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CLINICAL PATHOLOGY

# Improving Patient Outcomes Through Antibiotic Stewardship

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Antibiotic resistance is an issue faced by virtually all veterinary clinicians. Veterinarians commonly manage infections caused by bacteria such as methicillin-resistant *Staphylococcus* species and extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae. Furthermore, one of the most urgent antibiotic-resistance threats to human public health, carbapenem-resistant Enterobacteriaceae (CRE), is potentially emerging in companion animal medicine, detected in antimicrobial resistance surveillance studies and isolated cases in hospitalized patients.[1-4]

Complicating matters even more, many resistant pathogens in companion animal medicine have zoonotic potential, making antibiotic resistance and stewardship truly a One Health (cdc.gov/onehealth) concern. In human medicine, an estimated 30% of antibiotic use is either unnecessary or inappropriate.[5] Although accurate statistics for companion animal medicine are not available, it has been suggested that rates of unnecessary or inappropriate use in companion animal medicine are similar.[6]

No single clinical strategy can be expected to prevent all antibiotic resistance; however, antibiotic stewardship is a systematic effort that all clinicians can undertake to combat resistance and increase the likelihood of positive outcomes for their patients. The American Veterinary Medical Association defines antimicrobial stewardship as "the actions veterinarians take individually and as a profession to preserve the effectiveness and availability of antimicrobial drugs through conscientious oversight and responsible medical decision-making while safeguarding animal, public, and environmental health."[7] The goal of this article is to give veterinarians tools to help increase antibiotic stewardship in their daily practice, which will ultimately lead to improved patient outcomes.

## COMMENSAL BACTERIA

A major component of clinical antibiotic stewardship is simply considering commensal bacteria before prescribing an antibiotic. The most common bacterial isolates submitted to veterinary diagnostic laboratories for

**WIN-WIN SCENARIO**
Practicing antibiotic stewardship is not only responsible from a One Health perspective but will also ultimately lead to improved patient outcomes.

**BOX 1 Some Clinical Scenarios for Which Systemic Antibiotics Are Not Needed**[11,12]

- Routine, uncomplicated dental cleanings
- Uncomplicated acute upper respiratory tract infections
- Uncomplicated acute diarrhea
- Sterile cystitis in cats
- Prophylaxis for routine surgeries (e.g., spays/neuters)
- Animals that are seropositive for vector-borne pathogens but otherwise healthy
- Healthy animals before breeding
- Juvenile vaginitis in puppies
- Subclinical (asymptomatic) bacteriuria

identification and antibiotic susceptibility testing include *Staphylococcus pseudintermedius*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus* species, and *Enterococcus* species.[8] These pathogens have one major factor in common: they are all opportunistic commensal pathogens in dogs and cats. These pathogens live in or on healthy patients as well as patients with active infections; therefore, selection pressure associated with systemic antibiotic administration and these "bystander" bacteria is widely recognized as a problem and an unintended consequence of antibiotic use. Although administration of any antibiotic is associated with potential selection pressure for resistance, for commensal opportunistic pathogens, specific classes or types of antibiotics are associated with specific types of resistance. For example, fluoroquinolone administration is a widely known risk factor for carriage of methicillin-resistant *Staphylococcus* species, and third-generation cephalosporin administration is a risk factor for carriage and spread of ESBL-producing Enterobacteriaceae.[9] Although not all commensal bacteria are pathogenic, many share resistance genes with pathogenic strains (e.g., horizontal gene transfer between different strains of Enterobacteriaceae), making antibiotic stewardship important, even when dealing with nonpathogenic commensal bacteria.[10]

## PATIENT OUTCOMES

Historically, antibiotics have been used in clinical scenarios that do not necessitate their administration (**BOX 1**).[11,12] Staying up-to-date with the most recent evidence on treatment options for these common scenarios will help clinicians improve antibiotic stewardship.

Administration of a systemic antibiotic is not harmless. Well-documented consequences include disruption of normal bacterial flora and selection pressure for antibiotic resistance.[9,13] If antibiotics are not likely to improve a patient's outcome, they should not be prescribed.

## CLIENT COMPLIANCE

### Systemic Therapy

Crucial to successful antibiotic therapy and antibiotic stewardship is client compliance. When deciding which antibiotic to prescribe, clinicians can typically choose from many antibiotics with varied dosing regimens. Although conventional wisdom suggests that compliance will improve for medications administered less frequently, this belief is not fully supported by research. A recent study found that rates of compliance with short-term administration of once-daily and twice-daily oral antibiotics are similar, making both dosing frequencies reasonable choices for many veterinary patients.[14] Of note, the authors of that study suggested that antibiotics administered twice daily may be superior to antibiotics administered once daily because a missed twice-daily dose results in only a 12-hour lapse in therapy versus a missed once-daily dose resulting in a 24-hour lapse. However, for medications to be administered more often than twice daily, client compliance is markedly reduced.[14] Therefore, dosing regimens that require clients to administer medications more often than twice daily should be avoided unless the clinical scenario necessitates a specific medication and administration frequency (e.g., chloramphenicol administered q8h for methicillin-resistant *S pseudintermedius* infection).

### Topical Therapy

Strong evidence supports the use of topical therapy alone for many superficial infections.[15] Given the antibiotic-resistance challenges faced by companion animal clinicians, veterinary dermatologists on a consensus panel widely agreed that "topical therapy should be used as the sole on-animal antibacterial treatment for surface and superficial infections whenever a pet and owner can be expected to be compliant."[15] A veterinarian's perception regarding therapy for infectious diseases may differ from that of

the client. You may feel pressured by clients to prescribe systemic antibiotics, as they simply want the "best" treatment for their pet.[16]

Fortunately, many clients are aware of antibiotic-resistance challenges. Broad community-based awareness programs for antimicrobial stewardship in human medicine or mainstream media coverage have probably increased client awareness of terms such as "superbugs."[17] This awareness may improve compliance with topical therapy, such as chlorhexidine shampoo for superficial pyoderma. To minimize antibiotic resistance while providing a high probability of clinical resolution of their pet's infection, clients may be amenable to less convenient topical therapy in lieu of traditional systemic therapy.

## TREATMENT DURATION

In human medicine, research has led to shorter recommended durations of antibiotic treatment for many conditions.[18] In veterinary medicine, treatment duration has not been well studied, but recent reports support a trend toward shorter courses of antibiotics in companion animal medicine.[19-21] For example, historic recommendations for treatment of sporadic uncomplicated bacterial cystitis in dogs were typically 10 to 14 days of antibiotic therapy; however, for most patients, 3 to 5 days may be sufficient.[12,20,22] Unnecessarily long courses of systemic antibiotic therapy probably contribute to the emergence of antibiotic resistance. Ironically, a common misconception among the public is that preventing antibiotic resistance requires completing a minimum duration of antibiotic therapy.[18] Antibiotics should not be continued if clinical and/or microbiological evidence indicates resolution of the infection.[19] However, many types of infections (e.g., deep pyoderma) require long courses of antibiotics, such as 4 to 6 weeks or 2 weeks beyond clinical resolution. Clinicians must distinguish between the different treatment durations for different clinical conditions.[15]

## CHOOSING THE BEST ANTIBIOTIC

Choosing the best antibiotic for every clinical scenario is not easy. The appropriate antibiotic should have a high probability of safely producing a positive clinical outcome while simultaneously minimizing promotion of antibiotic resistance. Fortunately, choosing the antibiotic most likely to produce a positive clinical outcome and considering the principles of antibiotic stewardship are not mutually exclusive: antibiotic stewardship is good medicine. Things to consider include expected pathogens, minimal inhibitory concentrations (MICs), and breakpoints, as well as first-line systemic therapy, second-line systemic therapy, and last-resort therapy.

### Considerations for Expected Pathogens, MICs, Breakpoints, and Interpretive Categories

When deciding which antibiotic to prescribe, always consider which pathogens are most likely causing the infection. For example, nearly all superficial bacterial folliculitis infections in dogs are caused by *Staphylococcus* species, and empiric therapy should target bacteria of this genus. Avoid antibiotics not likely to be effective against staphylococcal skin infections, such as amoxicillin (without clavulanic acid).

Correctly interpreting antibiotic susceptibility testing results requires knowledge of numerous and often confusing terms, including MICs, breakpoints, and interpretive categories. *MIC* describes the lowest concentration of an antibiotic needed to inhibit bacterial growth in a laboratory setting.[23] *Breakpoints* are predetermined antibiotic concentrations at which particular types of bacteria are susceptible in a clinical setting: that is, breakpoints are used to determine susceptibility at antibiotic doses typically used in practice. Breakpoints are often patient-specific (e.g., dogs versus cats), bacteria-specific (e.g., *E coli* versus *S pseudintermedius*), and sometimes infection-site–specific (e.g., urine versus tissue).[24] *Interpretive categories* (susceptible, intermediate, or resistant) are

Broad community-based awareness programs for antimicrobial stewardship in human medicine or mainstream media coverage have probably increased client awareness of terms such as "superbugs."[17]

what clinicians ultimately use to guide antibiotic therapy based on antibiotic susceptibility testing.

Laboratories use MICs and breakpoints to interpret the category to which the submitted bacterial isolates belong. Use of the correct breakpoint is crucial when interpreting reported antibiotic susceptibility MICs. Therefore, when submitting samples for antibiotic susceptibility testing, always provide detailed information about the infection location (e.g., specify pyelonephritis if suspected) to ensure that the laboratory uses the most appropriate breakpoint to determine the interpretive category.[12] For example, the breakpoint for an antibiotic used to treat bacterial cystitis caused by *E coli* in dogs is much higher for some antibiotics (e.g., amoxicillin) than the breakpoint for the same antibiotic in other tissue (e.g., wound infection). This difference in breakpoint between infection sites is because amoxicillin concentrates much higher in urine than in infected tissue, such as wounds. Similarly, because antibiotics concentrate at tissue levels in prostatitis and pyelonephritis, breakpoints used for these conditions are much lower than those for lower urinary tract infections, even though they are all part of the urinary system.

## Considerations for First-Line Systemic Therapy

First-line systemic antibiotics should be preferentially used when their likelihood of being effective is high. Antibiotics commonly used as first-line therapy usually have a relatively low risk for adverse events, reasonable dosing regimens that facilitate administration compliance, and reasonable cost. Although use of any systemic antibiotic is associated with selection pressure for resistance, a core strategy of antibiotic stewardship is avoiding use of second- and third-line antibiotics that can increase risk for resistance selection pressure (e.g., fluoroquinolones) in lieu of first-line therapy.[9] First-line systemic therapy in companion animal medicine varies according to patient species and location/type of infection. In general, the most common antibiotics designated and used as first-line systemic therapy are amoxicillin, amoxicillin/clavulanic acid, clindamycin, doxycycline, and first-generation cephalosporins (TABLE 1). Several first-line antibiotics are available as chewable flavored tablets, which facilitate administration compliance for many clients.[27]

From the perspective of antibiotic-resistance selection pressure and efficacy, reasonable first-line systemic

**TABLE 1 First-line Systemic Antibiotics***

| INFECTION | SPECIES | ANTIBIOTIC |
|---|---|---|
| Sporadic uncomplicated urinary tract infection | Canine | **Amoxicillin**[12]<br>Amoxicillin/clavulanate[12]<br>Potentiated sulfonamide[12] |
| | Feline | **Amoxicillin**[12]<br>Amoxicillin/clavulanate[12]<br>Potentiated sulfonamide[12] |
| Superficial bacterial folliculitis | Canine | Amoxicillin/clavulanate[9]<br>Cephalexin[9]<br>Cefadroxil[9]<br>**Clindamycin**[9]<br>Lincomycin[9] |
| | Feline | **Amoxicillin/clavulanate**[22]<br>Cephalexin[22]<br>Cefadroxil[22]<br>Clindamycin[22] |
| Soft tissue wound/abscess | Canine | Amoxicillin[22]<br>**Amoxicillin/clavulanate**[22]<br>Clindamycin[22] |
| | Feline | **Amoxicillin**[22,25]<br>Amoxicillin/clavulanate[22]<br>Clindamycin[22] |
| Upper respiratory tract infection of >10-day duration or infection with mucopurulent discharge plus fever, lethargy, or inappetence | Canine | Amoxicillin/clavulanate[26]<br>**Doxycycline**[26] |
| | Feline | Amoxicillin[26]<br>**Doxycycline**[26] |

**Boldface indicates authors' preferred first-line antibiotic.*

therapy for many conditions is potentiated sulfonamide antibiotics. However, because of increased risk for significant adverse drug reactions with potentiated sulfonamides compared with other first-line therapy options, many clinicians prefer to use potentiated sulfonamides only when specifically indicated (i.e., guided by culture and antibiotic susceptibility results).[9,12]

## Considerations for Second-line Systemic Therapy or Specific Diseases

Several types of antibiotics should be reserved for specific disease indications or as second-line therapy (i.e., guided by culture and antibiotic susceptibility results), primarily because of their risks for specific types of antibiotic-resistance selection pressure. When prescribed empirically, second-line antibiotics should be substantially more likely than first-line antibiotics to be effective. The companion animal antibiotics that most commonly fall into this category are fluoroquinolones and second-/third-generation cephalosporins, but other examples include nitrofurantoin and azithromycin[9,12] (**TABLE 2**). Although some guidelines suggest that nitrofurantoin may be an acceptable second-line treatment option for bacterial cystitis, there is no reliable published evidence of its efficacy in dogs and cats. In addition, client compliance may be a concern because of the q8h dosing.[12,23,28] For patients with renal impairment, nitrofurantoin should be avoided due to increased toxicity risks and decreased efficacy.[28] Azithromycin has been used to treat respiratory tract infections, but reported data do not support its use over that of the commonly recommended first-line therapies.[26]

Examples of infections for which fluoroquinolones are indicated as initial empiric therapy (in addition to culture and antibiotic susceptibility–guided therapy) include pyelonephritis, prostatitis, pneumonia with evidence of sepsis, infections of the central nervous system, and infections suspected to be caused by *Pseudomonas* species. Published data suggest increased risks for resistance selection pressure when fluoroquinolones are prescribed, particularly at low doses.[15,29,30] Thus, for most infections, when individual patient tolerance permits, fluoroquinolones should be dosed at the upper end of published dose ranges. In addition, infections with some bacteria (e.g., *Pseudomonas* species) necessitate high doses of fluoroquinolones for effective treatment.[23] Note, however, that feline patients are particularly susceptible to the retinal side effect of enrofloxacin; dosages in excess of published feline-specific guidelines *should not be used for cats*.[12] Later generation fluoroquinolones (e.g., pradofloxacin) have more activity against anaerobes and gram-positive bacteria than earlier-generation fluoroquinolones (e.g., enrofloxacin). Use of later-generation fluroquinolones should be reserved for mixed infections or infections that indicate the need for expanded coverage (i.e., increased activity against anaerobes and gram-positive bacteria), such as aspiration pneumonia with evidence of sepsis.[26,31]

Because second- and third-generation cephalosporins may increase selection pressure for ESBL-producing

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**TABLE 2 Second-line, Last Resort, and Strongly Discouraged Systemic Antibiotics**

| SECOND-LINE[9,12,25] | LAST RESORT[9,12,25] | STRONGLY DISCOURAGED[9,12,15,25] |
|---|---|---|
| ▪ Azithromycin<br>▪ Cephalosporins (second- and third-generation)<br>▪ Fluoroquinolones (enrofloxacin, marbofloxacin, orbifloxacin, pradofloxacin*)<br>▪ Nitrofurantoin | ▪ Aminoglycosides (amikacin, gentamicin)<br>▪ Chloramphenicol<br>▪ Rifampin | ▪ Anti-MRSA cephalosporins<br>▪ Carbapenems (imipenem, meropenem)<br>▪ Glycopeptides (vancomycin, teicoplanin, telavancin)<br>▪ Linezolid |

**Pradofloxacin should be reserved for infections that require expanded-coverage antibiotic therapy.*
*MRSA = methicillin-resistant* Staphylococcus aureus.

Antibiotics such as chloramphenicol, amikacin, and rifampin are sometimes required for the treatment of antibiotic-resistant infections, but they must be used with caution because of increased risks for adverse drug reactions.

Enterobacteriaceae, these antibiotics should be used for routine infections only when they are specifically indicated by culture and antibiotic susceptibility results. If regional antibiogram data are supportive, third-generation cephalosporins may be a reasonable empiric choice for life-threating conditions (e.g., pyelonephritis) while awaiting culture and antibiotic susceptibility test results.[12] Although for routine infections it may be tempting to choose a third-generation cephalosporin with less frequent dosing regimens, such as cefpodoxime q24h, remember that once-daily dosing may not be superior to twice-daily dosing with regard to client compliance during short-term antibiotic administration.[14]

## Considerations for Systemic Antibiotics of Last Resort

As rates of antibiotic resistance increase, clinicians can find themselves needing to use systemic antibiotics of last resort. Antibiotics of last resort often have increased risks for adverse events, challenging dosage regimens, increased costs, and selection pressure for specific types of resistant bacteria (e.g., CRE). Recent surveillance reports indicate that CRE are potentially an emerging problem in veterinary medicine.[1-4] It has been postulated that these pathogens of urgent public health concern in human medicine have emerged because of the increased use of carbapenems (imipenem/meropenem). Although numerous different types of antibiotics cause selection pressure for CRE, limiting the use of carbapenems is critically important to avoid specific selection pressure for CRE infections in veterinary patients. Although imipenem and meropenem have been used to treat antibiotic-resistant infections, their use must be carefully justified because of the risk for selection pressure for CRE. Fortunately, CRE have not been commonly identified as clinical isolates from companion animals; nevertheless, they are of major public health concern and are potentially zoonotic.[32]

Antibiotics such as chloramphenicol, amikacin, and rifampin are sometimes required for the treatment of antibiotic-resistant infections, but they must be used with caution because of increased risks for adverse drug reactions. Chloramphenicol has been associated with bone marrow suppression, amikacin with renal toxicity, and rifampin with hepatic toxicity.[9]

Several antibiotics of last resort are of great importance in human medicine, which results in societal pressure to limit their use in veterinary medicine. Antibiotics that are critically important to human health for the treatment of serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections include families such as glycopeptides (e.g., vancomycin, teicoplanin, telavancin), linezolid, and anti-MRSA cephalosporins. Use of these drugs in companion animal medicine is strongly discouraged.[9,15] Before prescribing any antibiotic of last resort, carefully evaluate risks versus benefits; consultation with a veterinary specialist is recommended.[12]

## SUMMARY

In choosing an antibiotic and dosage, there are many factors to consider in addition to convenience and the patient's weight, including:

- the most common pathogens for an infection site
- breakpoint of expected pathogen given the patient species and infection location, expected or documented pathogen MIC, and distribution of the antibiotic to the infection site
- underlying patient health conditions, client finances, and expected client/patient compliance

Antibiotic stewardship *is* good medicine. Veterinarians and clients should continue to work toward producing a positive clinical outcome while simultaneously minimizing the promotion of antibiotic resistance. TVP

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