TREATMENT OF THE CHRONIC CANINE CHF PATIENT

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BEFORE WE GET STARTED…

▸ EPIC study results
▸ Large, randomized, multicenter, double blinded study to investigate pimobendan therapy for dogs with asymptomatic mitral valve disease
▸ Could pimobendan delay onset of CHF or cardiac related death/euthanasia in dogs?
▸ 360 dogs with preclinical disease enrolled
▸ > 6 years of age, 4-15 kg body weight, moderate murmur, cardiomegaly (VHS > 10.5, LA/Ao > 1.6, LVIDdn > 1.7)

EPIC STUDY RESULTS

▸ Final analysis found time to primary endpoint (CHF or cardiac death) for pimobendan group was 1228 days vs 766 days for placebo group (P value 0.0038)
▸ Pimobendan well tolerated with no difference of adverse effects with placebo group
▸ Time to secondary endpoint (composite of CHF, euthanasia or death due to non-cardiac reason) favored pimobendan (640 days vs 406 days for placebo)
How to Apply These Results?

- Not all dogs with murmurs should be treated with pimobendan.
- Considerations to the following patients:
  - Small breed dogs with moderate mitral murmur with evidence of cardiomegaly (radiographic and echo).
  - If criteria not met, re-evaluate in 6-12 months.
  - If echo is not possible, initiate therapy when VHS exceeds 11.5 or an incremental increase of > 0.5 vertebral bodies per 6 months is documented.

**Congestive Heart Failure**

- Occurs when the heart cannot meet the demands of the tissues (diastolic, systolic impairment).
- Occurs in patients with underlying cardiac disease:
  - Degenerative mitral valve disease.
  - Dilated cardiomyopathy.
  - Congenital cardiac disease (PDA, SAS, mitral valve dysplasia).
**REMINDER: PRESENTING COMPLAINTS OF CHF**

- Dyspnea, coughing, orthopnea, tachypnea
- Syncope
- Lethargy, exercise intolerance, weakness
- Many dogs will have a reduced appetite
- Abdominal distension
  - Ascites, hepatomegaly

**REMINDER: PHYSICAL EXAM FINDINGS IN CHF**

- Slow CRT, mucous membrane cyanosis
- Cool extremities
- Harsh lung sounds, crackles
- Thrill/cardiomegaly on precordial palpation
- Heart murmur, gallop sound
- Weak pulses (DCM), pulse deficits (if arrhythmia)
- Arrhythmias
- Ascites, hepatomegaly (right sided CHF)

**REMINDER: THORACIC RADIOGRAPHS**

- Evaluate for cardiomegaly
- Evaluate for pulmonary venous/artery distension
- Evaluate for pulmonary infiltrates
  - Thoracic radiographs are our gold standard for the diagnosis of CHF in veterinary patients
    - Echocardiography cannot diagnose CHF
REMINDER: DEVELOPMENT OF PULMONARY EDEMA

1. Cardiomegaly
   - Left atrial enlargement
2. Pulmonary venous distension
   - Leads to capillary hypertension
3. Interstitial pulmonary edema
   - Peribronchial and interstitial changes (mild-moderate CHF)
4. Alveolar pulmonary edema
   - Air bronchograms (advanced, severe CHF)

APPEARANCE & DISTRIBUTION OF PULMONARY EDEMA

- Interstitial edema most common in mild-moderate CHF cases
  - Peribronchial pattern may also be noted
- Appears first in the central peri-hilar region progressing outward and caudodorsally
- On the DV/VD view, often affects right caudal lung lobe (dogs with MR)
- Changes are often symmetric on DV/VD

Pulmonary venous distension? Lungs too white?
Heart too wide?
Localized cardiac enlargement?
Lungs too white?

Vicious Circle of Congestive Heart Failure

Cardiac Output
Vascular resistance
Blood Volume

GOALS OF CHF THERAPY

- Reduce Preload
  - Diuretics, ACE inhibitors, venodilators, pimobendan
- Reduce Afterload
  - Diuretics, ACE inhibitors, pimobendan
- Enhance contractility
  - Pimobendan
- Control any arrhythmias
### STANDARD OF CARE CHF THERAPY IN DOGS

- Furosemide
- ACE inhibitor
- Pimobendan
- +/- spironolactone
- Salt restriction
- Adjunctive therapies: amlodipine, hydralazine, hydrochlorothiazide

### PRELOAD REDUCERS

- Diuretics
  - Furosemide, torsemide, hydrochlorothiazide (HCTZ), spironolactone
  - Goal = attain lowest effect dose to control congestion while maintaining renal function
  - Due to progression of underlying cardiac disease, dose is generally uptitrated based on clinical signs and/or thoracic radiographs

### FUROSEMIDE

- Loop diuretic
- Blocks water reabsorption in the thick segment of the ascending loop of Henle
- Enhanced excretion of Na, Cl, K
- Weak bronchodilating, anti-tussive effects
- Goal: Reduces preload to help resolve pulmonary edema by reduced pulmonary capillary wedge pressures (hydrostatic pressure)
FUROSEMIDE

- Adverse effects:
  - Potential ototoxicity
  - Pre-renal azotemia, severe dehydration can lead to renal failure
  - Hypotension if volume depleted
- Dosing: 1-4 mg/kg PO q. 8-12 hrs
- Monitoring: Renal values, electrolytes

CARDIAC VS RENAL - THE CAREFUL BALANCE

<table>
<thead>
<tr>
<th>Balancing renal and pulmonary issues</th>
<th>Renal Status</th>
<th>Urea/Creat: Normal</th>
<th>Urea/Creat: Abnormal or increasing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Edema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolving (mild)</td>
<td></td>
<td>Reduce diuretics +</td>
<td>Increase forward blood flow: reduce diuretics +++ increase water intake; positive inotrope</td>
</tr>
<tr>
<td>Progressing (severe)</td>
<td></td>
<td>Increase diuretics; positive inotrope; arterial vasodilator</td>
<td>Increase forward blood flow: maintenance fluid; strong pos. inotrope + strong art. vasodilator</td>
</tr>
</tbody>
</table>

* Ongoing rate control if atrial fibrillation is present

PRELOAD & AFTERLOAD REDUCERS

- Mixed vasodilators
  - ACE inhibitors
  - Pimobendan
- Arterial vasodilators
  - Amlodipine
  - Hydralazine
REMINDER – RENIN ANGIOTENSIN ALDOSTERONE SYSTEM (RAAS)

ACE INHIBITORS

▸ Block the negative effects of long term RAAS activation (which are unrelated in CHF and in patients receiving furosemide)
  ◆ Angiotensin II
    ▸ Increases afterload = increased myocardial oxygen demand
    ▸ Activates vasopressin/ADH system
    ▸ Causes myocardial necrosis
  ◆ Aldosterone
    ▸ Increases preload
    ▸ Causes myocardial fibrosis

ACE INHIBITORS

▸ Generally started after stabilization of acute CHF in a patient who is eating
  ◆ Benazepril
    ▸ Dosed at 0.5 mg/kg PO q. 12-24 hrs
    ▸ Partial liver metabolism (55%) and renal (45%)
  ◆ Enalapril
    ▸ Dosed at 0.5 mg/kg PO q. 12-24 hrs
    ▸ Renal metabolism (95%)
    ▸ Comes in a smaller tablet size - 2.5 mg
EVIDENCE BASED MEDICINE & ACE INHIBITORS

- COVE trial (1995 JVIM) - QOL in dogs with MR or DCM & CHF
  - QOL parameters were improved in enalapril group vs placebo

- LIVE trial (1998 JAVMA) - Survival in dogs with MR or DCM & CHF
  - Mean time to endpoint in MR
    - Enalapril 159.5 days; placebo 86.6 days
  - Mean time to endpoint in DCM
    - Enalapril: 143 days; placebo 57 days

EVIDENCE BASED MEDICINE & ACE INHIBITORS

- BENCH Trial (JVC 1999) - ACE inhibitor improves survival in dogs with CHF due to MR or DCM
  - Randomized, double blind, placebo multicenter study
  - MR dogs (125):
    - Benazepril group (70): 436 days
    - Placebo group (55): 151 days
  - DCM (37):
    - Benazepril group (17): 394 days
    - Placebo group (20): 164 days

SPIRONOLACTONE

- Potassium sparing diuretic, aldosterone antagonist
  - Competitively inhibits binding of aldosterone to its receptors in many tissues
  - WEAK diuretic effect
  - Benefits: possible reduced cardiac remodeling and fibrosis; sequential nephron blockade in refractory CHF; vasodilator properties by aldosterone antagonism
  - Side effects: Hyperkalemia, GI signs
  - Dose: 1-2 mg/kg PO q. 12-24 hrs
**AMLODIPINE**

- Calcium channel blocker which produces arteriolar vasodilation
- Little effect on conduction
- Negative inotropic effect offset by afterload reduction
- Useful in dogs with MR, especially when hypertension is present (> 150-160 mmHg systolic)
- Dosed at 0.1-0.25 mg/kg PO q. 24 hrs

**HYDRALAZINE**

- Direct acting arterial vasodilator
- MR studies revealed that it significantly decreased arterial blood pressure, systemic vasculature resistance index and pulmonary capillary wedge pressures
- Side effects are very common: hypotension, anorexia, vomiting, diarrhea and reflex tachycardia
  - Therefore generally reserved for acute CHF therapy
  - Increases aldosterone levels, angiotensin levels
    - If used, combine with ACE inhibitor
  - Dose: 0.5 mg/kg PO q. 12 hrs

**PIMOBENDAN (VETMEDIN)**

- Positive inotrope and balanced vasodilator (inodilator)
- Inotropy due to:
  - Calcium sensitization, PDE-3 inhibition
  - Arterial & venous dilation
    - PDE-3,5 inhibition (PDE-5 inhibition may be helpful with PH)
- Other actions:
  - Increases appetite in some and improves other indices of well-being
- Dose: 0.50 mg/kg daily dose divided (does not have to be equal doses)
- Indications: MR dogs (pre-clinical and clinical), DCM dogs (pre-clinical and clinical)
Dilated Cardiomyopathy

Fuentes et al JVIM 2002 - Dobermans & Cocker Spaniels with DCM & CHF

Objective: increase survival & QOL when pimobendan added to conventional therapy (diuretics, ACE inhibitors, digoxin)

Results:
- Dobermans: Pimobendan 329 days, placebo 50 days
- Cocker Spaniels: Pimobendan 1037 days, placebo 537 days
- Improvement in QOL scores in both groups

Mitral Valve Disease

QUEST Trial (JVIM 2008)

Dogs with MR & CHF to determine if pimobendan when added to conventional therapy of a diuretic will extend time to sudden death, euthanasia for cardiac reasons or treatment failure when compared to benazepril when added to the same conventional therapy

Results (median time to primary endpoint)
- All dogs: 188 days
- Pimobendan dogs (124): 267 days
- Benazepril dogs (125): 140 days

ARRHYTHMIAS

Atrial fibrillation - common in canine patients with CHF

Rapid arrhythmia which contributes to increased left atrial pressures, reduced stroke volume (forward flow) and increased myocardial oxygen consumption

Will often decompensate a previously stable patient

Rates generally exceed 200 bpm
ATRIAL FIBRILLATION TREATMENT

- Two strategies: rate control vs rhythm control
- Rate control:
  - Combination of diltiazem (0.5-3 mg/kg PO q. 8 hrs - uptitrate slowly based on rate control) and digoxin (0.003-0.005 mg/kg PO q. 12 hrs)
  - In large dogs, can use Dilacor XR 2-4 mg/kg PO q. 12 hrs (extended release)
  - Goal rate is 130-160 bpm (patient dependent)

ATRIAL FIBRILLATION & RHYTHM CONTROL

- Electrical cardioversion for rhythm restoration
- Useful in patients who are failing medical management (rate control)
- In people, rhythm control associated with improved exercise capacity
- Heart failure can be better managed when in sinus rhythm
### TREATMENT SUMMARY

- **Preload: too high**
  - Diuretics, ACE inhibitors, pimobendan
- **Afterload: too high**
  - ACE inhibitors, pimobendan, arterial dilators
- **Enhance contractility**
  - Pimobendan
- **Neurohormonal activation**
  - ACE-inhibitors, spironolactone
- **Control any arrhythmias**

### PATIENT MONITORING

- **Within 2 weeks of starting CHF therapy**
  - Renal panel (BUN, creatinine, Na, K, Cl)
  - Thoracic radiographs
    - Re-evaluate for pulmonary edema
  - Blood pressure
    - Ensure no deleterious effects of vasodilators

### PATIENT MONITORING CONTINUED

- **Dose of furosemide is titrated to the lowest effective dose to control clinical signs/pulmonary edema without deleterious effects on renal function - should still be dosed twice daily**
- **Re-assessment in one month, then every 3 months thereafter if doing well**
- **Owner education regarding at-home monitoring and clinical signs to prompt re-evaluation**
- **Better educated clients = better compliance & better quality of life for our patients**
PROGNOSIS

- Prognosis depends on severity of disease at time of diagnosis
- Cardiologist can help provide this information
- CHF should be considered a chronic condition requiring long-term management strategies
- Adjustments in medications when complications occur/disease progresses
- MR & CHF survival times can generally be between 12-24 months
- DCM & CHF survival times can generally be between 6-12 months

CLIENT EXPECTATIONS

- Manage client expectations
  - Even with successful management, not all signs (such as cough) will disappear
    - Concurrent small airway disease
    - Concurrent joint disease may limit activity levels
  - Once CHF managed, we can work on other issues to improve & optimize quality of life
  - Cost - similar to other chronic health problems
    - Online pharmacies, Costco, dividing larger pimobendan tablets

AT-HOME MONITORING

- What to coach your clients to monitor:
  - SRR > 35 bpm suggestive of CHF
    - Monitor daily to several times weekly; if consecutively > 20% baseline, re-evaluate
    - Have owners recheck SRR increases in 10-60 minutes - real increases are consistent and that way spurious results are not over-interpreted
  - Phone Apps: Your Dogs Heart, Cardalis
  - PetPace Collar: Tracks heart rate, respiratory rate
AT-HOME MONITORING

- What to coach your clients to monitor:
  - Cough - not always sensitive to CHF
  - Exercise capacity - not always sensitive
  - Orthopnea - a change in sleeping habits or body positions with sleep can be suggestive of CHF
  - Appetite

COUGHING

- Continued coughing common in small breed dogs with severe MR and history of CHF
  - Can be due to recurrence of CHF, left mainstem bronchus compression secondary to left atrial enlargement (with concurrent tracheal-bronchial malacia), primary small airway disease
  - Chronic bronchitis, collapsing trachea

LEFT MAINSTEM BRONCHUS COMPRESSION MANAGEMENT

- To achieve therapeutic goals:
  - Afterload reduction: ACE inhibitors, arterial vasodilator
  - Cough suppression: bronchodilators, antitussives
  - Preload reduction: increasing furosemide dose, limit salt intake
WHY DO PATIENTS DECOMPENSATE WITH STANDARD THERAPY?

- Inherent progression of disease
- Worsening MR, chordal rupture
- Systolic dysfunction
- Secondary pulmonary hypertension
- Arrhythmias
- Right sided CHF affecting absorption of medications
- Owner/patient compliance
- Diuretic resistance
- Systemic hypertension, other extra-cardiac disorders

MITRAL REGURGITATION CONSIDERATIONS

- If patient is refractory, consider additional vasodilation especially if systemic hypertension noted
- ACE inhibitor + amlodipine
- Maximize pimobendan dosing
  - Can increase to 0.3 mg/kg PO q. 8-12 hrs (off-label)
- Address any complications
  - Sildenafil for PH, treat any arrhythmias, address hypokalemia

DILATED CARDIOMYOPATHY CONSIDERATIONS

- Maximize pimobendan dosing
- Treat any documented arrhythmias
  - Treat concurrent hypokalemia
- Thoracocentesis/abdominocentesis for any effusions
WHAT TO DO WHEN REFRACTORY?
- Careful history taking
  - Evaluate medication compliance - if an issue, consider compounding & other strategies for administration
- Careful physical examination
  - Evidence of development of right sided CHF (ascites) may suggest an inability to absorb medications well due to gut wall edema
  - Consider SQ furosemide?

DIURETIC RESISTANCE – WHY?
- Hypertrophy of the distal tubule (aldosterone secretion contributes)
- Increased sodium and subsequent water reabsorption
- Rebound sodium and water retention
  - RAAS activation
- Decreased GFR leads to decreased furosemide reaching the loop of Henle
  - Poor cardiac output, azotemia, hypotension, NSAIDs, high diuretic dosing

DIURETIC RESISTANCE – WHAT TO DO?
- Generally expected in patients receiving chronic diuretic therapy (>9-12 months)
- May note inappropriate urine specific gravity in a patient on diuretics
- Increase/maximize furosemide dosing
  - 4 mg/kg PO q. 8 hrs
- Add additional diuretics - sequential nephron blockade
  - Spironolactone, hydrochlorothiazide
- Change furosemide to torsemide
DIURETIC RESISTANCE - WHAT TO DO?

- Concurrent use of an NSAID? Consider alternatives
  - Tramadol, CBD, other modalities for osteoarthritis
- Ensure therapy with an ACE inhibitor
  - As long as patient tolerates
- Evaluate diet and avoid sodium excess

DIET & SODIUM

- Owners should be instructed to avoid high sodium foods:
  - Cheese, baby food, lunch meats, cold cuts, rawhides
- Recommended sodium content in diet:
  - <80 mg sodium/100 kcal
- Help owners administer medications without need for food
  - Pill guns, empty gelatin capsules
- Use low Na foods for medication administration
  - Meat or fish (home cooked without salt); low sodium canned pet food; fresh fruit (bananas, melons, berries); no-salt peanut butter; marshmallows; go easy on the pill pockets!

ADDITIONAL DIURETICS

- Hydrochlorothiazide (HCTZ)
  - Thiazide diuretic
  - Inhibits Na/Cl co-transporter in the distal convoluted tubule
  - Low ceiling diuretic: achieve maximal response at a relatively low dose
  - Longer duration of action than loop diuretics
  - Decreased capacity to work well in face of renal insufficiency
  - Dose: 1-2 mg/kg PO q. 12-24-48 hrs
**ADDITIONAL DIURETICS**

- Torsemide
  - Potent loop diuretic
  - Ten times more potent than furosemide
  - Longer duration of effect than furosemide
  - Possesses anti-aldosterone effects
  - Associated with development of azotemia, hypokalemia is common

**TORSEMIDE DOSING**

- Reported dosage in dogs is 0.2 mg/kg PO q. 12 hrs
- When transitioning from furosemide, many will take the total daily dose of furosemide x 1/10, given divided twice daily
  - ie: if furosemide daily dose is 50 mg, torsemide dose is 5 mg/day, divided (2.5 mg twice daily)
- When in doubt, round down to tablet size (smallest tablet size is 5 mg)

**WHEN TO TRANSITION TO TORSEMIDE**

- Furosemide dose is maximized and heart failure persists
- Concern regarding diuretic resistance
- When longer duration of effect is needed and owners are unable to administer q. 8 hrs diuretic therapy
- Some cardiologists have used an injectable furosemide dose in a patient still receiving torsemide
  - Generally an advanced, refractory patient
ARRHYTHMIAS

- Tachyarrhythmias can contribute to refractory CHF
- In some dogs, can result in tachyarrhythmia induced cardiomyopathy
- Consider Holter monitors for dogs considered at risk for arrhythmias and treat significant arrhythmias
  - SVT, VT

PULMONARY HYPERTENSION

- Common in patients with mitral regurgitation
- Due to chronically increased LA pressures
- Pulmonary hypoxia and co-existing pulmonary disease can contribute
- Can result in right sided CHF (ascites > pleural effusion) which contributes to cachexia, poor appetite
- Reduced quality of life parameters

PULMONARY HYPERTENSION

- Diagnosed via echocardiography
- Should only be treated under guidance of a cardiologist as treatment could lead to significant increase in left heart preload and worsening pulmonary edema
- Treatment:
  - Maximize pimobendan
  - Sildenafil - low dose (0.5-2 mg/kg PO q. 8-12 hrs)
  - Ensure optimized diuretic dosing
  - Centesis for patient comfort
CARDIAC CACHEXIA

- Contributes to clients perception of poor quality of life
- Due to production of TNF and other inflammatory cytokines; poor appetite (food aversion, medications, azotemia, right sided CHF, pancreatitis); protein loss
- Ensure good nutrition
  - Enticing foods, appetite stimulates, anti-nausea therapy
  - Manage azotemia
  - Omega fatty acid supplementation
  - 45 mg/kg of EPA:DHA per day
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- Manage azotemia
- Omega fatty acid supplementation
- 45 mg/kg of EPA:DHA per day
- Consider consultation with a veterinary nutritionist
- Formulate diet to maximize caloric intake (> 60 kcal/kg) and minimize sodium intake and optimize protein intake
  - Renal diets should be avoided in cardiac patients unless they have concurrent renal disease
  - Tufts - offers phone consults
  - Consider feeding tube placement

OTHER CONSIDERATIONS FOR THE REFRACTORY CHF PATIENT

- Consider admission to the hospital for more aggressive CHF therapy for 24-48 hrs:
  - Oxygen, Positive inotropes such as dobutamine, IV furosemide
  - Blood pressure control in a patient with chordal rupture
  - Treatment of hypotension
  - Treatment of significant azotemia
  - Replace one of the oral furosemide doses with a SQ dose