

Population Pharmacokinetic/Pharmacodynamic Analysis of Cefiderocol in Chinese Patients with Complicated Urinary Tract Infections

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INTRODUCTION

- Cefiderocol, a siderophore cephalosporin, demonstrates potent activity against Gram-negative bacteria, including carbapenem-resistant isolates. It has been approved in the USA for the treatment of complicated urinary tract infections (cUTI) and hospital-acquired and ventilator-associated bacterial pneumonia. In Europe, it is approved for the treatment of infections caused by susceptible Gram-negative bacteria in adult patients with limited treatment options.
- Its standard dosing regimen (2 g every 8 h, 3 h infusion) is adjusted for renal function (i.e., creatinine clearance <60 or ≥120 mL/min). However, evidence supporting adequate exposure in Chinese patients with cUTI is lacking.
- The objective of this study was to investigate the pharmacokinetics/pharmacodynamics (PK/PD) of cefiderocol in Chinese patients with cUTI, and to compare differences in PK/PD versus Caucasian patients with cUTI.

METHODS

- A published population pharmacokinetic model (3,427 plasma concentrations from 91 uninfected subjects and 425 patients with pneumonia, bloodstream infection/sepsis, or cUTI) was updated with 763 concentrations from 12 Chinese healthy subjects and 94 patients with cUTI from a Phase III clinical trial in Chinese patients (Trial #: 2021P0005) (**Figure 1**).
- The *in vitro* susceptibility results of cefiderocol were derived from the 2023 surveillance of its *in vitro* antibacterial activity against Gram-negative bacilli isolated from clinical samples in China (unpublished data).
- The model evaluated renal-adjusted dosing, probability of target attainment (PTA), cumulative fraction of response (CFR) against pathogens, and correlations between proportion of the dosing interval that the unbound drug concentration exceeded the minimum inhibitory concentration (%T>MIC) and clinical/microbiological outcomes in relation to estimated cefiderocol plasma concentrations.

RESULTS

- The exposure differences, falling between 0.8 and 1.25, were bioequivalent between Chinese and Caucasian patients with cUTI (**Figure 2**).
- Renal-adjusted dosing was validated for Chinese patients, achieving >90% PTA for MIC ≤4 µg/mL and CFR >98% against all species considered, including *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Stenotrophomonas maltophilia* (**Figure 3**).
- Most patients achieved 100% fT>MIC, precluding quantitative exposure–response relationships (**Figure 4**).

Figure 1. Overview of workflow for the study (A) and baseline demographic characteristic of Chinese patients with complicated urinary tract infections (B). Continuous data in Figure 1B are shown as median (min; max) and categorical data are shown as number of subjects (proportion)

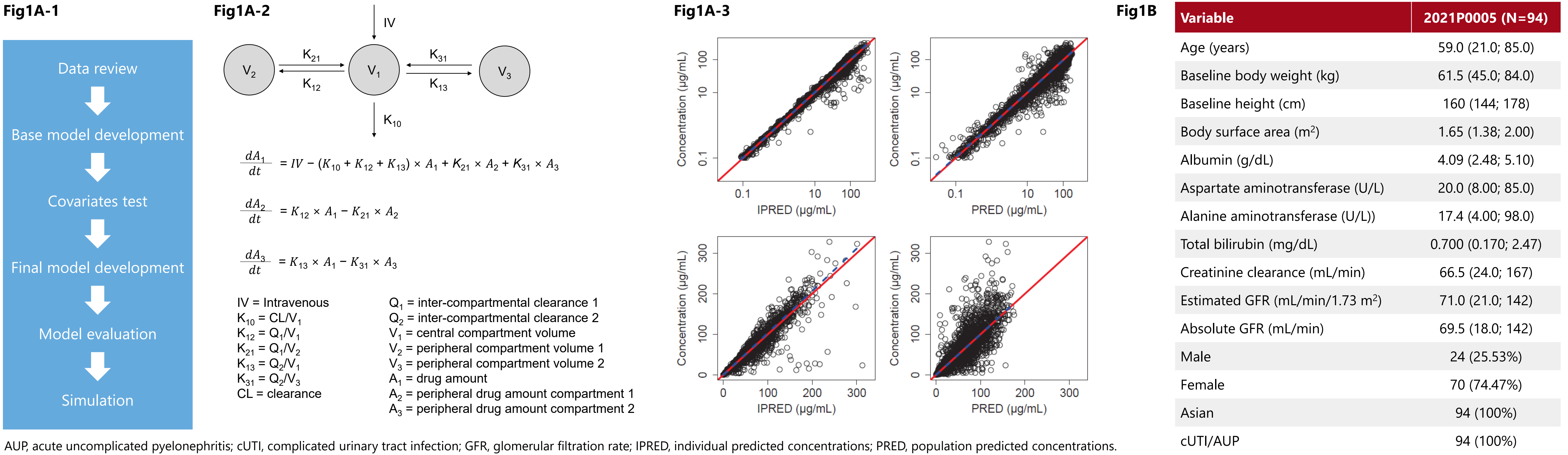


Figure 2. Cefiderocol exposure in Chinese patients with cUTI (N=94) compared with global patients with cUTI (N=238)

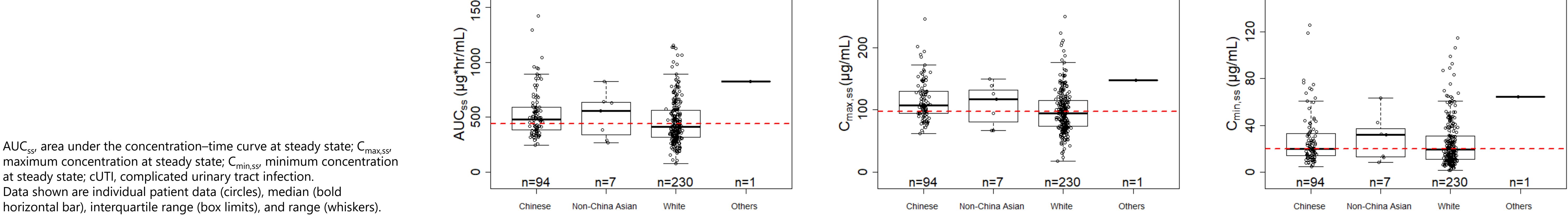


Figure 3. Simulated cefiderocol exposure in Chinese patients with cUTI under renal-adjusted dosing regimens (A), simulated probability of target attainment (B) and cumulative fraction of response (C) of cefiderocol against different Gram-negative pathogens

Fig3-A

Renal function	CrCL (mL/min)	Dosing regimen	C _{max,ss} (µg/mL) ^a	AUC _{T,ss} (µg/mL × h) ^a	C _{min,ss} (µg/mL) ^a
Augmented	≥120	2g q6h	74.36 (31)	1115.57 (35)	17.02 (63)
Normal	90 to <120	2g q8h	82.22 (30)	1035.17 (35)	12.08 (70)
Mild impairment	60 to <90	2g q8h	95.03 (30)	1282.06 (35)	19.30 (62)
Moderate impairment	30 to <60	1.5g q8h	91.67 (31)	1382.37 (37)	28.34 (57)
Severe impairment	15 to <30	1g q8h	85.18 (31)	1462.21 (37)	39.37 (48)
ESRD	5 to <15	0.75g q12h	76.03 (33)	1262.36 (40)	34.29 (52)

Simulation setting: n=1000; weight = 60.6 kg (CV: 30%, range 40–85 kg); albumin = 2.96 g/dL (CV: 30%, range 2.62–3.35 g/dL). Proportion of renal function: augmented (18%), normal (46%), mild impairment (18%), and moderate impairment (18%).
AUC_{T,ss}, area under the concentration–time curve over the dosing interval (=tau) at steady state; CFR, cumulative fraction of response; C_{max,ss}, maximum concentration at steady state; C_{min,ss}, minimum concentration at steady state; CrCL, creatinine clearance; cUTI, complicated urinary tract infection; ESRD, end-stage renal disease; PTA, probability of target attainment; q6/8/12h, every 6/8/12 hours.
^a Data is presented as Mean (CV%).

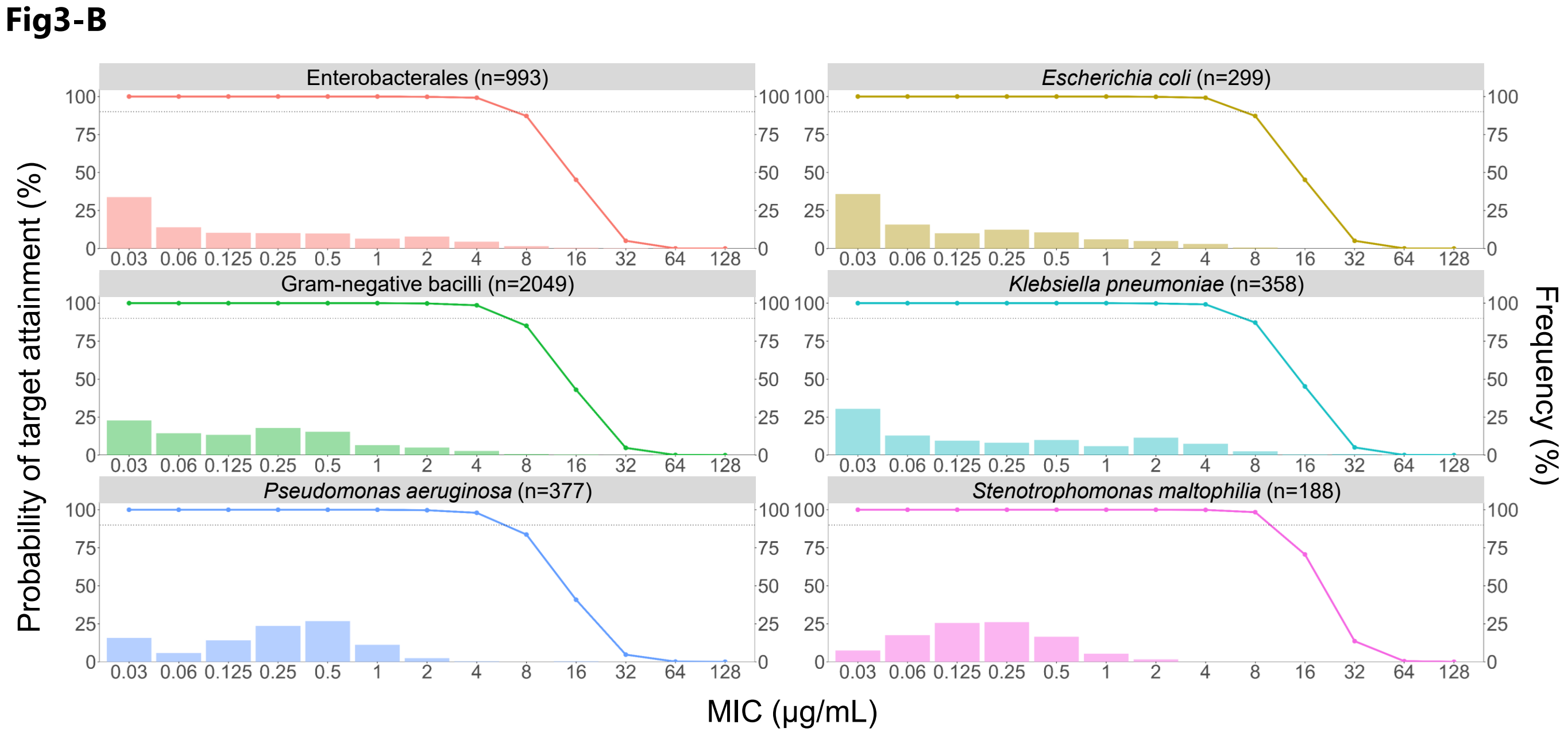


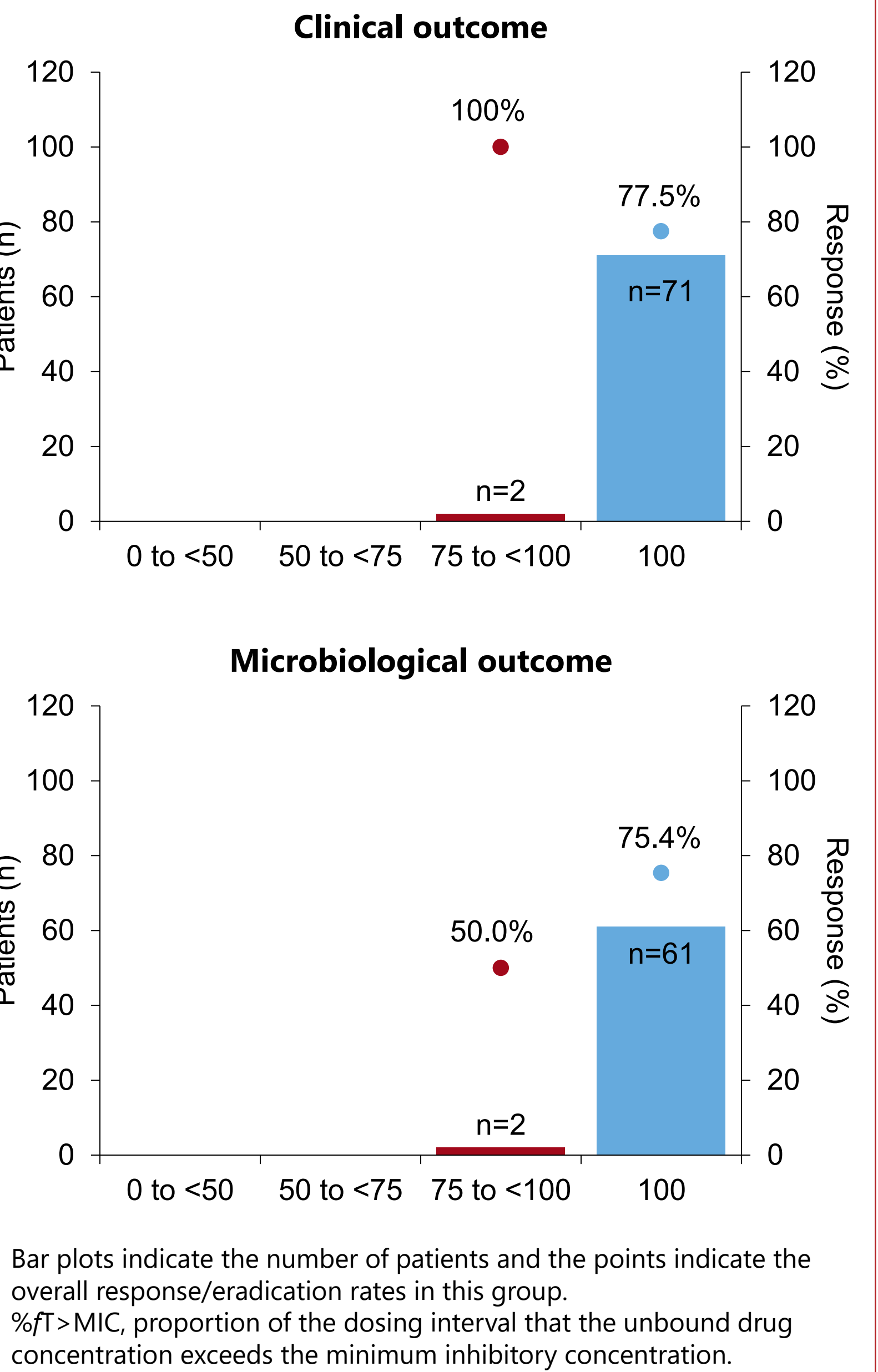
Fig3-C

Strain (n)	PK/PD target (%fT>MIC)	CFR
Gram-negative bacilli (2049)	75.0%	99.23%
Enterobacterales (993)	73.3%	98.67%
E. coli (299)	73.3%	99.21%
K. pneumoniae (358)	73.3%	98.22%
P. aeruginosa (377)	77.2%	99.85%
S. maltophilia (188)	53.9%	100%

CONCLUSIONS

- The PK/PD characteristics of cefiderocol were comparable between Chinese and Caucasian populations, without meaningful differences.
- The renal-adjusted cefiderocol regimen was appropriate for Chinese patients with cUTI, with expected robust microbiological efficacy.

Figure 4. Distribution of patients in %fT>MIC categories and rates of clinical and microbiological outcomes



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Conflict of interest: TK, NX, HD, and JY are employees of the Shionogi GROUP.