**Objectives**

- Discuss the problem of congestion
- Describe current and new medications
- Describe current and new device approaches

**Clinical Evidence of Congestion 4 to 6 Weeks after Hospitalization & Survival**

- Orthopnea
- JVD
- Weight gain > 2 lbs in one week
- Increase diuretic dose on visit
- Edema

Adapted from Gheorghiade M et al. JAMA. 2004; 291: 1963

**In-Hospital PCWP Predicts Subsequent Mortality in Advanced HF**

- PCWP >16 mm Hg
- CI >2.6 L/min-m²

456 HF patients after tailored vasodilator therapy

Predictors of Rehospitalization after the 1st Admission for HF*

HF-rEF: N=168
39 reached the endpoint within 1 year (23.2%)
- Low sodium (HR: 0.856)
- High BUN (HR: 1.045)
- High BNP levels at discharge (HR: 1.003)
- Absence of beta-blocker prescription (HR: 0.395)

HF-pEF (EF ≥ 50 %): N=142
43 reached the endpoint within 1 year (30.3%)
- Depression (HR: 7.185)
- High BNP levels at discharge (HR: 1.003)
- Dilated inferior vena cava (HR: 1.100)

N=310. Assessed medical Hx, VS, ECG, chest X-ray, blood tests and echocardiograms

Treatment of Congestion

- Diuretics, vasodilators, ultrafiltration, vasopressin antagonists, & aldosterone antagonists
- Potential novel agents:
  - Gut sequesterants
  - Serelaxin
- Uncertainty regarding an appropriate decongestion strategy approach for different patients

Treatment of Congestion

Evidence-based initial approach:
1. High-dose IV diuretics + vasodilators for dyspnea relief, if blood pressure allows
2. Enhance diuresis / overcome diuretic resistance with:
   - Dual nephron blockade with thiazide diuretics
   - Natriuretic doses of aldosterone antagonist
   - Vasopressin antagonist to improve aquarexis and relieve dyspnea
3. Consider ultrafiltration if # 1 and 2 unsuccessful (adequate kidney function)

Loop Diuretics – Pre 2010

- ? benefits outweigh harm
- ? new drug(s) to remove fluid with greater safety
- ? evidence that diuretic clinics benefit patients
  - Poor quality and low strength of evidence
- ? If continuous IV infusion produces more diuresis than IV bolus
  - ? leads to better clinical outcomes?
- ? does high-dose vs low-dose diuretics create more effective diuresis, cause renal toxicity and improve symptoms

IV DIURETICS-2x Day vs. Continuous

- RCT, open label, single-center trial in hospitalized pts. with fluid overload (N=41)
- No differences between groups in:
  - Serum creatinine level, \( p=0.18 \)
  - Urine output, \( p=0.64 \)
  - Change in weight, \( p=0.27 \)
  - Change in systolic BP, \( p=0.11 \)
  - Change in serum Na+ or K+, \( p=0.30 / 0.08 \)
  - Hypokalemia rate (K\(<\,3.5 \,\text{mEq/L}\), \( p=0.44 \)
  - Hospital LOS, \( p=0.69 \)

DOSE Trial - Furosemide

Prospective, RCT (N=308); compared:
1. Bolus vs. continuous IV furosemide
2. High-dose (2.5 x previous oral dose) vs. low-dose (previous oral dose)

Continuous IV diuresis clinics may cost time (RN care delivery) and not change outcomes

- High dose:
  - Trend toward greater improvement in global assessment of symptoms
  - Greater diuresis
  - Transient worsening of renal function

Treatment of Congestion
- IV nesiritide beyond dyspnea relief and ↓ PAOP during decompensation/hospitalization
- Renal Optimization Strategies Evaluation [ROSE] Acute HF RCT
  - 360 pts; GFR of 15-60 mL/min/1.73 m²
  - Low-dose dopamine vs. nesiritide
- Results:
  - Low-dose dopamine (vs. placebo) had no effect on 72-hour urine volume; p = 0.59
  - Low-dose nesiritide (vs. placebo) had no effect on 72-hour urine volume; p = 0.36
  - No effect of either on decongestion, renal function, or clinical outcomes

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Aldosterone Antagonists (MRA) in HF-pEF
- 10,570 hospitalized older pts; mean age, 80 yrs
  - 492 ordered MRA and 487 matched pairs without MRA, followed for 2.4 years
  - Balanced on 116 factors


ALDO-DHF Trial
HF CLINICAL RESULTS:
- Did not improve HF symptoms
- Did not improve QoL
- Slightly reduced 6MWD
  - -15 m; 95% CI, -27 to -2 m; P = .03
- Increased serum K+
  - +0.2 mEq/L; 95% CI, +0.1 to +0.3; P < .001
- Decreased eGFR
  - -5 mL/min/1.73/m²; 95% CI, -8 to -3; P < .001
- No effect on hospitalizations


Aldosterone Antagonist / MRA
EMPHASIS-HF trial: eplerenone in mild HF symptoms (NYHA-FC II) and EF < 30% or EF 30-35% + a high-risk feature:
- Age > 55 years
- QRS duration > 130 msec (if LVEF 31% - 35%)
- HF hospitalization within 6 months
- Elevated B-type natriuretic peptide level
- After ~ 21 months, eplerenone reduced:
  - (Primary endpoint) CV death or HF hospitalization
    - HR 0.63, 95% CI 0.54 - 0.74, P < .001
  - All cause mortality
    - HR 0.76, 95% CI 0.62 - 0.93, P < .008


Relaxin to Serelaxin
- Relaxin: A naturally occurring peptide hormone
  - Named for it’s action of relaxing the female reproductive tract
- CV tissues have relaxin receptors
  - Activated by circulating relaxin or regionally generated relaxin


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Serelaxin
- Recombinant human relaxin-2
- A naturally occurring peptide
  - Regulates maternal adaptations to pregnancy
- A vasoactive peptide hormone with biologic and hemodynamic effects in ADHF:
  - Increased arterial compliance
  - Increased cardiac output
  - Increased renal blood flow
Serelaxin: RELAX-AHF
- RCT; international study
- Serelaxin administered IV for 48 hours
  30 mcg/kg/day within 16 hours from presentation to the hospital
- Patients enrolled were:
  - Congested on Chest X-ray; had dyspnea
  - ↑ BNP or NTproBNP
  - Mild-moderate renal insufficiency
  - SBP > 125 mmHg
- Primary endpoints: Dyspnea improvement to day 5 (VAS) and dyspnea improvement via Likert scale during 1st 24 hours

RELAX-ADF
- Results in 1161 patients
- Despite no difference in change in body weight, and significantly higher use of IV diuretics ($p=0.006$) and vasoactive drugs ($p=0.01$) up to 5 days in the placebo group, serelaxin treated patients had improved S/S of congestion:

RELAX-AHF
- At 60 days, no differences between groups in:
  - CV death
  - Hospital readmission for HF or renal failure
  - Days alive out of the hospital
- At 180 days, serelaxin was associated with:
  - Fewer deaths
  - HR (95% CI): 0.63 (0.42, 0.93), $p=0.019$

Pre-RELAX-AHF + RELAX-AHF
- Risk for Mortality by Early Changes in Markers of Organ Function, Damage & Congestion

PARADIGM Trial- LCZ696
- LCZ696 200 mg bid (combo agent) was superior to enalapril 10 mg bid in mortality and morbidity in patients with NYHA FC II-IV HF-rEF
- Valsartan: blocks Ang II AT₁ receptor
  - vasodilatation + excretion of Na+/H₂O via the kidneys (by ↓ aldosterone prod.)
- AHU-377: (a prodrug that is activated to LBQ657) inhibits the enzyme neprilysin, preventing degradation of ANP and BNP – causing reduced blood volume
**Abdominal Contributions to Congestion**

- **Splanchnic venous & interstitial congestion**
  - Compromised capacitance function of the splanchnic vasculature and deficient abdominal lymph flow
    - Results in interstitial edema
  - Might increase cardiac filling pressures and renal dysfunction

**Abdominal Contributions to Congestion**

- Liver and spleen alterations contribute to systemic congestion in HF
- Gut derived hormones *might* influence sodium homeostasis
- Entrance of bowel toxins into the circulatory system (from impaired intestinal barrier function secondary to congestion) *might* further depress cardiac and renal function
  - Toxins are mainly produced by microorganisms in the gut lumen

**Abdominal Contributions to Congestion**

- Crosstalk between the abdomen, heart, and kidneys in congestive HF
  - * Might offer new diagnostic opportunities & treatment strategies
    - Paracentesis
    - Ultrafiltration
    - Peritoneal dialysis
    - Oral sodium binders
    - Vasodilator therapy
    - Renal sympathetic denervation
    - Agents targeting gut microbiota

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**Serelaxin and LCZ696** (NOT FDA approved)

- ZERO new drugs for ADHF (serelaxin) and chronic HF (LCZ696) in the last 10 years
- With improvement in outcomes
- Without harm to end-organ function
  - Vaptans for hyponatremia in 2010
  - Adenosine-1 receptor antagonist in 2010
- Both awaiting FDA approval
- Nurses need to understand expected effects, side effects (i.e., systolic BP may drop and require treatment) and how to use/adjust Tx

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**DEVICES**

- Internal Cardiac Monitoring – Impedance
  - CardioMEMS
- Ultrafiltration

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ULTRAFILTRATION

HOW DOES IT WORK:

- *Aquapheresis* works by:
  - Pulling a small amount of venous blood from the body (10-40 mL/min in increments of 5 mL/min)
  - AKA: Blood flow rate
  - Filtering out the excess salt and water (10-500 mL/hour in increments of 10 mL/hour)
  - AKA: Ultrafiltration rate
  - Returning filtered blood back to the patient

UNLOAD

- 200 adults > 18 years of age
- HYPERVOLEMIC HF with 2+ of the following:
  - Peripheral edema (≥ 2+)
  - Enlarged liver or ascites
  - X-ray pulmonary edema or pleural effusion
  - Jugular venous distention ≥ 7 cm
  - Pulmonary rales, paroxysmal nocturnal
dyspnea (PND), or orthopnea
  - Randomized within 24 hours of admission

UNLOAD: RESULTS

<table>
<thead>
<tr>
<th>Variable</th>
<th>UF arm</th>
<th>Usual care</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt loss, Kg (M ± SD)</td>
<td>5.0 ± 0.68</td>
<td>3.1 ± 0.75</td>
<td>0.001</td>
</tr>
<tr>
<td>Net fluid loss, L</td>
<td>4.6 ± 0.29</td>
<td>3.3 ± 0.29</td>
<td>0.001</td>
</tr>
<tr>
<td>Dyspnea score</td>
<td>6.4 ± 0.11</td>
<td>6.1 ± 0.15</td>
<td>0.35</td>
</tr>
<tr>
<td>Worsening HF:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pts rehospitalized, %</td>
<td>18</td>
<td>32</td>
<td>0.022</td>
</tr>
<tr>
<td>- Rehospitalizations/pt</td>
<td>0.22</td>
<td>0.46</td>
<td>0.037</td>
</tr>
<tr>
<td>- Days rehospitalized</td>
<td>123</td>
<td>330</td>
<td>0.022</td>
</tr>
<tr>
<td>- # rehospitalization days/pt</td>
<td>1.4</td>
<td>3.8</td>
<td>0.022</td>
</tr>
</tbody>
</table>

UNLOAD SUMMARY

- Early ultrafiltration produced greater weight and fluid loss than IV diuretics
  - Without adverse impact on renal function
- Early ultrafiltration reduced 90 day:
  - Rehospitalization for HF
  - Number of HF rehospitalizations/patient
  - Days of rehospitalization for HF
  - Emergency care and unscheduled office visits

Ultrafiltration: CARRESS Inclusion Criteria

- New cardio-renal syndrome: ≥ 0.3 mg/dl ↑ in sCr:
  - ≤ 7 days of hospital admission after receiving IV diuretics
  - ≤ 6 weeks before hosp. in the setting of escalating doses of OPD loop diuretics
- Evidence of persistent volume overload
  - No PA catheter:
    - ≥ 2+ peripheral edema
    - JVP or CVP >10 cm
  - or pulmonary edema or pleural effusions on CXR
  - PA catheter: PAWP >22 mmHg + 1 clinical sign

CARRESS Study

Ultrafiltration was *inferior to diuretic Tx*
CARRESS Study

- UF gp had higher sCr at 96 hrs ($P=0.003$)
- No difference in weight loss at 96 hrs ($P=0.58$)
- More UF gp pts had serious AEs (72% vs. 57%, $P=0.03$)


Stepped Pharmacologic Treatment Arm at Randomization

At 24 hours, if UO < 3L/day: advance to next step on table

At 48 hours, if UO < 3L/day: advance to next step on table; consider dop. or dobut IV if BP < 110 mmHg syst. or RV dysfunct. If BP > 120 mmHg, or severe symptoms, consider NTG or nesiritide symptoms

At 72 and 96 hours, if UO < 3L/day: same as 48 hours and consider hemodynamic guided IV Tx, LVAD, dialysis or ultrafiltration cross-over

Aquapheresis Versus Intravenous Diuretics and Hospitalizations for HF

Study type To be performed using the FDA Approved Aquadex System
Study Design Controlled multicenter, prospective, non-blinded, one to one randomized trial.
No Investigational sites Minimum of 25 sites
No patients
Study stopped before enrollment completed
Target population Patients who have failed outpatient oral diuretic therapy and are admitted to the hospital with a primary diagnosis of acute decompensated heart failure (ADHF)
Study duration (per subject) Followed up every 30 days after discharge from index HF hosp. for a maximum of 90 days
First/last patient Enrolled March 2012 / March 2013

Internal Cardiac Monitoring

65 yr old male pt w DCM; NYHA FC II; EF 23%; QRS 160 ms
Patient made contact
a) ↓ impedance
b) ↑ fluid index verified by remote data review
c) ↓ in patient activity led to telephone FU
Patient reported worse HF symptoms
- ↑ diuretic dose and a transmission in 1 wk
d) ongoing ↑ in impedance/ activity & remission of symptoms

Intrathoracic Impedance & PCWP

Impedance and PCWP During CHF Hospitalization

Medtronic data on file
**Home-Based Telemonitoring Clinical Practice Implications**

- Data can be used for trending of hemodynamics and volume parameters
- Must be used with other data:
  - Subjective assessment
    - Changes in/adherence to medication, diet, fluid intake; recent illness or other history
  - In poor historians or those who do not recognize worsening status, can objectively assess worsening HF
- Telemonitoring increases response / treatment time

**Agreement between ICD-Measured Intrathoracic Impedance and PCWP**

- 23 patients
  - Assessed ICD-measured intrathoracic impedance and PCWP by validated ECHO-doppler method
  - Followed patients for 23 months
  - 45 paired assessments of impedance/PCWP
  - Kappa analysis: 0.701, SE 0.113, \( P < 0.001 \)
  - Impedance alert detected clinical HF deterioration with 92% sensitivity and 67% positive predictive value
  - Combination of ↓impedance & ↑PCWP had a 92% PPV and 92% sensitivity

**Agreement Between ICD Measured Intrathoracic Impedance and PCWP**

- Fluid index threshold crossings and HF hospitalization

**Fluid Index Above Threshold and HF Hospitalization**

- Pts. with > 3 threshold crossing events/year during the 1st 4 months of follow-up:
  - ↑likelihood of experiencing a subsequent ADHF hospitalization during the remaining follow-up period (35% ↑risk)

**Relationship of Atrial Tachycardia/ Atrial Fib and Volume Overload**

- Clinical Implications:
  - Worsening pulmonary congestion is associated with increased susceptibility to temporary atrial tachycardia events
  - Activation of RAS, promoting fibrosis?
  - Increased atrial stretch?
  - Elevated circulating catecholamines?
  - Atrial tachycardia events may be responsible for triggering episodic pulmonary congestion
  - Cardiac remodeling?
Internal Assessment of Congestion

CardioMEMS®

FDA approved May 28, 2014

CardioMEMS®

Wireless PA pressure sensitive capacitor in a capsule, covered by silicone
- No batteries or wires
- 2 nitinol loops for anchoring in the PA

External antenna is held against the pts body; provides power to the device
- Resonant frequencies are converted into pressure waveforms
- Patients are instructed to transmit daily readings from home

CardioMEMS®

Catheter-based delivery system

Radio Frequency Communication
- Externally powered
- No battery

CardioMEMS®

Hospitalizations For HF During Randomized Access

Hosp LOS Tx vs. Control groups = 2.2 (SD 6.8) vs. 3.8 (11.1) days; P=0.02

Abraham WT et al. Lancet 2011;377:658

CardioMEMS®

Survival During Randomized Access

Abraham WT et al. Lancet 2011;377:658

CardioMEMS®

Freedom from Death or First HF Hospitalization – Randomized Access

Abraham WT et al. Lancet 2011;377:658
Effect access to PAPs without nurse communications
Hospitalization for HF During Open Access

<table>
<thead>
<tr>
<th>Number of Hospitalizations For Heart Failure</th>
<th>Annualized Rates of Hospitalization for Heart Failure</th>
<th>Hazard Ratio (95% CI) [p-value]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Former Control [Open Access - Part 1]</td>
<td>64</td>
<td>0.36 (0.56-1.34)</td>
</tr>
<tr>
<td>Former Treatment [Open Access - Part 2]</td>
<td>78</td>
<td>0.45</td>
</tr>
</tbody>
</table>

p=0.2176

Implications
- Who is paying attention to details?
- Who is making recommendations for GDMT optimization?
- Do nurses know how to read a PAP reading (a and v waves; x and y descents...)?
- Will we get the same effect in clinical practice achieved during randomized access?
- How long will the effects last? VALUE?

Wearable Devices.... External
- Corventis: monitors HR, HR variability, RR, fluid status and activity
- Perminova: aims to monitor chest fluid
- Zoe fluid status monitor