ACVIM Consensus Statement

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Guidelines for the Diagnosis and Treatment of Canine Chronic Valvular Heart Disease

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This is the report of the American College of Veterinary Internal Medicine (ACVIM) Specialty of Cardiology consensus panel convened to formulate guidelines for the diagnosis and treatment of chronic valvular heart disease (CVHD, also known as endocardiosis and myxomatous valve degeneration) in dogs. It is estimated that approximately 10% of dogs presented to primary care veterinary practices have heart disease, and CVHD is the most common heart disease of dogs in many parts of the world, accounting for approximately 75% of canine cases of heart disease cases seen by veterinary practices in North America.

CVHD most commonly affects the left atrioventricular or mitral valve, although in approximately 30% of cases the right atrioventricular (tricuspid) valve also is involved. The disease is approximately 1.5 times more common in males than in females. Its prevalence is also higher in smaller (<20 kg) dogs, although large breeds occasionally are affected.[1] In small breed dogs, the disease generally is slowly but somewhat unpredictably progressive, with most dogs experiencing the onset of a recognizable murmur of mitral valve regurgitation years before the clinical onset of heart failure. When large breed dogs are affected by CVHD, the progression of the disease appears to be more rapid than that observed in small breed dogs.[2] Cavalier King Charles Spaniels are predisposed to developing CVHD at a relatively young age, but the time course of their disease progression to heart failure does not appear to be markedly different from that of other small breed dogs except for the early age of onset.[3,4]

Abbreviations:

ACEI	angiotensin converting enzyme inhibitors
ACVIM	American College of Veterinary Internal Medicine
CRI	constant rate infusion
CVHD	chronic valvular heart disease
ECG	electrocardiography
LA	left atrium
LV	left ventricle
MR	mitral regurgitation

The cause of CVHD is unknown, but the disease appears to have an inherited component in some breeds studied.[5,6] CVHD is characterized by changes in the cellular constituents as well as the intercellular matrix of the valve apparatus (including the valve leaflets and chordae tendineae).[7,8] These changes involve both the collagen content and the alignment of collagen fibrils within the valve.[9,10] Endothelial cell changes and subendothelial thickening also occur,[11] although affected dogs do not appear to be at increased risk for arterial thromboembolism or infective endocarditis. Mitral valve prolapse is a common complication of myxomatous valve degeneration and represents a prominent feature of CVHD in some breeds.[6,12] Progressive deformation of the valve structure eventually prevents effective coaptation and causes regurgitation (valve leakage). Progressive valvular regurgitation increases cardiac work, leading to ventricular remodeling (eccentric hypertrophy and intercellular matrix changes) and ventricular dysfunction.

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Abnormal numbers or types of mitogen receptors (eg, any of the subtypes of serotonin, endothelin, or angiotensin receptors) on fibroblast cell membranes in the valves of affected dogs may play a role in the pathophysiology of the valvular lesions.[13] Systemic or local metabolic, neurohormonal or inflammatory mediators (eg, endogenous catecholamines and inflammatory cytokines) also may influence progression of the valve lesion or the subsequent myocardial remodeling and ventricular dysfunction that accompany long-standing, hemodynamically significant valvular regurgitation. However, these factors are poorly understood at this time.[14]

The prevalence of CVHD increases markedly with age in small breed dogs (with up to 85% showing some evidence of the lesion at necropsy by 13 years of age), but the presence of the pathologic lesion does not necessarily indicate that a dog will develop clinical signs of heart failure. Like the underlying cause of the disease, the factors that determine the progression of the lesion remain unknown, although age, left atrial size, and heart rate have been shown to predict outcomes.[15,16]

Classification of Heart Disease and Heart Failure

Heart failure is a general term that describes a clinical syndrome that can be caused by a variety of specific heart diseases, including CVHD. Heart failure from any cause is characterized by cardiac, hemodynamic, renal, neurohormonal, and cytokine abnormalities. The classification systems for heart failure most familiar to veterinarians are the modified New York Heart Association (NYHA)[17] and International Small Animal Cardiac Health Council[18] functional classification systems, both of which were designed to provide a framework for discussing and comparing the clinical signs of patients in heart failure.

These functional classification systems vary in their details, but both serve as semiquantitative schemes for judging the severity of a patient's clinical signs. Such categorization aids in teaching therapeutic protocols and constitutes a basis for stratification of subjects in clinical trials. The modified NYHA functional classification of heart failure can be summarized as follows:

- *Class I* describes patients with asymptomatic heart disease (eg, CVHD is present, but no clinical signs are evident even with exercise).
- *Class II* describes patients with heart disease that causes clinical signs only during strenuous exercise.
- *Class III* describes patients with heart disease that causes clinical signs with routine daily activities or mild exercise.
- *Class IV* describes patients with heart disease that causes severe clinical signs even at rest.

Functional classification systems share a common problem in that they are based on relatively subjective assessments of clinical signs that can change frequently and dramatically over short periods of time. Furthermore, treatments may not differ substantially across the functional classes.

A newer classification system that might more objectively categorize patients in the course of their heart disease has been developed, and this scheme was used by the panel for consensus recommendations. The goal was to link severity of signs to appropriate treatments at each stage of illness. In formulating these guidelines, the consensus panel adapted the 2001 American College of Cardiology/American Heart Association classification system for the treatment of heart disease and failure in human patients to the management of canine CVHD.[19] In this approach, patients are expected to advance from 1 stage to the next unless progression of the disease is altered by treatment.

The classification system presented below and used in these guidelines is meant to complement, not replace, functional classification systems. The new system describes 4 basic stages of heart disease and failure:

- *Stage A* identifies patients at high risk for developing heart disease but that currently have no identifiable structural disorder of the heart (eg, every Cavalier King Charles Spaniel without a heart murmur).
- *Stage B* identifies patients with structural heart disease (eg, the typical murmur of mitral valve regurgitation is present), but that have never developed clinical signs caused by heart failure. Because of important clinical implications for prognosis and treatment, the panel further subdivided *Stage B* into *Stage B1* and *B2*.
  - *Stage B1* refers to asymptomatic patients that have no radiographic or echocardiographic evidence of cardiac remodeling in response to CVHD.
  - *Stage B2* refers to asymptomatic patients that have hemodynamically significant valve regurgitation, as evidenced by radiographic or echocardiographic findings of left-sided heart enlargement.
- *Stage C* denotes patients with past or current clinical signs of heart failure associated with structural heart disease. Because of important treatment differences between dogs with acute heart failure requiring hospital care and those with heart failure that can be treated on an outpatient basis, these issues have been addressed separately by the panel. Some animals presenting with heart failure for the 1st time may have severe clinical signs requiring aggressive therapy (eg, with additional afterload reducers or temporary ventilatory assistance) that more typically would be reserved for those with refractory disease (see Stage D).
- *Stage D* refers to patients with end-stage disease with clinical signs of heart failure caused by CVHD that are refractory to "standard therapy" (defined later in this document). Such patients require advanced or specialized treatment strategies in order to remain clinically comfortable with their disease. As with Stage C, the panel has distinguished between animals in Stage D that require acute, hospital-based therapy and those that can be managed as outpatients.

This classification system emphasizes that there are risk factors and structural prerequisites for the development of heart failure in CVHD. The use of this classification system is meant to encourage veterinary cli-

nicians to think about heart disease in a way analogous to the current clinical approach to cancer. This classification system is designed to aid in:

- Developing screening programs for the presence of CVHD in dogs known to be at risk.
- Identifying interventions that may (now or in the future) decrease the risk of disease development.
- Identifying asymptomatic dogs with CVHD early in the course of their disease, comparable to "in situ" cancer, so that they can perhaps be treated more effectively.
- Identifying symptomatic dogs with CVHD so that these patients can be treated medically and either potentially cured (interventionally or surgically) or managed with their chronic disease.
- Identify symptomatic dogs with advanced heart failure from CVHD and refractory to conventional therapy—these patients require aggressive or new treatment strategies or potentially hospice-type end-of-life care.

Evaluating the Evidence for Efficacy and Safety

In classifying dogs with CVHD according to their disease stage and clinical status and matching them with diagnostic, pharmacologic, and dietary treatment recommendations, the consensus panel considered both the quantity and quality of evidence available to inform the diagnostic and therapeutic decisions made in these patients. The heading "Consensus recommendation" preceding a diagnostic, therapeutic, or dietary recommendation indicates that the panelists were unanimous in their opinion that the combination of available clinical trial evidence, other published experimental or anecdotal evidence, clinical experience, and expert opinion indicate that the potential benefit of the approach under discussion clearly outweighs the potential risks to the patient and minimizes financial impact on the client.

In situations in which the available evidence regarding the efficacy of a diagnostic or therapeutic maneuver was conflicting, weak, or absent and no consensus on a recommended course of action could be reached by the panelists based on the available evidence and their collective clinical experience, the panel's opinions and reasoning on clinically important issues are briefly summarized. These bulleted summary statements are grouped together and summarized under the heading "No consensus."

The panel recognized that there is considerable variation in the scientific quality of the evidence available to support clinical decision making, and sought to include topically relevant references. Whereas the status of a particular recommendation (consensus versus no consensus) reflects the collective judgment of the panel on each question addressed, no attempt was made to assign a specific scientific grade or value to each included citation.

Guidelines for Diagnosis and Treatment of CVHD

- *Stage A*—Dogs at high risk for development of heart failure, but *without apparent structural abnormality* (no heart murmur is heard) at the time of examination.

Diagnosis for Stage A

Consensus recommendations:

- Small breed dogs, including breeds with known predisposition to develop CVHD (eg, Cavalier King Charles Spaniels, Dachshunds, Miniature and Toy Poodles) should undergo regular evaluations (yearly auscultation by the family veterinarian) as part of routine health care.
- Owners of breeding dogs or those at especially high risk, such as Cavalier King Charles Spaniels, may choose to participate in yearly screening events at dog shows or other events sponsored by their breed association or kennel club and conducted by board-certified cardiologists participating in an ACVIM-approved disease registry.

Therapy for Stage A

Consensus recommendations:

- No drug therapy is recommended for any patient.
- No dietary therapy is recommended for any patient.
- Potential breeding stock should no longer be bred if mitral regurgitation (MR) is identified early, during their normal breeding age of <6–8 years.

- *Stage B*—These patients *have a structural abnormality indicating the presence of CVHD, but have never had clinical signs of heart failure*. These patients are generally recognized during a screening or routine health examination with a heart murmur typical of mitral valve insufficiency.

Diagnosis for Stage B

Consensus recommendations:

- Thoracic radiography is recommended in all patients to assess the hemodynamic significance of the murmur and also to obtain baseline thoracic radiographs at a time when the patient is asymptomatic for CVHD.
- Blood pressure measurement is recommended for all patients.
- In small breed dogs with typical murmurs, echocardiography is recommended to answer specific questions regarding either cardiac chamber enlargement or the cause of the murmur if those questions are not answered adequately by auscultation and thoracic radiography.
- Echocardiography generally is indicated in larger breed dogs because the murmur of MR is more likely to be related to other causes (eg, dilated cardiomyopathy).
- Basic laboratory work (a minimum of hematocrit, total protein concentration, serum creatinine concentration, and urinalysis) is indicated in all patients.

Because their prognosis and therapy may differ substantially, asymptomatic patients with murmurs of

mitral valve insufficiency are further subcategorized into 2 groups based on the results of the above evaluation:

- *Stage B1*: *Hemodynamically insignificant MR* (defined as radiographically or echocardiographically normal or equivocally enlarged LA, LV, or both, with normal LV systolic function; normal vertebral heart score on radiography; normotensive, normal laboratory results).

Therapy for Stage B1 (both pharmacologic and dietary) is identical for both small and large breed dogs.

Consensus recommendations:

Small and large breed dogs:

  - No drug or dietary therapy is recommended.
  - Re-evaluation is suggested by either radiography or echocardiography with Doppler studies in approximately 12 months (some panelists recommend more frequent follow-up in large dogs).

- *Stage B2: Hemodynamically significant MR with cardiac remodeling* (defined as clearly enlarged LA, LV, or both); normotensive.

Therapy for Stage B2 (both pharmacologic and dietary) is controversial, and no consensus could be reached with currently available evidence.

No consensus:

Small breed dogs:

  - *Angiogensin converting enzyme inhibitor (ACEI)*: For patients with clinically relevant left atrial enlargement on either initial examination, or those in which the left atrium has increased in size dramatically on successive monitoring examinations, a majority of the panel members recommend initiation of therapy with an ACEI. Clinical trials addressing the efficacy of ACEI for the treatment of dogs in Stage B2 have had mixed results—either no effect or a small positive effect delaying the onset of congestive heart failure.[20–22] A minority of the panel members recommend no therapy for asymptomatic animals pending further clinical trials to examine the efficacy of therapy in this setting.
  - β blockers: For patients with clinically relevant left atrial enlargement on either initial examination, or when the left atrium has increased in size dramatically on successive monitoring examinations, a minority of the panel members recommend initiation of therapy with a low dosage of a β blocker, titrating to the highest tolerated dose over a period of approximately 1–2 months depending on the specific medication recommended. A majority of the panel members recommend no β-blocker therapy for asymptomatic animals pending further clinical trials to examine the efficacy of therapy in this setting. Clinical trials addressing the efficacy of β blockers for the treatment of dogs in Stage B2 are in progress.
  - No other pharmacologic treatments were recommended in Stage B2 by a majority of panelists. A few panelists considered the use of the following medications for patients in Stage B2 under specific circumstances: pimobendan, digoxin, amlodipine, and spironolactone. The panel felt in general that these treatment strategies needed additional investigation into their efficacy and safety in this patient population before a consensus recommendation could be made.
  - Dietary treatment was recommended by a majority of panelists in Stage B2, a minority of the panel recommended no dietary changes. Principles guiding dietary treatment at this stage include mild dietary sodium restriction and provision of a highly palatable diet with adequate protein and calories for maintaining optimal body condition.

Larger breed dogs:

  - Generally, panelists who recommended treatment in smaller breed dogs strengthened their recommendations promoting the use of both ACEI and β blockers in larger breed dogs in Stage B2.
  - Dietary treatment recommendations for larger breed dogs were the same as those for small breeds, emphasizing mild sodium restriction and adequate protein and caloric intake if changes were recommended.

- *Stage C*—Patients have a *structural abnormality and current or previous clinical signs of heart failure* caused by CVHD. Stage C includes all patients that have had an episode of clinical heart failure. Such patients stay in this stage despite improvement of their clinical signs with standard therapy (even if their clinical signs resolve completely). Guidelines for standard pharmacotherapy are provided for both in-hospital (acute) management of heart failure and for home care (chronic) management of heart failure, as well as recommendations for chronic dietary therapy. Some patients that present in Stage C may have life-threatening clinical signs, and require more extensive acute therapy than is considered standard therapy. These acute care patients may share some medical management strategies with dogs that have progressed to Stage D (refractory heart failure, see below). In Stage C, heart failure secondary to CVHD, the panel did not make clinically relevant therapeutic distinctions between small and larger breed dogs for either acute or chronic medical management.

For both Stages C and D (CVHD patients with symptomatic heart failure), the acute care of heart failure is focused on regulating the patient's hemodynamic status by monitoring (as well as possible under clinical circumstances) and pharmacologically optimizing preload, afterload, heart rate, and contractility to improve cardiac output, decrease the extent of mitral valve regurgitation if possible, and relieve clinical signs associ-

ated with either low cardiac output or excessively increased venous pressures (preload). The broad goals of chronic (home care) management are focused on maintaining these hemodynamic improvements to the extent possible, while providing additional treatments aimed at slowing progression, prolonging survival, decreasing clinical signs of congestive heart failure, enhancing exercise capacity, and otherwise improving quality life.

Diagnosis for Stage C

Consensus recommendations:

- Because of the relatively high prevalence of chronic tracheobronchial disease in the same population at risk for CVHD, the presence of a typical left apical regurgitant murmur in a coughing dog does not necessarily mean that the clinical signs are the result of CVHD.
- A clinical database (including chest radiographs and preferably an echocardiogram and basic laboratory tests) must be obtained and examined carefully to accurately determine the cause of clinical signs in animals with CVHD.
- Serum N-terminal pro-B-type naturetic peptide (BNP) concentrations should become increasingly useful in determining the cause of clinical signs in dogs with CVHD. Although there is no doubt that, as a group, dogs with clinical signs caused by heart failure have higher serum BNP concentrations than those with clinical signs caused by primary pulmonary disease, the positive predictive value of any single BNP concentration, obtained by a commercially available test, has not been adequately characterized at the time of this writing (August 2009) to make a consensus recommendation with regard to BNP testing.
- The signalment and physical examination can be helpful in determining the pretest probability of heart failure as a cause of clinical signs in patients with CVHD. For example, obese dogs with no history of weight loss are less likely to be in heart failure secondary to CVHD; dogs with marked sinus arrhythmia and relatively slow heart rates also are less likely to have clinical signs attributable to CVHD.
- Most of these dogs are middle-aged or older, and it is always prudent to complete the database with a CBC, serum biochemical profile, and urinalysis, especially if therapy for CHF is anticipated.

Acute (Hospital-Based) Therapy of Stage C

Consensus recommendations:

- Furosemide—The specific dosing of furosemide in a dog with CHF should be related to the severity of clinical signs and the response to initial therapy. Lower or higher doses (eg, 1–4 mg/kg) may be appropriate in specific cases. Repeated IV boluses or a constant rate IV infusion may be indicated for poorly responsive dogs.
- For life-threatening pulmonary edema (expectoration of froth associated with severe dyspnea; diffuse pulmonary opacity on thoracic radiographs; poor initial response to furosemide bolus with failure of dyspnea and respiratory rate to improve over 2 hours), furosemide is administered as a constant rate infusion (CRI) at a dose of 1 mg/kg/h after the initial bolus.[23]
- Allow patient free access to water once diuresis has begun.
- Pimobendan, 0.25–0.3 mg/kg PO q12h—Although the clinical trial evidence supporting the chronic use of pimobendan in the management of Stage C heart failure from CVHD is stronger than for the acute situation, the recommendation to use pimobendan in acute heart failure therapy is strongly supported by hemodynamic and experimental evidence[24–27] as well as the anecdotal experience of the panelists.
- Oxygen supplementation, if needed, can be administered via a humidity and temperature-controlled oxygen cage or incubator or via a nasal oxygen canula.
- Mechanical treatments (eg, abdominal paracentesis and thoracocentesis) are recommended to remove effusions judged sufficient to impair ventilation or cause respiratory distress.
- Provide optimal nursing care, including maintenance of an appropriate environmental temperature and humidity, increase in the head on pillows, and placement of sedated patients in sternal posture.
- Sedation—Anxiety associated with dyspnea should be treated. Narcotics, or a narcotic combined with an anxiolytic agent, are most often used by panelists. Butorphanol (0.2–0.25 mg/kg) administered IM or IV was the narcotic most often utilized for this purpose; combinations of buprenorphine (0.0075–0.01 mg/kg) and acepromazine (0.01–0.03 mg/kg IV, IM, or SQ) as well as other narcotics, including morphine and hydrocodone, also have been utilized.
- CRI of sodium nitroprusside for up to 48 hours is often useful for life-threatening, poorly responsive pulmonary edema (refer to Class D below for specific dosing recommendations).

No consensus was reached on the following acute care Stage C issues:

- Care must be taken to monitor the blood pressure and respiratory response to narcotics and tranquilizers in the setting of acute heart failure. No specific treatment or dosage regimen was used by all panelists.
- ACEI (eg, enalapril 0.5 mg/kg PO q12h). Although treatment with ACEI is a consensus recommendation for chronic Stage C heart failure and a majority of panelists also treat acute heart failure with ACEI, the evidence supporting ACEI efficacy and safety in acute therapy when combined with furosemide and pimobendan is less clear. There is, however, clear evidence that the acute administration of enalapril plus

furosemide in acute heart failure results in substantial improvement in pulmonary capillary wedge pressure when compared with the administration of furosemide alone.
- Nitroglycerin 2% ointment, approximately 1/2'' paste per 10 kg body weight for 24–36 hours. Some panelists recommend administering the ointment in intervals (eg, 12 hours on, 12 hours off). Other panelists do not use nitroglycerin in this setting.

Home-Based (Chronic) Therapy for Stage C

Consensus recommendations:

- Continue PO furosemide administration to effect, commonly at a dosage of 2 mg/kg q12h. The daily furosemide dosage for dogs with CHF is wide and can be as low as 1–2 mg/kg PO q12h to 4–6 mg/kg PO q8h. The dosage must be titrated to maintain patient comfort and with attention to effects on renal function and electrolyte status.
- Chronic oral furosemide (doses $\geq$6 mg/kg q12h) needed to maintain patient comfort in the face of appropriate adjunct therapy indicates disease progression to Stage D.
- Continue or start ACEI (eg, enalapril 0.5 mg/kg, PO q12h) or equivalent dose of another ACEI if approved for use. The labeled dosage range of enalapril is 0.25–0.5 mg/kg PO q12h; most panelists treat at the upper end of this range. Measurement of serum creatinine and electrolyte concentrations 3–7 days after beginning an ACEI is recommended for animals with Stage C heart failure.
- Continue pimobendan (0.25–0.3 mg/kg PO q12h).[28–30]
- Panelists recommend against starting a β blocker in the face of active clinical signs of heart failure (eg, cardiogenic pulmonary edema) caused by CVHD.
- None of the panelists routinely use nitroglycerin in the chronic treatment of Stage C heart failure.
- Participation in a structured, home-based extended care program to facilitate body weight, appetite, respiratory, and heart rate monitoring while providing client support to enhance medication compliance and dosage adjustments in patients with heart failure is encouraged.

No consensus was reached regarding the following home-based (chronic) treatment strategies in Stage C:

- Spironolactone (0.25–2.0 mg/kg PO q12–24h) was recommended by a majority of panelists as an adjunct for the chronic therapy of dogs in Stage C heart failure. The primary purpose of spironolactone in this situation is thought to be aldosterone antagonism. No clinically relevant diuretic effect should be anticipated. This treatment now is approved in Europe at a dosage of 2 mg/kg/d.
- Digoxin (0.0025–0.005 mg/kg PO q12h) with target plasma concentration 8 hours postpill of 0.8–1.5 ng/mL. For the chronic management of Stage C heart failure, a majority of panelists recommended the addition of digoxin in cases complicated by persistent atrial fibrillation to slow the ventricular response rate. Some panelists also prescribe digoxin at this dosage for patients in Stage C heart failure in the absence of sustained supraventricular tachyarrhythmia, as long as no contraindication to digoxin is evident (eg, increased serum creatinine concentration, ventricular ectopy, concerns over owner compliance, chronic GI disease resulting in frequent or unpredictable bouts of vomiting or diarrhea).
- Once heart failure signs have resolved, a stable medication regimen has been instituted, and the patient is eating and apparently feeling well, a minority of panelists recommend attempting a low dose, slow up-titration regimen of a β blocker. There is no clinical trial evidence in dogs to support this recommendation. If prescribed, there is no consensus regarding which specific β blocker to use (carvedilol, atenolol, or metoprolol is the most frequently prescribed). The purpose of β blockade in this setting is related to potential long-term protective effects on myocardial function and remodeling. These effects have been demonstrated in some experimental animal models[31] and in humans with heart failure, but not in clinical trials.
- The presence of atrial fibrillation strengthens the indication for β blockade (to slow the ventricular response to atrial fibrillation) for those panelists who recommended a β blocker.
- In patients taking a β blocker before the onset of Stage C heart failure, the majority of panelists continue β blockade; some panelists would consider dosage reduction if needed clinically because of clinical signs of low cardiac output, hypothermia, or bradycardia.
- Some panelists prefer administration of oral diltiazem (several formulations are available, some sustained release) for chronic heart rate control in atrial fibrillation.
- Some panelists find cough suppressants useful in occasional patients in Stage C heart failure from CVHD.
- Some panelists find bronchodilators useful in occasional patients in Stage C heart failure from CVHD.

Dietary Therapy for Stage C

Cardiac cachexia is defined as the unintentional loss of $>$7.5% of the patient's normal, predisease weight, not including weight loss associated with the resolution of edema or the removal of body cavity effusions. Cachexia has substantial negative prognostic implications, and is much easier to prevent that to treat.[32]

Consensus recommendations:

- Maintain adequate calorie intake (maintenance calorie intake in Stage C should provide approximately 60 kcal/kg body weight) to minimize weight

loss (specifically muscle mass loss) that often occurs in CHF.
- Specifically address and inquire about the occurrence of anorexia, and make efforts to treat any drug-induced or other identifiable causes of anorexia that occur.
- Record the accurate weight of the patient at every clinic visit, and investigate the cause of weight gain or loss.
- Ensure adequate protein intake and avoid low-protein diets designed to treat chronic kidney disease, unless severe concurrent renal failure is present.
- Modestly restrict sodium intake, taking into consideration sodium from all dietary sources (including dog food, treats, table food, and foods used to administer medications) and avoid any processed or other salted foods.
- Monitor serum potassium concentrations and supplement the diet with potassium from either natural or commercial sources if hypokalemia is identified. Hyperkalemia is relatively rare in patients treated for heart failure with diuretics, even in those concurrently receiving an ACEI in combination with spironolactone.[33] Diets and foods with high potassium content should be avoided when hyperkalemia has been identified.

No consensus was reached on the following dietary therapy for Stage C:

- Consider monitoring serum magnesium concentrations, especially as CHF progresses and in animals with arrhythmias. Supplement with magnesium in cases in which hypomagnesemia is identified.
- Consider supplementing with n-3 fatty acids, especially in dogs with decreased appetite, muscle mass loss, or arrhythmia.[34]

- *Stage D*—Patients have clinical signs of failure refractory to standard treatment for Stage C heart failure from CVHD, as outlined above. Stage D heart failure patients therefore should be receiving the maximal recommended (or tolerated) dosage of furosemide, an ACEI, and pimobendan, as outlined in the Stage C guidelines above. Any indicated and tolerated antiarrhythmic medication, needed to maintain sinus rhythm (if possible) or regulate the ventricular response to atrial fibrillation in a heart rate range of 80–160/min, also should be used before a patient is considered refractory to standard therapy.

Not surprisingly, there have been very few clinical trials addressing drug efficacy and safety in this patient population. This leaves cardiologists treating patients with heart failure refractory to conventional medical therapy with a perplexing variety of treatment options. Because of the relative lack of clinical trial evidence and the diverse clinical presentations of patients with end-stage heart failure, development of meaningful consensus guidelines regarding the timing and implementation of individual pharmacologic and dietary treatment strategies for Stage D patients proved difficult. As with Stage C, guidelines for drug treatment are provided for both in-hospital (acute) and for home care (chronic) management of heart failure, and recommendations for chronic dietary therapy are also given.

Diagnosis for Stage D

- Because Stage D heart failure patients are, by definition, refractory to the treatments for Stage C patients, defining refractory congestive heart failure involves the same diagnostic steps outlined for Stage C plus the finding of failure to respond to treatments outlined in the Stage C guidelines.

Acute (Hospital-Based) Therapy for Stage D (Refractory Heart Failure)

Consensus recommendations:

- In the absence of severe renal insufficiency (ie, serum creatinine concentrations > 3 mg/dL), additional furosemide is administered IV as a bolus at a dosage of 2 mg/kg followed by either additional bolus doses, or a furosemide CRI at a dosage of 1 mg/kg/h until respiratory distress (rate and effort) has decreased, or for a maximum of 4 hours. As indicated above, the dosage or furosemide is a range and higher or lower doses may be appropriate for a given case.
- Continue to allow patient free access to water once diuresis has begun.
- Fluid removal (eg, abdominal paracentesis, thoracocentesis) as needed to relieve respiratory distress or discomfort.
- In addition to oxygen supplementation as in Stage C (above), mechanical ventilatory assistance may be useful to make the patient more comfortable, to allow time for medications[35] to have an effect; and to provide time for left atrial dilatation to accommodate sudden increases in mitral valve regurgitant volume in patients with acute exacerbation of CVHD (eg, ruptured chordae tendinae with severe cardiogenic pulmonary edema) and impending respiratory failure.
- More vigorous afterload reduction in patients that can tolerate arterial vasodilation. Drugs potentially beneficial include sodium nitroprusside (starting at 0.5–1 μg/kg/min), hydralazine (0.5–2.0 mg/kg PO), or amlodipine (0.05–0.1 mg/kg PO). Direct vasodilators should be started at a low dosage and up-titrated hourly until adequate clinical improvement accompanied by a decrease of approximately 5–10% in systolic blood pressure is observed. These drugs are recommended in addition to an ACEI and pimobendan. The clinician should be mindful that any decline in blood pressure will also depend on specific vasodilator drug. For example, vasodilation effects are rapid onset with nitroprusside, but slower with amlodipine. Caution is warranted to avoid serious, prolonged hypotension (ie, monitor blood pressure and main-

tain systolic arterial blood pressure > 85 mmHg or mean arterial blood pressure > 60 mmHg. Serum creatinine concentration should be measured before and 24–72 hours after administration of these drugs. Patients in Stage D have life-threatening heart failure, and a trial of additional afterload reduction is warranted. The panel emphasized that because afterload reduction may increase cardiac output substantially in the setting of severe MR and heart failure, administration of an arterial dilator in this setting does not necessarily decrease blood pressure.

No consensus was reached regarding the following acute care Stage D recommendations:

- Pimobendan dosage may be increased (off-label) to include a 3rd 0.3 mg/kg daily dose. Some panelists administer an additional dose of pimobendan on admission of Stage D patients with acute pulmonary edema. Because this dosage recommendation is outside of the FDA-approved labeling for pimobendan, this use of the drug should be explained to and approved by the client.
- In animals judged to be too sick to wait for the effects of oral afterload reduction or inotropic support (eg, pimobendan with or without hydralazine or amlodipine), nitroprusside (for afterload reduction in life threatening pulmonary edema) or dobutamine (for inotropic support of the hypotensive patient) must be administered by CRI. Both drugs can be administered at dosages of 0.5–1.0 μg/kg/min and up-titrated every 15–30 minutes to a maximum of approximately 10 μg/kg/min. These drugs, either separately or in combination, can be used for 12–48 hours to improve hemodynamic status and control refractory cardiogenic pulmonary edema. Continuous electrocardiographic and blood pressure monitoring is recommended to minimize the potential risks of this therapy.
- Sildenafil (1–2 mg/kg PO q12h) is used by a minority of panelists to treat acute exacerbations of Stage D heart failure caused by CVHD, even in the absence of diagnosed pulmonary hypertension.
- Bronchodilators are recommended as an adjunct therapy in treating cardiogenic pulmonary edema in hospitalized patients by a minority of panelists.

Home-Based (Chronic) Stage D Therapy

Consensus recommendations:

- Furosemide dosage should be increased as needed to decrease pulmonary edema or body cavity effusions, if use is not limited by renal dysfunction (which generally should be monitored 12–48 hours after dosage increases). The specific strategy and magnitude of dosage increase (eg, same dose increased to 3 times per day versus 2 higher doses, substituting 1 SC dose for a PO dose q48h, or flexible SC dose supplementation based on body weight or girth measurements) varied widely among the panelists.
- Spironolactone, if not already started in Stage C, is indicated for chronic treatment of Stage D patients.
- β blockade generally should not be initiated at this stage unless clinical signs of heart failure can be controlled, as outlined in Stage C.

No consensus was reached regarding the following chronic Stage D therapeutic recommendations:

- Hydrochlorthiazide was recommended by several panelists as adjunctive therapy with furosemide, utilizing various dosing schedules (including only intermittent use every 2nd–4th day). Some panelists warned of the risk of acute renal failure and marked electrolyte disturbances, based on personal experience.
- Pimobendan dosage is increased by some panelists to include a 3rd 0.3 mg/kg daily dose (off-label use, explanations and cautions apply as listed for in-hospital care, above).
- Digoxin, at the same (relatively low) dosages recommended by some panelists for Stage C heart failure, was recommended for treatment of atrial fibrillation for patients in Stage D, with the same cautions listed in Stage C above.
- Digoxin, at the same (relatively low) dosages recommended by some panelists for Stage C heart failure, also was recommended by a minority of panelists for all patients in Stage D in sinus rhythm, assuming no clear contraindication was present.
- Sildenafil (1–2 mg/kg PO q12h) is used by some panelists to treat Stage D heart failure caused by CVHD or to treat advanced CVHD complicated by pulmonary hypertension.
- The majority of panelists felt that β blockade initiated at an earlier stage of heart failure in CVHD should not be discontinued, but that dose reduction may be needed if shortness of breath could not be controlled by the addition of other medications or if bradycardia, hypotension, or both were present.
- β blockade still may be useful to decrease the ventricular response rate in atrial fibrillation after stabilization and digitalization.
- Cough suppressants are recommended by a minority of panelists to treat chronic, intractable cough in Stage D patients receiving home care.
- Bronchodilators are recommended by a minority of panelists to treat chronic, intractable coughing in Stage D patients receiving home careanelists.

Home-Based (Chronic) Dietary Therapy for Stage D

Consensus recommendations:

- All of the dietary considerations for Stage C (above) apply.
- In patients with refractory fluid accumulations, attempts should be made to further decrease dietary

sodium intake if it can be done without compromising appetite or renal function.

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