

**MINISTRY OF HEALTHCARE OF UKRAINE  
HSEEU "Ukrainian Medical Stomatological Academy"**

**"Approved"**  
at the meeting of internal  
medicine №1 department  
Head of Department  
**Prof. Skrypnyk I.M.**

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Protocol № 4 from 13.10.2016

**GUIDELINES  
FOR STUDENTS  
INDEPENDENT WORK  
IN THE PRACTICAL CLASSES PREPARING**

<i>Academic discipline</i>	Internal medicine
<i>Module</i>	Current practice of internal medicine
<i>Content module</i>	Management of the patients with main symptoms and syndromes in nephrology clinic
<i>Study subject</i>	<b>Management of the patients with chronic kidney disease</b>
<i>Course</i>	VI
<i>Faculty</i>	of foreign students training

## **1. The aims of the training course:**

### **To Know:**

1. Definition and classification.
2. Etiological factors.
3. The term chronic kidney disease.
4. Classification.
5. Pathogenesis of lesions in organs and systems, their clinical manifestations.
6. Clinic and laboratory parameters.
7. Differential treatment at different stages.
8. Renal replacement therapy: hemodialysis, kidney transplantation.
9. Indications and contraindications for dialysis, complications.
10. Primary and secondary prevention.

### **To be able to:**

- Conduct surveys and examination of patients with major nephrological syndromes
- Know the basic invasive and noninvasive diagnostic techniques used in nephrology, indications and contraindications for their conduct, possible complications
- identify major and atypical variants of the course and complications of urinary system diseases
- draft examination of patients with major nephrological syndromes
- Based on analysis of laboratory and instrumental examination to conduct differential diagnosis, justify and formulate diagnoses for diseases of urinary system
- prescribe treatment, determine prognosis, to conduct primary and secondary prevention
- diagnose and assist in chronic kidney disease

### **The contents of topic:**

## **Text**

*Merck Manual Professional Version <http://www.merckmanuals.com/professional>*

*Last full review/revision April 2013 by James I. McMillan, MD*

Chronic kidney disease (CKD) is long-standing, progressive deterioration of renal function. Symptoms develop slowly and include anorexia, nausea, vomiting, stomatitis, dysgeusia, nocturia, lassitude, fatigue, pruritus, decreased mental acuity, muscle twitches and cramps, water retention, undernutrition, peripheral neuropathies, and seizures. Diagnosis is based on laboratory testing of renal function, sometimes followed by renal biopsy. Treatment is primarily directed at the underlying condition but includes fluid and electrolyte management, erythropoietin for anemia, and often dialysis or transplantation.

## ***Etiology***

CKD may result from any cause of renal dysfunction of sufficient magnitude. The most common cause in the US is diabetic nephropathy, followed by hypertensive nephroangiosclerosis and various primary and secondary glomerulopathies. Metabolic syndrome, in which hypertension and type 2 diabetes are present, is a large and growing cause of renal damage.

## *Pathophysiology*

CKD can be roughly categorized as diminished renal reserve, renal insufficiency, or renal failure (end-stage renal disease). Initially, as renal tissue loses function, there are few abnormalities because the remaining tissue increases its performance (renal functional adaptation); a loss of 75% of renal tissue causes a fall in GFR to only 50% of normal.

Decreased renal function interferes with the kidneys' ability to maintain fluid and electrolyte homeostasis. Changes proceed predictably, but considerable overlap and individual variation exist. The ability to concentrate urine declines early and is followed by decreases in ability to excrete phosphate, acid, and K. When renal failure is advanced ( $\text{GFR} \leq 10 \text{ mL/min/1.73 m}^2$ ), the ability to dilute urine is lost; thus urine osmolality is usually fixed close to that of plasma (300 to 320 mOsm/kg), and urinary volume does not respond readily to variations in water intake.

Plasma concentrations of creatinine and urea (which are highly dependent on glomerular filtration) begin a hyperbolic rise as GFR diminishes. These changes are minimal early on. When the GFR falls below  $10 \text{ mL/min/1.73 m}^2$  (normal =  $100 \text{ mL/min/1.73 m}^2$ ), their levels increase rapidly and are usually associated with systemic manifestations (uremia). Urea and creatinine are not major contributors to the uremic symptoms; they are markers for many other substances (some not yet well defined) that cause the symptoms.

Despite a diminishing GFR, Na and water balance is well maintained by increased fractional excretion of Na and a normal response to thirst. Thus, the plasma Na concentration is typically normal, and hypervolemia is infrequent unless dietary intake of Na or water is very restricted or excessive. Heart failure can occur from Na and water overload, particularly in patients with decreased cardiac reserve.

For substances whose secretion is controlled mainly through distal nephron secretion (eg, K), adaptation usually maintains plasma levels at normal until renal failure is advanced. K-sparing diuretics, ACE inhibitors,  $\beta$ -blockers, NSAIDs, cyclosporine, tacrolimus, trimethoprim/sulfamethoxazole, pentamidine, or angiotensin II receptor blockers may raise plasma K levels in patients with less advanced renal failure.

Abnormalities of Ca, phosphate, parathyroid hormone (PTH), vitamin D metabolism, and renal osteodystrophy can occur. Decreased renal production of calcitriol contributes to hypocalcemia. Decreased renal excretion of phosphate results in hyperphosphatemia. Secondary hyperparathyroidism is common and can develop in renal failure before abnormalities in Ca or phosphate concentrations occur. For this reason, monitoring PTH in patients with moderate CKD, even before hyperphosphatemia occurs, has been recommended.

Renal osteodystrophy (abnormal bone mineralization resulting from hyperparathyroidism, calcitriol deficiency, elevated serum phosphate, or low or normal serum Ca) usually takes the form of increased bone turnover due to hyperparathyroid bone disease (osteitis fibrosa) but can also involve decreased bone turnover due to adynamic bone disease (with increased parathyroid suppression) or osteomalacia. Calcitriol deficiency may cause osteopenia or osteomalacia.

Moderate acidosis (plasma  $\text{HCO}_3^-$  content 15 to 20 mmol/L) and anemia are characteristic. The anemia of CKD is normochromic-normocytic, with an Hct of 20 to 30% (35 to 40% in patients with polycystic kidney disease). It is usually caused by deficient erythropoietin production due to a reduction of functional renal mass. Other causes include deficiencies of iron, folate, and vitamin B<sub>12</sub>.

### *Symptoms and Signs*

Patients with mildly diminished renal reserve are asymptomatic. Even patients with mild to moderate renal insufficiency may have no symptoms despite elevated BUN and creatinine. Nocturia is often noted, principally due to a failure to concentrate the urine. Lassitude, fatigue, anorexia, and decreased mental acuity often are the earliest manifestations of uremia.

With more severe renal insufficiency (eg, creatinine clearance < 10 mL/min for patients without diabetes and <15 mL/min for those with diabetes), neuromuscular symptoms may be present, including coarse muscular twitches, peripheral sensory and motor neuropathies, muscle cramps, hyperreflexia, restless legs syndrome, and seizures (usually the result of hypertensive or metabolic encephalopathy). Anorexia, nausea, vomiting, weight loss, stomatitis, and an unpleasant taste in the mouth are almost uniformly present. The skin may be yellow-brown. Occasionally, urea from sweat crystallizes on the skin (uremic frost). Pruritus may be especially uncomfortable. Undernutrition leading to generalized tissue wasting is a prominent feature of chronic uremia.

In advanced CKD, pericarditis and GI ulceration and bleeding are common. Hypertension is present in > 80% of patients with advanced CKD, is usually related to hypervolemia, and is occasionally the result of activation of the renin-angiotensin-aldosterone system. Heart failure caused by hypertension or coronary artery disease and renal retention of Na and water may lead to dependent edema.

### *Diagnosis*

- Electrolytes, BUN, creatinine, phosphate, Ca, CBC, urinalysis (including urinary sediment examination)
- Ultrasonography
- Sometimes renal biopsy

CKD is usually first suspected when serum creatinine rises. The initial step is to determine whether the renal failure is acute, chronic, or acute superimposed on chronic (ie, an acute disease that further compromises renal function in a patient with CKD). The cause of renal failure is also determined. Sometimes determining the duration of renal failure helps determine the cause; sometimes it is easier to determine the cause than the duration, and determining the cause helps determine the duration.

Testing includes urinalysis with examination of the urinary sediment, electrolytes, urea nitrogen, and creatinine, phosphate, Ca, and CBC. Sometimes specific serologic tests are needed to determine the cause. Distinguishing acute from chronic renal failure is most helped by a history of an elevated creatinine level or abnormal urinalysis. Urinalysis findings depend on the nature of the underlying disorder, but broad (> 3 WBC diameters wide) or especially waxy (highly refractile) casts often are prominent in advanced renal failure of any cause.

An ultrasound examination of the kidneys is usually helpful in evaluating for obstructive uropathy and in distinguishing acute from chronic renal failure based on kidney size. Except in certain conditions, patients with chronic renal failure have small shrunken kidneys (usually < 10 cm in length) with thinned, hyperechoic cortex. Obtaining a precise diagnosis becomes increasingly difficult as renal function reaches values close to those of end-stage renal disease. The definitive diagnostic tool is renal biopsy, but it is not recommended when ultrasonography indicates small, fibrotic kidneys.

## **Classification**

Staging CKD is a way of quantifying its severity. CKD has been classified into 5 stages.

- Stage 1: Normal GFR ( $\geq 90 \text{ mL/min/1.73 m}^2$ ) plus either persistent albuminuria or known structural or hereditary renal disease
- Stage 2: GFR 60 to 89 mL/min/1.73 m<sup>2</sup>
- Stage 3: GFR 30 to 59 mL/min/1.73 m<sup>2</sup>
- Stage 4: GFR 15 to 29 mL/min/1.73 m<sup>2</sup>
- Stage 5: GFR < 15 mL/min/1.73 m<sup>2</sup>

GFR (in mL/min/1.73 m<sup>2</sup>) in CKD can be estimated by:  $186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203}$ . The result is multiplied by 0.742 if the patient is female and by 1.21 if the patient is African American. For female African Americans, the result is multiplied by  $0.742 \times 1.21$  (0.898). This calculation is not very accurate for patients who are older and sedentary, very obese, or very thin. Alternatively, GFR can be estimated using the Cockcroft-Gault equation; this equation tends to overestimate GFR by 10 to 40%.

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula is more accurate than the MDRD and Cockcroft and Gault formulas, particularly for patients with a GFR near

normal values. The CKD-EPI equation yields fewer falsely positive results indicating chronic kidney disease and predicts outcome better than the other formulas.

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### ***Prognosis***

Progression of CKD is predicted in most cases by the degree of proteinuria. Patients with nephrotic-range proteinuria (> 3 g/24 h or urine protein/creatinine > 3) usually have a poorer prognosis and progress to renal failure more rapidly. Progression may occur even if the underlying disorder is not active. In patients with urine protein < 1.5 g/24 h, progression usually occurs more slowly if at all. Hypertension, acidosis, and hyperparathyroidism are associated with more rapid progression as well.

### ***Treatment***

- Control of underlying disorders
- Possible restriction of dietary protein, phosphate, and K
- Vitamin D supplements
- Treatment of anemia and heart failure
- Doses of all drugs adjusted as needed
- Dialysis for severely decreased GFR, uremic symptoms, or sometimes hyperkalemia or heart failure
- Maintaining  $\text{NaHCO}_3$  level at >20

Underlying disorders and contributory factors must be controlled. In particular, controlling hyperglycemia in patients with diabetic nephropathy and controlling hypertension in all patients substantially slows deterioration of GFR. Target BP should be about 110 to 130/ < 80 mm Hg. ACE inhibitors and angiotensin II receptor blockers decrease the rate of decline in GFR in

patients with most causes of CKD, particularly those with proteinuria. Increasing evidence suggests that, compared with either drug alone, combined use of ACE inhibitors and angiotensin II receptor blockers increases incidence of complications and does not slow decline in renal function, even though combined use does reduce proteinuria more.

Activity need not be restricted, although fatigue and lassitude usually limit a patient's capacity for exercise. Pruritus may respond to phosphate binders if serum phosphate is elevated. If patients do not respond, ultraviolet phototherapy may help.

## **Nutrition**

Severe protein restriction in renal disease is controversial. However, moderate restriction (0.8 g/kg/day) is safe and easy for most patients to tolerate. Some experts recommend 0.6 g/kg/day for patients with diabetes and, for patients without diabetes, > 0.8 g/kg/day if GFR is 25 to 55 mL/min/1.73 m<sup>2</sup> or 0.6 g/kg/day if GFR is 13 to 24 mL/min/1.73 m<sup>2</sup>. Many uremic symptoms markedly lessen when protein catabolism and urea generation are reduced. Sufficient carbohydrate and fat are given to meet energy requirements and prevent ketosis. Patients for whom < 0.8 g/kg/day has been prescribed should be closely followed by a dietician.

Because dietary restrictions may reduce necessary vitamin intake, patients should take a multivitamin containing water-soluble vitamins. Administration of vitamin A and E is unnecessary. Vitamin D in the form of 1,25-dihydroxyvitamin D (calcitriol) or its analogs should be given as indicated by PTH concentrations. Dose is determined by stage of CKD, PTH concentration, and phosphate concentrations. Target levels for Ca are 8.4 to 9.5 mg/dL (2.10 to 2.37 mmol/L); for the Ca-phosphate product, < 55 mg<sup>2</sup>/dL<sup>2</sup>.

A typical starting dose is calcitriol (or a calcitriol analog) 0.25 µg po once/day or 1 to 4 µg 2 times/wk. PTH levels are not corrected to normal because doing so risks precipitating adynamic bone disease.

Dietary modification may be helpful for hypertriglyceridemia. In patients with hypercholesterolemia, a statin is effective. Fibric acid derivatives (clofibrate, gemfibrozil) may increase risk of rhabdomyolysis in patients with CKD, especially if taken with statin drugs, whereas ezetimibe (which reduces cholesterol absorption) appears relatively safe. Correction of hypercholesterolemia may slow progression of the underlying renal disease and reduce coronary risk.

## **Fluid and electrolytes**

**Water intake** is restricted only when serum Na concentration is < 135 mmol/L or there is heart failure or severe edema.

**Na restriction** of 1.5 g/day benefits patients, especially those with edema, heart failure, or hypertension.

**K intake** is closely related to meat, vegetable, and fruit ingestion and usually does not require adjustment. However, foods (especially salt substitutes) rich in K should generally be avoided. Hyperkalemia is infrequent (unless there is hyporeninemic hypoaldosteronism or K-sparing diuretic therapy) until end-stage renal failure, when K intake may need to be restricted to  $\leq 50$  mmol/day. Mild hyperkalemia ( $< 6$  mmol/L) can be treated by reducing K intake and correcting metabolic acidosis. More severe hyperkalemia ( $> 6$  mmol/L) warrants urgent treatment.

**Phosphate** restriction to  $< 1$  g/day is often sufficient to maintain phosphate level in the target range during the early phase of stages 3 and 4 CKD. However, in the later phases, phosphate binders, such as Ca salts (acetate or carbonate but avoid citrate) or non-Ca-containing phosphate binders (sevelamer) are often necessary. No more than 1500 mg/day of elemental Ca should be given as binders (2000 mg/day of total Ca; binders plus dietary Ca).

Mild **acidosis** (pH 7.30 to 7.35) requires no therapy. However, most patients with chronic metabolic acidosis who have a pH  $< 7.3$  have a plasma  $\text{HCO}_3$  content  $< 15$  mmol/L and symptoms of anorexia, lassitude, dyspnea, and exaggerated protein catabolism and renal osteodystrophy.  $\text{NaHCO}_3$  1 to 2 g po bid is given and amount is increased gradually until  $\text{HCO}_3$  concentration is about 20 mEq/L or until evidence of Na overloading prevents further therapy.

### **Anemia and coagulation disorders**

Anemia is treated to keep the Hb between 11 and 12 g/dL. Anemia slowly responds to recombinant human erythropoietin (eg, epoetin alfa 50 to 150 units/kg sc 1 to 3 times/wk). Because of increased iron utilization with stimulated erythropoiesis, iron stores must be replaced, often requiring parenteral iron. Iron concentrations, iron-binding capacity, and ferritin concentrations should be followed closely. Target transferrin saturation (TSAT), calculated by dividing serum Iron by total Iron binding capacity and multiplying by 100%, should be  $> 20\%$ , Target ferritin in patients not on dialysis is  $> 100$  ng/mL. Transfusion should not be done unless anemia is severe (Hb  $< 8$  g/dL) or causes symptoms.

The bleeding tendency in CKD rarely needs treatment. Cryoprecipitate, RBC transfusions, desmopressin 0.3 to 0.4 mcg/kg (20 mcg maximum) in 20 mL of isotonic saline IV over 20 to 30 min, or conjugated estrogens 2.5 to 5 mg po once/day help when needed. The effects of these treatments last 12 to 48 h, except for conjugated estrogens, which may last for several days.

## Heart failure

Symptomatic heart failure is treated with Na restriction and diuretics. If left ventricular function is depressed, ACE inhibitors and  $\beta$ -blockers (carvedilol or metoprolol) should be used. Digoxin may be added, but the dosage must be reduced. Diuretics such as furosemide usually are effective even when renal function is markedly reduced, although large doses may be needed. Moderate or severe hypertension should be treated to avoid its deleterious effects on cardiac and renal function. Patients who do not respond to sodium restriction (1.5 g/day), should receive diuretic therapy (furosemide 80 to 240 mg po bid). Hydrochlorothiazide 12.5 mg (starting dose) to 25 mg (rarely up to 50 mg) po once/day or metolazone 5 to 10 mg po once/day or bid may be added to high-dose furosemide therapy if hypertension or edema is not controlled. Even in renal failure, the combination of a thiazide with a loop diuretic is quite potent and must be used with caution to avoid overdiuresis. Occasionally, dialysis may be required to control heart failure. If reduction of the ECF volume does not control BP, conventional antihypertensives are added. Azotemia may increase with such treatment and may be necessary for adequate control of heart failure and/or hypertension.

## Drugs

Renal excretion of drugs is often impaired in patients with renal failure. Common drugs that require revised dosing include penicillins, cephalosporins, aminoglycosides, fluoroquinolones, vancomycin, and digoxin. Hemodialysis reduces the serum concentrations of some drugs, which should be supplemented after hemodialysis. It is strongly recommended that physicians consult a reference on drug dosing in renal failure before prescribing drugs to these very vulnerable patients.

Certain drugs should be avoided entirely in patients undergoing dialysis. They include nitrofurantoin, metformin, and phenazopyridine.

## Dialysis

Dialysis is usually initiated at the onset of any uremic symptoms (eg, anorexia, nausea vomiting, weight loss, pericarditis, pleuritis), or difficulty controlling fluid overload, hyperkalemia or acidosis. These problems typically occur when the estimated GFR reaches  $\leq 10$  mL/min in a patient without diabetes or  $\leq 15$  mL/min in a patient with diabetes; patients whose estimated GFR values are near these values should be closely monitored so that these signs and symptoms are recognized early. Dialysis is best anticipated so that preparations can be made and urgent insertion of a hemodialysis catheter can be avoided. Such preparations usually begin when the patient is in early to mid stage 4 CKD; preparation allows time for patient education, selection of the type of dialysis, and timely creation of an arteriovenous fistula or placement of a peritoneal dialysis catheter.

## Transplantation

If a living kidney donor is available, better long-term outcomes occur when a patient receives the transplanted kidney early, even before beginning dialysis. Patients who are transplant candidates but have no living donor should receive a cadaveric kidney transplant as early after initiating dialysis as possible

### Key Points

- Common causes of CKD in the US are diabetic nephropathy, (the most common), nephroangiosclerosis, glomerulopathies, and metabolic syndrome.
- Effects of CKD can include hypercalcemia, hypophosphatemia, metabolic acidosis, anemia, secondary hyperparathyroidism, and renal osteodystrophy.
- Distinguish CKD from acute kidney injury based on history, clinical findings, routine laboratory tests, and ultrasonography.
- Control underlying disorders (eg, diabetes) and BP levels (usually with an ACE inhibitor or angiotensin II receptor blocker).
- Give supplemental vitamin D and  $\text{NaHCO}_3$  and restrict phosphate as needed.
- Treat heart failure, anemia, and other complications.
- Arrange dialysis for severely decreased GFR, uremic symptoms, and sometimes hyperkalemia or heart failure.
- Prepare for dialysis early whenever possible (eg, for severely decreased GFR).

*Last full review/revision April 2013 by James I. McMillan, MD*

### **Self preparation at class:**

Listen information;

Work with patients;

Ask about the problems that have not been found in information given.

### **Self preparation at home:**

Compose the plan of your answer;

Answer the questions to the topic;

Do the test given above.

### Questions

1. Indicate GFR typical for Stage V Chronic Renal Diseases:
  - a) 60-89 ml/min;
  - b) 30-59 ml/min;
  - c) 15-29 ml/min;
  - d) less than 15 ml/min
2. A 54-year-old patient has an over 20-year history of femoral osteomyelitis. Over the last month she has developed progressing edemata of the lower extremities. Urine test reveals: proteinuria at the rate of 6,6 g/l; in blood: dysproteinemia in form of hypoalbuminemia, elevation level of

alpha-2 and gamma-globulin, ESR - 50 mm/h. What is the most likely diagnosis?

- A** Secondary renal amyloidosis
  - B** Acute glomerulonephritis
  - C** Myelomatosis
  - D** Chronic glomerulonephritis
  - E** Systemic lupus erythematosus
3. What drugs can make CKD worse?

**Recommended literature:**

**A. Main:**

1. "Harrison's principles of internal medicine", Editors: Anthony S. Fauci, Dennis L. Kasper, Stephen L Hauser, Dan L. Longo, Joseph Loscalzo, McGraw-Hill Education / Medical; 19 edition (April 8, 2015), 1-2 volumes, 3000 p.
2. CURRENT Medical Diagnosis and Treatment 2012, Fifty-First Edition (LANGE CURRENT Series) by Stephen McPhee, Maxine Papadakis and Michael W. Rabow (Paperback - Sep 12, 2011)
3. Davidson's Principles and Practice of Medicine: With STUDENT CONSULT Online Access, 21e (Principles & Practice of Medicine (Davidson's)) by Nicki R. Colledge BSc FRCP(Ed), Brian R. Walker BSc MD FRCP(Ed) and Stuart H. Ralston MB ChB MD FRCP FMedSci FRSE (Paperback - Mar 11, 2010)Kumar and Clark's Clinical Medicine, 7e (Kumar, Kumar and Clark's Clinical Medicine) by Parveen J. Kumar (Paperback - Jul 2, 2009)
4. CURRENT Diagnosis and Treatment Emergency Medicine, Seventh Edition (LANGE CURRENT Series) by C. Keith Stone (May 23, 2011)
5. Goldman's Cecil medicine / [edited by] Lee Goldman, Andrew I. Schafer.—24th ed. Elsevier Sanders. Rev. ed. of: Cecil medicine. 23rd ed. – 2012. p.
6. Sonographer's Handbook of Diagnostic Ultrasound by Jason R. Young M.D. (Feb 23, 2011)

**Additional literature:**

- 1.Kovalyova O.M., Asheulova T.V. Propedeutics to internal medicine. Part 1, Diagnostics. Vinnytsya, Nova Knyha, 2006, 424 p

Answer

1. d) less than 15 ml/min
2. **A** Secondary renal amyloidosis
3. All patients with CKD should have a medication review.  
The advice of a current copy of the British National Formulary (BNF) should be followed. The priorities for this medication review should be:
  - Stop unnecessary medication which may impair renal function. For example, many patients may be on non-steroidal anti-inflammatory drugs (NSAID) which should be discontinued.
  - Angiotensin converting-enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) are the best drugs to treat hypertension in proteinuric CKD, although they can sometimes reduce renal perfusion. (See Q26)
  - Renal metabolism and excretion of drugs might be impaired. For example, patients on analgesics, certain B-blockers (including atenolol), digoxin and allopurinol may all need their dose reducing.

- In diabetes sulphonylureas may accumulate and therefore short acting drugs are preferred. Metformin should only be used under specialist advice when eGFR is below 30mL/min/1.73m<sup>2</sup> (Stage 4 and 5 CKD). When eGFR is between 30 and 60mL/min/1.73m<sup>2</sup> the risk/benefit ratio of metformin should be assessed on an individual basis.

Methodical recommendations consisted by

Kulishov S.K.