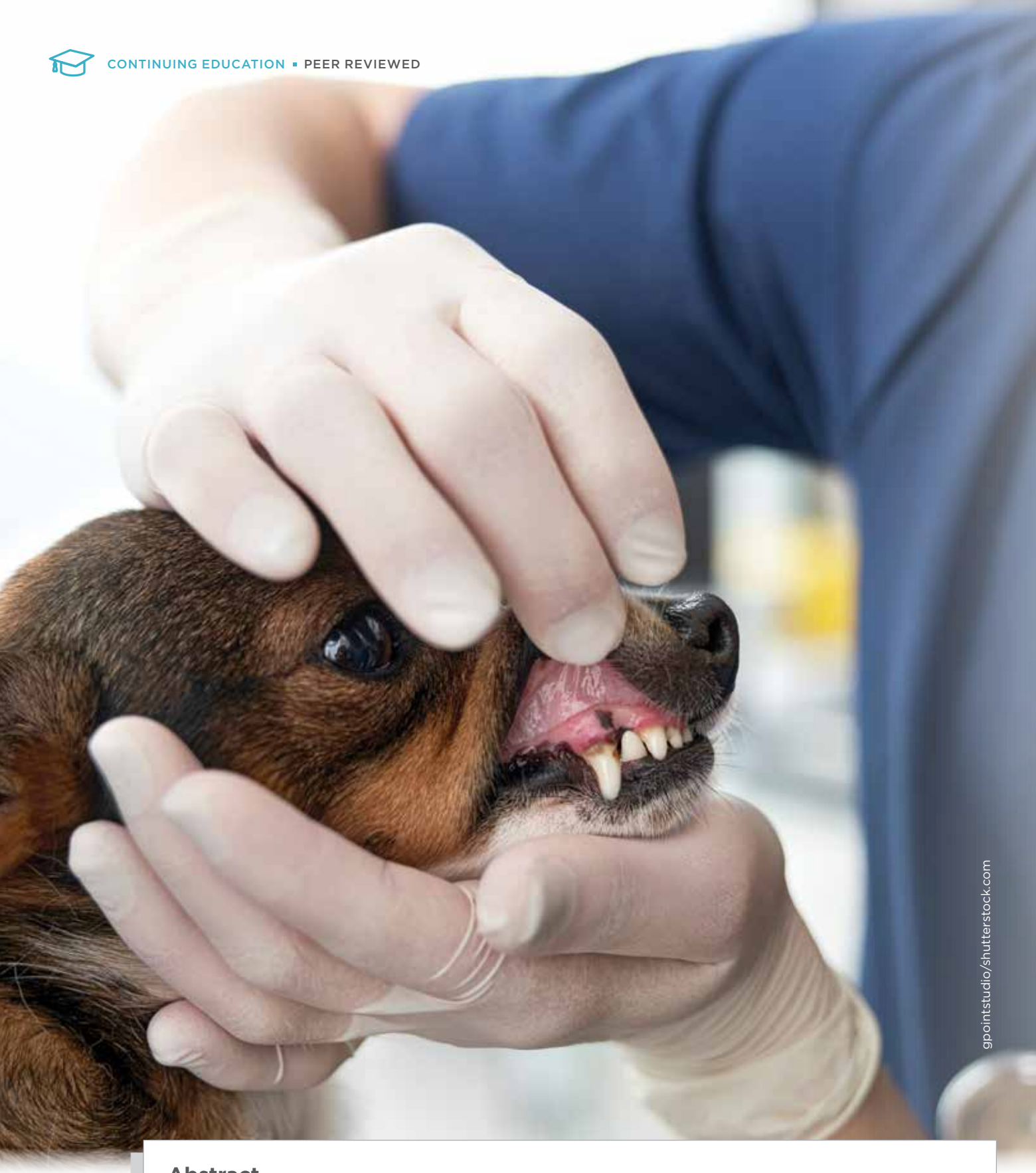

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## Abstract

This article describes new perspectives on periodontal disease and its treatment in light of recent advances in molecular biology. Specific indications and contraindications for the administration of systemic antimicrobial drugs to veterinary patients with periodontal disease are described.

CONTINUING EDUCATION

DENTISTRY

# The Use of Antibiotics in Veterinary Dentistry

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Oral and dental diseases are among the most common health problems recognized in small animal veterinary practice today.[1] Although improving, education in veterinary dentistry and instruction in basic oral surgery skills by veterinary schools remain inadequate.[2] As a result, new graduates often learn how to practice dentistry from their employer or from colleagues who themselves may have had little training in oral medicine and surgery.

Older concepts relating to the treatment of periodontal disease remain entrenched, particularly with regard to antibiotic use. Overuse and misuse of antimicrobial drugs are believed to be leading causes of bacterial

## Take-Home Points

- Overuse and misuse of antimicrobial drugs are believed to be leading causes of bacterial resistance, which has resulted in ineffectiveness of drugs that previously provided life-saving treatment for human and veterinary patients.
- Antimicrobial drugs should be reserved to treat serious infections of known bacterial etiology rather than to prevent a possible infection.
- Although nearly 1000 different microbial species are present in the mouths of dogs and cats, host immune surveillance mechanisms tolerate them and they do not cause disease or provoke an inflammatory response in healthy animals.
- When changes in the oral environment due to host and microbial factors alter the microbial composition (dysbiosis), immune tolerance is disrupted, resulting in an inflammatory response.
- Periodontitis is a destructive inflammatory process against which systemic antimicrobial therapy has a limited effect. Treatment of periodontitis involves surgical debridement. Systemic antimicrobial drugs should not be used as a substitute for surgical treatment.
- Rather than attempting to target putative pathogenic species that thrive in diseased oral tissues, prophylactic antimicrobial therapy should be directed against organisms most commonly associated with bacteremia and infective endocarditis.
- In dogs and cats, the risk for developing infective endocarditis after oral surgery is extremely low, and prophylactic antimicrobial therapy for patients not regarded as high risk is not warranted.
- For high-risk patients, intravenous prophylactic antimicrobial therapy should begin 30 to 60 minutes prior to oral surgery and should be readministered intraoperatively based on the drug's half-life. Postoperative antimicrobial treatment is rarely indicated and not recommended.

resistance, which has resulted in ineffectiveness of drugs that previously provided life-saving treatment.[3] A recent systematic review estimated that 4.95 million people died of bacterial diseases because of antimicrobial resistance in 2019.[4] Therefore, it is incumbent upon all healthcare providers to consider antimicrobial drugs as precious resources that should be reserved to treat serious infections of known bacterial etiology rather than to prevent a possible bacterial infection.

## HISTORICAL USE OF ANTIBIOTICS IN DENTISTRY

Since the 1960s, gram-negative anaerobic bacteria, including *Porphyromonas gingivalis, Tannerella forsythia,* and *Treponema denticola,* have been consistently cultured from sites of oral inflammation in humans, which implicated those organisms as "causative agents" of periodontitis.[5] Sensitivity testing showed that amoxicillin and clindamycin were effective antibiotics against these species; therefore, these drugs were frequently prescribed by dentists for human patients. Gram-negative bacteria (*Porphyromonas* species) were also cultured from periodontal lesions in companion animals, which suggested that periodontitis in humans and animals might share a common etiology. However, it soon became apparent that periodontitis could not be cured by antibiotics alone like other diseases that fulfilled Koch's postulates (criteria necessary to demonstrate a causal relationship between a microorganism and a disease).[6] Several theories to explain the pathogenesis of periodontitis have since been proposed; however, a single, all-encompassing hypothesis has yet to be generally accepted.[7]

## THE ORAL MICROBIOME

The original definition of "microbiome" referred to the collective genes and genomes of all microbial inhabitants on or in a defined location.[8] Conceptually, the term has evolved, and it is now understood that a microbiome exists as a community of multiple species in a defined environment that compete with each other for resources but also share genetic information, including virulence factors and antimicrobial resistance genes. The relative abundance of species in a microbiome is influenced by local conditions in the host, and can also influence the host's response to its presence.

### Current Research

Progress in molecular biology and bioinformatics over the past 20 years has contributed to a new appreciation for the indigenous microbial inhabitants of the healthy oral cavity and revised the collective understanding of the conditions under which oral health transitions to inflammation. Whereas standard bacterial culture can only detect organisms that readily grow on artificial media in vitro, gene sequencing technology allows detection and taxonomic identification of microbial species from contaminated environments in vivo based on their unique RNA or DNA sequences.[9] This technology has demonstrated that the healthy oral cavity of mammalian hosts is inhabited by hundreds of different bacterial species, as well as archaea, fungi, protozoa, and viruses.[10] Analysis of gene sequences has led to the detection of previously uncultured microorganisms and thereby enables a more accurate assessment of the richness (total number of species) and diversity (relative abundance of each species) of microbial life in a defined environment.

Although bacteria are the most abundant and best-studied oral inhabitants, culture-independent diversity surveys of archaea, fungi, and viruses have also been recently published.[10-12] The composition of the oral microbial community in patients with oral health compared with that in patients with various oral diseases has been studied in humans and veterinary species. In 1 study, gene sequences of a total of 714 bacterial species were detected in dogs with and without periodontal disease.[13] In a survey of cats with and without odontoclastic resorption, sequences of a total of 441 bacterial taxa were detected.[14] At the time of this writing, the expanded Human Oral Microbiome Database contains the gene sequences of approximately 750 species-level oral taxa found in the human oral cavity, of which only 57% have been officially named and 30% are still uncultivated.[15]

### Relationship With the Host

Clearly, the healthy oral cavity contains an enormous number and variety of microorganisms that coexist with the host without causing clinical evidence of inflammation or disease. While many of the mechanisms to explain this are not fully understood, it is thought that crosstalk between commensal microorganisms and host immune surveillance occurs, which allows the indigenous microbial inhabitants to remain without provoking an inflammatory response.[16]

Such symbiosis involves adaptations by both the commensal microorganisms and the host that benefit

both parties. In return for a suitable habitat and nutrients, commensal species benefit the host by providing a "first line of defense" against colonization of exogenous species by limiting attachment sites and competing for nutrients.[17] Some commensal bacteria express antimicrobial molecules (bacteriocins) that directly inhibit the growth of exogenous species.[18] Meanwhile, host regulatory T cells ($T_{reg}$ cells) in the oral mucosa have pattern recognition receptors that allow discrimination between commensal species and exogenous microrganisms.[19] Depending on which signals are received, $T_{reg}$ cells can express cytokines that inhibit secretion of proinflammatory mediators to maintain homeostasis or can initiate an inflammatory response by releasing cytokines that promote recruitment of additional immune cells.[20]

## Influencing Factors

The conditions within a microbiome are dynamic, and the relative abundance of different species changes in response to local environmental conditions.[21] Age (i.e., neonate versus adult), systemic health (e.g., diabetes, infectious disease), oral hygiene, and diet are examples of host factors that can influence the composition of the oral microbiome. Examples of microbial factors that can influence local conditions in the oral environment include depletion of oxygen and other nutrients, accumulation of metabolic waste products, and altered pH. Such factors drive competition between microbiome constituents and thereby influence its composition.[22] The surfaces of the tongue, buccal mucosa, and palatal rugae, as well as the supra- and subgingival surfaces of the teeth, each represent a unique environmental niche (biogeography) that is occupied by a distinct microbiome.[23]

## Survival and Protection

The oral microbiome is attached to the teeth and oral soft tissue surfaces as a biofilm. A biofilm is a protective 3-dimensional barrier composed of proteins, lipids, polysaccharides, and DNA expressed by the microbiome constituents and is referred to as the extracellular polymeric matrix (EPM).[23,24] Biofilm formation occurs rapidly as pioneer species attach to specific oral surfaces, followed by coaggregation of secondary colonizers, which allows the biofilm to mature and expand.[24] A biofilm protects the embedded microbial community from mechanical disruption, diffusion of topical disinfectants, and systemic antibiotics that cannot penetrate the EPM.[25] Bacteria within a biofilm have slower growth and altered gene expression compared with planktonic (free-living) organisms of the same species. Because the minimum inhibitory concentration of antimicrobial drugs is based on bacterial cells cultured in vitro, recommended dose and duration guidelines generally fail to achieve lethal drug concentrations against bacteria within a biofilm.[26]

Biofilm, attached to the supra- and subgingival surfaces of the teeth, accumulates over time and becomes mineralized as calculus. Calculus forms when the biofilm becomes saturated by calcium–phosphate salts present in saliva and thickens as successive layers of viable biofilm cover the mineralized surfaces and porosities, which in turn become mineralized.[27]

## Common Bacterial Species

Despite the torrent of microbes that enter the oral cavity through eating, drinking, grooming, and other behaviors, only certain microbial groups have evolved unique adaptations that enable them to attach, survive, and reproduce within the harsh oral environment.[28,29] Gene sequencing techniques have established that just a few bacterial phyla are consistently detected in the oral cavities of various hosts.[30] Although similar at the phylum level, the species composition of the oral microbiome varies significantly between different mammalian host species. For example, only 16.4% of oral bacterial taxa in dogs matched the gene sequences of oral bacteria in humans.[31]

The most abundant bacteria in the healthy human oral cavity are gram-positive aerobic species, including *Streptococcus oralis* and *Streptococcus sanguinis*.[32] By contrast, the most abundant bacterial taxa in the healthy oral cavity of dogs are gram-negative anaerobes, including *Porphyromonas cangingivalis*, *Moraxella* species, *Bergeyella* species, and *Neisseria* species.[33] In human patients with periodontitis, the most abundant bacterial taxa were gram-negative anaerobes, including *P gingivalis, T forsythia,* and *T denticola*. In dogs with periodontitis, the most abundant bacterial taxa were gram-positive anaerobes (*Peptostreptococcus canis*) and gram-negative anaerobes (*Porphyromonas gulae*).[13,33] The observation that health-associated taxa in one host are disease-associated taxa in another host suggests that categorizing taxa as "pathogenic" may be an oversimplification. Furthermore, "pathogenic" species are commonly found in the absence of disease, while health-associated species are often found in sites of periodontitis.[34]

To shed light on the definition of a pathogen, a systematic review and meta-analysis published in 2020 compared various species of *Porphyromonas* from healthy and diseased sites in humans, dogs, cats, cattle, sheep, pigs, and monkeys.[35] The study found that *Porphyromonas* species were just as likely to be found in healthy tissues as diseased tissues. Variation in the expression of certain genes was discovered among different species, which influenced their ability to thrive in inflamed or noninflamed tissues. For example, *P gingivalis* in humans and *P gulae* in dogs lacked the genetic machinery to acquire iron from sources other than heme, an iron-rich molecule that is released from decomposing blood and tissue found at sites of inflammation. By contrast, commensal species such as *P cangingivalis* had genes that enabled the acquisition of iron from other environmental sources, which allowed that species to thrive in low-heme, noninflamed tissues.[36] Such findings highlight the complexity of factors that determine the relative abundance of different microbial species within different host environments.

### Role in Periodontal Disease

It has long been presumed that certain bacterial species are responsible for triggering the host inflammatory response in periodontitis. However, that paradigm is shifting toward the view that periodontitis is a multifactorial disease that involves a complex interplay between oral microbial inhabitants and host immune surveillance.[37] Periodontal tissue destruction is not triggered solely by the presence of specific bacterial species, but rather is the result of synergy between the host inflammatory cascade and microbial communities whose composition has been altered in response to local environmental changes (dysbiosis).[38]

Gingivitis is a reversible inflammatory response confined to gingival tissue that is not associated with attachment loss. Gingivitis does not always progress to periodontitis, but gingivitis is commonly present in periodontitis.[39] Periodontitis is a more destructive process in which components of the tooth attachment apparatus, including gingiva, alveolar bone, periodontal ligament, and cementum, are irreversibly damaged. It has been determined that most of the tissue destruction is the result of the host inflammatory response, in which dying neutrophils release potent intracellular enzymes such as collagenase and elastase, which contribute to degradation of host connective tissues.[40] The process leading to periodontitis has been described as an "unremitting positive feedback loop" in which inflammation and proteolysis provide an enriched environment that favors growth of microbial species best suited to thrive in those conditions, which then leads to further tissue destruction and inflammation.[41]

## ANTIMICROBIAL STEWARDSHIP IN VETERINARY DENTISTRY

Gingivitis and periodontitis are inflammatory diseases, and antimicrobial therapy neither prevents nor effectively resolves inflammation resulting from disrupted homeostasis between the microbiome and the host. Furthermore, the multitude of oral taxa embedded within a protective biofilm limits the benefit of systemic antimicrobial drugs in the treatment of periodontal disease.[42]

### Antimicrobial Therapy for Periodontitis

Scaling and root planing (SRP) remains the generally accepted treatment for mild to moderate periodontitis in humans and veterinary species, and there is conflicting evidence whether adjunctive administration of systemic antimicrobial drugs provides substantial clinical benefit. For example, a systematic review and meta-analysis published in 2022 compared SRP alone with SRP plus adjunct amoxicillin and metronidazole for the treatment of aggressive periodontitis in humans.[43] Studied criteria included changes in probing depth and mean clinical attachment level. The overall mean difference in reduction of probing depth with adjunctive antibiotics was 0.42 mm and the mean improvement in clinical attachment level was 1.04 mm compared to SRP without antibiotics.[43] Although statistically significant, the value of improvement by 1 millimeter is of questionable clinical benefit.

### Current Guidelines on Antimicrobial Prophylaxis for Dental Procedures

Beyond their limited value in treating periodontal disease, systemic antimicrobial drugs are commonly prescribed prophylactically to human and veterinary patients undergoing various dental and oral surgical procedures. In this context, prophylaxis is the administration of an antimicrobial to an individual to mitigate the risk of acquiring disease or infection that is anticipated based on history, clinical judgment, or epidemiological knowledge.[44] Multiple reviews in human patients have evaluated the risk to benefit ratio

of antimicrobial drugs given to prevent oral bacteremia and infective endocarditis (IE) compared to the risk of adverse drug reactions and increased antimicrobial resistance.[45-47] On the basis of the evidence to date, the American Heart Association (AHA) and American Dental Association (ADA) have issued guidelines to dentists advising that prophylactic antimicrobial drugs are neither necessary nor recommended except for high-risk patients such as those with certain underlying cardiac conditions or with a prior history of bacterial infection from joint replacement surgery.[48]

Guidelines on the use of antimicrobial prophylaxis have also been published for veterinary patients. For example, the American Veterinary Dental College issued a 2019 position statement on the use of antibiotics in veterinary dentistry that stated "use of a systemically administered antibiotic is recommended to reduce bacteremia for animals that are immune compromised, have underlying systemic disease (such as certain clinically-evident cardiac disease [sub-aortic stenosis] or severe hepatic or renal disease) and/or when severe oral infection is present."[49] However, such recommendations are exceedingly broad, provide little specific guidance, and therefore include a large percentage of veterinary patients for whom antimicrobial prophylaxis is prescribed but is likely unnecessary. Furthermore, such broad guidelines are inconsistent with the current recommendations for human patients. More limited criteria for antimicrobial prophylaxis in veterinary patients undergoing oral procedures have been published and recommend treatment only for high-risk patients such as those with patent ductus arteriosus, subaortic or aortic stenosis, unrepaired cyanotic heart disease, previous IE, and implanted pacemaker leads.[50]

The 2022 antimicrobial stewardship guidelines sponsored by the American Association of Feline Practitioners and the American Animal Hospital Association state, "Systemic antimicrobials are usually not indicated for routine dental prophylaxis or after tooth extractions. In cases of periodontitis, systemic antimicrobials are not a substitute for surgical treatment. In most cases of periapical tooth root abscesses, debridement of infective tissue is sufficient to control infection."[44] It is has been shown that transient bacteremia occurs with any type of oral activity, including chewing, toothbrushing, and flossing.[51] Therefore, the risk for complications such as IE associated with dental procedures, including extractions, is considered low for the vast majority of patients.

## Risk of Infective Endocarditis in Dental Patients

In humans, the association between invasive dental procedures, antibiotic prophylaxis, and the development of IE was evaluated using data collected from employer-provided health insurance coverage of nearly 8 million Americans.[52] High-risk patients who received antimicrobial prophylaxis prior to extractions or oral surgery had a significantly lower risk of developing IE within 30 days of the procedure compared with high-risk patients who did not receive prophylactic therapy.[52] The author's conclusion is that prophylactic antimicrobial therapy was not justified for all patients undergoing invasive dental procedures but was justified for high-risk patients, which supported the current recommendations of the AHA and ADA.[48,52]

Despite such high-quality evidence, a study that examined prescribing habits of U.S. dentists found that 78.5% of prescriptions for antibiotic prophylaxis in 2018 were inconsistent with current guidelines and were therefore considered unnecessary.[53,54] Furthermore, a cross-sectional study of 115 625 890 outpatient visits from Veterans Affairs medical facilities and clinics found that dentists wrote 10% of all outpatient antibiotic prescriptions, which was 1.7 times the prescription-per-visit rate of physicians, nurse practitioners, and physician assistants.[55] Clearly, improvements are necessary to reiterate antimicrobial stewardship strategies to dentists (and veterinarians) to reduce the unnecessary prescribing of antimicrobial prophylaxis to patients least likely to benefit from their use.

In dogs and cats, the incidence of IE is also very low (<0.5%); however, the disease is challenging to diagnose and is typically associated with high morbidity and mortality. One comparative study showed that none of 76 dogs diagnosed with IE had a history of undergoing a dental or oral procedure in the 3 months prior to the diagnosis of endocarditis.[56] Similarly, dental treatment was not identified as a predisposing risk factor in dogs and cats diagnosed with IE in 3 recent retrospective studies.[57-59] For example, of 120 150 dogs presented to a tertiary referral center, IE was diagnosed in 233 dogs over a 15-year period (0.09% prevalence).[59] The predominant bacteria associated with IE in dogs were gram-positive cocci (*Staphylococcus pseudointermedius, Streptococcus canis,* and *Staphylococcus aureus*) and gram-negative rods (*Escherichia coli*). In that study, *Bartonella* species were detected in 15% of IE cases.[59]

## Use of Antimicrobial Therapy in High-Risk Dental Patients

While high-level data are lacking, there is little to suggest that IE is a common clinical issue for veterinary patients undergoing dental cleaning or extraction procedures. Nevertheless, if prophylactic antimicrobial therapy is deemed appropriate for at-risk veterinary patients, treatment should be directed against organisms most likely to be associated with bacteremia and IE rather than against putative pathogens associated with periodontal disease.[60]

To preemptively reduce the potential for bacteremia, an appropriate antimicrobial drug should be administered intravenously 30 to 60 minutes prior to oral surgery.[60] Whereas ampicillin and clindamycin are generally effective against gram-positive bacteria like staphylococci and streptococci, neither drug is particularly effective against gram-negative coliform species.[61] Cefazolin, a first-generation cephalosporin, is a good option due to its efficacy against streptococci and most β-lactamase–producing bacteria, and it is moderately effective against gram-negative species. Following intravenous administration of the preoperative dose, the same drug should be readministered intraoperatively based on its half-life. For time-dependent drugs such as ampicillin and cefazolin, intravenous administration every 2 hours during the procedure is recommended.[62] However, for most dogs and cats that are not in a high-risk category, there is limited evidence supporting the need for antimicrobial therapy following dental cleaning, extractions, or other types of oral surgery. Therefore, postoperative antimicrobial treatment is rarely indicated and not recommended. TVP

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## Eric M. Davis

Dr. Davis received his veterinary degree from Cornell University in 1979 and became a diplomate of the American Veterinary Dental College in 2005. He started the Dental Referral Service at Cornell, which has since developed into a faculty-level program. In 2005, he started Animal Dental Specialists of Upstate New York, a referral practice for dentistry and oral surgery near Syracuse, New York. He is the author of several review papers published in scientific journals. Most recently, he collaborated with Dr. Scott Weese from the Ontario Veterinary College to write a chapter in the Veterinary Dentistry and Oral Surgery edition of *Veterinary Clinics of North America* about the oral microbiome in dogs and cats and the utility of antimicrobial therapy in the treatment of periodontal disease.

CONTINUING EDUCATION

# The Use of Antibiotics in Veterinary Dentistry

## TOPIC OVERVIEW

This article reviews the use of antimicrobial therapy in veterinary dentistry and describes specific indications and contraindications for the administration of systemic antimicrobials to veterinary patients with periodontal disease.

## LEARNING OBJECTIVES

After reading this article, practitioners should be able to explain why systemic antimicrobial therapy has limited efficacy in veterinary dentistry and is unnecessary for most patients. Readers should be able to identify which patients are at higher risk for developing infective endocarditis and use prophylactic antimicrobials that target species most frequently associated with infective endocarditis rather than species associated with periodontitis.

This article has been submitted for **RACE approval for 1 hour of continuing education credit** and will be opened for enrollment upon approval. To receive credit, take the test at **vetfolio.com** by searching the name of the article or scanning the QR code below. Free registration is required. Questions and answers online may differ from those below. Tests are valid for 2 years from the date of approval.

1. **A microbiome is best described as:**
   a. A defined location inhabited by microorganisms
   b. A microscopic environment composed of proteins, lipids, polysaccharides, and bacteria
   c. A collection of bacteria that reside in or on a defined location
   d. The collective genes and genomes of all microbial inhabitants on or in a defined location
   e. All of the above

2. **Antibiotic stewardship refers to:**
   a. Strategies to enhance the use of antimicrobial drugs
   b. Guidelines to select the best antimicrobial agents to treat a specified disease
   c. Evidence-based prescribing advice to curb the overuse of antimicrobial drugs with the goal of reducing antimicrobial resistance
   d. Ensuring that there are no shortages in the supply of antimicrobial drugs to treat human and animal diseases
   e. A global initiative to study the effects of microbial resistance to antibiotics

3. **Why do antimicrobial drugs have limited efficacy in the treatment of periodontal disease in dogs and cats?**
   a. There are hundreds of different species of microorganisms present in the oral cavity and antimicrobial drugs can only kill some of them.
   b. Bacteria and other microbes are embedded within a biofilm that protects them from systemically administered antimicrobial drugs.
   c. Bacteria within a biofilm have slower growth and altered gene expression compared with planktonic organisms of the same species, reducing antimicrobial efficacy.
   d. Antimicrobial drugs do not prevent or resolve inflammation caused by disrupted homeostasis between the microbiome and host.
   e. All of the above

4. **Antimicrobial therapy to prevent infective endocarditis after dental procedures should be limited to which of the following veterinary patients?**
   a. Healthy dogs and cats requiring dental extractions
   b. Patients with an acquired heart murmur
   c. Patients with a fractured tooth with pulp exposure that might get infected
   d. None of the above
   e. All of the above

5. **Periodontitis is best described as a:**
   a. Disease caused by specific bacteria that can be controlled with antimicrobial drugs
   b. Destructive inflammatory process that requires surgical treatment, including mechanical disruption of the biofilm by scaling, root planing, and extractions
   c. Disease that requires adjunctive antimicrobial therapy in addition to surgical treatment
   d. Reversible inflammatory response that can be managed by scaling, root planing, extractions, or periodontal surgery
   e. Process in which tissue destruction is the direct result of metabolism by the oral microbiome

6. **Which of the following patients are at high risk for developing infective endocarditis?**
   a. Patients with a patent ductus arteriosus
   b. Patients with unrepaired cyanotic heart disease
   c. Patients with subaortic or aortic stenosis

d. Patients with a prior history of infective endocarditis
e. All of the above

7. **Which statement best represents the current understanding of the pathogenesis of periodontitis?**
   a. Periodontitis is a multifactorial disease that involves a complex interplay between oral microbial inhabitants and host immune surveillance.
   b. Periodontitis is caused by a complex interplay involving the bacteria that continuously enter the oral cavity through eating, drinking, and other oral activities.
   c. Subgingival bacteria express antimicrobial resistance genes that allow for an increased relative abundance of pathogenic species.
   d. Periodontitis is caused by immune-mediated tissue destruction, with limited influence from the oral microbiome.
   e. None of the above

8. **Which antimicrobial agent has broad efficacy against the most common bacteria associated with endocarditis in dogs and cats?**
   a. Ampicillin
   b. Clindamycin
   c. Cefazolin
   d. Doxycycline
   e. All of the above

9. **Infective endocarditis in dogs and cats is a:**
   a. Common risk factor following invasive dental procedures like extractions
   b. Rare disorder that is easily diagnosed
   c. Common disorder that has high morbidity but low mortality
   d. Rare disorder that is associated with high morbidity and high mortality
   e. Common disorder that should be prevented by prophylactic antimicrobial drugs that target periodontal pathogens

10. **Prophylactic antimicrobial therapy in veterinary dentistry is indicated for which of the following patient groups?**
    a. All patients that require surgical extractions
    b. Only patients with severe periodontitis for which surgical treatment cannot be performed
    c. Patients with high-risk factors for infective endocarditis, including congenital heart disease and implanted pacemaker leads
    d. All patients with gingivitis, to prevent development of periodontitis
    e. All of the above

# VETORYL® CAPSULES
## (trilostane)

**5 mg, 10 mg, 30 mg, 60 mg and 120 mg strengths**
Adrenocortical suppressant for oral use in dogs only.

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**BRIEF SUMMARY** (For Full Prescribing Information, see package insert.)

**CAUTION:** Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

**DESCRIPTION:** VETORYL Capsules are an orally active synthetic steroid analogue that blocks production of hormones produced in the adrenal cortex of dogs.

**INDICATION:** VETORYL Capsules are indicated for the treatment of pituitary and adrenal-dependent hyperadrenocorticism in dogs.

**CONTRAINDICATIONS:** The use of VETORYL Capsules is contraindicated in dogs that have demonstrated hypersensitivity to trilostane. Do not use VETORYLCapsules in animals with primary hepatic disease or renal insufficiency. Do not use in pregnant dogs. Studies conducted with trilostane in laboratory animals have shown teratogenic effects and early pregnancy loss.

**WARNINGS**: In case of overdosage, symptomatic treatment of hypoadrenocorticism with corticosteroids, mineralocorticoids and intravenous fluids may be required. Angiotensin converting enzyme (ACE) inhibitors should be used with caution with VETORYL Capsules, as both drugs have aldosterone-lowering effects which may be additive, impairing the patient's ability to maintain normal electrolytes, blood volume and renal perfusion. Potassium sparing diuretics (e.g. spironolactone) should not be used with VETORYL Capsules as both drugs have the potential to inhibit aldosterone, increasing the likelihood of hyperkalemia.

**HUMAN WARNINGS:** Keep out of reach of children. Not for human use. Wash hands after use. Do not empty capsule contents and do not attempt to divide the capsules. Do not handle the capsules if pregnant or if trying to conceive. Trilostane is associated with teratogenic effects and early pregnancy loss in laboratory animals. In the event of accidental ingestion/overdose, seek medical advice immediately and take the labeled container with you.

**PRECAUTIONS:** Hypoadrenocorticism can develop at any dose of VETORYL Capsules. A small percentage of dogs may develop corticosteroid withdrawl syndrome within 10 days of starting treatment. Mitotane (o,p'-DDD) treatment will reduce adrenal function. Experience in foreign markets suggests that when mitotane therapy is stopped, an interval of at least one month should elapse before the introduction of VETORYL Capsules.
It is important to wait for both the recurrence of clinical signs consistent with hyperadrenocorticism, and a post-ACTH cortisol level of > 9.1 µg/dL (> 250 nmol/L) before treatment with VETORYL Capsules is initiated. Close monitoring of adrenal function is advised, as dogs previously treated with mitotane may be more responsive to the effects of VETORYL Capsules.
The use of VETORYL Capsules will not affect the adrenal tumor itself. The safe use of this drug has not been evaluated in lactating dogs and males intended for breeding.

**ADVERSE REACTIONS:** The most common adverse reactions reported are poor/reduced appetite, vomiting, lethargy/dullness, diarrhea, elevated liver enzymes, elevated potassium with or without decreased sodium, elevated BUN, decreased Na/K ratio, weakness, elevated creatinine, shaking and renal insufficiency. Occasionally, more serious reactions, including severe depression, hemorrhagic diarrhea, collapse, hypoadrenocortical crisis or adrenal necrosis/rupture may occur, and may result in death. **Owners should be advised to discontinue VETORYL Capsules and contact their veterinarian immediately in the event potential drug intolerance is observed.**

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