Canine Prostate Disease

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KEYWORDS

- Prostate • Benign prostatic hyperplasia (BPH) • Prostatitis • Prostatic neoplasia
- Canine prostate-specific arginine esterase (CPSE)

KEY POINTS

- All intact, male dogs eventually develop benign prostatic hyperplasia and a subset will develop clinical signs associated with subfertility, discomfort, or infection.
- Any male dog may develop neoplasia associated with the prostate, with a higher proportion of neutered males being affected.
- Ultrasound imaging and prostatic tissue cytology remain the most reliable diagnostic tests for canine prostate disease, but canine prostate-specific arginine esterase shows value as a supporting diagnostic test.
- Older recommendations to treat prostatitis for 4 to 8 weeks with appropriate antibiotics have been updated to now recommend a truncated 4-week treatment regime for acute cases.
- Medical treatments for benign prostatic hyperplasia have variable effects on prostate size and function, and may affect androgen production.

Video content accompanies this article at http://www.vetsmall.theclinics.com/.

INTRODUCTION

The prostate is the only accessory sex organ in dogs. Diseases of the canine prostate are relatively common. The canine prostate is constantly developing and growing under androgenic influence throughout the life of the intact male dog. This androgenic influence seems to have a protective effect in the case of neoplastic disease,[1–3] but the increase in size under androgens also predisposes the canine prostate to infection and cystic disease.[4–6] The consequences of these diseases range from mild discomfort to varying effects on semen quality to very painful or life-threatening illness. An evolving understanding of the way the canine prostate functions has led to expanded diagnostic options and recent changes in treatment recommendations for some of these conditions. Each prostatic condition is discussed separately.

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PROSTATIC ANATOMY AND PHYSIOLOGY

The prostate in the dog is a bilobed, oval to spherical-shaped organ with both a dorsal and ventral sulcus that sits in the cranial pelvic canal or in the caudal abdomen. The proximal urethra runs through the prostate between the 2 lobes. Testosterone is converted to dihydrotestosterone (DHT) via the enzyme 5α-reductase and it is this androgen, DHT, that stimulates prostatic development, growth, and secretions.[7] The enzyme 5α-reductase is found in 2 isoenzymes in the body, types 1 and 2. Each isoenzyme is encoded by a different chromosome, but common coding sequences indicate a common evolutionary precursor. Isoenzyme type 1 is found throughout the body, including the skin, liver, and prostate. Isoenzyme type 2 is found predominantly in the prostate and other genital tissue. Testosterone and DHT both bind to the same androgen receptors and cause the same effects. The binding of DHT to the androgen receptor, however, is much tighter and of longer duration than that of testosterone. The resultant effect is that lower concentrations of DHT cause an amplified response compared with testosterone.[8,9] This mechanism is important to consider when discussing medical treatment of BPH elsewhere in this article.

Benign Prostatic Hyperplasia

The disorder consists of both cellular hyperplasia and hypertrophy.[10] The prostate exhibits continual, androgen-dependent growth, eventually exhibiting hyperplasia and hypertrophy that is, sensitive to estrogens, which increase androgen receptors, leading to more hyperplasia.[11,12] Although benign prostatic hyperplasia (BPH) can be present as early as 1 year of age, it does become increasingly more prevalent as intact dogs age (**Table 1**).[13] Approximately one-half of intact male dogs will have histologic signs of BPH by 4 years of age and more than 90% by 8 years of age. Most dogs with BPH do not show any clinical signs and, therefore, require no immediate treatment, although preventative treatment has been advocated and is discussed elsewhere in this article. Clinical signs may include sanguinous prostatic fluid dripping from the prepuce, hematospermia, hematuria, dysuria, constipation, or tenesmus.[14]

Dogs with BPH will show signs of subfertility, often accompanied by a marked number of red blood cells in the prostatic fluid. Spermatozoa from dogs with BPH have

Table 1 Prevalence of BPH by age	
Age Range (y)	**Total Prevalence of Canine, n/N BPH (%)**
0.1–1.0	0/25 (0)
1.1–2.0	3/19 (16)
2.1–3.0	8/25 (32)
3.1–4.0	9/21 (43)
4.1–5.0	5/9 (56)
5.1–6.0	34/39 (87)
6.1–7.0	15/18 (83)
7.1–8.0	9/10 (90)
8.1–9.0	27/28 (96)
9.1–10+	25/27 (93)

Abbreviation: BPH, benign prostatic hyperplasia.

Modified from Berry SJ, Strandberg JD, Saunders WJ, et al. Development of canine benign prostatic hyperplasia with age. Prostate 1986;9(4):363–73; with permission.

increased DNA fragmentation and increased numbers of primary morphologic defects.[15] Dogs with BPH are predisposed to prostatitis and cystic disease (discussed elsewhere in this article); indeed, these conditions are extremely rare in neutered male dogs with smaller prostates.

BENIGN PROSTATIC HYPERPLASIA DIAGNOSIS

The prostate should be digitally, transrectally palpated. In some dogs with advanced BPH, the prostate will have fallen cranially into the abdomen and cannot be palpated initially transrectally. In these cases, it is often helpful to gently lift up on the caudal abdomen to push the prostate back into the pelvis where it can be reached transrectally with the clinician's finger. Each of the 2 lobes of the prostate should be symmetric in size and shape. The consistency should be firm, but not hard. Gentle palpation of the prostate should not be painful to the dog with simple BPH. In this way, it is possible to gain a subjective opinion about the size, shape, and consistency of the prostate.

Objective measurements must be done with transabdominal ultrasound evaluation. Three-dimensional measurements can be taken of length, width, and height. A linear or curvilinear probe (5.0–8.0 mHz) may be used (Fig. 1, Video 1). Clipping is usually not necessary because of the scarcity of hair in the inguinal region. Acoustic gel and alcohol should be applied to obtain diagnostic images. The dog may be in a standing position, but can also be placed in lateral or dorsal recumbency. The probe is placed lateral to the prepuce in both transverse and sagittal orientations to obtain length (sagittal), width (transverse), and height (both transverse and sagittal) measurements. Accurate sagittal images are confirmed by observing the hypoechoic urethral tract. At least 3 views in each orientation should be obtained and the average measurement for each dimension used. The volume of the prostate may then be calculated by using the ellipsoid formula of length × width × height × 0.523 (where height is the average of the transverse and sagittal measurements). Normal prostatic measurements for dogs of
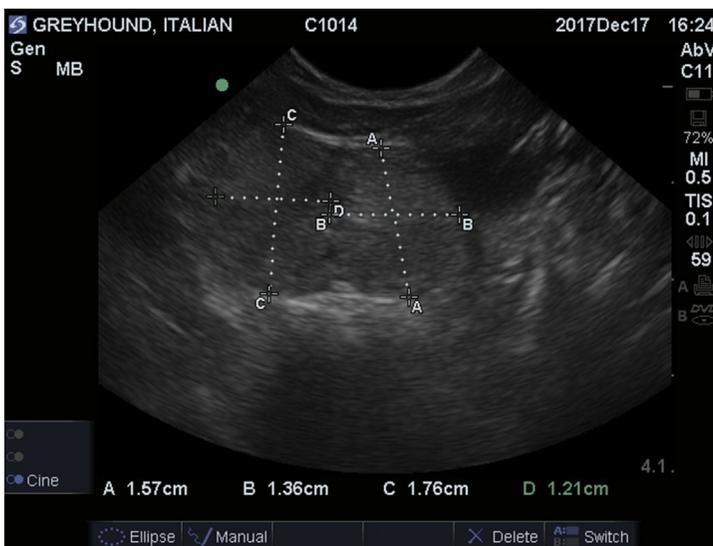
Fig. 1. Cross-sectional view of the prostate from a 6-year-old, intact Italian Greyhound. The bladder is visible to the right. The prostate is enlarged, but homogeneously echogenic, consistent with benign prostatic hyperplasia.

different ages and weights have been published.[16,17] The maximum predicted value (containing 97.5% of the normal population) for prostate volume may be calculated by using the following formula,[16] where BW is body weight and A is age:

$$V = (0.867 \times BW) + (1.885 \times A) + 15.88$$

The echogenic texture and uniformity should also be evaluated with ultrasound imaging. Normal prostatic parenchyma is uniformly echogenic throughout the organ (see **Fig. 1**). The hypoechoic urethra may be located between the 2 lobes. Any distinct hyperechoic or hypoechoic areas should be evaluated closely and likely indicate pathologic changes, like neoplasia, inflammation, or cystic disease. Enlargement of the prostate with a uniformly echogenic parenchyma is consistent with BPH.

Prostatic fluid evaluation is highly diagnostic for prostatic disease.[18] Prostatic fluid may be obtained through massage and aspiration or through collection and fractionation of an ejaculate. Fluid may be obtained by passing a lubricated, flexible catheter, such as a red rubber catheter, up the urethra to the level of the prostate (palpable transrectally). Then, 1 to 2 mL of sterile saline are infused slowly while the prostate is massaged transrectally and then aspirated back into the syringe.

Simply collecting and fractionating an ejaculate can obtain an even more voluminous sample with greater concentration of potentially diagnostic material. The canine ejaculate consists of 3 fractions. The second fraction comes from the epididymis and is the sperm-rich fraction. The first and third fractions come from the prostate, with the third fraction being the greatest in volume. Most intact, male dogs can be stimulated to ejaculate with manual stimulation into either an artificial vagina or into funnels, although males with painful prostatic conditions may be reluctant to ejaculate. The artificial vagina or funnel should have a plastic reservoir attached for collecting the fluid. By switching the collection device after each subsequent stage of ejaculation, the prostatic portion of the ejaculate may be separated from the sperm-rich fraction. The third fraction from a normal prostate is clear. Any detectable turbidity or color indicates cellular material or fat.

Recovered fluid is centrifuged at $1000 \times g$ for 10 minutes and the resultant pellet can be used for both culture and cytology. The culture sample should be submitted for both aerobic growth. The portion used for cytology can be rolled gently onto a slide, air dried, and stained with a Romanowsky stain, such as Diff-Quik. 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) and spermatozoa from the second fraction. Dogs with BPH may have dramatically increased numbers of RBC's (>20 per high-power field) in semen, which generally appears pinkish to red before centrifugation. Large numbers of prostatic epithelial cells are obtained and have a mosaic appearance.[19]

If cytology samples cannot be obtained via ejaculation or massage and aspiration, ultrasound-guided fine needle aspiration can also be used to obtain prostatic samples for histologic analysis.[18] Concerns for spreading infection or neoplastic cells are often raised, but there is a lack of evidence of this actually occurring in either human or veterinary literature. This technique is commonly used because many veterinarians are comfortable with ultrasound examinations, but lack experience in manual collection of ejaculates. Evidence also suggests that prostatic tissue sample culture is more specific than culture of prostatic fluid.[20]

Studies of canine prostate-specific arginine esterase have indicated that elevated serum concentrations of this enzyme correlate well with histologic evidence of BPH.[21,22] This assay may be used if other diagnostics are not available or

inconclusive. Canine prostate-specific arginine esterase may also help to screen dogs with preclinical cases of BPH for proactive, preventative treatment options. A commercial laboratory test, using an enzyme-linked immunosorbent-type immunoassay, has been developed that can diagnose BPH using a blood sample (Odelis canine prostate-specific arginine esterase, Virbac, Carros, France). This assay is sensitive (97.1%), specific (92.1%) and shows good repeatability (intraassay coefficient of variation of <3.1%; interassay coefficient of variation of <6.7%).[23] The specific hardware necessary to process the assay is available in Europe and currently undergoing market trials in North America.

BENIGN PROSTATIC HYPERPLASIA TREATMENT

Treatment for BPH focuses on eliminating or decreasing androgen stimulation of the prostate. Orchidectomy is clearly the most effective treatment because it will remove all androgenic stimulation. For nonbreeding males, castration is the treatment of choice and results in marked decrease in size of the prostate (80% by 12 weeks after castration) and dramatic decrease in serum DHT concentrations within days to weeks of surgery.[24,25] For the breeding male, medical options are available. Resolution of BPH is achieved by removing the androgen source of prostatic stimulation. This review considers treatments including 5α-reductase inhibitors, androgen receptor inhibitors, androgen antagonists, aromatase inhibitors and other antiestrogen therapies, and gonadotropin-releasing hormone (GnRH) agonists. Treatments of the past that are no longer in widespread use owing to serious adverse effects, such as estrogens, are not discussed in this review. In men, lower urinary tract symptoms are common sequelae of BPH and an effective treatment is the use of α_1-adrenergic receptor antagonists to relax smooth muscle in the lower urinary tract.[26] Because this issue is not usually a concern in dogs owing to a relative lack of smooth muscle in the canine prostate, this treatment is not used and is not discussed herein.

BENIGN PROSTATIC HYPERPLASIA TREATMENT: ANTIANDROGENS
Finasteride

In North America, the best medical choice for treatment of BPH in dogs is finasteride, an azasteroid that at selectively inhibits the action of 5α-reductase type 2, thus, reducing the conversion of testosterone to DHT,[8] preserving testosterone concentrations while eliminating the production of DHT. The removal of DHT significantly decreases androgenic stimulation to the prostate, which consequently reduces in size owing to apoptosis of prostatic cells.[27] The prostate will reduce by nearly one-half (43%) by 16 weeks of treatment (0.1 mg/kg orally once per day, not to exceed 5 mg per dog per day).[28] A 50% to 70% decrease in prostatic volume has been noted after 16 to 53 weeks of treatment.[29–33] This is enough of a reduction in size and function to cause a resolution of clinical signs in most cases. Treatment can then be tapered to administration every 2 to 3 days, but must be continued for the life of the dog or the prostate will again increase in size and predispose the dog to recurrent clinical signs. Because testosterone itself is not inhibited, its effects on libido and spermatogenesis are preserved.

In humans, side effects include erectile or ejaculatory dysfunction and teratogenic effects in pregnant women, predictably with regard to sexual differentiation in male fetuses. Problems with libido and fertility have not been reported with dogs. In fact, reports indicate normal fertility and libido in dogs on finasteride.[32] Teratogenic effects should not be an issue in dogs because female dogs do not receive finasteride directly. Some veterinary clinicians have reported concerns about male dogs passing

the drug onto females through the semen in mating, but passage of the drug in the semen has not been shown to be a concern in humans, the half-life of finasteride is short enough to not be a teratogenic concern even if it were passed in the semen, and humans may have sexual relations during pregnancy, whereas dogs do not. Semen in natural mating in canines is deposited in the cranial vagina and then it is thought that the continual secretion of large volumes of prostatic fluid during ejaculation of the third fraction pushes the sperm-rich fraction through the cervix into the uterus. The use of finasteride greatly decreases the volume of the third fraction, raising the concern that fertility will be decreased in natural matings using male dogs that are receiving finasteride. This concern has led to a variety of anecdotal dosing strategies among clinicians, including discontinuing the use of finasteride a week or two before an anticipated mating, reducing the dosing schedule to once every few days, or only putting the male on finasteride once a year for a few months. One study has tested the fertility of dogs on an active finasteride protocol and found no effect on fertility,[32] so although the concern regarding use of finasteride during natural mating programs makes sense, it may be unwarranted. Certainly, more studies on appropriate dosing regimens for finasteride are needed in the dog. The conventional wisdom at this point would be to continue finasteride treatment (somewhat) continuously until the breeding career of the dog is over, and then consider castration.

Osaterone Acetate

Osaterone acetate (Ypozane, Virbac) is a testosterone analogue with potent antiandrogenic activity attributed to competitive binding to androgen receptors, as well as the overall reduction of androgen receptors, reduction of 5α-reductase, and the inhibition of testosterone transport into prostate cells.[34] In 1 trial, osaterone was administered at a dose of 0.25 mg/kg orally once daily for 7 days to 73 dogs with clinical signs of BPH. By 14 days after the start of the trial, nearly one-half of the dogs had resolution of clinical signs and a 38% average reduction in prostate volume was noted. By 6 months after the start of the trial, 84% of dogs had resolution of clinical signs.[34] Using this same dosing regimen, it was determined that peak serum concentrations were reached by day 7, which may explain the initial rapid effect and then slow tapering of effects in the following weeks.[35] Semen quality and fertility do not seem to be negatively affected by osaterone and may, in some cases, improve.[36] Ypozane is marketed in France and available in some countries in the European Union. It is not licensed in the United States.

BENIGN PROSTATIC HYPERPLASIA TREATMENT: PROGESTINS
Medroxyprogesterone Acetate

Progestins exhibit antiandrogen activity and, therefore, have been used to treat BPH. The antiandrogenic action of progestins is likely due to competitive binding with the androgen receptors and/or suppression of luteinizing hormone secretion via negative feedback.[37] Dogs in 1 study were treated for BPH with medroxyprogesterone acetate and, although 84% showed a decrease in clinical signs, only 53% showed a decrease in prostate volume after 6 weeks of treatment.[38] No effect was noted on semen quality or libido. Concerns regarding the development of diabetes mellitus or mammary nodules have precluded its popular use for BPH treatment.

Delmadinone Acetate

Delmadinone acetate (Tardak, Pfizer Animal Health, Sandwich, Kent, UK) is a progestin with 17 times more potent antiandrogenic activity than progesterone.[34] Treatment of 69 dogs with clinical signs of BPH using a single intramuscular or subcutaneous injection of

3 mg/kg of delmadinone resulted in complete remission of clinical signs by 14 days after the injection in nearly one-half of the dogs and in 83% of the dogs by 6 months after the injection. At 14 days after the injection, a 28% decrease in prostate volume was noted.[34] One of the 69 dogs in the trial developed hypoadrenocorticism, which required treatment to resolve. In another study, delmadinone was administered at a dose of 1.5 mg/kg as a subcutaneous injection at 0, 1, and 4 weeks; adrenocorticotropic hormone and cortisol concentrations were measured during the trial. Adrenocorticotropic hormone stimulation tests were also conducted. There was a significant decrease in basal and 2 hours after adrenocorticotropic hormone stimulation concentrations of cortisol in treated dogs compared with control dogs. The authors concluded that treated dogs may be at risk for developing glucocorticoid insufficiency during treatment if subjected to stressful events.[39] Other side effects were of minimal importance, transient, and affected very few of the dogs; these included increases in appetite, behavior changes, vomiting, diarrhea, asthenia, polyuria, and polydipsia. In a separate study, male beagle dogs given an single injection of 1 mg/kg of delmadinone showed a temporary change in the maturation of epididymal spermatozoa.[33] Tardak is marketed in the UK and currently licensed in Austria, Belgium, Finland, France, Luxemburg, the Netherlands, and the UK. It is not licensed in the United States.

BENIGN PROSTATIC HYPERPLASIA TREATMENT: ANTIESTROGEN THERAPY
Tamoxifen Citrate

Estrogens have been thought to play either a causative or permissive role in the pathogenesis of BPH.[11] Tamoxifen citrate is an antiestrogen drug, marketed under various trade names for breast cancer treatment in women, that has been given at a dose of 2.5 mg per dog once daily for 28 days in male dogs with clinical BPH.[40,41] Prostatic volume decreased by 28% to 50% during the treatment period and volume of the third fraction decreased to a few drops or was absent. Prostate size returned rapidly to or less than pretreatment size after treatment ceased. Testicular size, spermatozoal motility, and normal morphology, libido, and serum testosterone concentration all showed dramatic decreases during treatment, some disappearing altogether, but all gradually returned to pretreatment levels by the end of the monitoring period. Bitches bred to 3 of the male dogs conceived and whelped normal litters. No systemic side effects were noted during the treatment period. Tamoxifen may represent a treatment option. It offers a rapid prostatic response and an apparently reversible contraceptive effect, at least with limited use.

Anastrazole

Anastrazole (Arimidex, AstraZeneca, Cambridge, UK) is a potent, highly selective aromatase inhibitor with no intrinsic hormonal activity that has replaced tamoxifen in many breast cancer treatment protocols for women.[42] Given to dogs at a dose of 0.25 to 1 mg per dog once daily for 28 days, a rapid decrease in prostate volume of 21% was noted with no significant changes in libido, testicular consistency, scrotal diameter, semen volume, count, motility, or morphologic abnormalities.[41] No hematologic or other clinical abnormalities were noted. Anastrazole is available in North America and may present veterinary practitioners with a more rapid alternative to protocols using finasteride.

BENIGN PROSTATIC HYPERPLASIA TREATMENT: GONADOTROPIN-RELEASING HORMONE AGONISTS
Deslorelin Acetate

Deslorelin acetate (Suprelorin, Virbac) and azagly-nafarelin (Gonazon, Intervet, Angers Technopole, France) are potent GnRH agonists that shut down luteinizing hormone

release by desensitizing the pituitary gonadotrophs to GnRH and the Leydig cells to luteinizing hormone.[43] GnRH agonists have been used in domestic dogs and in wild carnivores as a reversible contraceptive.[44–48] With no testosterone available, spermatogenesis and libido are suspended after an initial stimulatory period (and therefore no reproduction) and DHT cannot be produced; the prostate gland and testes decrease in volume by up to 60%.[49] These parameters remain suppressed throughout the duration of the treatment, slowly returning to normal ranges usually 2 to 3 months after cessation of the treatment.[44,48,50–53] Male fertility seems to be unaffected after recovery from the treatment.[50,52] Suprelorin must be administered every 6 to 12 months, depending on the formulation used, for as long as suppression is desired. GnRH agonists may be very useful in treating dogs for BPH in situations when nonsurgical, reversible contraception is also a goal during the treatment period. Clients should be aware that reversal times are highly variable, unpredictable, but may be hastened by removal of the implant. GnRH implants are not available commercially for use in dogs in North America at the present time.

PROSTATITIS

Dogs experiencing BPH are predisposed to developing prostatitis. Reports of prostatitis in castrated male dogs are rare and often have a history of recent castration before presentation. Clinical signs of prostatitis will vary largely depending on the chronicity of the infection, with acute cases showing more serious, painful clinical signs and chronic cases often presenting as subclinical. Clinical signs relate to pain, but may manifest as back pain, abdominal pain, a painful, stiff gait, or depression. Semen quality and libido may be diminished. Hematospermia, hematuria, pyospermia, and fever may be present. Because prostatic fluid constantly flows both retrograde into the bladder as well as antegrade out the prepuce, these cases can be misdiagnosed as urinary tract infections. Transrectal digital palpation of the prostate will likely elicit pain in acute cases, but may not in chronic cases. The prostate will feel enlarged in acute cases and may not be bilaterally symmetrical, especially if abscessation is present. Some chronic cases of prostatitis may not have an obvious enlargement because fibrosis may have reduced the size of the prostate. Evaluation of the third fraction of the ejaculate is very helpful, if the dog is not too painful to cooperate with manual collection. Contaminant bacteria (usually Gram-positive cocci) are usually few in number and extracellular. The third fraction of the ejaculate in cases of prostatitis generally is associated with large numbers of Gram-negative rods (although less commonly Gram-positive may be present in large numbers), many of which are inside degenerative neutrophils. Chronic cases of prostatitis also have large numbers of macrophages, with plasma cells and lymphocytes.[19,54] The collection of a sample directly from the prostate via fine needle aspiration has been discouraged because of the concern for seeding the needle track with the infectious agent, but actual evidence of this is lacking.[20] The prostatic fluid will often have a marked number of neutrophils that may show degenerative changes and may have intracellular bacteria. A lack of neutrophils in the third fraction does not entirely rule out prostatitis, because neutrophils may be in a distinct segment of the prostate, not communicating with the secretory ducts. Culture of the third fraction to determine the causative agent should be performed if prostatitis is suspected. Although *Escherichia coli* is the most common pathogen in canine prostatitis, any opportunistic bacteria ascending from the urethra may cause the infection.

Fungal causes are possible, but much less common, and usually part of a systemic fungal infection.[4,55] A complete blood count will often reveal a regenerative

leukocytosis, but some dogs may be leukopenic. Ultrasound evaluation of the prostate is valuable and usually shows a heterogenous echogenic appearance to the prostatic parenchyma; distinct hypoechoic regions correspond to abscessation.

Prostatitis Treatment

Because BPH predisposes dogs to prostatic infections, treatment aimed at reduction of the hyperplasia is warranted. For dogs without valuable breeding potential and no signs of systemic infection, castration coupled with antibiotic therapy is the preferred treatment. Otherwise, choose from one of the medical options discussed in this review for BPH treatment. Antibiotic therapy should be based on culture and sensitivity results (or be targeted to *E coli* without culture results) and should consider the unique physiology of the prostate. Owing to the profound inflammation present in acute prostatitis, the blood–prostate barrier is less functional and allows adequate diffusion of drugs that otherwise would not reach therapeutic concentrations in the prostate. Drugs such as broad-spectrum penicillin derivatives or a third-generation cephalosporin may initially be used to good effect. Once the blood–prostate barrier heals after initial improvement, however, diffusion across the barrier is limited to drugs containing specific pharmacokinetic properties and the antibiotic choice must be switched to an antibiotic with those properties. Drug penetration occurs via passive mechanisms of concentration gradients and diffusion. The blood–prostate barrier permits access only to lipophilic drugs and those not highly bound to proteins. In addition, the pH of the prostate is more acidic than the blood (canine prostatic pH ranges from 6.1 to 6.5[56,57]). The phenomenon of ion trapping further determines the concentrations of drugs across the membrane. Each drug will have a charged fraction (ionized) and an uncharged fraction. The uncharged fraction of a lipophilic drug, in a stable system, will equilibrate on both sides of the membrane. The charged portion of the drug, however, will concentrate more on one side or the other, depending on the differing pH on each side. The drug will be most concentrated on the side with the greatest ionization (the greatest charge).[58] Weak bases will, therefore, concentrate in the acidic canine prostatic fluid.

Antibiotic drugs that have proven efficacy in treating prostatic infections are discussed elsewhere in this article. Conventional recommendations have been that treatment for prostatitis should continue for between 4 to 6 weeks in acute cases and 6 to 8 weeks in chronic cases. Those recommendations are currently under review by the International Society for Companion Animal Infectious Diseases, which after review of available veterinary and human medical literature is recommending that antibiotic treatment be 4 weeks for acute cases and 6 weeks for chronic cases or cases with abscessation. Antibiotic treatment for acute cases may be even shorter if accompanied by castration, although objective data on these recommendations are lacking. The dog should be reexamined after the end of the treatment to confirm resolution of the infection.

Trimethoprim

Trimethoprim has the necessary properties to allow diffusion across the blood–prostate barrier and is a weak base with a pK_a of 7.4, therefore concentrating well in the acidic environment of the canine prostate.[59] Trimethoprim has good broad-spectrum activity, but is not effective against anaerobic infections. Pairing with a sulfa drug does not seem to affect prostate penetration.[60] Long-term treatment with trimethoprim, as is required for prostatitis cases, can lead to deleterious side effects, such as keratoconjunctivitis sica, anemia, and folate deficiency.

Fluoroquinolones The fluoroquinolones are amphoteric or zwitterionic in that they are neither purely acidic nor basic, but have qualities of both in clinical settings. They essentially have 2 ionizing groups, one positively charged and one negatively charged. At a pH somewhere in between the 2 groups, there is a minimal amount of charged drug. This is the isoelectric point. At pH values higher or lower than the isoelectric point, the amount of charged drug increases. So, if an amphoteric drug has an isoelectric point close to the pH of plasma, the drug will tend to concentrate in areas where the pH is higher or lower than that of plasma. This is the case with fluoroquinolones and why their concentrations are higher in the prostatic environment.[58] The fluoroquinolones have a good broad spectrum of activity and enrofloxacin is effective against mycoplasma infections. Some studies have indicated that ciprofloxacin may have poor bioavailability owing to decreased prostate penetration,[61–63] but other work suggests that ciprofloxacin can attain therapeutic concentrations in canine prostates.[64] The author is not aware of studies evaluating the efficacy of marbofloxacin in treating prostatitis. Fluoroquinolones do not act efficiently against anaerobic infections.

Macrolides

The macrolides diffuse very well into the prostate, but have poor action against gram-negative bacteria.[65] They should not be used until a sensitivity analysis has been obtained to show that the pathogenic bacteria are gram-positive organisms sensitive to the drug. Examples for veterinary use include erythromycin and tylosin.

Chloramphenicol

Chloramphenicol obtains good concentrations in the prostate and exhibits good activity against many anaerobes. It is highly protein bound, so high doses are required. The toxicity of chloramphenicol in humans is most likely not a concern in adult male dogs. Chloramphenicol, therefore, may be a good choice for an anaerobic prostatic infection.

PROSTATIC ABSCESSATION

Dogs with prostatic abscesses are diagnosed as prostatitis cases with signs of abscessation on ultrasound examination (**Fig. 2**, Video 2). Prostatic abscesses should be treated with the same protocols as dogs with prostatitis, using treatment targeted at BPH (castration or medical) and appropriate antibiotics for the infection. In addition, active drainage of the abscess (if the diameter is >1 cm) is often necessary either via surgical procedures or percutaneous, ultrasound-guided drainage.

Surgical drainage may be accomplished by marsupialization, Penrose drainage, or omentalization. Detailed description of each of these techniques is beyond the scope of this review, but information is available in the literature and in veterinary surgical texts.[66] A summary of each technique is presented herein.

Prostatic Abscessation Treatment

Prostatic omentalization

Omentalization is the current procedure of choice for surgical drainage of prostatic abscesses.[66] The omentum provides an alternate vascular and lymphatic supply and functions well in the presence of infection. As such, it has been used in multiple small animal surgical procedures.[67] The procedure of placing the omentum through the capsule of 20 dogs with prostatic abscessation (intracapsular omentalization) resulted in complete resolution in 19 dogs, with 1 dog showing recurrent abscessation and requiring Penrose drain placement.[68] Minimal to no postoperative complications were reported and most dogs were discharged to their owners 48 hours after surgery.

Fig. 2. Cross-sectional view of both lobes of the prostate from an 8-year-old, intact Italian Greyhound showing anechoic pockets of fluid, one in each lobe, consistent with either prostatic cysts or abscesses.

If the abscess is a paraprostatic retention cyst, and not intracapsular, omentalization may still be used to good effect.[69]

Penrose drainage
Penrose drain placement was the treatment of choice before the advent of omentalization techniques. Placement of a Penrose drain within the abscess and leading out through the abdominal wall allows continuous drainage of the abscess. Various techniques are described that differ in the exact placement of the Penrose drains.[70] The duration of time during which the drains are left in place varies with the technique from a few days to a few weeks. Active postoperative monitoring and care are necessary until drainage resolves, the drains are removed, and the wounds close. Complications may include recurrent abscessation, urinary incontinence, subcutaneous edema, anemia, sepsis, shock, hypokalemia, and hypoproteinemia.[71–74]

Marsupialization
Marsupialization is not commonly performed owing to the better postoperative results achieved by omentalization techniques. Marsupialization involves opening the abscess and suturing the edges to the skin to prevent the abscess from closing, allowing continual drainage to the exterior. For treatment of prostatic abscessation, the edges of the opened abscess may be sutured to the external abdominal skin adjacent to the prepuce, or ventral or lateral to the anus.[70] The abscess is thus allowed continual drainage as long as necessary and antibiotic or antiseptic treatments may be placed directly into the abscess. Drainage reportedly continues for 1 to 2 months, but may continue for many months in complicated cases. Active postoperative monitoring and care are necessary until drainage resolves, the drains are removed, and the wounds close. Complications potentially are the same as for Penrose drainage, and may also include fistula formation.[71–73]

PROSTATIC CYSTS

Prostatic cysts may be located within the prostatic parenchyma (retention cysts; see **Fig. 2**) or in a paraprostatic position. Prostatic cysts may not cause any clinical signs or may result in difficulties in urination or defecation. Prostatic cysts may predispose the dog to developing abscessation and, therefore, removal is often recommended, even in the absence of clinical signs. Removal of retention cysts may be done using the techniques described for abscessation, preferably omentalization. Paraprostatic cysts or abscesses do not communicate directly with the prostatic parenchyma and, therefore, local resection is often the treatment of choice.[70] Omentalization may also a good alternative.[69] Concurrent and ongoing treatment for BPH (castration or medical) is recommended.

PROSTATIC NEOPLASIA

Dogs are the only animal, besides man, with a known, significant occurrence of prostatic neoplasia. Adenocarcinomas and transitional cell carcinomas are the most common canine prostatic neoplastic diseases. Evidence suggests that prostatic neoplasia in dogs largely originates from the urothelium or ductular epithelium rather than the acinar epithelium. Neutered male dogs are predisposed to developing urinary bladder transitional cell carcinoma, prostate adenocarcinoma, prostate transitional cell carcinoma, prostate carcinoma, and general prostate tumors.[2] Genetic predispositions exist, making the risk variable for each breed.

Although there are apparent similarities in the disease between dogs and men, important differences also exist. As a result, many screening and treatment modalities used successfully in human medicine fail to be applicable in veterinary medicine. Prostatic neoplasia in men is often diagnosed in the early stages, thanks to heightened awareness and effective diagnostic screening tests (eg, the prostate specific antigen test), and depends on androgens as growth factors. Androgen deprivation therapy is a foundation therapy for men with prostate cancer and they usually respond rapidly and favorably. Most prostatic neoplasia in men is benign or slow growing. In dogs, however, prostatic neoplasia tends to be highly aggressive and metastatic. Canine prostatic neoplasia is not androgen dependent and is more commonly diagnosed in castrated males than intact males.[1–3] Reasons for the increased incidence of prostatic neoplasia in castrated dogs are unknown, but hypotheses include a loss of protective effects of androgens; a shift in the prostatic stroma from actin-positive smooth muscle cells to vimentin-positive mesenchymal cells, which may favor tumor formation; and increased longevity of castrated animals, predisposing them to age-related neoplastic diseases.[6,75] Clinical signs of prostatic neoplasia in dogs resemble those of other prostatic diseases including dysuria, dyschezia, and pain associated with the gait, back, or abdomen. Diagnosis is by history, clinical signs, an irregular painful prostate on transrectal palpation, heterogenous prostatic echogenicity on ultrasound evaluation, neoplastic cells found on cytology, or biopsy results. Cytology from prostatic wash is more likely to yield a diagnosis than an ejaculated sample. Fine needle aspiration can produce a diagnostic sample, but concern has been expressed about seeding the needle track with neoplastic cells. Usually, diagnosis is made at very late stages of the disease and survival times range from days to weeks after diagnosis.[6,76,77] Because of these differences, treatments are palliative and in some cases result in an increased quality of life for only a short time. Many treatment modalities, however, have potential, serious side effects that may result in the death or euthanasia of the dog. This underscores the need to tailor each recommendation to each specific

clinical scenario. Clients should be made aware of potential complications, that treatments may not extend the life of the dog, but may alleviate clinical signs.

Prostatic Neoplasia Treatment

Surgery

Prostatic tumors tend to be highly aggressive and metastatic. If, however, there are no signs of metastasis, total prostatectomy may be a suggested therapy. There are some considerations, however, that make total prostatectomy in the dog less likely to produce an acceptable outcome. Even if metastasis has not been documented, there is a high likelihood that it has happened and will manifest itself shortly. Owing to the location of the urethra inside the prostate, urinary incontinence is a common postoperative complication with total prostatectomy. Surgery has also not been shown to increase survival in many cases.[71,72]

Subtotal intracapsular prostatectomy has also been tested, both using traditional surgical instruments and an Nd:YAG laser. In general, survival may be up to 5 times longer than with total prostatectomy and with a lower incidence of urinary incontinence.[78–81] Survival times and postoperative complications are comparable to treatment with piroxicam alone (discussed elsewhere in this article).[77]

Transurethral resection of the prostate has been reported in 3 dogs. Palliation of clinical signs postoperatively was rapid, but survival times remained short and complications included urinary tract infection, seeding of the tumor, and urethral perforation.[82]

Surgical therapy may alleviate clinical signs in some cases, but is associated with an increased risk for complications associated with poor quality of life, and is not associated with increased survival times. The decision to use surgery should be based on individual cases. Postoperative follow-up with systemic therapies to slow the spread of disease will likely aid in a more positive outcome.

Radiation

Radiation therapy has been tried in dogs without extending quality of life and resulting in some cases in severe adverse effects, including chronic colitis, gastrointestinal stricture or perforation, necrotic drainage/ulceration in the skin and subcutaneous tissues, osteopenia, urinary bladder thickening, chronic cystitis, urethral stricture, ileosacral osteosarcoma, pelvic limb edema, and perianal pain.[6,83,84] Survival time was not affected by the adverse effects, but quality of life decreased and owner expense increased. Radiation may play a role in future treatment regimes, but more work must be done to determine the best protocols.

Chemotherapy

The benefits of traditional chemotherapeutic agents have not been well-documented with canine prostatic neoplasia. Work has been done to investigate the chemotherapeutic properties of some nonsteroidal antiinflammatory drugs (NSAIDs). It is thought that cyclooxygenase (COX)-2 inhibition plays a key role through inhibition of angiogenesis, stimulation of apoptosis, and altering immune function.[85] One study evaluating the use of NSAIDs in the treatment of canine prostatic neoplasia noted that a majority of normal and neoplastic prostatic cells expressed COX-1 and that only neoplastic cells expressed COX-2. The study also retrospectively evaluated dogs with prostatic neoplasia that were treated with NSAIDs and those that were not and found that survival time was significantly different between the 2 groups, with 6.9 months in the former group and 0.7 months in the latter.[77] The 2 NSAIDs evaluated were piroxicam and carprofen.

Bisphosphonates

Bisphosphonates are osteoclast inhibitors used in human medicine for treatment of skeletal metastasis of prostatic carcinoma. They have been tested in dogs and seem to have similar benefits of increasing bone density and decreasing pain in some patients.[86] Inhibiting osteoclast activity strengthens bone, which reduces pain and the risk of fracture. It also controls the humoral hypercalcemia of malignancy. Other benefits of bisphosphonates in cancer treatment include inhibition of cancer cell proliferation, induction of apoptosis of cancer cells, angiogenesis inhibition, matrix metalloproteinase inhibition, and cytokine expression alteration.[87]

Samarium-153-ethylenediamine-tetramethylene-phosphonic acid

An injectable radiopharmaceutical, samarium-153-ethylenediamine-tetramethylene-phosphonic acid palliates and may have some curative properties in some restricted cases of canine skeletal metastatic disease (tumors <2 cm in diameter, not invading cortical bone, tumors in the axial skeleton, mineralized tumors, and those with high uptake of technetium (^{99m}Tc) medronic acid during scintigraphy).[88] The drug is not currently easily accessible.

Dysuria Therapy

Because dysuria is a common effect of prostatic neoplasia, treatment may be focused on relieving this clinical sign. Tube cystotomy may be used, but owners should be aware of complications, including urinary tract infection and dissemination of the tumor.[89] The presence of the tumor may also cause incontinence to persist. Placement of a metallic urinary stent has been reported, which resulted in immediate restoration of urinary function. The treatment is costly and complications may include loss of the stent, reobstruction, and incontinence. In 1 study, 7 of 12 dogs were scored as having an excellent outcome and mean survival time for all dogs was 20 days.[90]

Prostatic Neoplasia Treatment Summary

No standard protocol for the treatment of prostatic neoplasia in dogs exists, nor is it likely that a standard protocol ever will exist as long as most diagnoses are in the late, terminal stages of the disease, and because individual patient variation and client wishes will always play an important role in deciding the correct treatment regime. At the current time, the best treatment to extend both life expectancy and improve quality of life (for 6 months on average) is the use of COX-2 inhibitors. Some treatments do seem to offer palliative measures to decrease pain and other clinical signs and should be considered as available options on a case-by-case basis, considering owner expectations and concerns, and the current quality of life of the patient.

DISEASE SCREENING

A retrospective survey of intact dogs determined that the most useful time to begin screening intact male dogs for prostatic disease, using ultrasound imaging, was at 40% of that breed's life expectancy.[91] At this time, there was a high probability of detecting prostatic disease before other clinical signs being evident. This measure would allow for early intervention and treatment. No such recommendations have been given for screening neutered males for neoplasia.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.cvsm.2018.02.012.

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