

Rifampin co-administration with clindamycin can result in failure to reach the PKPD targets in staphylococcal osteoarticular infections

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Introduction

Background

- In staphylococcal osteoarticular infections (OAI), the oral combination of clindamycin and rifampin, is a relevant choice [1,2]
- Rifampin induces CYP3A4, which suggests a pharmacokinetic interaction with clindamycin [3]

Objectives

- To describe the pharmacokinetics of clindamycin before and during rifampin co-administration
- To estimate the rifampin effect on pharmacokinetics parameters of clindamycin and on the probability to reach the minimal inhibitory concentrations (MIC)-based PKPD targets

Methods

Clinical trial, design

- The DALARI clinical trial (NCT02782078 — Principal investigator: Tiphaine Goulenok, MD — Sponsored by Assistance Publique Hôpitaux de Paris) was started in 2017 in three French hospitals, in adult patients with staphylococcal OAI
- After an initial antibiotherapy, oral clindamycin was started: 1800mg (low) or 2400mg (high) in 3 daily doses, followed by rifampin 36 hours after clindamycin introduction. Clindamycin plasma concentrations were measured on day 2 and 14 (without and with rifampin, respectively), each patient being his own control (Figure 1)

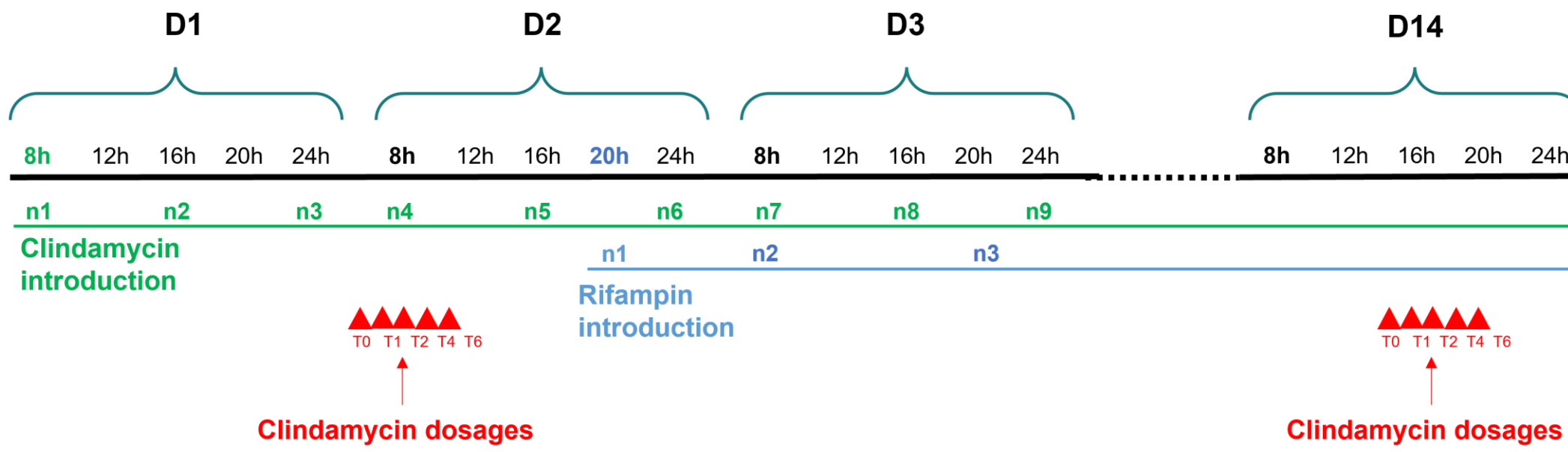


Figure 1: Design of the DALARI clinical trial

Statistical model for a parameter p

$\log(\theta_{p_{ik}}) = \log(\mu_p) + \eta_{p_i} + \eta_{p_{ik}} + \beta_{p_{RIFAM}} \times I_{RIFAM_{ik}}$
 μ , fixed effect; η , random effect; i , individual; k , occasion; β , covariate effect; I_{RIFAM} , rifampin indicator (0 if without rifampin, 1 if with rifampin)

Table 1: PKPD markers and targets

PKPD Marker	Notation	Target(s)
Residual concentration	C_{res}/MIC	> 2
Exposure	AUC_8 or AUC_{24}/MIC	$AUC_{24}/MIC > 60$ or > 120
Fraction of time above MIC between two doses	$\%fT_{>MIC}$	100%

Clindamycin population pharmacokinetic model

- Parameters estimated with SAEM (Monolix 2020R1) [4]
- Model selection (structure, random and error models) was based on BICc and goodness of fits
- Rifampin was investigated as a binary covariate effect (backward selection on all parameters with inter-occasion variability, Wald test, $p < 0.05$)
- Model evaluation: NPDE and prediction-corrected VPC (pcVPC) from 1000 Monte Carlo simulations

Pharmacokinetic-Pharmacodynamic (PKPD) targets — simulations

- From empirical Bayes estimates (EBE) and individual MIC, PKPD markers (Table 1) were calculated
- Model-based simulations ($n=1000$) were performed (low or high clindamycin dose, with or without rifampin)

Results

Data

- Clindamycin PK was measured in 19 patients (Figure 2)
- Median MIC was 0.047 mg/L

Pharmacokinetic model, parameters & evaluation

- Clindamycin PK at steady state ($t_{1/2} = 3h$) was described by a two-compartment model
- Rifampin co-administration increased the clindamycin clearance (CL) by a factor 15 and the intercompartmental clearance (Q) by a factor 3 (Table 2)
- Both NPDE and pcVPC showed that the model adequately described the clindamycin PK (Figure 3)

Table 2: Estimated PK parameters of clindamycin and relative standard errors (rse)

Parameter	Estimate (rse in %)	p-value of Wald test
Fixed & covariate effects		
k_a (h^{-1})	1.2 (16)	
V_1 (L)	60 (14)	
Q (L/h)	13 (28)	
$\beta_{Q_{RIFAM}}$	1.1 (36)	$< 2.2E-16$
V_2 (L)	180 (60)	
CL (L/h)	15 (13)	
$\beta_{CL_{RIFAM}}$	2.7 (5)	0.006
Between-subject variability		
ω_{k_a} (%)	64 (20)	
ω_{V_2} (%)	215 (24)	
ω_{CL} (%)	40 (24)	
$corr(k_a, CL)$	-0.73 (26)	
Between-occasion variability		
γ_{V_1} (%)	48 (21)	
γ_Q (%)	76 (23)	
γ_{CL} (%)	39 (15)	
Residual variability		
σ_{add} (mg/L)	0.03 (39)	
σ_{prop} (%)	11 (15)	

β_{PCOV} , COV effect on p

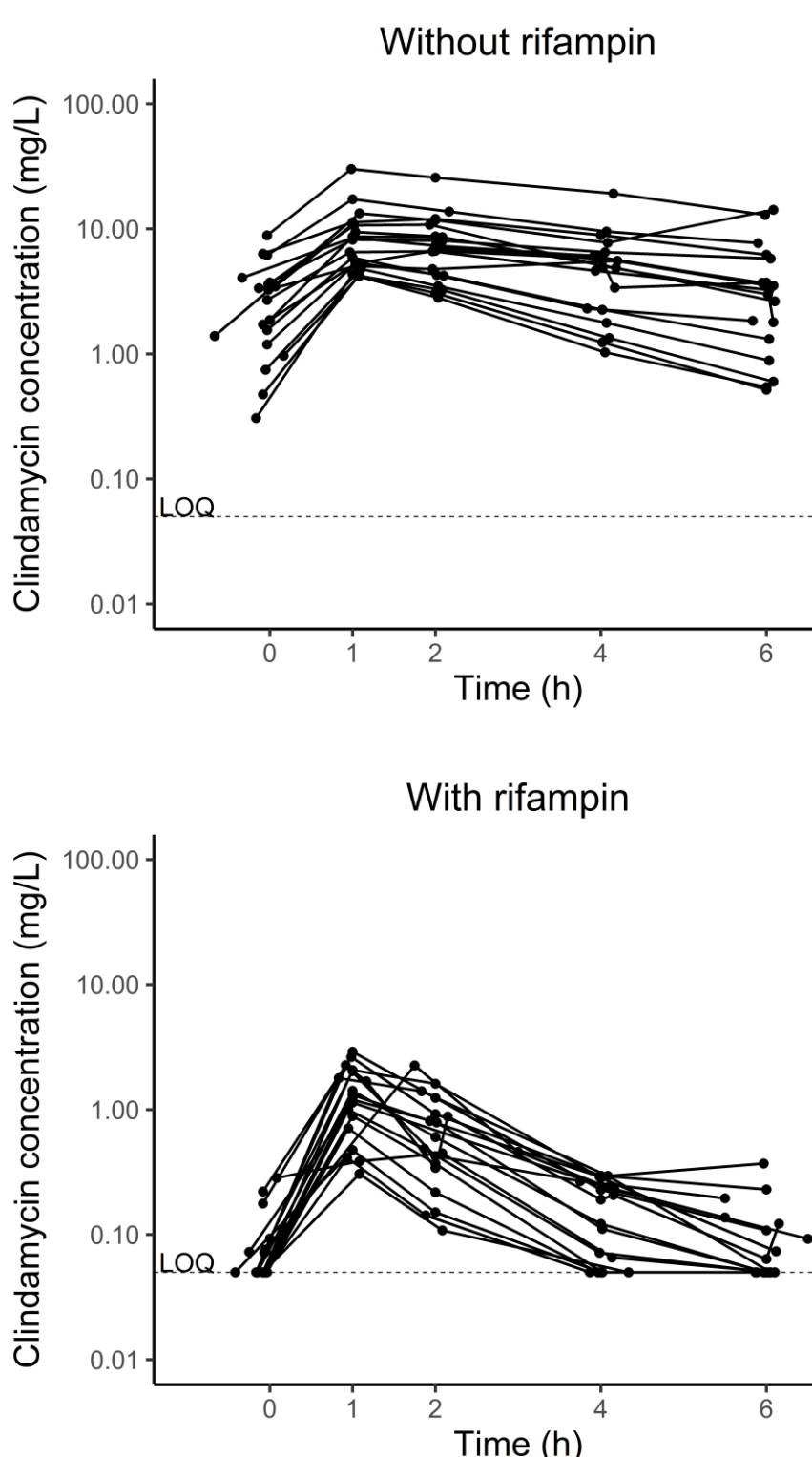


Figure 2: Observed clindamycin plasma concentrations, without (top) and with rifampin (bottom)

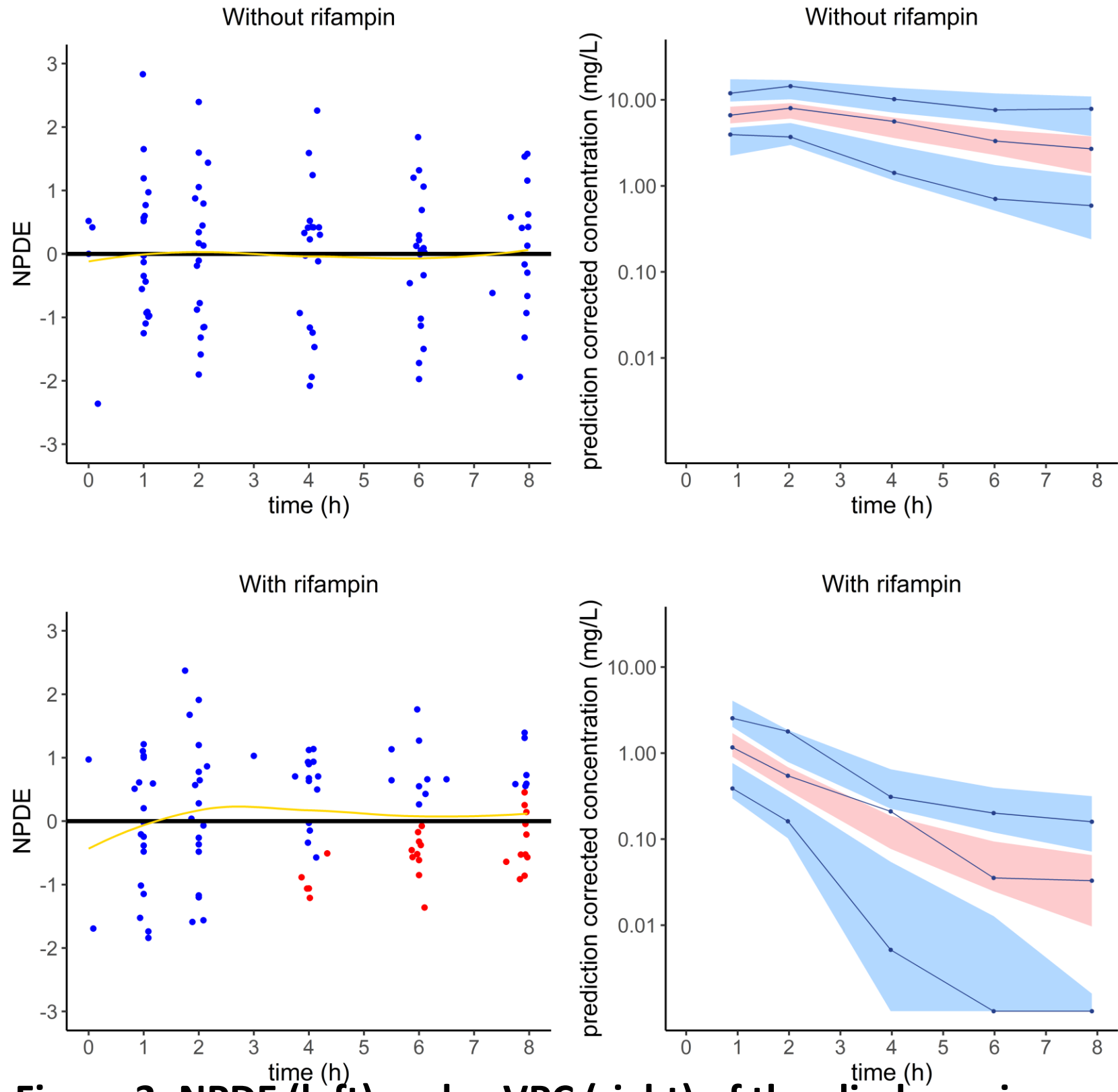


Figure 3: NPDE (left) and pcVPC (right) of the clindamycin PK model, without (top) and with rifampin (bottom)

Red dots are NPDE of below limit of quantification data

Individual PKPD parameters

- Rifampin co-administration reduced clindamycin PKPD parameters (Table 3)

Table 3: Derived PKPD parameters

Parameter	Without rifampin	With rifampin	Ratio without/with rifampin
AUC_8/MIC	1180 (268-4780)	71.8 (18.2-182)	14.0 (7.2-33.7)
C_{res}/MIC	64.7 (11.0-438)	0.3 (< 0.05 -5.5)	97.6 (27.5-1120.0)
$\%fT_{>MIC}$	100 (100-100)	82.9 (34.5-100)	1.5 (1.0-2.9)

Parameters are reported as median (min-max)

Model based simulations of probability to reach PKPD targets

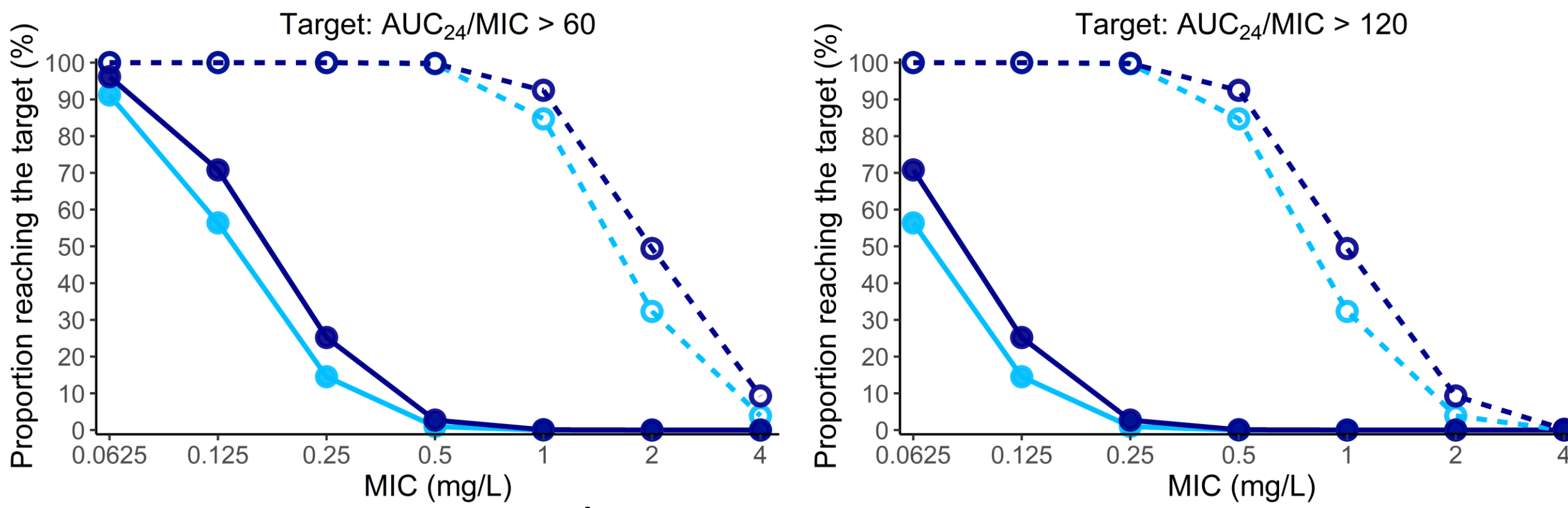


Figure 5: Probability to reach AUC/MIC targets vs. MIC

For a low (light blue) or a high dose (dark blue) of clindamycin, without (dashed lines) or with rifampin (solid lines)

- Against a susceptible strain ($MIC = 0.25$ mg/L), more than 90% reached all the proposed PKPD targets without rifampin, whereas the proportion reaching $AUC_{24}/MIC > 60$ was 25% with rifampin and high dose of clindamycin (Figure 5)

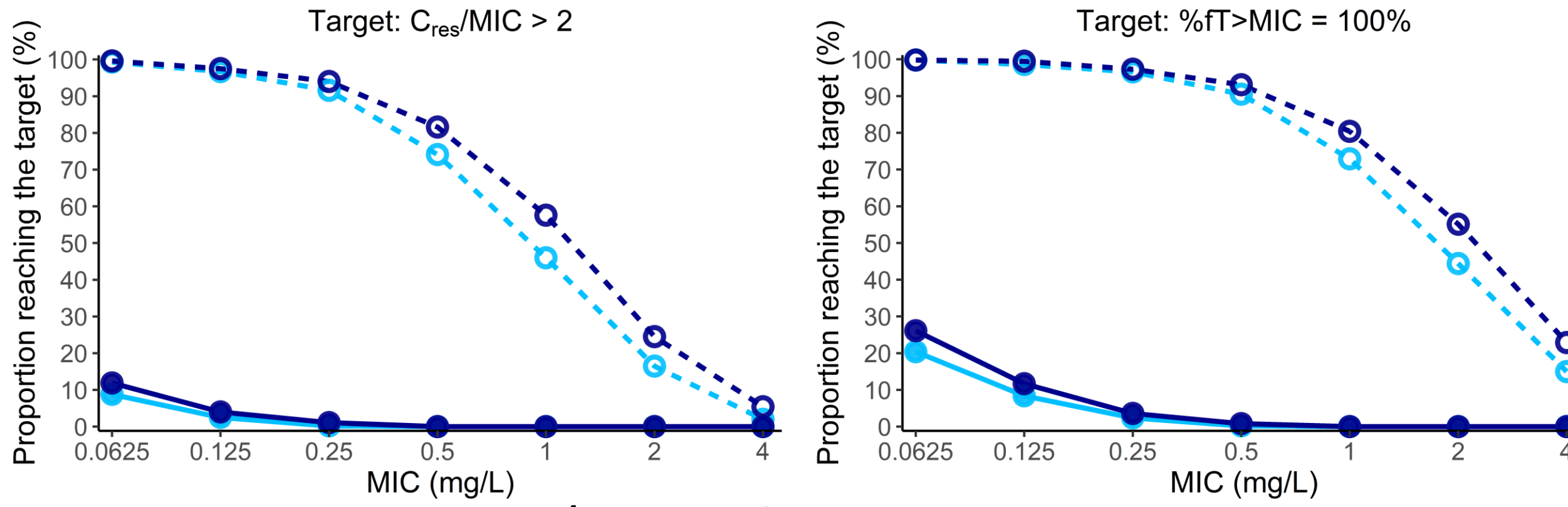


Figure 6: Probability to reach C_{res}/MIC and $\%fT_{>MIC}$ targets vs. MIC

For a low (light blue) or a high dose (dark blue) of clindamycin, without (dashed lines) or with rifampin (solid lines)

- Against a more resistant strain ($MIC = 1$ mg/L), a high dose of clindamycin increased the probability to reach $C_{res}/MIC > 2$ to 58% vs. 46% for a low dose without rifampin, whereas 0% of individuals reached any of the PKPD targets with rifampin (Figure 6)

Conclusions

- Our study quantifies the interaction of rifampin with clindamycin PK in OAI patients
- Although our small sample size does not allow to make dose recommendations, our results suggest that a high dose of clindamycin would be preferable in case of intermediary bacterial strain
- Although different PKPD targets have been proposed for clindamycin, it is necessary to define which one is the most relevant [5]
- An extension of this work would be to analyse the PK data of rifampin and develop a semi-mechanistic model such as the global pharmacodynamic interaction model [6]

References

[1] Courjon V, et al., *Eur J Clin Microbiol Infect Dis*. 2017. ; [2] Muller-Seriesys C, et al. *Antimicrob Agents Chemother*. 2009. ; [3] Niemi M, et al. *Clin Pharmacokinet*. 2003. ; [4] Kuhn E, et al. *Comput Stat Data Anal*. 2005. ; [5] Curis E, et al. *Infection*. 2015. ; [6] Wicha S, et al. *Nat Commun*. 2017.