"Precision” medicine

- The “Precision Medicine Initiative” defines precision medicine as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person”.

- The principle underlying precision medicine is that the same treatment may not be effective for all patients.

- Perhaps the most successful area of precision medicine is cancer treatment. Tumors tend to arise from genetic variants, often somatic variants, in a limited set of genes; and several new treatments target these variants successfully.

Puiy BM, et al. JAMA. 2018;320:751-752
What is precision medicine? Available from: https://gho.slm.nih.gov/primen/precisionmedicine/definition

Personalized medicine in RRT

 Connie Rhee Semin Nephrol 2018
I. Incremental PD

PD Prescription: Dose of dialysis

- Target $\text{Kt/V} > 1.7$ (PD + renal)
  if symptom (+) or $\text{Kt/V} < 1.7 \rightarrow$ then, increase dialysis dose.

- Ccr no longer recommended for CAPD

- Clinical Assessment
  Appetite, sleep, work/school, volume control, BP, Ca/P/PTH

- Try to preserve residual renal function. Check RRF every 3-6 months
- Overall fluid balance is more important than absolute UF volume

Adequacy target of peritoneal dialysis

Recommendations: 잔여신기능의 존재 유무와 상관없이 total $\text{Kt/Vurea}$ 를 최소 1.7/week 이상 유지하도록 한다.

2005 ISPD Guideline on Dialysis Adequacy
Incremental approach to PD

- Less than full dose (e.g., 1-2 dwell-times per day)
- Minimum weekly Kt/V target of 1.7 must be reached
- Initiation of dialysis gradually such that the RRF is contributing to blood depuration in conjunction with the added dialysis.
- First developed in the late 90s.
- Sometimes mistakenly presented as a way to start dialysis “earlier”

Incremental vs Full-dose PD

[Graph showing incremental vs full-dose PD]

Oh et al. Essentials of Dialysis

Incremental PD vs Full dose PD

<table>
<thead>
<tr>
<th>Full dose PD</th>
<th>Incremental PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start PD with 3-4 exchanges/day</td>
<td>Start with x 2 exchanges/day</td>
</tr>
<tr>
<td></td>
<td>Step-wisely, increase the exchange number</td>
</tr>
<tr>
<td>Lower risk of inadequate dialysis</td>
<td>Better QoL, Stepwise adjustment to PD, Time saving, economical</td>
</tr>
<tr>
<td></td>
<td>Lower risk of peritonitis and peritoneal membrane damage</td>
</tr>
</tbody>
</table>

Page 5
Incremental PD (1-2 exchange CAPD) vs. standard PD (3-5 CAPD or APD)

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>6th mo</th>
<th>P value</th>
<th>Initial vs 6th</th>
</tr>
</thead>
<tbody>
<tr>
<td>IncrPD</td>
<td>2.02±0.38</td>
<td>2.40±0.58</td>
<td>0.008</td>
<td>2.13±0.45</td>
</tr>
<tr>
<td>SkPD</td>
<td>2.02±0.47</td>
<td>5.61±0.49</td>
<td>0.169</td>
<td>6.62±0.02</td>
</tr>
</tbody>
</table>

Hospitalization
P = 0.021

3 versus 4 exchanges in CAPD patients - RCT

Figure 1. Flow of patients in the study. Abbreviations: HD, hemodialysis; MHD, maintenance hemodialysis; RRF, residual kidney function.

3 versus 4 exchanges in CAPD patients - RCT

CAPD regimens with 3 and 4 exchanges had similar effects on residual GFR, urine volume, and time to anuria.
Retrospective analysis in SNUH

545 patients from a cohort of patients who commenced PD
January 2007 - December 2015

- 115 Excluded
  - 52 Drop-out of PD < 5 months
  - 15 Relocation of PD to another hospital
  - 12 Change volume > 200 ml per day
  - 14 Peritoneal hemolysis
  - 22 Incomplete study data

- 433 Included (follow-up until July 2017)

254 Incremental PD
- 100 Anuria
- 50 Kidney transplantation
- 72 Transfer to HD
- 15 Death
  (1 due to PD-related complication)

139 Full-dose PD
- 73 Anuria
- 23 Kidney transplantation
- 38 Transfer to HD
- 5 Death
  (1 due to PD-related complication)

Figure 1. Flow of patients in the cohort. PD: peritoneal dialysis. HD: hemodialysis.

(See YH, OP-KH et al. submitted)

Retrospective analysis from SNUH

Inversed probability weighted, adjusted anuria-free survival
using time-dependent Cox proportional hazards model

HR 0.71 (95% CI 0.55-0.95, p=0.023)

(See YH, OP-KH et al. submitted)

Proven Benefits of incremental PD

- Improves quality of life
- Reduces health-related costs
- Comparable survival rates to standard PD prescriptions
- Lower hospitalization rates and costs
- Better preserve RRF (needs to be confirmed)

Auguste et al. Semin Nephrol 2018
Drawbacks of incremental PD

- Increased risk of uremia, hypervolemia, and other dangerous, electrolyte disturbances
- Warrant frequent assessments in incremental dialysis.
- Incremental PD patients may be reluctant to adhere to increases in prescription dose as kidney function declines.

Auguste et al. Semin Nephrol 2018

Extended Use of PD

- PD remains feasible and can be applied to more extended range of patients

Refractory Heart Failure  Advanced Liver Disease  Combined Therapy of PD and HD

II. Combined Therapy with PD and HD
- Hybrid dialysis -
Case : M/56

- ESRD due to unknown cause
- 68 kg, 170cm
- CAPD since 2003, progressively lost RRF
- Feb, 2012 : Kt/V 1.47 (peritoneal) + 0 (renal) = 1.47 (total)
- 2012, PET : Low average
- Poor P control → secondary hyperparathyroidism → subtotal parathyroidectomy
- Fatigue due to sustained insufficient dialysis, but insists on PD

Combination therapy with PD+ HD

- Benefits of PD : continuous therapy, RRF preservation
- Standard PD may, when RRF declines, not be sufficient to avoid the risk of uremic complications
- PD + HD for prevalent patients in whom RRF has declined
- Combination regimen is used as an alternative to increasing the dose of PD
- General prescription : 5-6 days of PD weekly and 1 session of HD weekly
- 10.5% of total PD patients in Japan (JSDT 2006)

Indications of combination therapy

**Insufficient dialysis dose**
- Insufficient small-solute clearance resulting in uremic symptoms;
- Any combination of excessive K, Na, P or protein intake concerns.

**Fluid overload**
- Ultrafiltration failure,
- Difficult-to-manage fluid balance because of poor self-management, or severe HF.

Kawashima et al, PDI 2007
Indications of combination therapy (cont’d)

- **Avoiding an increase in dialysate volume**
  - Limited peritoneal capacity, hernia, hydrothorax.

- **Severe mental stress, PD holiday.**

- **Peritoneal rest**
  - With expectation of improved peritoneal function
  - Postponement of membrane deterioration

- **Cardiovascular instability in HD patients**
  - Avoid the intermittency of HD

---

**SNUH experience of combined therapy**

<table>
<thead>
<tr>
<th>Gender</th>
<th>8:2 (M:F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at the start of PD (yr)</td>
<td>51 (10)*</td>
</tr>
<tr>
<td>Duration of PD at the start of combined therapy (mo)</td>
<td>19 (34)*</td>
</tr>
<tr>
<td>Duration of Combined therapy (mo)</td>
<td>10 (9)*</td>
</tr>
<tr>
<td>Cause of choosing combined therapy</td>
<td></td>
</tr>
<tr>
<td>Low Kt/V</td>
<td>6</td>
</tr>
<tr>
<td>Volume overload</td>
<td>1</td>
</tr>
<tr>
<td>Both Low Kt/V and volume overload</td>
<td>3</td>
</tr>
<tr>
<td>Peritoneal rest</td>
<td>0</td>
</tr>
<tr>
<td>Kt/V at the start of combined therapy</td>
<td>1.43 (0.16)*</td>
</tr>
<tr>
<td>UF volume at the start of combined therapy (ml/day)</td>
<td>1217 (568)*</td>
</tr>
</tbody>
</table>

Average(S.D.)*
3% of total PD population at SNUH;
Source: SNUH PD Registry

---

**Number of PD patients in Japan**

**TABLE 1. Number of PD patients at the end of 2012**

<table>
<thead>
<tr>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD patients</td>
</tr>
<tr>
<td>Patients with a catheter for PD such as those who underwent only peritoneal lavage</td>
</tr>
<tr>
<td>New patients who were started on PD in 2012 but introduced to other methods in the same year</td>
</tr>
<tr>
<td><strong>Patients who underwent PD+HD(F)</strong></td>
</tr>
</tbody>
</table>

Hybrid dialysis
Comparison of technique survival

![Graph showing comparison of technique survival between PD+HD and PD alone.](image)

Kawanishi et al. Perit Dial Int 2007

---

Echo parameters before and after combination therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>50±11</td>
<td>117±28</td>
<td>0.01</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>56.5±15.0</td>
<td>56.2±13.5</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>46.0±4.6</td>
<td>43.9±3.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>38.3±4.4</td>
<td>36.0±3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Interventricular septum thickness (mm)</td>
<td>10.8±0.2</td>
<td>10.5±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Posterior wall thickness (mm)</td>
<td>10.8±0.2</td>
<td>10.5±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Physical and laboratory tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>73.8±7.6</td>
<td>57.8±7.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>136±17</td>
<td>139±15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>8.7±1.6</td>
<td>9.0±1.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.4±0.2</td>
<td>3.4±0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.2±0.8</td>
<td>1.1±0.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Serum parathyroid hormone (pg/mL)</td>
<td>271 (50–771)</td>
<td>121 (20–401)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Calcium × phosphate × calcium (mg/dL)²</td>
<td>0.7 (0.6–0.9)</td>
<td>0.3 (0.2–0.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Daily ultrafiltration volume (mL)²</td>
<td>200 (0–400)</td>
<td>310 (0–800)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Tanaka et al. Perit Dial Int 2011

---

Beneficial effect on the peritoneal membrane

<table>
<thead>
<tr>
<th>Parameter</th>
<th>At the start</th>
<th>After 1 year</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bwt</td>
<td>62.6</td>
<td>61.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP</td>
<td>145</td>
<td>138</td>
<td>0.03</td>
</tr>
<tr>
<td>DBP</td>
<td>84</td>
<td>78</td>
<td>0.12</td>
</tr>
<tr>
<td>Anti-HT drugs</td>
<td>2.6</td>
<td>2.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ANP</td>
<td>123</td>
<td>60</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>D/P Cr</td>
<td>0.65</td>
<td>0.59</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Effluent IL-6</td>
<td>21.0</td>
<td>10.3</td>
<td>0.03</td>
</tr>
<tr>
<td>CRP</td>
<td>0.05</td>
<td>0.02</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Matsuo et al. Clin Nephrol 2010
Future trend for combination therapy

- Initiate PD as soon as to maintain RRF as long as possible
- When RRF declines:
  - Combination therapy considered
  - PD for 5-6 days and HD x1/week
- Increase HD and reduce PD
  - HD x3/wk and low volume PD on non-HD days

Start of PD

RRF disappears

Pent Dial Int 2007

III. PD for congestive heart failure

PD for Short-Term Management of Refractory CHF

- Fluid removal rates of 67–568 ml/h can be achieved (not different from CRRT)
- Reduction of plasma volume
- An improvement in hyponatremia
- Reduction in pulmonary capillary wedge pressure.
- No consistent effects on cardiac output
- An improvement in diuretic responsiveness (improved renal hemodynamics)

<table>
<thead>
<tr>
<th>Report</th>
<th>Patients</th>
<th>Prescription</th>
<th>Toxicity, %</th>
<th>UF ml/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxwell et al. [18]</td>
<td>1</td>
<td>2 l/hr x 6</td>
<td>10</td>
<td>1.08</td>
</tr>
<tr>
<td>Berry [19] (1962)</td>
<td>1</td>
<td>2 l/hr x 30</td>
<td>4.25</td>
<td>67</td>
</tr>
<tr>
<td>Lund and Hughes [22]</td>
<td>2</td>
<td>2 l/hr x 12</td>
<td>1.5-4.5</td>
<td>568</td>
</tr>
<tr>
<td>Cork et al. [27] (1960)</td>
<td>16</td>
<td>2 l/hr x 30-45 min</td>
<td>1.5-4.25</td>
<td>200</td>
</tr>
<tr>
<td>Ruz and Hoppin [26]</td>
<td>1</td>
<td>every 30 min</td>
<td>6.25</td>
<td>112</td>
</tr>
<tr>
<td>Cheprat et al. [25]</td>
<td>4</td>
<td>every 30 min</td>
<td>6.36</td>
<td>286</td>
</tr>
<tr>
<td>Shis et al. [20] (1975)</td>
<td>9</td>
<td>1 l/hr x 33</td>
<td>1.5-4.5</td>
<td>100</td>
</tr>
</tbody>
</table>

Mehrotra et al. Cardiology 2001
PD for Long-Term Management of Refractory CHF

- Continuous longstanding extracorporeal UF is not feasible
- Intermittent HD complicated by hypotension
- When PD is initiated solely for the management of CHF
  - as renal dysfunction is not severe enough to start dialysis
  - PD therapy can be modified to achieve adequate ultrafiltration
  - 1~3 hypertonic exchanges/day or one icodextrin bag/day

Mahrota et al. Cardiology 2001

PD for Long-Term Management of Refractory CHF: Systematic review

LVEF

Hospitalization

Lu et al. CardioRenal Med 2015

Refractory HF: Outcome of APD over 1 yr

20 Patients with severe CHF Sx (NYHA IV) refractory to drug therapy

CVVH

(2-4 sessions)

Start PD

Tunehoff catheter implanted

Three APD sessions/week (each 8hr)

Stroke volume index (pre to 1yr)

Left cardiac work index

Thoracic fluid content index (pre to 1yr)

Gottlob et al JDT 2005
Other benefits of PD in CHD

- Reduction in need for diuretics
- Improved QoL
- Limited evidence on the survival benefit
- Mortality is most likely determined by the underlying cardiac disease
- PD-related complications such as peritonitis, malnutrition because of protein loss, increased intra-abdominal pressure, and socio-economic influences are minimal

Mechanism of Therapeutic Actions of PD

- Continuously draws UF
  - More physiologic, lesser risk of hypotension
  - Preserves RBF
  - Less stimulation of RAAS and sympathetic n. system

- Decreases the amount of interstitial edema

- Correction of nutrition and anemia
  - Glucose load, correction of acidosis

- Removal of proinflammatory factors
  - TNFα, IL-1, IL-6, ANP, myocardial depressant factor (MDF)

- Removes more Na than diuretics
  - Na level about 100mmol/L vs 60-70 mmol/L

Summary: PD in CHF

- PD needs to be considered as a novel therapeutic option in type II cardiorenal syndrome (CRS)

- In non-uremic patients with CHF, simple use of icodextrin solution once daily could benefit

- Prospective research is warranted to elucidate the clinical significance and possible risk associated with PD in refractory CHF