6.3.2 *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp.

Breakpoints for gram-positive cocci can generally be extrapolated to other gram-positive cocci (eg, *Staphylococcus* spp., *Streptococcus* spp.), but there may be differences for *Enterococcus* spp. See Table 8 in Subchapter 3.3 for a list of antimicrobial agents for which *Enterococcus* spp. may have intrinsic resistance.

Table 17. Extrapolating Feline-Specific Breakpoints Approved for Specific Bacteria to Other Bacterial Species

Gram Reaction	Bacteria With Feline-Specific Breakpoints	May Extrapolate Breakpoints to Other Bacteria	May Not Extrapolate Breakpoints to Other Bacteria
Gram-negative bacteria	*E. coli*	*Other Enterobacteriaceae*	
	Enterobacteriaceae and *P. aeruginosa*		One fluoroquinolone may not be predictive of other fluoroquinolones.
	P. aeruginosa	Other *Pseudomonas* spp.	Nonfermenting gram-negative species
	P. multocida	Other *Pasteurellaceae*	
Gram-positive bacteria	*Staphylococcus felis*	Other staphylococci	
	Streptococcus spp.	β-hemolytic streptococci (eg, β-hemolytic streptococci, group C or *S. agalactiae*)	

6.4 Applying Feline-Specific Breakpoints to Other Infection Sites in Cats

As described in Subchapter 2.1.1, breakpoints and interpretive categories derived for skin and soft-tissue infections can generally be extrapolated and applied to infections in other body sites. Table 2 lists tissues in the body that have barriers to diffusion. Breakpoints should therefore not be relied on to predict susceptibility in the absence of clinical efficacy data or PK data.

IMPORTANT NOTE:

It is not appropriate to indiscriminately apply the breakpoint for a drug to any other dose, route, frequency, or duration.

6.5 Applying Feline-Specific Breakpoints to Other Doses, Routes, Frequencies, or Durations of Therapy

Dose, route, frequency, and duration of therapy are integral components of breakpoint determination, because these factors determine the concentrations of drug in the animal. The dosage regimens for approved feline-specific breakpoints are based on oral or injectable administration for systemic use. Therefore, it is not appropriate to indiscriminately apply the breakpoint for a drug to any other dose, route, frequency, or duration.

Some antimicrobial agents listed may occasionally be applied to cats by other routes of administration (eg, otic or topical). Many agents are active on the skin surface, but there are no breakpoints or interpretive categories for agents applied topically (eg, skin, ears, or eyes). There is no assurance that antimicrobial agents that test as susceptible will be effective when applied topically. However, because of the high concentrations achieved by these topical methods of administration or by regional infusion, effective antimicrobial activity is anticipated but not validated.

NOTE:

There are no breakpoints or interpretive categories for agents applied topically (eg, skin, ears, or eyes).

NOTE:

There is only one antimicrobial agent with urine-specific breakpoints for urine isolates from cats, ie, cefovecin.

NOTE:

Azithromycin AST results **should not** be extrapolated to other macrolides.

6.6 Applying Human or Other Species' Breakpoints for Interpreting Antimicrobial Susceptibility Testing Results for Cats

Examples of antimicrobial agents that may be tested and results extrapolated from other species are listed in Table 18. These agents do **not** have CLSI-approved breakpoints or interpretive categories for cats. They may be considered for testing and reporting when primary agents listed for cats (see Subchapter 3.2, Table 7) are not available, or the isolate is resistant to the agent listed for primary testing. Dosage regimens for antimicrobial agents in Table 18 may be found on product labels or in reputable consensus documents, treatment guidelines, or reference books. Breakpoints not specific to cats may be applied cautiously, in consultation with a clinical microbiologist or clinical pharmacologist, to bacteria for which there are no feline-specific breakpoints (see Table 19).

Although several antimicrobial agents listed in Table 18 have canine-specific or human breakpoints for interpreting AST results from urine isolates, there is only one antimicrobial agent with urine-specific breakpoints for urine isolates from cats, ie, cefovecin. Although it is likely that the antimicrobial agents with urine-specific breakpoints for dog UTIs concentrate in the urine of most cats, there are no published data to support this assumption (see CLSI document VET08[4]). Additionally, the canine-specific breakpoints for urine isolates were established using isolates from dogs with uncomplicated UTIs. In cats, bacterial infections of the lower urinary tract are typically defined as complicated because there is a frequent occurrence of comorbidities and a higher incidence in older cats. It is unusual for cats to have lower UTIs if no other conditions are present. Therefore, the definition of an uncomplicated UTI used in the tables of CLSI document VET08[4] for some antimicrobial agents cannot be easily applied to cats. It is also recognized that most cats with clinical signs of a lower UTI do not have bacterial cystitis.[77-79]

Table 18. Considerations for Using Antimicrobial Agents With Human or Other Species' Breakpoints for Interpreting AST Results for Cats

Antimicrobial Agents With Human (H) or Dog (D) Breakpoints	Antimicrobial Susceptibility Predicted in Cats	Considerations for or Against Use	Body Site		
			Resp	SST	Ur
Amikacin (D)	Amikacin	Amikacin may be considered for aerobic gram-negative bacteria (eg, *Enterobacteriaceae*) if the isolate tests as S based on the canine breakpoints and if there are no other options available.	X	X	X
Azithromycin (H)	Azithromycin	• Azithromycin may be considered for *Staphylococcus* spp. or *Streptococcus* spp. if the isolate tests as S based on the human breakpoints and if there are no other options available. • Azithromycin AST results **should not** be extrapolated to other macrolides.	X		

Table 18. (Continued)

Antimicrobial Agents With Human (H) or Dog (D) Breakpoints	Antimicrobial Susceptibility Predicted in Cats	Considerations for or Against Use	Body Site		
			Resp	SST	Ur
Cefazolin (D)	Cefazolin	Cefazolin may be considered for some gram-positive and some gram-negative bacteria if the isolate tests as S based on the canine breakpoints and if there are no other options available.	X	X	X
Cefotaxime (H)	Cefotaxime	• Cefotaxime may be considered for *Enterobacteriaceae* if the isolate tests as S based on the human breakpoints and if there are no other options available. • Note that susceptibility to cefotaxime or ceftazidime does not predict susceptibility to other 3rd-generation cephalosporins (eg, cefovecin, cefpodoxime).	X	X	X
Ceftazidime (H)	Ceftazidime	• Ceftazidime may be considered for *Enterobacteriaceae* and *P. aeruginosa* if the isolate tests as S based on the human breakpoints and if there are no other options available. • Note that susceptibility to cefotaxime or ceftazidime does not predict susceptibility to other 3rd-generation cephalosporins (eg, cefovecin).	X	X	X
Cephalexin Cephalothin (D)	1st-generation cephalosporins*	Other 1st-generation cephalosporins (eg, cefadroxil or cefazolin) may be considered for some gram-positive and gram-negative species if the isolate tests as S to cephalexin or cephalothin based on canine breakpoints and if there are no other options available.	X	X	X
Clindamycin (D)	Clindamycin	Clindamycin may be considered if the isolate tests as S to clindamycin based on canine breakpoints and if there are no other options available.	X	X	X
Doxycycline (D)	Doxycycline	Doxycycline may be considered if the isolate tests as S to doxycycline based on canine breakpoints and if there are no other options available.	X	X	X
Erythromycin (H)	Azithromycin Erythromycin	Azithromycin or erythromycin may be considered for *Staphylococcus* spp. and *Streptococcus* spp. if the isolate tests as S to erythromycin based on human breakpoints.	X	X	
Gentamicin (D)	Gentamicin	Gentamicin may be considered for aerobic gram-negative bacteria (eg, *Enterobacteriaceae*) if the isolate tests as S to gentamicin based on canine breakpoints and if there are no other options available.	X	X	X
Imipenem (H)	Imipenem Meropenem	Imipenem or meropenem may be considered for *Enterobacteriaceae* and *P. aeruginosa* if the isolate tests as S based on the human breakpoints and if there are no other options available.	X	X	X
Linezolid (H)	Linezolid	Linezolid may be considered for *Staphylococcus* spp. or *Enterococcus* spp. if the isolate tests as S based on the human breakpoints and if there are no other options available.	X	X	X

Table 18. (Continued)

Antimicrobial Agents With Human (H) or Dog (D) Breakpoints	Antimicrobial Susceptibility Predicted in Cats	Considerations for or Against Use	Body Site		
			Resp	SST	Ur
Minocycline† (D)	Minocycline	Minocycline can be considered for respiratory and intracellular isolates if the isolate tests as S based on the canine breakpoints and if there are no other options available.	X	X	X
Nitrofurantoin (H)		• Nitrofurantoin may be considered for isolates from the **lower urinary tract,** using human breakpoints with caution, if the isolate tests as S and if there are no other options available. • There are no clinical studies that predict efficacy or guide dosage regimens for nitrofurantoin use in cats.			X
Penicillin (H)	Amoxicillin Amoxicillin-clavulanate Ampicillin Cephalosporins, 1st-generation* Penicillin	Penicillin may be considered for gram-positive organisms (eg, *Staphylococcus* spp., *Streptococcus* spp., *Enterococcus* spp.) if the isolate tests as S based on the human breakpoints.	X	X	X
Piperacillin-tazobactam (D)	Piperacillin-tazobactam	Piperacillin-tazobactam combination may be considered for gram-negative and gram-positive bacteria and anaerobes if the isolate tests as S based on the canine breakpoints.	X	X	X
Rifampin (H)	Rifampin	• *Staphylococcus* spp. isolates that test as S to rifampin based on the human breakpoints may be clinically susceptible based on clinical experience and published clinical studies. • There is a lack of evidence that combining rifampin with other agents is necessary to decrease the emergence of resistance when staphylococcal infections are treated.	X	X	
Trimethoprim-sulfamethoxazole (H)	Trimethoprim-sulfadiazine Trimethoprim-sulfamethoxazole	Trimethoprim-sulfamethoxazole and trimethoprim-sulfadiazine may be considered for gram-positive and gram-negative bacteria if the isolate tests as S based on the human breakpoints.	X	X	X
Vancomycin (H)	Vancomycin	• Vancomycin may be considered for *Staphylococcus* spp. or *Enterococcus* spp. if the isolate tests as S based on the human breakpoints and if no other options are available. • Therapeutic drug monitoring of patients is encouraged to ensure that adequate patient plasma drug concentrations are maintained.	X	X	X

* First-generation cephalosporins include cefadroxil, cefazolin, cephalexin, cephalothin, and cephapirin.
† Minocycline breakpoints apply only to dogs administered minocycline under fasting conditions; administering minocycline with food will significantly reduce drug availability and may result in clinical failure.
Abbreviations: AST, antimicrobial susceptibility testing; resp, respiratory; S, susceptible; SST, skin and soft tissue; ur, urinary tract.

Table 19. Sources of AST Methods and Breakpoints for Interpreting AST Results of Bacteria Without Feline-Specific Breakpoints

Organism	Information Available in CLSI Document			
	M11[73]	M24,[74] M62[75]	M100[72]	VET06[76]
Actinomycetaceae (eg, *Actinomyces* spp., *Nocardia* spp.)		X		X
Anaerobes	X		X	
Campylobacter spp.				X
Corynebacterium spp.				X
Enterococcus spp.			X	
Gram-negative nonfermenters (eg, *Neisseria* spp.)			X	
L. monocytogenes				X
Mycobacterium spp.		X		X

Abbreviation: AST, antimicrobial susceptibility testing.

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Chapter 7

Equine-Specific and Other Breakpoints and Factors Affecting Antimicrobial Susceptibility Testing Result Interpretations for Horses

This chapter includes information on:

- Confidence in applicability of breakpoints for interpreting AST results for horses
- Approved equine-specific breakpoint dosage regimens and tissue infection sites
- Application of equine-specific breakpoints to other:
  - Bacteria in horses
  - Infection sites in horses
  - Doses, routes, frequencies, or durations of therapy
- Application of human breakpoints for interpreting AST results for horses

IMPORTANT NOTE:

If a **different dosage regimen** is being used rather than the dosage regimen used to set an approved breakpoint, the breakpoint and interpretive categories cannot be routinely or reliably applied to susceptibility test result interpretation (see Subchapter 7.5).

REMINDER:

See CLSI document VET08,[4] Tables 2A to 2J to interpret AST results for bacterial isolates from the tissues or body sites indicated for each antimicrobial agent in Table 20.

7 Equine-Specific and Other Breakpoints and Factors Affecting Antimicrobial Susceptibility Testing Result Interpretations for Horses

7.1 Confidence in Applicability of Breakpoints for Interpreting Antimicrobial Susceptibility Testing Results for Horses

This chapter focuses on interpreting AST results on bacterial isolates from horses. If a horse has an infection at the same site caused by the same bacterial organism(s) as a CLSI-approved equine-specific breakpoint, confidence in the organism susceptibility test result interpretation should be high (see Subchapter 7.2). See Appendix C for an index, sorted by infection site (ie, Table C1) and organism (ie, Table C2), of approved equine-specific breakpoints that are available in CLSI document VET08.[4]

If an equine-specific breakpoint is applied to a **different bacterial species** than the approved breakpoint (see Subchapter 7.3) or to a **different indication or infection site** than the approved breakpoint (see Subchapter 7.4), then confidence in the applicability to susceptibility test result interpretation is lower.

If a breakpoint for a **different animal species or humans** (see CLSI document M100[72]) is applied to a susceptibility test result, there are some valid and evidence-based extrapolations that can be made, but susceptibility test result interpretation should be made with very low confidence (see Subchapter 7.6).

If a **different dosage regimen** is being used rather than the dosage regimen used to set an approved breakpoint, the breakpoint and interpretive categories cannot be routinely or reliably applied to susceptibility test result interpretation (see Subchapter 7.5). If an isolate is identified as intermediately susceptible, in some cases, increasing the dose may improve the likelihood of treatment success, but this strategy cannot be applied to all drugs or bacteria. Consultation with a clinical microbiologist or clinical pharmacologist is recommended if the breakpoints will be applied to different dosage regimens (ie, dose, route, frequency, or duration).

7.2 Approved Equine-Specific Breakpoint Dosage Regimens and Tissue Infection Sites

Dosage regimens used for determining equine-specific breakpoints, approved by the CLSI Subcommittee on VAST, for antimicrobial agents used in horses are listed in Table 20. Importantly, the tissue sites applied to the equine-specific breakpoints are also listed in Table 20, because drug concentrations may not be equivalent across all body sites (see Subchapter 2.1.1). AST results for

bacterial isolates from the tissues or body sites indicated for each antimicrobial agent in Table 20 may be interpreted with the breakpoints available in CLSI document VET08,[4] Tables 2A to 2J. Refer to Figure 11 for an example of reporting AST results on *P. aeruginosa* isolated from an equine eye. Note that an antimicrobial agent listed may not be approved for an indication to treat infections in these tissue sites, so veterinarians are advised to review drug labels and relevant regulations on extralabel drug use when making drug choices (see Subchapter 2.4).

NOTE:

An antimicrobial agent listed may not be approved for an indication to treat infections in these tissue sites.

Table 20. Dosage Regimens and Tissue Sites Applicable to Equine-Specific Breakpoints

Antimicrobial Agent	Dosage Regimen Used for Breakpoint Analysis	Applicable Tissue, Body Site				
		Bone	Gen*	Joints	Resp	SST
Amikacin	Horses (adult): 10 mg/kg IM or IV every 24 hours	X	X	X	X	X
	Horses (foals < 11 days of age): 20 mg/kg IV every 24 hours				X	X
Ampicillin	22 mg/kg IM or IV every 12 hours (ampicillin sodium)	X	X	X	X	X
Cefazolin	25 mg/kg IV every 6 hours	X	X	X	X	X
Ceftiofur	2.2–4.4 mg/kg IM every 24 hours (ceftiofur sodium) or 6.6 mg/kg IM twice 4 days apart (ceftiofur crystalline free acid)		X		X	X
Doxycycline	20 mg/kg PO every 12 hours		X	X	X	X
Enrofloxacin	7.5 mg/kg PO every 24 hours (intermediate range MIC values may be attained with higher doses)	X	X	X	X	X
Gentamicin	Horses (adult): 6.6 mg/kg IM or IV every 24 hours	X	X	X	X	X
Minocycline	5 mg/kg PO every 12 hours		X	X	X	X
Penicillin G	22 000 IU/kg IM every 24 hours	X	X	X	X	X

* Refers to the site of infection and not the intrauterine route of administration.
Abbreviations: gen, genital; IM, intramuscular; IU, international unit(s); IV, intravenous; MIC, minimal inhibitory concentration; PO, oral; resp, respiratory; SST, skin and soft tissue.

Important caveats apply to the approved equine-specific breakpoints in CLSI document VET08,[4] Tables 2A to 2D for the following antimicrobial agents:

- **Amikacin:** The breakpoints for amikacin apply to systemic use of the drug and are not applicable to the intrauterine route of administration of amikacin.
- **Enrofloxacin:**
  - The equine-specific enrofloxacin breakpoints should not be applied to other fluoroquinolones and should not be used for foals.
  - The dose listed in Table 20 is applicable to the equine-specific enrofloxacin breakpoints listed in CLSI document VET08,[4] Tables 2A to 2D. However, this dose may be exceeded for conditions in which the veterinarian's judgment is that higher doses are needed because of the specific pathogen, tissue treated, or severity of infection. Higher doses also may be needed if the isolate tests as intermediate in the range of the interpretive categories.

IMPORTANT NOTE:

The equine-specific enrofloxacin breakpoints should not be applied to other fluoroquinolones and should not be used for foals.

- **Gentamicin:**
  - The equine-specific gentamicin breakpoints cannot be reliably applied to use of gentamicin in foals because the drug disposition, and therefore dosage regimen, are very different in foals (< 2 weeks of age) than in adult horses.
  - The breakpoints for gentamicin apply to systemic use of the drug and are not applicable to the intrauterine route of administration of gentamicin.
- **Penicillin:** The equine-specific penicillin G breakpoints are based on the commonly used extralabel regimen of 22 000 IU/kg IM of procaine penicillin G. Therefore, the prediction of efficacy for an isolate identified as susceptible to penicillin relies on the use of that extralabel dose.
  - Veterinarians should understand that the equine-specific penicillin breakpoints are **not** applicable if the labeled dose is used, and that extralabel drug regulations apply. That is, if a penicillin AST result is reported as S in a laboratory report, it implies susceptibility using the extralabel dose rather than the labeled dose. If penicillin is administered SC at 20 000 IU/kg, however, confidence in the S result is lower, because the drug concentrations achievable with SC dosing can be different than penicillin that is administered IM.
  - The equine-specific penicillin breakpoints do **not** apply to the formulation of penicillin that is a combination of benzathine and procaine penicillin G, because dosing of these formulations results in very different drug concentrations from the dosing listed in Table 20.

When AST results are interpreted, it is important to understand that laboratories cannot feasibly test all available antimicrobial agents and that some agents may be used to predict susceptibility to other agents in the same drug class. Table 21 lists agents that are typically tested for horses and predictability of susceptibility to other agents in the same class. It also provides instances in which predictions should not be made, ie, from cefazolin, gentamicin, fluoroquinolones, and tetracyclines.

NOTE:

Equine-specific penicillin breakpoints are **not** applicable if the labeled dose is used.

NOTE:

The equine-specific penicillin breakpoints do **not** apply to the formulation of penicillin that is a combination of benzathine and procaine penicillin G.

Table 21. Predictability of AST Result Interpretations Applied to Other Antimicrobial Agents

Antimicrobial Agent	Predicts Susceptibility to Other Antimicrobial Agent(s)	Predicts Susceptibility to Which Other Antimicrobial Agent(s)
Amikacin	No	
Ampicillin	Yes	Amoxicillin Amoxicillin-clavulanate (only if ampicillin is S) Ampicillin-sulbactam (only if ampicillin is S)
Cefazolin	No	Susceptibility to cefazolin does not predict susceptibility to other 1st-generation cephalosporins in horses.
Ceftiofur	No	
Doxycycline	No*	
Enrofloxacin	No†	
Gentamicin	Yes	All aminoglycosides, except streptomycin
Minocycline	Yes	Isolates resistant to minocycline will also be resistant to doxycycline and tetracycline.

* If a strain is resistant to doxycycline or tetracycline, it can be minocycline-susceptible, eg, when it carries a *tet*(K) gene coding for an efflux protein that can export doxycycline and tetracycline but not minocycline.
† Susceptibility or resistance to one fluoroquinolone may not indicate the same category for other fluoroquinolones. It is possible to have resistance to one and susceptibility to another fluoroquinolone. Additionally, isolates that are intermediate or resistant to any fluoroquinolone may be at risk of developing resistance to all fluoroquinolones. Susceptibility to any fluoroquinolones listed should not be used to predict susceptibility to ciprofloxacin because PK-PD analysis does not support its use in horses.
Abbreviations: AST, antimicrobial susceptibility testing; PK-PD, pharmacokinetic-pharmacodynamic; S, susceptible.

7.3 Applying Equine-Specific Breakpoints to Other Bacteria in Horses

Breakpoints listed in CLSI document VET08,[4] Tables 2A to 2J are established for specific organisms or groups (see Appendix C, Table C2 for a list of equine-specific breakpoints sorted by organism). However, in most instances for horses, these breakpoints also may be applied to other bacteria not listed, as outlined in Table 22. Such an extrapolation can be considered because the PK-PD principles (see Subchapter 2.1.2) that were used to determine the breakpoints apply to many bacteria, regardless of species.