Stage D Heart Failure

- Refractory Heart Failure
- Requiring Specialized Interventions

Characteristics of Refractory Heart Failure

- Marked symptoms at rest
- On maximal medical therapy
- Recurrent hospitalizations
- Unable to stabilize in hospital for discharge

Characteristics of Refractory Heart Failure Patients

- Profound fatigue
- Cannot perform most activities of daily living
- Cardiac cachexia
- Require repeated and/or prolonged hospitalizations for intense therapy

Specialized Management in Heart Failure - Goals

• Optimize standard medical therapy
  – **Lifestyle therapy**: diet (Na, nutrients) and activity (rest), smoking, alcohol, drugs
  – **Medications**: ACE/ARB, B-Blocker, diuretic (solo or combination), Aldo-Antag, Dig, Hydralaz/nitrate
  – **Devices**: ICD, Biventricular pacing

• **Realism**: appropriate level of care

Meticulous Management of Fluid Status During Hospitalization - 1

- Critical step in management
- Diuretic resistance
  - Decline in renal perfusion
  - Second diuretic with complementary action
  - Addition of dopamine or dobutamine
  - Ultrafiltration or hemofiltration
The Nephron in HF

Braunwald’s heart disease, Ch 25, Fig 9, 2008.
### Diuretics for Treating Fluid Retention in Chronic Heart Failure*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose(s)</th>
<th>Maximum Total Daily Dosage</th>
<th>Duration of Action (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>0.5 to 1.0 mg once or twice</td>
<td>10 mg</td>
<td>4 to 6</td>
</tr>
<tr>
<td>Furosemide</td>
<td>20 to 40 mg once or twice</td>
<td>600 mg</td>
<td>6 to 8</td>
</tr>
<tr>
<td>Torsemide</td>
<td>10 to 20 mg once</td>
<td>200 mg</td>
<td>12 to 16</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>250 to 500 mg once or twice</td>
<td>1000 mg</td>
<td>6 to 12</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>12.5 to 25 mg once</td>
<td>100 mg</td>
<td>24 to 72</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>25 mg once or twice</td>
<td>200 mg</td>
<td>6 to 12</td>
</tr>
<tr>
<td>Indapamide</td>
<td>2.5 mg once</td>
<td>5 mg</td>
<td>36</td>
</tr>
<tr>
<td>Metolazone</td>
<td>5 mg once</td>
<td>20 mg</td>
<td>12 to 24</td>
</tr>
<tr>
<td>Potassium-sparing diuretic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiloride</td>
<td>12.5 to 25 mg once</td>
<td>20 mg</td>
<td>24</td>
</tr>
<tr>
<td>Triamterene</td>
<td>50 to 75 mg twice</td>
<td>200 mg</td>
<td>7 to 9</td>
</tr>
<tr>
<td>AVP antagonist†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satavaptan</td>
<td>25 mg once</td>
<td>50 mg once</td>
<td>NS</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>30 mg once</td>
<td>60 mg once</td>
<td>NS</td>
</tr>
<tr>
<td>Lixivaptan</td>
<td>125 mg twice</td>
<td>250 mg twice</td>
<td>NS</td>
</tr>
<tr>
<td>Conivaptan (IV)</td>
<td>20-mg IV loading dose, followed by 20 mg</td>
<td>40 IV infusion/day</td>
<td>7 to 9</td>
</tr>
<tr>
<td>Sequential nephron blockade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metolazone</td>
<td>2.5 to 10 mg once plus loop diuretic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>25 to 100 mg once or twice plus loop diuretic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide (IV)</td>
<td>500 to 1000 mg once plus loop diuretic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Unless indicated, all dosages are for oral diuretics.

†As of 2007, this class of agents is not FDA-approved for the management of patients with heart failure.

NS = not specified.


Sorting out Diuretic Resistance

• Is the patient taking the drug?
• Is the drug being absorbed?
  – JVP elevation indicates poor absorption
• Is the blood pressure adequate to provide renal flow?
• Is renal function adequate?
Mechanisms of Diuretic Resistance

- **Braking phenomenon**: diuretics decrease extracellular fluid volume and activate adaptations that reduce responsiveness
  - Increase in proximal reabsorption
  - Sympathetically-mediated reduction in RBF and renin release (increase in Na reabsorption)
- Hypotension and **renal hypoperfusion**
- Distal convoluted **tubular hypertrophy** and hyperplasia due to increased delivery
- **Cardiorenal syndrome**

Braunwald’s heart disease, Ch 25, 2008.
Braking Phenomenon

(Modified from Ellison DH: Diuretic therapy and resistance in congestive heart failure. Cardiology 96:132, 2001.)

Braunwald’s heart disease, Ch 25, 2008.
Diuretic Usage

- **Furosemide**, max 160-200 mg dose IV, or 600 mg/da (20-40 mg IV over 1-2 minutes, then 10-40 mg/hr, or even 80-160/hr but at risk of more adverse effects)

- **Second agent** (later, perhaps best 3 times/wk)
  - Distal convoluted tubule: Metolazone 2-10 mg/d
  - Distal convoluted tubule: Hctz 25-100 mg/d
  - Distal convoluted tubule: Chlorothiazide 500-1000 mg IV (once or twice a day)
  - Proximal: acetazolamide 250-375 mg/da or up to 500 mg IV (up to 4 times per day) – good for alkalosis and hypokalemia
  - Collecting duct: spironolactone 100-200 mg/d
  - Collecting duct: amiloride 5-10 mg/d

Diuretic Usage

### Table 2. Combination diuretic therapy

To a ceiling dose of a loop diuretic (table 1) add:

- **DCT diuretics**
  - metolazone 2.5–10 mg per os daily\(^1\)
  - hydrochlorothiazide (or equivalent) 25–100 mg per os daily
  - chlorothiazide 500–1,000 mg intravenously

- **Proximal tubule diuretics**
  - acetazolamide 250–375 mg daily or up to 500 mg intravenously

- **Collecting duct diuretics**
  - spironolactone 100–200 mg daily
  - amiloride 5–10 mg daily

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\(^1\) Metolazone is generally best given for a limited period of time (3–5 days) or should be reduced in frequency to 3 times per week once ECF volume has declined to the target level. Only in patients who remain volume expanded should full doses be continued indefinitely, based on the target weight.
Diuretic Usage

Fig. 6. Comparison of continuous-infusion versus bolus furosemide treatment of patients with chronic congestive heart failure. The squares indicate Na excretion during infusion of 2.5–3.3 mg/h furosemide following a loading dose of 30–40 mg. The circles depict urinary Na excretion following 30–40 mg of furosemide every 8 h. Total urine output was 18.5% higher during continuous infusion than bolus administration. Data are drawn from Lahav et al. [51].
### Table 3. Continuous infusion of loop diuretics

<table>
<thead>
<tr>
<th></th>
<th>Bolus mg</th>
<th>Infusion rate, mg/h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;25 ml/min</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40</td>
<td>20 then 40</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>1</td>
<td>1 then 2</td>
</tr>
<tr>
<td>Torsemide</td>
<td>20</td>
<td>10 then 20</td>
</tr>
</tbody>
</table>

At high continuous doses, toxicity may develop, especially during furosemide infusion in patients with impaired renal function. Doses derived from Brater [56].
Meticulous Management of Fluid Status During Hospitalization - 2

- Requirements for hospital discharge
  - Stable diuretic regimen
  - Euvolemia
- Increased risk for readmission if goals not met

Meticulous Management of Fluid Status After Hospitalization

- Weigh daily
- Diuretic dose adjustments may be made by patients based on weight changes
- Sodium restriction 2 gm Na/da
- Possibly 2 liter/da fluid restriction
• ACE-inhibitor: increased risk for hypotension and renal insufficiency
• Beta-blocker: increased risk for exacerbation of HF symptoms
• Even low doses are beneficial
• Do not initiate use if SBP<80 or if signs of hypoperfusion
• Do not initiate beta-blocker
  – Ongoing fluid retention
  – Recent need for IV inotropes

Use of Neurohormonal Inhibitors - 2

- Nitrate-hydralazine combination
  - Beneficial in patients not taking beta-blocker or ACE-I but less symptomatic patients than Stage D
  - Utility in Stage D unknown, but an option
  - Side-effects: headache and GI distress

- Aldosterone antagonists beneficial only if renal function is adequate and K+ is OK

- ARB beneficial if intolerant of ACE-I due to cough (and maybe angioedema) but no advantage if hypotension or renal insufficiency
Use of IV Agents

- **Inotropic agents**
  - Dopamine
  - Dobutamine
  - Milrinone

- **Vasodilator agents**
  - Nitroglycerine
  - Nitroprusside
  - Nesiritide

- Generally hospitalization should continue at least 48 hr after infusions
# Hemodynamics of Shock

## Table 3

Hemodynamic parameters in shock

<table>
<thead>
<tr>
<th>Type of shock</th>
<th>CO</th>
<th>PCWP</th>
<th>CVP</th>
<th>SVR</th>
<th>PAP</th>
<th>SVo2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>LV failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV failure</td>
<td></td>
<td>←or↑</td>
<td>↑↑</td>
<td>↑</td>
<td>←or↑</td>
<td>↓</td>
</tr>
<tr>
<td>Hypovolemic</td>
<td>↓↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>←or↑</td>
<td>↓</td>
</tr>
<tr>
<td>Vasodilatory (septic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>↑↑</td>
<td>↓</td>
<td>↓</td>
<td>↓or↓↓</td>
<td>↓</td>
<td>↑or↑↑</td>
</tr>
<tr>
<td>Late</td>
<td>←or↓</td>
<td>↓ or ←</td>
<td>↓ or ←</td>
<td>↓or↓↓</td>
<td>↓</td>
<td>↑or↑↑</td>
</tr>
<tr>
<td>Extracardiac Compressive</td>
<td>↓or↓↓</td>
<td>←or↓</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Neurogenic</td>
<td>↑or← or ↓</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: CO, cardiac output; CVP, central venous pressure; LV, left ventricle; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RV, right ventricle; SVo2, mixed venous oxygen saturation; SVR, systemic vascular resistance.  
↓-decrease, ↑-increase, ←-equal.*
## Vasoactive Drugs in HF

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Dose</th>
<th>( \alpha )</th>
<th>( \beta )</th>
<th>DA</th>
<th>CV effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>Direct agonist</td>
<td>1–12 µg/min</td>
<td>+++</td>
<td>++</td>
<td>0</td>
<td>( \uparrow ) SBP, DBP</td>
<td>Primary vasopressor used in VD shock</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( \leftrightarrow ) CO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( \leftrightarrow ) VC most vascular beds</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Direct agonist</td>
<td>1–200 µg/min</td>
<td>++</td>
<td>+++</td>
<td>0</td>
<td>( \uparrow ) HR, SV, CO</td>
<td>( \uparrow ) MVo₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( \uparrow ) SBP, DBP, PP, PAP</td>
<td>May induce tachyarrhythmias</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( \leftrightarrow ) VC most vascular beds</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>Direct agonist</td>
<td>1–2 µg/kg/h</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>( \uparrow ) CO, ( \leftrightarrow ) SVR</td>
<td>Causes NE release from nerve terminals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2–10 µg/kg/h</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10–20 µg/kg/h</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>( \uparrow ) SVR, VC most vascular beds</td>
<td>May induce tachyarrhythmias and ( \uparrow ) MVo₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( \leftrightarrow ) VC most vascular beds</td>
<td>2\textsuperscript{nd} line agent in VD shock</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Direct agonist</td>
<td>20–200 µg/min</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>( \uparrow ) SVR</td>
<td>Limited role in VD shock</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>May cause reflex bradycardia</td>
<td>Primary agent in neurogenic shock</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Potentially ( \downarrow ) CO</td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Direct agonist</td>
<td>2–20 µg/kg/min</td>
<td>+</td>
<td>+++</td>
<td>0</td>
<td>( \uparrow ) contractility, automaticity, CO, SV</td>
<td>Primary inotrope in cardiogenic shock or in VD shock</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( \downarrow ) CO</td>
<td></td>
</tr>
<tr>
<td>Milrinone</td>
<td>Phosphodiesterase inhibitor</td>
<td>50 µg/kg load 0.25–1 µg/kg/min</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>( \uparrow ) contractility, CO</td>
<td>Long half-life (30–60 min) limits usefulness in acute setting</td>
</tr>
</tbody>
</table>

Abbreviations: CO, cardiac output; CV, cardiovascular; DA, dopamine; DBP, diastolic blood pressure; HR, heart rate; MVo₂, myocardial oxygen consumption; NE, norepinephrine; PAP, pulmonary artery pressure; PP, pulse pressure; SBP, systolic blood pressure; SV, stroke volume; SVR, systemic vascular resistance; VC, vasoconstriction; VD, vasodilation.
Patients who cannot be weaned despite repeated attempts

Agents that have been tried

- Dobutamine
- Milrinone
- Nesiritide

Generally in patients awaiting transplant

Also for those who cannot otherwise be discharged
Use of IV Agents as Outpatient - 2

- Disadvantages
  - Burden on family
  - Burden on health services
  - May increase mortality

- Advantage - may allow palliation to allow patient to die in comfort at home
Use of Mechanical Therapies - 1

- Established: cardiac transplantation
  - Fewer than 2,500/year in US
    - Currently on the transplant list 2,861 (UNOS data)
    - 2007: 2,210 transplants in US
    - 2008: 2,192
    - 74% male, 54% over 50 yo
    - 86%, 77%, 70% (1-yr, 3-yr, 5-yr survival)
  - Indications: severe functional impairment or dependence on IV inotropic support (refractory ventricular arrhythmia or angina)
Table 10. Indications for Cardiac Transplantation

Absolute Indications in Appropriate Patients

For hemodynamic compromise due to HF
- Refractory cardiogenic shock
- Documented dependence on IV inotropic support to maintain adequate organ perfusion
- Peak VO₂ less than 10 mL per kg per minute with achievement of anaerobic metabolism

Severe symptoms of ischemia that consistently limit routine activity and are not amenable to coronary artery bypass surgery or percutaneous coronary intervention

Recurrent symptomatic ventricular arrhythmias refractory to all therapeutic modalities

Relative Indications

- Peak VO₂ 11 to 14 mL per kg per minute (or 55% predicted) and major limitation of the patient’s daily activities
- Recurrent unstable ischemia not amenable to other intervention
- Recurrent instability of fluid balance/renal function not due to patient noncompliance with medical regimen

Insufficient Indications

- Low left ventricular ejection fraction
- History of functional class III or IV symptoms of HF
- Peak VO₂ greater than 15 mL per kg per minute (and greater than 55% predicted) without other indications

HF indicates heart failure; IV, intravenous; and VO₂, oxygen consumption per unit time.
Heart Transplantation

Heart Transplantation

Number of heart transplant procedures reported to the registry by year, according to reporting source. Reporting of transplants is mandatory for Eurotransplant, UK Transplant and UNOS. Transplant reports from other organ-exchange organizations and from individual transplant centers are non-mandatory.

Age Distribution of Heart Transplant Recipients by Era

- 1982–1988 (N = 9,672)
- 1989–1993 (N = 19,386)
- 1994–1998 (N = 20,624)
- 1999–2004 (N = 19,679)

UNOS Status Definitions

- 1A: Inpatient mechanical circ support, ventilator, high-dose inotrope (dobutamine >7.5, milrinone >0.5)
- 1B: LVAD or inotropes
- 2: All others
- 7: Temporarily unsuitable
Figure 1  Historical Perspective of Heart Transplantation

The figure describes the major landmarks of heart transplantation associated with progressive improvement in survival. FDA = Food and Drug Administration; MMF = mycophenolate mofetil. Adapted, with permission, from Hunt (1).
Heart Transplantation

ADULT HEART TRANSPLANTATION

All comparisons significant at p < 0.0001

SURVIVAL (%)

100
80
60
40
20
10
0

YEARS

0 1 2 3 4 5 6 7 8 9 10 11 12

1982–1988 (N = 9,071)
1989–1993 (N = 17,685)
1994–1998 (N = 18,758)
1999–6/2004 (N = 16,227)


Braunwald, Ch. 27, Fig 13A, 2008.
Figure 2 Steps in T Cell Activation

The alloimmune response often requires activation of multiple signaling pathways. The first signal is provided when antigen-presenting cells and antigens activate the T cell receptor. Costimulation (signal 2) occurs when CD80 (B7-1) and CD86 (B7-2) on the antigen-presenting cells engage CD28. Both signals activate important signal transduction pathways (calcineurin, RAS-mitogen-activated protein kinase [MAP-K] pathway, and the nuclear factor-kappa B [NF-KB] pathway). These pathways lead to the expression of many molecules, including interleukin (IL)-2 and IL-15. Interleukin-2 and other cytokines then activate the "target of rapamycin" pathway to provide the trigger for cell proliferation (signal 3). AP-1 = activating protein 1; CDK = cyclins-dependent protein kinase; IKK = serine-threonine protein kinase; JAK3 = Janus kinase 3; MHC = myosin heavy chain; mRNA = messenger ribonucleic acid; mTOR = mammalian target of rapamycin; NFAT = nuclear factor of activated T cells; PKC = protein kinase C; S-1-P = sphingosine-1-phosphate; TCR = T cell receptor. Adapted, with permission, from Halloran (28).
<table>
<thead>
<tr>
<th>Imunosuppressive Agent</th>
<th>Target Class</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucorticosteroid</td>
<td>Multiple targets including inhibition of APC and nuclear transcription</td>
<td>Usually weaned during the first year</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Cyclophillin</td>
<td>Cyclosporine favored in patients with poorly controlled diabetes mellitus; tacrolimus may be associated with decreased rejection episodes</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>FKBp12</td>
<td></td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Purine synthesis inhibitors</td>
<td>Has replaced azathioprine in combination regimens</td>
</tr>
<tr>
<td>Proliferation signal inhibitors</td>
<td>Target-of- rapamycin</td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus (not yet FDA approved)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyclonal antibody: horse or rabbit antithymocyte globulin</td>
<td>Depleting antibodies against T cells</td>
<td>Selective use in the treatment of severe cellular rejection or in induction therapy</td>
</tr>
<tr>
<td>Rituximab</td>
<td>B-cell–depleting monoclonal anti-CD20 antibody</td>
<td>Selective use in the treatment of humoral rejection</td>
</tr>
<tr>
<td>Daclizumab, basiliximab</td>
<td>Anti-CD25 antibody</td>
<td>Selective use for induction therapy</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Anti-CD52 antibody</td>
<td>Selective use for induction therapy (preliminary experience in heart transplantation), case reports of its use in refractory rejection</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>Multiple sites of actions including interference with Fc receptors on the cells of the reticuloendothelial system</td>
<td>Selective use in the treatment of humoral rejection or sensitized patients</td>
</tr>
<tr>
<td>CTLA-4-Ig (LEA29) (fusion protein)</td>
<td>Costimulation signal inhibitor</td>
<td>In phase III trials in renal transplantation</td>
</tr>
</tbody>
</table>
### Table 2

**Maintenance Regimens Used in Heart Transplantation**

<table>
<thead>
<tr>
<th>Regimens*</th>
<th>Indication or Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcineurin inhibitor and mycophenolate mofetil, <strong>Cyclosporine, tacrolimus</strong></td>
<td>Most common regimen used; older transplant patients may still be on a calcineurin inhibitor and azathioprine combination</td>
</tr>
<tr>
<td>Calcineurin inhibitor and proliferation signal inhibitor, <strong>Sirolimus, everolimus</strong></td>
<td>Regimen often considered in patients with established allograft vasculopathy or malignancy</td>
</tr>
<tr>
<td>Mycophenolate mofetil and proliferation signal inhibitor</td>
<td>Calcineurin-free regimen considered in patients with severe renal insufficiency</td>
</tr>
<tr>
<td>Tacrolimus monotherapy</td>
<td>Preliminary data suggest the safety of tacrolimus monotherapy in heart transplantation (45)</td>
</tr>
</tbody>
</table>

*Corticosteroids usually part of all regimens during the first year.*

Table 3  Immune and Functional Monitoring of Heart Transplant Recipients

<table>
<thead>
<tr>
<th>Monitoring Tool</th>
<th>Type</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endomyocardial biopsy</td>
<td>Histology and immunohistochemistry</td>
<td>Time-honored gold standard for the diagnosis of rejection; disadvantage of being invasive and susceptible to sampling errors and variability in interpretation</td>
</tr>
<tr>
<td>Drug monitoring and pharmacogenomics</td>
<td>Drug level or AUC</td>
<td>Trough levels are usually monitored for practical reasons although peak levels usually correlate better with AUC; gene polymorphisms of CYP3A5 and MDR1 correlate with calcineurin inhibitor levels</td>
</tr>
<tr>
<td>Functional monitoring</td>
<td>Diastolic parameters</td>
<td>Moderate correlation with significant rejection</td>
</tr>
<tr>
<td></td>
<td>Tissue Doppler</td>
<td>δ tissue Doppler systolic velocities are sensitive although less specific for the diagnosis of significant rejection</td>
</tr>
<tr>
<td></td>
<td>BNP</td>
<td>Correlates with significant rejection; no specific threshold has good discrimination capacity</td>
</tr>
<tr>
<td>Genomic markers of rejection</td>
<td>AlloMap* gene expression profiling test</td>
<td>Sensitive marker for cellular rejection although lower specificity; not validated for AMR</td>
</tr>
<tr>
<td>T cell functional assays</td>
<td>1) ImmuKnow</td>
<td>Marker of T cell activation, currently under validation in heart transplantation</td>
</tr>
<tr>
<td></td>
<td>2) Elispot</td>
<td>Marker of cytokine-producing T cells; currently under validation</td>
</tr>
<tr>
<td>Antibody monitoring</td>
<td>DSA</td>
<td>The presence of DSA has been associated with an increased risk of rejection and allograft vasculopathy</td>
</tr>
</tbody>
</table>

*XDx, Brisbane, California.
AMR = antibody-mediated rejection; AUC = area under the curve; BNP = B-type natriuretic peptide; DSA = donor-specific antibodies.

Maybe just first 5 years
Issues in Transplantation

- Graft vasculopathy – most common cause of late graft failure, second cause of late death
- Malignancies – most common cause of late death; lymphoproliferative, aggressive skin
- Renal failure (CNI-free regimens)
- Induction of organ tolerance
Use of Mechanical Therapies - 2

• Developing:
  – Mitral surgery for annular dilation for symptoms (no proof for symptoms, LV fcn, mort)
  – Cardiomyoplasty, LV aneurysmectomy
  – Mechanical circulatory assist devices (intense investigation) – best for short term reversible (acute MI, myocarditis, postcardiotomy)
Mechanical Assist Devices

- **First Generation** pulsatile volume displacement pumps, large, designed for about 1 year durability
  - Heartmate I (5,000 pts)
  - Thoratec PVAD (paracorporeal VAD, 3,000 pts, now an IVAD=implantable)
  - Novocor (1,600 pts)

- **Second Generation** axial flow pumps, smaller, nonpulsatile
  - Heartmate II (1,200 pts)
  - Jarvik 2000
  - Berlin Heart Incor
  - MicroMed DeBakey VAD

- **Third Generation** bearingless continuous flow pumps with impeller that is magnetic levitation or hydrodynamically suspended
  - Heartware
  - Ventrassist
  - Duraheart VAD
  - Terumo

Birks EJ. Heart. July 16, 2009 on line.
Mechanical Assist Devices

Heartmate I

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Mechanical Assist Devices

Heartmate II

Birks EJ. Heart. July 16, 2009 on line.
Mechanical Assist Devices

Heartmate II

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Mechanical Assist Devices

Jarvik 2000: placed in the LV

Figure 3b

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Mechanical Assist Devices

Heartware

Figure 4

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Mechanical Assist Devices

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Assist Device Indications - 1

- **Bridge to transplant** when transplant unavailable or when patient complications are prohibitive for transplant (renal failure, nutritional status, pulmonary vascular resistance improvements may take weeks to months) – improves probability of survival to transplant

- **Bridge to recovery** – small number of patients (clenbuterol induces hypertrophy)

Birks EJ. *Heart*. July 16, 2009 on line.
**Assist Device Indications - 2**

- **Destination therapy:** Heartmate VE
  - Nov 2002 FDA approved
  - Oct 2003 Medicare approved
  - Not funded in UK

- **Bridge to decision:** Moribund patients short term VAD (Levitronix CentriMag LVAS – not yet US approved for longer than 6 hr) to see if recovery to level of candidacy for LVAD occurs

Birks EJ. *Heart*. July 16, 2009 on line.
Mechanical Circulatory Assist

- Established efficacy as destination therapy: Rematch trial (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure)
  - 129 patients randomized
  - 2-year survival: medical=6%, device=23% (Heartmate I)
  - Complications: bleeding, infection, thromboembolism, device failure (sepsis 41% and device failure 17% of deaths)
  - Anticipated to benefit those with expected 1-year survival<50%
  - Bridge to recovery?
Heart Mate II

- 281 patients with 18 mo f/u or endpoint
- 54 yo, mostly men, mostly nonischemic CM, most on inotropes, 45% IABP
- Death: 20%, Sepsis 4%, stroke 4% (equal hemorrhagic and ischemic), right heart failure 3%, device failure 3% (7 patients: 2 pump thrombosis, 1 twisted inflow graft, 1 outflow disconnect, 1 severed percutaneous lead, 2 power loss), MSOF 2%, bleeding 1%, other 3%
- Nonfatal adverse events: bleeding requiring transfusion and surgery, stroke, esp ischemic,

Heart Mate II

Is nonpulsatile flow acceptable to the human body long-term?
Assist Device Complications

- Acute: periop hemorrhage, right heart failure, abdominal complications
- Later: infection, thromboembolism, hemolysis, device failure
- All except heartmate I require anticoagulation (warfarin)

Birks EJ. Heart. July 16, 2009 on line.
Specialized Intervention in Heart Failure - Options

- Compassionate end-of-life care/hospice
- Extraordinary measures
  - Heart transplant
  - Chronic inotropes
  - Permanent mechanical support
  - Experimental surgery or drugs

Predictors of Adverse Outcome

- BUN elevation
- lower SBP
- male gender
- previous hospitalizations
- worse NYHA class
- Hyponatremia
- elevated RA pressure and PAW pressure

- S3 as outpatient
- narrow pulse pressure
- Tachycardia
- positive troponin
- BNP>1100
- failure of BNP to fall with inpatient treatment
- discharge BNP>430

His next development was a new type of storage battery, which Edison hoped would replace conventional batteries in the rapidly growing automobile industry. It is typical of him that even after his first 8,000 experiments failed, he said, "Well, at least we know 8,000 things that don't work." Although Edison's battery turned out to be unsuitable for cars, it did succeed in railroad and marine shipping applications, which required batteries with longer life and greater durability.
Things that don’t work in HF

- Calcium sensitizers – levosimendan
- Nitric oxide synthase inhibitors – tilarginine acetate (L-NMMA) in shock
- Vasopressin antagonists - -vaptans
- Endothelin antagonists - -sentans
- ?EECP
Tidbits in Heart Failure

- Sauna bathing may be beneficial
- Moxonidine, a central sympathetic inhibitor, is adverse
ADHF Management Summary
from Braunwald 2005

• Begin with IV diuretics
• If poor perfusion or poor response, add dobutamine or nesiritide (milrinone only if EDP>15 because of vasodilation lowering preload, but choice if β-blocker)
• If poor response – PA catheter, consider dobutamine plus milrinone
• After optimization of inotropes, can add vasodilator if SVR or PVR high – NTP or NTG can be used instead of inotrope if SVR is high
• If BP is too low, dopamine, but its beta is weak and tachyphylaxis is in 12 hr, or vasopressin

Questions?
NYHA (New York Heart Association) Functional Classification

- **Class I** – symptoms at level of exertion that would cause symptoms in normal people
- **Class II** – symptoms at ordinary exertion
- **Class III** – symptoms at less than ordinary exertion
- **Class IV** – symptoms at rest
Factors Affecting Symptoms in HF

- LV systolic function
- LV diastolic function
- RV function
- Pericardial restraint
- Valvular regurgitation
- Noncardiac factors (peripheral vascular, pulmonary, muscular, neurohormonal, autonomic)