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CLSI Veterinary Antimicrobial Susceptibility Testing Subcommittee (VAST)

CLSI
Generic Antimicrobial Agents Working Group

Subcommittee on Veterinary Antimicrobial Susceptibility Testing

January 24-25, 2019

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

CLSI-VAST
Generic Drug Working Group

CLSI
Generic Antimicrobial Agents Working Group

Members (2019):

Cory Langston, Vijay Singu, Virginia Sinnott-Stutzman, Ching Ching Wu, Shabbir Simjee, Lacie Johansen, Sara Lawhon, Virginia Fajt, Mark Papich, John Turnidge, Stefan Schwarz, Marilyn Martinez, Amanda Kreuder, & Tara Bidgood.

CLSI-VAST
Interpretive Categories and Breakpoints for Susceptibility Testing:

- Overall: breakpoints for approximately 180 drug-bug combinations

- Since 2015: 35 new breakpoints; 28 developed by the Generic Drug Working Group

CLSI Veterinary-Specific Breakpoint Additions/Revisions Since 2015*

Antimicrobial Agent	Table	Organism(s)	Animal Species	Body Site	Data Source Presentation
Ampicillin	2A	*Escherichia coli*	Cats	SST, UTI	GWG (January 2018)
Cefovecin	2A	*E. coli*	Cats	UTI	Sponsor (January 2018)
Ampicillin	2A	*E. coli*	Cattle	Metritis	GWG (January 2018)
Cefazolin	2A	*E. coli* *Klebsiella pneumoniae* *Proteus mirabilis*	Dogs	UTI	GWG (January 2017)
Cefovecin	2A	*E. coli* *P. mirabilis*	Dogs	UTI	Sponsor (January 2018)
Cefpodoxime	2A	*E. coli* *K. pneumoniae* *P. mirabilis*	Dogs	UTI	GWG (January 2017)
Cephalexin	2A	*E. coli*	Dogs	SST	GWG (June 2015)
Cephalexin	2A	*E. coli* *K. pneumoniae* *P. mirabilis*	Dogs	UTI	GWG (January 2017)
Piperacillin-tazobactam	2A	*Enterobacteriaceae*	Dogs	SST, UTI	GWG (June 2015)
Doxycycline	2A	*E. coli*	Horses	Resp, SST	GWG (January 2017)
Enrofloxacin	2A	*E. coli*	Horses	Resp, SST	GWG (January 2017)
Minocycline	2A	*E. coli*	Horses	Resp, SST	GWG (January 2018)
Piperacillin-tazobactam	2B	*Pseudomonas aeruginosa*	Dogs	SST, UTI	GWG (June 2015)
Enrofloxacin	2B	*P. aeruginosa*	Horses	Resp, SST	GWG (January 2017)
Ampicillin	2C	*Staphylococcus* spp.	Cats	SST, UTI	GWG (January 2018)
Cefovecin	2C	*Staphylococcus pseudintermedius*	Dogs	SST	Sponsor (January 2018)
Cephalexin	2C	*Staphylococcus aureus* *S. pseudintermedius*	Dogs	SST	GWG (June 2015)
Minocycline	2C	*S. pseudintermedius*	Dogs	SST	GWG (June 2015)
Piperacillin-tazobactam	2C	*Staphylococcus* spp.	Dogs	SST, UTI	GWG (June 2015)
Doxycycline	2C	*S. aureus*	Horses	Resp, SST	GWG (January 2017)
Enrofloxacin	2C	*S. aureus*	Horses	Resp, SST	GWG (January 2017)
Minocycline	2C	*S. aureus*	Horses	Resp, SST	GWG (January 2017)
Ampicillin	2D	*Streptococcus* spp.	Cats	SST, UTI	GWG (January 2018)

CLSI Veterinary-Specific Breakpoint Additions/Revisions Since 2015* (Continued)

Antimicrobial Agent	Table	Organism(s)	Animal Species	Body Site	Data Source Presentation
Cefovecin	2D	*Streptococcus* β-hemolytic group	Dogs	SST	Sponsor (January 2018)
Cephalexin	2D	*Streptococcus* β-hemolytic group	Dogs	SST	GWG (June 2015)
Doxycycline	2D	*Streptococcus equi* subsp. *equi* and *zooepidemicus*	Horses	Resp, SST	GWG (January 2017)
Enrofloxacin	2D	*S. equi* subsp. *equi* and *zooepidemicus*	Horses	Resp, SST	GWG (January 2017)
Minocycline	2D	*Streptococcus* spp.	Horses	Resp, SST	GWG (January 2017)
Ampicillin	2G	*Mannheimia haemolytica*	Cattle	Resp	GWG (January 2018)
Danofloxacin	2G	*M. haemolytica*	Cattle	Resp	Sponsor (January 2016, I and R breakpoints)
Ampicillin	2H	*Pasteurella multocida*	Cats	SST, UTI	GWG (January 2018)
Cefovecin	2H	*P. multocida*	Cats	SST, UTI	Sponsor (January 2018)
Ampicillin	2H	*P. multocida*	Cattle	Resp	GWG (January 2018)
Danofloxacin	2H	*P. multocida*	Cattle	Resp	Sponsor (January 2016, I and R breakpoints)
Ampicillin	2J	*Histophilus somni*	Cattle	Resp	GWG (January 2018)

Abbreviations: GWG, Generic Drug Working Group; I, intermediate; R, resistant; resp, respiratory; SST, skin and soft tissue; UTI, urinary tract infection.

CLSI
Generic Antimicrobial Agents Working Group

Updates from the Generic Drug Working Group

CLSI
Generic Antimicrobial Agents Working Group

Amoxicillin / Ampicillin in Cats
January 2018

Protein Binding

- Estimated at 20% in our analysis, based on other animals and people, but data was not available for cats.

Amoxicillin Protein Binding in Cat Plasma (10 µg/mL)	
Replicate	% protein binding
1	20.17
2	13.2
3	15.79
Mean	16.39

New Evidenct that Supports Previous CLSI-VAST GWG Breakpoints

- Population PK Analysis
- 78 dogs
- Goal: "to compute PK/PD cutoff values and establish a clinical breakpoint for cefazolin in dogs"

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 09 October 2018
doi: 10.3389/fphar.2018.01137

Population Pharmacokinetic Study of Cefazolin Used Prophylactically in Canine Surgery for Susceptibility Testing Breakpoint Determination

Petra Cagnardi[1], Federica Di Cesare[1], Pierre-Louis Toutain[2], Alain Bousquet-Mélou[3], Giuliano Ravasio[4] and Roberto Villa[1]*

[1] Department of Health, Animal Science and Food Safety, Università degli Studi di Milano, Milan, Italy, [2] The Royal Veterinary College, University of London, London, United Kingdom, [3] INTHERES, Université de Toulouse, INRA, ENVT, Toulouse, France, [4] Department of Veterinary Medicine, Università degli Studi di Milano, Milan, Italy

This study aimed to determine the population pharmacokinetic (Pop PK) parameters of cefazolin administered prophylactically at 25 mg/kg intravenously (IV) 30 min before surgery in a canine population of 78 dogs and assess whether covariates, such as sex, age, body weight (BW), breed, health status, creatinine level, and surgery time, have an influence on cefazolin disposition. The ultimate goal was to compute PK/PD cut off values and subsequently establish a specific clinical breakpoint (CBP) for the development of an antimicrobial susceptibility test (AST) of cefazolin in dogs according to the VetCAST approach. Two to 11 blood samples were collected from each dog from 5 to 480 min after cefazolin administration. A two-compartment model was selected, and parameterization was in terms of serum clearance (CL), intercompartmental CL(s) (Q) and volume(s) of distribution (V). The percentage of cefazolin binding to serum protein was 36.2 ± 5.3%. Population primary parameter estimates V1, V2, CL, and Q were (typical value ± SE) 0.116 ± 0.013 L/kg, 0.177 ± 0.011 L/kg, 0.0037 ± 0.0002 L/kg/min, and 0.0103 ± 0.0013 L/kg/min, respectively. Cefazolin presented rapid distribution and elimination half-lives (mean ± SE) 4.17 ± 0.77 min and 57.93 ± 3.11 min, respectively. The overall between-subject variability (BSV) for estimated primary parameters ranged from 36 to 42%, and none of the seven explored covariates were able to reduce this variability by an amplitude clinically relevant. By Monte Carlo simulation, the probability of a PK/PD target attainment (here to achieve a free serum concentration exceeding the MIC for 50% of the dosing interval in 90% of dogs) was computed with a dosage of 25 mg/kg administered IV every 6 h for 4 administrations in 24 h. The computed PK/PD cut off value was 2 mg/L. In conclusion, cefazolin administered prophylactically in surgical dogs at 25 mg/kg IV every 6 h was deemed effective against pathogens with a MIC value ≤ 2 mg/L and from a PK/PD perspective, can be recommended in a wide range of canine patient populations with no necessary dose adjustment for special dog subpopulations.

Keywords: cefazolin, dog, prophylactic administration, surgery, population pharmacokinetics, PK/PD cut off value

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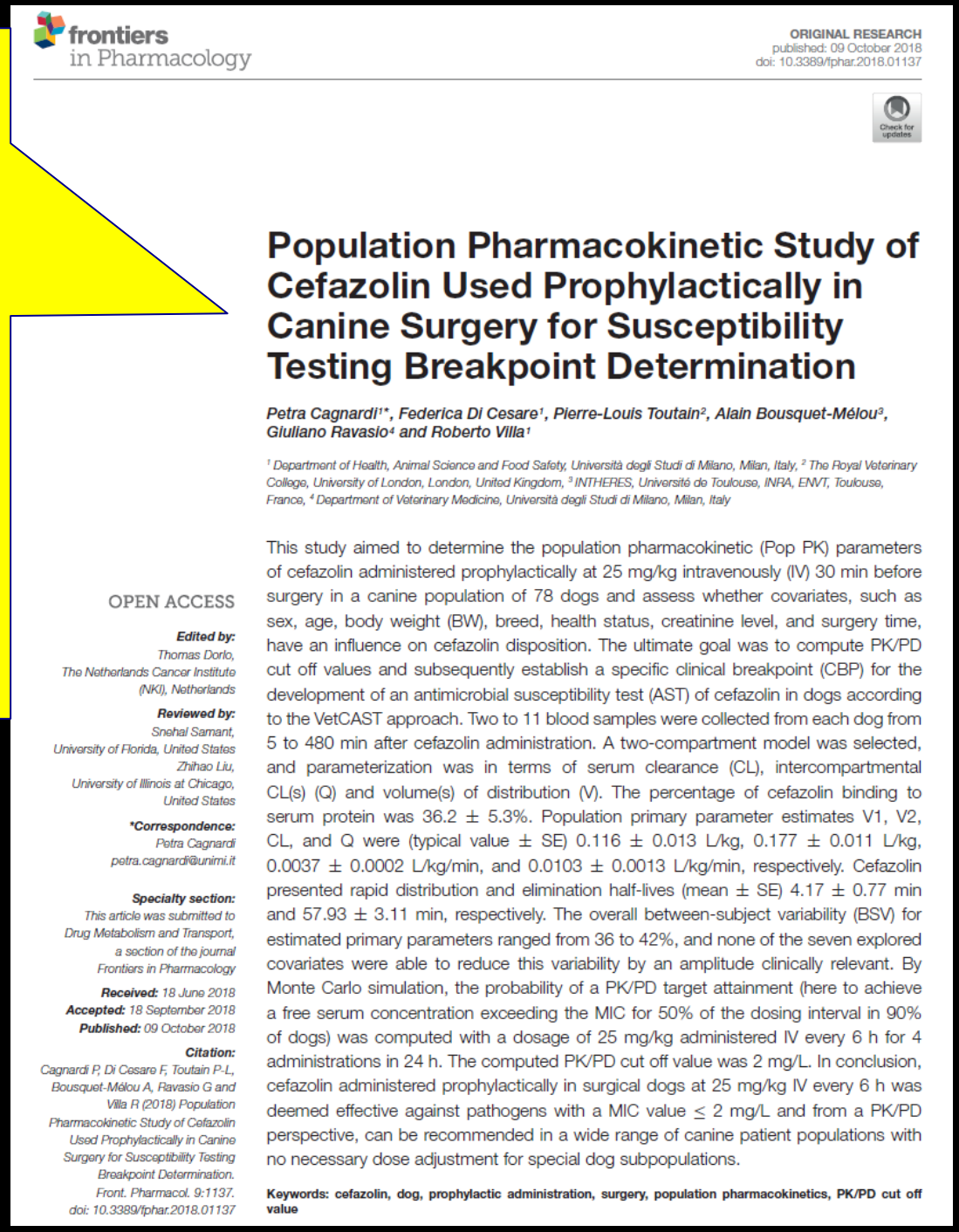
Table 2A. Enterobacteriaceae (From CLSI VAST Vet08, 2018)

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.
							–	≤ 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.
							≤ 17	≤ 2	4	≥ 8	See comment (26).

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.

Conclusion:

- At a dose of 25 mg/kg IV every 6 hours, the PK/PD cutoff value was 2 µg/mL.
- No changes necessary based on age, surgery, health status, weight, creatinine, and time.
- "The present trial is consistent with CLSI breakpoint."



frontiers in Pharmacology

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Keywords: cefazolin, dog, prophylactic administration, surgery, population pharmacokinetics, PK/PD cut off value

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DOI: 10.1111/jvim.15078

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

An evaluation of serum gentamicin concentrations and bacterial susceptibility to gentamicin in equine practice

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Background: Therapeutic drug monitoring and minimum inhibitory concentration (MIC) data allow more informed use of gentamicin.

Hypothesis/Objectives: To measure peak and trough serum gentamicin concentrations in horses after a 6.6 mg/kg dose of gentamicin given IV and the MIC of gentamicin of bacteria for which gentamicin might be selected.

Methods: Retrospective analysis of hospital records. Peak and trough plasma gentamicin concentrations were measured after 6.6 mg/kg gentamicin IV in 339 hospitalized horses. The MIC of gentamicin was measured for 503 isolates from ambulatory practice and 33 from hospital practice. The distribution of gentamicin concentrations and MIC results were compared to current recommendations for MIC breakpoints.

Results: The median serum gentamicin concentration at 60 minutes after administration (C_{60min}) was 21.4 μg/mL with a distribution indicating that bacteria with MIC ≥2 μg/mL were unlikely to be exposed to sufficient gentamicin for effective killing. Approximately 90% of isolates from ambulatory practice and 36% of hospital isolates had MICs at or below breakpoints for susceptibility with most of the remainder unlikely to be responsive, even to higher IV doses.

Conclusions and Clinical Importance: Gentamicin at a dosage of 6.6 mg/kg IV is likely to be effective against the majority of infections encountered in ambulatory practice, but less effective in an equine hospital. Because there was a dichotomy of most bacteria as being clearly susceptible or clearly resistant to gentamicin, it appears unlikely that higher doses would have been more efficacious, especially in the hospitalized population in our study.

Table 2A. *Enterobacteriaceae* (Continued)

Test/ Report Group	Body Site	Antimicrobial Agent	Organism	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL			Comments
					S	I	R	S	I	R	
Aminoglycosides/Aminocyclitols											
Dogs											
A		Amikacin	*E. coli*	–	–	–	–	≤4	8	≥16	**(5)** Breakpoints were derived from microbiological, PK (using accepted clinical doses), and PD data. For dogs, the dose of amikacin modeled was 15 mg/kg, every 24 hours IM, IV, or SC.
								≤2	4	≥8	**(6)** Breakpoints were derived from microbiological, PK (using accepted clinical doses), and PD data. For dogs, the dose of gentamicin modeled was 10 mg/kg every 24 hours IM.
								≤2	4	≥8	**(7)** Breakpoints were derived from microbiological, PK (using accepted clinical doses), and PD data. For foals <11 days of age, the dose of amikacin modeled was 20 mg/kg, every 24 hours IV.
Horses (adu											
A			*E. coli*	–	–	–	–	≤4	8	≥16	**(8)** Breakpoints were derived from microbiological, PK (using accepted clinical doses), and PD data. For adult horses, the dose of amikacin modeled was 10 mg/kg, every 24 hours, IM or IV.
A		Gentamicin	*Enterobacteriaceae*	10 µg	≥16	13–15	≤12	≤2	4	≥8	**(9)** Breakpoints were derived from microbiological, PK (using accepted clinical doses), and PD data. For horses, the dose of gentamicin modeled was 6.6 mg/kg every 24 hours IM.

- Gentamicin Breakpoint for Horses
- ≤ 2 µg/mL (S)
- Dose: 6.6 mg/kg once daily

Received: 9 October 2017 | Revised: 27 September 2017 | Accepted: 23 January 2018
DOI: 10.1111/jvim.15078

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access
ACVIM American College of Veterinary Internal Medicine

An evaluation of serum gentamicin concentrations and bacterial susceptibility to gentamicin in equine practice

Background: Therapeutic drug monitoring and minimum inhibitory concentration (MIC) data allow more informed use of gentamicin.

Hypothesis/Objectives: To measure peak and trough serum gentamicin concentrations in horses after a 6.6 mg/kg dose of gentamicin given IV and the MIC of gentamicin of bacteria for which gentamicin might be selected.

Methods: Retrospective analysis of hospital records. Peak and trough plasma gentamicin concentrations were measured after 6.6 mg/kg gentamicin IV in 339 hospitalized horses. The MIC of gentamicin was measured for 503 isolates from ambulatory practice and 33 from hospital practice. The distribution of gentamicin concentrations and MIC results were compared to current recommendations for MIC breakpoints.

Results: The median serum gentamicin concentration at 60 minutes after administration (C_{60min}) was 21.4 μg/mL with a distribution indicating that bacteria with MIC ≥2 μg/mL were unlikely to be exposed to sufficient gentamicin for effective killing. Approximately 90% of isolates from ambulatory practice and 36% of hospital isolates had MICs at or below breakpoints for susceptibility with most of the remainder unlikely to be responsive, even to higher IV doses.

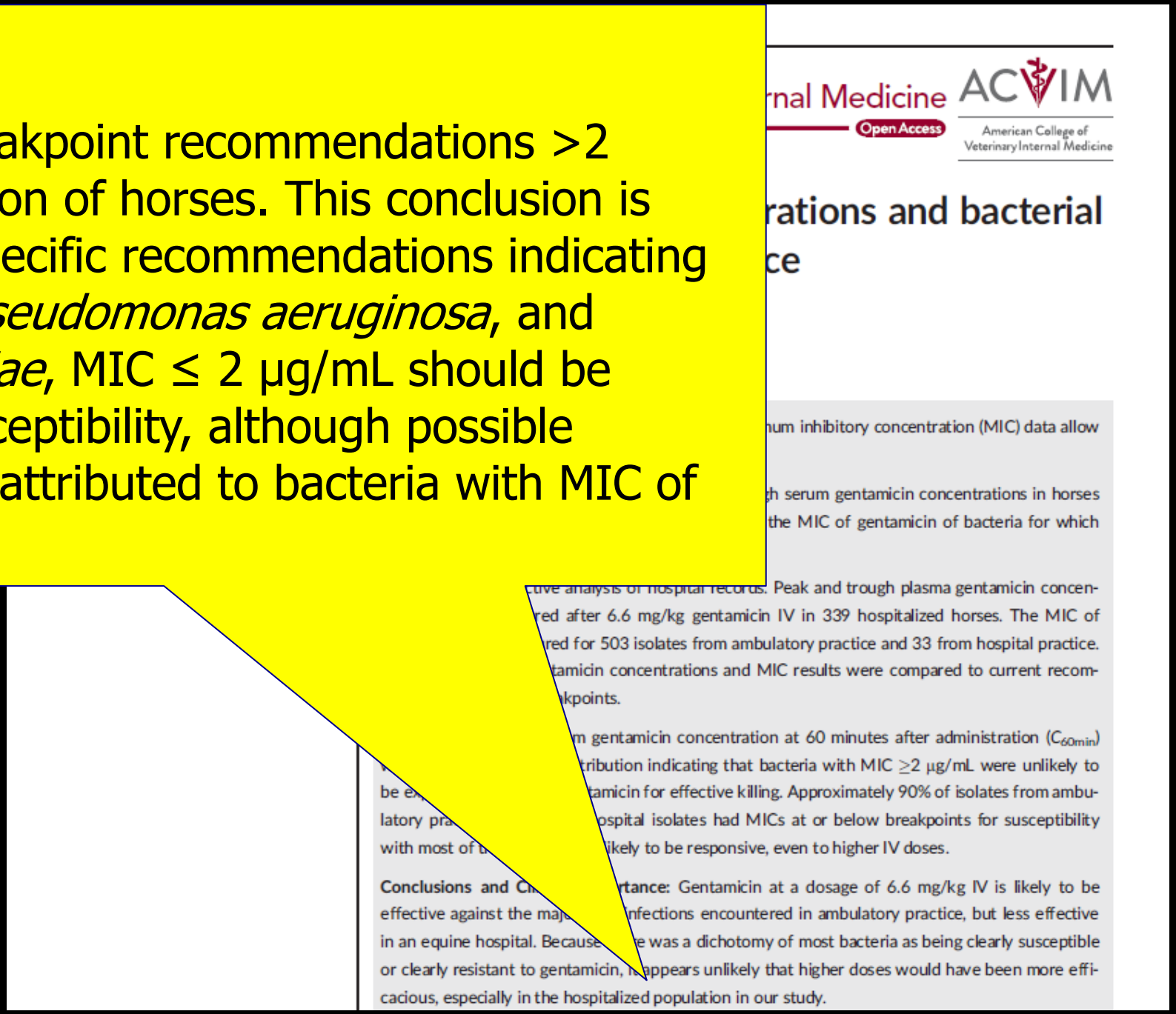
Conclusions and Clinical Importance: Gentamicin at a dosage of 6.6 mg/kg IV is likely to be effective against the majority of infections encountered in ambulatory practice, but less effective in an equine hospital. Because there was a dichotomy of most bacteria as being clearly susceptible or clearly resistant to gentamicin, it appears unlikely that higher doses would have been more efficacious, especially in the hospitalized population in our study.

Study Design:

- 339 hospitalized horses.
- MIC measured from 503 isolates in ambulatory practice and 33 from hospitalized horses.
- Dose: 6.6 mg/kg once daily.

Conclusion:

"it is difficult to justify MIC breakpoint recommendations >2 µg/mL, at least in this population of horses. This conclusion is consistent with CLSI equine-specific recommendations indicating that for Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Actinobacillus pleuropneumoniae*, MIC ≤ 2 µg/mL should be taken to indicate probable susceptibility, although possible susceptibility (intermediate) is attributed to bacteria with MIC of 4 µg/mL."



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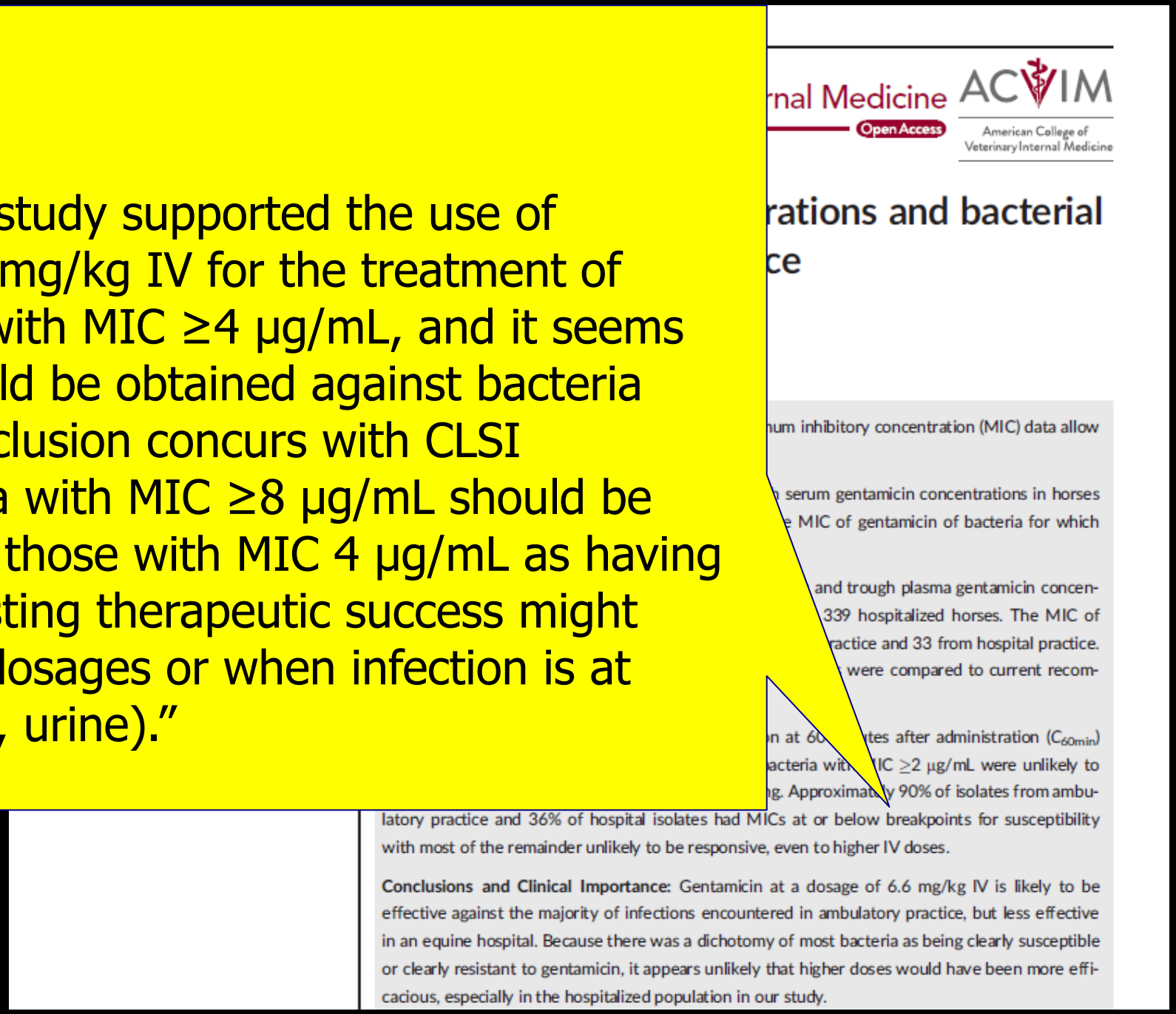
Conclusion:

[citing other studies] "Neither study supported the use of gentamicin at a dosage of 6.6 mg/kg IV for the treatment of infections caused by bacteria with MIC ≥4 µg/mL, and it seems inconceivable that success could be obtained against bacteria with MIC ≥8 µg/mL . This conclusion concurs with CLSI recommendations that bacteria with MIC ≥8 µg/mL should be regarded as resistant and that those with MIC 4 µg/mL as having intermediate sensitivity suggesting therapeutic success might only be possible using higher dosages or when infection is at sites of drug accumulation (eg, urine)."



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CLSI Rationale Document

Fluoroquinolone Breakpoints for Enterobacteriaceae and *Pseudomonas aeruginosa,* April 2018.

Breakpoint revisions:

Revised CLSI Fluoroquinolone MIC Breakpoints (last reviewed, January 2018) to be published in M100S 29th Edition*)

Organism Group	Antimicrobial Agent	S	SDD	I	R
Enterobacteriaceae	Ciprofloxacin	≤0.25	–	0.5	≥1
	Levofloxacin	≤0.5	–	1	≥2
Pseudomonas aeruginosa	Ciprofloxacin	≤0.5	N/A	1	≥2
	Levofloxacin	≤1	N/A	2	≥4

*pending approval of disk diffusion breakpoints in June 2018

Replaces CLSI Fluoroquinolone MIC Breakpoints (last published in M100S 28th Edition)

Organism Group	Antimicrobial Agent	S	SDD	I	R
Enterobacteriaceae	Ciprofloxacin	≤1	–	2	≥4
	Levofloxacin	≤2	–	4	≥8
Pseudomonas aeruginosa	Ciprofloxacin	≤1	N/A	2	≥4
	Levofloxacin	≤2	N/A	4	≥8

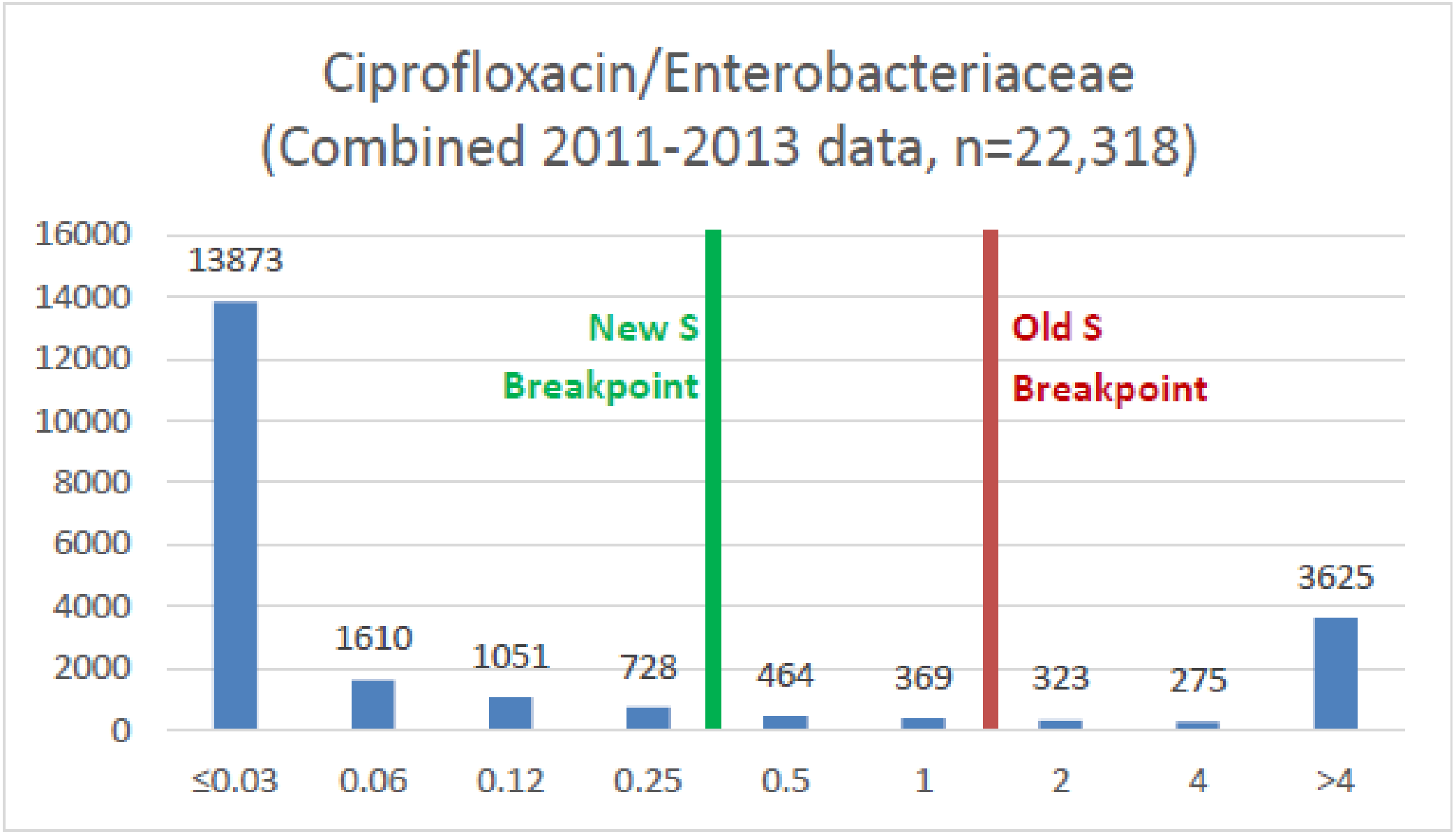


Figure 4.1. MIC distribution for Enterobacteriaceae and ciprofloxacin.

CLSI AST Agenda Item

Amoxicillin & Amox/Clavulanate Breakpoints *Enterobacteriaceae* & Anaerobes

Breakpoints Too High Based on Drug Dosage PK/PD

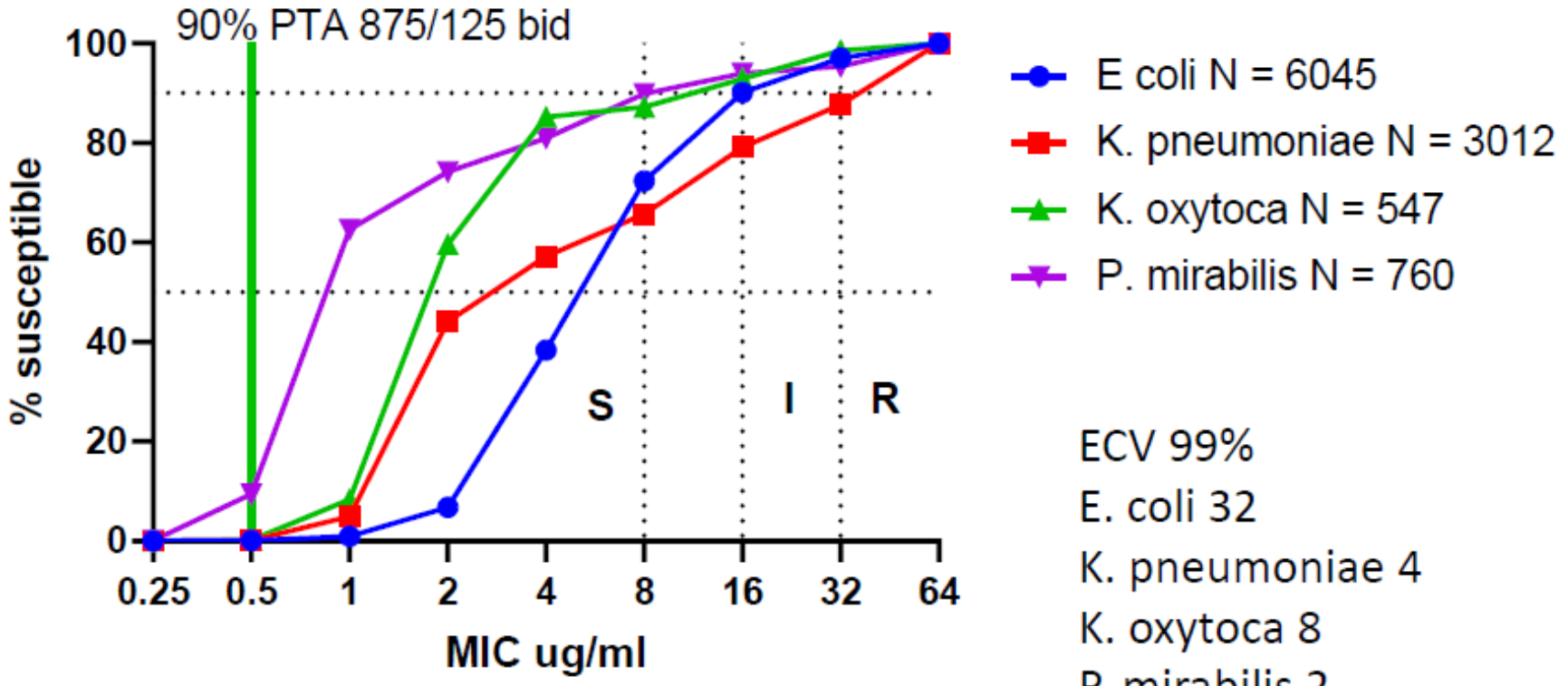
P. Edelstein Sept 2018

M100-S28 Breakpoints - *Enterobacteriaceae*

Drug	S	I	R
Ampicillin	≤ 8	16	≥ 32
Amoxicillin/ clavulanate	≤ 8/4	16/8	≥ 32/16
Ampicillin/ sulbactam	≤ 8/4	16/8	≥ 32/16

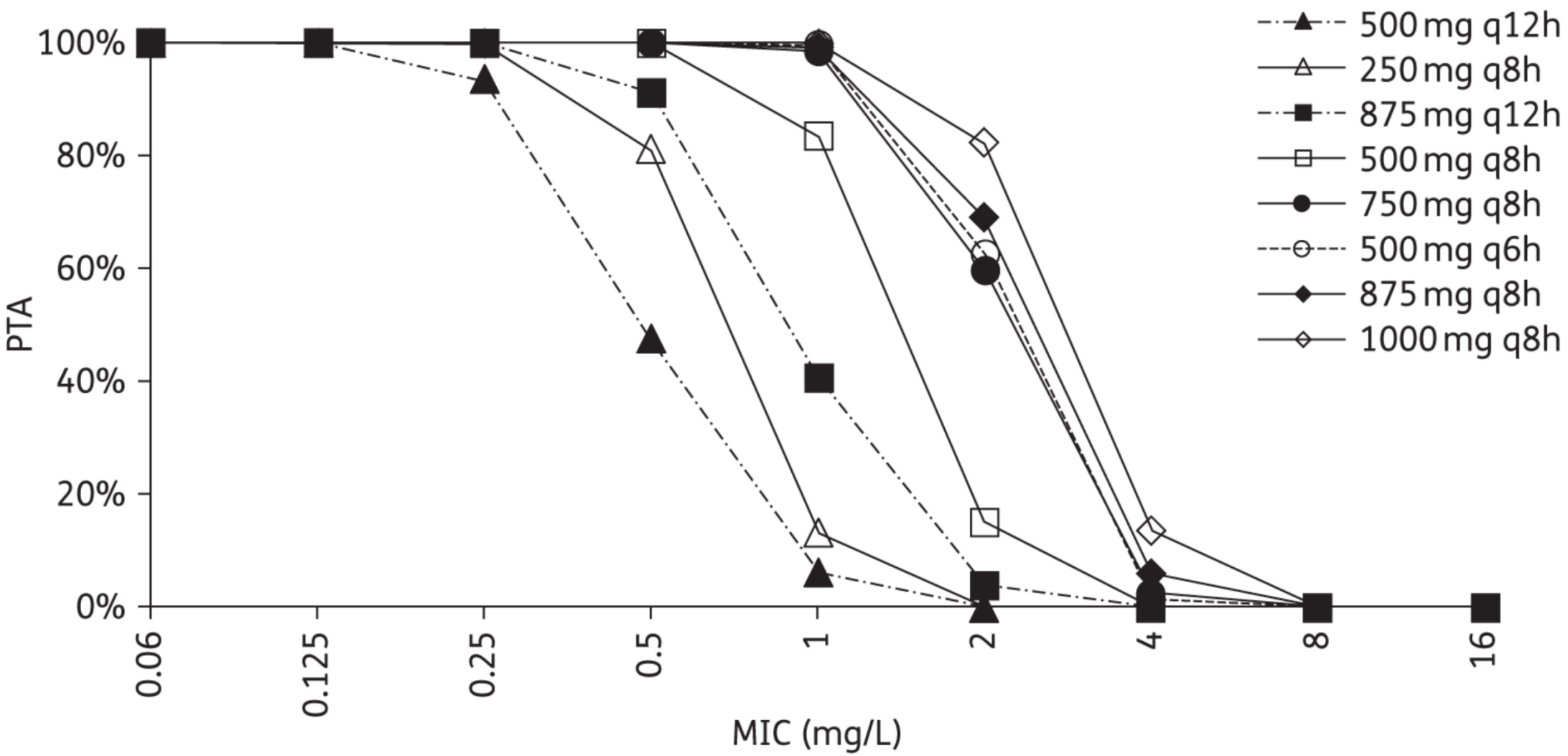
Almost No "Susceptible" Enterobacteriaceae Using 90% PTA

Amoxicillin-clavulanate MICs of Contemporary Isolates



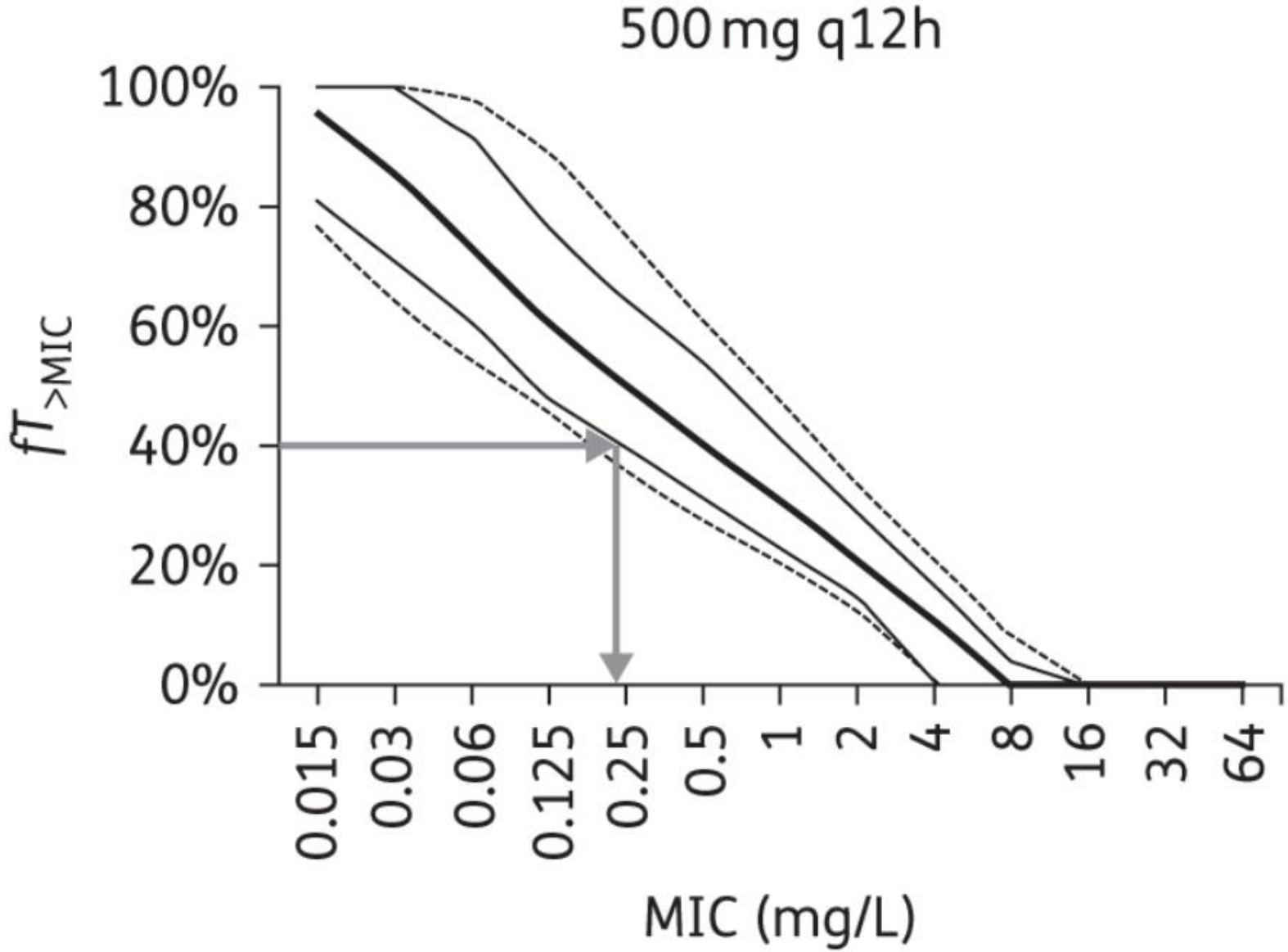
ECV 99%
E. coli 32
K. pneumoniae 4
K. oxytoca 8
P. mirabilis 2

JMI Labs - Maria Castanheira 2018



From: Non-linear absorption pharmacokinetics of amoxicillin: consequences for dosing regimens and clinical breakpoints

J Antimicrob Chemother. 2016;71(10):2909-2917. doi:10.1093/jac/dkw226


500 mg q12h
100%
80%
60%
40%
20%
0%
$fT_{>MIC}$
0.015
0.03
0.06
0.125
0.25
0.5
1
2
4
8
16
32
64
MIC (mg/L)

Planned New Breakpoints

CLSI-VAST
Generic Drug Working Group
New Breakpoints

Agent	Species	Status
Chloramphenicol	Dogs, Horses	• C. Langston compiling data
Trimethoprim-sulfamethoxazole	Dogs, Cats, Horses	• PK data available • Still need PK-PD targets defined • Difficult to define due to combination product
Rifampin	Dogs, Horses	• PK data available for horses, but scarce for dogs. • PK-PD targets need to be defined.

Generic Drug Working Group
New Breakpoints

Agent	Species	Status
Other 3rd-Generation Cephalosporins?	Dogs, Cats, Horses	✓ Ceftazidime • Cefotaxime
Carbapenems?	Dogs, Cats	• PK data available • PK-PD targets defined • Just use human breakpoint?
Tylosin	Cattle, Pigs	• Collecting data and PK-PD targets
Amoxicillin, Amoxicillin-Clavulanate	Cat-urine	• Studies are planned to collect data

Table 2A. *Enterobacteriaceae* (Continued)

Test/ Report Group	Body Site	Antimicrobial Agent	Organism	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL			Comments
					S	I	R	S	I	R	
Aminoglycosides/Aminocyclitols (Continued)											
Humans **(10) Warning: For *Salmonella* spp. and *Shigella* spp., aminoglycosides may appear active *in vitro* but are not effective clinically and should not be reported as susceptible.**											
		Amikacin		30 µg	≥17	15–16	≤14	≤16	32	≥64	
		Gentamicin		10 µg	≥15	13–14	≤12	≤4	8	≥16	
		Kanamycin		**30 µg**	**≥18**	**14–17**	**≤13**	**≤16**	**32**	**≥64**	
		Streptomycin		**10 µg**	**≥15**	**12–14**	**≤11**	–	–	–	**(11) There are no MIC breakpoints.**
Penicillins											
Dogs											
A	Skin, soft tissue	Ampicillin	*E. coli*	–	–	–	–	≤0.25	0.5	≥1.0	**(12) Systemic breakpoints were derived from microbiological and PK-PD data. The dosage regimen used for PK-PD analysis of amoxicillin was 22 mg/kg every 12 hours orally.** **(13) Except for lower UTI, *E. coli* and other *Enterobacteriaceae* will test resistant to ampicillin and amoxicillin.**
A	UTI	Ampicillin	*E. coli*	–	–	–	–	≤8	–	–	**(14)** This breakpoint for UTIs was derived from published literature in which orally administered ampicillin 25.6 mg/kg and amoxicillin 11 mg/kg was administered to healthy dogs at 8-hour intervals for 5 consecutive doses and produced urine concentrations in dogs > 300 µg/mL.

Table 2A. *Enterobacteriaceae* (Continued)

Test/ Report Group	Body Site	Antimicrobial Agent	Organism	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL			Comments
					S	I	R	S	I	R	
Penicillins (Continued)											
Cats											
A	Skin, soft tissue, UTI	Ampicillin	*E. coli*	–	–	–	–	≤0.25	0.5	≥1.0	(15) Ampicillin breakpoints were determined from an examination of MIC distribution data and PK-PD analysis of amoxicillin in cats. The dosage regimen used for PK-PD analysis of amoxicillin was 12.5 mg/kg administered every 12 hours orally.
Cattle											

Any others?

Thank you.

Any Questions?

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