# Reproductive microbiome alterations: canine prostatitis

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## Abstract

Prostate is the only accessory sex gland in dog. During periods of sexual rest, prostatic fluid is continuously and constitutively secreted into the proximal urethra where a small amount flows antegrade to exert bactericidal effects and to prevent ascent of lower urinary tract bacteria. Pathologic conditions of the prostate gland are common in dogs and their incidence increases with age. Bacterial prostatitis and benign prostatic hyperplasia account for ~ 85% of all prostatic disorders. Bacterial prostatitis can develop as an acutely fulminating emergency condition or as a chronic disorder in conjunction with benign prostatic hyperplasia. Although signalment, clinical signs and pathogenesis vary between these 2 disease forms, diagnosis and treatment are similar. All dogs with suspected prostatitis should have a complete physical examination, including transrectal palpation and abdominal ultrasonography, as well as a minimum database with complete blood count, chemistry panel, and prostatic fluid analysis and culture (with sensitivity). Most common isolate in bacterial prostatitis is *Escherichia coli* (there are various subpathotypes that promote prostatic virulence). In addition, a variety of other gram-negative and gram-positive bacterial and fungal organisms can cause prostatitis in dogs. Successful treatment of prostatitis depends upon which form of the disease is present. Acute prostatitis requires aggressive systemic therapy with sensitive antimicrobials. For chronic prostatitis, treatment goals must include both reducing prostatic hyperplasia (to eliminate the predisposing cause) as well as antimicrobials (selected based upon sensitivity as well as pharmacokinetics). Trimethoprim-sulfadiazine, erythromycin, chloramphenicol, and enrofloxacin are all suitable choices.

**Keywords:** Acute prostatitis, benign prostatic hyperplasia, chronic prostatitis, *Escherichia coli*

## Introduction

Prostate is located in the retroperitoneal space and completely encircles the proximal urethra and the neck of the urinary bladder.[1] Numerous prostatic ducts open into the proximal urethra.[2] Age, androgenic stimulus, disease, and degree of urinary bladder distention affect its position. Beginning at ~ 8 months of age, androgenic stimulation arising from sexual maturity results in prostatic enlargement. Prostatic enlargement repositions prostate cranially over the pelvic brim as it increases in size, to a total or partial intra-abdominal position.[3] Prostatic size (volume in $cm^3$) is also correlated with body weight (BW), and volume of a normal intact dog's prostate can be accurately calculated from the equation 0.867 * BW (kg) + 1.885 * age (years) + 15.88.[4] Length, width, and depth of prostate gland can be determined ultrasonographically and followed over time.[5] Following castration, prostate atrophies and returns to intrapelvic position. Degree of urinary bladder distention also affects prostate position such that a full bladder displaces the prostate intraabdominally, whereas an empty bladder facilitates an intrapelvic position.[6]

Prostate gland is the only accessory sex gland in the dog. Normal prostatic fluid is clear and slightly acidic (pH 6.15 - 6.5), owing to the presence of prostatic acid phosphatase.[7] However, > 90% of T protein secreted in prostatic fluid is canine prostatic specific esterase (CPSE).[8-9] Enzyme CPSE is an arginine esterase present mainly on the apical regional of prostatic secretory epithelial cells. Serum concentrations of CPSE are elevated in all forms of prostate disease.[10-11] During erection and ejaculation, parasympathetic stimulation increases rate of prostatic fluid production. Sympathetic stimulation ejects prostatic secretions into urethra to become seminal plasma.[12] Prostatic secretions account for > 97% of total ejaculate volume and aid in sperm transport by stimulating uterine contractions.[13-14]

During rest, prostatic fluid is continuously and constitutively secreted into proximal urethra where majority of fluid refluxes retrograde into the bladder.[15-16] A small amount of the prostatic secretion flows antegrade where it exerts bactericidal effects to prevent ascent of lower urinary tract bacteria.[17] In humans, antimicrobial activity of prostatic fluid is primarily attributable to its high zinc concentration.[18]

However, unlike in men, zinc does not have an important role in resolving bacterial prostatitis in dogs.[9,19] Pathological alterations of glandular tissue may result in changes in prostatic fluid composition and loss of its physiological role.[17] Bacterial prostatitis occurs when host defense mechanisms are compromised by concurrent predisposing conditions (benign prostatic hyperplasia) or primary urinary tract infections (cystitis). These conditions allow virulent microorganisms to ascend into prostate, adhere and multiply.[5,20]

Pathologic conditions of the prostate gland are common in dogs and their incidence increases with age. Approximately 8% of all male dogs > 10 years old had prostatic disease, whereas only 0.6% of male dogs < 4 years old had prostatic disease. Large breed dogs (over 20 kg) are overrepresented in all prostatic diseases except neoplasia.[21] Breeds most frequently identified to have prostatic disease include Doberman Pinscher, German Shepherd dog, Rottweiler, American Staffordshire Terrier, Berger de Beauce dog, and Bernese Mountain dog.[21-22] Bacterial prostatitis and benign prostatic hyperplasia account for ~ 85% of all prostatic disorders.[21-22] Bacterial prostatitis can develop as an acutely fulminating emergency condition or as a chronic disorder in conjunction with benign prostatic hyperplasia. Although signalment, clinical signs, and pathogenesis vary between these 2 disease forms, diagnosis and treatment are similar. All dogs with suspected prostatitis should have a complete physical examination, including transrectal palpation and abdominal ultrasound, as well as a minimum database with complete blood count, chemistry panel, and prostatic fluid analysis and culture (with sensitivity).[5]

**Acute Prostatitis**

Acute prostatitis is rare in dog. Acute prostatitis can occur in dogs of any age or sex status but young, intact males are overrepresented. Clinical signs include anorexia, fever, depression, vomiting, and gait abnormalities. Abdominal palpation and/or transrectal palpation may not be possible due to moderate to extreme pain emanating from inflamed prostate. A neutrophilia with a left shift will be present on a complete blood count.[5] Urinalysis will typically reveal pyuria and evidence of bacteria.[5] Acute prostatitis most likely develops secondary to a cystitis or from a hematogenous origin. In cases of acute prostatitis, collection of a prostatic fluid sample for culture is be made via a fine needle aspirate to avoid the uncertainty as to whether prostatic fluid has been expressed. Ultrasonographic appearance of a prostate with acute prostatitis is a normal size with a hypoechoic parenchyma, instead of the normal homogeneous echodense appearance.[23] Because prostatic-blood barrier has been breached by infection, acute prostatitis can be treated with any appropriate antibiotic as determined by culture and sensitivity.[22]

**Chronic Prostatitis**

Chronic prostatitis is common in older, intact male dogs. Benign prostatic hyperplasia has a key role in development of chronic prostatitis (refer below). Clinical signs associated with chronic prostatitis are variable, depending on degree of prostatomegaly.[5,24] Unlike acute prostatitis, systemic signs (e.g. fever, depression) and pain are not present. Most common clinical signs associated with chronic prostatitis include urethral discharge, hematuria, and tenesmus. Urethral discharge can be clear, purulent or hemorrhagic.[2,16] In a 14-year retrospective study of prostatic disease, hemorrhagic urethral discharge was the only clinical sign observed in 23% of cases, which could be exacerbated by sexual arousal.[25] In addition, urinary symptoms (hematuria, pollakiuria, stranguria, dysuria, pyuria, polyuria) are exhibited in > 50% of dogs experiencing chronic prostatitis.[21] Although widely described as a clinical sign associated with prostatitis, tenesmus is only present when the prostate is morbidly enlarged. It is important to mention that many dogs with chronic prostatitis are asymptomatic.[21] Laboratory findings are generally within normal limits or inconclusive for prostatic disease. Ultrasonographic appearance of a dog with chronic prostatitis is coarsely hyperechoic throughout the parenchyma with regions of heterogenous echotexture and dystrophic mineralization resulting from fibrosis and chronic inflammation.[23,26]

Benign Prostatic Hyperplasia

Prostate undergoes continual, androgen-dependent growth, leading to both glandular epithelial cell hyperplasia and hypertrophy (referred to as benign prostatic hyperplasia (BPH).[17,27-28] Ninety percent of dogs > 9 years old have BPH. With increasing age, a modest decrease in serum testosterone

concentrations combined with no change in serum estradiol-17  concentrations result in a relative decrease in the serum androgen:estrogen ratio.[30] In addition, transiently proliferating/amplifying cells are more abundant in the prostate of older males. Both of these conditions may contribute to the age-related increase in size.[17] Prostatic enlargement is both uniform and diffuse. Although the condition is described as "benign", hypervascularization of hypertrophic/hyperplastic tissue can result in vascular leakage or hemorrhage into the gland.[13,31-32] Blood in preputial discharge, urine and/or seminal plasma is the most frequently reported clinical sign of BPH. Additional clinical signs involving the urinary tract (e.g. dysuria, stranguria), gastrointestinal tract (e.g. constipation, tenesmus) or systemic (e.g. abdominal pain, limping) are infrequently reported.[17,32-33] Regardless, nearly half of histologically confirmed cases of BPH were asymptomatic.[22]

Within the prostatic parenchyma, testosterone of testicular origin is metabolized to dihydrotestosterone (DHT) by the enzyme 5 -reductase.[34] Although both androgens stimulate prostate growth and secretions, DHT is far more biologically active in that it binds to the androgen receptor with twice the affinity of testosterone and has a 5 fold slower rate of dissociation.[34] In addition to glandular epithelial cell hyperplasia and hypertrophy, intraparenchymal cyst formation may result from obstruction of parenchymal ducts, causing accumulation of prostatic secretions.[27-28] Prevalence of intraparenchymal cysts in asymptomatic dogs with BPH is 14%.[4,35] In addition to glandular epithelial cell hyperplasia and hypertrophy, intraparenchymal cysts may predispose prostate to bacterial infection.[27-28]

**Diagnosis of Prostatitis**

Prostatic fluid collection and evaluation

Collection and analysis of prostatic fluid is an essential part of diagnosing prostatitis. Prostatic fluid may be obtained by ejaculation, prostatic wash, or fine-needle aspiration.[5] Prostatic fluid can be collected aseptically by ejaculation as long as care is taken to change collection containers following collection of combined sperm-rich fraction and that the tip of the penis does not touch inside of sterile collection container. Technique for prostatic massage has been previously described.[36] Unlike with ejaculation, there can be uncertainty as to whether a prostatic fluid has been collected using prostatic massage. Technique of fine-needle aspiration for collecting prostatic fluid samples has been described.[2] In many instances, fine-needle aspirate samples are nondiagnostic. To improve success with sample collection, aspiration should be performed as needle is redirected several times within the prostate gland. In addition, negative pressure should be slowly released before needle is withdrawn. Complications associated with fine-needle aspiration include periprostatic haemorrhage and abscess formation.[36-38] It is important to note that urine bacterial culture results are well correlated with prostatic fluid culture results, such that a cystocentesis may be a safer alternative to a fine needle aspirate of the prostate if prostatic fluid could not be collected by other methods.[7] There is a strong correlation ($r = 1$) between urine and prostatic fluid culture when compared to culture of prostatic tissue (all dogs with a positive fluid culture had *Escherichia coli* (*E. coli*) isolated from the prostatic tissue and all dogs with negative fluid cultures had negative prostatic tissue cultures).[19]

Prostatic fluid evaluation is highly diagnostic for prostatitis. However, in contrast to humans, prostatic fluid pH, specific gravity and cholesterol zinc concentrations are not reliable indicators for chronic prostatitis.[39] Prostatic fluid should be assessed by culture and cytologic evaluation. Recovered fluid should be centrifuged at 1000 x g for 10 minutes and the resultant pellet used for both culture and cytology.[24] Sample should be submitted for aerobic culture and sensitivity.[20] It is important to isolate the type of bacteria present, as well as quantify bacterial count, in order to correctly interpret findings.[40-41] Quantitative bacterial cultures yielding > 100,000 bacteria of a single species/ml of prostatic fluid or > 2 $\log_{10}$ one or more bacterial species in prostatic fluid samples over the number of colonies of the same species in paired urethral or urine samples are indicative of prostatic infection.[11,14,41] Heavy growth of a pure culture of gram-negative bacteria occurs in > 70% of cases.[2,5,40]

Remaining sample should be used for cytology.[24] Normal prostatic cytology will have parabasal epithelial cells usually with very low numbers of red blood cells and neutrophils (typically < 5 red blood cells or polymorphonuclear neutrophils per high-power field). In prostatitis with BPH, cytology evaluation of prostatic fluid reveals epithelial dysplasia with a significant number of neutrophils that may have degenerative changes and perhaps intracellular bacteria.[24] However, a lack of neutrophils on prostatic cytology does not entirely rule out prostatitis, because neutrophils may be in a distinct segment of the prostate that is not communicating with the secretory ducts.[24] In cases of chronic prostatitis, inflammatory component may be reduced or confined to predominately mononuclear cells (macrophages, lymphocytes, plasma cells).[5,7,42-44] Inflammatory changes in prostatic fluid are associated with histological inflammation in > 80% of cases.[2,19,41,45-46]

Etiologic agents

Most common isolate in bacterial prostatitis is *E. coli*.[5,20] However, a reliable discriminatory typing scheme to differentiate commensal nonvirulent strains commonly found in the lower urinary tract from specific pathotypes of *E. coli* does not exist for dogs.[47] In humans, *E. coli* isolates that infect the prostate have several virulence attributes (e.g. a group I or group II capsule synthesis gene and some of the iron uptake related genes (such as *irp*, *fyuA*, or *iutA*), as well as at least 1 of the following adhesin related genes: *pap* (P fimbriae), *sfa* or *foc* (S/F1C fimbriae), *afa* or *dra* (Dr binding adhesins).[48] Presence of adhesin-associated genes (*fimA*, *fimH*, *papC*, and *sfaD*) was positively associated with a hospital stay for 1 or more days at the time of infection.[49] In addition, a uropathogenic *E. coli* subpathotype has been positively associated with development of prostatitis in men.[49] To be classified as uropathogenic *E. coli*, isolates must contain the hemolysin gene *hlyA*, cytotoxic necrotizing factor *cnf1*, uropathogenic-specific protein *usp*, and iron uptake related genes. Investigations in dogs are needed to identify specific factors and/or genes that promote prostatic virulence.

In addition to *E. coli*, any opportunistic bacteria ascending from the urethra can cause prostatitis. In decreasing order of incidence: *Staphylococcus* sp., *Pseudomonas* sp., *Klebsiella* sp., *Proteus* sp., *Enterobacter* sp., *Pasteurella* sp., and *Hemophilum* sp., *Streptococcus* sp., and *Ureaplasma* sp. have all been isolated from cases of bacterial prostatitis in dogs.[2,15-16,22,30,41] Infections with anaerobic bacteria have not been reported.[16,22,31] *Brucella canis* has been isolated in cases of both acute and chronic prostatitis.[5,15,50] A pure culture of *Mycoplasma canis* has also been isolated from the ejaculate of a dog with chronic prostatitis.[51] However, several *Mycoplasma* species are commensal to the lower urinary tract of healthy dogs.[52-54] *Borrelia burgdorferi* has been detected by PCR in urine from dogs with prostatitis, but more research is needed to determine if this organism can contribute to prostatitis.[55-56] Additionally, histologic examination of a biopsy from a dog with chronic prostatitis yielded *Leishmania* sp., although bacterial culture was negative.[57] Prostatitis from *Trueperella pyogenes* has been usually described in cattle, goats, sheep, and horses, but not in dogs, which may be because these bacteria are not a normal flora of this species.[58-61] Although not bacterial, prostate infections with fungal organisms (*Blastomyces dermatitidis*, *Cryptococcus neoformans*, or *Coccidioides immitis*) occur infrequently and usually part of a systemic fungal infection.[15,61-63]

## Treatment

Successful treatment of prostatitis depends upon which form of the disease is present. Acute prostatitis requires aggressive therapy.[17] Intravenous fluid and nonsteroidal anti-inflammatory drug (NSAID) administration are usually used. In acute prostatitis, blood–prostate barrier is broken, resulting in an easy penetration of antibiotics and other drugs into the gland, independent of pH and oil solubility of the active compound.[2] Therefore, any antimicrobial selected based upon culture and sensitivity results would be appropriate.[20] Drugs such as broad-spectrum penicillin derivatives or a third-generation cephalosporin may initially be used to good effect.[24] Antimicrobials must be selected more carefully in cases of chronic prostatitis because the blood-prostate barrier is generally intact[20] (refer below). Castration is not recommended in the immediate management of acute prostatitis because of the increased

risk for formation of scirrhous spermatic cords and therefore should be postponed for 4 weeks after clinical resolution.[15]

For chronic prostatitis, treatment goals must include both antimicrobials (to treat infection) as well as reducing prostatic hyperplasia (to eliminate the predisposing cause). For chronic prostatitis, antimicrobial selection must be based upon culture and sensitivity (or targeted to *E. coli* without culture results), in addition to the pharmacokinetics of the antimicrobial.[5] Most antimicrobial agents useful against uropathogenic bacteria diffuse poorly into prostatic tissue (blood-prostate barrier). Blood-prostate barrier prevents diffusion of drugs that are highly protein bound in plasma from entering prostatic fluid in therapeutic concentrations.[15] In addition, ability of an antimicrobial to cross an epithelial membrane depends on its lipid solubility and its pKa (acid dissociation constant).[16,64] Blood-prostate barrier permits access only to lipophilic drugs and those not highly bound to proteins.[24] Drugs with low lipid solubility do not cross epithelial membranes (e.g. ampicillin, penicillin, cephalothin). The pKa is the pH at which a drug exists equally in both ionized and non-ionized forms. Only nonionized forms can cross epithelial membranes. Basic drugs (e.g. trimethoprim-sulfamethoxazole, erythromycin) diffuse easily from blood (pH 7.4) to the more acidic prostatic environment (pH 6.1 - 6.5).[5,7,65-68] These drugs become concentrated on the side with the greatest ionization (greatest charge; e.g. the acidic canine prostatic fluid).[69] However, when surveyed, 30% of veterinarians said that they would prescribe amoxicillin-clavulanate, a drug with poor penetration into prostate tissues.[70] Both chloramphenicol and enrofloxacin (a fluorinated quinolone) can readily cross epithelial membranes regardless of their pH, due to their zwitterion characteristics.[5,64,71] Zwitterions are neither purely acidic nor basic because they have 2 ionizing groups, one positively charged and one negatively charged.[24] Zwitterions have 2 or more pKa values and at their isoelectric point, least amount of the drug is uncharged; whereas at higher or lower pH values, more drug is ionized and is therefore less diffusible.[72]

Trimethoprim has good broad-spectrum activity, but is not effective against anaerobic infections.[17,24] Pairing with a sulfa drug (trimethoprim-sulfadiazine 15 mg/kg every 12 hours orally) does not seem to affect prostate penetration.[20,73] Long-term treatment with trimethoprim, as is required for prostatitis cases, can lead to deleterious idiosyncratic and immune-mediated adverse effects, such as keratoconjunctivitis sicca, hepatopathy, anemia, folate deficiency, hypersensitivity, and skin eruptions.[20,24] With prolonged therapy, a baseline Schirmer tear testing is recommended with periodic reevaluation and owner monitoring for ocular discharge. Erythromycin crosses the prostate epithelium similar to trimethoprim but has poor action against gram negative bacteria.[74] Erythromycin should not be used until a culture and sensitivity show that the pathogenic bacteria are gram-positive organisms and are sensitive to this drug.[24] Chloramphenicol (40 - 50 mg/kg every 8 hours orally) is often reserved for multidrug-resistant infections or anaerobic bacterial infections.[20] Not only can myelosuppression occur in dogs with long-term therapy, humans are at risk for developing idiosyncratic aplastic anemia from the chloramphenicol.[20] In general, chloramphenicol is antagonistic with enrofloxacin and other fluoroquinolones.[75]

Enrofloxacin has a low molecular weight, which favors tissue penetration. Enrofloxacin penetrates prostate well and distributes not only into extracellular fluid but also into the intracellular space.[76-79] Enrofloxacin has an antimicrobial spectrum that includes most bacteria that cause prostatitis.[80] In general, enrofloxacin has excellent activity against *Enterobacteriaceae* sp. and *Pseudomonas* sp.; good to moderate activity against *Staphylococci*, *Mycobacteria* sp., *Chlamydia* sp., *Mycoplasma* sp., and *Ureaplasma* sp.; and little or no activity against *Streptococci* sp., *Enterococci* sp., and anaerobic bacteria.[74] Minimum inhibitory concentration (MIC) of enrofloxacin is low (range: 0.01 to 2.0 μg/ml).[81] Enrofloxacin is approved for use in dogs for treatment of urinary tract infections, although it is used in an extralabel manner for treatment of prostatitis (e.g. doses of 10 - 20 mg/kg once daily orally).[20] Enrofloxacin achieves maximum prostatic fluid and tissue concentrations (1.4 pg/ml) that exceeded serum concentrations and remained above MIC for at least 6 hours.[81] Enrofloxacin has anecdotally increased frequency and intensity of seizures in epileptic dogs.[82] After repeated administration of enrofloxacin, hepatic clearance is decreased and elimination half-life of theophylline and caffeine are increased, reportedly by decreasing demethylation of theophylline by hepatic P450 enzymes, 4-oxoquinolone

metabolite.[83-85] In addition, crystalluria can occur in dogs at high doses of enrofloxacin.[75] Noninflammatory, erosive arthropathies can be observed in growing animals treated with enrofloxacin or other fluoroquinolones.[75] These erosions are preferentially located at weight-bearing joints.[86] Articular cartilage forms vesicles after several moderately large doses, which can then progressively rupture and produce cartilaginous erosions.[75] This observation is due to an early phase burst in oxidative metabolism in immature (but not mature) chondrocytes that may precipitate cell death.[87-88] For this reason, immature large breed dogs should not be treated with fluoroquinolones.[75]

It is of interest to point out that ciprofloxacin does not concentrate in prostate the same way enrofloxacin does.[81,89] Fluoroquinolones differ from each other by substitutions in their chemical ring structure, which can affect the particular isoelectric point and therefore, their tissue penetration.[81] In addition, it is also possible that differences in serum protein binding of each quinolone may account for lack of tissue penetration.[81] In dogs, a therapeutically equivalent dose of ciprofloxacin has been suggested to be 4 - 5 times the dose (on a mg/kg basis) of enrofloxacin.

Antimicrobial treatment of chronic prostatitis requires prolonged treatment for 6 - 12 weeks, regardless of earlier disappearance of clinical signs.[5,24] Potential side effects of a long-term antibiotic treatment include bacterial resistance, liver dysfunction, renal dysfunction, anemia (high risk for chloramphenicol, fluoroquinolones), arthropathy (fluoroquinolones) and some possible complications of trimethoprim administration (e.g. hypothyroidism), urolith formation or keratoconjunctivitis sicca.[16,90] Follow-up urine and prostatic fluid cultures should be performed prior to ending and 30 days after ending therapy to assure resolution of infection.[5]

Prostatic hyperplasia can be reduced by castration in dogs without valuable breeding potential.[24] Prostatic size is significantly reduced (> 70%) within 7 - 14 days following castration and completely involuted in 4 months.[5,16,91] As a result of rapid prostatic atrophy, clearance of infection from cases of chronic prostatitis occurs more than twice as fast compared to intact dogs.[19] Although medical management of BPH is not as effective as castration in reducing prostatic size, it is a viable option for valuable breeding dogs.[92] Finasteride, a 5 -reductase inhibitor, prevents conversion of testosterone to DHT[93-94] and produces a dose-dependent regression in prostate size.[95] At a daily oral dose of 0.1 - 0.5 mg/kg (maximum 5 mg per dog per day) for 16 weeks, finasteride decreases prostatic diameter, prostatic volume, and serum DHT concentration by 20, 43, and 58%, respectively.[16,91]
A 50 - 70% decrease in prostatic volume has been noted after 16 - 53 weeks of treatment.[92-93,96-98] This is enough of a reduction in size and function to cause a resolution of clinical signs in most cases.[24] Treatment can then be tapered to administration every 2 - 3 days, but must be continued as effects of finasteride are reversible in < 8 weeks after treatment is discontinued.[91] Therefore, the recommendation is to continue finasteride treatment continuously until breeding career of dog is over and castration can be performed. Unlike GnRH agonist or immunotherapies available in other countries for treating canine BPH, finasteride does not alter LH secretion, so semen quality or quantity and fertility are not adversely affected.[5,98] Semen volume, however, is significantly reduced. Finasteride is teratogenic to male fetuses especially during early gestation so pregnant women should have someone else medicate their dogs. However, teratogenic effects should not be an issue in dogs because female dogs are not treated with finasteride and the half-life of finasteride in semen is low enough to not be a teratogenic concern at the time of breeding.[24]

Ancillary therapies for treatment (or prevention) of prostatitis

D-mannose is a sugar that competitively binds to mannose-fimbriae on uropathogenic strains of *E. coli*, thereby inhibiting adhesion to epithelium.[99] It has been used to prevent recurrent urinary tract infections in humans, but there have been no studies of clinical efficacy in veterinary patients for urinary tract or prostatic infections.[20] An extrapolated anecdotal dose for dogs is one-quarter teaspoon per 20 pounds of body weight orally 3 times daily.[20]

Proanthocyanidin is the “active ingredient” in cranberry. It alters phenotypic expression of fimbriae on uropathogenic *E. coli*, which subsequently inhibits bacterial adherence to epithelial cells.[100] A meta-analysis reviewed effects of supplementing with cranberry products in 1049 human subjects, and

treated group had fewer urinary tract infections over 12-month observation period compared to placebo.[101] However, there has not been adequate research using cranberry products in dogs.[102] In addition, quality and potency among over-the-counter products is extremely variable, making it impossible to provide recommendations on safety or efficacy of this method.

In humans, there is great interest in the use of probiotics. Probiotics are a form of bacterial interference and recommended as a treatment and preventive measure for recurrent urinary tract infections in women. *Lactobacillus* sp. create an acidic environment that inhibits uropathogenic *E. coli* colonization, modulates host immune function, and may also downregulate virulence factor expression in pathogenic bacteria.[103] Two studies in dogs evaluated efficacy of probiotics and reported no significant differences in vaginal microflora.[104-105] However, prospective studies are needed in male dogs to evaluate potential role of probiotics for treatment and prevention of prostatitis.

A biofilm is composed of organisms adhered together by a self-produced polysaccharide matrix.[106] Some bacteria have the capacity for biofilm formation, which facilitates colonization.[106-107] It has been suggested that as bacteria within biofilm become sessile, they are protected from immune system. They are also immune to antimicrobial treatment and are inherently resistant to even shear force removal.[106] Strategies used to prevent biofilm formation have included silver coating, nanoparticles, iontophoresis, urease and other enzyme inhibitors, liposomes, bacteriophages, quorum sensing inhibitors, and vibroacoustic stimulation.[20] Research is needed in understanding how biofilms contribute to pathogenesis of canine prostatitis.

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