End Stage Renal Disease and Hypertension: Connecting the Disconnect with Spironolactone

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At the end of this presentation, the learner should be able to:

1. Explain the correlation between end-stage renal disease (ESRD) and hypertension
2. Describe the role of aldosterone in the renin-angiotensin-aldosterone system (RAAS) and in resistant hypertension
3. Explain the mechanism of aldosterone antagonists in decreasing blood pressure
4. Evaluate literature concerning the efficacy, renal protective properties, and safety of spironolactone
5. Discuss the role of aldosterone antagonists in patients with ESRD and hypertension
1. Chronic Kidney Disease (CKD)\(^1-4\)
   a. CKD is a major public health problem that often progresses to kidney failure
      i. CKD is defined according to the presence or absence of kidney damage and the level of
         kidney function (see Table 1)
      ii. 33 million American adults diagnosed with CKD
         1. Millions more at risk, but unaware of this risk
         2. More than 50,000 (8.6%) of the 576,000 Americans who have kidney failure are Texans
         3. Number of dialysis patients in Texas has more than tripled since 1990
            a. At the end of 2011, over 39,000 patients were receiving dialysis treatments
      iii. Average cost of dialysis treatment or renal transplant is $66,000 per patient per year
   2. Kidney Failure and ESRD\(^5-8\)
      a. Definition of Renal Failure and ESRD
         i. Two independent criteria for renal failure
            1. GFR < 15mL/min/1.73m\(^2\) accompanied in most cases by signs and symptoms of uremia
            2. Need to initiate kidney replacement therapy (dialysis or transplant) to treat complications
               of decreased GFR
         ii. ESRD is an administrative term used in the US for Medicare billing purposes and includes
             patients treated by dialysis or transplant irrespective of GFR
      b. Diabetes and hypertension are the most common causes of renal failure in the United States

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR mL/min/1.73m(^2) (Kidney Function)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60-89</td>
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<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
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<td>4</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

3. Renal Physiology\(^7-8\) (see Appendix A)
   a. Kidneys are located in the retroperitoneal area
      i. Approximately 25% of cardiac output goes to the kidney
         1. Renal artery and renal vein supply blood flow to the kidney
      ii. The anatomic unit of kidney function is the nephron which consists of the glomerulus and
           renal tubule (see Figure 1)
         1. Functions of the kidney
            a. Regulate water and electrolyte balance
            b. Excrete metabolic waste
            c. Excrete bioactive substances (i.e. hormones and many foreign substances, specifically drugs)
            d. Regulate arterial blood pressure (BP)
            e. Regulate red blood cell production (erythropoietin synthesis)
            f. Activate Vitamin D
            g. Gluconeogenesis
         2. Nephron processes
            a. Filtration
            b. Reabsorption
            c. Secretion
            d. Excretion
      iii. Renal microvasculature organized into two capillary beds: the glomerular capillary convolute
           and the peritubular capillary network
            a. These capillary beds create a balance between glomerular filtration and tubular
               reabsorption (glomerulo-tubular balance)
            b. The glomerulo-tubular balance maintains pressure required for filtration and
               reabsorption
b. Regulation of blood pressure\textsuperscript{6-13}
   i. Kidneys play a major role through their effect on sodium and water balance
      1. RAAS
         a. Controls fluid and electrolyte balance through coordinated effects on the heart, blood vessels, and kidneys (see Appendix B)
      2. Angiotensin II
         a. Plays a role in the short- and long-term regulation of arterial BP
         b. Modest increases in angiotensin II acutely raise BP
         c. Has a slow pressor response and a role in altering cardiovascular structure
         d. Signals the adrenal cortex to secrete more aldosterone
      3. Aldosterone
         a. Regulates sodium channel activity
         b. Effects vary by the specific cell type
         c. Primarily promotes the reabsorption of sodium and the secretion of potassium in the distal nephron
   c. Renal Disease\textsuperscript{14-15}
      i. Main mechanisms of renal injury are based on immunologic reactions, tissue hypoxia/ischemia; often in reaction to exogenous or endogenous substances, etc.
      ii. Disease Progression
         1. Glomerular, tubular, and vascular injury are all involved in progressive renal disease
            a. Progressive renal disease is characterized by glomerulosclerosis, interstitial leukocyte infiltration, tubular atrophy, and tubulointerstitial fibrosis
            b. Damage to one part of the nephron will in part affect the other through several different mechanisms (see Appendix C)
iii. Renal Failure\textsuperscript{14-16}
   1. Stressors such as high blood pressure cause injury to nephron
   2. Stress Adaptation/Compensatory Mechanisms
      a. Glomerular capillary hypertrophy
         i. Each nephron can increase its filtration rate by 25-50%.
      b. Once the capacity for stress adaptation is exceeded, injury becomes irreversible and cell death occurs
   3. Sets off a cascade of adaptations that cause damage
      a. The loss of nephrons increases the pressure on remaining nephrons, resulting in glomerular capillary hypertension
         i. Elevated glomerular pressure increases net filtration
            1. Compensates for the loss of nephrons
            2. Afferent arteriole vasodilates which will increase GFR due to a very high capillary pressure
      4. Allows the kidney to adapt but eventually damages the remaining nephrons if stressor is not corrected or removed
         a. Can cause or worsen systemic hypertension; glomerular perfusion increases more from even higher systemic pressure
         b. Causes a positive feedback cycle
   iv. Renal replacement therapy (RRT) is the only life-supporting treatment available when the kidney’s fail\textsuperscript{16}
      1. Types of RRT can include hemodialysis, peritoneal dialysis, or transplantation
      2. Initiation of RRT requires evaluation of benefits, risks, and disadvantages
         a. Individual factors such as dialysis accessibility, vascular access, age, declining health, fluid balance, and compliance-often influences the timing of dialysis initiation
   4. Hemodialysis (HD)\textsuperscript{16-17}
      a. Most common form of RRT for kidney failure
         i. Usually initiated when GFR ≤ 15mL/min/1.73m\textsuperscript{2}
         ii. Does not provide a cure
      b. Relies on the principle of solute diffusion across a semi-permeable membrane
         i. Metabolic waste moves down a concentration gradient provided by the dialysate
         ii. Procedure is targeted at removing both low- and high-molecular-weight solutes
         iii. Majority of ESRD patients require between 9-12 hours of dialysis per week
      c. Four essential components to hemodialysis (see Appendix D)
         i. Dialyzer
            1. Plastic chamber that perfuses blood and dialysate compartments simultaneously at very high flow rates
         ii. Dialysate
            1. Chemical bath used to draw fluids and toxins out of the bloodstream
            2. Composition and delivery is adjusted for each patient
         iii. Blood delivery system
            1. Composed of the extracorporeal circuit in the dialysis machines and the dialysis access
            2. The circuit consists of a blood pump, dialysis solution delivery system, and various safety monitors
            3. The pump moves blood from the access site, through the dialyzer, and back to the patient
         iv. Dialysis Access (see Appendix E)
            1. Blood obtained from fistula, graft, or catheter for hemodialysis
               a. Fistula: connection of an artery to a vein
               b. Arteriovenous graft: prosthetic material linking an artery and a vein
   5. Cardiovascular disease and ESRD
      a. Atherosclerotic and cardiovascular disease has been shown to be more prevalent in dialysis patients than in the general population\textsuperscript{8}
Cardiovascular disease constitutes the major cause of death in patients with ESRD and cardiovascular event rates are higher in dialysis patients. Underlying cause is unclear, but likely related to shared risk factors (e.g., diabetes, hypertension, vascular disease), chronic inflammation, massive changes in extracellular volume, inadequate treatment of hypertension, alterations in cardiovascular dynamics during treatment, etc.

ESRD and hypertension

i. Hypertension differs from other causes of ESRD because it can also act as a co-morbid condition affecting outcome
   1. Hypertension is also a consequence of renal disease

ii. Cardiovascular confounders
   1. 50-80% of patients begin dialysis with pre-existing left ventricular hypertrophy (LVH)
      a. The risk for death from cardiovascular causes increases approximately threefold with LVH
      b. The degree of LVH correlates with morbidity and mortality as well as the severity of hypertension
      c. Some reversal of LVH in dialysis patients is possible with good blood pressure control
   2. Volume expansion is an important driving factor in developing and sustaining elevated blood pressure, especially in dialysis patients
      a. Volume expansion leads to increased BP through increases in cardiac output and inappropriately high systemic vascular resistance
         i. Results from activation of RAAS or secretion sodium-potassium pump inhibitors (increased intracellular sodium)
   3. Sympathetic over-activity is common in ESRD
      a. Correlates with increases in vascular resistance and systemic BP

d. Most experts recommend conventional cardio-protective strategies in dialysis patients including management of blood pressure

i. Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (see Appendix F)
   1. Target pre-dialysis BP < 140/90mmHg
   2. Lifestyle modifications (LSM) should emphasize sodium restriction
   3. Achieve dry weight and reduce extracellular volume
   4. Initiate antihypertensive drugs if LSM are unsuccessful
      a. First line agents are angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)
         i. Selection of other drugs based on compelling indications (see Appendix F)
   5. Resistant hypertension is defined as uncontrolled BP after an adequate and appropriate three-drug regimen
      a. Regimen should include optimal doses of at least three different agents selected from ACEI, calcium channel blockers, beta-blockers, anti-adrenergic agents, or direct vasodilators

Some experts suggest that blockade of RAAS by direct aldosterone antagonism may be beneficial, especially in patients who demonstrate resistance to conventional therapies.

i. Aldosterone
   1. Minearalocorticoid hormone that acts as a key determinant of volume status and BP
   2. Hyperaldosteronism is associated with renal injury, the development of CKD, and progression to ESRD (see Figure 2)
      a. Aldosterone escape
         i. Despite treatment with ACEI/ARB, aldosterone concentrations remain elevated in up to 50% of patients
         ii. Once patients have progressed to ESRD, aldosterone levels may remain elevated or may revert to normal concentrations

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Aldosterone Antagonists

3. Aldosterone is associated with increased cardiac fibrosis, vascular inflammation, oxidative stress, apoptosis, and sympathetic nervous system activity. These effects worsen cardiovascular outcomes and can lead to end-stage organ dysfunction. Stratified multivariate analysis in LURIC trial showed increased morbidity/mortality even at normal plasma aldosterone concentrations.

4. Aldosterone blockade is an important but often overlooked component in controlling blood pressure. The wide-ranging effects of aldosterone increase in significance when viewed in the context of heart failure, hypertension, and/or renal disease. As such, specifically targeting aldosterone may play a critical role in treating these disease states in patients with ESRD.

Figure 2. Negative effects of aldosterone on various systems.
6. Aldosterone antagonists\textsuperscript{8-13, 31}
   a. Spironolactone and eplerenone
      i. Pharmacological properties listed in Appendix G
   b. Competitively inhibit aldosterone binding to the mineralcorticoid receptor (MR)
      i. Blocks aldosterone-induced-protein synthesis, which blocks reabsorption of sodium and the secretion of potassium in the distal nephron
      ii. Effects on urinary excretion are a function of endogenous levels of aldosterone
   c. Do not require adequate renal function for action
      i. Do not require access to the tubular lumen to induce diuresis

   \textbf{Figure 3.} Effects of aldosterone and diuretic mechanism of aldosterone antagonists\textsuperscript{5}

   d. In recent years, clinical trials have shown that aldosterone antagonism is beneficial in specific populations
      i. Use of spironolactone for heart failure has been shown to significantly reduce mortality in landmark trials
         1. Spironolactone also been shown to favorably affect myocardial fibrosis and improve endothelial dysfunction
      ii. Meta-analyses show spironolactone is effective for lowering blood pressure and slowing the progression of CKD
      iii. Aldosterone antagonism has also been shown to attenuate proteinuria and renal damage
   e. Concern about using these agents arises from the risk for provoking hyperkalemia\textsuperscript{24}
      i. Dialysis patients are already at risk for hyperkalemia due to impaired handling of potassium
      ii. Assumption is aldosterone antagonists will enhance this risk
         1. However, it is unlikely that renal potassium clearance could be further compromised
      iii. Guidelines caution against the use of aldosterone antagonists in patients with baseline elevations of serum potassium or with GFR < 30mL/min/1.73m\textsuperscript{2}
         1. KDOQI guidelines specifically caution against using spironolactone in dialysis patients

7. Aldosterone antagonists in ESRD\textsuperscript{24-30}
   a. In most ESRD patients, aldosterone levels are normal or nominally elevated\textsuperscript{24}
      i. Normally, elevated serum potassium stimulates an increase in plasma aldosterone, which causes a compensatory increase in urinary potassium excretion
      1. In anuric renal disease plasma aldosterone cannot increase urinary potassium excretion
b. The body’s response to aldosterone can be dissociated from circulating aldosterone levels\textsuperscript{23}
   i. Horiuchi et al. suggested that increased mineralocorticoid response may occur in the absence of an increase in plasma aldosterone levels
   ii. Takeda et al. observed that there was increased response to aldosterone despite aldosterone levels

c. Aldosterone antagonism protects against end-organ damage\textsuperscript{22}
   i. Recall that aldosterone has negative effects on multiple organs
   ii. Aldosterone antagonism in ESRD has been shown to provide additional extrarenal benefits
      1. A study by Vukusich et al. showed that 50mg of spironolactone used three times a week significantly reduced the progression of carotid intima-media thickness (a measurement of atherosclerosis progression) in hemodialysis patients\textsuperscript{30}
      2. Decreases in BP, improved vascular function, and reduction in LVH have also been shown in ESRD patients\textsuperscript{23, 27-29}

8. Literature Evaluation

<table>
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<tr>
<th>Study</th>
<th>Design</th>
<th>Primary objective</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saudan\textsuperscript{33} (2003)</td>
<td>Prospective, nonrandomized, nonblinded study of HD patients</td>
<td>Incidence of hyperkalemia in HD patients on low-dose spironolactone</td>
<td>Spironolactone 12.5-25 mg 3 times/week on HD days for 4 weeks</td>
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<td>Hussain\textsuperscript{34} (2003)</td>
<td>Prospective, single-arm cohort</td>
<td>Effect of spironolactone in modulating extrarenal disposition of potassium loads</td>
<td>Spironolactone 25 mg/day for 4 weeks</td>
</tr>
<tr>
<td>Michea\textsuperscript{35} (2004)</td>
<td>Prospective, double-blind, placebo-controlled, crossover</td>
<td>Potassium balance in HD patients treated with spironolactone</td>
<td>Spironolactone 50mg 3 times/week for 2 weeks</td>
</tr>
<tr>
<td>Gross\textsuperscript{36} (2005)</td>
<td>Prospective, randomized, double-blind, placebo-controlled, crossover</td>
<td>Effect of high-dose spironolactone on blood pressure and RAAS in oligoanuric HD patients</td>
<td>Spironolactone 50mg twice daily for 2 weeks</td>
</tr>
<tr>
<td>Taheri\textsuperscript{37} (2009)</td>
<td>Prospective, randomized, double-blind, placebo-controlled</td>
<td>Outcomes and incidence of hyperkalemia in patients with moderate-to-severe heart failure on HD</td>
<td>Spironolactone 25mg 3 times/week after dialysis for 6 months</td>
</tr>
<tr>
<td>Smith (2012)</td>
<td>Retrospective, pre-post cohort study</td>
<td>Efficacy and safety of spironolactone in stage 3-5 CKD</td>
<td>Spironolactone 25mg daily</td>
</tr>
</tbody>
</table>

a. Saudan et al. (2003)\textsuperscript{33}
   i. Assess incidence of hyperkalemia in HD patients on low-dose spironolactone
   ii. Design
      1. 2-week baseline period, followed by 4-week treatment period
2. Spironolactone initiated at 12.5 mg three times/week then increased to 25 mg three times/week after HD

iii. Results
1. 14 patients received low dose spironolactone; compared with 21 controls (n = 35)
2. Low-dose spironolactone did not change mean serum potassium (4.9 ± 0.7 vs. 4.9 ± 0.3 mmol/L)
3. Spironolactone treatment was associated with a modest reduction in serum potassium (-0.2 mmol/mL, p = 0.016) in a multivariate analysis

iv. Conclusion
1. Cautious administration should not be contraindicated in hemodialysis patients
2. Cannot conclude that spironolactone (25 mg three times/week) will be equally safe under other conditions

b. Hussain et al. (2003)34
i. Evaluate safety of spironolactone administration in HD patients
ii. Design
1. HD patients with a mean serum potassium < 5.6 mEq/L (for preceding four months) were treated with spironolactone (25 mg daily) for 28 days
2. Serum potassium measured before every HD session
iii. Results
1. 15 HD patients served as their own controls
2. Mean serum potassium was 4.6 ± 0.6 mEq/L at baseline and 4.9 ± 0.9 mEq/L at study completion (p = 0.14)
3. 13 patients completed trial with no potassium levels > 6.0 mEq/L, 4 had measurements between 5.6 and 6.0 mEq/L, and one patient was withdrawn after developing hyperkalemia (7.6 mEq/L)

iv. Conclusion
1. Spironolactone can safely be administered to stable, compliant HD patients with heart disease
2. Additional studies will be required to determine whether if there is a risk reduction in cardiovascular morbidity and mortality

c. Michea et al. (2004)35
i. Evaluate the effects of spironolactone on the extrarenal regulation of potassium and validate the effectiveness of spironolactone in aldosterone blockade in HD patients
ii. Design
1. Two-week baseline period; followed by spironolactone treatment for 15 days (50 mg three times/week); followed by two-week washout period; and then a two-week placebo period
2. Administration of an oral potassium load before and after spironolactone initiation
iii. Results
1. Nine patients met inclusion criteria; peripheral sodium channel expression was assessed in 6 subjects
2. No subjects developed hyperkalemia during spironolactone treatment
3. Maximal plasma potassium following oral potassium load was 5.33 ± 0.88 mEq/L in the control phase; 5.23 ± 0.68 mEq/L in the spironolactone phase; and 5.38 ± 0.61 mEq/L placebo
4. Expression of peripheral sodium channels was significantly decreased from baseline in the selected patients who had this measurement (p < 0.05)

iv. Conclusion
1. Spironolactone may be considered for treatment of selected HD patients
2. Effect of the drug on expression of sodium channels demonstrates effectiveness of aldosterone blockade in non-epithelial tissues
   a. Could be used to monitor effectiveness of treatment

d. Gross et al. (2005)36
i. Assess the effect of spironolactone on BP and RAAS in oligo-anuric HD patients
ii. Design
   1. Administer spironolactone (50 mg) or placebo orally twice daily for two weeks; followed by a three-week washout period, after which patients crossed over for two more weeks

iii. Results
   1. 8 HD patients
   2. Administration of spironolactone for 2 weeks, decreased pre-dialysis systolic blood pressure from 142.0 ± 19.6 to 131.4 ± 18.2 mmHg (p < 0.05)
   3. Compared with placebo, spironolactone had no effect on pre-dialysis or post-dialysis plasma potassium

iv. Conclusion
   1. Spironolactone administration decreases pre-dialysis SBP in oligo-anuric hemodialysis patients by a non-diuretic mechanism without producing hyperkalemia

e. Taheri et al. (2009)37
   i. Assess whether low-dose spironolactone could be administered in HD patients with moderate-to-severe heart failure to improve cardiovascular function and reduce hospitalization without leading to hyperkalemia
   ii. Design
      1. Randomized patients to receive placebo or 25 mg of spironolactone after each dialysis session for six months
      2. Performed echocardiography to assess ejection fraction and left ventricular mass at beginning and end of study
      3. Measured pre-dialysis serum potassium every four weeks
   iii. Results
      1. A significant increase in mean ejection fraction was seen in the spironolactone group compared to placebo (6.2 ± 1.64 vs 0.83 ± 4.9, p = 0.046)
      2. There was also a statistically significant difference in mean LV mass between spironolactone and placebo groups (-8.4 ± 4.72 vs 3 ± 7.97; p = 0.021)
      3. Incidence of hyperkalemia was not statistically significantly in either group
   iv. Conclusions
      1. Administration of spironolactone in HD patients with moderate-to-severe heart failure substantially improved cardiac function and decreases in left ventricular mass without development of significant hyperkalemia

f. Smith et al. (2012)
   i. Assess efficacy and safety of spironolactone in stage 3-5 CKD patients
   ii. Design
      1. Retrospective, pre-post cohort analysis
   iii. Results
      1. 92 patients in efficacy cohort; 83 patients in safety cohort
      2. Median change from baseline in SBP was -16.5 (95% CI -20 to -12, p < 0.0001); DBP -7 (95% CI -8 to -3, p < 0.001); and potassium +0.3 (95% CI 0.2 to 0.4, p < 0.0001)
      3. 3.6% incidence of hyperkalemia (> 5.5 mEq/L) and no incidence of hyperkalemia (> 6.0 mEq/L)
   iv. Conclusion
      1. Spironolactone may be an effective and safe option to reduce blood pressure in patients with stage 3-5 CKD

Conclusions of Literature Evaluation
1. Spironolactone can be used safely in HD patients
2. Spironolactone may be effective in reducing systolic blood pressure in HD patients
3. Spironolactone has been shown to improve cardiac function and effectively blocks aldosterone in non-epithelial tissues
9. Retrospective Analysis in ESRD: Smith et al. (2013)
   a. Objectives
      i. Primary
         1. Determine if adding spironolactone to antihypertensive regimen (defined as 2 or more antihypertensive medications) can control blood pressure in dialysis patients
            a. Determine if addition of spironolactone decreases number of anti-hypertensive medications
         2. Determine if addition of spironolactone increases serum potassium levels
      ii. Secondary
         1. Identify patient characteristics (weight, age, sex, etc.) that might have an effect on spironolactone efficacy in controlling blood pressure
         2. Identify if co-morbid disease states (e.g., diabetes) have an effect on the efficacy of spironolactone to control blood pressure
   b. Study design
      i. Retrospective, pre-post cohort study
   c. Study population
      i. Inclusion criteria
         1. Hemodialysis patients
         2. >18 years old
         3. Spironolactone (25-50mg) prescribed as ‘add-on’ therapy to control BP
            a. ‘Add-on’ implies 2 or more antihypertensive medications without achieving goal BP (< 130/80mmHg)
      ii. Exclusion criteria
         1. SBP/DBP < 130/80mmHg
         2. Prescription of spironolactone prior to study initiation
         3. Discontinuation of spironolactone prior to completion of 8 week study period
   d. Data collection
      i. Patients identified using e-prescribing records at 3 private dialysis clinics in San Antonio, TX
      ii. Review of medical charts to determine if patients are eligible for inclusion
      iii. Data points: patient characteristics, pre-dialysis SBP/DBP, labs, weight, medications
      iv. Blood pressure data points will be averaged for each week
   e. Data Analysis
      i. JMP 9.0 analytical software
      ii. Descriptive statistics for demographics and co-morbidity data
      iii. Appropriate statistical tests will be used to determine differences in outcomes after initiation of spironolactone
   f. Study Limitations/Strengths
      i. Limitations
         1. Convenience sampling
         2. Retrospective study: cause and effect cannot be determined
         3. Cannot account for confounders and bias
      ii. Strengths
         1. Largest population studied to date (approximately 120)
         2. Study design
   10. Conclusion
      a. Spironolactone has been used safely in ESRD patients
         i. Also been shown to reduce cardiovascular risk factors by improving cardiac function, reducing LVH etc.
      b. Spironolactone may be an effective option to reduce systolic and diastolic blood pressure in ESRD
      c. Large scale outcome trials needed
         i. Confirm efficacy and safety in this patient population
         ii. Provide morbidity and mortality data


Appendix A. Renal Physiology

Figure 4. Blood supply to the kidneys

Figure 5. Functions of the Nephron

Images accessed at: http://www.austincc.edu/apreview/PhysText/Renal.html
Appendix B. Renin-Angiotensin-Aldosterone System\textsuperscript{10}
APPENDIX C. Factors and Pathways Contributing to Progression of Renal Disease

- Toxic or metabolic: glucose, lipids, paraproteins
- Inflammatory injury
- Delivery of proinflammatory mediators from glomerular immune cells
- Ischemia/hypoxia secondary to decreased postglomerular blood flow or interstitial fibrosis
- Loss of endothelial growth factors by infiltrating leukocytes
- Generation of proapoptotic cell apoposis
- Replacement by fibrous tissue
- Endothelial rarefaction
- Exocytosis
- Interstitial damage
- Toxic and metabolic: glucose, lipids, paraproteins
- Immunological injury
- Ischemia/hypoxia secondary to capillary rarefaction
- Fibroblast activation and proliferation
- Altered matrix turnover and fibrosis

- Glomerular damage
  - Intracapillary hypertension
  - Glomerulosclerosis
  - Intraglomerular thrombosis
  - Hyperplasia of mesangial cells

- Tubular damage
  - Toxic or metabolic: glucose, lipids, paraproteins
  - Filtrated cytokines
  - Ischemia/hypoxia

- Interstitial damage
  - Toxic and metabolic: glucose, lipids, paraproteins
  - Immunological injury
  - Ischemia/hypoxia secondary to capillary rarefaction
  - Fibroblast activation and proliferation

- Fibroblast activation and proliferation

- Altered matrix turnover and fibrosis
APPENDIX D. Components of a Dialysis System

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APPENDIX E. Types of Vascular Access for Dialysis

Graft

Fistula

Catheters

Cephalic vein
Basilic vein

Arteriovenous anastomosis

Artery
Vein
Graft

http://www.cvtsa.com/MediaServer/MediaItems/MediaItem_209.jpg
APPENDIX F. KDOQI Guidelines Treatment Algorithm and Drug Therapy Options

Step 1: Lifestyle Modifications
Achieve dry weight

Step 2: Initial Drug Choices

Hypertension Without Compelling Indications
- Stage 1 Hypertension
  (BP 140-159/90-99 mm Hg)
  Start an ACEI, or ARB

Hypertension With Compelling Indications
- Stage 2 Hypertension
  (BP > 160/100 mm Hg)
  Start a 2-Drug combination
  (Usually an ACEI or ARB and a CCB)

Step 3: Not at Goal BP
Add a β-blocker or clonidine

Step 4: Work-up for secondary causes
If w/u neg, add minoxidil

Table 12. Antihypertensive Drug Therapy in Dialysis: Guidelines for Selection

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Preferred</th>
<th>Relatively or Absolutely Contraindicated</th>
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<tbody>
<tr>
<td>Angina pectoris</td>
<td>β-Blockers, CCBs</td>
<td>Direct vasodilators</td>
</tr>
<tr>
<td>Post-MI</td>
<td>Non-ISA β-blockers</td>
<td>Direct vasodilators</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy with diastolic dysfunction</td>
<td>β-Blockers, diltiazem, verapamil</td>
<td>Direct vasodilators, α1 -blockers</td>
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<td>Bradyarrhythmia, heart block, sick sinus syndrome</td>
<td></td>
<td>β-blockers, labetalol, verapamil, diltiazem</td>
</tr>
<tr>
<td>Heart failure (decreased LV ejection fraction)</td>
<td>ACE inhibitors, ARBs, β-blockers</td>
<td>CCBs</td>
</tr>
<tr>
<td>Peripherals vascular disease</td>
<td>ACE inhibitors, ARBs</td>
<td>β-blockers</td>
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<td>Cyclosporine-induced hypertension</td>
<td>CCBs, labetalol</td>
<td>Nicardipine, verapamil, diltiazem</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Calcium antagonists</td>
<td>Labetalol, methyldopa</td>
</tr>
<tr>
<td>Erythropoietin-induced hypertension</td>
<td></td>
<td>ACE inhibitors</td>
</tr>
</tbody>
</table>

* May increase serum levels of cyclosporine
* May increase erythropoietin production
### APPENDIX G. Pharmacological Properties of Aldosterone Antagonists

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Spironolactone</th>
<th>Eplerenone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical indication</td>
<td>Severe (NYHA class III–IV) CHF with LV systolic dysfunction</td>
<td>Severe (NYHA class III–IV) CHF after myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Essential hypertension</td>
<td>Essential hypertension</td>
</tr>
<tr>
<td></td>
<td>Primary hyperaldosteronism</td>
<td></td>
</tr>
<tr>
<td>Receptor binding affinity (aldosterone=1)</td>
<td>1.1×10^{-1}</td>
<td>5.1×10^{-3}</td>
</tr>
<tr>
<td>Sex-steroid receptor cross-reactivity</td>
<td>Yes</td>
<td>Minimal</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic</td>
<td>Cytochrome P450, isoenzyme CYP3A4</td>
</tr>
<tr>
<td>Conversion to metabolites for effect</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>1.4</td>
<td>4–6</td>
</tr>
<tr>
<td>Excretion</td>
<td>Renal and bile</td>
<td>Renal and GI</td>
</tr>
<tr>
<td>Administration</td>
<td>With food to maximize absorption</td>
<td>With or without food</td>
</tr>
<tr>
<td>Recommended dose, mg/d</td>
<td>Hypertension, 50–100; CHF, 25–200</td>
<td>Hypertension, 50–100; CHF, 25–50</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Potentiate hyperkalemia: ACE-I, NSAIDs</td>
<td>Potentiate hyperkalemia: ACE-I, NSAIDs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP3A4 inhibitors increase eplerenone:itraconazole, ribonavir, clarithromycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP3A4 inducers decrease eplerenone: St John’s Wort</td>
</tr>
<tr>
<td>Side effects</td>
<td>Hyperkalemia, Gynecomastia, breast tenderness, Erectile dysfunction, Dysmenorrhea</td>
<td>Hyperkalemia, Abdominal pain, diarrhea</td>
</tr>
</tbody>
</table>

***GI indicates gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs.***