Inhibiteurs de β-lactamases

Un des premiers articles…

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Antimicrob Agents Chemother 2013;57:2809–2814

Pharmacokinetics-Pharmacodynamics of Tazobactam in Combination with Ceftolozane in an *In Vitro* Infection Model

Brian VanScoy,[a] Rodrigo E. Mendes,[b] Anthony M. Nicasio,[c] Mariana Castanheira,[b] Catharine C. Bulik,[a] Olanrewaju O. Okusanya,[a] Sujata M. Bhavnani,[a] Alan Forrest,[a] Ronald N. Jones,[b] Lawrence V. Friedrich,[d] Judith N. Steenbergen,[d] Paul G. Ambrose[a,e]

Institute for Clinical Pharmacodynamics, Latham, New York, USA[a]; JMI Laboratories, North Liberty, Iowa, USA[b]; Albany College of Pharmacy and Health Sciences, Albany, New York, USA[c]; Cubist Pharmaceuticals, Lexington, Massachusetts, USA[d]; University of Oxford, Oxford, United Kingdom[e]

Objectives:

1. identify the exposure measure (e.g., area under the concentration-time curve[AUC], maximal concentration [C_{max}], or the percentage of the dosing interval that the drug concentration remains above a threshold concentration [%Timethreshold]) that best predicts tazobactam efficacy in combination with ceftolozane

2. determine the magnitude of the exposure measure associated with net bacterial stasis and a 1- and 2-log10 CFU reduction in bacteria at 24 h.

3. determine the impact of various -lactamase transcription levels on the magnitude of the exposure measure associated with efficacy.

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Antimicrob Agents Chemother 2013;57:2809–2814

Pharmacokinetic
with Ceftolozane

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Sujata M. Bhavnani,[a] Alan Forre

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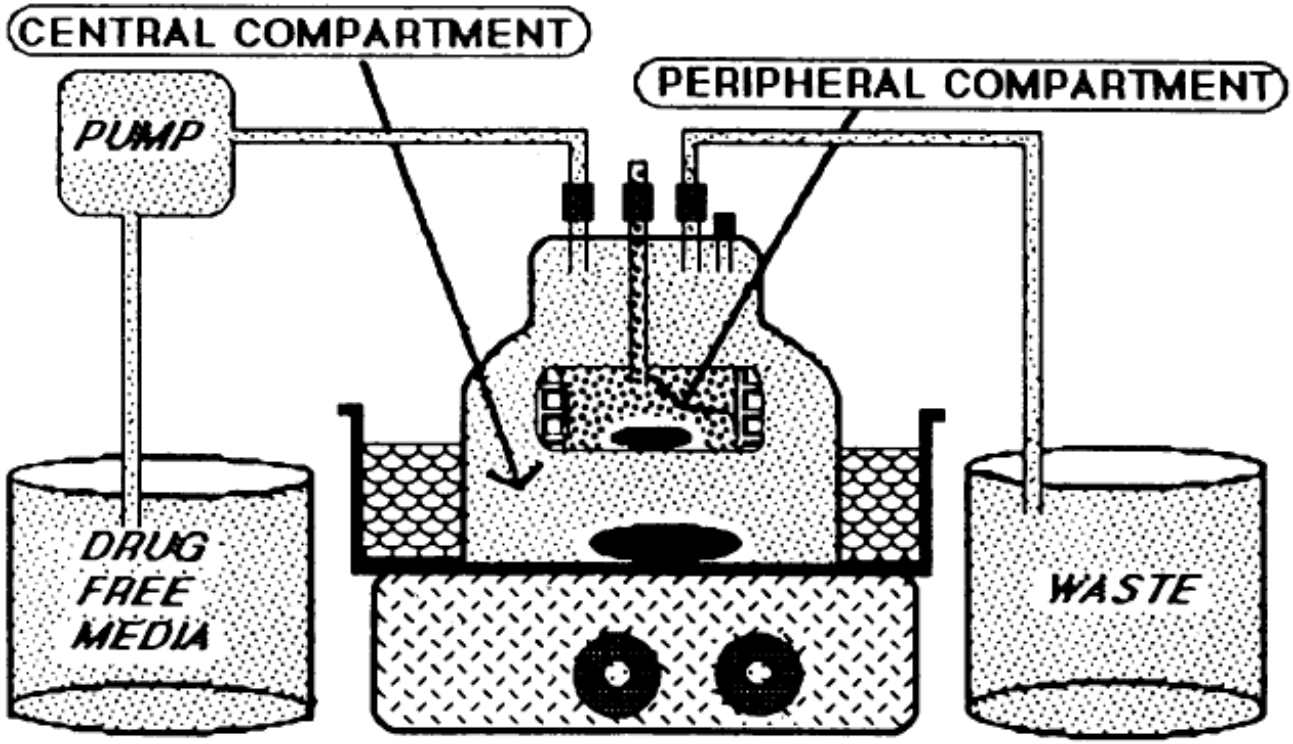

FIG. 1. Diagram of the in vitro pharmacodynamic model used in this study.

Un des premiers articles…

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Antimicrob Agents Chemother 2013;57:2809–2814

Pharmacokinetics-Pharma
with Ceftolozane in an *In*

Brian VanScoy,[a] Rodrigo E. Mendes,[b] Anthony M
Sujata M. Bhavnani,[a] Alan Forrest,[a] Ronald N. Jo

Institute for Clinical Pharmacodynamics, Latham, New York, U
New York, USA[c]; Cubist Pharmaceuticals, Lexington, Massach

TABLE 1 Susceptibility testing results and hydrolytic activity rates for ceftolozane alone and in combination with tazobactam at 4 μg/ml against *E. coli* strains producing different levels of CTX-M-15[a]

	MIC (μg/ml)			
E. coli strain	Ceftolozane alone	Ceftolozane + TAZ[b] (4 μg/ml)	Hydrolytic activity[c]	qRT-PCR[d]
Control	0.25	0.25	−3	ND
Low producer	4	0.25	36	1
Moderate producer	16	0.25	120	8.3
High producer	64	0.25	580	43.9

[a] The transcription levels of $bla_{\text{CTX-M-15}}$ are also shown.
[b] TAZ, tazobactam.
[c] Hydrolytic activity rates expressed as the amount (mg) of ceftolozane hydrolyzed per minute per milligram of protein.
[d] Expression of $bla_{\text{CTX-M-15}}$ relative to the *E. coli* strain demonstrating the lowest CTX-M-15 production based upon MIC results and hydrolysis assays for β-lactams. ND, not detected.

Un des prem

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Antimicrob Agents Chemother 2013;57:2809

Pharmacokinetics-Pharmacodynamics of Ta with Ceftolozane in an *In Vitro* Infection M

Brian VanScoy,[a] Rodrigo E. Mendes,[b] Anthony M. Nicasio,[c] Mariana Castanheira,[b] Sujata M. Bhavnani,[a] Alan Forrest,[a] Ronald N. Jones,[b] Lawrence V. Friedrich,[d] Judi

Institute for Clinical Pharmacodynamics, Latham, New York, USA[a]; JMI Laboratories, North Liberty, Iowa, New York, USA[c]; Cubist Pharmaceuticals, Lexington, Massachusetts, USA[d]; University of Oxford, Oxford, U

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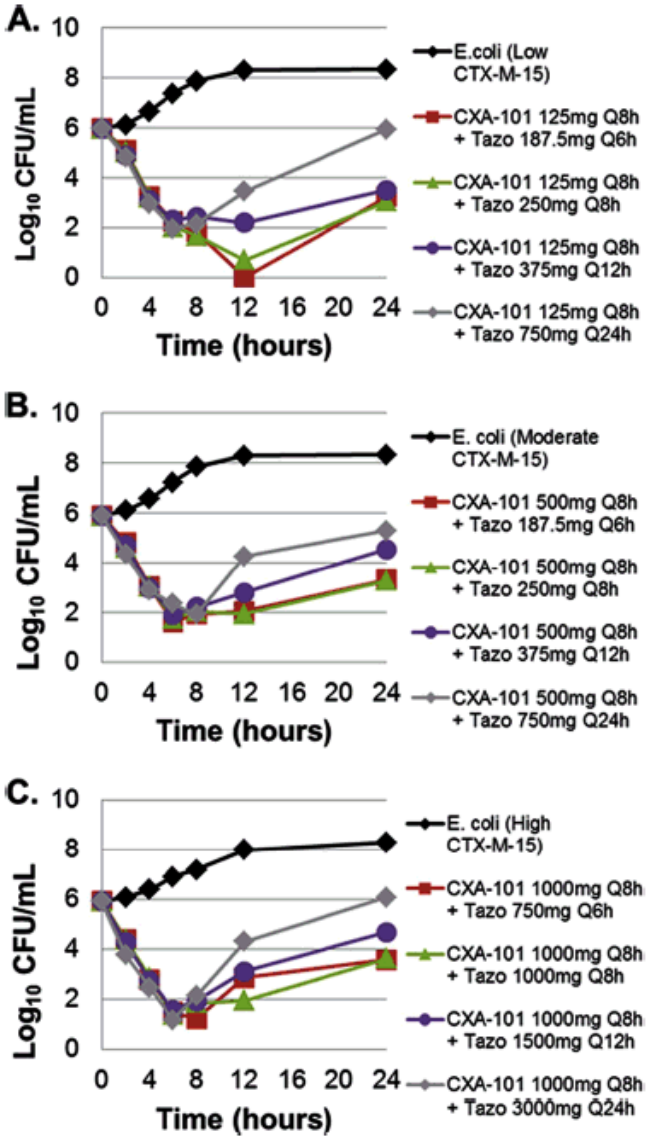
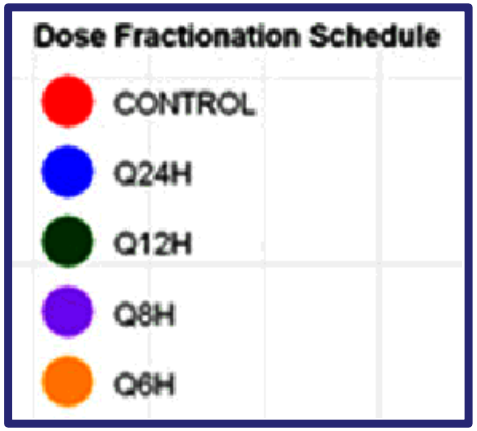
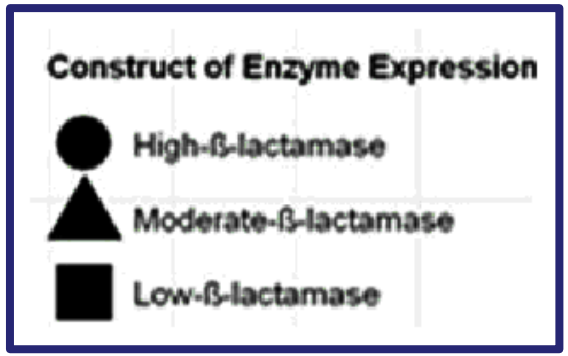


FIG 2 Dose fractionation study results for the low- (A), medium- (B) and high-level (C) CTX-M-15-producing *E. coli*. The effect of each active regimen is shown relative to the no-treatment controls. CXA-101, ceftolozane; Tazo, tazobactam; Q8h, every 8 h.

Un des premiers articles…

Antimicrob Agents Chemother 2013;57:2809–2814





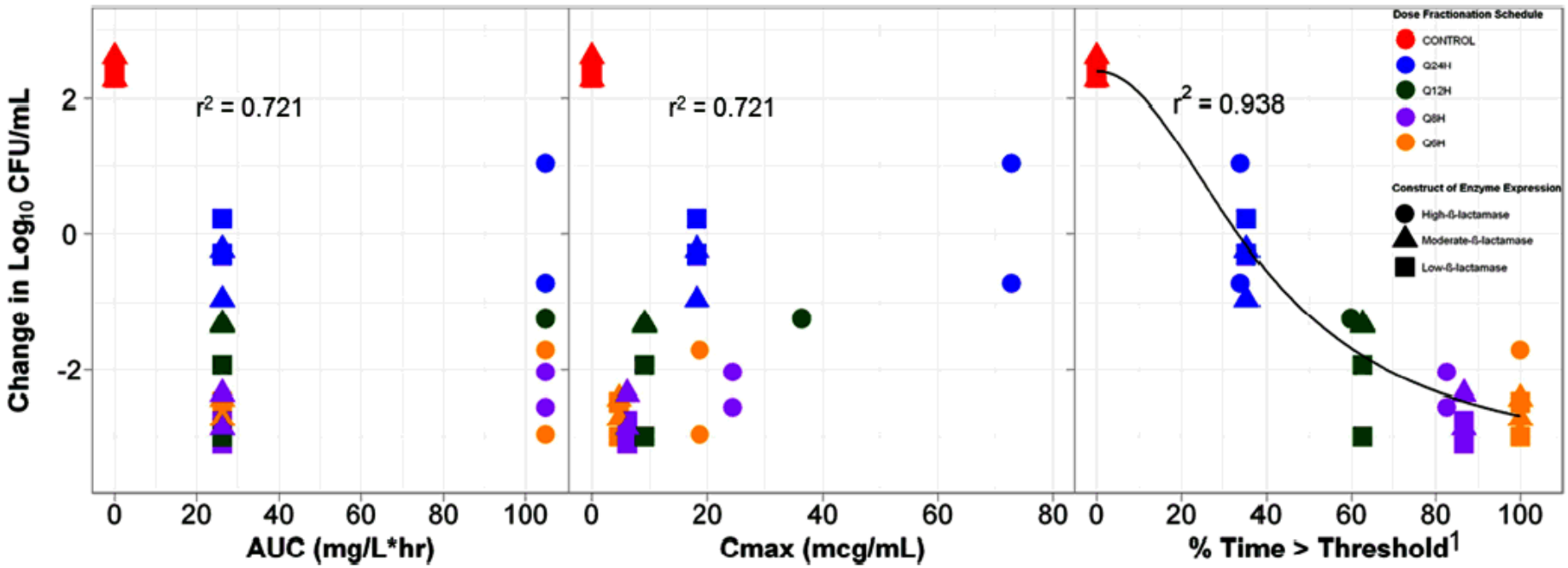
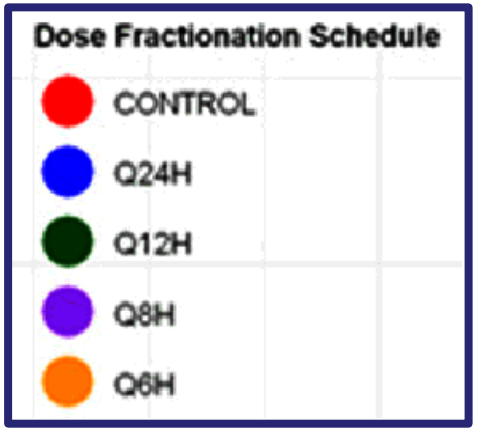


FIG 3 Relationships between three tazobactam exposure measures, AUC, C_{max}, and %Time>threshold, and the change in $\log_{10}$ CFU of isogenic CTX-M-15-producing *E. coli* after 24 h of therapy in a PK-PD *in vitro* infection model. The color of the symbols represent the different dose fractionation schedules, while the shape of the symbol represents the level of β-lactamase production. C_{max} is shown in micrograms per milliliter. [1], the threshold concentration was 0.05 μg/ml for the low- and moderate-β-lactamase genetic constructs and 0.25 μg/ml for the high-β-lactamase genetic construct.

Un des premiers articles…

Antimicrob Agents Chemother 2013;57:2809–2814



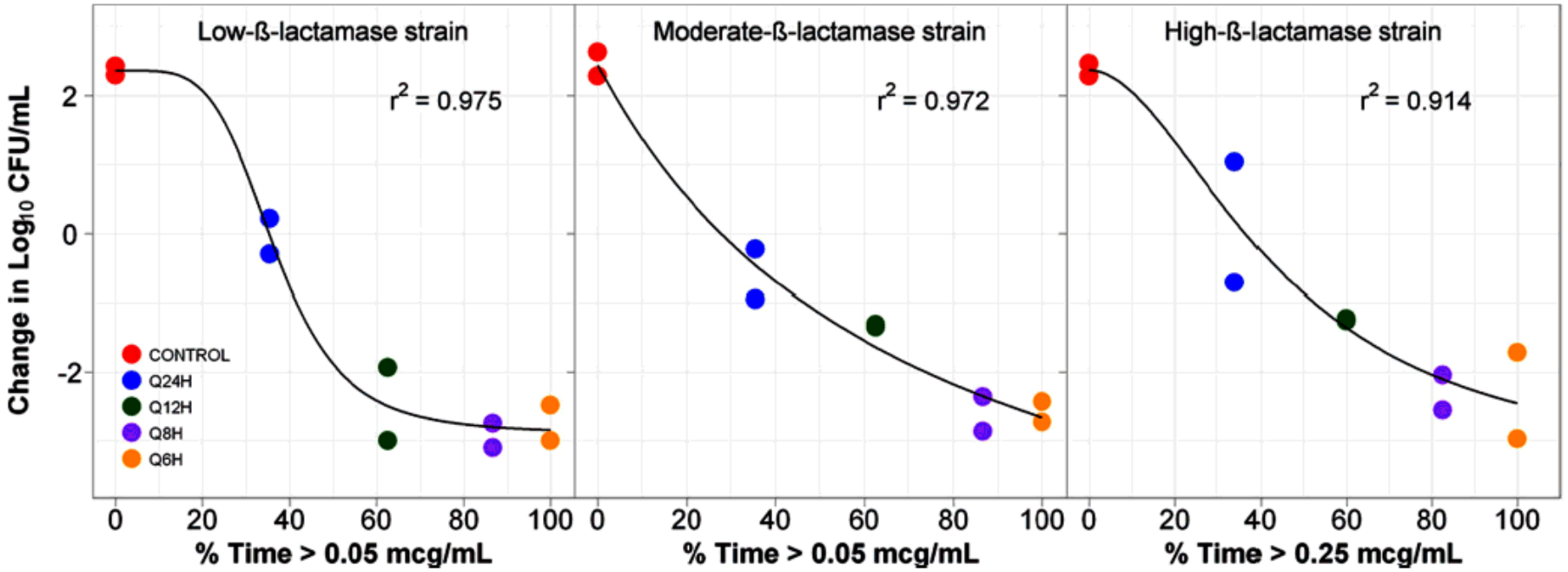


FIG 4 Relationships between tazobactam %Time>threshold and the change in $\log_{10}$ CFU of low-, medium- and high-level CTX-M-15-producing *E. coli* after 24 h of therapy in a PK-PD *in vitro* infection model. The threshold concentrations are given in micrograms per milliliter.

Qu'apporte le premier article ?

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Antimicrob Agents Chemother 2013;57:2809–2814

Pharmacokinetics-Pharmacodynamics of Tazobactam in Combination with Ceftolozane in an *In Vitro* Infection Model

Brian VanScoy,[a] Rodrigo E. Mendes,[b] Anthony M. Nicasio,[c] Mariana Castanheira,[b] Catharine C. Bulik,[a] Olanrewaju O. Okusanya,[a] Sujata M. Bhavnani,[a] Alan Forrest,[a] Ronald N. Jones,[b] Lawrence V. Friedrich,[d] Judith N. Steenbergen,[d] Paul G. Ambrose[a,e]

Institute for Clinical Pharmacodynamics, Latham, New York, USA[a]; JMI Laboratories, North Liberty, Iowa, USA[b]; Albany College of Pharmacy and Health Sciences, Albany, New York, USA[c]; Cubist Pharmaceuticals, Lexington, Massachusetts, USA[d]; University of Oxford, Oxford, United Kingdom[e]

Observations:

1. The exposure measure associated with efficacy was the percentage of the dosing interval that tazobactam concentrations remained above a threshold (%Time>threshold), regardless of enzyme expression
2. The threshold concentrations identified were 0.05 µg/ml for low and moderate and 0.25 µg/ml for the high-β-lactamase expression strain constructs.
3. The magnitudes of %Time>threshold for tazobactam associated with net bacterial stasis and a 1- and 2-log10 CFU reduction in bacteria at 24 h were approximately 35, 50, and 70%, respectively.

Un deuxième article … avec des souches cliniques…

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Antimicrob Agents Chemother 2013;57:5924–5930

Pharmacological Basis of β-Lactamase Inhibitor Therapeutics: Tazobactam in Combination with Ceftolozane

Brian VanScoy,[a] Rodrigo E. Mendes,[b] Jennifer McCauley,[a] Sujata M. Bhavnani,[a] Catharine C. Bulik,[a] Olanrewaju O. Okusanya,[a] Alan Forrest,[a] Ronald N. Jones,[b] Lawrence V. Friedrich,[c] Judith N. Steenbergen,[c] Paul G. Ambrose[a,d]

Institute for Clinical Pharmacodynamics, Latham, New York, USA[a]; JMI Laboratories, North Liberty, Iowa, USA[b]; Cubist Pharmaceuticals, Lexington, Massachusetts, USA[c]; University of Oxford, Oxford, United Kingdom[d]

Objectives:

1. to characterize the relationship between tazobactam %Time>threshold and efficacy for 4 β-lactamase-producing clinical ***E. coli*** isolates.
2. identify a translational relationship that would allow for comodeling of the relationship between %Time>threshold and efficacy.
3. to evaluate the translational relationship to other ESBL-producing Enterobactriaceae by including 3 well-characterized β-lactamase-producing clinical ***Klebsiella pneumoniae*** isolates.
4. to allow for the forecasting of effective and noneffective clinical regimens from preclinical models systems based upon in vitro susceptibility test results.

Un deuxième article … avec des souches cliniques…

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Antimicrob Agents Chemother 2013;57:5924–5930

Pharmacological Bas
Tazobactam in Com

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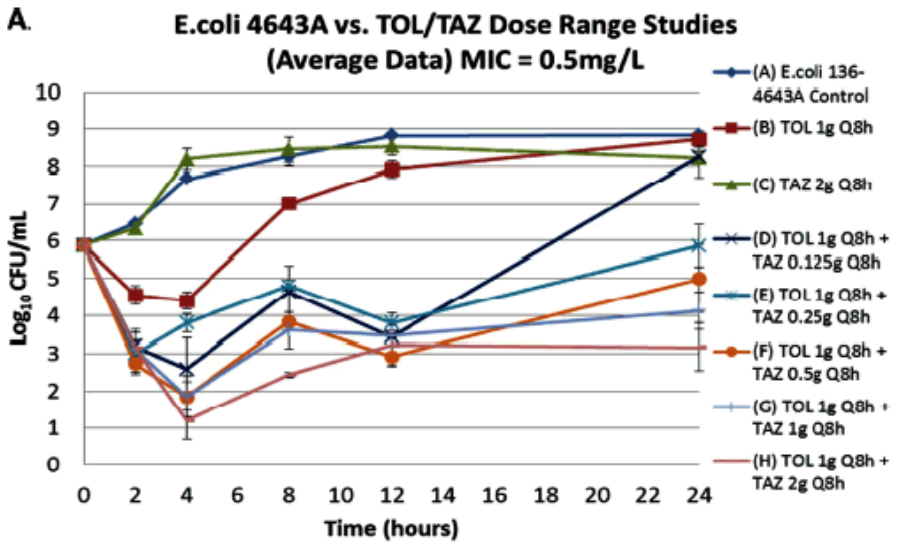
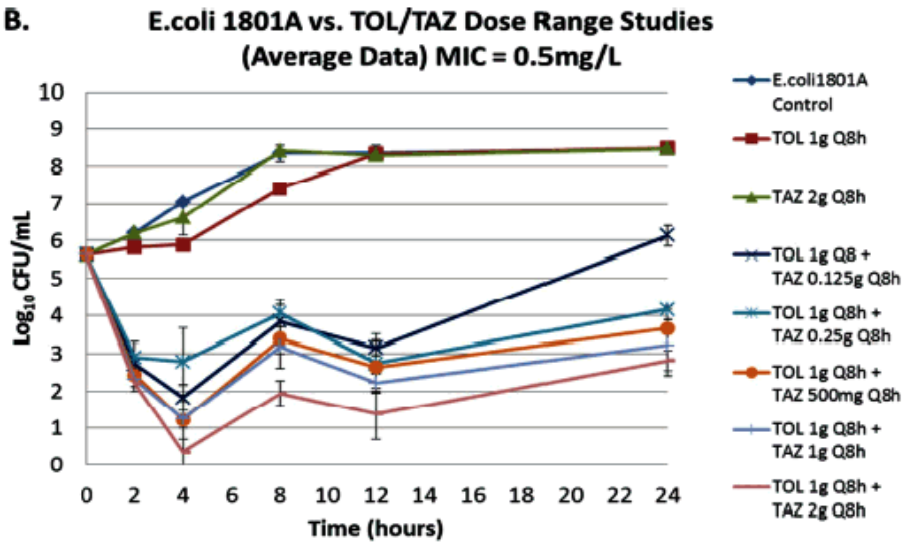
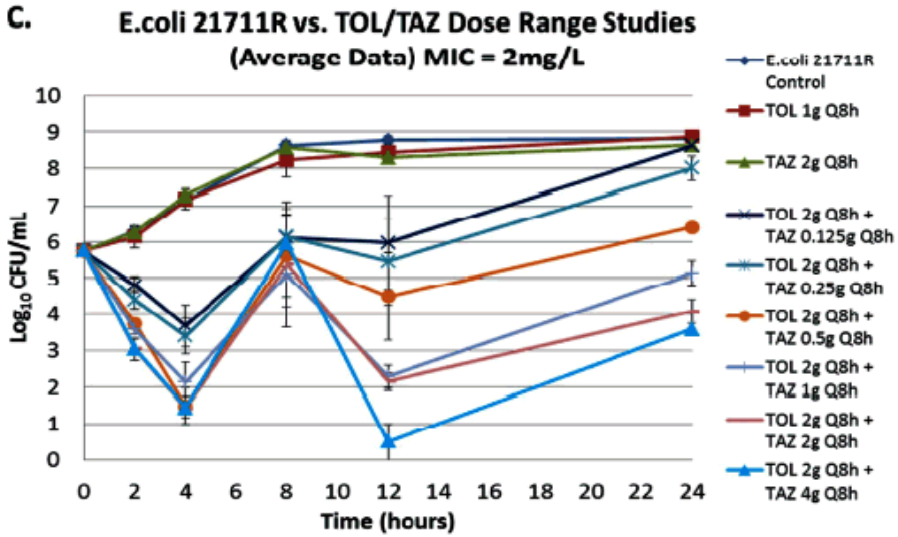
University of Oxford, Oxford, United Kingdom[d]

TABLE 1 Susceptibility testing results for ceftolozane and ceftolozane combined with tazobactam against an *E. coli* ATCC control strain and seven clinical isolates

Species and isolate	Microtiter MIC (mg/liter)		MBC (mg/liter), ceftolozane-tazobactam (4 mg/liter)
	Ceftolozane alone	Ceftolozane-tazobactam (4 mg/liter)	
E. coli			
ATCC 25922	0.5	0.5	0.5
4643A	128	0.5	0.5
1801A	128	0.5	1
21711R	256	2	4
13319R	512	4	4
K. pneumoniae			
604C	256	1	2
21904E	512	2	2
4812E	512	4	4







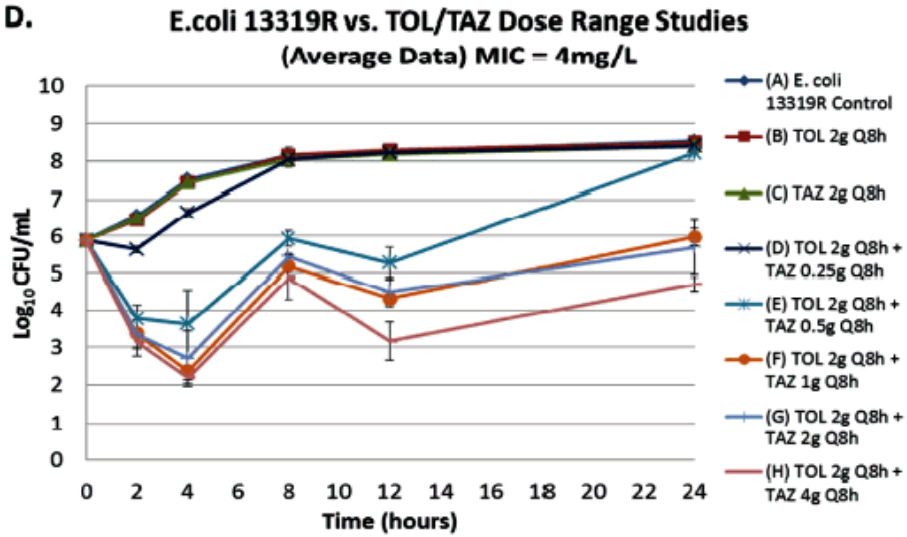
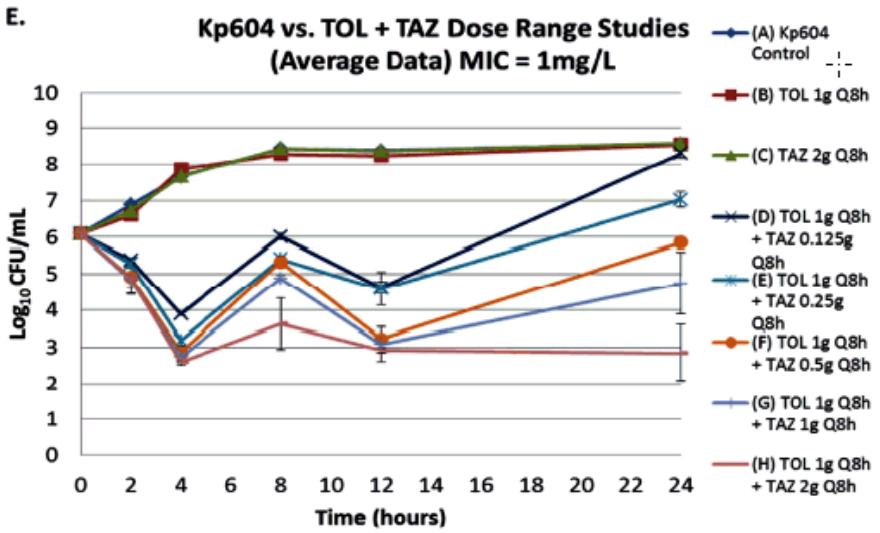
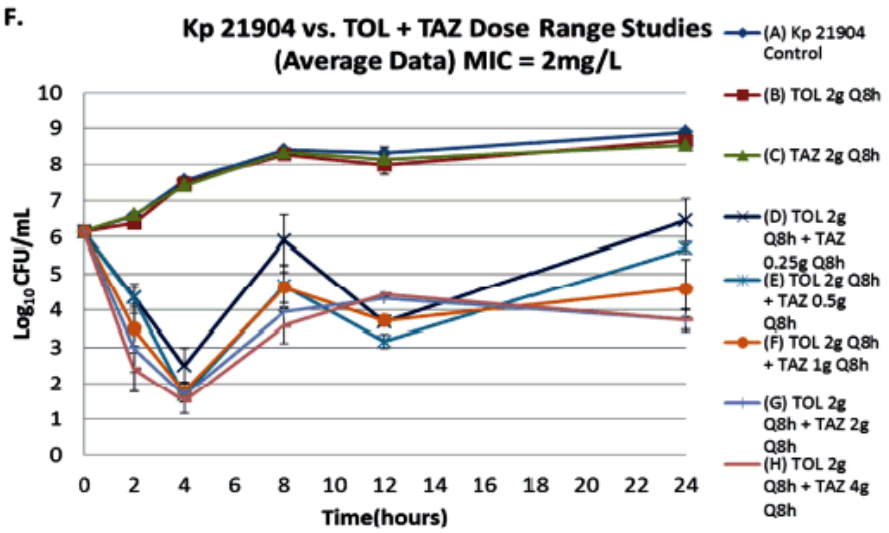


FIG 2 Dose-ranging study results for each of the four *E. coli* (A to D) clinical isolates. The effect of each active regimen relative to the no-treatment controls is shown. TOL, ceftolozane; TAZ, tazobactam. Error bars represent the range of data over two studies.





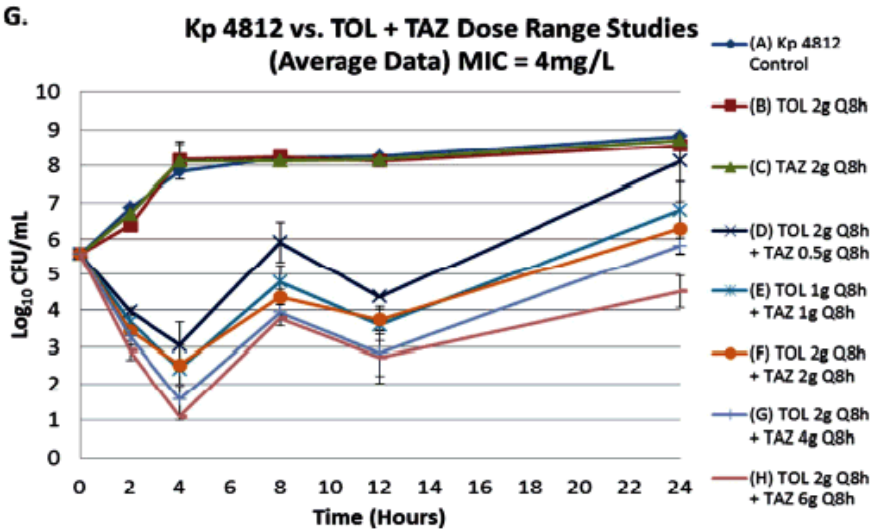


FIG 2 Dose-ranging study results for each of the three *K. pneumoniae* (Kp) (E to G) clinical isolates. The effect of each active regimen relative to the no-treatment controls is shown. TOL, ceftolozane; TAZ, tazobactam. Error bars represent the range of data over two studies.

Un deuxième article … avec des souches cliniques…

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Antimicrob Agents C

Pharmacological Basis of β-I
Tazobactam in Combination

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all *E. coli* individually

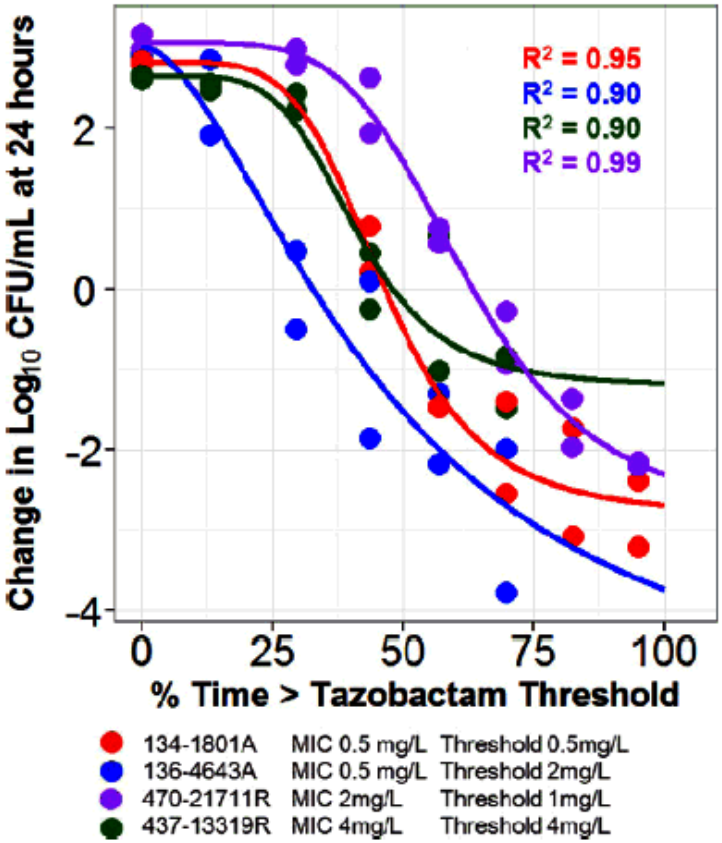

FIG 3 Relationships between tazobactam %Time>threshold and change in $\log_{10}$ CFU from baseline at 24 h for the four *E. coli* clinical isolates in a PK-PD *in vitro* infection model. Data points and fitted functions for each isolate are represented by different colors. The threshold for each isolate was identified using an iterative process which allowed for evaluation of dispersion of data along the %Time>threshold axis and optimization of r^2 values.

Un deuxième article … avec des souches cliniques…

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Antimicrob Agents Chem

Pharmacological Basis of β-Lact
Tazobactam in Combination wi

Brian VanScoy,[a] Rodrigo E. Mendes,[b] Jennifer McCauley,[a] S
Alan Forrest,[a] Ronald N. Jones,[b] Lawrence V. Friedrich,[c] Juc

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University of Oxford, Oxford, United Kingdom[d]

all *E. coli* together with treshold = MIC x 0.5

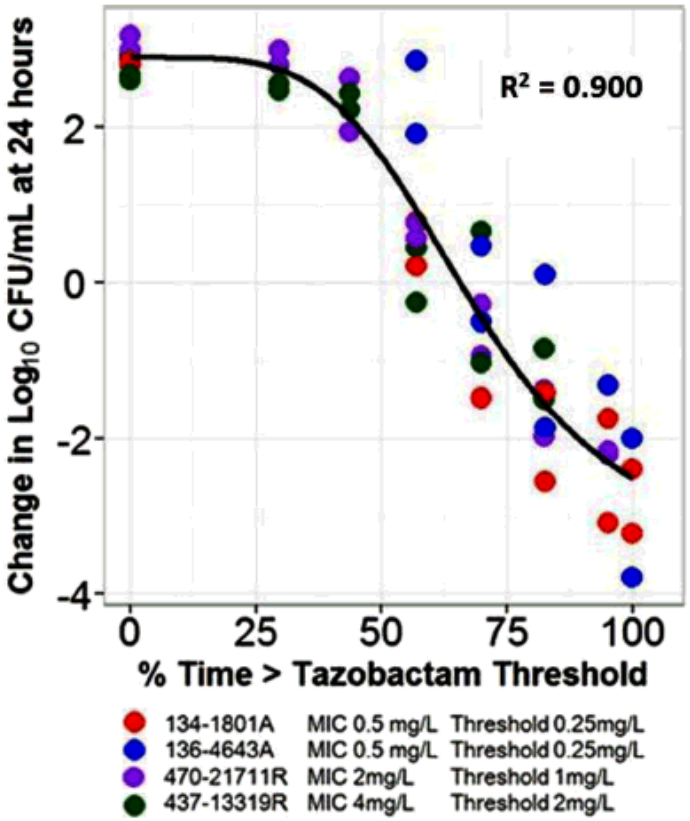

FIG 4 Relationship between tazobactam %Time>threshold and change in $\log_{10}$ CFU from baseline at 24 h for the four *E. coli* clinical isolates in a PK-PD *in vitro* infection model. Isolates are represented by different colors. The black line represents the fitted function for the pooled data across isolates. The threshold for each isolate represented the product of the ceftolozane-tazobactam MIC for the individual isolate and 0.5.

Un deuxième article … avec des souches cliniques…

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Antimicrob Agents Chem

Pharmacological Basis of β-Lact
Tazobactam in Combination wi

Brian VanScoy,[a] Rodrigo E. Mendes,[b] Jennifer McCauley,[a] S
Alan Forrest,[a] Ronald N. Jones,[b] Lawrence V. Friedrich,[c] Juc

Institute for Clinical Pharmacodynamics, Latham, New York, USA[a]; JMI Labo
University of Oxford, Oxford, United Kingdom[d]

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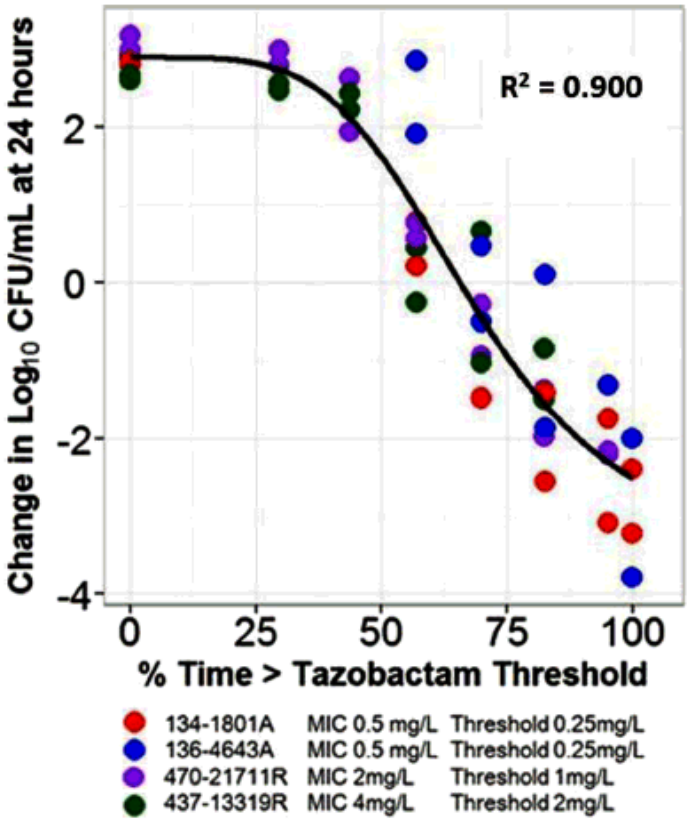

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Un deuxième article … avec des souches cliniques…

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Antimicr

Pharmacological B
Tazobactam in Co

Brian VanScoy,[a] Rodrigo E. Mendes
Alan Forrest,[a] Ronald N. Jones,[b] La
Institute for Clinical Pharmacodynamics, Lat
University of Oxford, Oxford, United Kingdo

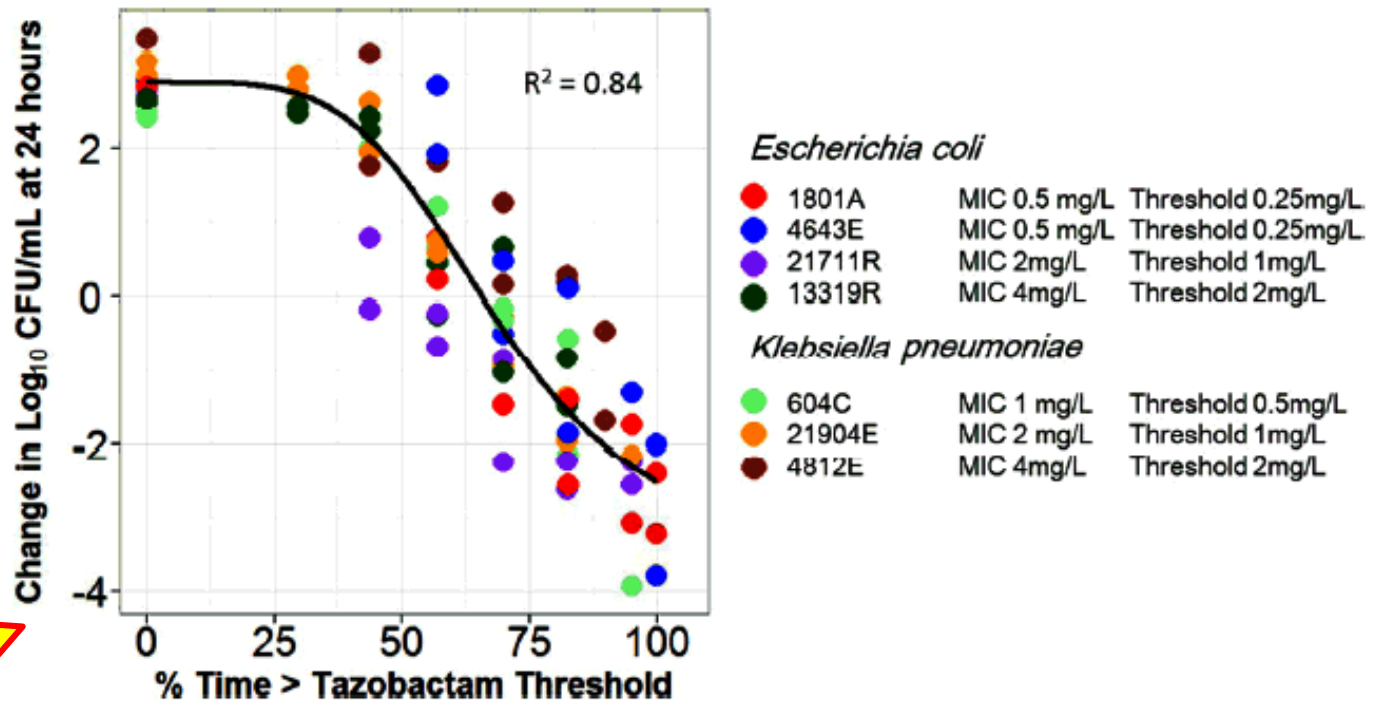

FIG 5 Relationship between tazobactam %Time>threshold and change in $\log_{10}$ CFU from baseline at 24 h for the four *E. coli* and three *K. pneumoniae* clinical isolates in a PK-PD *in vitro* infection model. Isolates are represented by different colors. The black line represents the fitted function for the pooled data across isolates. The threshold for each isolate represented the product of the ceftolozane-tazobactam MIC for the individual isolate and 0.5.

all *E. coli* and K. pneumoniae with treshold = MIC x 0.5

Un deuxième article … Les conclusions …

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Antimicrob Agents Chemother 2013;57:5924–5930

Pharmacological Basis of β-Lactamase Inhibitor Therapeutics: Tazobactam in C

Brian VanScoy,[a] Rodrigo E. Me
Alan Forrest,[a] Ronald N. Jones
Institute for Clinical Pharmacodynamic
University of Oxford, Oxford, United Ki

Observations:

1. The data were well described by fitted functions describing the relationship between the tazobactam %Time>threshold and change in $\log_{10}$ CFU from baseline
2. We identified an enabling translational relationship for the tazobactam threshold that allowed comodeling of all four clinical isolates, which was the product of the **individual isolate's ceftolozane-tazobactam MIC value and 0.5.**
3. The translational relationship for the tazobactam threshold performed well for the expanded data set (seven isolates in total; four E. coli and three K. pneumoniae)
4. This simple translational relationship is especially useful as it is directly linked to in vitro susceptibility test results, which are used to guide the clinician's choice of drug and dosing regimen.

Un modèle animal (souris neutropénique)

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

2016;60:368 –375.

Pharmacodynamics of Ceftazidime and Avibactam in Neutropenic Mice with Thigh or Lung Infection

Johanna Berkhout,[a] Maria J. Melchers,[b] Anita C. van Mil,[a] Seyedmojtaba Seyedmousavi,[b] Claudia M. Lagarde,[b] Virna J. Schuck,[c]* Wright W. Nichols,[c] Johan W. Mouton[b,d]

Department of Medical Microbiology and Infectious Diseases, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands[a]; Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, The Netherlands[b]; AstraZeneca Pharmaceuticals, Waltham, Massachusetts, USA[c]; Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands[d]

Objectives and means:

1. to use the neutropenic mouse infection models (thigh infection and pneumonia) with ceftazidime-resistant Pseudomonas aeruginosa to determine the exposure-response relationship of ceftazidime alone and to derive estimates of pharmacodynamic indices (PDI) over 24 h for avibactam in combination with ceftazidime.

2. Use the the notional threshold concentration (CT), that represents an approximation of the threshold concentration of avibactam during a declining concentration-time curve, below which β-lactamase is no longer effectively inhibited *in vivo* (determined to be 1 mg/L in previous studies)

Un modèle animal (souris neutropénique)

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

2016;60:368 –375.

TABLE 1 *P. aeruginosa* strains used for pharmacodynamic studies of ceftazidime and avibactam, including magnitude of the PDI %*f*T>MIC of monotherapy ceftazidime

Isolate no.	Resistance summary[a]	MIC (mg/liter)		Static % *f*T>MIC (ceftazidime)	
		Ceftazidime	Ceftazidime-avibactam[b]	Thigh	Lung
1	Nitrocefinase activity, ++; AmpC transcript, overexpressed; β-lactamase genotype, bla_{AmpC}; class A^-, class B^-	128	8	Not done	0
3	Nitrocefinase activity, baseline; AmpC transcript, basal; β-lactamase genotype, bla_{AmpC} bla_{TEM-24} (CAZ-6); class B^-	64	2	0	0
5	Nitrocefinase activity, ++++; AmpC transcript, overexpressed; β-lactamase genotype, bla_{AmpC}; class A^-, class B^-	128	8	0	0
7	Nitrocefinase activity, +++; AmpC transcript, overexpressed; β-lactamase genotype, bla_{AmpC}; class A^-, class B^-	64	4	0	0
11	$OprD^-$, $AmpC^{con}$, class A^-, class B^-	128	16	No stasis[c]	0
18	$OprD^-$, $AmpC_{ind}$?, class A^-, class B^-	32	2	28.6	27.0
19	$OprD^-$, $AmpC^{con}$, class A^-, class B^-	64	4	29.6	0

[a] con, constitutive; ind, inducible; $OprD^-$, outer membrane protein deficiency causing resistance to carbapenems in *Pseudomonas* species; bla_{AmpC}, possesses β-lactamase gene coding for AmpC; bla_{TEM-24}, possesses β-lactamase gene coding for TEM_{24}.

[b] The MIC of ceftazidime-avibactam was the value of the ceftazidime MIC measured in the presence of a fixed concentration of avibactam of 4 mg/liter.

[c] The highest dose used did not result in a bacteriostatic effect.

Un modèle animal (souris neutropénique)

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

2016;60:368 –375.

Pharmacodynamics of Ceftazidime and Avibactam in Neutropenic Mice with Thigh or Lung Infection

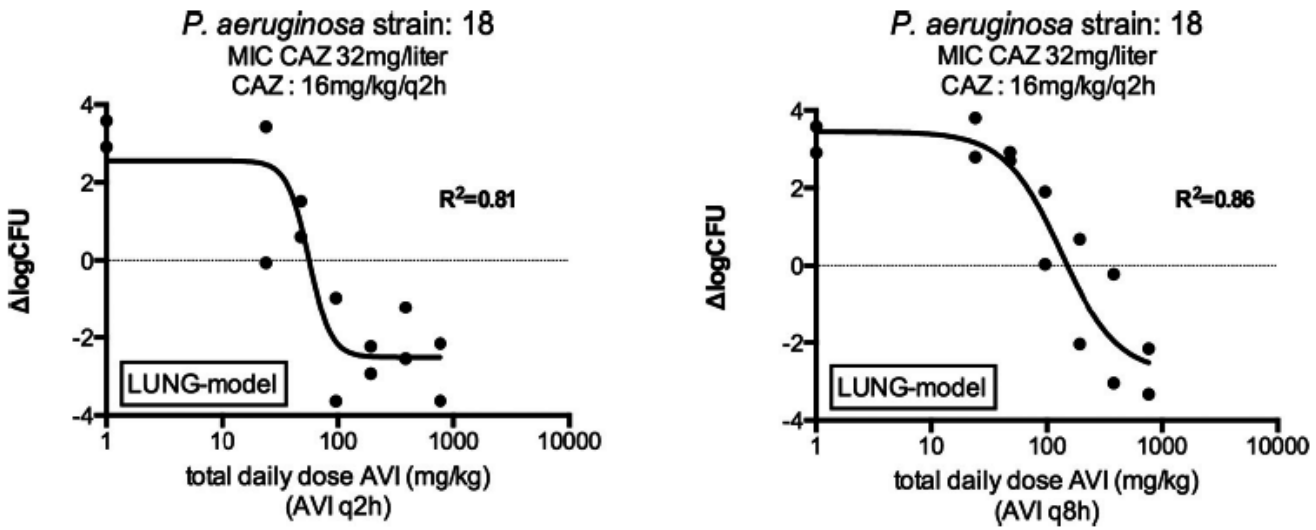

FIG 1 Change in $\log_{10}$ CFU in lung-infected mice treated with ceftazidime dosing q2h and avibactam q2h or q8h., = ceftazidime; AVI, avibactam; ΔlogCFU, change in $\log_{10}$ CFU compared to the initial inoculum The ΔlogCFU values for controls treated with ceftazidime for 24 h but with zero avibactam are plotted on the vertical axis.

Un modèle animal (souris neutropénique)

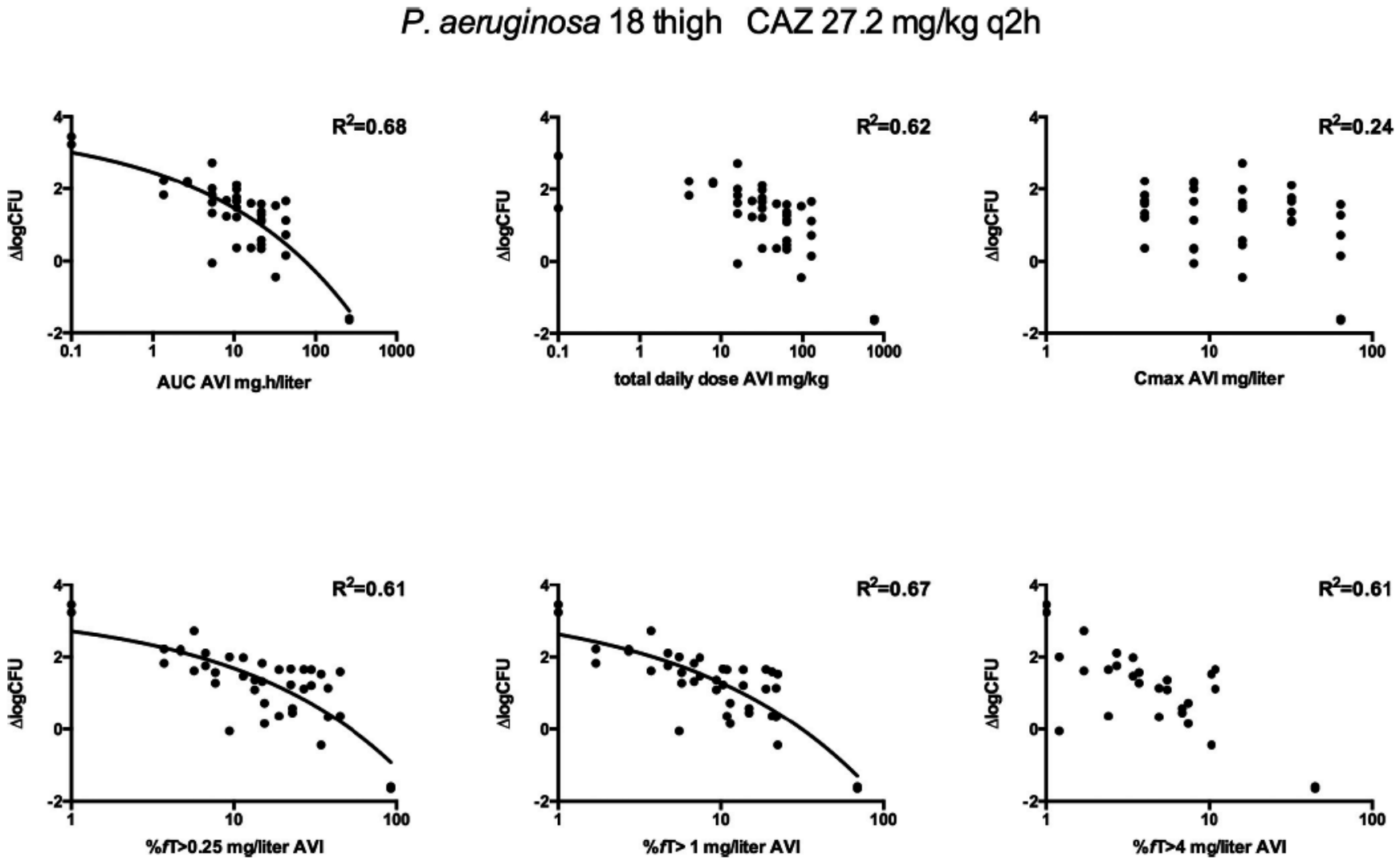

FIG 2 Example of exposure-response, dose fractionation studies of avibactam in thigh-infected neutropenic mice treated with ceftazidime q2h. CAZ, ceftazidime; AVI, avibactam; ΔlogCFU, change in $\log_{10}$ CFU compared to the initial inoculum.

Un modèle animal (souris neutropénique)

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2016;60:368 –375.

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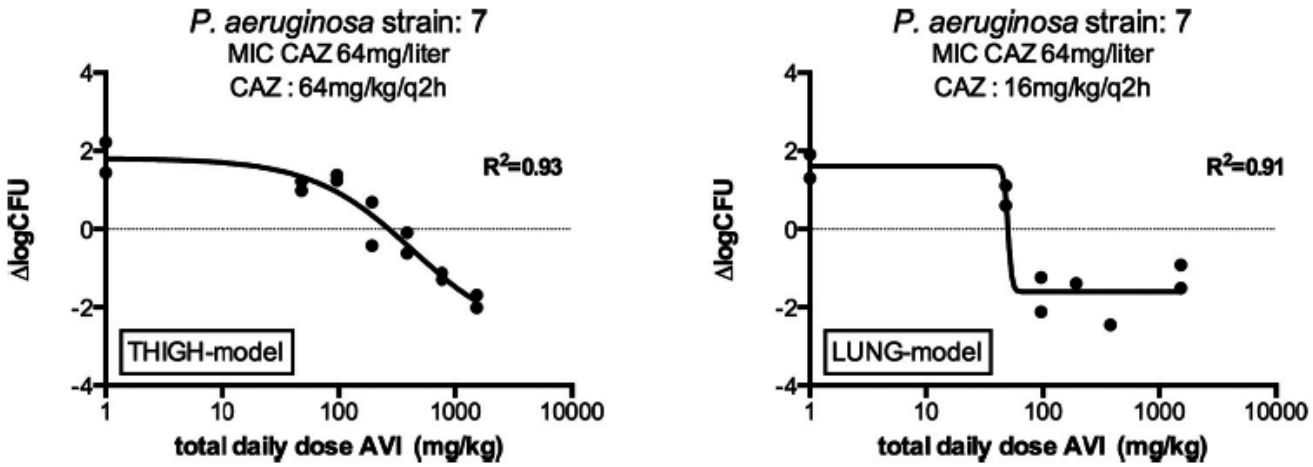

FIG 3 Example of exposure response of avibactam in neutropenic thigh- and lung-infected mice treated with ceftazidime and various doses of avibactam q2h. CAZ, ceftazidime; AVI, avibactam; ΔlogCFU, change in $\log_{10}$ CFU compared to the initial inoculum. MIC of ceftazidime-avibactam versus this strain, 4 mg/liter.

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Pharmacodynamics of Ceftazidime and Avibactam in Neutropenic Mice with Thigh or Lung Infection

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Observations and conclusions:

1. Dose fractionation studies of avibactam in both the thigh and lung models indicated that the effect of avibactam correlated well with %fT>CT 1 mg/liter.
2. Addition of avibactam enhanced the effect of ceftazidime, which was more pronounced at frequent dosing and well related with %fT>CT 1 mg/liter.
3. The thigh model appeared more stringent, with higher values, ranging up to 62.5% fT>CT 1 mg/liter, required for a static effect

Analyse d'une population spéciale: patients atteints de mucoviscidose

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2017;61:e00988-17.

Pharmacokinetic-Pharmacodynamic Target Attainment Analyses To Determine Optimal Dosing of Ceftazidime-Avibactam for the Treatment of Acute Pulmonary Exacerbations in Patients with Cystic Fibrosis

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Background, objectives and means:

1. Altered pharmacokinetics (PK) of several beta-lactam antibiotics have been reported in CF patients.
2. The aim was to characterize the PK of ceftazidime-avibactam (CZA) and perform target attainment analyses to determine the optimal treatment regimen.
3. The PK of ceftazidime and of avibactam in 12 adult CF patients administered 3 intravenous doses of 2.5 g every 8 h infused over 2 h were determined.
4. Population modeling utilized the maximum likelihood expectation method. Monte Carlo simulations determined the probability of target attainment (PTA).
5. Criteria: For ceftazidime: fT>MIC = 50% – For avibactam: fT>1 mg/L = 100%

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Pharmacokinetic-Pharma
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1. ceftazidime

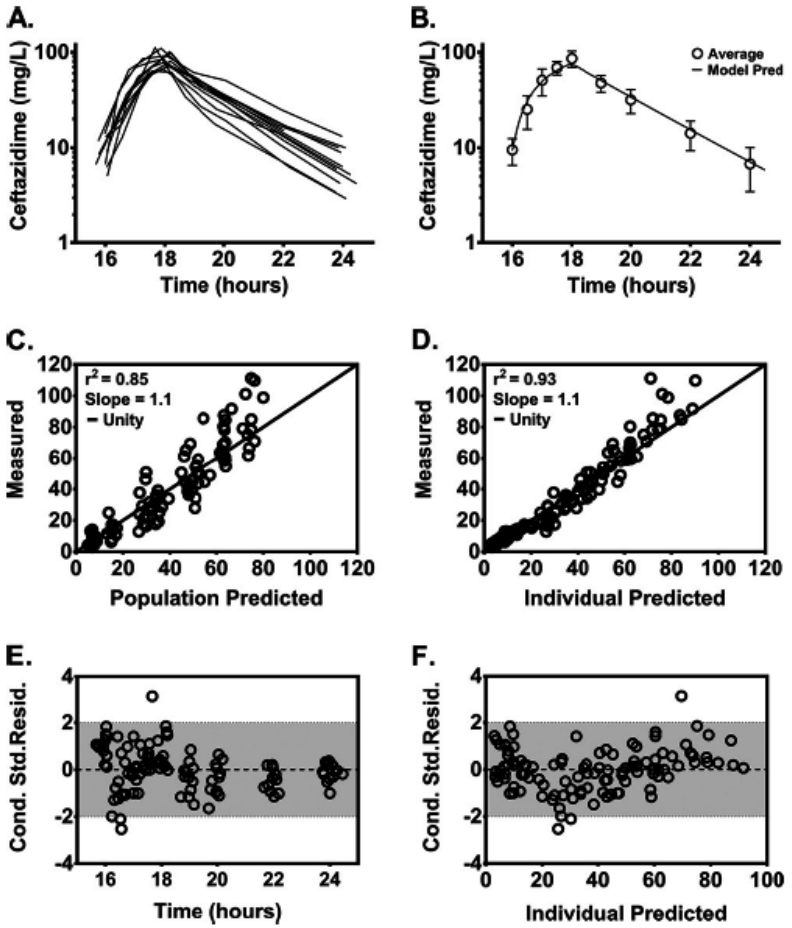

FIG 1 Observed CAZ plasma concentrations, model-predicted CAZ plasma concentrations, and goodness-of-fit of CAZ plasma concentrations after multiple administrations of CZA i.v. via a 2-h infusion in adults with CF. (A) Spaghetti plot of CAZ concentrations. (B) Summary of observed CAZ concentration-time profiles after the 3rd dose overlaid with the mean of the individual model predictions (Model Pred). (C to F) Goodness-of-fit plots of final population PK model: individual measured CAZ concentrations versus population prediction (C) or individual prediction (D), conditional standardized residuals (Cond. Std. Resid.) versus time after dose (E), and conditional standardized residuals versus individual prediction (F). Drug concentrations are plotted on a $\log_{10}$ scale. Summarized observed data are presented as the mean ± SD (n = 12).

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2. avibactam

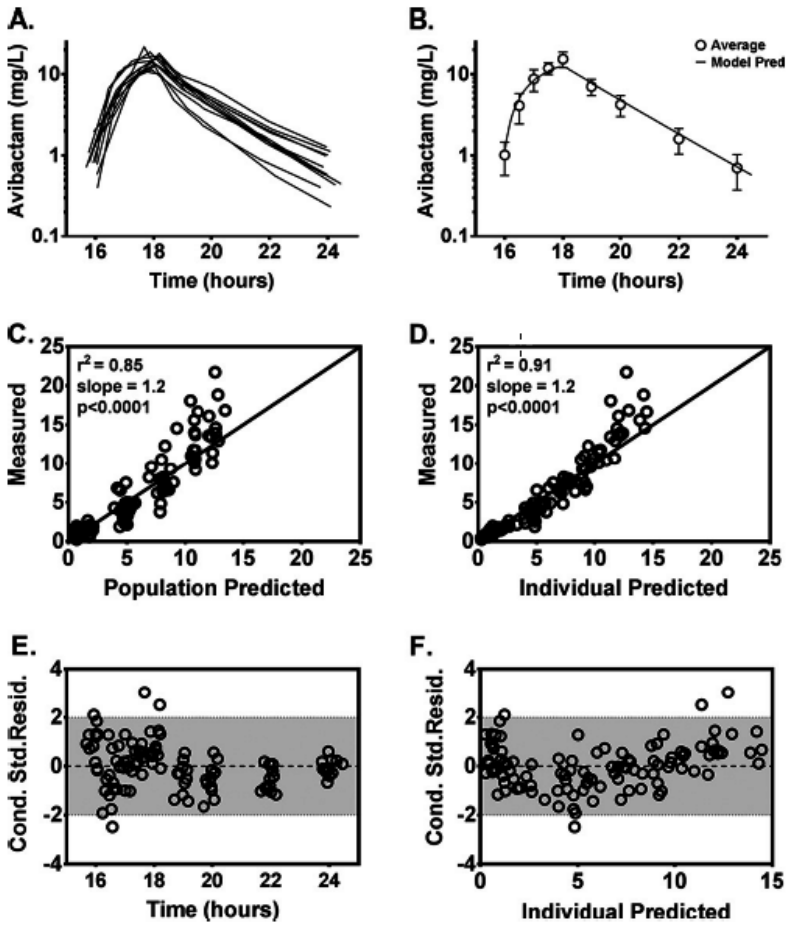

FIG 2 Observed AVI plasma concentrations, model-predicted AVI plasma concentrations, and goodness-of-fit of AVI plasma concentrations after multiple administrations of CZA i.v. with a 2-h infusion in adults with CF. (A) Spaghetti plot of AVI concentrations. (B) Summary of observed AVI concentration-time profiles after the 3rd dose overlaid with the mean of the individual model predictions (Model Pred). (C to F) Goodness-of-fit plots of final population PK model: individual measured AVI concentrations versus population prediction (C) or individual prediction (D), conditional standardized residuals (Cond. Std. Resid.) versus time after dose (E), and conditional standardized residuals versus individual prediction (F). Drug concentrations are plotted on a $\log_{10}$ scale. Summarized observed data are represented as the mean ± SD (n = 12).

Analyse d'une population spéciale: patients atteints de

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Pharmacokinetic-P Target Attainment Optimal Dosing of for the Treatment Exacerbations in Pa Fibrosis

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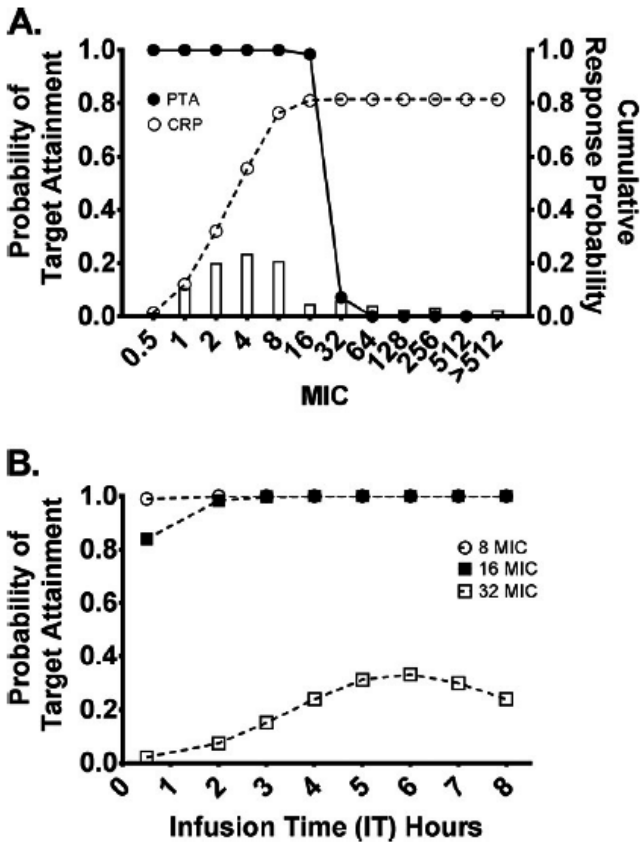
PTA / CRP of caz-avi



cumulative response probability: overall likelihood of a therapeutic effect

FIG 3 Probability of target attainment for discrete CZA MICs for *Pseudomonas aeruginosa* isolates recovered from CF patients under steady-state conditions. (A) Probability of target attainment and cumulative response of *P. aeruginosa* to CZA over the MIC distribution for CZA at 2.5 g infused over 2 h every 8 h. (B) Probability of target attainment dependent on infusion time for discrete MICs of 8, 16, and 32 mg/liter using a 1,000-patient Monte Carlo simulation trial incorporating PK variability from a one-compartment base model derived from data for 12 adult CF patients. The target was defined as an $fT_{>MIC}$ of 50% for CAZ and an $fT_{>1\ mg/liter}$ of 50% for AVI. The distribution of the CZA MICs for *P. aeruginosa* isolates from patients with CF was digitized from previously published data (10).

Analyse d'une population spéciale: patients atteints de mucoviscidose: 3. PTA / CRP

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Cumulative response probability: overall likelihood of a therapeutic effect:

1. A PTA of ≥ 0.9 is selected as threshold for optimal treatment.

2. The cumulative response probability (CRP) tells about the overall likelihood of a therapeutic effect in a population given
   - the empirical dosing regimen of CZA (2.5 g q8h infused over 2 h),
   - the pharmacokinetic variability, and
   - the susceptibility of *P. aeruginosa* isolates obtained from a representative population of patients with CF.

3. Briefly, CRP was calculated as the product of the probability of target attainment and isolate frequency at each discrete MIC and the values obtained for each MIC then summed