CLINICAL AND LABORATORY STANDARDS INSTITUTE®

CLSI Veterinary Antimicrobial Susceptibility Testing Subcommittee (VAST)

CLSI
Generic Antimicrobial Agents Working Group

Subcommittee on Veterinary Antimicrobial Susceptibility Testing

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CLINICAL AND LABORATORY STANDARDS INSTITUTE®

CLSI-VAST
Generic Drug Working Group

CLSI
Generic Antimicrobial Agents Working Group

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CLSI
Generic Antimicrobial Agents Working Group

Ceftazidime in Dogs

Objective

- To define the interpretive categories and breakpoints for ceftazidime against Enterobacteriaceae and *Pseudomonas aeruginosa* bacteria isolates from dogs.

Formulations

Ceftazidime 1gm Injection for dogs cats and reptiles

Login/Register

Ceftazidime for Injection for dogs, cats, and reptiles.

(Sef-taz-i-deem) – 3rd Generation Cephalosporin for dogs, cats, and reptiles.

Ceftazidime injection is a 3rd generation cephalosporin that has the potential to be useful in treating gram-negative bacterial infections with respects to susceptible Enterobacteriaceae as well as Pseudomonas aeruginosa in dogs, cats, and reptiles.

As part of Specialty Veterinary Pharmacy's program you can now purchase Ceftazidime

inventory control

one vial at a time. There is no need to purchase a dozen vials just so they can set on your shelf and collect dust. This service will help you free up vital cash that can be used for more important things like equipment and staff.

Your patient may experience pain when administering Ceftazidime intro-muscular. Subcutaneous injection may produce less pain.

There has been some reports of gastrointestinal adverse effects when given to canines subcutaneously.

Other names: Ceptaz®, Fortaz® and Tazicef®

For Intravenous or Intramuscular Use

Each vial contains Ceftazidime Pentahydrate equivalent to 1 gram of Ceftazidime and 118 mg of Sodium Carbonate (Sodium content is approximately 54 mg or 2.3 mEq per gram of Ceftazidime activity).

Important: This vial is under reduced pressure. Addition of diluent generates a positive pressure. Before reconstituting, see Instructions for Reconstitution. To prepare IM solution, add 3 mL of an approved diluent. To prepare IV solution, add 10 mL of Sterile

INVITED ARTICLE MEDICAL MICROBIOLOGY

L. Barth Reller and Melvin P. Weinstein, Section Editors

Clinical Infectious Diseases 2013; 56: 1301

Background and Rationale for Revised Clinical and Laboratory Standards Institute Interpretive Criteria (Breakpoints) for Enterobacteriaceae and *Pseudomonas aeruginosa*: I. Cephalosporins and Aztreonam

Michael N. Dudley,[1] Paul G. Ambrose,[2] Sujata M. Bhavnani,[2] William A. Craig,[3] Mary Jane Ferraro,[4] and Ronald N. Jones;[5] for the Antimicrobial Susceptibility Testing Subcommittee of the Clinical and Laboratory Standards Institute

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Widespread resistance in Enterobacteriaceae and *Pseudomonas aeruginosa* to cephalosporin and monobactam antibiotics due to extended-spectrum β-lactamases (ESBLs) has resulted in the need for reassessment of the interpretative criteria (breakpoints) established for these agents more than 2 decades ago. Following extensive evaluation, the Clinical and Laboratory Standards Institute recently adopted and published new breakpoints for these agents for use in clinical laboratories and provided updated recommendations for use of the ESBL screening test. This paper summarizes the background and supportive rationale for new interpretative criteria for cephalosporins and aztreonam for testing Enterobacteriaceae.

Keywords. breakpoints; Enterobacteriaceae; cephalosporins; *Pseudomonas*; CLSI.

Revised Breakpoint for Cephalosporins and Aztreonam
Dudley, et al. Clinical Infectious Diseases 2013; 56: 1301

Enterobacteriaceae

Drug (Dosage)[a]	MIC (µg/mL)					
	Revised			Pre-2010		
	S	I	R	S	I	R
Aztreonam (1 g q8h)	≤4	8	≥16	≤8	16	≥32
Cefotaxime (1 g q8h)	≤1	2	≥4	≤8	16–32	≥64
Ceftazidime (1 g q8h)	≤4	8	≥16	≤8	16	≥32
Ceftizoxime (1 g q12h)	≤1	2	≥4	≤8	16–32	≥64
Ceftriaxone (1 g q24h)	≤1	2	≥4	≤8	16–32	≥64

Revised Breakpoint for Cephalosporins and Aztreonam
Dudley, et al. Clinical Infectious Diseases 2013; 56: 1301

Pseudomonas aeruginosa

Drug	Dosage	MIC Breakpoints		
		Susceptible	Intermediate	Resistant
Ceftazidime	1 g q6h or	≤8	16	≥32
	2 g IV q8h			
Aztreonam	1 g q6h or	≤8	16	≥32
	2 g IV q8h			
Cefepime	1 g IV q8h or	≤8	16	≥32
	2 g IV q12h			

Clinical Use

1. Third-generation cephalosporin
2. Used primarily for treatment of infections caused by
   - Enterobacteriaceae (especially *Escherichia coli*)
   - *Pseudomonas aeruginosa*
3. Species: dogs, cats, reptiles, zoo animals

Clinical Use

Table 1: List of published doses of ceftazidime for dogs		
Dose	**Interval**	**Reference**
30 mg/kg, SC	Every 4 hours	Moore et al, 2000
4.4 mg/kg IV loading dose, then 4.1 mg/kg/hr	Constant rate infusion	Moore et al, 2000
20 mg/kg IV	Every 8 hours	Monfrinotti, et al. 2009
25 mg/kg IM or SC	Every 8 hours	Monfrinotti, et al. 2009

Generic Drug Working Group

Vet02-A4 Guidelines

Section 2.4: Development of Breakpoints for Generic or Unsponsored Compounds

- Regulatory approval documentation will be accepted as sufficient evidence of efficacy
- Alternatively, the committee will accept other evidence of clinical efficacy if it is of sufficient quality
- The subcommittee recognizes that isolates from clinical trials may not be available (hence, there can be no CO_{CL})

Generic Drug Working Group

Vet02-A4 Guidelines

- Requests for establishing veterinary-specific breakpoints for these generic or unsponsored compounds must include PK-PD data.
- If the dosage upon which the susceptibility breakpoint will be established differs from the dosage appearing on the regulatory authority-approved label, the sponsor should justify this alternative dosage.
- The generation of a CO_{PD} is anticipated.

Generic Drug Working Group

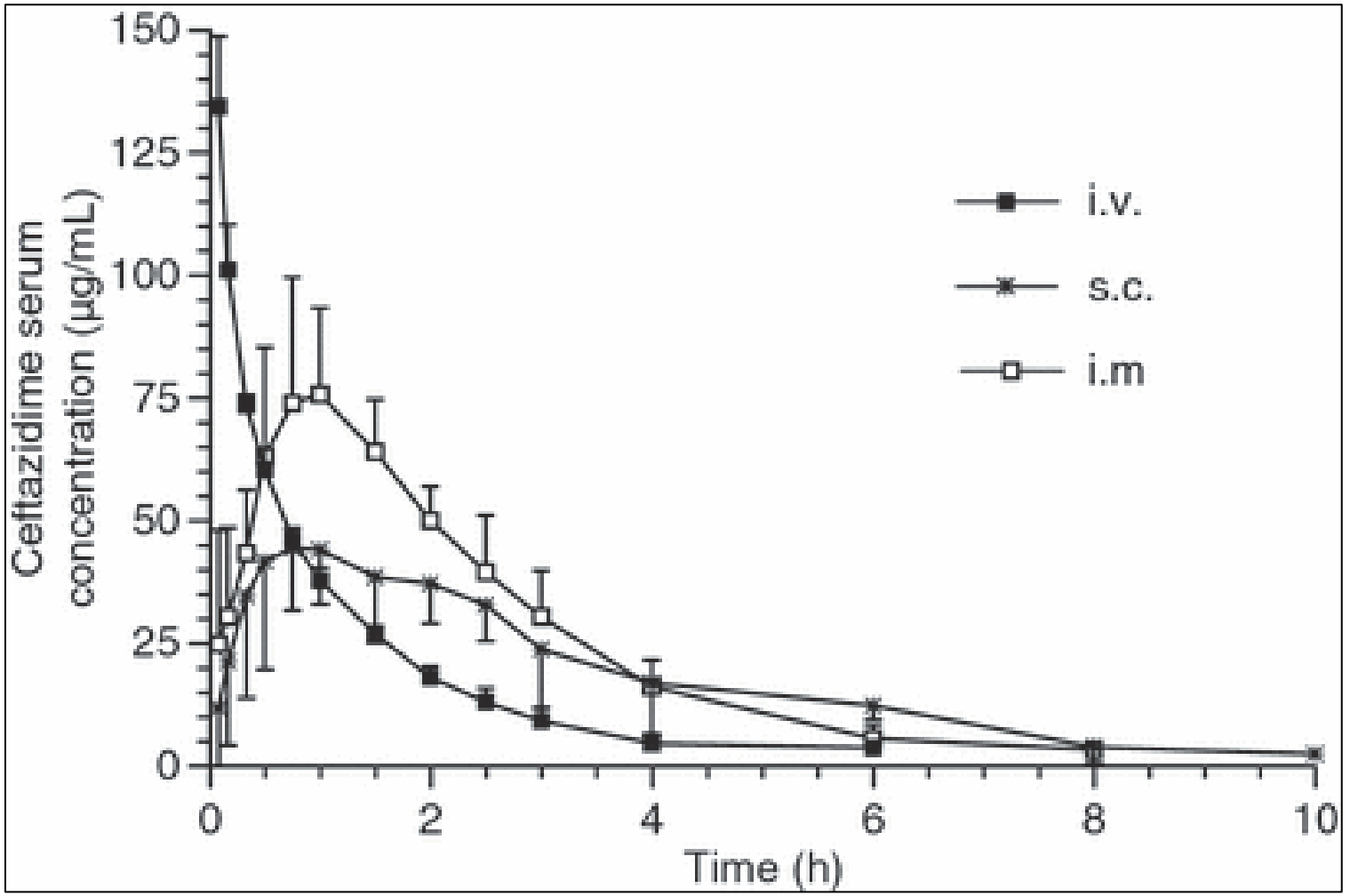
- Vet02-A4 Guidelines

- Microbiological data should be generated using CLSI standardized testing methods, including the proper use of QC organisms, and should be limited to clinically relevant isolates appropriate for the class of compound being evaluated.
- A CO_{WT} should be proposed

Pharmacokinetic Data

Ceftazidime Pharmacokinetics in Dogs (mean values and std.dev; nr = not reported from study											
	n	dose	T½	Kel	VD	CL	AUC	Cmax	Tmax	Reference	Assay
		mg/kg	hr	/hr	L/kg	L/kg/hr	ug hr/mL	ug/mL	hr		
Dogs SC injection	5	30	0.8	0.9	0.246	.	122	42.2	1	Moore et al, 2000	HPLC
Std. Dev.			0.1	0.2	0.044	.	22	7.1	0.3		
Dogs IV infusion	5	4.4 bolus,4.1 mg/kg/hr	0.54	.	0.13	0.19	.	.	.	Moore et al, 2000	HPLC
Std. Dev.			0.12	.	0.05	0.05	.	.	.		
Dogs IV bolus	5	20	1.09	.	0.353	0.228	89	105	na	Sakamoto, et al, 1993	Bioassay
Std. Dev			0.03	.	0.02	0.009	3.8	19.5			
Dogs IM injection	6	15	0.82	0.845	nr	nr	nr	35.6	0.5	Acred, 1983	Bioassay
Std. Dev			nr	nr	.	.	.	nr	nr		
Dogs IV injection	6	20	1.02	0.71	0.233	0.161	126	.	.	Monfrinotti, et al. 2010	Bioassay
Std. Dev			0.27	0.15	0.045	0.01	9.04	.	.		
Dogs IV injection	3	20	0.82	.846	0.218	0.215	93.0	208	.	Matsui, et al 1984	Bioassay
Std. Dev			0.02	0.024	0.007	0.003	1.0	79	.		
Dogs SC injection	6	25	1.68	0.52	0.141	.	177	52.5	1.12	Monfrinotti, et al. 2010	Bioassay
Std. Dev			0.79	0.29	0.049	.	61.1	17.5	0.54		
Dogs IM injection	6	25	1.13	0.651	0.119	.	210	80.2	1	Monfrinotti, et al. 2010	Bioassay
Std. Dev			0.29	0.18	0.014	.	24.6	20.7	0.27		
Dogs IM injection	6	25	1.1	0.63	0.104	.	.	104.3	0.72	Monfrinotti, et al. 2010	Bioassay
Std. Dev			0.3	.	0.025	.	.	25	0.4		
Dogs IV injection	5	20	0.86		0.21	0.194	105	.	.	Kita, et al. 1992	Bioassay
Std. Dev			nr	nr	nr	nr	nr	.	.		

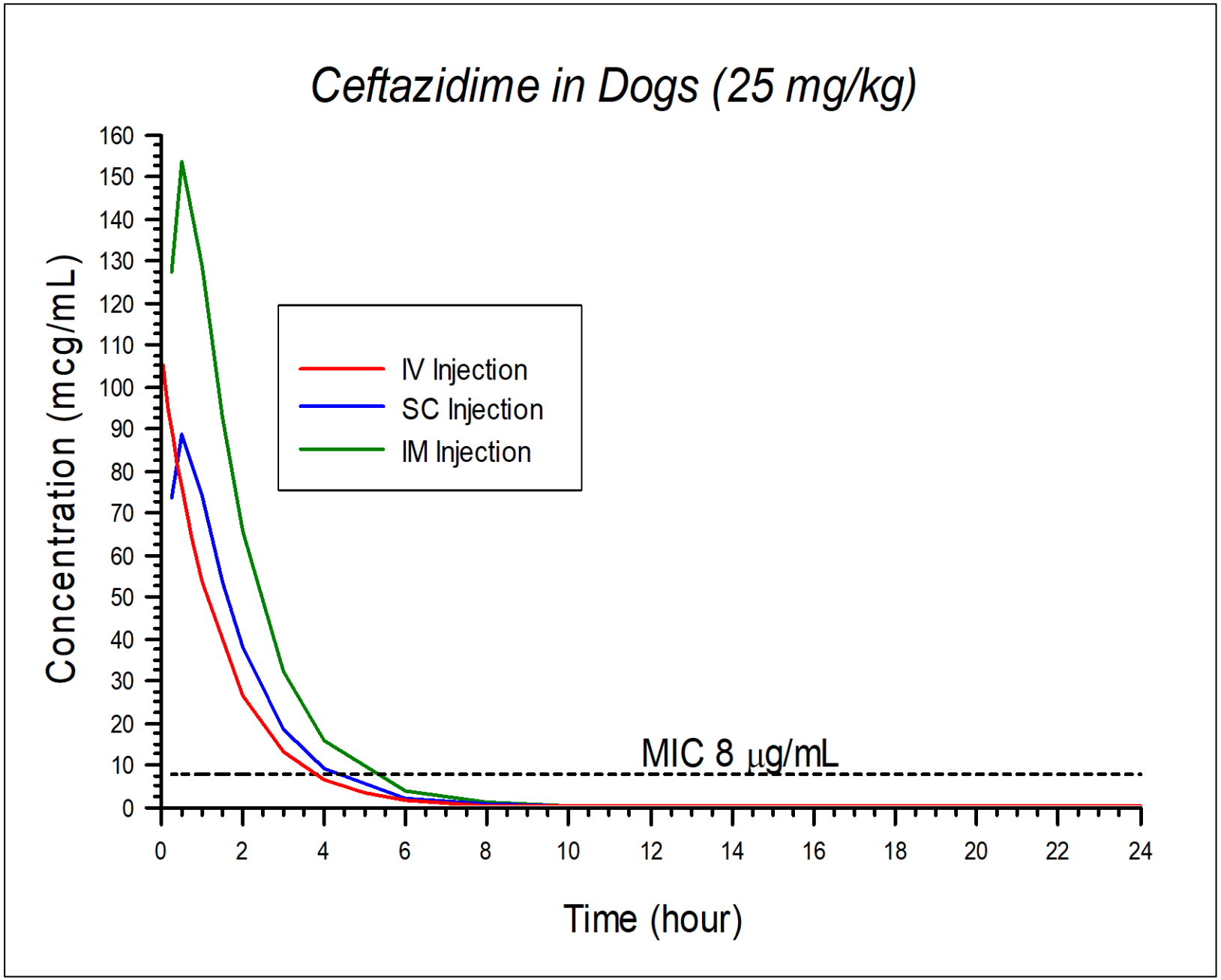
Pharmacokinetics of ceftazidime after intravenous, intramuscular and subcutaneous administration to dogs



Pharmacokinetics of ceftazidime after intravenous, intramuscular and subcutaneous administration to dogs, Volume: 33, Issue: 2, Pages: 204-207, First published: 08 March 2010, DOI: (10.1111/j.1365-2885.2009.01104.x)

Ceftazidime Pharmacokinetics in Dogs (mean across all studies)							
	T½	Kel	VD	CL	AUC	Cmax	Tmax
	hr	/hr	L/kg	L/kg/hr	ug hr/mL	ug/mL	hr
Mean overall	1.004	0.7093	0.192	0.19325	152.77	69.97	0.868
Std. Deviation	0.271	0.205	0.035	0.023	29.59	17.96	0.378
Mean IV	0.866	0.778	0.229	0.1976	103.25	156.5	
Std. Deviation	0.11	0.087	0.03	0.018	4.6133	49.25	
Mean IM	1.017	0.7087	0.112	.	225.2	73.37	0.74
Std. Deviation	0.295	0.18	0.019	.	40.8	22.85	0.335
Mean SC	1.24	0.71	0.194	.	149.5	47.35	1.06
Std. Deviation	0.445	0.245	0.047	.	41.55	12.3	0.42
Bioavailability (F): 134% (IM) and 70.3% (SC), from Monfrinotti, et al. 2009.							

Simulated plasma concentrations in dogs after IV, SC, and IM injection



Ceftazidime Pharmacokinetic Values Used for Monte Carlo Simulations		
	T½	VD
	hr	L/kg
Mean	1.0	0.19
Std. Deviation	0.33	0.06

Protein Binding

- Necessary to calculate free drug fraction *(fu):*

- 10.2% in dogs (*Sakamoto, et al. 1993*)
- free fraction (*fu*) is 0.898
- In most animals, and humans, the protein binding of ceftazidime is approximately 10%

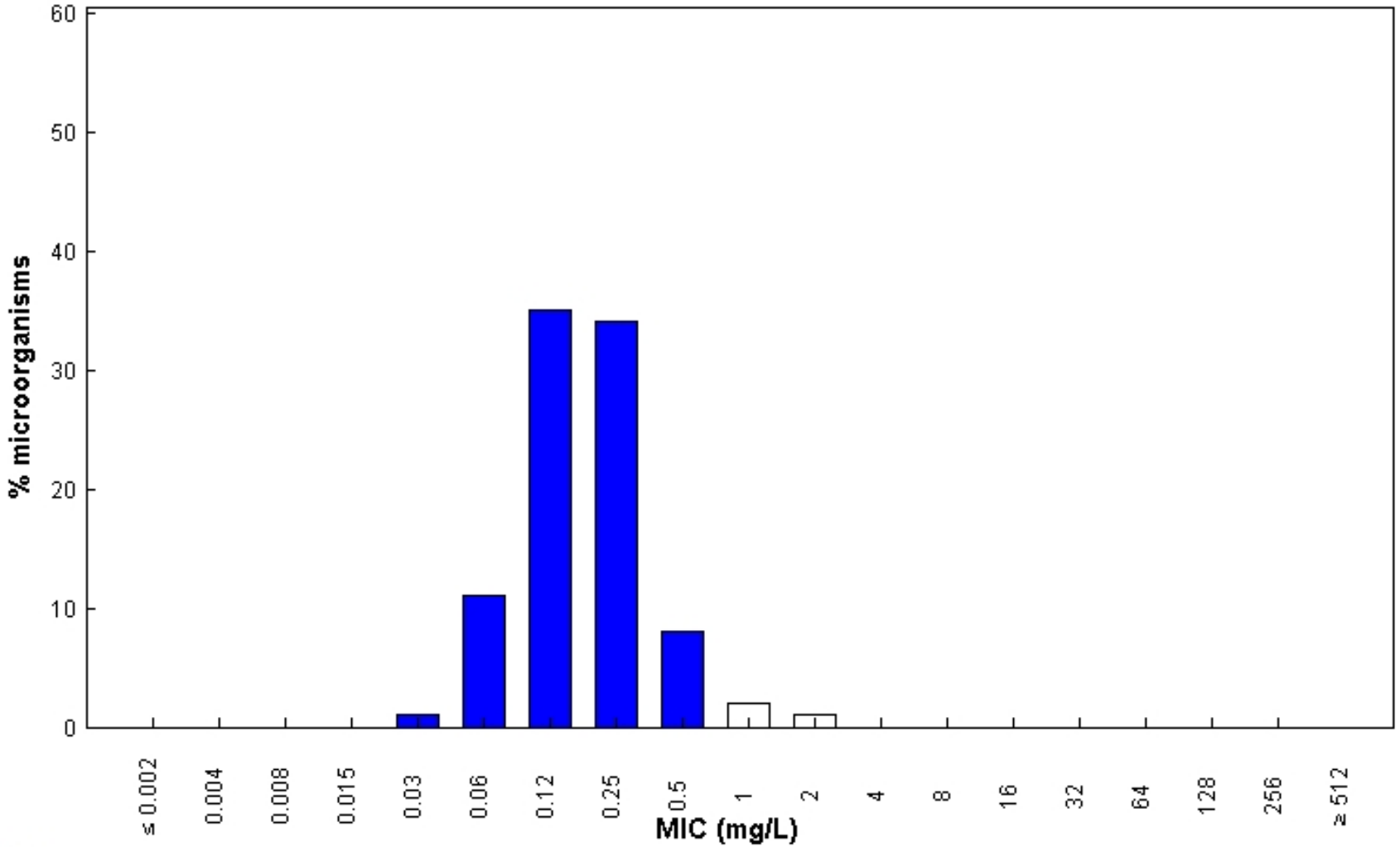
Microbiology Data

EUCAST Data
www.EUCAST.org

Ceftazidime / Escherichia coli

International MIC Distribution - Reference Database 2018-12-12

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC
Epidemiological cut-off (ECOFF): 0.5 mg/L
Wildtype (WT) organisms: ≤ 0.5 mg/L

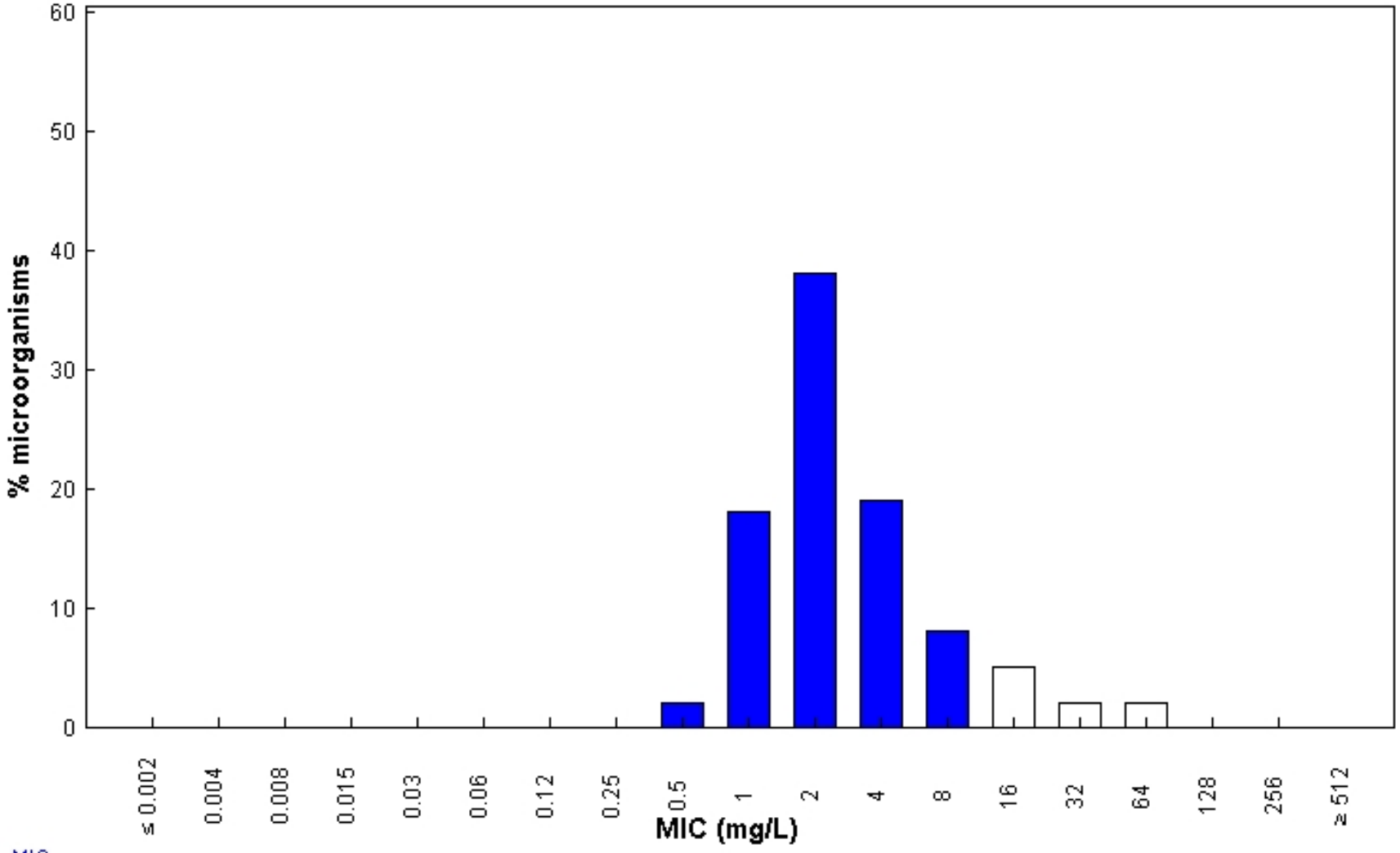
15162 observations (82 data sources)

EUCAST Data
www.EUCAST.org

Ceftazidime / Pseudomonas aeruginosa

International MIC Distribution - Reference Database 2018-12-12

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC
Epidemiological cut-off (ECOFF): 8 mg/L
Wildtype (WT) organisms: ≤ 8 mg/L

32276 observations (84 data sources)

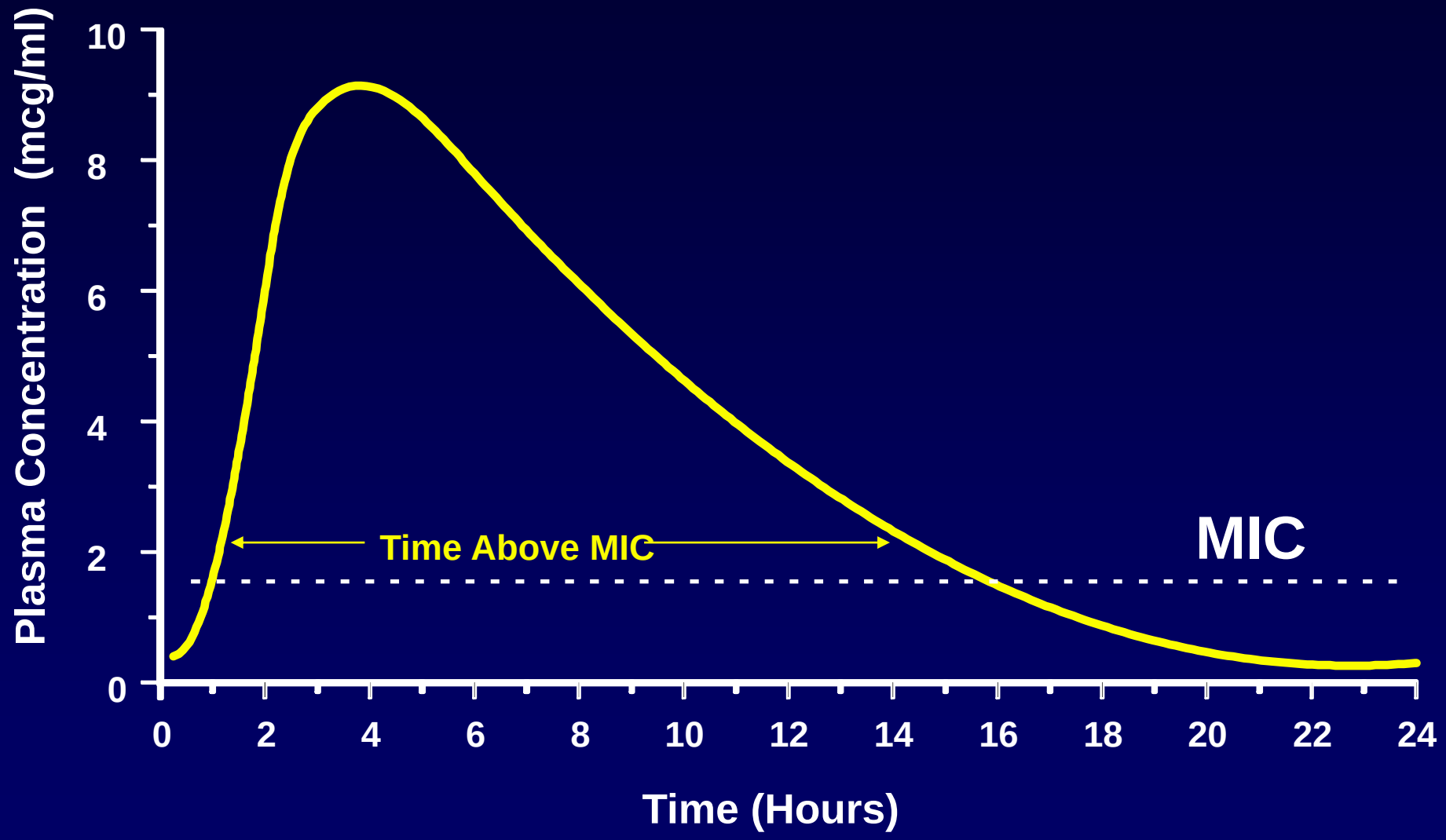
Pharmacokinetic-Pharmacodynamics (PK-PD)

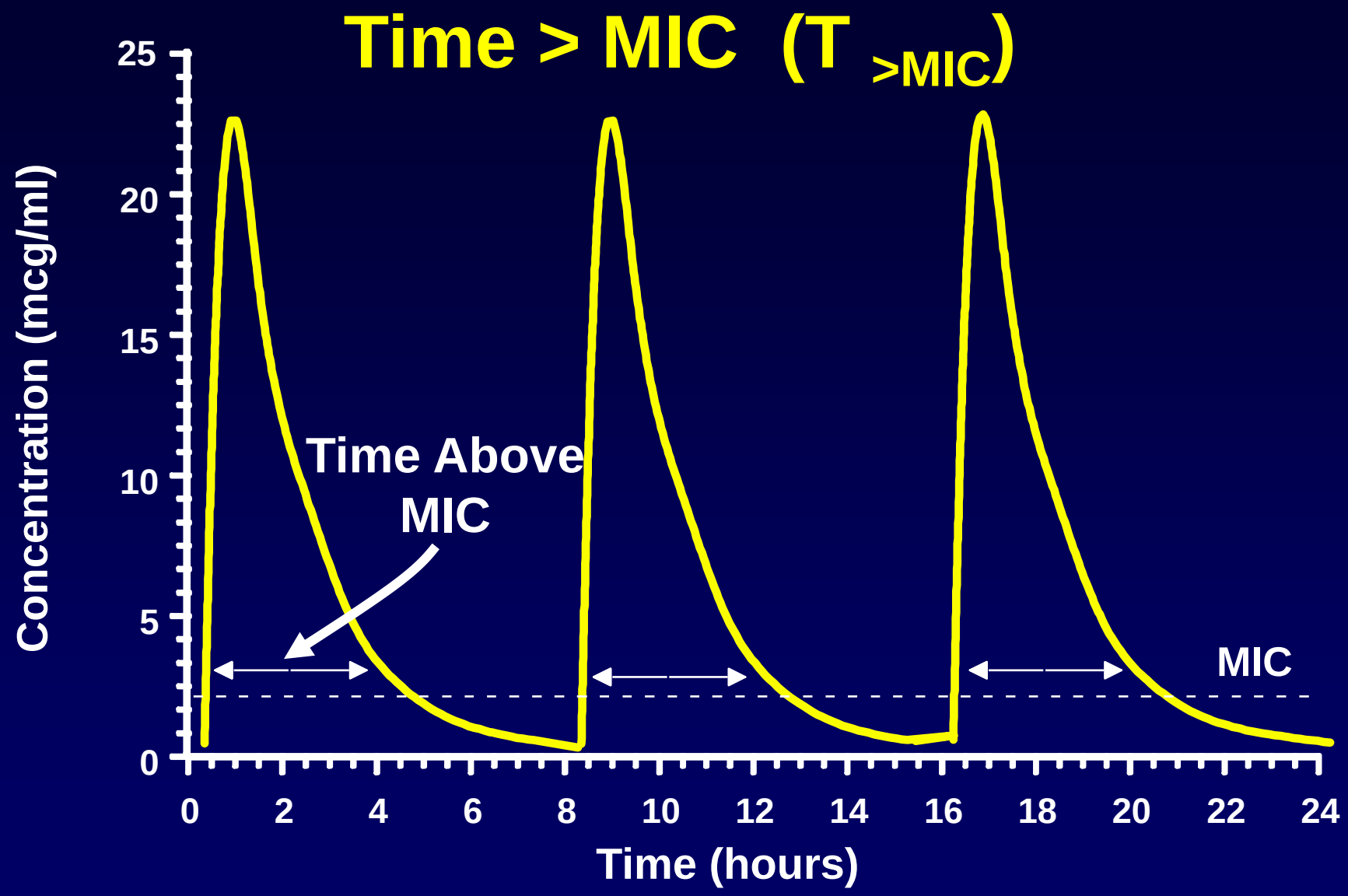
Beta-Lactam Antibiotics

Antibacterial Features

- Bactericidal
- Time-dependent activity

Time > MIC ($T_{>MIC}$)




Time > MIC (T >MIC)
Concentration (mcg/ml)
25
20
15
10
5
0
Time Above MIC
MIC
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (hours)

PK-PD Targets for ß-lactam Antibiotics

(Turnidge Clin Infect Dis 27: 10, 1998)

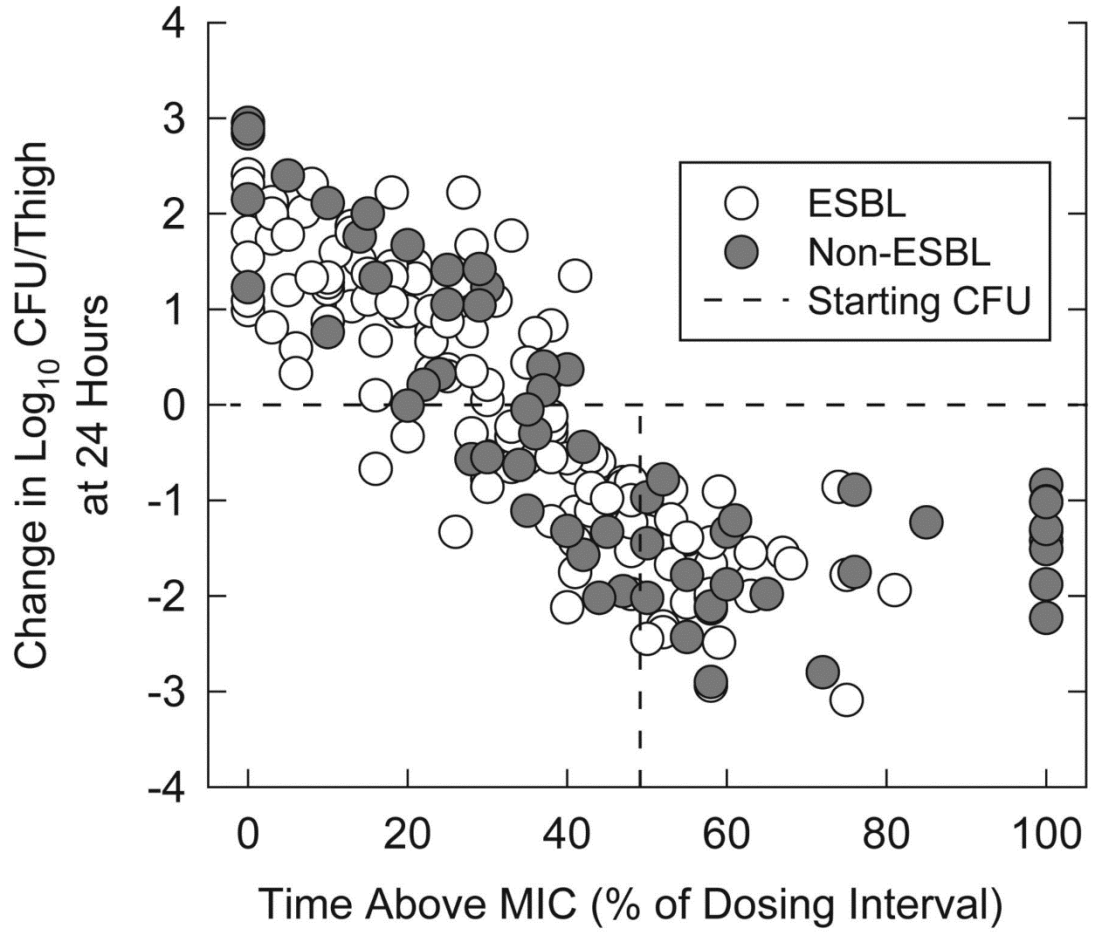
- T > MIC is best predictor of outcome.
- Neutropenic animals
  - T > MIC 90-100% of dosing interval
  - T > MIC 50-60% of dosing interval when there is a PAE
- Non-Neutropenic animals
  - T > MIC 20% for carbapenems
  - T > MIC 25-30% for penicillins
  - T > MIC 25-40% for cephalosporins

PK-PD Target for T > MIC for Cephalosporin Antibiotics

CLSI Vet02-A4 Section 4.4.3 "Establishing a Pharmacokinetic-Pharmacodynamic Target"

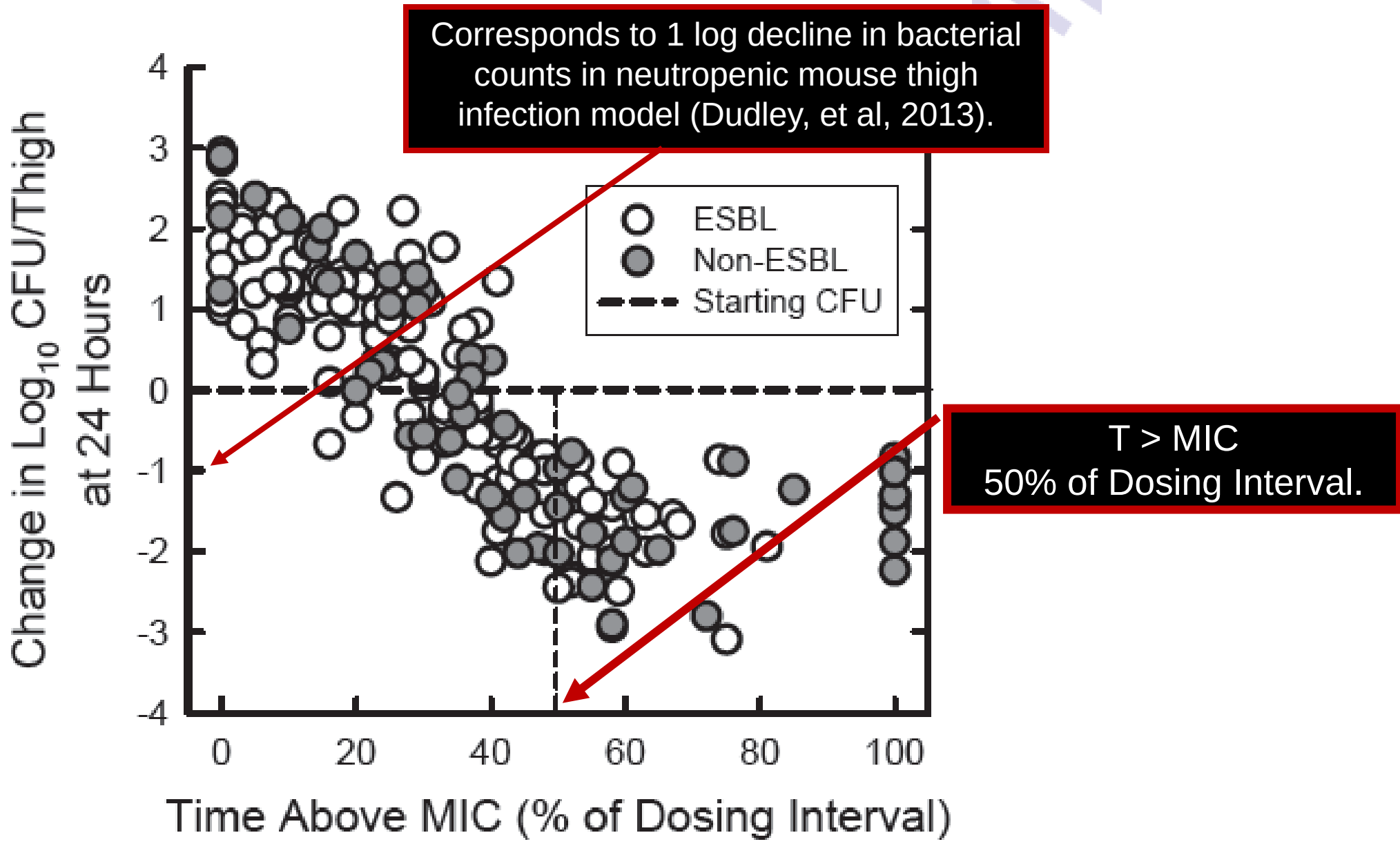
Table C2:

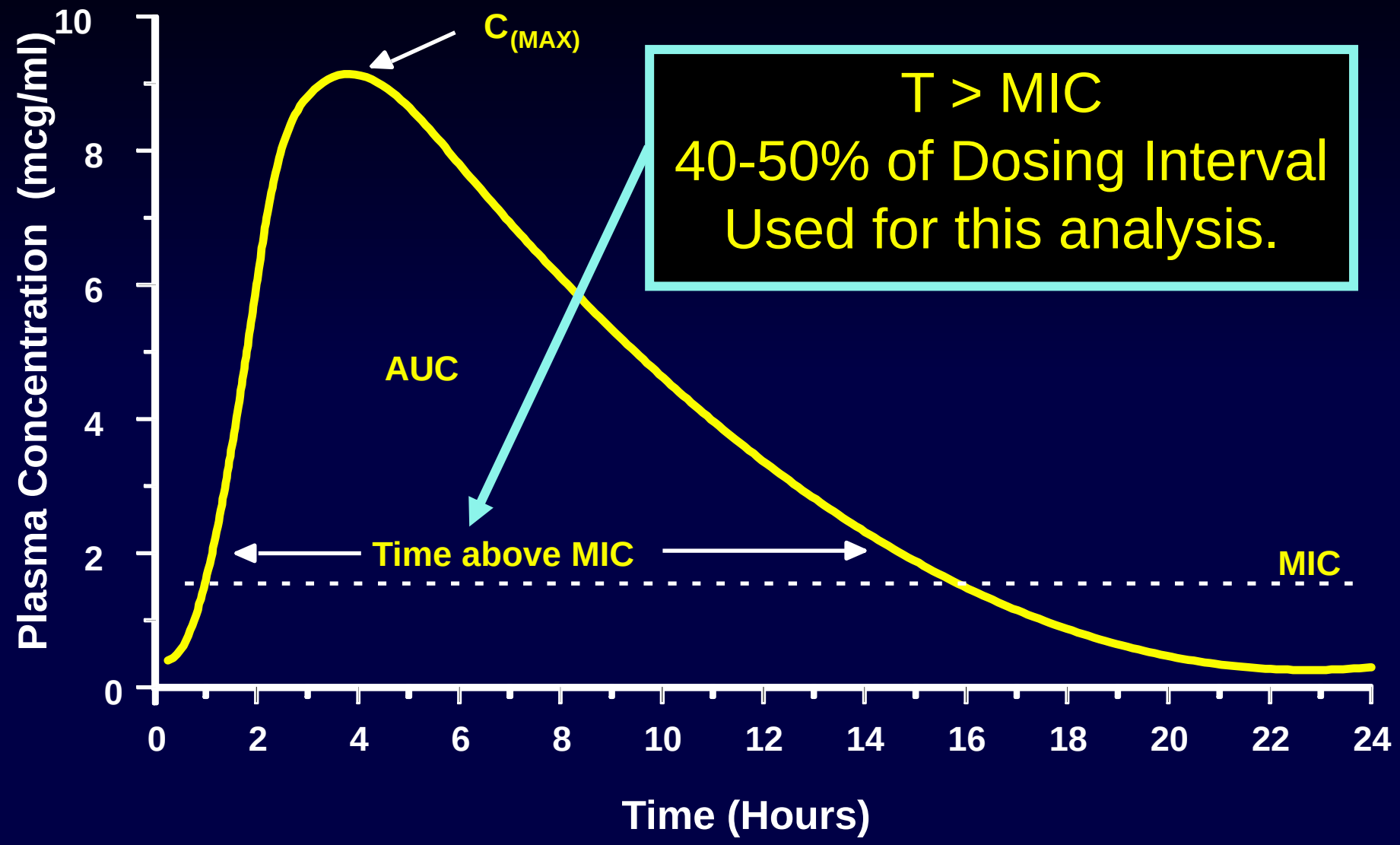
- *Gram-negative & Streptococci*
  - *f* T>MIC = 40-50% (stasis)
  - *f* T>MIC = 70-80 (max kill)
- *Staphylococcus* spp.
  - *f* T>MIC = 20-30 (stasis)
  - *f* T>MIC = 40-50 (max kill)



From: Background and Rationale for Revised Clinical and Laboratory Standards Institute Interpretive Criteria (Breakpoints) for Enterobacteriaceae and Pseudomonas aeruginosa: I. Cephalosporins and Aztreonam

Clin Infect Dis. 2013;56(9):1301-1309. doi:10.1093/cid/cit017


Corresponds to 1 log decline in bacterial counts in neutropenic mouse thigh infection model (Dudley, et al, 2013).
T > MIC
50% of Dosing Interval.
ESBL
Non-ESBL
Starting CFU
Change in Log10 CFU/Thigh at 24 Hours
Time Above MIC (% of Dosing Interval)
4
3
2
1
0
-1
-2
-3
-4
0
20
40
60
80
100


Plasma Concentration (mcg/ml)
10
8
6
4
2
0
$C_{(MAX)}$
AUC
Time above MIC
MIC
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (Hours)
T > MIC
40-50% of Dosing Interval
Used for this analysis.

PK-PD Data

Determination of T > MIC

- % T > MIC =
  ln (Dose/[VD x MIC]) x (T ½ / ln2) x (100 / DI)

- VD = volume of distribution
- T ½ = half-life
- DI = dose interval

Monte Carlo Simulations

- % T > MIC
- Crystal Ball software v. 11.1.1.1 (Oracle)
- 1,000 random trials simulated
- Input
  - MIC (range from 0.03 µg/mL– 128 µg/mL)
  - Dose interval (12, 8, and 6 hours tested)
  - VD (mean & variance)
  - T ½ (mean & variance)
  - Protein binding (10.2 %)

Results

Target Attainment Monte Carlo Simulation (T>MIC) for Ceftazidime in Dogs
% Probability of attaining 50% T>MIC.

	MIC (µg/mL)										
Dose 25 mg/kg	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Every 6 hours	100	100	100	99.56	99.26	97.47	91.79	75.66	43.37	9.4	0.72
Every 8 hours	99.8	99.79	99.31	96.37	94.65	85.79	70.38	42.38	14.68	2.16	0.04
Every 12 hours	96.24	91.88	86.31	76.11	62.02	42.85	24.17	9.46	1.51	0.09	0.01

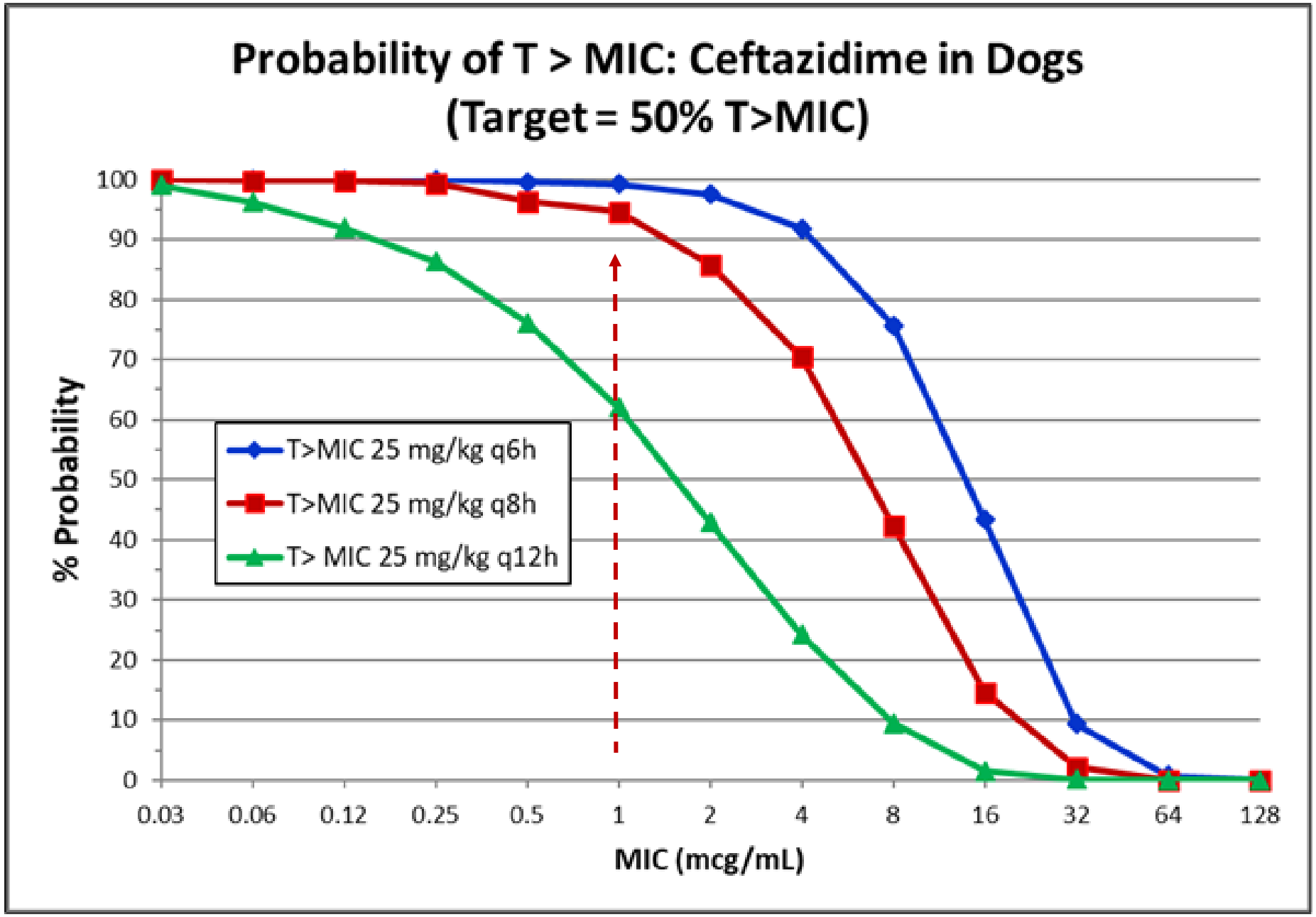


Figure 5: *Probability of Target Attainment (PTA) for Ceftazidime in Dogs for 50% T>MIC*

Target Attainment Monte Carlo Simulation (T>MIC) for Ceftazidime in Dogs
% Probability of attaining 40% T>MIC.

	MIC (µg/mL)										
Dose 25 mg/kg	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Every 6 hours	100	100	100	100	99.85	99.72	97.55	91.71	66.81	23.29	2.35
Every 8 hours	100	100	99.84	99.31	98.6	95.25	88.57	65.56	32.26	7.08	0.38
Every 12 hours	99.27	98.47	95.82	91.61	84.32	67.69	48.76	23.27	6.22	0.89	0.05

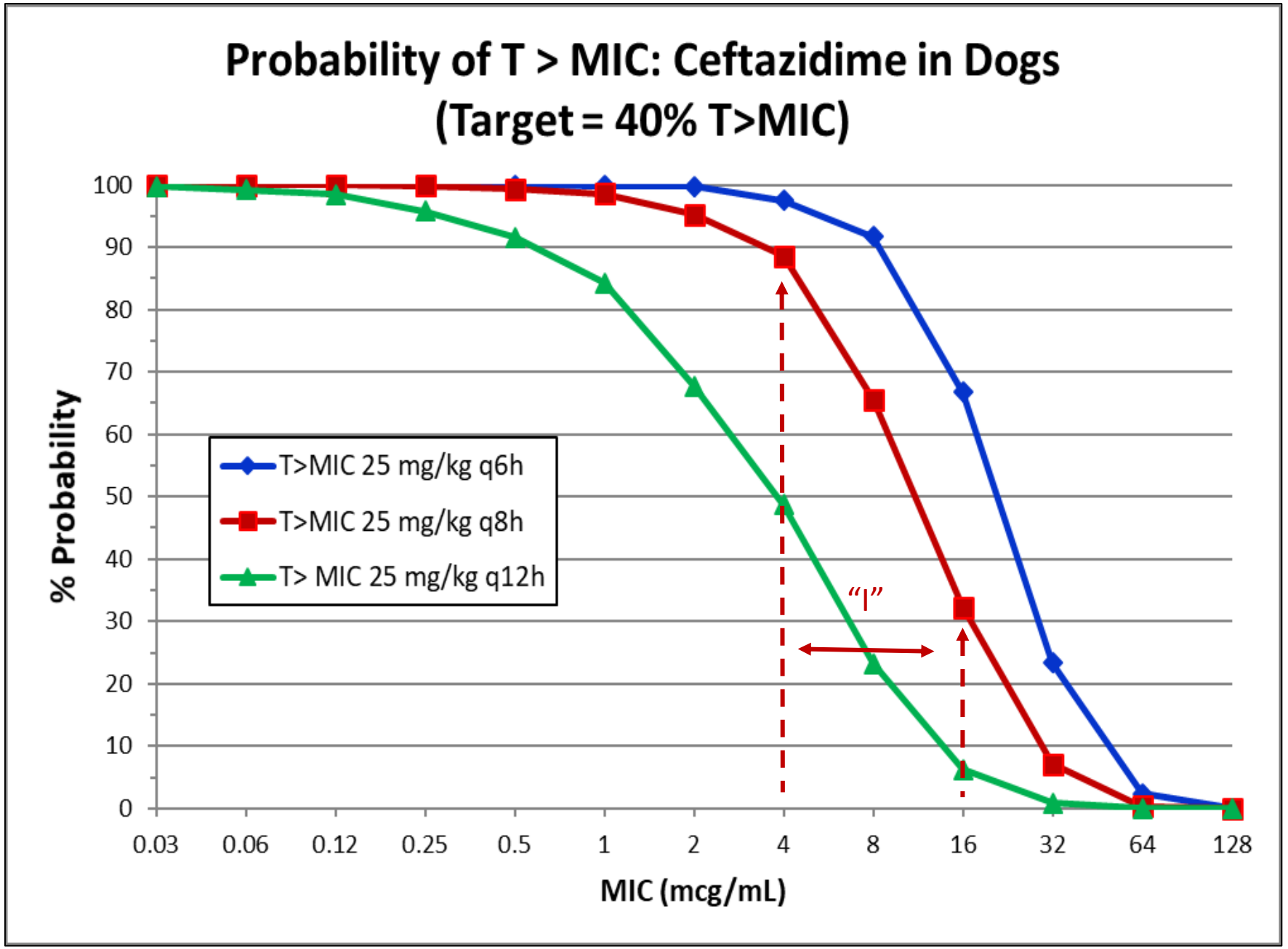


Figure 6: *Probability of Target Attainment (PTA) for Ceftazidime in Dogs for 40% T>MIC*

Revised Breakpoint for Cephalosporins and Aztreonam
Dudley, et al. Clinical Infectious Diseases 2013; 56: 1301

Enterobacteriaceae

Drug (Dosage)[a]	MIC (µg/mL)					
	Revised			Pre-2010		
	S	I	R	S	I	R
Aztreonam (1 g q8h)	≤4	8	≥16	≤8	16	≥32
Cefotaxime (1 g q8h)	≤1	2	≥4	≤8	16–32	≥64
Ceftazidime (1 g q8h)	≤4	8	≥16	≤8	16	≥32
Ceftizoxime (1 g q12h)	≤1	2	≥4	≤8	16–32	≥64
Ceftriaxone (1 g q24h)	≤1	2	≥4	≤8	16–32	≥64

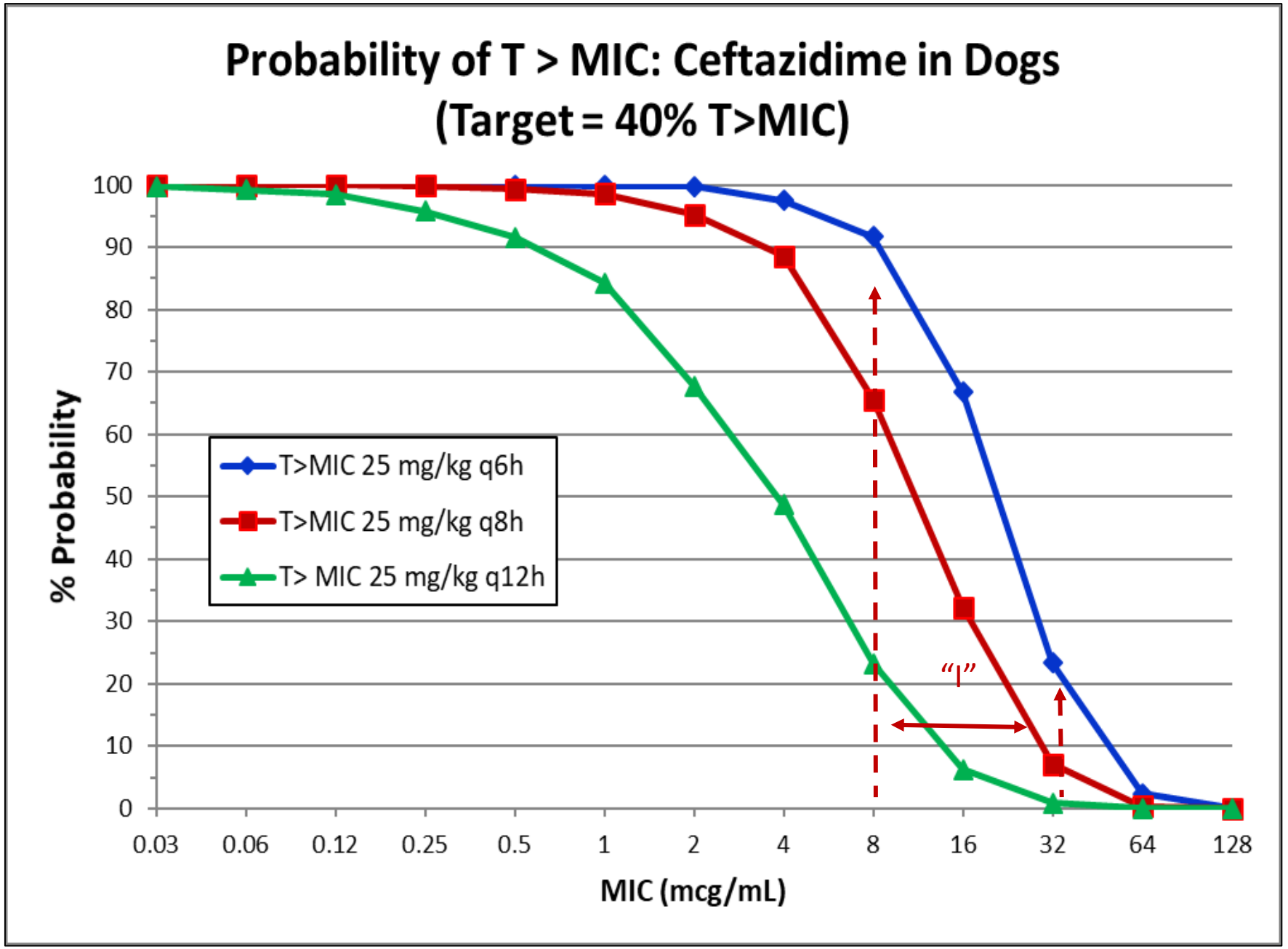


Figure 6: *Probability of Target Attainment (PTA) for Ceftazidime in Dogs for 40% T>MIC*

Revised Breakpoint for Cephalosporins and Aztreonam
Dudley, et al. Clinical Infectious Diseases 2013; 56: 1301

Pseudomonas aeruginosa

Drug	Dosage	MIC Breakpoints		
		Susceptible	Intermediate	Resistant
Ceftazidime	1 g q6h or	≤8	16	≥32
	2 g IV q8h			
Aztreonam	1 g q6h or	≤8	16	≥32
	2 g IV q8h			
Cefepime	1 g IV q8h or	≤8	16	≥32
	2 g IV q12h			

VET 02-A4 Guidelines

Table C10: Decision Table When Only 2 Cutoff Values Available (CO_{WT} and [CO_{PD} or CO_{CL}])

Abbreviations: CL, clinical cutoff value (CO_{CL}); PD, pharmacodynamic cutoff value (CO_{PD}); WT, wild type cutoff value (CO_{WT}).

Ranking of Cutoffs	Suggested Breakpoint	Comments
WT > PD	PD	Could accept CO_{WT} as breakpoint if CO_{WT} only 1 dilution higher than CO_{PD}
PD > WT	PD	
WT = PD	WT = PD	
WT > CL	CL	Could accept CO_{WT} as breakpoint if CO_{WT} only if 1 dilution higher than CO_{CL}
CL > WT	CL	
WT= CL	WT= CL	

Recommendation from the Generic Drug Working Group

Conclusion

*f*T>MIC can be maintained for at least 40% of the dose interval when administering ceftazidime at 25 mg/kg

- Every 6 hours (*Pseudomonas aeruginosa*)
- Every 8 hours (*E. coli*)

Recommendations

Canine-specific ceftazidime breakpoint*

Enterobacteriaceae

- ≤ 4 µg/mL (S)
- 8 µg/mL (I)
- ≥ 16 µg/mL (R)

*Based on 90% PTA, 3 times daily dose of 25 mg/kg IV, IM, or SC, 10.2% protein binding, and T>MIC for 40% of dose interval

Table 2A. Enterobacteriaceae (From CLSI VAST Vet08, 2018)

Test/ Report Group	Body Site	Antimicrobial Agent	Organism	Disk Content	Zone Diameter Breakpoints and Interpretive Categories (nearest whole mm)			MIC Breakpoints and Interpretive Categories (µg/mL)			Comments
					S	I	R	S	I	R	
Cephalosporins											
Dogs											
A	Skin, soft tissue	Cephalexin	E. coli	–	–	–	–	≤ 2	4	≥ 8	Cephalexin breakpoints were determined from an examination of MIC distribution data, efficacy data, and PK-PD analysis of cephalexin in dogs. The dosage regimen used for PK-PD analysis of cephalexin was 25 mg/kg administered every 12 hours orally.
A	Skin, soft tissue	Cefazolin	*E. coli*	–	–	–	–	≤ 2	4	≥ 8	Cefazolin breakpoints were determined from an examination of MIC distribution data and PK-PD analysis of cefazolin. The dosage regimen used for PK-PD analysis of cefazolin was 25 mg/kg administered every 6 hours IV in horses and dogs.
A	Wounds, abscesses	Cefpodoxime	*E. coli* *P. mirabilis*	10 µg	≥ 21	18–20	≤ 17	≤ 2	4	≥ 8	See comment (26).
A	**Skin, soft tissue**	**Ceftazidime**	~~***E. Coli***~~ ***Enterobacteriaceae***	30 µg	≥ 21	18–20	≤ 17	**≤ 4**	**8**	**≥ 16**	**Ceftazidime breakpoints were determined from an examination of MIC distribution data and PK-PD analysis of ceftazidime. The dosage regimen used for PK-PD analysis of ceftazidime was 25 mg/kg administered every 8 hours IM, IV, or SC in dogs.**
Humans											
		Ceftazidime	*Enterobacteriaceae*	30 µg	≥ 21	18-20	≤ 17	≤ 4	8	≥ 16	Based on a dose of 1 gram every 8 hours

Recommendations

Canine-specific ceftazidime breakpoint*

Pseudomonas aeruginosa

- ≤ 8 µg/mL (S)
- 16 µg/mL (I)
- ≥ 32 µg/mL (R)

*Based on 90% PTA, 4 times daily dose of 25 mg/kg IV, IM, or SC, 10.2% protein binding, and T>MIC for 40% of dose interval

Table 2B *Pseudomonas aeruginosa* (From CLSI VAST Vet08, 2018)											
Test/ Report Group	**Body Site**	**Antimicrobial Agent**	**Organism**	**Disk Content**	**Zone Diameter Breakpoints and Interpretive Categories (nearest whole mm)**			**MIC Breakpoints and Interpretive Categories (µg/mL)**			**Comments**
					S	**I**	**R**	**S**	**I**	**R**	
Cephalosporins											
Dogs											
A	**Skin, soft tissue**	**Ceftazidime**	***Pseudomonas aeruginosa***					**≤8**	**16**	**≥32**	**Ceftazidime breakpoints were determined from an examination of MIC distribution data and PK-PD analysis of ceftazidime. The dosage regimen used for PK-PD analysis of ceftazidime 25 mg/kg administered every 6 hours in dogs.**
Humans											
		Ceftazidime	*Pseudomonas aeruginosa*	30 µg	≥18	15-17	≤14	≤8	16	≥32	Based on a dose of 1 gram every 6 hours, or 2 grams every 8 hours.

Additional Recommendations:

1. Include ceftazidime (dogs only) in VET08, Table 1* for testing for ceftazidime for *Enterobacteriaceae* and *Pseudomonas aeruginosa* in Dogs
2. In addition to the breakpoint, include the dose and dosing route used for PK-PD analysis in the Comment sections of Table 2A and 2B.
3. Include the human breakpoint zone diameters also

* Location to be determined by VET08 WG

Thank you.

Any Questions?

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