Peritoneal Dialysis (PD)

APSN Continuing Medical Education (CME)  as of June 3, 2014
Date : July 3, 2014
Venue : PACIFICO YOKOHAMA, Conference Center 「411+412」

Division of Nephrology
Japanese Red Cross Medical Center
Yoshitaka Ishibashi
Peritoneal Dialysis

1. Past
2. Present
3. Future
1. Past
(a) Discovery of Principles of Dialysis
Osmosis: the movement of water through membranes that hamper the passage of solutes but allow the passage of water down concentration gradients of salts.

Henri Dutrochet (French, 1776-1846) “grandfather of dialysis”
Diffusion

Thomas Graham (Scotland, 1805-1869) “father of modern dialysis”

\[
\text{Rate}_\text{effusion} \propto \frac{1}{\sqrt{\text{density}}} \propto \frac{1}{\sqrt{\text{MM}}}
\]
(b) The Peritoneal Cavity and the Peritoneal Membrane
The Peritoneal Cavity

1. First described by Egyptian morticians as early as 3000 B.C.
   1. The observation was recorded in the Ebers papyrus.
Extensive knowledge started to accumulate in the last half of the nineteenth century, as the abdomen was often explored due to developments in the abdominal surgery.

Natural Functions of the Peritoneum as follows:

(a) to regulate fluid for nutrient and mechanical purposes:
(b) to facilitate motion:
(c) to minimize friction:
(d) to conduct vessels and nerves to the viscera.

Byron Robinson  
The Peritoneum: Histology and physiology  
Chicago Medical Book Company, 1897 – 503
(c) The Birth of Clinical Dialysis

The first human hemodialysis was done in 1924 in Germany by George Haas.

(d) First Attempts at Peritoneal Dialysis

George Ganter treated a young man with glomerulonephritis using pleural lavage in 1918.

Thereafter, he treated a woman with acute uremia from bilateral ureteral obstruction due to uterine carcinoma using intraperitoneal saline infusion.
Early Experience in PD (1923-1950)

- 101 reported patients treated by PD between 1923 and 1948.
  - Causes of renal failure
    - Sixty-three of the patients had reversible causes,
    - 32 had irreversible renal lesions, and
    - two had an indeterminate renal diagnosis.
  - Only 36 survived. The most common causes of death were
    - Pulmonary edema (40%),
    - Uremia (33%), and
    - peritonitis (15%).
• Technique applied in a very diverse way:
  – 22 patients received intermittent treatments and
  – 75 patients received continuous treatments.

• PD solutions:
  – a great variety of solutions used with 14 different types reported.
Closed system reported from group of Beth Israel Hospital
Paul Doolan treated a 33-year-old black woman with renal failure from San Francisco who had complications from a recent childbirth.

She was kept on intermittent PD for 7 months.
(g) Introduction of The Tenckhoff Catheter

PIONEERS IN PERITONEAL DIALYSIS

HENRY TENCKHOFF: THE FATHER OF CHRONIC PERITONEAL DIALYSIS

Perit Dial Int 1983

Figure 1: Henry Tenckhoff MD.
Characteristics of Tenckhoff catheter

① Shape of Catheter Tip
② Silicone Rubber
③ Cuff

Deep cuff (Inner Cuff)
Superficial cuff (Outer cuff)
(h) The Growth of and Disappointment with Intermittent Peritoneal Dialysis

• The difficulties in providing the adequate supply of sterile peritoneal dialysis fluids.

• Patients’ problem was handling the large and heavy bottles.

Introduction of PD using fluid in plastic bags
Continuous Ambulatory Peritoneal Dialysis: Three-Year Experience at One Center

KARL D. NOLPH, M.D.; MICHAEL SORKIN, M.D.; JACK RUBIN, M.D.; DARIUSH ARFANIA, M.D.; BARBARA PROWANT, R.N.; LEONOR FRUTO, R.N.; and DEE KENNEDY, R.N.

(j) Introduction of The Y-set Technique
Decreased Peritonitis

Perit Dial Int 1989 159-163

![Graph showing cumulative probability of survival peritonitis free over study months. The graph compares Y-SET (N=61) and STANDARD (N=63) groups. The Chi-Sq = 9.34 with p = .0022.]
(K) Introduction of Automated PD

- Thirty percent of the 149000 global PD patients and 60% of the U.S. patients were on APD at the end of 2004.
2. Present
(a) Functional Structure of Peritoneum as Dialyzing Membrane
Functional Structure of Peritoneum as dialyzing membrane

Liver

Peritoneal catheter

dialysate

Solute and Fluid

Osmosis and Diffusion
The Peritoneal Membrane

- Mesothelial cells
- Basement membrane
- Interstitial tissue
- Fat cells
- Lymphatic vessels
- Capillary
- Fibroblast
- Basement membrane
Schematic representation of the peritoneal membrane
(b) The physiology of Peritoneal Solute Transport
Mechanism of Solute Transport

- Fick’s law of diffusion
- (England, 1855)

- \( J_s = \text{rate of transfer} = \text{MTAC}(P-D) \)

- MTAC:
  - the mass transfer area of coefficient
    - \( P \): plasma concentration of a solute
    - \( D \): Dialysate concentration of a solute
    - \( J_s \): rate of transfer
    - \( D_f \): free diffusion coefficient
    - \( \Delta x \): diffusion distance
    - \( A \): surface area
    - \( \Delta C \): concentration gradient

- \( J_s = D_f/\Delta x \times A \Delta C \)
- the mass transfer area of coefficient: MTAC: \( D_f/\Delta x \)
Power relationships of MTAC of low- and middle-molecular-weight solutes with their molecular weights

\[ \text{MW} = \frac{4\pi r^3}{3} \]
\[ D_f = \frac{RT}{6\pi \eta r N} \]  
(Einstein-Stokes equation)
R is Boltzmann’s gas constant
T is absolute temperature
\( \eta \) is viscosity of solvent
N is Avogadro’s number

\[ D_f = a \text{MW}^{-0.33} \]
a is a constant
\[ y = ax^b \text{ or } \ln y = b \ln x + \ln a \]
(c)PD solutions (PDS)

Glucose based dialysate.

Icodextrin: Glucose polymer solution.

Nutrineal: 1.1% amino acid containing solution.
Glucose degradation products (GDPs) is generated during heat sterilization.

D-glucose is easily degraded to GDPs.

D-glucose + protein $\rightarrow$ AGE (e.g. CML, CEL, OMA, imidazolones) $\rightarrow$ + protein

D-glucose $\rightarrow$ GDPs

1-DG $\leftrightarrow$ D-fructose $\leftrightarrow$ 4-DG
Reduced GDPs content

<table>
<thead>
<tr>
<th>GDP</th>
<th>Concentration in PDS (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,4-Dideoxyglucosone-3-ene</td>
<td>9–22</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>120–420</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>4–15</td>
</tr>
<tr>
<td>2-Furaldehyde</td>
<td>0.05–2</td>
</tr>
<tr>
<td>Glyoxal</td>
<td>3–14</td>
</tr>
<tr>
<td>5-Hydroxymethylfuraldehyde</td>
<td>6–30</td>
</tr>
<tr>
<td>Methylglyoxal</td>
<td>2–23</td>
</tr>
<tr>
<td>3-Deoxyglucosone</td>
<td>118–324</td>
</tr>
</tbody>
</table>

PDI 2006
(d) Adequacy

- Solute clearance (CANUSA: during the latter 1990s)
  
  **ADEMEX study (2002)**

- Total management
CRA syndrome
MIA syndrome
Fluid management in PD patients

47 Pts hypertensive

4 weeks of salt restriction

20 Pts (152/92→121/77)

17 Pts (164/100→119/79)

Salt restriction +UF

7 Pts

3 Pts

37 Pts normotensive without antihypertensive

Still hypertensive

+ Normotensive with Enalapril

Am J Kidney Dis 2001;37:588
Mechanism of heart failure in ESRD patients

Fluid Excess

<table>
<thead>
<tr>
<th>Volume overload</th>
<th>Pressure overload</th>
</tr>
</thead>
<tbody>
<tr>
<td>• AV fistula</td>
<td>• Hypertension</td>
</tr>
<tr>
<td>• Na+/H₂O retention</td>
<td>• Arteriosclerosis</td>
</tr>
<tr>
<td>• Chronic anemia</td>
<td>• Aortic stenosis</td>
</tr>
<tr>
<td>- increased stroke volume</td>
<td></td>
</tr>
<tr>
<td>- increased heart rate</td>
<td></td>
</tr>
</tbody>
</table>

If fluid excess is not corrected, Eccentric LVH does not improve
Relation between fluid excess and peritoneal permeability

Chronic over hydration can result in increase peritoneal permeability.

Adequate Dialysis

1. Sufficient small solute clearance; renal + peritoneal
2. Strict fluid control
3. good nutrition
4. Inflammation
5. Anemia
6. Control of Phosphate & Calcium levels
   ● 2, 3, and 6 are achieved by thorough patient education.
   ● When signs of malnutrition, inflammation, anemia, or fluid retention were suspected, we increased the dose of PD or switched to hybrid therapy (combination of daily PD and once a week of HD) especially for oligouric/anuric patients.
Policy of treatment: Patient Education

We firmly believe patient education to be essential for successful therapy.

We mostly emphasize the importance of fluid management, and explain to patients and families the reason for its importance.

1. The Rationale
   Chronic volume overload leads finally to;
   1. Cardiovascular complications
   2. Peritoneal damage

2. The Practice
   1. Sodium restriction; 4-5g/day
   2. Achievement of normal BP (below 130/80) without use of antihypertensives except diuretics and/or ACE-I/ARB.

3. Cather management
   1. Helping patients manage the peritoneal catheter
(e) Comparing survival outcome in PD and HD
Head-to-head randomized controlled trial directly comparing PD to HD survival have never been successfully completed.
Similar Outcomes With Hemodialysis and Peritoneal Dialysis in Patients With End-Stage Renal Disease

Rajnish Mehrotra, MD; Yi-Wen Chiu, MD; Kamyar Kalantar-Zadeh, MD; Joanne Bargman, MD; Edward Vonesh, PhD

Integrative care approach

1. Timely referral
2. Timely preparation
3. Timely initiation

Peritoneal dialysis

Transplant

Hemodialysis

Combined Therapy

Mendelsen et al. Perit Dial Int 2002
Case:
81 year old male with ESRD on HD for 7 years was converted to Combined therapy (PD plus once a week HD for 10 years)
## Clinical course of the patient

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>2003</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD</td>
<td>→ PD&lt;sub&gt;(+HD)&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alb</td>
<td></td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>B.P.</td>
<td></td>
<td>170/90</td>
<td>128/79</td>
</tr>
<tr>
<td>LVM-i</td>
<td></td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>iP × Ca</td>
<td></td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>D/P creat</td>
<td></td>
<td>0.82</td>
<td>0.60</td>
</tr>
</tbody>
</table>

### Changes over time

- **CTR53%**
  - HD: 2003
  - PD<sub>(+HD)</sub>: 2011
  - Alb: 3.4 → 4.1
  - B.P.: 170/90 → 128/79
  - LVM-i: 240
  - iP × Ca: 50
  - D/P creat: 0.82

- **CTR43%**
  - HD: 2003
  - PD<sub>(+HD)</sub>: 2011
  - Alb: 4.1 → 4.0
  - B.P.: 128/79 → 112/67
  - LVM-i: 150
  - iP × Ca: 30
  - D/P creat: 0.60

### Notes
- HD: Hemodialysis
- PD: Peritoneal Dialysis
- CTR: Control Rate
(f) Peritoneal change during long-term PD
Peritoneal damage during PD with previous clinical practice (~2000)

- 55 year old male at start of PD with ESRD due to CGN
- 57 year old male with ESRD on PD for 3 years with bioincompatible dialysate. Because his fluid management was poor, he was converted to HD.

Multilyaering of PMCs

Multiplication of Endothelium
EMT
(Epithelial-to-Mesenchymal Transition of mesothelial cells)
Cytology of PMCs in long-term PD patients

30 year old female with ESRD on PD with acidic pH and high GDPs dialysate
Electron microscopy of Flattened Large PMCs
ORIGINAL INVESTIGATIONS

Morphological Studies of Mesothelial Cells in CAPD Effluent and Their Clinical Significance

Tadashi Yamamoto, PhD, Tsuyoshi Izumotani, MD, Tatsuyuki Otoshi, MD, and Masao Kim, MD

Table 2. Morphological Classification of Mesothelial Cells

<table>
<thead>
<tr>
<th>Type</th>
<th>Cell Area (µm²)</th>
<th>Nucleocytoplasmic Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal cell</td>
<td>335.6 ± 31.0</td>
<td>0.663 ± 0.051</td>
</tr>
<tr>
<td>Dyskaryotic cell</td>
<td>570.5 ± 35.9*</td>
<td>0.583 ± 0.056</td>
</tr>
<tr>
<td>Giant cell</td>
<td>1,821.0 ± 68.8*</td>
<td>0.059 ± 0.003*</td>
</tr>
</tbody>
</table>

Table 3. Comparison of Area Parameter (AαTM, AαNM, AαDM, and RαAM)

<table>
<thead>
<tr>
<th>Type</th>
<th>SEP (n = 3)</th>
<th>PS (n = 5)</th>
<th>Other (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AαTM (µm²)</td>
<td>709.3 ± 125.4*</td>
<td>586.6 ± 55.2†</td>
<td>388.2 ± 36.4</td>
</tr>
<tr>
<td>AαNM (µm²)</td>
<td>371.7 ± 103.8†</td>
<td>340.9 ± 16.3†</td>
<td>257.6 ± 11.1</td>
</tr>
<tr>
<td>AαDM (µm²)</td>
<td>1030.0 ± 58.2*</td>
<td>597.9 ± 151.5†</td>
<td>455.3 ± 20.6</td>
</tr>
<tr>
<td>RαAM (%)</td>
<td>62.7 ± 14.0*</td>
<td>38.6 ± 13.5</td>
<td>31.3 ± 2.6</td>
</tr>
</tbody>
</table>

NOTE: Data are expressed as mean ± standard error of the mean.
*P < 0.0001, SEP v other.
†P < 0.01, SEP or PS v other.
Monitoring the functional status of peritoneal damage

① Cytology of peritoneal mesothelial cells

② Peritoneal equilibration test: PET

↑D/P creat (Increased MTAC of creat)
Laparoscopic view of peritoneal cavity

60 year old male patient

PD duration 12 years with acidic high GDPs dialysate

Tanned peritoneum Suggestive of AGE
Multilayered PMCs and hyaline degeneration of capillaries were observed.
Abdominal X-ray
One year after catheter removal.

This patient died from ileus after this surgery.
Conventional dialysate vs Current Japanese PD clinical Practice: D/P creat

PD with conventional dialysate.
Acidic pH, high GDPs content

Current Japanese PD clinical practice.
Neutral pH, less GDPs content,
Introduction of combined therapy

Davis et al. Kidney Int 2004
Ayuzawa N et al. Perit Dial Int 2012
Normal Peritoneum After Nine-years of Peritoneal Dialysis with biocompatible dialysate: A Case Report.

Yuka Kamijo, Hidekazu Iida, Chiaki Kawabata, Katsunori Saito, Rie Furutera, Yoshihaka Ishibashi

Division of Nephology, Japanese Red Cross Medical Center, Tokyo, Japan

Guidelines on PD practice: http://ispd.org/

- **Adequacy**
  - Guidelines on Solute and Fluid Removal 2006

- **Infection**
  - ISPD Position Statement on Reducing the Risks of Peritoneal Dialysis–Related Infections 2011

- **Peritoneal Access**
  - Clinical Practice Guidelines for Peritoneal Access 2010

- **Avoidance of Peritoneal EPS**
  - Length of time on PD and Encapsulating Peritoneal Sclerosis 2009

- **Education**
  - Peritoneal Dialysis Training 2006
Other issues

1. Achieve Adequacy
   1. Fluid management
   2. Control of uremia

2. Peritonitis
   1. Intraluminal
   2. Periluminal
      1. Exit-Site and Tunnel Infection
   3. Enteric
   4. Iatrogenic (enteric, bacteremiac, gynecologic)

3. Non infectious Complication of PD
   1. Inflow and Outflow failure
   2. Hernia & Leak
Exit-Site and Tunnel Infections

ISPD GUIDELINES/RECOMMENDATIONS

PERITONEAL DIALYSIS-RELATED INFECTIONS
RECOMMENDATIONS: 2010 UPDATE

In the present article, exit-site and tunnel infections are collectively referred to as catheter infections.
Epithelium Is Absent from the Subcutaneous Tunnel in Long-Term Peritoneal Dialysis Patients

Ishibashi Y et al. Perit Dial Int 2012

### TABLE 1
Clinical Background of the Study Patients

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Cause of ESRD</th>
<th>PD duration (years)</th>
<th>Epithelialization (mm)</th>
<th>Reason for surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>85</td>
<td>Male</td>
<td>Non-DM</td>
<td>8</td>
<td>6</td>
<td>Patient choice</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>Male</td>
<td>DM</td>
<td>6</td>
<td>8</td>
<td>Peritonitis (touch contamination)</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>Male</td>
<td>Non-DM</td>
<td>4</td>
<td>0</td>
<td>Patient choice</td>
</tr>
<tr>
<td>4</td>
<td>71</td>
<td>Male</td>
<td>Non-DM</td>
<td>3</td>
<td>8</td>
<td>Catheter malposition</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>Female</td>
<td>Non-DM</td>
<td>10</td>
<td>0</td>
<td>Patient choice</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>Male</td>
<td>DM</td>
<td>5</td>
<td>0</td>
<td>Tunnel infection</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>Male</td>
<td>Non-DM</td>
<td>4</td>
<td>9</td>
<td>Tunnel infection</td>
</tr>
<tr>
<td>8</td>
<td>59</td>
<td>Female</td>
<td>Non-DM</td>
<td>8</td>
<td>5</td>
<td>Tunnel infection</td>
</tr>
<tr>
<td>9</td>
<td>54</td>
<td>Male</td>
<td>DM</td>
<td>2</td>
<td>2</td>
<td>Tunnel infection</td>
</tr>
<tr>
<td>10</td>
<td>63</td>
<td>Female</td>
<td>Non-DM</td>
<td>1</td>
<td>5</td>
<td>Tunnel infection</td>
</tr>
</tbody>
</table>

ESRD = end-stage renal disease; PD peritoneal dialysis; DM = diabetes mellitus.

Exit-site

Subcutaneous Tunnel

5mm ~ 10mm
Treatment Plan of Exit-site and Tunnel Infection (proposal)

Start Antibiotics

3 weeks

Not improve

Outer cuff infection negative positive

Exit site conversion Catheter removal

improve

Continue antibiotics

In cases with bacteria: Muraoka K, Ishibashi Y PDI 2012
In cases with NTM: Jo A, Ishibashi Y PDI 2012
Break away the Tenckhoff cather between inner and outer cuff.
Partial Catheter Reimplantation (2)
Inflow and Outflow failure

- **Causes**
  1. Dislocation and Kink of the Tenckhoff catheter
     - Cooperation with surgeon about design before surgery
  2. Obstruction of side holes of the Tenckhoff catheter
     - In cases with fibrin clots, we can dissolve them with heparin of urokinase.
     - In cases with internal organ, surgery is recommended.
Incarnation of Fallopian Tube

40 year old female on PD
Incarnation of colon wall

Kink of catheter after tunnel conversion

Mori E, Ishibashi Y. Perit Dial Int
3. Future
Progress so far

- Advances in natural science (medicine)
  - made it possible for patients to live with ESRD

1. Paradigm of ESRD treatment in Japan

Start of RRT

Live longer with several cycles of RRT

Need of individualized medicine
46 year old male. PD duration 9 years.

98 year old male. PD duration 9 years.
# Reasons of PD technique failure

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>16%</td>
</tr>
<tr>
<td>Fluid management</td>
<td>16%</td>
</tr>
<tr>
<td>Uremia</td>
<td>13%</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>28%</td>
</tr>
<tr>
<td>Catheter infection</td>
<td>8%</td>
</tr>
<tr>
<td>Patient selection</td>
<td>3%</td>
</tr>
</tbody>
</table>

Self-management
Directional Movement of ISPD

ISPD 2012 in Kuala Lumpur
PD first, the way forward

ISPD 2013 in Taipei
Live longer, Live better
2. Academic approaches to individualized medicine

- Introduction of Narrative Based Medicine and Behavioral Science (humanities, cultural science)
The rationale behind this concept derives mainly from the humanities, including **phenomenology**, **logology**, **psychology**, and other fields of study.

The human is a creature whose body and mind are integrated. When seeing patients with chronic disease, caregivers should keep in mind a good integrated balance of natural science and the humanities.
Collaborative research with humanities

University of Tokyo
Phenomenology (1)

- Established by Edmund Husserl (1859-1938) at the beginning of the 20th century.

- Since the 1980’s it has been applied to the nursing theory and practice in order to elucidate and ground the nursing care, firstly in American and European countries and then in Japan, Korea, and Taiwan.
Phenomenology (2)

- Phenomenology gives us some important viewpoints, for example, embodiment, background meaning, concern, temporality, and life world. They are very effective to understand patients with chronic disease individually and integratedly, and to enhance them to be what they want to be.

- [One of the Japanese leading philosophers in the field of Phenomenology of Nursing or Clinical Phenomenology is Professor Tetsuya Sakakibara at the University of Tokyo, with whom I am now working together to develop the Total Renal Care project.]
Phenomenology (3): Ex. Temporality

*Time* is a linear success on moments
Category of natural science.

*Temporality* means “being anchored in a present made meaningful by past experience and ones’ anticipated future.
Category of humanities (Phenomenology).

Temporality creates an individual life story, it is an important concept of individualized medicine.
Behavioral Science

• ACT (Acceptance and Commitment Therapy)
  – To the way to live a better life
    • Bringing out the patients’ constructive attitude toward their own life.
      – Ex. To verbalize aim in life

• CBT (Cognitive Behavioral Therapy)
  – straighten out the patients’ behavior
  – Ex. Salt restriction, Exit-site care
CBT aiming for control of B.P.
Take-home Messages

1. Past:
   1. Thanks to the valuable knowledge obtained over the years, mainly from the natural sciences, continuous PD was made possible in the 1980s.

2. Present:
   1. Current PD clinical practice has shifted from emphasis on solute clearance to a more comprehensive approach.
   2. The position PD occupies in ESRD treatment is now clear, and collaboration with other modes of ESRD treatment is mandatory.

3. Future:
   1. Self-management and maintaining the health of patients with declining renal function is the mainstay of PD therapy. Professionals in the field should try to establish an interdisciplinary approach focusing on both natural science and the humanities.