DIALYSIS THERAPY IN THE 21ST CENTURY

John Sweeney, BS, CHT
United States Transplant Data

<table>
<thead>
<tr>
<th>Year</th>
<th>Transplants</th>
<th>Waiting List</th>
<th>Deaths while waiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>12,318</td>
<td>53,315</td>
<td>2528</td>
</tr>
<tr>
<td>2007</td>
<td>16,119 (up 31%)</td>
<td>94,741 (up 78%)</td>
<td>4452 (up 76%)</td>
</tr>
</tbody>
</table>

Kidney allograft failure is now the third most common cause of incident ESRD

5 year nonrenal organ transplantation leading to ESRD is running 7% to 21% depending on the organ

Urine protein test predicts early failure
- Offers opportunity to eliminate biopsies
- Protein profiles identified for
  - Interstitial fibrosis and tubular atrophy
  - Chronic antibody-mediated rejection w/ kidney dysfunction
- 100% of patients correctly identified from group of 50 which included healthy individuals and stable kidney transplants

ImmuKnow Blood Test (Cylex, Inc)
- Predicts potential early acute transplant rejection in patients in the first 90 days following transplantation
- Measures vitality of the patients immune systems

*New test can predict transplant rejection*, Nephrology News and Issues, April 2008, p. 26
*Urine protein test detects kidney dysfunction in transplant patients*, N N & I, Jan 2009, p. 26
Xenotransplantation

- Need based on lack of human donors
- Practical Challenges
  - Rejection
  - Correct functioning across species barriers
  - Minimize new infection agents into humans
  - Primates ruled out in countries allowing transplants
- Rejection
  - Hyper acute Rejection – Human antibodies and complement
  - Acute Vascular rejection
  - T cell response
  - Chronic Xenograft rejection

**Diabetes Statistics**

- **NIH data: Diabetes Care – February, 2009**
  - 13% of all adults 20 years and older have diabetes
  - 40% of those have not been diagnosed
  - For those over 65 years of age nearly one third have diabetes and another 30% are pre-diabetes
  - Study base: Oral Glucose Tolerance Test (OGTT) which is better than a Fasting Blood Glucose Test (FBG) especially with older people

- **25 year projection: Diabetes Care – December, 2009**
  - USA Population: 2009 = 23.7 million, 2034 = 44.1 million
  - Cost: 2009 - $113 billion, 2034 - $336 billion
  - Medicare population: 2009 – 6.5 million, 2034 – 14.1 million
  - Medicare costs: 2009 - $45 billion, 2034 - $171 billion
New Class: DPP-4 Inhibitors (Oral hypoglycemics)

DPP-4 = Dipeptidyl peptidase – 4

Decreasing DPP-4 prolongs the activity of incretins which regulate insulin secretion and blood glucose levels.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic Name</th>
<th>Company</th>
<th>Status</th>
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<tbody>
<tr>
<td>Januvia</td>
<td>sitagliptin</td>
<td>Merck</td>
<td>FDA approved 10/2006</td>
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<tr>
<td>Onglyza</td>
<td>saxagliptin</td>
<td>Bristol – Myers Squibb</td>
<td>FDA approved 6/2009</td>
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<tr>
<td>Galvus</td>
<td>vildagliptin</td>
<td>Novartis</td>
<td>EU approved 2008</td>
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<tr>
<td>----</td>
<td>alogliptin</td>
<td>Takeda Pharmaceutical</td>
<td>FDA suspended 6/2009</td>
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<tr>
<td>Ondero</td>
<td>linagliptin</td>
<td>Boehringer Ingelheim</td>
<td>Phase III clinical trials</td>
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</table>
Alzheimer’s patient’s brains are resistant to insulin the same way as diabetes type 2 patients. Toxic proteins ADDLs ("amyloid beta-derived diffusible ligands") attach to brain synapse’s insulin receptors, disabling communication resulting in memory loss.

Damage to neurons by ADDLs is blocked by insulin. Anti-diabetic drugs shield synapses against ADDLs. Implication is that weight loss and exercise which reduces the chance of developing diabetes may also work for Alzheimer’s Disease.

Survival vs. Treatment Time

- **Study:** 451 patients
  - Patients started: Jan 1, 1996 – Dec 31, 2001
  - Study ended November 30, 2008

- **Survival at 10 years (p < 0.0001):**
  - Tx Time > 4.0 hours = 39.7%
  - Tx Time (3.75 – 4.0 hours) = 18.9%
  - Tx Time < 3.75 hours = 15.4%

- **Time and Adequacy vs. Survival:**
  - Kt/V > 1.6 + t > 4.0 hours = 54.3%
  - Kt/V > 1.6 + t < 4.0 hours = 38.9% \( (p < 0.04) \)
  - Kt/V < 1.6 + t > 4.0 hours = 17.9%
  - Kt/V < 1.6 + t < 4.0 hours = 3.1% \( (p < 0.0001) \)

Long Term Patient Survival on Hemodialysis: Association with Time, Singh S, Ashby D, et al., Poster at ASN. West London Renal and Transplant Centre, London, United Kingdom
Home Hemodialysis

- **Top 10 Providers (about 80% of US ESRD population)**
  - 1,736 HHD patients (2008), 2,836 HHD patients (2009)
  - Increase in number = 63.3%
  - Still less than 1% of the total ESRD population

- **Benefits due to daily HHD**
  - Regression of Left Ventricular Hypertrophy
  - Reduced Hypertension
  - Improved fluid overload status
  - Improved anemia status/reduced drugs
  - Treatment tolerance and quality of life

http://www.nxstage.com/chronic_renal_care/index.cfm
Most present machines were designed for in center use on multiple patients.

Home machines need to be smaller, more automated, and user friendly.

- DaVita has an exclusive relationship with NxStage Medical and their SystemOne HHD machine.
- Fresenius has purchased Renal Solutions and their Allient sorbent HD machine.
- Baxter Healthcare has invested in an HHD machine being developed by DEKA who acquired the assets of Aksys Ltd and their PhD machine.

The Bioartificial Kidney

- David Humes MD – University of Michigan
- William Fissell MD – Cleveland Clinic

Stage 1 filter lined with blood vessel cells.

Stage 2 reabsorbing unit lined with tubule cells.

Next stage
Add oxygen sensing cells to produce EPO

Research at Columbia Univ. Medical Center
Urine test used to detect small protein, NGAL (neutrophil gelatinase associated lipocalin)
Test done for those with sudden kidney failure
May detect kidney failure 1 -2 days sooner than standard creatinine test
May also distinguish between acute and chronic failure
Results for patients with positive NGAL tests:
- 65% need care of a nephrologist
- 32% would need dialysis
- 29% would require care in the ICU
Northwestern Univ. Feinberg School of Medicine

- Type 1 diabetics avoid insulin injections through infusion of their own stem cells
- Done for early stage type 1 patients (within 1st 6 months of detection)
- 20 of 23 cases were insulin free for at least a few months
- 12 patients averaged 31 months without insulin need
- Next step: Compare stem cell success to intensive insulin injection therapy.
Stem Cell Research

- **Intermountain Medical Center and AlloCure**
  - Modified stem cells used on patients with acute renal failure
  - Cells administered following surgery.
  - Injured organ sends chemical signals that attract cells
  - Cells work to boost kidney repair and are then flushed from the patient’s system after about 72 hours
  - Kidney improvements include:
    - Decreased apoptosis (cell death)
    - Increased mitogenesis (cell generation)
    - Decreased expression of pro-inflammatory cytokines
    - Increased expression of anti-inflammatory cytokines
  - Clinical trial phase I ends in the spring of 2009 and phase II begins.

*Utah researchers test stem cells in patients to improve risk for kidney failure*, Macha A., NN&I, Nov 2008, p.29
Bioelectrical Impedance Analysis (BIA) or Bioimpedance Spectroscopy (BIS)

Body ICF and ECF ratios to total body fluid and body electrical impedance are related to voltage frequency.

Used to measure electrical impedance of body tissues to provide estimate of total body water (TBW).

Fat-free mass (FFM), Fat mass (FM) and Body mass index (BMI) can be determined from BIA results using various algorithms.

Typical current frequency range is 5 - 1000 kHz.

More frequencies used – better results
- XiTRON Hydra 4200 = 50 frequencies
- ImpediMed SFB7 = 256 frequencies
Advantages

- Identifies volume of fluid space (total body water), thus: **Quantifies actual state of hydration**
- Non-invasive test
- 3 minutes/test

Disadvantages

- Cost
  - Machine
  - Electrode/sensor pads
- Dubious accuracy in dialysis patients
  - Unable to accurately measure trunk volume
  - Currently acceptable only for measuring acute Δ in ECW

Current producing electrode

Voltage sensing electrode

Current = 800 µA

Frequency Range = 5 - 1000 kHz

XiTRON Hydra 4200
XiTRON Technologies – San Diego CA
Electronics Evolution

- Moore’s Law (1975) –
  - Complexity of circuits doubles every 2 years
- Today –
  - Transistor is 32 nanometers wide
  - Lithography limit is 22 nanometers
  - AMD Phenom X4 processor has 758 million transistors on a surface area of less than 0.5 square inch
- Hewlett Packard –
  - Developing crossbar design of nanowires
  - Wire intersections create “memristors” = 10 to 15 transistors
- The Challenge –
  - The more compact, the higher the operating temperature
  - Transistors breakdown at high temperatures

“The next twenty years of Microchips”, Scientific American, January 2010, pp 82-89
• MacBook Air Notebook – Case acts as a heat sink made of thermally conductive Aluminum

• Apple Power Mac G5 – Uses microchannels on the underside of the processor to run liquid coolant.

• Intel – Builds a thin-film superlattice of bismuth telluride a thermoelectric material into the chip case. It converts a temperature gradient into electricity and acts as a refrigerant.

• Purdue University - makes a solid state fan using the Corona wind effect. Live wires generate a microplasma of ions that are driven to a plate. This is the same effect used in silent home air purifiers.

“The next twenty years of Microchips”, Scientific American, January 2010, pp 82-89
The Next Generation

- **Optical Computing** – connecting processors using light instead of wires – Hewlett-Packard, UC – Santa Barbara
- **Molecular Computing** – Molecules replace transistors. Referred to as “molelectronics”. – Yale and Rice Universities
- **Biological Computing** – replacing transistors with DNA and RNA molecules. – An area occupied by a billion transistors could hold a trillion DNA strands. – Weizmann Institute of Science – Israel
- **Quantum Computing** – Transistor made from individual atoms, electrons, or photons. Can have “on”, “off” and “quasi” states. $2^8 = 256$, $3^8 = 6561$ – Univ. of Maryland, National Institute of Standards and Technology

“The next twenty years of Microchips”, Scientific American, January 2010, pp 82-89
Need for Improvement

- Present Environment
  - Mortality exceeds 20% annually
  - Costs are running $34 billion
  - Patient Rehabilitation is less than 20%
  - Hospital costs are greater than $20K per patient per year

- Leading cause of death
  - Infection who’s main source is catheters
  - Cardiovascular disease due to left ventricular hypertrophy (LVH)

- What to do
  - Longer treatments, more frequent treatments (DHHD, SNHD)
  - Better initial care for new patients
  - Get rid of catheters

20th century – linear, 21st century – exponential

Assume linear growth of knowledge increase at 5% of known information in 2000 for each year successive year
- By 2010 the knowledge base would be 50% greater
- By 2020 it would double
- By 2100 it would have increased by 500%

Assume exponential growth of knowledge at 5% of known information compounding each year
- By 2010 the knowledge base would be 63% greater
- By 2020 it would be 165%
- By 2100 it would be 13,050% !!

Put yourself in “Education Mode” if you want to keep up.
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Registered Nurse</td>
<td>581,500</td>
<td>$62,450</td>
<td>Associate’s degree</td>
</tr>
<tr>
<td>Home Health Aid</td>
<td>460,900</td>
<td>$20,460</td>
<td>Short term - OJT</td>
</tr>
<tr>
<td>Personal and Home Care Aids</td>
<td>375,800</td>
<td>$19,180</td>
<td>Short term - OJT</td>
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<tr>
<td>Medical Assistants</td>
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<td>$28,300</td>
<td>Moderate - OJT</td>
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<tr>
<td>Physician Assistant</td>
<td>29,200</td>
<td>$81,230</td>
<td>Master’s degree</td>
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