Management of Refractory Heart Failure
Reaching Beyond the Triple Threat

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Standard CHF therapy

**Dogs**
- Furosemide
- Pimobendan
- ACE-inhibitor

**Cats**
- Furosemide
- ACE-inhibitor
- Clopidogrel (Plavix)
- Pimobendan*

*Reina-Doreste et al. Case control study of the effects of pimobendan on survival in cats with HCM and CHF, JAVMA 2014

Prognosis for CHF

- K9 valve disease 12-18 months average
- K9 DCM 3-12 months average
- Feline HCM 12-18 months
Causes of Recurrent CHF

Disease progression → Rads, Echo, ECG/Holter
- Valve regurgitation, progressive valve pathology, chordal rupture
- Progressive myocardial failure
- Arrhythmias
- Pulmonary hypertension

Causes of Recurrent CHF

Medication issues
- Owner / pet compliance
- Diuretic resistance
Anamnesis
Compounding trial
Dosage assessment

Causes of Recurrent CHF

Concurrent medical diseases
- Systemic hypertension – persistent or intermittent
- Thyroid disease
- Pneumonia
- Pancreatitis
Thoracic radiographs
Blood pressure
Bloodwork
Addressing Recurrent CHF

More diuresis
- Increase / maximize furosemide
- Add 2nd or 3rd diuretic
  - Spironolactone
  - Hydrochlorothiazide
- Switch diuretics
  - Replace furosemide with torsemide

Addressing Recurrent CHF

More vasodilation to reduce afterload for MR
- Start ACE-I if not already on board
- Amlodipine
- Maximize pimobendan dose
- Treat complications
- Sildenafil to treat pulmonary hypertension
- Control arrhythmias
- Treat concurrent conditions
- Cats – withdraw or lower dose of β-blocker

Clinical Cases of Recurrent or Refractory CHF
“Ginger” 2yr Mc DSH

First onset CHF (HCM) 2 months ago
Hospitalized 4 times for severe pulmonary edema

Current medications after 4th hospitalization
- Furosemide 18.75 mg PO BID with 12.5 mg midday
- Benazepril 1.25 mg PO SID
- Clopidogrel 18.75 mg PO SID
- Pimobendan 1.25 mg PO BID

Bloodwork
- BUN 32
- Creat 2.0
- K 4.2
Diuretic Resistance - What causes it?

- Glomerular Filtration Rate results in decreased delivery of furosemide to the nephron

1. Decreased cardiac output
   - Myocardial dysfunction
   - Dehydration
2. Renal insufficiency (Cardiorenal syndrome)
3. NSAIDs
4. Hypotension
5. Diuretic use...bummer

More Causes of Diuretic Resistance

- Rebound Na and water retention
  - Decreased GFR
  - SNS stimulation
  - Short acting diuretics

- Loss of responsiveness to endogenous natriuretic peptides

- Ascending Loop of Henle hypertrophy (overexpression of Na/K/Cl cotransporter)

Options to Address Diuretic Resistance

- Sequential nephron blockade
  - Thiazides (early distal tubule)
  - Spironolactone (late distal tubule)

- Alternatives to NSAIDS

- Avoid rebound Na retention
  - Frequent furosemide dosing
  - Furosemide CRI
  - Switch to longer acting diuretic (torsemide)
**“Ginger”**

Treatment options?
Oral furosemide is already maximized...

- Parenteral furosemide
- Add a 2nd diuretic
  - Spironolactone
  - Hydrochlorothiazide
- Replace furosemide with torsemide

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**Torsemide**

Loop diuretic with anti-aldosterone action

- Approximately 10x more potent than furosemide
- Longer duration of action than furosemide
- Reduced mortality/morbidity in people
- Less diuretic resistance
- Oral dosing only
- 5mg, 10mg, 20mg, 100mg

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**He is Mr. Puff**

Tormax-10

Distress to Delighted

- Mr. Puff is a very snuggly and lovable cat
- He is a friendly and fun-loving pet
- Mr. Puff loves to play and is always up for a good time
- He is very affectionate and will cuddle with his owner

**Torsemide studies**

*Uehi et al J Vet Med Sci 2003*
- Cats (experimental) 0.3 mg/kg PO SID
- Dogs (experimental) 0.2 mg/kg PO SID
- Increased urine output
  - Onset 1 hr, peak 2-4 hrs, duration 12 hrs (furosemide duration 6 hrs)
- Increased plasma aldosterone

*Hori et al AJVR 2007*
- Dogs (experimental) 2 mg/kg PO BID furosemide vs. 0.2 mg/kg PO BID torsemide
- Higher urine volume after 14 days compared to furosemide
- Higher aldosterone compared to furosemide

*Peddle et al JVC 2012*
- 7 MR dogs with CHF, 14 day crossover study
- Torsemide dose 1/10 furosemide dose, divided BID
- Higher BUN, creat, PO4, TCO2, albumin compared to furosemide
- Lower USG than furosemide, no difference in potassium
- Similar control of CHF signs

*Giatis et al ACVIM Forum Presentation 2014*
- Retrospective - torsemide in 17 cats with refractory / rapidly recurrent CHF
- Creatinine higher (2.2 pre, 2.4 post) and K lower (4 pre, 3.6 post) after torsemide

**Clinical Use**
- Clinical success with refractory cases
- Potential for dehydration / azotemia
- Hypokalemia requiring K+ supplementation is common
- Compounding into liquid is often necessary for cats, small dogs
- When to make the switch is evolving.....
“Ginger”

Torsemide – what dose??
- Current furosemide dose 18.75 mg PO BID with 12.5 mg midday (CHF controlled)
- 50 mg/day furosemide + 10 = 5.0 mg
- 5.0 mg torsemide/day + 2 = 2.5 mg
- Torsemide 2.5 mg PO BID (use 5 mg tabs or compound for greater future dosing precision)

“Ginger”

Follow-up
- BUN 43 (was 32)
- Creat 2.9 (was 2.0)
- K 3.3 (was 4.2)

“Ginger”

Additional medications
- Spironolactone 6.25 mg PO BID
- Potassium supplementation
1 week later
- BUN 45 (was 43)
- Creat 2.9 (was 2.9)
- K 3.8 (was 3.3)

No CHF for a year!
Take home points from “Ginger”

- Diuretic resistance can be challenging
- Torsemide dosing / potency
- Hypokalemia is common
- Currently used as rescue therapy – will this change?

“Gabe” 8yr Mc Boxer

Chief Complaint

- Cough
- Dyspnea
- Syncope

“Gabe”

Hospitalized for CHF treatment with CRI furosemide and O2
“Gabe”

Blood pressure 120 mmHg
CBC/Chem – unremarkable
T4 2.3
Whole blood taurine - pending

“Gabe”

Diagnosis – Dilated Cardiomyopathy
- Furosemide
- Pimobendan
- Benazepril
- Taurine supplementation until test returned as normal (not deficient)

2 recurrent episodes of CHF in 1 month → maximized doses
- Furosemide (4 mg/kg PO TID) and pimobendan (0.3 mg/kg PO TID)

Further diagnostics?

“Gabe”

In-house telemetry
Differential diagnoses
- Arhythmogenic Right Ventricular Cardiomyopathy of Boxers (ARVC, aka
  Boxer Cardiomyopathy) with DCM phenotype (myocardial dysfunction)
- ARVC of Boxers with the primary VT and secondary myocardial failure
  (tachycardia-induced cardiomyopathy)

What oral antiarrhythmic medications can Gabe receive in addition to CHF meds?
- Ideally avoid β-blockers
- Amiodarone
  - Class III (I, II, IV) K channel blocker
  - Side effects - liver, thyroid
- Mexilitine
  - Class I Na channel blocker
  - Side effects - GI, neuro

Mexilitine prescribed 150 mg PO TID
+Furosemide, benazepril, pimobendan
Marked tremors occurred after 3 doses
Dosing decreased to BID with no improvement
Switched to amiodarone
- 300 mg PO BID x 1 week
- 200 mg PO SID
“Gabe”

Recheck in 3 weeks
- CBC, Chemistry panel, T4 – wnl
- Holter – sinus rhythm, 350 VPCs, no VT
- Radiographs – no edema, slightly smaller heart

“Gabe”

Recheck at 3 months
- CBC – wnl
- T4 – wnl
- Chemistry panel – ALT 467, AST 589, AP 753
- ECG – sinus rhythm
- Radiographs – no CHF, normal heart size

Recheck 3 months later
Echocardiogram

At presentation  | After 3 months of treatment

“Gabe”
Amiodarone liver toxicity
Tachycardia-induced cardiomyopathy (underlying Boxer ARVC)

Change to sotalol because hepatotoxicity has occurred and systolic function has normalized

“Gabe” 1 month later
Chemistry panel – liver values normalized
Recheck Holter monitor – good control
505 VPCs, 2 slow ventricular couplets, no VT
Take home points from “Gabe”

- Importance of cardiac rhythm assessment and control to aid in CHF control
- Antiarrhythmic drug toxicities

Questions?

“Max” 10 yr Mc Shepherd mix

2 year history of left sided CHF, well controlled on furosemide, pimobendan and benazepril

“Max” At home monitoring

- Respiratory rate
- Attitude, appetite

Recheck exams

- Radiographs
- Renal panel
- Blood pressure
Why monitor BP in valve disease?

- Hypotension is bad for the kidneys and organ perfusion
- Hypertension is bad for progression of valve disease and end-organ damage

![Diagram showing high and low resistance in the heart and its effects on pressure and pulmonary edema.]

“Max”
Sudden development of ascites after 2 years of stability

Tricuspid PG 58 mmHg
+ Est. PA press 70 mmHg
= Est. RA press 12 mmHg
= Est. PA press 70 mmHg

Mod/Severe PHT
+ Severe TR
= RHF
Why does Pulmonary Hypertension develop in Mitral Valve Disease?

Chronic MR
- LA pressure
- Pulm. venous pressure
- Pulm. arterial constriction
- Structural changes

Hypoxia → pulmonary vasoconstriction
Primary lung disease
Genetics
  - Stern et al JAVM 2014. Identification of PDE5A mutation resulting in lower cGMP levels - susceptibility to PHT?

“Max” – Treating PHT
Decrease pulmonary vascular resistance
  - Sildenafil inhibits cGMP specific PDE-5A
    - Selective pulmonary vasodilation (more cGMP)
    - Enhancement of natriuretic peptide vasodilation
    - Some (not all) studies have shown decreased PHT (10-15%) with consistent improvement in quality of life and symptoms
    - 1.7-2.0 mg/kg PO BID-TID
    - No systemic hypertension
    - Minimal side effects excepting SSS
"Max" - Treating PHT

Pimobendan
- PDE3 inhibition & Ca++ sensitization
- Atkinson et al JVIM 2009 – Pimobendan improved PHT, improved quality of life and lowered BNP in dogs with PHT secondary to mitral valve disease
  - Peripheral vasodilation and improved contractility resulting in lower left sided filling pressures
  - ? Direct pulmonary vasodilation?
- 0.25-0.3 mg/kg PO BID-TID

"Max" - Treating PHT

Right sided congestive heart failure treatment
- Continue benazepril
- Maximize furosemide → switch to torsemide
- Add spironolactone
- Periodic abdominocentesis
  - Every 3 weeks for 1.5 years
  - 1.5-2 liters/tap

"Max"

Progressive cachexia
- Cardiac cachexia
  - TNFα and other inflammatory cytokines
  - Freeman LM et al. Nutritional alterations and the effect of fish oil supplementation in dogs with CHF. JVIM 1998
- Inappetence
  - Medications
  - Azotemia
  - Ascites
  - Pancreatitis (Han et al. cPLI in dogs with CHF and MR. JVIM 2015)
- Protein loss through ascites
Fighting Cachexia

- Optimize nutrition
  - Enticing foods [http://vet.tufts.edu/heartsmart/diet/reduced_sodium_diet.html]
  - Appetite stimulants (e.g. mirtazapine)
  - Anti-nausea / anti-vomiting meds (e.g. maropitant, ondansetron)
  - Nutrition consultation
  - Feeding tubes
- Manage azotemia
- Fish oil supplementation*  
  - 45 mg/kg of EPA/DHA (3:2)


Take home points from “Max”

- Treatment of pulmonary hypertension secondary to chronic MR
- Role of abdominoentesis
- Managing cardiac cachexia
- Some CHF patients can live for an extended time if complications are closely managed (3.5 years for Max)

Questions?