Objectives

- Review the 5 Subtypes of the Cardiorenal Syndrome (CRS)
- Discuss the epidemiology and discriminating features of the CRS
- Assist in helping to understand the complexity of physiological, biochemical and neurohormonal derangements that complicate patient care
- Discuss treatment considerations in clinical management
Heart Failure Hits Home

Heart Failure Death Rates, 2007-2009
Adults Ages 35+, by County

ACC/AHA Guidelines: Management of Fluid Status

• Patients should not be discharged from the hospital until a stable and effective diuretic regimen is established, and ideally, not until euolemia is achieved

• Patients who are sent home before these goals are reached are at high risk of recurrence of fluid retention and early readmission because unresolved edema may itself attenuate the response to diuretics


The dilemma - we know what needs to be achieved but we have not been able to accomplish the desired outcome with any consistency or sustainability in many acutely decompensated heart failure patients

Inadequate Diuresis During ADHF Treatment (Adhere Registry)

Change in Weight From Admission to Discharge

Note: For the chart, n represents the number of patients who have both baseline and discharge weight, and the percentage is calculated based on the total patients in the corresponding column. Patients without a baseline or discharge weight are omitted from the histogram calculations.

ADHERE® Database

TheNation=26,757, 68%

Change in Weight (lb)

(>20) (15 to 20) (10 to 15) (5 to 10) (0 to 5) (-5 to 0) (-10 to -5) (-15 to -10) (-20 to -15) (-20)
Renal Disease Affects Readmissions and Mortality

- Majority (71%) of CHF patients with SCr >2.5 mg/dL (10% of CHF patients) will be readmitted within 6 months\(^1\)

- Concurrent renal disease, seen in 6.5% of acute CHF patients in a Canadian study, is a significant independent predictor of 30-day and 1-year mortality\(^2\)

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Impact of Renal Function on Survival in HF Ibopamine Trial \(n=1906\)

Definitions

- Cardiorenal Syndrome (CRS)
  - A condition in which there is dysfunction of both the cardiac and renal function
    - Seen in heart failure patients who have renal dysfunction
    - Seen in renal patients that develop cardiac dysfunction
  - Risk Factors that increase chances for both
    - HTN, Diabetes, Atherosclerosis
Schematic Overload

CRS Classifications

- Type 1 CRS reflects an abrupt worsening of cardiac function (e.g., acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury.
- Type 2 CRS describes chronic abnormalities in cardiac function (e.g., chronic congestive heart failure) causing progressive and permanent chronic kidney disease.
- Type 3 CRS consists in an abrupt worsening of renal function (e.g., acute kidney ischemia or glomerulonephritis) causing acute cardiac disorder (e.g., heart failure, arrhythmia, ischemia).
- Type 4 CRS describes a state of chronic kidney disease (e.g., chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events.
- Type 5 CRS reflects a systemic condition (e.g., diabetes mellitus, sepsis) causing both cardiac and renal dysfunction.

Type I CRS reflects an abrupt worsening of cardiac function (e.g., acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury.

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CRS Type I – Key concepts

- Acute
- Generally, four broad subsets of heart failure:
  - Acutely decompensated failure
  - Hypertensive failure with preserved EF and pulmonary edema
  - Cardiogenic shock
  - Right ventricular failure
- Consider pre-existing risk factors, such as:
  - Underlying renal insufficiency
  - Worsening heart failure class
  - Tachyarrhythmias
  - Hypo/Hypertension
  - High-dose diuretic therapy
- Primary clinical observation is inadequate renal perfusion leading to low cardiac output with marked elevation of venous pressures resulting in renal congestion.

CRS Type I – Treatment Considerations

- Decongestion is paramount
- If this is a relatively new condition the traditional approaches are often successful:
  - Diuretics
  - Vasodilators
  - And, in the case of cardiogenic shock -- pressors
- If acute on chronic, then it is often more difficult due to refractory treatment responsiveness.

References:

2. Pasquale Congest Heart Fail. 2007;13(2):93-98.
CRS Type 1 – Treatment Considerations cont.

- **Diuretics**
  - Loop diuretic preferred and intravenously
    - Bolus vs Continuous – Dose Trial
    - Augmented with low dose Dopamine – DAD-HF

- **Ultrafiltration – To Be or Not to Be**
  - UNLOAD, CARRESS, AVOID-HF – Up in the Air

- **Consider plasma refill rate/hemoconcentration**


CRS Type 1 – Treatment Considerations cont.

- **Vasodilators**
  - Nitroglycerin and nitropreside
    - Limited data and cautious recommendations
  - Nesiritide
    - Initially looked good but fell out of favor


CRS Type 1 – Treatment Considerations cont.

- **Inotropes/pressors**
  - More symptomatic relief, palliative measures, or bridge to decision – overall associated with high morbidity and mortality, especially arrhythmogenic death
  - More novel agents
    - Vasopressin
    - Levosimendan
    - Relaxin

2. Konstam MA, Jama. 2007-2012(12);1319-1331.
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**CRS Type 2 – Key Concepts**

- Chronic abnormalities – Cardiac is Primary (Type 2 and Type 4 are often very difficult to distinguish)
- Make an effort to discern which is primary – cardiac vs renal
- Very few chronic heart failure patients present without some degree of renal dysfunction (ADHERE); furthermore, this co-existent relationship is associated with poor outcomes.¹

¹ Heywood JT, J Card Fail. 2007;13(6):422-430.

**CRS Type 2 – Treatment Considerations**

- Primary goal is evidence based care of the patient
  - Aggressively prudent up-titration of ACE/ARB
    - Hypotension, NSAIDS
  - Carvedilol may have a more favorable effect on renal function²
  - Spironolactone should be considered with attention to hyperkalemia
  - How does PARADIGM fit into the CRS paradigm
    - Possibly more favorable renal effects²
  - Diuretics and diuretic resistance

Elevated Neurohormone Levels Cause Diuretic Resistance

- Glomerulus
  - Norepinephrine (and endothelin) decreases renal blood flow and GFR
- Proximal Tubule
  - Angiotensin II increases sodium reabsorption
- Collecting Duct
  - Aldosterone increases sodium reabsorption

Elevated neurohormone levels cause diuretic resistance. Angiotensin II increases sodium reabsorption in the proximal tubule, while aldosterone increases sodium reabsorption in the collecting duct. Norepinephrine (and endothelin) decreases renal blood flow and GFR in the glomerulus.
CRS Type 2 – Treatment Considerations cont

• Diuretic Resistance
  – Short-term (braking phenomena)
    • Poorly understood
  – Long-term distal nephron hypertrophy
    • May be benefited by combination therapy


Short-Term (Braking Phenomena)

Long Term tolerance

Tubular hypertrophy to compensate for salt loss
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CRS Type 3—Key Concepts

• Acute Kidney Injury
  – Contrast induced kidney injury
  – Drug-induced nephropathies
  – Kidney injury post major surgery
  – Rhabdomyolysis
  – Post-infectious glomerulonephritis

CRS Type 3 – Treatment Considerations

• Avoid the insult
  – Assess for vulnerable patient populations
  – Hydrate

• Novel therapies
  – Avert System Technology (AVERT clinical trial [NCT 01976299])

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CRS Type 4—Key Concepts

- Chronic abnormalities – Renal vs Primary (Type 2 and Type 4 are often very difficult to distinguish)
- Principle concept is clinical management aimed at slowing the progression of renal dysfunction

CRS Type 4 – Treatment Considerations

- Appreciate the degree of renal insufficiency when considering medications and dosage, i.e. digoxin
- Be mindful of over diuresis
- Consider the possibility of chronic anemia
  - No benefit in RED-HF(epo)\(^1\)
  - Interesting benefits of FAIR-HF (iron)\(^2\)


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CRS Type 5—Key Concepts

• Essentially, a simultaneous acute/chronic dysfunction of both the cardio and renal systems

• Limited studies and least understood; however, as more organs fail outcomes are obviously worse

CRS Type 5—Treatment Considerations

• Prompt identification and treatment of the offending source

• Hydration
  – Conservative vs Liberal\(^1\)

• Pressor consideration
  – Norepinephrine and vasopressor dopamine are both associated with high mortality but norepinephrine may have less adverse events\(^2\)


CRS – Complicated

• Cardio-Renal Syndrome is very real and very complicated

• It is a marker for Advanced Management

• It is a tremendous burden leading to readmissions and death

• Effective treatment must be unique to the patient