%, 10/75) and five (7%, 5/75) patients were infected by *E. faecalis* and staphylococci, respectively. MIC data were available for 68 patients and are reported in Fig. S2. The determined MIC range was 0.008–0.38 mg/L for streptococci, 1– 6 mg/L for *E. faecalis*, and 0.064–0.125 mg/L for staphylococci. The composite outcome occurred in six patients (8%, 6/75).

Table 1
Demographic and clinical data of the study population

Total patients, *N*	75
Male, *n* (%)	50 (66.7)
Female, *n* (%)	25 (33.3)
Characteristic,[a] median (IQR)	
Age (y)	69 (64–76.5)
Body weight (kg)	78 (65.3–89.5)
BMI (kg/m^2)	24.9 (23.5–28.4)
Creatinine clearance (mL/min)	74.8 (53.0–92.5)
Pathogen, *n* (%)	
Streptococci	59 (78.7)
Enterococcus faecalis	10 (13.3)
Staphylococci	5 (6.7)
Unknown[b]	1 (1.3)
Outcome,[c] *n* (%)	6 (8.0)

BMI, body mass index; IQR, interquartile range.
[a] Body weight, height, and creatinine data were missing for one patient each, making BMI calculations impossible for two patients and creatinine clearance estimation impossible for one.
[b] Microbiological data were unavailable for one patient.
[c] The composite outcome in the Partial Oral Endocarditis Treatment study included all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteraemia with the primary pathogen.

Population PK analysis

A total of 291 plasma concentrations of benzylpenicillin were available for analysis. A two-compartment model with the first-order elimination adequately described the data. The population PK estimates are reported in Table S1. Large inter-individual variation was observed. We observed significant correlations between clearance, inter-compartmental clearance, and volume of central compartment, which were kept in the final model and the simulations. The residual variability was best described by a proportional error model.

Inclusion of estimated creatinine clearance as a covariate for clearance caused a significant improvement of the model (change in objective function value = −49.11, $p < 0.0001$) and was retained in the final model. No significant improvement was observed including body weight as a covariate.

Goodness-of-fit plots are presented in Fig. S3. They showed an acceptable fit with no visible structural misspecifications. The performed visual predictive check is provided in Fig. S4, further demonstrating an adequate fit with no systematic trends.

Individual target attainment and PK/PD analyses

The individual target attainment with targets of 50% fT > MIC and 50% fT > 4 × MIC was 100% (56/56) and 94.6% (53/56) for streptococci, 100% (3/3) for staphylococci, and only 66.7% (6/9) and 33.3% (3/9) for *E. faecalis*, although only three patients with staphylococcal IE were evaluated (Table 2). Using stricter thresholds of 100% fT > MIC and 100% fT > 4 × MIC, the individual target attainment was 89.3% (50/56) and 75.0% (42/56) for streptococci, 100.0% (3/3) and 66.7% (2/3) for staphylococci, and 33.3% (3/9) and 11.1% (1/9) for *E. faecalis*, respectively.

Among the six patients who reached an endpoint, five patients achieved 50% fT > MIC, five patients achieved 100% fT > MIC and 50% fT > 4 × MIC, and four patients achieved 100% fT > 4 × MIC.

Model-based simulations assuming the median creatinine clearance of 74.8 mL/min showed that high PTAs (>90%) were

Table 2
Individual target attainment

Patient group	50% fT > MIC	100% fT > MIC	50% fT > 4 × MIC	100% fT > 4 × MIC
All patients with available MIC ($N = 68$)	95.6% (65/68)	82.4% (56/68)	86.8% (59/68)	66.2% (45/68)
Streptococci ($N = 56$)	100.0% (56/56)	89.3% (50/56)	94.6% (53/56)	75.0% (42/56)
Enterococcus faecalis ($N = 9$)	66.7% (6/9)	33.3% (3/9)	33.3% (3/9)	11.1% (1/9)
Staphylococci ($N = 3$)	100.0% (3/3)	100.0% (3/3)	100.0% (3/3)	66.7% (2/3)

The letter f indicates the free unbound concentration; e.g. fT > MIC means the time above MIC of the unbound concentration. T, time.

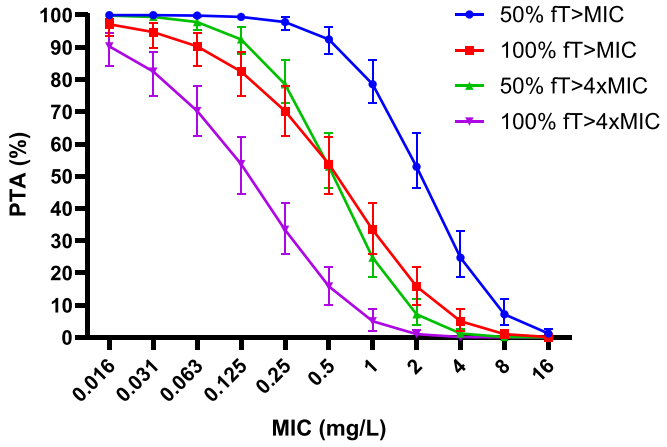

Fig. 1. PTA from Monte-Carlo simulations. A median creatinine clearance of 74.8 mL/min was assumed. The letter f indicates the free unbound benzylpenicillin concentration; e.g. fT > MIC means the time above MIC of the unbound concentration. The error bars indicate the 90% CIs for the estimates. PTA, probability of target attainment; T, time.

achieved for MIC values ≤ 0.5 mg/L with a standard target of 50% fT > MIC, and for MIC values ≤ 0.063 mg/L with targets set at 100% fT > MIC or 50% fT > 4 × MIC (Fig. 1). The strictest target of 100% fT > 4 × MIC did only result in a high PTA if a low MIC of 0.016 mg/L was assumed.

Simulating patients with varying degrees of renal function yielded significant shifts in the estimated PTAs, as illustrated in Fig. 2. Reduced renal function (creatinine clearance = 40.8 mL/min) resulted in high PTAs for MIC ≤1.0 mg/L with the standard target of 50% fT > MIC, for MIC ≤0.25 mg/L with targets set at 50% fT > 4 × MIC or 100% fT > MIC, and even for MIC ≤0.063 mg/L with a stringent 100% fT > 4 × MIC target. Conversely, higher renal function (creatinine clearance = 103.2 mL/min) led to a notable decrease in PTA. High PTAs were only observed with the standard target and MIC values ≤ 0.25 mg/L, a target of 50% fT > 4 × MIC and MIC values ≤ 0.063 mg/L, or a target of 100% fT > MIC with a low MIC of 0.016 mg/L.

Discussion

The evaluation of antibiotic plasma concentrations and infecting bacterial MICs in the POET trial enabled us to perform thorough PK/PD analyses [5]. Previously, we evaluated individual target attainment using standard targets of the major oral antibiotics included in the POET trial [25]. In the present study, we analysed the target attainment of intravenous benzylpenicillin (3000 mg q6h) in 75 patients from the POET trial and found that most patients achieved the target levels, particularly those infected with streptococci or susceptible staphylococci. However, target attainment in the nine patients infected with *E. faecalis* was notably low (11–67%). This finding can be explained by the elevated expression of low-affinity penicillin-binding proteins, particularly PBP5, in enterococcal species, leading to high MICs [26]. Thus, the low PTA for *E. faecalis* corresponds to the elevated epidemiological cut-off value reported by European Committee on Antimicrobial Susceptibility Testing (8 mg/L), in contrast to streptococci and staphylococci, which have epidemiological cut-off values of <1 mg/L [27]. Furthermore, high renal function was found to significantly reduce PTA.

Although six patients reached an endpoint in this POET substudy, four of them achieved the high PK/PD target of 100% fT > 4 × MIC. This suggests that factors other than benzylpenicillin treatment may have influenced the outcome, underlining the complexity of IE. However, it is well established that achieving sufficient antibiotic plasma levels is strongly correlated with clinical outcomes in critically ill patients, particularly those with bloodstream infections, and the consequences of underexposure can be devastating [8]. A recent systematic review evaluated optimal PK/PD targets in patients with IE and concluded that although T > MIC is important, no single PK/PD target can be

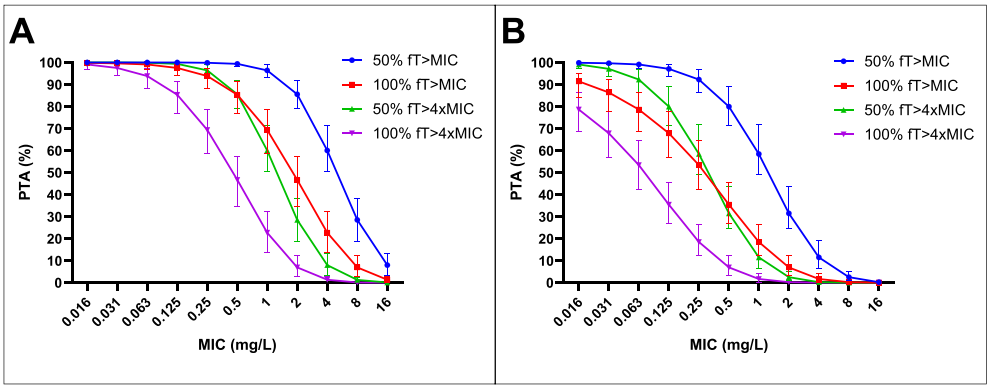

Fig. 2. PTA with reduced (a) and high renal function (b). A creatinine clearance of 40.8 mL/min (a) or 103.2 mL/min (b) was assumed, corresponding to the 10th and 90th percentile of estimated creatinine clearance. The letter f indicates the free unbound benzylpenicillin concentration; e.g. fT > MIC means the time above MIC of the unbound concentration. The error bars indicate the 90% CIs for the estimates. PTA, probability of target attainment; T, time.

established based on the current level of evidence and suggested more clinical trials validating defined therapeutic targets [13].

A previous study evaluating benzylpenicillin in 46 patients with IE reported that 96% achieved 50% fT > MIC, and 71% achieved 100% fT > MIC [21]. Consistent with our results, the authors concluded that enterococcal IE was associated with a poor PTA. Another study involving 25 patients with streptococcal IE conducted population PK analysis of benzylpenicillin and found that a trough plasma concentration exceeding 60 × MIC to be associated with a positive outcome proposing an optimal dose of 1 million IU/h continuously [20].

Identifying patients at risk of underexposure to penicillin is crucial, as these patients could experience worse clinical outcomes and might benefit from therapeutic drug monitoring or an increase in dosage [7]. In our study, the inter-individual variation of PK parameters was substantial, consistent with previous studies of critically ill patients [28,29]. If underexposure of benzylpenicillin is identified, possible solutions include appropriately increasing the dose or switching to alternative antibiotics with a better PK/PD profile. Alternatively, co-administering an antibiotic from a different class can be considered. Furthermore, some studies suggest that extended or continuous infusions of β-lactams may improve the PTA and clinical outcome compared with short infusions [30], as they optimize time-dependent bacterial killing. This approach also reduces the burden on nursing staff by requiring fewer venous line manipulations.

The present study has limitations. First, the POET study was not designed for subgroup analyses, and because of the limited sample size of 75 patients, of whom only six patients reached an endpoint, no PK/PD analysis evaluating clinical outcome could be performed. Second, the free unbound plasma concentrations were estimated based on the measured total concentrations and a previously reported unbound fraction. The magnitude of protein binding in this study population may differ, and inter-individual variation may have influenced the results, although substantial bias seems unlikely. Third, the potential impact of body weight on the PK of benzylpenicillin could not be quantified, as body weight did not significantly improve the PK model, likely because of limited variability in body weight among patients. Fourth, the penetration and distribution of benzylpenicillin within the bacterial vegetations were not investigated. Understanding these aspects is important for achieving target concentrations at the site of infection. Fifth, benzylpenicillin was administered as short infusions over approximately 30 minutes, but the individual infusion times were not recorded, which may have influenced the analyses. To investigate this, we performed simulations assuming infusion times of 15 or 45 minutes, which did not substantially alter the PTA values (Fig. S5).

In conclusion, most patients with IE achieve the target levels of intravenously administered benzylpenicillin (3000 mg q6h), especially those with streptococcal or susceptible staphylococcal infections. The low individual target attainment observed in patients with IE caused by *E. faecalis* aligns with existing evidence and guidelines that suggest benzylpenicillin may have limitations in treating enterococcal IE, especially in patients with preserved renal function.

Author contributions

K.I., N.I., J.H.-L., C.M., and H.B. designed the Partial Oral Endocarditis Treatment trial and wrote the protocol. K.I. and H.B. lead the Partial Oral Endocarditis Treatment trial. The benzylpenicillin pharmacokinetic/pharmacodynamic study was planned by C.M., M.B., K.I., N.I., S.G., U.C., H.E., J.A.P., N.E.B., D.E.H., E.L.F., J.H.-L., L.K., M.M.P.-H., C.T.P., N.T., J.J.C., F.S.R., K.F., and H.B. Pharmacokinetic analyses were conducted by M.B. and J.G.C.V.H. M.B. did first manuscript writing. All co-authors contributed to the manuscript and approved the final version. All authors had access to data.

Transparency declaration

Potential conflict of interest

J.G.C.V.H. reports unpaid board membership of Pharmacometrics Network Benelux Foundation and Foundation for Advancement of Systems Pharmacology. C.T.P. reports a grant from Bayer for a randomized study, and a grant from Novo Nordisk for an epidemiological study. L.K. reports payment for speaking engagements from AstraZeneca, Boehringer, Novartis, and Novo Nordisk. All other authors report no potential conflicts.

Financial report

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2025.04.025.

References

[1] Delgado V, Ajmone Marsan N, de Waha S, Bonaros N, Brida M, Burri H, et al. 2023 ESC Guidelines for the management of endocarditis. Eur Heart J 2023;44:3948–4042. https://doi.org/10.1093/eurheartj/ehad193.
[2] Holland TL, Baddour LM, Bayer AS, Hoen B, Miro JM, Fowler Jr VG. Infective endocarditis. Nat Rev Dis Primers 2016;2:16059. https://doi.org/10.1038/nrdp.2016.59.
[3] Werdan K, Dietz S, Löffler B, Niemann S, Bushnaq H, Silber RE, et al. Mechanisms of infective endocarditis: pathogen-host interaction and risk states. Nat Rev Cardiol 2014;11:35–50. https://doi.org/10.1038/nrcardio.2013.174.
[4] Park LP, Chu VH, Peterson G, Skoutelis A, Lejko-Zupa T, Bouza E, et al. Validated risk score for predicting 6-month mortality in infective endocarditis. J Am Heart Assoc 2016;5:e003016. https://doi.org/10.1161/JAHA.115.003016.
[5] Iversen K, Ihlemann N, Gill SU, Madsen T, Elming H, Jensen KT, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med 2019;380:415–24. https://doi.org/10.1056/NEJMoa1808312.
[6] Pries-Heje MM, Wiingaard C, Ihlemann N, Gill SU, Bruun NE, Elming H, et al. Five-year outcomes of the Partial Oral Treatment of Endocarditis (POET) trial. N Engl J Med 2022;386:601–2. https://doi.org/10.1056/NEJMc2114046.
[7] Abdul-Aziz MH, Alffenaar JC, Bassetti M, Bracht H, Dimopoulos G, Marriott D, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a position paper. Intensive Care Med 2020;46:1127–53. https://doi.org/10.1007/s00134-020-06050-1.
[8] Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 2014;58:1072–83. https://doi.org/10.1093/cid/ciu027.
[9] Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol 2004;2:289–300. https://doi.org/10.1038/nrmicro862.
[10] Berry AV, Kuti JL. Pharmacodynamic thresholds for beta-lactam antibiotics: a story of mouse versus man. Front Pharmacol 2022;13:833189. https://doi.org/10.3389/fphar.2022.833189.
[11] Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26. https://doi.org/10.1086/516284. quiz 11-2.
[12] Ciofu O, Moser C, Jensen PØ, Høiby N. Tolerance and resistance of microbial biofilms. Nat Rev Microbiol 2022;20:621–35. https://doi.org/10.1038/s41579-022-00682-4.
[13] Robson C, Tan B, Stuart R, Nicholls S, Rogers BA, Sandaradura I. A systematic review of optimal pharmacokinetic/pharmacodynamic parameters for beta-lactam therapy in infective endocarditis. J Antimicrob Chemother 2023;78:599–612. https://doi.org/10.1093/jac/dkad005.

[14] Delattre IK, Taccone FS, Jacobs F, Hites M, Dugernier T, Spapen H, et al. Optimizing beta-lactams treatment in critically-ill patients using pharmacokinetics/pharmacodynamics targets: are first conventional doses effective? Expert Rev Anti Infect Ther 2017;15:677–88. https://doi.org/10.1080/14787210.2017.1338139.
[15] Li C, Du X, Kuti JL, Nicolau DP. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother 2007;51:1725–30. https://doi.org/10.1128/AAC.00294-06.
[16] McKinnon PS, Paladino JA, Schentag JJ. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents 2008;31:345–51. https://doi.org/10.1016/j.ijantimicag.2007.12.009.
[17] Iversen K, Høst N, Bruun NE, Elming H, Pump B, Christensen JJ, et al. Partial oral treatment of endocarditis. Am Heart J 2013;165:116–22. https://doi.org/10.1016/j.ahj.2012.11.006.
[18] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro 3rd AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006.
[19] Bos JC, van Hest RM, Misticio MC, Nunguiane G, Lang CN, Beirão JC, et al. Pharmacokinetics and pharmacodynamic target attainment of benzylpenicillin in an adult severely ill sub-Saharan African patient population. Clin Infect Dis 2018;66:1261–9. https://doi.org/10.1093/cid/cix961.
[20] Komatsu T, Inomata T, Watanabe I, Kobayashi M, Kokubun H, Ako J, et al. Population pharmacokinetic analysis and dosing regimen optimization of penicillin G in patients with infective endocarditis. J Pharm Health Care Sci 2016;2:9. https://doi.org/10.1186/s40780-016-0043-x.
[21] Öbrink-Hansen K, Wiggers H, Bibby BM, Hardlei TF, Jensen K, Kragh Thomsen M, et al. Penicillin G treatment in infective endocarditis patients—does standard dosing result in therapeutic plasma concentrations? Basic Clin Pharmacol Toxicol 2017;120:179–86. https://doi.org/10.1111/bcpt.12661.
[22] Shah RV, Kipper K, Baker EH, Barker CIS, Oldfield I, Philips BJ, et al. Population pharmacokinetic study of benzylpenicillin in critically unwell adults. Antibiotics (Basel) 2023;12:643. https://doi.org/10.3390/antibiotics12040643.
[23] Nguyen TH, Mouksassi MS, Holford N, Al-Huniti N, Freedman I, Hooker AC, et al. Model evaluation of continuous data pharmacometric models: metrics and graphics. CPT Pharmacometrics Syst Pharmacol 2017;6:87–109. https://doi.org/10.1002/psp4.12161.
[24] Colin P, Eleveld DJ, Jonckheere S, Van Bocxlaer J, De Waele J, Vermeulen A. What about confidence intervals? A word of caution when interpreting PTA simulations. J Antimicrob Chemother 2016;71:2502–8. https://doi.org/10.1093/jac/dkw150.
[25] Bock M, Theut AM, van Hasselt JGC, Wang H, Fuursted K, Høiby N, et al. Attainment of target antibiotic levels by oral treatment of left-sided infective endocarditis: a POET substudy. Clin Infect Dis 2023;77:242–51. https://doi.org/10.1093/cid/ciad168.
[26] Zapun A, Contreras-Martel C, Vernet T. Penicillin-binding proteins and beta-lactam resistance. FEMS Microbiol Rev 2008;32:361–85. https://doi.org/10.1111/j.1574-6976.2007.00095.x.
[27] MIC and zone diameter distributions and ECOFFs: European committee on antimicrobial Susceptibility testing (EUCAST). http://eucast.org. [Accessed 14 April 2025].
[28] Gonçalves-Pereira J, Póvoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. Crit Care 2011;15:R206. https://doi.org/10.1186/cc10441.
[29] Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 2014;14:498–509. https://doi.org/10.1016/S1473-3099(14)70036-2.
[30] Hong LT, Downes KJ, FakhriRavari A, Abdul-Mutakabbir JC, Kuti JL, Jorgensen S, et al. International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics: endorsed by the American college of clinical pharmacy, British society for antimicrobial chemotherapy, cystic fibrosis foundation, European society of clinical microbiology and infectious diseases, infectious diseases society of America, society of critical care medicine, and society of infectious diseases pharmacists. Pharmacotherapy 2023;43:740–77. https://doi.org/10.1002/phar.2842.