Kidney Transplantation
Part of the Continuum of care of Kidney Disease

A story of Failure and Success

Indian Health Service - California Region Health Care Conference - May 22, 2013
Sacramento, CA

William H. Marks, MD., Ph.D., FACS, MHA
Executive Medical Director
Alexion Pharmaceuticals
Conflict of Interest

• I am employed by Alexion Pharmaceuticals as a clinical researcher
• My talk does not address the use of Alexion products or the off label use of other pharmaceutical products
• I have no conflicts of interest
Agenda

• Introduction
  – Some terminology – Healthcare and Success

• Beginning with the punch line –
  – Renal Replacement Therapy - Transplantation as the preferred option

• Chronic Kidney Disease
  – A continuum of care through the lens of transplantation

• Questions
What is Success when dealing with a Disease?

Prevention -
Successful prevention: disease never occurs... Healthcare

Treatment - dealing with failure... Medicine/Healthcare
Successful treatment: benefits a target population and consistently yields best possible outcome

Successful treatments share specific characteristics
1. Testable -------- scientifically vetted
2. Equitable ------ apply equally to affected group
3. Cost effective -- pharmacoeconomic argument
4. Available -------- generally available
Kidney Function(s)

1. Oxidize detoxified compounds
2. Regulate ECF: Na⁺, K⁺, Cl⁻, Ca²⁺, HPO₄²⁻ solutes
3. Acid-base balance of H⁺/HCO₃⁻
4. Regulate ECF H₂O volume
5. Process metabolic end products: secrete uric acid & creatine
6. Endocrine: erythropoietin, renin-angiotensin axis
   + Vit D₃ → liver → kidney processes it → gut to a
# The Early NHANES III Study

## Analysis of Prevalence of CKD by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>eGFR Range (ml/min/ 1.73 m²)</th>
<th>Population (1,000’s)</th>
<th>Population (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or increase GFR</td>
<td>≥ 90</td>
<td>5,900</td>
<td>3.3 %</td>
</tr>
<tr>
<td>2</td>
<td>Moderately decreased GFR</td>
<td>60-89</td>
<td>5,300</td>
<td>3.0 %</td>
</tr>
<tr>
<td>3</td>
<td>Severe decreased GFR</td>
<td>30-59</td>
<td>7,600</td>
<td>4.3 %</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15-29</td>
<td>400</td>
<td>0.2 %</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure</td>
<td>&lt; 15</td>
<td>300</td>
<td>0.1 %</td>
</tr>
</tbody>
</table>

- Adapted from NHANES III (2000)
CKD Management – Thinking Ahead
Renal Replacement Therapy

• Palliative care

• Peritoneal Dialysis

• Hemodialysis

• Transplantation
Hemodialysis
Then and Now

Artificial Kidney: 1947
Hemodialysis

Advantages
1. Target electrolytes
2. Tight control of fluid status
3. Professional contact
4. Community interaction

Disadvantages
1. Surgical / wound complications
2. Infection
3. Peak and valley results
4. Time / availability
5. Access to facilities/certified assist

Types of Access for Hemodialysis:
- Graft
- Fistula

Peritoneal Dialysis

Advantages:
1. Independent (Can do on own)
2. Portable
3. Consistent quality of life

Disadvantages:
1. Requires Meticulous technique – risk of infection
2. Surgical complications
3. Weight gain
4. Diabetic control
Kidney Functions

- Metabolic End Products
  - Removal of Urea, Creatinine etc.

- Bone Structure
  - Calcium Balance
  - Vitamin D Activation

- Blood Formation
  - Erythropoietin Synthesis
  - Water Balance

- Cardiac Activity

- Potassium Balance

- Recovery of Bicarbonate

- Sodium Removal

- Blood Pressure

- Regulation of Blood pH

Adapted from NephroCare 2013
Fears - Safety – Efficacy – Expectations

Transplant – safe alternative

<table>
<thead>
<tr>
<th>Year of transplant</th>
<th>Graft survival after first adult kidney only transplant from a DBD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. at risk on day 0</td>
</tr>
<tr>
<td>1998-2000</td>
<td>2890</td>
</tr>
<tr>
<td>2001-2003</td>
<td>2773</td>
</tr>
<tr>
<td>2004-2006</td>
<td>2469</td>
</tr>
<tr>
<td>2007-2010</td>
<td>2868</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year of transplant</th>
<th>Patient survival after first adult kidney only transplant from a DBD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. at risk on day 0</td>
</tr>
<tr>
<td>1998-2000</td>
<td>2890</td>
</tr>
<tr>
<td>2001-2003</td>
<td>2773</td>
</tr>
<tr>
<td>2004-2006</td>
<td>2469</td>
</tr>
<tr>
<td>2007-2010</td>
<td>2868</td>
</tr>
</tbody>
</table>
Survival Benefit
Transplant versus Dialysis

USRDS annual report 2011
Improved Quality of Life

Transplant versus Dialysis

Short form health survey - SF36

Tonelli M, et al., AJT 2011; 11(10)
Cost Effective
Transplant versus Dialysis
What is the Success when dealing with ESRD?

Prevention: Ideal but limited

✓ Successful treatment: benefits the target population and consistently yields best possible outcome

Characteristics of a successful treatment:

✓ 1. Testable -------- scientifically vetted
✓ 2. Equitable ------ apply equally to affected group
✓ 3. Cost effective -- pharmacoeconomic argument
✓ 4. Available -------- generally available

Transplantation is the preferred treatment for ESRD

What about the rest of ‘Kidney Disease?’
Kidney Disease = Chronic Kidney Disease

- Many terms used interchangeably to describe a state of chronic reduced kidney function
  - Chronic Renal Insufficiency
  - Chronic Renal Failure
  - Renal Insufficiency
  - Renal dysfunction
  - Diabetic nephropathy*
  - Chronic rejection (if patient had prior transplant)
  - Chronic nephropathy
  - Hypertensive nephrosclerosis*
  - Etc. etc. etc.
Chronic Kidney Disease (CKD)
Kidney Disease Outcome Quality Initiative (KDOQI)

– Anatomical or Structural Defect
  • Abnormal imaging study
    – (i.e. Polycystic Kidney Disease, nephrosclerosis)
  • Abnormal Renal Biopsy
    – (i.e., MPGN, TMA)
  • Proteinuria (spot UProt/creat >30 mg/g)

– Functional Component
  • Abnormal eGFR (Low or High)
    – A biomarker (calculated measure) of kidney function

– Time Component (chronic)
  • Finding present ≥ 3months
KDOQI CKD Definition

- eGFR < 60 ml/min/1.73 m² ≥3 months

  OR

- Spot urine albumin/creatinine ratio of >30 mg/g in at least 2 urine samples
Chronic Kidney Disease

Quality of life
Length of life
Social impact
Financial impact
Family
Community
CKD – Risk Factors

- Diabetes Mellitus
- Hypertension
- Cardiovascular Disease
- Obesity
- Metabolic Syndrome
- Age and Race
- Acute Kidney Injury
- Malignancy
- Family history of CKD
- Infections like Hep C and HIV

- Kidney Stones
- Autoimmune diseases
- Nephrotoxic drugs
  - like NSAIDS
  - Calcineurin inhibitors (CNI)
- Prior transplant
  - Chronic rejection
- History of antibody mediated rejection (AMR)
- History of delayed graft function (DGF)
CKD – Most Common Etiologies

Graph showing the number of patients (in thousands) affected by different causes of CKD from 1980 to 2002:
- Diabetes
- Glomerulonephritis
- Hypertension
- Cystic kidney

The graph indicates an increase in the number of patients affected by these conditions over time.
# High Blood Pressure

## Endemic Native American Healthcare Risk for CKD

### Hypertension

*CDC data is not available.*

#### Age-adjusted percentage of persons 18 years of age and over who have high blood pressure, 2004-2008.

<table>
<thead>
<tr>
<th></th>
<th>American Indian/Alaska Native</th>
<th>Non-Hispanic White</th>
<th>American Indian/Alaska Native/Non-Hispanic White Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men and Women</td>
<td>34.5</td>
<td>25.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Men</td>
<td>38.7</td>
<td>26.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Women</td>
<td>30.2</td>
<td>24.7</td>
<td>1.2</td>
</tr>
</tbody>
</table>


Percent of adults age 18 and over with hypertension whose blood pressure is under control *Not available at this time.*

#### Age-adjusted percentage of persons 18 years of age and over who have high blood pressure, 2010. National Health Interview Survey (NHIS)

<table>
<thead>
<tr>
<th></th>
<th>American Indian/Alaska Native</th>
<th>Non-Hispanic White</th>
<th>American Indian/Alaska Native/Non-Hispanic White Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30.0</td>
<td>23.9</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Native Americans CKD
Etiology

Diabetes (DM) = #1 cause of kidney failure
Native Americans have a high incidence of diabetes
13-15% of Native Americans >18y have diabetes

High Blood Pressure (HTN) = #2 cause of kidney failure
~30% of adult Native Americans have HTN

Together: DM and HTN = ~ 75% of kidney failure
Kidney Disease - Therapeutic Windows

• Prevention
  prevent and/or treat CKD risk factors

• Management of CKD
  stages 1 & 2 (eGFR >60): management guidelines DM and HTN and patient education
  stages 3 & 4 (eGFR 15-60) therapeutic guidelines for related complications (anemia, ESRD preparation)

• Renal replacement therapy (RRT)
  Patient education, evaluation and collaboration with dialysis and/or transplant center
Kidney Disease - Continuum of Care

At Risk Population
26,000,000+
people

Kidney insult due to large number of factors

Primary Care

CKD

ESRD

Primary Care Nephrologist

Primary Care Nephrologist
Care Team

Dialysis Center

Transplant Center

500,000+
People

1965

1998

Modified – Fresenius Corporation 2012
CKD Patients Need Special Attention

CKD “Death Before Dialysis” is Prominent

- Early recognition and intervention for CKD can prevent early death before dialysis
- In one study of a large HMO, CKD patients were more likely to die than reach RRT

*Modified/Fresenius corporation*

![Chart showing the progression of CKD stages and outcomes:](chart)

- **Stage 2**: 73.5% Stable CKD, 11.2% Death
- **Stage 3**: 64.2% Stable CKD, 24.3% Death
- **Stage 4**: 27.8% Stable CKD, 17.6% Death, 45.7% Death, 0% Lost to Follow Up

Total for each stage includes the percentage of patients remaining stable, those who died, those who required dialysis, and those lost to follow-up.
CKD Patients Need Special Attention

eGFR & Mortality

eGFR < 60 ml/min/m2 ➔ Increase Risk of Death

![eGFR Adjusted Mortality Graph]

<table>
<thead>
<tr>
<th>eGFR (ml/min/1.73 m²)</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;59</td>
<td>25,803</td>
</tr>
<tr>
<td>45-59</td>
<td>11,603</td>
</tr>
<tr>
<td>30-44</td>
<td>7,802</td>
</tr>
<tr>
<td>15-29</td>
<td>4,408</td>
</tr>
<tr>
<td>&lt;15</td>
<td>1,842</td>
</tr>
</tbody>
</table>
CKD - Management

The graph illustrates the progression of GFR (glomerular filtration rate) over time for different treatment scenarios:

- **No Treatment** (black line)
- **Current Treatment** (red line)
- **Early Treatment** (gray line)

Key points:
- **Kidney Failure** is indicated as the area where GFR drops below 10.
- Time (years) is marked at 4, 7, 9, and 11 years.
Chronic Kidney Disease
through the lens of transplantation

Assumptions
The patient will progress to ESRD
The initial treatment will be dialysis (often for years)

Goals for Treatment of CKD
Prolong the dialysis free course
   Protect the kidneys (remember that the same factors that affect native kidneys affect transplants)
Maintain health while on dialysis
   (6% year over year mortality)
Prepare patient and family for transplantation
   Protect the patient from treatments that may adversely affect his/her ability to obtain a transplant

ESRD - treatment of choice is Transplantation
CKD Management
Key areas of focus (Eye to the Future)

1. Hypertension
2. Anemia
3. Diabetic control
4. Preparation for RRT
CKD – Hypertension
Thinking ahead – Hypertension injures ALL kidneys

• Single most important measure is BP control
  – Target BP <130/80 with minimal proteinuria
  – Lower (125/70) if significant proteinuria (1g)

• ACEIs and ARBs slow the progress of CKD (both diabetic and non-diabetic)

• Decrease the sodium intake - 2.5g/day

• Most patients require 2+ agents
CKD – Anemia

• Associated with a decrease in quality of life
  – Subjective Diagnosis
  – Most apparent in later stage disease

• Due to decrease in EPO production in the kidney.
CKD Management – Anemia - think ahead
Correct Anemia with an Eye to the Future

• Erythropoietin
  Epoetin alfa: Procrit®, Epogen®
  Darbepoietin Alpha: ARANESP®

• Recommended target Hb 11-12g (<13)
  ≥13g Hb associated with increased mortality due to CHF

• Correct iron stores

• AVOID transfusions
  – Sensitize patients –
    • Decrease opportunity for future transplant
    • Decrease success of future transplant
  – If transfusion necessary - insist on LEUKOREDUCTED blood only (Leukofiltration)
    • Defend your patient’s opportunity for future transplant

*CHOIR study
(correction hemoglobin and outcomes in renal insufficiency)
CKD Management – Think Ahead
Diabetic Control in a Changing Renal Environment

• Kidneys metabolize LMW proteins
• When kidney loses function
  – Ability to metabolize small proteins decreases and insulin is a small protein
  – Endogenous or exogenous insulin lasts longer
  – Oral therapies may have prolonged affect
  – CKD patients may suffer severe hypoglycemic episodes
  – Patient education and/or insulin dose adjustment
  – Close attention to oral therapy dosing
• Prepare patient to expect the opposite with successful transplant
  – A transplant does not make diabetes worse
  – may require greater attention to maintain tight control
CKD Management – Thinking Ahead
Renal Replacement Therapy

• Palliative care

• Peritoneal Dialysis

• Hemodialysis

• Transplantation
CKD Management – Thinking Ahead
Renal Replacement Therapy - RRT

• Preparation
  1. Peritoneal Dialysis
     • Abdominal operations – communicate with the surgical team
     • Diet/weight loss
     • Early training
     • Early placement
  2. Hemodialysis
     • Avoid needless Veni-puncture & insertion of catheters – patient and staff education
     • Early placement of vascular access
       – HD/PD
         • Opportunity to CHANGE MIND
CKD Management – Thinking Ahead
Renal Replacement Therapy - RRT

Options – what’s best for your patient’s situation?

1. Peritoneal Dialysis
   - Prior abdominal operations
   - Home environment
   - Bathing – Swimming

2. Hemodialysis
   - Access
   - Transportation
   - Assistance
   - Cardiovascular status

3. Transplantation
   - Malignancy – Spectrum from in situ to Melanoma
   - Infection – active / bacterial / viral
   - Recurrent disease risk (ie., MGPN II, C3 nephropathy, FSGS)
   - Environment – Access
   - Personal responsibility - Compliance
CKD Management – Thinking Ahead
Renal Replacement Therapy - RRT
Options – what’s best for your patient’s situation?

1. Peritoneal Dialysis
   • Prior abdominal operations
   • Home environment
   • Bathing – Swimming

2. Hemodialysis
   • Access
   • Transportation
   • Assistance
   • Cardiovascular status

3. Transplantation
   • Malignancy – Spectrum from in situ to Melanoma
   • Infection – active / bacterial / viral
   • Recurrent disease risk (ie., MGPN II, C3 nephropathy, FSGS)
   • Environment – Access
   • Personal responsibility - Compliance
Transplantation Renal Replacement Therapy
Option of choice? The Issues...

1. High success rate post-transplant
   a. High incidence of renal disease
   b. Highest referral rate to transplant centers
   c. Once listed – transplanted at same rate as rest of list
   d. Once transplanted – 1, 3, 5 y graft survival high compared to other races

2. Low percapita rate of transplantation
   a. Cost: Medicare but no non-direct transplant costs and 80% reimbursement
   b. PsychoSocial issues
   c. Location – location – location