CRS Objectives

• Definitions & classification
• Pathophysiology
• Biomarkers
• Management
• Fluid management
• Emerging therapies
Tower of Babel
CRS Defined

• Condition characterized by kidney failure and heart failure; the failing organ precipitates failure in the other; the bidirectional interaction of these organs can create a nexus of deterioration of both
CRS Classification

- **Type 1:** Acute worsening of heart function leading to kidney injury
- **Type 2:**
- **Type 3:**
- **Type 4:**
- **Type 5:**

Cardiorenal Syndrome
Update 2012

Samuel Snyder, D.O.
snyderdo@nova.edu
CRS Classification

- Type 1: Acute worsening of heart function leading to kidney injury
- Type 2: Chronic abnormalities of heart function leading to kidney injuries or dysfunction
- Type 3:
- Type 4:
- Type 5:

CRS Type 2
CRS Classification

- **Type 1:** Acute worsening of heart function leading to kidney injury
- **Type 2:** Chronic abnormalities of heart function leading to kidney injuries or dysfunction
- **Type 3:** Acute worsening of kidney function leading to heart injury or dysfunction
- **Type 4:**
- **Type 5:**

CRS Type 3
CRS Classification

• Type 1: Acute worsening of heart function leading to kidney injury
• Type 2: Chronic abnormalities of heart function leading to kidney injuries or dysfunction
• Type 3: Acute worsening of kidney function leading to heart injury or dysfunction
• Type 4: Chronic kidney disease leading to heart injury, disease or dysfunction
• Type 5:

CRS Classification

• Type 1: Acute worsening of heart function leading to kidney injury
• Type 2: Chronic abnormalities of heart function leading to kidney injuries or dysfunction
• Type 3: Acute worsening of kidney function leading to heart injury or dysfunction
• Type 4: Chronic kidney disease leading to heart injury, disease or dysfunction
• Type 5: **Systemic conditions leading to simultaneous injury or dysfunction of heart and kidney**

Heart failure

- Sympathetic system activation
- Neurohormonal stress
- Inflammation
- Hemodynamic changes
- Hypoperfusion
- ↓Perfusion pressure
- ↑RVR
- Ischemia/reperfusion
- Hypoxia
- Oxidative stress
- Toxemia
- Exogenous toxins
- Heme proteins, antibiotics
- Contrast media
- LPS/endotoxin
- Monocyte activation
- Cytokines

Organ damage/dysfunction

Renal insufficiency

Systemic diseases
- Diabetes
- Amyloidosis
- Vasculitis
- Sepsis

CRS Type 5
Serum Creatinine as Biomarker in CRS versus
Don’t we measure renal function with Serum Creatinine?
Association between S Cr and other renal biomarkers

Biomarkers in CRS

Cystatin C

- Cysteine protease inhibitor produced by all cell nuclei
- Measured in blood and urine
- Appears sooner, superior diagnostic accuracy compared to S Cr, sensitive to lesser degrees of AKI or CIN, also in AHF
- Predicted readmission and mortality in AHF (1 yr all cause, sens 75%, spec 68%) even with mild AKI
KIM-1

- Transmembrane glycoprotein belonging to immunoglobulin gene superfamily
- Expressed on proximal tubule apical membrane cilia with injury, found in urine
- Detectable within 2-6 hr after AKI, where S Cr is up in 72 hr (CABG)
- Best predictive value compared with NGAL, NAG, cystatin C post CABG; little data in CIN; increased risk of death or hospitalization in AHF regardless of GFR
NGAL

- Human neutrophil gelatinase associated lipocalin, expressed by neutrophils and epithelial cells, involved in ischemic injury and repair, and in iron trafficking
- Measured in blood and urine
- Low sensitivity but high specificity (81%) for AKI after CPB, elevated as early as 2 hours; plasma appears superior to urinary values; good sens and spec for early dx in CIN; in AHF, associated with very high spec (87%) and sens (100%) for CRS; also correlated with NYHA class and BNP in chronic CHF
NAG

- Lysosomal enzyme from proximal convoluted tubule
- Enhances predictive power when used with KIM-1 & NGAL
- Correlates with GFR, RPF, BNP
- Associated with increased risk of death or hospitalization in HF, regardless of GFR
Natriuretic Peptides

• Released in response to ventricular wall stress, volume expansion, pressure overload in HF
• Increase GFR & Na⁺ & water excretion, vasodilation, inhibit RAAS
• Expanding role in diagnosis & prognosis of HF & CRS
## Biomarkers in CRS

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Associated Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHE3</td>
<td>Ischemia, pre-renal, post-renal AKI</td>
</tr>
<tr>
<td>Cytokines (IL-6, IL-8, IL-18)</td>
<td>Toxic, delayed graft function</td>
</tr>
<tr>
<td>Actin-actin depolymerizing F</td>
<td>Ischemia and delayed graft function</td>
</tr>
<tr>
<td>α-GST</td>
<td>Proximal T injury, acute rejection</td>
</tr>
<tr>
<td>π-GST</td>
<td>Distal tubule injury, acute rejection</td>
</tr>
<tr>
<td>L-FABP</td>
<td>Ischemia and nephrotoxins</td>
</tr>
<tr>
<td>Netrin-1</td>
<td>Ischemia and nephrotoxins, sepsis</td>
</tr>
<tr>
<td>Keratin-derived chemokine</td>
<td>Ischemia and delayed graft function</td>
</tr>
</tbody>
</table>

Adapted from Cruz DN et al, Seminars in Nephrol, Jan 2012.32(1):79-92.
Inflammatory Mediators in CRS

- TNF-α
- IL-6, IL-18
- Other cytokines
- C-reactive protein
- Adhesion molecules

Leading to:
- Cachexia
- Anemia
- Endothelial dysfunction
- Oxidative stress
- Distant organ dysfunction
Inflammation in CRS

**Acute or Chronic Heart Failure**

**Neurohormonal Activation**
- SNS
- RAAS
- AVP
- Endothelins

**Immune Activation**
- Complement
- Cytokines
- TNF
- Adhesion Molecules
- Immune cells

**Systemic Inflammatory Effects**
- Cachexia
- Anemia
- Depression
- Muscle Weakness
- Distant organ dysfunction
- Endothelial dysfunction
- Oxidative stress

**Left ventricular remodeling**
- Myocyte dysfunction
- Fibrosis

**Worsening Heart Failure**
Pathways of Immune Mediated Inflammation

- Direct antigenic stimulation, e.g., viral myocarditis or cardiac allograft rejection
- New antigenic peptides present on myocardium 2° to acute injury trigger immune response
- Local or systemic cytokine release
- Chronic ongoing injury, e.g., chronic HF
- Activation 2° to hemodynamic overload
Inflammation and Acute Kidney Injury

Ischemia-Reperfusion

Endothelial Cell activation
Dendritic Cell activation
DAMP Signaling

Impaired Vasodilation
Complement Activation
Coagulation
Leukocyte Infiltration

Capillary Obstruction and Continued Ischemia

Extension of AKI

Inflammation

Source: Seminars in Nephrology 2012; 32:70-78 (DOI:10.1016/j.semnephrol.2011.11.010)
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The cardiorenal anemia syndrome. Congestive heart failure (CHF) is a cause and consequence of CKD. First, CHF inflames the heart, liver, and vasculature, creating an influx of circulating cytokines that depress erythropoiesis and perturb iron metabolism [44]. Second, CHF directly induces kidney damage, in which GFR can deteriorate by as much as one mL/min/month [45–47]. In response to reduced cardiac output, blood pressure (and renal perfusion) is maintained by activation of the renin-angiotensin-aldosterone system. Angiotensin II-mediated renal vasoconstriction and increased metabolic demands of the kidney result in renal ischemia and ultimately tubular cell death [1]. Renal cell death in turn hastens anemia through loss of endocrine function. In addition, aldosterone-induced salt and water retention leads to an increased preload on the heart, which increases its rate in an attempt to increase output.

Vitamin D Receptor Activators in CRS

Pathophysiology of BMD in CKD
Role of Selective VDRA in CKD
Impact of VDRA on markers of CV disease

VDR Activators

Decreased:
- Hypertension
- Heart weight
- Left ventricular hypertrophy
- Posterior wall thickness
- Left ventricular end-diastolic pressure
- Brain Natriuretic Protein, Atrial Natriuretic Factor
- Renin and Angiotensin
- Vascular Endothelial Growth Factor
- Plasminogen Activator Inhibitor-1

Increased:
- Fractional shortening
- Vascular relaxation
- Thrombomodulin
Diagnosis & Management of Volume Overload in CRS

Wet or Dry?

Nephrologist

Cardiologist
Table 1. Common Clinical Features of Fluid Overload in ADHF

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Presentation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>87-93</td>
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<tr>
<td>Exertional</td>
<td>86-97</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>10-59</td>
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<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>13-39</td>
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<tr>
<td>At rest</td>
<td>1-6</td>
</tr>
<tr>
<td>Weight gain</td>
<td>5-15</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
</tr>
<tr>
<td>Jugular venous distention</td>
<td>5-54</td>
</tr>
<tr>
<td>Abdominal jugular reflex</td>
<td>6</td>
</tr>
<tr>
<td>Edema</td>
<td>35-70</td>
</tr>
<tr>
<td>Gallop</td>
<td>1-26</td>
</tr>
<tr>
<td>Rales</td>
<td>25-45</td>
</tr>
<tr>
<td>Ascites</td>
<td>3-17</td>
</tr>
</tbody>
</table>

Bioimpedance Vectorial Analysis

Source: Seminars in Nephrology 2012; 32:100-111 (DOI:10.1016/j.semnephrol.2011.11.013)
BIVA

Transthoracic

Intrathoracic
BIVA Tolerance Ellipses
- **Normally hydrated**: Tissue H2O 72.7% - 74.3%

- **Dehydration**: 72.7-71% = slight
  - 71-69% = moderate
  - <69% = severe

- **Hyperhydration**: 74.3-81% = slight
  - 81 and 87% = moderate
  - >87% = severe water overload (subclinical edema)
  - >87% = severe water overload (tissue edema)
BNP in relation to Hydration Status

Acute Volume Management

- Volume overloaded hypertensive patients
- Volume overloaded normotensive patients
- Volume overloaded hypotensive patients
- Preload reduction
- Afterload reduction
Diuretics

- Mainstay of pharmacologic therapy
- No clear evidence of improved long-term mortality
- Rapidly efficacious in volume reduction
- Increase activation of RAAS & SNS
- Compromise renal perfusion, renal underfilling
How to Diurese?

• Low dose v. high dose
• High dose: longer LOS, higher mortality, more azotemia, more ICU admissions in ADHF registry
• Continuous infusion
• Combination with nitrates, nesiritide
Fluid Removal by RRT

- **Intermittent:**
  - IHD

- **CRRT**
  - CVVH, SCUF
  - CVVHD, CVVHDF
  - SLEDD
  - PD: APD, CCPD
The Candidates

- Azotemia, baseline or progressive
- CKD or AKI
- Oliguria, absolute or relative
- Diuretic resistance
- CRS class?
Figure 4

CRS and Ultrafiltration

Ultafiltration

Creatinine

Day 0  Day 1  Day 2  Day 3  Day 4  Day 5

0 500 1000 1500 2000

0 0.8 1.2 1.4 1.6

BNP  Ultrafiltration

Source: Seminars in Nephrology 2012; 32:100-111 (DOI:10.1016/j.semnephrol.2011.11.013)
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Effects of CRRT in CRS

• Substantial weight loss
• Improvement in pulmonary congestion
• Increased diuresis at lower diuretic doses

However ...

• Conversion of nonoliguria to oliguria
• Increased neurohumoral activation
• Reduced renal perfusion pressure

Hemofiltration might ...

- Reduced lung water, improvement in dyspnea, cardiac function, gas exchange, edema, ascites, effusions, cardiac filling pressures, heart rate, BP, SVR
- Preserved effective circulating volume
- Reduced NE, PRA, aldosterone, increased renal perfusion and diuresis

Lack of Standardized ...

• Definitions
• Patient populations
• Therapies
• Trials
Lack of Standardized...

• Definitions
• Patient populations
• Therapies
• Trials
• Results
What about PD?
“5B” Approach to Management

- Balance of fluids
- Blood pressure
- Biomarkers
- Bioimpedance
- Blood volume

Innovations
Unifying Hypothesis?

Diabetes and Hypertension

Mineral and Bone Disorder

Proteinuria

Cachexia

Uremic Solute Retention

Obesity/Cardiometabolic

Iron Reutilization Defect/Relative EPO Deficiency/Anemia

Normal, ↑Risk, Damage, ↓GFR, Failure, Death

Impaired Renal Reserve, Partial Recovery

Ronco C, JACC.2012.01.077.