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CARDIOLOGY

Degenerative Valve Disease: Classification, Diagnosis, and Treatment of Mitral Regurgitation

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Degenerative valve disease (DVD) is the most common heart disease and the most common cause of congestive heart failure (CHF) in dogs. Although it may be seen in dogs of all sizes, it is typically seen in elderly, small-breed dogs, with almost 85% affected by 13 years of age.¹ It is a chronic, slowly progressive process, potentially affecting dogs for more than 5 years before resulting in heart failure and death. The mitral valve is most commonly and severely affected, although the tricuspid valve is concurrently involved in 30% of cases.¹⁻⁵

ETIOLOGY

The causes of DVD are unknown. A heritable basis has been reported in dachshunds and cavalier King Charles spaniels, suggesting a polygenic mode of inheritance.⁶⁻⁸

ON THE LOOKOUT

Dachshunds, cavalier King Charles spaniels, chihuahuas, miniature and toy poodles, whippets, and most terriers are predisposed to degenerative valve disease.

PATHOLOGY AND PATHOPHYSIOLOGY

DVD often progresses over many years, and morbidity is directly related to the degree of valvular insufficiency and subsequent volume overload to the heart. The degree of valvular insufficiency is affected by degree of structural change in the valve leaflets, integrity of the chordae tendineae, myocardial contractility, and chamber dilation. Secondary changes related to valvular insufficiency contribute to progressive valvular insufficiency. Chamber and annular dilation reduce leaflet coaptation. Decreased myocardial contractility may develop (more common in large breeds). Arrhythmias can contribute to distorting the synchrony of contraction. All of these changes lead to progressive valvular regurgitation and subsequent greater volume overload, triggering additional chamber dilation and eventually heart failure.^{6,9-11}



As valve regurgitation worsens, forward cardiac output diminishes, thereby stimulating a variety of compensatory mechanisms. These compensatory mechanisms alter blood volume to ensure that circulatory needs of the body are met, primarily by an increase in preload (Frank-Starling relationship).^{4,12-14}

Compensatory changes in atrial and ventricular size and blood volume can allow patients to remain asymptomatic for years, and some patients never show clinical signs of CHF, despite severely affected valves. However, preload may eventually increase to the point where capillary homeostasis can no longer be maintained, and the patient develops edema or CHF. Certain events can induce acute clinical signs in patients that were previously asymptomatic. These include arrhythmias, left atrial perforation, and major chordae tendineae rupture.^{4,12-14}

HISTOPATHOLOGY

The histopathological change observed with DVD is described as myxomatous degeneration, which results in loss of collagen and other connective tissue within the valve leaflet and excessive accumulation of proteoglycans. This process results in loss of the normal support structure of the valve as well as a derangement of the leaflet morphology.^{10,11}

EPIDEMIOLOGY

DVD is common in middle-aged and older dogs. Smaller-breed dogs are affected much more often than large-breed dogs, sometimes at a younger age. Males are more commonly affected than females (1.5:1).^{1-5,9} Disease incidence in the general population is estimated at 1:7 dogs. The incidence is greater than 90% for predisposed breeds (**BOX 1**), especially senior animals.^{1-5,9}

CLINICAL SIGNS

A systolic murmur with its point of maximal intensity over the left apex is the most distinctive clinical finding in a dog with DVD. The intensity of the murmur does not correlate with the hemodynamic significance of valve insufficiency. A second auscultatory abnormality associated with DVD is a systolic click, a high-pitched sound heard in midsystole that is caused by mitral valve prolapse associated with elongation and/or tearing of the chordae.^{2-4,14}

Physical examination findings in mild cases of CHF may be limited to a murmur and a slightly increased respiratory rate, with increased bronchovesicular sounds noted on pulmonary auscultation. In more severe cases, dyspnea is evident, and crackles and wheezes may be heard on auscultation. Dogs with concurrent tricuspid insufficiency and pulmonary hypertension may have signs of right-sided CHF such as hepatomegaly, ascites, and pleural effusion. Dogs in active heart failure are generally tachycardic from a state of elevated sympathetic tone secondary to the heart disease.^{2-4,14}

Clinical signs in dogs with symptomatic disease usually result from the onset of left-sided CHF. Coughing, restlessness, respiratory distress, syncope, exercise intolerance, weight loss, and inappetence are common complaints. In the initial stages, coughing is nocturnal and/or occurs with rest. A common cause of coughing in patients with DVD is collapse of the left mainstem bronchus associated with left atrial enlargement, which may occur even without left-sided CHF.^{2-4,14}

Coughing, respiratory distress, and pulmonary crackles are common signs of several pulmonary diseases, especially chronic bronchitis. Crackles secondary to CHF usually occur only when pulmonary edema is severe and respiratory distress is clearly apparent. Patients with CHF often have sinus tachycardia, whereas dogs with chronic pulmonary disease frequently have a respiratory sinus arrhythmia (presumably because of a reflex increase in vagal tone).^{2-4,14}

DIAGNOSIS

Radiography

In the early stages of DVD, thoracic radiographs may be unremarkable. However, as the disease progresses, thoracic radiographs reveal a progressive increase in the size of the cardiac silhouette, with left atrial and ventricular enlargement predominating. Left-sided CHF is diagnosed when radiographic signs of pulmonary edema develop (progressive interstitial and even alveolar pulmonary infiltrate).

In dogs, infiltrates consistent with cardiogenic pulmonary edema have a fairly characteristic distribution (i.e., marked in the caudodorsal lung fields). If right-sided CHF is present, pleural effusion, a distended caudal vena cava, hepatomegaly, and/or ascites may be seen. Generally, the lobar pulmonary



veins are distended secondary to venous congestion. However, lack of venous distention does not rule out CHF.¹⁵⁻¹⁷

Electrocardiography

The electrocardiogram is often normal, especially in the early stages of DVD, although it may show changes consistent with left or biatrial enlargement (P wave changes) and left ventricular enlargement (tall R waves). In advanced stages, arrhythmias may be present. These are mainly supraventricular (atrial premature complexes, atrial tachycardia, atrial fibrillation), but ventricular ectopy may occur rarely.^{2-4,9}

Echocardiography

Two-dimensional echocardiography usually indicates chamber enlargement on either side of the affected valve(s). Prolapse, flail, and irregular thickening of the affected valve leaflets may be seen. In most dogs, M-mode echocardiography reveals hyperdynamic motion of the interventricular septum and left ventricular posterior wall. Doppler echocardiography (color-flow and/or spectral) interrogation of the valves reveals high-velocity, retrograde flow from the ventricles into the atria during systole.^{15,18,19}

TREATMENT

Definitive therapy of DVD involves surgical replacement or repair of the diseased heart valve(s). Open heart surgery is becoming more common in veterinary medicine, with a growing number of centers offering such procedures. However, costs and equipment needs drastically limit the number of patients referred for surgery.^{1,20-22}

The main goal of therapy is to provide symptomatic relief by controlling congestion and edema and delaying disease progression. Many dogs with advanced mitral insufficiency can be maintained for months to years with appropriate therapy.

Diagnosis and treatment guidelines provided below come from the American College of Veterinary Internal Medicine (ACVIM) 2019 consensus statement.¹ The ACVIM guidelines are based on a letter grade classification scheme evaluating the hemodynamic significance of the mitral regurgitation.

BOX 1 Breeds Predisposed to Degenerative Valve Disease

- Chihuahua
- Cavalier King Charles spaniel
- Dachshund
- Miniature and toy poodle
- Whippet
- Most terrier breeds

Stage A

Stage A patients do not have heart disease but are considered to be predisposed or at high risk for developing heart disease (**BOX 1**).

Diagnosis: Breeds that are predisposed should undergo yearly auscultations by their primary care veterinarian.

Treatment: No drug or dietary treatment is recommended. Breeding animals should not be bred if a murmur or echocardiographic evidence of mitral regurgitation is identified before 6 to 8 years of age.^{1,23,24}

Stage B

Stage B patients have developed mitral and/or tricuspid regurgitation but have not developed clinical signs of heart failure.

Diagnosis: Thoracic radiography is recommended to obtain baseline radiographs and assess for hemodynamic changes. Echocardiography is recommended to assess the severity of chamber enlargement and identify comorbidities.^{1,15} Blood pressure measurement is also recommended to identify systemic hypertension.

In some situations, treatment recommendations are being made solely based on thoracic radiographs without echocardiography. This approach is considered inferior, and caution is recommended as there is marked variation in thoracic conformation and breed difference in vertebral heart score (VHS).¹⁶

Stage B1

Stage B1 describes asymptomatic dogs with no



radiographic or echocardiographic evidence of remodeling or with remodeling changes not severe enough to meet clinical criteria to initiate treatment. In these patients, progression to heart failure is considered unlikely to occur within 12 months.

Treatment: No medication, supplements, or dietary modifications are proven effective at this stage. Reevaluation by echocardiography, thoracic radiography, and systemic blood pressure measurement is recommended in 6 to 12 months.¹

Stage B2

Stage B2 describes asymptomatic dogs with more advanced mitral valve regurgitation that has resulted in radiographic and echocardiographic evidence of left atrial/ventricular enlargement. These patients meet clinical criteria to initiate pharmacologic treatment to delay the onset of heart failure.

Diagnosis: Murmur intensity is typically 3/6 or greater; left atrial to aortic ratio (LA:Ao) in early diastole is 1.6 or greater; left ventricular internal diameter in diastole, normalized for body weight, is 1.7 or greater; and breed-adjusted radiographic VHS is greater than 10.5.^{1,15,25}

No reliable radiographic markers of stage B2 cardiac remodeling currently exist. However, in the absence of echocardiography, clear radiographic evidence of cardiomegaly (general VHS >11.5), or evidence of an accelerating interval change in radiographic cardiac enlargement patterns can substitute for quantitative echocardiography.^{1,15,25}

Treatment: Pimobendan is recommended at 0.25 to 0.3 mg/kg PO q12h. Dietary modifications are recommended, such as mild sodium restriction and adequate protein and caloric intake to maintain a body condition score of 5/9. Angiotensin-converting enzyme inhibitors (ACEI) are controversial at this stage, and studies of their preclinical efficacy show mixed results. Surgical intervention is possible and recommended by some ACVIM panelists. Reevaluation by echocardiography, thoracic radiography, and systemic blood pressure measurement is recommended every 4 to 6 months.^{1,15,25-28}

Stage C

Stage C patients have clinical signs secondary to their

heart disease. These animals are predominantly in CHF with pulmonary edema, pleural effusion, and/or ascites.

Diagnosis: Signalment, history, and physical examination are all beneficial in determining whether CHF is being caused by DVD. A clinical database including thoracic radiographs and echocardiography is recommended. There is a high prevalence of tracheal collapse in older small-breed dogs, the clinical signs of which can be mistaken for heart failure.^{2,3}

Echocardiography with Doppler studies is useful to confirm the presence of DVD, quantify chamber enlargement and cardiac function, and identify comorbidities. NT-proBNP (N-terminal pro-brain natriuretic peptide) can also provide adjunct evidence. Heart failure can be excluded in symptomatic dogs with normal NT-proBNP.^{1,15,29,30}

Serum creatinine, blood urea nitrogen, and electrolyte concentrations should be checked 1 to 2 weeks after initiation of or change in diuretic or ACEI therapy and every 3 to 4 months thereafter.¹ These patients should be reassessed by a veterinarian every 3 to 4 months, typically with thoracic radiography, bloodwork, and systemic blood pressure measurement.¹

Treatment, acute signs: For acute treatment, oxygen therapy is beneficial, not only for its vasodilatory effects but also to improve oxygen saturation while diuretic therapy is started. Furosemide is the staple treatment in resolving acute signs of CHF. A 2 mg/kg injection of furosemide should be administered IV or IM followed by hourly injections (IV or IM) of 1 to 2 mg/kg until respiratory signs have improved. Alternatively, a constant rate infusion (CRI) of 0.25 to 1 mg/kg/hr may be implemented in cases of severe respiratory distress.^{31,32} These patients should have free access to water.

Pimobendan at 0.25 to 0.3 mg/kg PO q12h should be initiated if not already prescribed and should be continued if already started.^{15,33} Mechanical treatments such as thoracocentesis or abdominocentesis may be necessary to improve ventilation and signs of respiratory distress.³⁴

Anxiety associated with respiratory distress should be managed with narcotics or anxiolytic agents. Care is recommended to not suppress respiratory drive or significantly affect blood pressure. One low dose of butorphanol is recommended at 0.1 to 0.15 mg/kg IV.³⁵⁻³⁷



In patients with poor forward output or that fail to respond to routine management, dobutamine (2.5 to 10 µg/kg/min CRI) can be initiated. Continued electrocardiography is recommended to monitor for arrhythmias.³⁵⁻³⁷

Nitroprusside, an arterial and venous vasodilator, can be used as a CRI (1 to 15 µg/kg/min) for poorly responsive pulmonary edema or in azotemic patients. Close monitoring of blood pressure is recommended while using this product. Nitroglycerin, a venous vasodilator, can be used transdermally to decrease pulmonary capillary wedge pressure and left atrial preload.^{35,38}

ACEI are controversial in the acute setting of heart failure. Although, in combination with furosemide, they decrease pulmonary capillary wedge pressure, they also decrease renal perfusion and can contribute to kidney injury. The author does not recommend them in the acute setting.³⁶⁻³⁸

Treatment, chronic management: Home management of heart failure includes furosemide, typically at doses of around 2 mg/kg PO q12h. Torsemide, given at one-tenth to one-twentieth of the furosemide dose once to twice daily, can be used instead. Studies on the safety and efficacy of torsemide for this use are ongoing. ACEI should be continued or started at this stage (enalapril or benazepril, 0.5 mg/kg PO q12h to q24h). Spironolactone (1 to 2 mg/kg PO q12h to q24h) is recommended for aldosterone antagonism. Pimobendan should be continued. Adjunct therapy can include diltiazem or digoxin for atrial fibrillation or atrial tachycardia.^{1,36,39-44}

In stage C heart failure, cardiac cachexia can become clinically relevant and is a poor prognostic indicator. Supplementation with fish oil is recommended to combat muscle wasting. Adequate caloric intake and measures to prevent anorexia (kidney value monitoring, dosage adjustments, appetite stimulants) should be addressed. Additionally, low-protein diets should be avoided (unless concurrent severe renal disease is present) and sodium intake should be moderately reduced (<90 mg/100 kcal).^{45,46}

Surgical intervention can prove beneficial in these patients.²⁰⁻²²

The main goal of therapy is to provide symptomatic relief by controlling congestion and edema and delaying disease progression.

Stage D

Stage D patients are in refractory heart failure, which is defined as the recurrence of edema while receiving proper heart failure therapy: furosemide, ACEI, and pimobendan.¹ Stage D patients require advanced or specialized treatment to remain clinically comfortable or pursue surgical repair of the valve. They should be reassessed every 1 to 2 months.¹

Treatment: Stage D patients are treated with higher doses of furosemide (4 mg/kg q8h to q12h) and the addition of other diuretics that target downstream regions of the nephron, such as hydrochlorothiazide (0.5 to 1 mg/kg q12h to q24h). Occasionally, furosemide is replaced by the more powerful loop diuretic, torsemide.^{40,47}

Off-label high-dose pimobendan (0.9 to 1.2 mg/kg q24h) has shown to increase survival times and quality of life in stage D patients. They may benefit from the addition of vasodilators such as amlodipine if blood pressure remains normal.¹ Digoxin or diltiazem may be used for antiarrhythmic treatment.^{41,44} Sildenafil is used cautiously to manage patients with ascites secondary to moderate or severe pulmonary hypertension.⁴⁸ This therapy should always be instituted in a hospital as it can exacerbate signs of left-sided heart failure, although this is rare. Cough suppressants and bronchodilators can be used to treat chronic, intractable cough.

PROGNOSIS

The prognosis for cases of DVD is unpredictable in the early stages (B1), as many patients never progress to advanced stages. Those that do progress may take a number of years to do so. Generally, B2 patients develop CHF within 1 to 4 years of diagnosis. The median time to development of CHF in B2 cases treated with pimobendan is 3.5 years.^{15,25} The median



survival time for stage C dogs has been reported as 9 to 15 months based on numerous studies. Approximately 25% of these dogs survive longer than 1.5 years; more than 2 years is somewhat common. Survival time for stage D patients is typically 3 to 6 months.^{1-3,9,15,25} **TVP**

Note: This article is adapted from the NAVC's 2020 VMX Conference Proceedings.

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easOtic

(hydrocortisone aceponate, miconazole nitrate, gentamicin sulfate)

Otic Suspension for Dogs

Anti-inflammatory, antifungal, and antibacterial

Rx

For Otic Use in Dogs Only

CAUTION

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

EASOTIC® Otic Suspension contains 1.11 mg/mL hydrocortisone aceponate, 17.4 mg/mL miconazole nitrate and 1.5 mg/mL gentamicin (as sulfate). The inactive ingredient is a semi-liquid petroleum jelly.

INDICATIONS

EASOTIC Otic Suspension is indicated for the treatment of otitis externa in dogs associated with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (*Staphylococcus pseudintermedius*).

DOSAGE AND ADMINISTRATION

Verify that the tympanic membrane is intact. **Shake well before each use.**

Priming the canister: Prior to the first use of the dosing container, press firmly on the pump several times until the product fills the nozzle (canula tip) with a full dose of product.

Carefully insert the canula into the affected external ear canal(s) and apply 1 mL (a single pump) of Otic Suspension once per day for 5 days. Wash hands after usage.

CONTRAINDICATIONS

Do not use in dogs with known tympanic membrane perforation.

EASOTIC Otic Suspension is contraindicated in dogs with known or suspected hypersensitivity to corticosteroids, imidazole antifungals, or aminoglycoside antibiotics.

WARNINGS

Human Warnings: Not for use in humans. Keep this and all drugs out of reach of children. In case of accidental skin contact, wash area thoroughly with water. Avoid contact with eyes.

Humans with known or suspected hypersensitivity to hydrocortisone, aminoglycoside antibiotics, or azole antifungals should not handle this product.

In case of accidental ingestion by humans, contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

Animal Warnings: As a class, aminoglycoside antibiotics are associated with ototoxicity, vestibular dysfunction and renal toxicity. The use of EASOTIC Otic Suspension in a dog with a damaged tympanic membrane can result in damage to the structures of the ear associated with hearing and balance or in transmission of the infection to the middle or inner ear. Immediately discontinue use of EASOTIC Otic Suspension if hearing loss or signs of vestibular dysfunction are observed during treatment (see **ADVERSE REACTIONS**).

PRECAUTIONS

Do not administer orally.

Concurrent administration of potentially ototoxic drugs should be avoided.

Use with caution in dogs with impaired hepatic or renal function (see **ANIMAL SAFETY**).

Long-term use of topical otic corticosteroids has been associated with adrenocortical suppression and iatrogenic hyperadrenocorticism in dogs (see **ANIMAL SAFETY**).

The safe use of EASOTIC Otic Suspension in dogs used for breeding purposes, during pregnancy, or in lactating bitches, has not been evaluated.

ADVERSE REACTIONS

In a field study conducted in the United States (see **EFFECTIVENESS**), there were no adverse reactions reported in 145 dogs administered EASOTIC Otic Suspension.

In foreign market experience, reports of hearing loss and application site erythema have been received. In most reported cases, the hearing loss and erythema were transient and resolved with discontinuation of EASOTIC® suspension.

To report suspected adverse drug events, contact Virbac AH, Inc at 1-800-338-3659 or the FDA at 1-888-FDA-VETS or www.fda.gov/reportinalmaae.

For technical assistance or to obtain a Safety Data Sheet, call Virbac at 800-338-3659 or visit us at us.virbac.com.

PHARMACOLOGY

Hydrocortisone aceponate is a glucocorticoid with anti-inflammatory effects. Miconazole nitrate is an imidazole antifungal. Gentamicin sulfate is an aminoglycoside antibiotic.

In the target animal safety study, hydrocortisone aceponate, miconazole and gentamicin were shown to be systemically absorbed from the ears of healthy dogs (see **ANIMAL SAFETY**); increased systemic absorption may be observed in inflamed ears.

MICROBIOLOGY

The compatibility and additive effect of each of the components in EASOTIC® Otic Suspension was demonstrated in a component effectiveness and non-interference study. An in vitro study of organisms collected from clinical cases of otitis externa in dogs and from dogs enrolled in the clinical effectiveness study for EASOTIC Otic Suspension determined that miconazole nitrate and gentamicin sulfate inhibit the growth of bacteria and yeast commonly associated with otitis externa in dogs. No consistent synergistic or antagonistic effect of the two antimicrobials was demonstrated. The addition of hydrocortisone aceponate to the combination did not impair antimicrobial activity to any clinically-significant extent. In a field study (see **EFFECTIVENESS**), the minimum of 10 isolates from successfully treated cases was met for *S. pseudintermedius* and *M. pachydermatis*.

EFFECTIVENESS

The effectiveness of this drug was evaluated in 157 dogs with otitis externa. The study was a double-masked field study with a placebo control. One hundred and four dogs were treated with EASOTIC Otic Suspension and 53 dogs were treated with the placebo control. Treatment was administered once daily for 5 consecutive days to the affected ear(s). The dogs were evaluated at 4 different intervals over the course of 1 month to determine response to therapy. The 6 clinical signs evaluated were: malodor, aural discharge, pruritus, erythema, swelling and pain. The individual clinical scores were assigned based on the severity of each sign. Success was based on clinical improvement at Day 28 ± 2 days. The success rates of the 2 groups

were significantly different ($p=0.0179$); 68.5% of dogs administered EASOTIC Otic Suspension were successfully treated, compared to 21.8% of the dogs in the placebo control group.

ANIMAL SAFETY

In the target animal safety study, EASOTIC Otic Suspension was administered at 0X, 1X, 3X and 5X the recommended dose for 15 consecutive days (3 times the recommended treatment duration) in laboratory Beagles, with 8 dogs per group. Hypersensitivity reactions in the external ear canal and inner pinnae were seen in all EASOTIC Otic Suspension groups and included mild to severe aural erythema (3X group), papules and ulceration (1X and 5X groups), otitis externa (3X and 5X groups), and otitis media (5X group). Renal tubular crystals were present in the cortex and medulla (0X, 1X, 3X, and 5X groups) and mild renal tubular basophilia and atrophy were present in one 5X group dog. Baseline cortisol values and the cortisol response to ACTH stimulation were lower in treated dogs compared to the control dogs. The ACTH stimulation test results are consistent with systemic absorption of topical corticosteroids causing suppression of the hypothalamic-pituitary-adrenal axis. Dogs in the 3X and 5X groups demonstrated elevations in AST and ALP, while dogs in the 1X, 3X, and 5X groups had elevated cholesterol, total protein, and albumin levels. Dogs in the 3X and 5X groups also had higher liver weights and greater food consumption.

STORAGE INFORMATION: Store at temperatures between 20° C-25° C (68° F-77° F), with excursions permitted between 15° C-30° C (59° F-86° F).

HOW SUPPLIED: EASOTIC Otic Suspension is supplied in a polyethylene canister, with a soft applicator canula. Each canister contains ten 1 mL doses. Made in the U.S.A.

Distributed by:
Virbac AH, Inc.
P.O. Box 162059
Fort Worth, TX 76161 USA



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