Uremic Syndrome
Acute Kidney Injury
Chronic Kidney Disease

Lecture 3: Genito-urinary system.
Uremic Syndrome
Acute Kidney Injury
Chronic Kidney Disease
nephron

the functional unit of the kidney

- capable of forming urine
- has two major components:
  - glomerulus
  - tubule:
    - proximal loop of Henle
    - distal
    - collecting

Interstitium
structural organization

renal parenchyma
cortex
medulla

nephrons
cortical
juxtamedullary
Renal Function:

Excretory
Regulatory
Endocrine

Excretory Function:

Glomerular

Glomerular Filtration Rate (GFR)
Creatinin Clearance.

UxV/P ml/min
GFR:

- inulin clearance
- EDTA isotop
- $^{99}$ Tc isotop
- Iohexal High Performance liquid chromatography

Clinical setting:

eGFR: Cockroft-Gault Formula
MDRD Formula
Cockroft-Gault Formula

Male:

\[
Ccr = \frac{1,23 \times (140 - \text{age}) \times \text{BW (kg)}}{\text{Scr (µ mol/min)}} \text{ ml/min}
\]

Or

\[
Ccr = \frac{140 - \text{age (yrs)} \times \text{BW (kg)}}{72 \times \text{Scr (mg/dl)}} \text{ ml/min}
\]

Female:

\[
Ccr = \frac{140 - \text{age (yrs)} \times \text{BW (kg)}}{72 \times \text{Scr (mg/dl)}} \text{ ml/min}
\]

Or

\[
Ccr(\text{ male}) \times 0.85.
\]
NKF-KDOQI recommendation

Adults
Cockcroft-Gault equation:
GFR (ml/min) = (140-age) X Weight /72 x Scr X(0.85 if female)

MDRD (modification of diet in renal disease) equation:
GFR (ml/min/1.73 m^2) = 186 X (SCr)^-1.154 X (Age)^-0.203 X
(0.742 if female) X (1.210 if black)

Children
Schwartz equation: GFR (ml/min) = 0.55 x length/Scr

Counahan-Barratt equation: GFR (ml/min/1.73m^2)= 0.43 X Length/Scr
Renal Function:

Excretory

Regulatory

Endocrine

Regulatory Function:

Tubulo-interstitial

* water and electrolyte balance
* acid-base balance
Renal Function:

Excretory

Regulatory

Endocrine

Endocrine Function:
renal parenchymal
renin, prostaglandin,
erithropoietin, calcitriol
Uremic Toxicity
Greek words: urine + blood = uremia
Uremia is the retention of excessive byproducts of protein metabolism in the blood and the toxic condition produced thereby.
Uremia-2

- Uremia is a toxic syndrome caused by severe glomerular insufficiency, associated with disturbances in tubular and endocrine functions of the kidney.

- It is characterized by retention of toxic metabolites, associated with changes in volume and electrolyte composition of the body fluids and excess or deficiency of various hormones (uremic syndrome).
Toxic effects of uremic plasma

- variety disturbances:
  anemia, immunologic deficiency, bleeding tendency, disorders of carbohydrate and lipid metabolism, and various membrane transport disturbances.
Uremia

An excess in the blood of urea, creatinine and other nitrogenous end products with signs and symptoms listed.

- **General**
  - Fatigue, weakness
  - Pruritus

- **Mental/neurologic status change**
  - Uremic encephalopathy
  - Seizures
  - Asterixis

- **GI disturbance**
  - Anorexia, early satiety, N/V,

- **Uremic Pericarditis**

- **Platelet dysfunction/bleeding**
Uremic toxins
Small, middle-sized, and large molecules

Size:
- Small: \(< 500 \) (or \(350\)) Da
- Middle: \(500 \sim 5,000\) Da
- Large: \(> 5,000\) Da
Toxicity of inorganic substances in uremia

- Water
- Sodium
- Potassium
- Hydrogen ions
- Magnesium
- Phosphate
- Sulfate
- Trace elements
Organic compounds of Low molecular weight

- Urea
- Creatinine
- Guanidines (other than creatinine)
- Methylguanidine
- Guanidinosuccinic Acid (GSA)
- Methylated Arginine Metabolites
- Other guanidines
- Products of Nucleic Acid Metabolism
Urea (1)

- The most important end product of nitrogen metabolism in mammals and account for 85% of the urinary nitrogen excretion.
- Blood concentration: glomerular filtration rate, nitrogen intake, balance between endogenous protein synthesis and breakdown.
Urea(3)

- High concentration: headache, fatigue, nausea, vomiting, glucose intolerance, and bleeding.
- The most severe uremic GI, CV, mental and neurologic changes were not seen.
- Considered “mild” uremic toxin.
- Role in the pathophysiology of uremia is not well defined.
Serum Creatinine

- Serum creatinine is a reflection of creatinine clearance.
- Creatinine production is determined by muscle mass and must be interpreted with respect to pt’s age, weight, and sex.
- Creatinine is filtered and secreted and tends to overestimate GFR.
- Certain diseases and medications interfere with correlation between serum Cr and GFR. (i.e., Acute glomerulonephritis, trimethoprim, cimetidine)
Serum Creatinine (cont.)

- None of the equations accurately determine GFR in ARF. (Assume Cr is stable)
- More accurate techniques involve nuclear medicine studies and GFR scans.
- New biochemical markers investigated (i.e., Cystatin C)
The concentrations of various guanidine compounds are higher in uremic patients.

Some toxic in vitro effects seem to have been obtained at concentrations similar to those in uremic body fluids.

Most in vitro and in vivo toxic effects have been observed at much higher concentrations than are found in uremic patients.

The role of guanidines as uremic toxins is still not well defined.
Product of Nucleic Acid Metabolism

- Uric acid and other purine derivatives
- Cyclic AMP
- Pyridine derivatives
- Amino acids, dipeptides, and tripeptides
- Sulfur amino acids
- Aliphatic amines
- Aromatic amines
- Polyamines
- Indoles
- Phenols
- Carbonhydrate derivatives
Middle molecules as uremic toxins

The middle molecule hypothesis:

- Peritoneal membrane was more leaky and thus more effective at removing middle molecules than the hemodialysis membranes.
- It is well established that CAPD patients may survive and thrive as well as HD patients do, even though their average weekly clearance of urea is considerably lower than that for HD patients.
Toxic effects of crude MM fractions

- Inhibition of proliferation of undifferentiated cell lines and hematopoietic cell lines, depression of several immune function, increase hemolysis, cardiotoxicity, inhibition of platelet aggregation, inhibition of glucose utilization, inhibit protein synthesis and amino acid transport, inhibition of mitochondrial respiration
- Inhibit osteoclast mitogenesis
- Some enzyme activities are also inhibited
Parathyroid hormone

- Increased in uremic patients as consequence of phosphate retention, decreasing ionized calcium stimulate parathyroid glands to increase PTH secretion

- PTH hypersecretion in uremic patients: encephalopathy, neuropathy, dementia, bone disease, soft tissue calcification, hypertension, cardiomegaly, carbohydrate intolerance, anemia, sexual dysfunction
High-molecular-weight peptides and proteins

- Ribonuclease
- Granulocyte-inhibiting proteins
- Complement factors
- **Beta2-Microglobulin** and Dialysis-related amyloidosis
Uremic Syndrome
Acute Kidney Injury
Chronic Kidney Disease

Lecture 3: Genito-urinary system.
acute kidney injury: definition

ARF is an abrupt decline in glomerular and tubular function, resulting in the failure of the kidneys to excrete nitrogenous waste products and to maintain fluid and electrolyte homeostasis.
Epidemiology

- 5% of hospitalized patients develop ARF.
- 0.5% of these patients require dialysis.
- 20% of critical care admissions develop ARF.
- Hospital acquired ARF usually develops in the setting of ICU secondary to multisystem organ failure.
RIFLE Classification

2004 ADQI group classification

- **Risk (R)** - Increase Cr x1.5 or Decrease GFR x 25% or UO <0.5 ml/kg/hr x 6hrs
- **Injury (I)** - Increase Cr x2.0 or Decrease GFR x 50% or UO <0.5 ml/kg/hr x 12hrs
- **Failure (F)** - Increase Cr x3.0 or Decrease GFR x75% or anuria x 12 hours
- **Loss (L)** - Persistent ARF, complete loss of kidney function x 4 weeks (needing RRT)
- **End Stage Kidney Disease (E)** - Loss of kidney function x 3 months
The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group
AKI

Pre-Renal
- Loss of intra-vas. vol
- Reduced cardiac-output
- Periferal Vasodilatation
- Increased reno-vascular resistance
- Reduced intra-glomerular pressure
- ACE-i

Renal

Post-Renal
ACUTE KIDNEY INJURY
Pre-renal

Loss of intra-vascular volume
- BLEEDING
- POLYURIA, SALT-LOOSING GN
- G-I TRACT FLUID LOSS
- PROFUSE SWEATING
- TISSUE TAUMA ETC

Reduced cardiac output
- CHF
- CARDIOGENIC SHOCK
- PERICARDIAL/TAMPONADE
- MASSIVE LUNG EMBOLI

Peripheral vasodilatation
- SEPSIS
- ANTI-HIPERTENSIVE DRUGS
- ANAPHYLAXIS

Increase renal-vascular resistance
- SURGERY
- ANESTHETICS
- HEPATORENAL SYNDROME
- VASOCONSTRICTIVE DRUGS

Reduced intraglomerular pressure
- ACE-i
BIG VESSELS

STENOSIS A.RENALIS
THROMBOSIS/EMBOLI

SMALL VESSELS

VASCULITIS, ATHEROEMBOLIC DIS.
THROMBOTIC MICROANGIOPATHY

GLOMERULAR:

Ix deposit glom. Disease
psgn, lupus nephritis, MPGN etc
RPGN

Acute interstitial nephritis
AB, Diuretics, NSAID, allopurinol dll

Goodpasture syndr

Non Ix deposit

Wegener’s granulomatosis, Polyarteriitis nodosa, Idiop. Cresc.GN

INTERSTITIUM

RENAL ISCHEMIA:

shock, bleeding, trauma, gram (-) bacteria,
pankreatitis dll.

Nefrotoxic drugs: AB, Anti-neoplastik, contrast, anesthetics etc

Endogen. Toxins: Mioglobin (rhabdomyolisis), Hb (Malaria falciparum,
mismatched bloo transf, uric acid etc.

TUBULAR:

Renal ischemia: shock, bleeding, trauma, gram (-) bacteria,
pankreatitis dll.

Nefrotoxic drugs: AB, Anti-neoplastik, contrast, anesthetics etc

Endogen. Toxins: Mioglobin (rhabdomyolisis), Hb (Malaria falciparum,
mismatched bloo transf, uric acid etc.

GLOMERULAR:

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psgn, lupus nephritis, MPGN etc
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INTERSTITIUM

Acute interstitial nephritis
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AKI

PRERENAL

RENAL

POST RENAL

- Stone, Crystals
- Prostate, Ureteric Stricture

bilateral or uni-lateral in single functioning kidney

MEDICAL

SURGICAL
Causes of ARF in Hospitalized Patients

45% ATN
- Ischemia, Nephrotoxins

21% Prerenal
- CHF, volume depletion, sepsis

10% Urinary obstruction

4% Glomerulonephritis or vasculitis

2% Acute Interstitial Nephritis

1% Atheroemboli

e tc
Pre Renal Azotemia

- Impaired renal blood flow as a result of true intravascular depletion, decreased effective circulating volume to the kidneys, or agents that impair renal blood flow.
- Urine and blood studies are helpful in diagnosing pre renal ARF.
- Hyaline casts can be seen (Not an abnormal finding).
- Treat with fluid boluses or continuous IVF, monitor urine output.
Post Obstructive Uropathy

- Occurs if both urinary outflow tracts are obstructed or outflow tract of solitary kidney is obstructed.
- Patients with SUDDEN ONSET of anuria are likely to have post obstructive uropathy.
- Primary causes include BPH, prostate and cervical cancer, stones, strictures and retroperitoneal fibrosis.
- Bladder catheterization and Renal U/S to assess hydronephrosis.
- Can have obstruction w/o hydronephrosis on U/S
- Monitor for post obstructive diuresis, hemorrhagic cystitis?
Intrinsic Acute Kidney Injury

1. Tubular (ATN)
2. Interstitial (AIN)
3. Glomerular (Glomerulonephritis)
4. Vascular
ATN

- Most common cause of ARF in hospitalized patients
- Contrast and aminoglycosides most often associated with nonischemic ATN.
- 3 phases:
  1) Initiation phase- Renal injury lasting hours to days.
  2) Maintenance phase- Lasts days to weeks. GFR and U.O at lowest.
  3) Recovery Phase- Postacute tubular necrosis diuresis. Can still exp. uremia and hypovolemia as tubular function not completely restored.
Acute Interstitial Nephritis

70% Drug hypersensitivity
- 30% Antibiotics: PCNs (Methicillin), Cephalosporins, Cipro
- Sulfa drugs
- NSAIDs
- Allopurinol...

15% Infection
- Strep, Legionella, CMV, other bact/viruses

8% Idiopathic

6% Autoimmune Dz (Sarcoid, Tubulointerstitial nephritis/Uveitis)
AIN from Drugs

Renal damage is NOT dose-dependent
May take wks after initial exposure to drug
- Up to 18 mos to get AIN from NSAIDS!
But only 3-5 d to develop AIN after second exposure to drug

- Fever (27%)
- Serum Eosinophilia (23%)
- Maculopapular rash (15%)

- Bland sediment or WBCs, sterile pyuria most commonly seen
- WBC Casts are common
- Urine eosinophils on Wright’s or Hansel’s Stain
  - Also see urine eos in RPGN, renal atheroemboli...

- Treatment is to remove offending agents. Most patients recover complete kidney function w/I one year.
Nephritic Syndromes

Type 1: Anti-GBM dz (Anti GBM Ab positive)
- Goodpasture’s Disease
- Anti-GBM

Type 2: Immune complex (Low compliment, elevated ESR)
- IgA nephropathy (Normal Compliment levels)
- Postinfectious glomerulonephritis
- Lupus nephritis
- Mixed cryoglobulinemia
- MPGN
- IBE

Type 3: Pauci-immune (ANCA positive, assoc with vasculitis)
- Wegner’s Disease
- Microscopic Polyangitis
- Churg-Strauss
Nephritic Syndromes

- Fever
- Oliguria
- Hematuria
- Htn
- RBC casts
- Proteinuria (1-2 grams usually)
- Treatment varies based on underlying disease
Renal Atheroembolic Dx

1% of Cardiac caths: atheromatous debris scraped from the aortic wall will embolize
- Retinal
- Cerebral
- Skin (Livedo Reticularis, Purple toes)
- Renal (ARF)
- Gut (Mesenteric ischemia)

- Cr will NOT improve with IVF
- Diagnosis of exclusion: will NOT show up on MRI or Renal U/S; WILL show up on renal bx
- Tx: supportive
acute renal failure: prevention

- recognize patients at risk (postoperative states, cardiac surgery, septic shock)

- prevent progression from prerenal to renal

- preserve renal perfusion
  - isovolemia, cardiac output, normal blood pressure
  - avoid nephrotoxins (aminoglycosides, NSAIDS, amphotericin)
Treatment

- Reverse underlying causes and correct fluid and electrolyte balances
- Treatment is supportive.
- Drugs such as mannitol, loop diuretics, dopamine and CCB successful in promoting diuresis in animals but not in humans.
- Dialysis as needed (IHD vs. CRRT)
acute renal failure: management

- treat the underlying diseases
- strictly monitor intake and output (weight, urine output, insensible losses, IVF)
- monitor serum electrolytes
- adjust medication dosages according to GFR
- avoid highly nephrotoxic drugs
nutrition

- provide adequate caloric intake
- limit protein intake to control increases in BUN
- minimize potassium and phosphorus intake
- Limit Na/fluid intake

*If adequate caloric intake can not be achieved due to fluid limitations, some form of dialysis should be considered*
acute renal failure: fluid therapy

If patient is fluid overloaded
- fluid restriction (insensible water losses)
- attempt furosemide 1-2 mg/kg (not evidence-based)
- Renal replacement/support therapy (see later)

If patient is dehydrated:
- restore intravascular volume first
- then treat as euvoletic (below)

If patient is euvoletic:
- restrict to insensible losses (30-35 ml/100kcal/24 hours) +
  other losses (urine, chest tubes, etc)
Daily fluid allowance:

\[
\text{ALLOWANCE} = \text{Volume Excreted} + \text{I W L}  \\
24 \text{ hrs}
\]

Volume Excreted: Urine, vomitus, diarrhea, drain, etc

I W L: 500 ml / 24 hrs ⇒ 50 kg BW T 37 °C
\uparrow 15 % ⇒ increment of 1 °C

Monitor daily BW
sodium

- most patients have dilutional hyponatremia which should be treated with fluid restriction

- severe hyponatremia ($Na< 125 \text{ mEq/L}$) or hypernatremia ($Na> 150 \text{ mEq/L}$): dialysis or hemofiltration
Treatment of Hyperkalemia

- Calcium Gluconate
- Glucose and Insulin
- Sodium Bicarbonate
- Diuretics (Lasix)
- Cation-exchange resins (Kayexalate)
- Dialysis
Acute Indications for Dialysis

AIUEO

- Acidosis (metabolic)
- Ingestion of drugs/Ischemia
- Uremic syndrome
- Electrolytes (hyperkalemia)
- Overload (fluid)
INDIKASI:
- Severe uremic symptoms
- Urea >200 mg%, Cr >8 mg%
- K > 7 mg%
- Pericarditis
- Severe Asidosis
- Pulmonary Oedema

MANAGEMENT
AKI

FLUID
DIET
DRUG
RRT/SUPPORT

DIALYSIS
PERITONEAL
HEMO
HEMOFILTRATION
- CAVH (d), CVVH (d)
- SCUF (d), SLEDD
Mortality/Morbidity

- Mortality rates range from 7-80% depending on patient’s other co morbidities.
- This rate has remained unchanged since the advent of dialysis because of increasing age and co morbidity conditions.
- Most common cause of death associated with ARF are sepsis, cardiac failure and respiratory failure.
- Mortality rates are lower for nonoliguric (>400ml/day) than oliguric ARF (<400 ml/day).
Features of the history and physical examination in addition to relevant lab and radiologic investigations help to determine the most likely cause(s) of ARF in a given patient.
Take Home Points

Management of a patient with ARF involves:
- Treating potentially life-threatening complications
- Reversing pre-renal and post-renal causes
- Minimizing further hemodynamic and toxic insults to the kidney
- Admission and appropriate consultation
- Lack of evidence for converting oliguric to non-oliguric ARF
Uremic Syndrome
Acute Kidney Injury
Chronic Kidney Disease
Population of Patients With End-stage Renal Disease (ESRD) Is Growing

US Renal Data System. USRDS 2000 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. 2000. Available at: http://www.usrds.org/2kpdf/pdf_parts/01_incid&_prev_part_2.pdf. Accessed May 21, 2002. The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government.
CKD

PARENCHYMAL
- GN
- Diabetic Nephropathy
- Nephrosclerotic/hypertension
- Policystic
- Lupus
- TBC

OBSTRUCTIVE
- urolithiasis
- Prostate
- Ureteric Stricture
Definition of Chronic Kidney Disease

1. Kidney damage for \(>3\) months, with or without decreased GFR, as manifest by either
   - pathologic abnormalities; or
   - markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests

2. GFR \(<60\) mL/min/1.73 m\(^2\) for \(>3\) months, with or without kidney damage

AJKD 2002: 39(2)
# Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney Damage with Normal or ↑ GFR</td>
<td>&gt;90</td>
</tr>
<tr>
<td>2</td>
<td>Mild ↓ GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
</tr>
<tr>
<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>
Improving on the Scr screening

Cockcroft-Gault (C-G) Method for Estimating Ccr

\[ Ccr = \frac{(140 - \text{age [yr]}) \cdot \text{(body wt [kg])}}{72 \times \text{SCr [mg/dL]}} \times 0.85^* \]

- Example:
  - 80-year-old woman, 50-kg body weight, 1.5 mg/dL SCr

- Formula result:
  - Ccr = 24 mL/min Severe dysfunction

* For women (x 1.0 for men)

NKF-KDOQI recommendation

Adults

MDRD (modification of diet in renal disease) equation:
GFR (ml/min/1.73 m^2) = 186 X (SCr)^{-1.154} X (Age)^{-0.203} X (0.742 if female) X (1.210 if black)

Children

Schwartz equation: GFR (ml/min) = 0.55 x length/Scr

Counahan-Barratt equation: GFR (ml/min/1.73m^2) = 0.43 X Length/Scr
Pivotal Role of Glomerular Hypertension in the Initiation and Progression of Structural Injury.

Systemic Hypertension

Primary Renal Disease

Aging, Diabetes Mellitus, Dietary Factors

GLOMERULAR HYPERTENSION

ENDOTHELIAL INJURY
- Release of vasoactive factors
- Vascular lipid deposition
- Intracapillary thrombosis

MESANGIAL INJURY
- Accumulation of macromolecules
- ↑Matrix production
- ↑Cell proliferation

EPITHELIAL INJURY
- Proteinuria
- ↓Permeability to water

GLOMERULAR SCLEROSIS

Protein leakage

Proteinuria

Protein load to Proximal tubules

Glomerular Hypertension

Ang II

TGF β 1, etc

Interstitium

• Gene expression for inflammation
• Transdifferentiation to myofibroblast

Fibrosis

Proliferation Hypertension Matrix synthesis

PROGRESSION of CKD
Stages of Kidney and Cardiovascular Disease

- Chronic Kidney Disease
  - Kidney failure (ESRD)
- Cardiovascular Disease
  - Heart failure

- Progression
  - Decreased GFR
  - Damage (Proteinuria)
- Initiation, injury
  - Age, DM, HBP, family history

- At ↑ risk
  - CAD, LVH
  - CVD events

DM = diabetes mellitus; HBP = high blood pressure; CVD = cardiovascular disease
CKD Predicts CVD

Age-Standardized Rate of Cardiovascular Events (per 100 person-yr)

Go, et al., 2004
Stage and prevalence of CKD in individuals older than 20 years

*GFR measurement in mL/min/1.73 m²
In normal “healthy” individuals, the eGFR will fall by up to 10 ml/min (ie 10%) per decade.

An 80 year old man will have an expected eGFR of 50-60 ml/min.
RISK FACTORS FOR CKD PROGRESSION

- Genetic
- Hyperglycemia
- Hypertension
- Proteinuria
- Hyperlipidemia
- Cigarettes
- Anemia
- RAAS Activity
- Homocysteine
- Salt Intake
- Hyperphosphatemia
- Protein Intake
- Endogenous Insulin Excess

Hebert et al: KI 2001 59:1211-26
Renal survival and level of proteinuria

- Proteinuria (g/24 h)
  - < 1
  - 1–3
  - > 3

Renal survival vs. Time (months)
Baseline Prevalence of LVH by Degree of Kidney Function

<table>
<thead>
<tr>
<th>Ccr (ml/min)</th>
<th>&gt;50</th>
<th>35–49</th>
<th>25–34</th>
<th>&lt;25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Hb (g/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>141</td>
<td>132</td>
<td>125</td>
<td>114**</td>
</tr>
</tbody>
</table>

**P<.0001
*P<.001; Ccr <25 vs all others
Cardiovascular disease in CKD

Damage to the heart
(Uraemic cardiomyopathy)

Damage to the arteries
(Uraemic arteriopathy)
Echocardiography
Starting Dialysis Therapy

- LV dilatation: 28%
- Systolic dysfunction: 16%
- Concentric LVH: 41%
- Normal: 16%

Kidney Int 1995
Comorbidities in CKD

- **All cardiovascular disease**
  - No CKD: 80%
  - Stage 3 CKD: 20%
  - Stage 4 CKD: 0%
  - Stage 5 CKD: 0%

- **Diabetes**
  - No CKD: 20%
  - Stage 3 CKD: 20%
  - Stage 4 CKD: 0%
  - Stage 5 CKD: 0%

- **Ischaemic heart disease**
  - No CKD: 60%
  - Stage 3 CKD: 20%
  - Stage 4 CKD: 0%
  - Stage 5 CKD: 0%

- **Heart failure**
  - No CKD: 20%
  - Stage 3 CKD: 20%
  - Stage 4 CKD: 0%
  - Stage 5 CKD: 0%

- **Peripheral vascular disease**
  - No CKD: 10%
  - Stage 3 CKD: 0%
  - Stage 4 CKD: 0%
  - Stage 5 CKD: 0%

- **Hypertension**
  - No CKD: 80%
  - Stage 3 CKD: 20%
  - Stage 4 CKD: 0%
  - Stage 5 CKD: 0%
Development of Anemia During Progression of Kidney Disease

Mean Hgb *(g/dL)

GFR (mL/min/1.73 m²)

> 91  98-41  39-30  29-20  19-10  <18

"Original study performance using hematocrit from Radtke et al, Blood 1979;54:877-884."
Pathophysiology of Anemia in CKD

- Erythropoietin deficiency
- Iron deficiency:
  - Bleeding diathesis: platelet dysfunction, gastrointestinal pathology
  - Possible nutritional deficiencies

CARDIAC REMODELLING RESULTING FROM ANEMIA AND HYPERTENSION

- CONCENTRIC LVH
- ECCENTRIC LVH
- DILATED LVH WITH HEART FAILURE

LVH = left ventricular hypertrophy; LVM = LV mass; LVEDV = LV end diastolic volume

Normal LVM: 126 g/m²
LVEDV: <90 ml/m²

Anemia associated with increased risk of stroke
In CKD patients/

Fig. 1. Stroke rates per 1000 person-years of follow-up according to creatinine clearance, in the entire sample, and stratified according to anemia status.

Prevalence of Calcium (<8.5 mg/dL) and PO₄ (>4.5 mg/dL) x Level of GFR: Canadian Cohort

Prevalence of low calcium and high phosphate by GFR category

Unadjusted prevalence

GFR mL/min

Ca <8.5 mg/dL
PO₄ >4.5 mg/dL

<15
15-29
30-44
45-60
Calcitriol Decline and iPTH Elevation as CKD Progresses

N = 150.
iPTH = intact PTH.

© 2005 The Johns Hopkins University School of Medicine.
Systolic Blood Pressure and Progression of CKD

AIPRD Study Group

Meta-analysis of 11 RCTs of ACEIs

5569 records with non-diabetic kidney disease

Jafar et al, Ann Intern Med 2003;139:244-252
Urine Protein Excretion and Progression of CKD
AIPRD Study Group

Meta-analysis of 11 RCTs of ACEIs

4685 records with non-diabetic kidney disease

Jafar et al, Ann Intern Med 2003;139:244-252
Synergistic effect of CKD, CHF and Anemia as risk factors for Death

2 yr mortality (n~ 200,000 5% Medicare sample)

Collins, Adv studies in Med 2003
Stages in Progression of CKD and Therapeutic Strategies

- **Normal**
  - Screening for CKD risk factors
- **Increased risk**
  - CKD risk factor reduction, screening for CKD
- **Damage**
  - Diagnosis and treatment, treat comorbid conditions, slow progression
- **GFR**
  - Estimate progression, treat complications, prepare for replacement
- **Kidney failure**
  - Replacement by dialysis and transplant
- **CKD death**

Complications
Recommended Screening Tests for Patients at Risk for CKD

Screening is the beginning of a complex management process for CKD

- Serum creatinine ($S_{cr}$) for estimated GFR
- Blood pressure
- Glucose
- Urinalysis
- Microalbuminuria/proteinuria

Who are at risk?

- Those who are hypertensive, diabetic, obese, renal stone.
- Those with family history of hypertension, diabetes, and renal disease/failure
A Multi-disciplinary Team Approach for CKD Care

<table>
<thead>
<tr>
<th>Stage</th>
<th>At-risk</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR ml/min</td>
<td>&gt;90</td>
<td>60-90</td>
<td>30-60</td>
<td>15-30</td>
</tr>
<tr>
<td>Detection</td>
<td>Primary Dz</td>
<td>BP</td>
<td>Anemia</td>
<td>Bone disease</td>
</tr>
<tr>
<td>CVD risk factor mod</td>
<td>Nutritional status</td>
<td>Protein restriction</td>
<td>Acidosis</td>
<td></td>
</tr>
<tr>
<td>Family Counseling</td>
<td>Modality selection</td>
<td>Vascular access</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Persons at-risk

Team members:
- PCP
- Dietician
- Nurse Clinician
- Nephrologist

CQIP opportunity
- OP
- claims/records
- Hospital charts
- HCFA 2728
- Form
Acute on Chronic

- Infection / UTI
- Dehydration
- Obstructive
- Electrolyte Disturb.
- Severe Hypertension
Decrement of residual renal function

Renal insufficiency

Renal failure

ESRD

Risk

Tx
Decisions in renal replacement

- Pre-dialysis care

- Active treatment
  - Peritoneal dialysis (PD)
  - Haemodialysis (HD)
  - Transplantation

- Conservative (non-dialytic) care. Symptom management.
• Blood pressure and proteinuria control
• Correction of hyperglycaemia
• Dietary management
• Correction of calcium-phosphate disorders
• Correction of hyperlipidaemia
• Correction of anemia and acidosis
• Cessation of smoking
• the importance of early referral to a nephrologist
Decisions in renal replacement

- Pre-dialysis care
  - Treat: hypertension
  - Hyperglycemia
  - Hyperlipidemia
  - Anemia

To target
Diet: Low Protein

Anti RAAS antihypertensives
Smoking and progression

<table>
<thead>
<tr>
<th></th>
<th>rel. risk vs. non-smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>smokers, no ACE inhibitors</td>
<td>10            0.001</td>
</tr>
<tr>
<td>smokers treated with ACE inhibitors</td>
<td>1.3            N.S.</td>
</tr>
</tbody>
</table>

Orth, Kidn Intern (1998) 54: 926
Fig 2. Mean slope of the calculated glomerular filtration rate (GFR) (left panel) and net increase in urine protein-to-creatinine (Pro/Cr) ratio (right panel) during follow-up in smokers and nonsmokers. *P < 0.0001 versus nonsmokers.
Pengaruh regular mild aquatic exercise selama 3 bulan pada pasien CKD (n=20) NDT 2003 18:624
Treating anemia early in renal failure patients slows the decline of renal function: A randomized controlled trial

Chariclia Gouva, Petros Nikolopoulos, John P.A. Ioannidis, and Kostas C. Siamopoulos

Division of Nephrology, Department of Internal Medicine, and the Clinical Trials and Evidence-Based Medicine Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece; and Division of Clinical Care Research, Tufts-New England Medical Center, Tufts University School of Medicine, Boston, Massachusetts

Fig. 1. Hemoglobin levels at baseline and during follow-up (at 2, 4, 6, 9, and 12 months) in the deferred (white boxes) and early (gray boxes) treatment groups. The box plots show the median (horizontal line), interquartile range (box), and range (whiskers), unless there are also outliers and/or extreme values with 1.5 to 3 and >3 box lengths, respectively, away from the edge of the box, in which case these are shown by circles and asterisks.
Fig. 2. Serum creatinine levels at baseline and during follow-up (at 2, 4, 6, 9, and 12 months) in the deferred (white boxes) and early (gray boxes) treatment groups. The box plots show the median (horizontal line), interquartile range (box), and range (whiskers), unless there are also outliers and/or extreme values with 1.5 to 3 and >3 box lengths, respectively, away from the edge of the box, in which case these are shown by circles and asterisks. Not shown are two creatinine values above 10 mg/dL.
Fig. 3. Kaplan-Meier plots for doubling of creatinine, renal replacement, or death (A), and renal replacement or death (B) in the early (thick line) versus deferred (thin line) treatment arms.
Early Treatment Makes a Difference
MANAGEMENT
CKD

CONSERVATIVE
Diet: Water + salt
Protein
Calori
Phosphate, K+

Risk-factors management

Symptomatic Medicament:
(minimize)

RRT
MANAGEMENT
CKD

Conservative

DIALYSIS
- Hemodialysa
- Peritoneal
  - CAPD
  - IPD
- Hemofiltration
- Hemodiafiltration

RRT

TRANSPLANT

Indication: vide AKI
Diabetes: The Most Common Cause of ESRD

Primary Diagnosis for Patients Who Start Dialysis

- Diabetes: 50.1%
- Hypertension: 27%
- Glomerulonephritis: 13%
- Other: 10%

No. of patients

- 1984: 243,524
- 1988: 281,355
- 1992: 480,125
- 1996: 515,240
- 2000: 520,240
- 2004: 525,555
- 2008: 530,870

No. of dialysis patients (thousands)

r²=99.8%

Cardiovascular Mortality in the General Population and in ESRD Treated by Dialysis

Annual mortality (%)

Age (years)

Dialysis

General population

Male
Female
Black
White
(Renal Replacement Therapy)

a. Dialysis
   1. Peritoneal dialysis
      (continuous ambulatory peritoneal dialysis = CAPD)
   2. Hemodyalisis (HD)

b. RENAL TRANSPLANTATION
   Donor : Living (related, un-related)
   Cadaver
   Recipient : Tissue Type - HLA-Match
Long term use of imuno-suppressive drugs to cope with rejection
Messages to Take Home

- Kidney Disease is a silent killer—(no signs or symptoms until you lose >70% of your kidney function,
- The risk of dying from a cardiovascular event, if you’ve lost 50% or more of your kidney function, is similar to that having had a heart attack.
- Proteinuria reduction needs to be a key part of blood pressure management.
Terima Kasih