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MANAGEMENT OF PATIENTS WITH CHRONIC KIDNEY DISEASE

Methodological recommendations
(based on KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease)

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Methodological recommendations are purposed for medical students, clinical ordinators, therapeutics, family physicians and doctors of other specialties who may deal with chronic kidney disease patients. Recommendations contain information about evaluation and management of this group of patients, based on the KDIGO guidelines and data from recent scientific publications.

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LIST OF ABBREVIATIONS

CKD – chronic kidney disease
CCr - creatinine clearance
GFR – Glomerular filtration rate
SCr – serum creatinine
CVD – cardiovascular disease
CRF – chronic renal failure
AER – albumin excretion rate
ACR – albumin-to-creatinine ratio
RBC – red blood cells
WBC - white blood cells
DM – diabetes mellitus
AKI - acute kidney injury
PCR – protein-to-creatinine ratio
BP - blood pressure
ARBs - angiotensin II receptor blockers
ACE – angiotensin-converting-enzyme
HR – hazard ratio
CCBs – calcium-channel blockers
HbA1c – glycated hemoglobin
EPO – erythropoietin
TSAT – serum transferrin saturation
ESAs – erythropoiesis-stimulating agents

A FEW WORDS ABOUT GLOMERULAR FILTRATION RATE

Nowadays Glomerular filtration rate (GFR) is the best overall index of kidney function. Normal GFR ranges from 90 to 120 ml/min/1.73m^2 but it varies according to age, sex, and body size. GFR is not constant through the life. It declines with an average speed 1 ml/min/1.73m^2 per year after 20-30 years of age due to normal ageing processes. The rate of decline may accelerate after age 50–60 years. This decline appears to be a part of the normal physiologic process of cellular and organ senescence and is associated with structural changes in the kidneys.

There are several formulas to calculate GFR based on serum creatinine level. One of the easiest one is Cockcroft-Gault equation (1).

Cockcroft-Gault equation

$$GFR = \frac{(140-A)\times W\times k}{72\times SCr} \times 0.85\ if\ female, \quad (1)$$

Where:

GFR – Glomerular filtration rate, mL/minute;

A – Age, years;

W – Weight, kg;

SCr – Serum creatinine;

k=1 if SCr in mg/dl, k=88.5 if SCr in μmol/l

The Cockcroft-Gault formula was developed in 1973 using data from 249 men with creatinine clearance (CCr) from approximately 30 to 130 mL/min. It is not adjusted for body surface area. This equation is **no longer recommended** for use because it has not been expressed using standardized creatinine values.

MDRD equation (2):

$$GFR = 186.3 \times (Scr)^{-1.154} \times (A)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}), \quad (2)$$

Where:

GFR – Glomerular filtration rate, mL/min/1.73 m²;

A – Age, years;

SCr – serum creatinine, mg/dl;

MDRD equation is recommended to use only for patients with confirmed chronic kidney disease (CKD). It is not accurate in case of acute renal failure. It was shown that this equation may underestimate the actual GFR in healthy patients by up to 29%.

CKD-EPI equation (3) is considered as the most accurate among available. It can be used for GFR calculation both in healthy subjects and in patients with CKD.

GFR (mL/min/1.73 m^2) $=141\times\min(SCr/\kappa,1)^{\alpha}\times\max(Scr/\kappa,1)^{-1.209}\times0.993^{Age}\times1.018$ [if female]×1.159 [if black] (3)

Where:

SCr – serum creatinine, mg/dl),

k is 0.7 for females and 0.9 for males,

α is 0.329 for females and 0.411 for males,

min is the minimum of SCr/k or 1,

max is the maximum of SCr/k or 1.

Using of serum creatinine levels alone without GFR calculation is not reliable method to evaluate kidney function because it varies greatly depending on many factors. Increased serum creatinine levels are seen in case of:

- impaired renal function,
- chronic nephritis,
- urinary tract obstruction,
- muscle diseases such as gigantism, acromegaly, and myasthenia gravis,
- congestive heart failure,
- shock.

On the other hand, creatinine levels may be **decreased** in:

- elderly patients,
- persons with small stature,
- decreased muscle mass,
- inadequate protein intake,
- muscle atrophy.

Despite CKD-EPI and MDRD equations are quite difficult to calculate manually there are many web services and applets for android and iOS devices. For instance, on National Kidney Foundation website you can find online GFR calculator (https://www.kidney.org/professionals/KDOQI/gfr_calculator).

As it was remarked before, GFR declines with age. This is worth to keep in mind especially when you deal with an elderly patient because dose adjusting may be needed for many drugs depending on the GFR values.

WHAT IS CHRONIC KIDNEY DISEASE?

Chronic kidney disease – or chronic renal failure (CRF), as it was historically termed – is a term that encompasses all degrees of decreased renal function, from damaged–at risk through mild, moderate and severe chronic kidney failure. CKD is a worldwide public health problem. It is associated with an increased risk of cardiovascular disease (CVD) and acute renal failure. CKD is a common condition that is more prevalent in the elderly population. There is a rising incidence and prevalence of kidney failure, with poor outcomes and high cost. Kidney disease is the ninth leading cause of death in the United States.

CKD is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health. CKD can be diagnosed in case of presence of kidney damage markers (present for more than 3 months) and/or decreased GFR (present for more than 3 months) (Table 1).

Table 1

Chronic kidney disease diagnostic criteria

Markers of kidney damage (one or more)	Albuminuria (AER>30mg/24 hours; ACR>30mg/g [>3mg/mmol])
	Urine sediment abnormalities
	Electrolyte and other abnormalities due to tubular disorders. Abnormalities detected by histology
	Structural abnormalities detected by imaging
	History of kidney transplantation
Decreased GFR	GFR <60ml/min/1.73 m^2 (GFR categories G3a-G5)
Where: AER – albumin excretion rate; ACR – albumin-to-creatinine ratio.	

Urine sediment abnormalities include the following:

- isolated non-visible (microscopic) hematuria with abnormal red blood cells (RBC) morphology (anisocytosis) in glomerular basement membrane disorders;
- RBC casts in proliferative glomerulonephritis;
- white blood cells (WBC) casts in pyelonephritis or interstitial nephritis;

- oval fat bodies or fatty casts in diseases with proteinuria;
- granular casts and renal tubular epithelial cells in many parenchymal diseases.

Electrolyte and other abnormalities due to tubular disorders include:

- renal tubular acidosis;
- nephrogenic diabetes insipidus;
- renal potassium wasting;
- renal magnesium wasting;
- fanconi syndrome;
- non-albumin proteinuria;
- cystinuria.

Abnormalities detected by histology include:

- glomerular diseases (diabetes, autoimmune diseases, systemic infections, drugs, neoplasia);
- vascular diseases (atherosclerosis, hypertension, ischemia, vasculitis, thrombotic microangiopathy);
- tubulointerstitial diseases (urinary tract infections, stones, obstruction, drug toxicity);
- cystic and congenital diseases.

Structural abnormalities detected by imaging include:

- polycystic kidneys;
- dysplastic kidneys;
- hydronephrosis due to obstruction;
- cortical scarring due to infarcts, pyelonephritis or associated with vesicoureteral reflux;
- renal masses or enlarged kidneys due to infiltrative diseases;
- renal artery stenosis;
- small and hyperechoic kidneys (common in more severe CKD due to many parenchymal diseases).

Epidemiology

Nathan R. et al. (2016) conducted a systematic review and meta-analysis of 100 clinical trials and showed that global CKD prevalence of between 11 to 13% with the majority stage 3. It is remarkable that there were almost no difference in prevalence between high-income and low-income countries.

The prevalence of CKD increases dramatically with age (4% at age 29-39 y; 47% at age >70 y), with the most rapid growth in people after 60 years. In the National Health and Nutrition Examination Survey (NHANES) study (USA), the prevalence of stage 3 CKD in this age group rose from 18.8% during the years 1988-1994 to 24.5%

during the years 200-2006. During the same period, the prevalence of CKD in people aged 20-39 years remained consistently below 0.5%.

Etiology

The most common causes of CKD are diabetes mellitus (DM) and arterial hypertension. Thus, according to literature more than 40 % of CKD patients have DM type II and almost 30% high blood pressure. Other causes of chronic kidney disease include the following:

- vascular disease;
- glomerular disease (primary or secondary);
- cystic kidney diseases;
- tubulointerstitial disease;
- urinary tract obstruction or dysfunction;
- recurrent kidney stone disease;
- congenital (birth) defects of the kidney or bladder;
- unrecovered acute kidney injury (AKI).

The percentage of these diseases in the CKD structure is less than 30%.

CKD classification.

CKD is classified into categories (stages) according to estimated GFR (eGFR) and albuminuria. There are five stages of CKD depending to eGFR (Table 2). Stage G3 is subdivided into G3a and G3b substages.

Table 2

GFR categories (stages) in CKD

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	>90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

Three albuminuria categories are defined (Table 3)

Table 3

Albuminuria categories in CKD

	AER	ACR (approximate equivalent)		
Category	(mg/24 hours)	(mg/mmol)	(mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

Abbreviations:
AER – albumin excretion rate;
ACR – albumin-to-creatinine ratio;
*Relative to young adult level.
**Including nephrotic syndrome (albumin excretion usually 4 2200 mg/24 hours [ACR 4 2220 mg/g; 4 220 mg/mmol])

The following measurements for initial testing of proteinuria (in descending order of preference) are suggested:

1) urine albumin-to-creatinine ratio (ACR);
2) urine protein-to-creatinine ratio (PCR);
3) reagent strip urinalysis for total protein with automated reading;
4) reagent strip urinalysis for total protein with manual reading.

In all cases an early morning urine sample is preferred. The term microalbuminuria should no longer be used. If significant non-albumin proteinuria is suspected, assays for specific urine proteins (e.g., α1-microglobulin, monoclonal heavy or light chains, [Bence Jones proteins]) must be used.

EXAMINATION OF THE PATIENT WITH CKD

A careful physical examination is imperative. It may reveal findings characteristic of the condition that is underlying CKD (e.g., lupus, severe arteriosclerosis, hypertension) or its complications (e.g., anemia, bleeding diathesis, pericarditis). However, the lack of findings on physical examination **does not exclude** kidney disease. In fact, CKD is frequently clinically silent, so screening of patients without signs or symptoms at routine health visits is important.

Unfortunately, patients with CKD stages 1-3 are frequently asymptomatic. They do not experience clinically evident disturbances in water or electrolyte balance or endocrine/metabolic derangements and have no specific complaints. In late stages all human organs and systems are involved in pathological process.

Renal and urologic changes. Initially, salt-wasting and consequent hyponatremia produce hypotension, dry mouth, and loss of skin turgor, fatigue and nausea. Later, somnolence and confusion develop. As the number of functioning nephrons decreases, so does the kidneys' capacity to excrete sodium, resulting in salt retention and overload. Accumulation of potassium causes muscle irritability, and then muscle weakness as the potassium level continues to rise. Fluid overload and metabolic acidosis also occur. Urine output decreases: urine is very dilute and contains casts and crystals.

Cardiovascular changes. Hypertension and arrhythmias, including life-threatening ventricular tachycardia or fibrillation, cardiomyopathy, uremic pericarditis, pericardial effusion with possible cardiac tamponade, heart failure and peripheral edema may be present.

Respiratory changes. Due to reduced pulmonary macrophage activity patients with CKD are highly susceptible to lung infections. Pulmonary edema, pleuritic pain, pleural friction rub and effusions, uremic pleuritis, uremic lung (or uremic pneumonitis) and dyspnea also occur.

Gastrointestinal changes include:

- stomatitis;
- gum ulceration and bleeding;
- esophagitis;
- gastritis;
- duodenal ulcers;
- lesions on the small and large bowel;
- uremic colitis;
- pancreatitis;
- proctitis.

Cutaneous changes. As usual the skin is pallid or yellowish bronze, dry and scaly. Skin changes are often accompanied with severe itching. Presence of purpura,

ecchymoses or petechiae reflect coagulation disturbances. In critically ill or terminal patients uremic frost is seen on the skin.

Neurological changes. Disorders of central and peripheral nervous system are common. Patient presents with pain, burning and itching in the legs and feet, which may be relieved by voluntarily shaking, moving or rocking them. Eventually, this condition progresses to paresthesia and motor nerve dysfunction (usually bilateral foot drop) unless dialysis is initiated. Patient may also experience:

- muscle cramping and twitching;
- shortened memory and attention span;
- apathy;
- drowsiness;
- irritability;
- confusion;
- coma;
- seizures.

Forty-five percent of adult patients with CKD have depressive symptoms at initiation of dialysis therapy, as assessed using self-report scales. However, these scales may emphasize somatic symptoms – specifically, sleep disturbance, fatigue, and anorexia – that can coexist with chronic disease symptoms.

Hematopoietic changes include:

- anemia;
- decreased RBC survival time;
- blood loss from dialysis and GI bleeding;
- mild thrombocytopenia and platelet defects;
- increased bleeding and clotting disorders, demonstrated by purpura, hemorrhage from body orifices, easy bruising, ecchymoses, and petechiae.

Skeletal abnormalities are developed due to calcium-phosphorus imbalance and consequent parathyroid hormone imbalances. These changes lead to muscle and bone pain, skeletal demineralization, pathologic fractures, calcifications in the brain, eyes, gums, joints, myocardium, and blood vessels. Arterial calcification may produce coronary artery disease.

MANAGEMENT OF THE PATIENT WITH CKD

Predicting prognosis of CKD

In predicting risk for CKD outcome, doctor has to identify the cause of CKD, GFR category, albuminuria category, other risk factors and comorbid conditions. The relative strength of each of these factors will vary for each complication or outcome of interest. Risk for kidney disease end points, such as kidney failure and AKI, is predominately driven by an individual patient's clinical diagnosis, GFR, and the degree of albuminuria or other markers of kidney damage and injury. For cardiovascular disease, risk will be determined by history of CVD and traditional and nontraditional CVD risk factors.

For other conditions, the risk is determined by risk factors specific for those conditions. For all conditions, the cause of CKD, GFR category, and albuminuria category have important influence as "risk multipliers", but will have smaller overall influence on disease prediction than risk factors specific for the condition.

The risk associations of GFR and albuminuria categories appear to be largely independent of one another. Therefore, neither the category of GFR nor the category of albuminuria alone can fully capture prognosis for a patient with CKD. The magnitude and gradients of risk across categories of GFR and albuminuria will likely differ for each specific adverse event (Table 4).

CKD progression. Definition and identification

GFR and albuminuria must be assessed at least annually in people with CKD. If individuals are at higher risk of progression, and/or where measurement will impact therapeutic decisions GFR and albuminuria have to be assessed more often. Small fluctuations in GFR are common and are not necessarily indicative of progression.

CKD progression is defined based on one or more of the following:

- Decline in GFR category. A certain drop in eGFR is defined as a drop in GFR category accompanied by a 25% or greater drop in eGFR from baseline.
- *Rapid progression* is defined as a sustained decline in eGFR of more than 5 ml/min/1.73 m^2/yr.
- The confidence in assessing progression is increased with increasing number of serum creatinine measurements and duration of follow-up.

In people with CKD progression current management must be reviewed. These patients have to be examined for the reversible causes of progression and considered for referring to a specialist (Table 4).

Table 4.

Prognosis of CKD by GFR and albuminuria category. Guide to Frequency of Monitoring (number of times per year)

				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73m^2) Description and range	G1	Normal or high	≥90	low risk (1 if CKD)	moderately increased risk (1)	high risk (2)
	G2	Mildly decreased	60-89	low risk (1 if CKD)	moderately increased risk (1)	high risk (2)
	G3a	Mildly to moderately decreased	45-59	moderately increased risk (1)	high risk (2)	very high risk (3)
	G3b	Moderately to severely decreased	30-44	high risk (2)	very high risk (3)	very high risk (3)
	G4	Severely decreased	15-29	very high risk (3)	very high risk (3)	very high risk (4+)
	G5	Kidney failure	<15	very high risk (4+)	very high risk (4+)	very high risk (4+)

The numbers in the boxes are a guide to the monitoring frequency (number of times per year).

Prevention of CKD progression

Lifestyle modification

People with CKD have to be encouraged to undertake physical activity compatible with cardiovascular health and tolerance (aiming for at least 30 minutes 5 times per week), achieve a healthy weight (body mass index 20 to 25 kg/m^2, according to country specific demographics), and smoking cessation.

Dietary recommendation

Protein intake. In adults with or without diabetes and GFR < 30 ml/min/ 1.73 m^2 protein intake must not exceed 0.8 g/kg/day. Adults with CKD at risk of progression have to avoid protein intake > 1.3 g/kg/day.

Salt intake. Lowering salt intake to < 90 mmol (< 2 g) per day of sodium (corresponding to 5 g of sodium chloride) in adults is recommended, unless contraindicated.

Additional dietary advice. In fact, individuals with CKD must receive expert dietary advice and information in the context of an education program, tailored to severity of CKD and the need to intervene on salt, phosphate, potassium, and protein intake where indicated.

Blood pressure control

Blood pressure (BP) targets and agents must be individualized according to age, coexistent comorbidities, risk of CKD progression, presence or absence of retinopathy (in CKD patients with diabetes), and tolerance of treatment. Consider age, comorbidities and other therapies in elderly patients with CKD, with gradual escalation of treatment. Close attention to adverse events related to BP treatment (including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects) is needed in elderly.

Target BP depends greatly on albumin excretion rate. For both diabetic and non-diabetic adults with CKD and urine albumin excretion <30 mg/24 hours BP must be as low as <140 mm Hg systolic and <90 mm Hg diastolic.

If albumin excretion >30 mg/24 hours BP-lowering drugs must be used to maintain a BP that is consistently <130 mm Hg systolic and <80 mm Hg diastolic (for both diabetic and non-diabetic adults).

Renin–angiotensin–aldosterone system interruption

Angiotensin II receptor blockers (ARBs) or angiotensin-converting-enzyme (ACE) inhibitors are the drugs of choice in majority of CKD patients. It is known that these agents help to control BP and have nephroprotective effect mainly due to reduction of proteinuria. Xie X. et al. (2016) conducted a bayesian network meta-analysis of 119 randomized controled clinical trials and showed that the use of ACE inhibitors or ARBs in people with CKD reduces the risk for kidney failure and cardiovascular

events. ACE inhibitors also reduced the risk for all-cause mortality and were possibly superior to ARBs for kidney failure, cardiovascular death, and all-cause mortality in patients with CKD, suggesting that they could be the first choice for treatment in this population.

Thus, these BP-lowering agents are recommended for adults with CKD on the background of DM if urine albumin excretion exceeds 30 mg/24 hours. For CKD patients without DM ARB or ACE inhibitors must be prescribed if urine albumin excretion exceeds 300 mg/24 hours.

There is no sufficient evidence to recommend combining an ACE-I with ARBs to prevent progression of CKD.

Lowering BP below indicated values in CKD patients is debatable. In the Systolic Blood Pressure Intervention Trial (SPRINT) with *n*=9361 participants was showed that among patients with CKD and hypertension without diabetes, targeting a systolic BP <120 mm Hg reduced rates of major cardiovascular events and all-cause death if compared with <140 mm Hg. However, in the intensive BP lowering group increased risks for hypokalemia (HR, 1.87; 95% CI, 1.02 to 3.43), hyperkalemia (HR, 1.36; 95% CI, 1.01 to 1.82), and acute renal failure (HR, 1.46; 95% CI, 1.10 to 1.95) compared with the standard treatment group were documented.

As it was indicated above ACE inhibitors and ARBs may reduce proteinuria. Regarding this, many clinical trials were conducted to evaluate the necessity of these drugs usage in normotensive patients with CKD. In one meta-analysis of randomized controlled trials was shown that in normotensive patients with microalbuminuria and type 1 DM ACE inhibitors reduced the risk of progression to macroalbuminuria. In normotensive patients with microalbuminuria and type 2 DM both ACE inhibitors and ARBs reduced the risk of progression to macroalbuminuria. At the same time ACE inhibitors and ARBs did not reliably affect serum creatinine levels. Recommendations are not available for normotensive patients without diabetes who have microalbuminuria.

It is also worth to remember the key features of ACE inhibitors and ARBs pharmacokinetics. For instance, most available ACE inhibitors have active moieties that are largely excreted in the urine. But, fosinopril and trandolapril are partially (in general, approximately 50%) excreted by the liver, such that the blood levels are less influenced by kidney failure than levels of other ACE inhibitors which are predominantly excreted by the kidneys.

In contrast, all ARBs are substantially excreted by the liver, with the proportion of drug elimination ranging from 40% (in case of candesartan) to >95% (in case of irbesartan and telmisartan). As with ACE inhibitors, the dose of ARBs is usually adjusted according to clinical effect rather than kidney function.

ACE inhibitors and ARBs should be used with caution or even avoided in certain CKD subgroups, particularly in patients with bilateral renal-artery stenosis or with

intravascular fluid depletion, because of the risk of a large reduction in GFR. If hyperkalemia occurs in CKD patients taking a renal excreted ACE inhibitors, possible interventions include dietary advice, reducing the dose, switching to fosinopril or trandolapril, or adding a potassium-losing diuretic.

In 50% of patients treated with ACE inhibitors or ARBs the aldosterone level comes back to the baseline after initial decreasing. This phenomenon is known as "aldosterone breakthrough". The mechanism is not fully understood but it is considered that angiotensin I to angiotensin II conversion occurs via other pathways and by the fact there may be other active receptors for angiotensin II that may have arange of roles.

In fact, aldosterone breakthrough is a frequent event. The post hoc analysis (Moranne O. et al., 2013) of prospective, randomized, double-blind, controlled, multicenter, parallel-group trial AMADEO (the A comparison of telMisartan versus losArtan in hypertensive type 2 DiabEtic patients with Overt nephropathy) showed that aldosterone breakthrough occurred 1 year after initiating renin-angiotensin-aldosterone system blockade, particularly in participants exposed to intensive lowering of BP with sodium depletion and short-acting ARBs. Short-term serum aldosterone level increases at 6 months are not associated with negative kidney outcomes between 6 months and 1 year.

Diuretics

Loop diuretics. In primary hypertension furosemide (also called frusemide), bumetanide, torsemide and ethacrynic acidare are effective in the short term but less so than thiazides in the long term. Loop diuretics are particularly useful when treating edema and high BP in CKD 4-5 stages patients in addition or as an alternative to thiazide diuretics.

Thiazides. Although thiazides are excreted by the kidney, no dose adjustment is recommended in patients with reduced GFR. These drugs reduce the risk of hyperkalemia, potentiate the action of ACE inhibitors and ARBs. In newly treated primary hypertensives, the thiazide-like diuretics are preferable to the thiazides, based on the larger volume of evidence for efficacy.

Potassium-sparing diuretics. Triamterene and amiloride are usually avoided in patients with CKD because of the risk of hyperkalemia. Aldosterone antagonists increase potassium levels in blood. In combination with ACE inhibitors or ARBs, these medication increase the antiproteinuric effect, but also increase the risk of hyperkalemia that can be partially controlled by thiazide or loop diuretics.

Beta-blockers

In patients with CKD beta-blockers or active metabolites may be accumulated witch may lead to exacerbation of their concentration-dependent side effects (such as

bradycardic arrhythmias). Such accumulation occurs with atenolol and bisoprolol, but not carvedilol, propranolol, or metoprolol.

Calcium-channel blockers

Most calcium-channel blockers (CCBs) do not accumulate in patients with impaired kidney function, with the exception of nicardipine and nimodipine. There are a few types of calcium channels but talking about kidney hemodynamic it is worth to keep in mind that T-type calcium channels are present both in afferent and efferent arterioles while L-type calcium channels are in afferent arteriole only. Regarding this, T-channel blockade (with non-dihydropyridine CCBs) leads to a dilation of afferent and efferent arterioles, reduction in intraglomerular pressure, and accordingly a fall in urine albumin levels. In contrast, blockade of L-channel receptors (with dihydropyridine CCBs) cause the dilation of afferent arteriole only, increase of intraglomerular pressure and subsequent increase in the urine albumin level. Therefore, in patients with albuminuria non-dihydropyridine CCBs are preferable.

Lipid status management

In adults with newly identified CKD (including those treated with chronic dialysis or kidney transplantation) evaluation with a lipid profile (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides) is recommend. Follow-up measurement of lipid levels is not required for the majority of patients.

Pharmacological cholesterol-lowering treatment in adults

In adults aged ≥ 50 years with eGFR < 60 ml/min/1.73 m^2 but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5) treatment with a statin or statin/ezetimibe combination is strongly recommend. If eGFR ≥ 60 ml/min/1.73 m2 (GFR categories G1-G2) treatment with a statin is recommended.

In adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation statin treatment is required in people with one or more of the following:

- known coronary disease (myocardial infarction or coronary revascularization);
- diabetes mellitus;
- prior ischemic stroke;
- estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%;

In adults with dialysis-dependent CKD statins or statin/ezetimibe combination should not be initiated. If patient already receives statins or statin/ezetimibe combination at the time of dialysis initiation these agents be continued.

The benefit of statins is similar in people with and without albuminuria. High-intensity statins were found to improve a decline in eGFR in population with CKD not requiring dialysis, but moderate- and low-intensity statins were not. Statins were not found to decrease proteinuria in patients with CKD.

Statins are contraindicated in pregnant or breast-feeding females; in people with active liver disease; in people with transaminase levels that are three times or more the upper limit of normal. There is no evidence that the risk of liver dysfunction differs in people with CKD, as compared to those without. Regardless of CKD severity baseline levels of transaminases must be measured before initiating statin treatment. Routine follow-up measurements of transaminases are not recommended.

Glycemic control

The intensive treatment of hyperglycemia, cause of vascular target organ complications, seems to prevent elevated albuminuria or delays the kidney failure progression, even in patients treated with normoglycemic approaches who may be at risk of severe hypoglycemia.

In people with CKD a target glycated hemoglobin (HbA1c) is recommended to be approximately 7.0% (53 mmol/mol) to prevent or delay progression of the microvascular complications of diabetes, including diabetic kidney disease. Patients who are at risk of hypoglycemia must not be treated to an HbA1c target of < 7.0% (< 53 mmol/mol). Target HbA1c can be extended above 7.0% (53 mmol/mol) in individuals with comorbidities or limited life expectancy and risk of hypoglycemia.

Metformine is continued in people with GFR > 45 ml/min/1.73m^2 (GFR categories G1-G3a); its use should be reviewed in those with GFR 30-44 ml/min/1.73m^2 (GFR category G3b); and it should be discontinued in people with GFR < 30 ml/min/1.73m^2 (GFR categories G4-G5).

Hyperuricemia

According to the KDIGO guideline there is insufficient evidence to support or refute the use of agents to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay CKD progression. Up to now there are lack of large randomized clinical trials designed to confirm the influence of hyperuricemia on the CKD development and progression as well as the efficacy of urate lowering therapy in these patients.

COMPLICATIONS ASSOCIATED WITH LOSS OF KIDNEY FUNCTION

Anemia in CKD

Anemia is a common and important complication of CKD because it contributes significantly to the heavy symptom burden of CKD. It is typically normocytic, normochromic, and hypoproliferative. Anemia in CKD patients is associated with poor outcomes. Despite it has a major impact on the lives of people with CKD it is potentially reversible with appropriate treatment. Predominant cause of anemia in these patients is erythropoietin (EPO) deficiency. The main stimulus for elevated synthesis of EPO is tissue hypoxia, which normally leads to an increase in serum EPO levels. This feedback is affected in patients with pathological conditions involving the kidneys and the developing anemia is not adequately compensated by a sufficient increase in the EPO production. The most important extrarenal source of EPO is the liver, which accounts for 10-15% of the total EPO production. Iron deficiency, or its limited availability for erythropoiesis, is also an important pathogenetic mechanism for the renal anemia development.

Diagnose anemia in adults with CKD when the Hb concentration is < 13.0 g/dl (< 130 g/l) in males and < 12.0 g/dl (< 120 g/l) in females.

To identify anemia in people with CKD measure Hb concentration:

- when clinically indicated in people with GFR > 60 ml/min/1.73 m^2 (GFR categories G1-G2);
- at least annually in people with GFR 30–59 ml/min/1.73 m^2 (GFR categories G3a-G3b);
- at least twice per year in people with GFR < 30 ml/min/1.73 m^2 (GFR categories G4-G5)

In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia:

- complete blood count (CBC), which should include Hb concentration, red cell indices, white blood cell count and differential, and platelet count;
- absolute reticulocyte count;
- serum ferritin level;
- serum transferrin saturation (TSAT);
- serum vitamin B_{12} and folate levels.

Treatment of anemia with iron and erythropoiesis-stimulating agents (ESAs) has an important positive role. Work-up for anemia in CKD should include assessment of secondary causes including iron deficiency. Iron replacement is often effective in anemia of CKD as initial therapy and routes of administration (intravenous or oral) must be determined by clinicians, patient preferences, and local available resources. ESAs therapy is not recommended in those with active malignancy, or recent history of malignancy. In most people with CKD, ESAs should not be used to intentionally increase the Hb concentration above 11.5 g/dl (115 g/1).

When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients.

For adult CKD patients with anemia who do not receive iron or ESA therapy a trial of IV iron (or in CKD non-dialysis patients alternatively a 1-3 month trial of oral iron therapy) if:

- an increase in Hb concentration without starting ESA treatment is desired and
- transferrin saturation is ≤ 30% and ferritin is ≤ 500 ng/ml (≤ 500 pg/1)

For adult CKD patients on ESA therapy who are not receiving iron supplementation, a trial of intravenous (IV) iron (or in CKD non-dialysis patients alternatively a 1-3 month trial of oral iron therapy) if:

- an increase in Hb concentration or a decrease in ESA dose is desired (based on patient symptoms and overall clinical goals including avoidance of transfusion and improvement in anemia-related symptoms, and after exclusion of active infection and other causes of ESA hyporesponsiveness) and
- transferrin saturation is ≤ 30% and ferritin is ≤ 500 ng/ml (≤ 500 pg/1)

For CKD non-dialysis patients who require iron supplementation, the route of iron administration is selected based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost.

Subsequent iron administration in CKD patients are guided based on Hb responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA treated patients, trends in each parameter, and the patient's clinical status.

IV iron administration must be avoided in patients with active systemic infections.

Metabolic bone disease including laboratory abnormalities

In adults with GFR < 45 ml/min/1.73 m^2 (GFR categories G3b-G5) measuring serum levels of calcium, phosphate, parathyroid hormone (PTH), and alkaline phosphatase activity is recommended at least once in order to determine baseline values. Routine bone mineral density testing is not suggested (information may be misleading or unhelpful). Serum phosphate concentrations have to be maintained in the normal range according to local laboratory reference values. Note that the optimal PTH level is not known in this group of CKD patients.

Vitamin D supplements or vitamin D analogs should not be routinely prescribed (unless there is suspected or documented deficiency) to suppress elevated PTH concentrations in people with CKD not on dialysis.

It is recommended to avoid bisphosphonate treatment in people with GFR < 30 ml/min/1.73 m^2 without a strong clinical rationale.

CKD and cardiovascular disease

It is well known that all people with CKD are considered at increased risk for cardiovascular disease. In adults with CKD at risk for atherosclerotic events treatment with antiplatelet agents is offered unless there is an increased bleeding risk that needs to be balanced against the possible cardiovascular benefits.

In people with CKD and heart failure, any escalation in therapy and/or clinical deterioration should prompt monitoring of eGFR and serum potassium concentration.

In people with GFR < 60 ml/min/1.73 m^2, serum concentrations of brain natriuretic peptide/N-terminal pro b-type natriuretic peptide (BNP/NT-proBNP) must be interpreted with caution and in relation to GFR with respect to diagnosis of heart failure and assessment of volume status.

In people with GFR < 60 ml/min/1.73m^2, serum concentrations of troponin should be interpreted with caution with respect to diagnosis of acute coronary syndrome.

MISCELLANEOUS

Medication management and patient safety in CKD

GFR should be taken into account when drug dosing because many drugs need dose adjustment depending on GFR.

It is recommended temporary discontinue of potentially nephrotoxic and renally excreted drugs in people with a GFR < 60 ml/min/1.73 m^2 (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk of AKI. These agents include, but are not limited to: renin–angiotensin–aldosterone system (RAAS) blockers (including ACE inhibitors, ARBs, aldosterone inhibitors, direct renin inhibitors), diuretics, nonsteroidal anti-inflammatory drugs, metformin, lithium, and digoxin.

Herbal remedies are not recommended in people with CKD.

Radiocontrast

All people with GFR < 60 ml/min/1.73 m^2 undergoing elective investigation involving the intravascular administration of iodinated radiocontrast media should be managed according to the KDIGO Clinical Practice Guideline for AKI including:

- avoidance of high osmolar agents;
- use of lowest possible radiocontrast dose;
- withdrawal of potentially nephrotoxic agents before and after the procedure;
- adequate hydration with saline before, during, and after the procedure;
- measurement of GFR 48-96 hours after the procedure.

Gadolinium-based contrast media are not recommended to use in people with GFR <15ml/min/1.73 m^2 (GFR category G5), unless there is no alternative appropriate test. It is suggested that people with GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5) who require gadoliniumcontaining contrast media are preferentially offered a macrocyclic chelate preparation.

Bowel preparation. Oral phosphate-containing bowel preparations are not recommend in people with a GFR <60 ml/min/1.73 m^2 or in those known to be at risk of phosphate nephropathy.

CKD and risk of infections

For all adults with CKD annual vaccination with influenza vaccine is offered, unless contraindicated.

All adults with eGFR < 30 ml/min/1.73 m^2 and those at high risk of pneumococcal infection (e.g., nephrotic syndrome, diabetes, or those receiving immunosuppression) are recommended to receive vaccination with polyvalent pneumococcal vaccine, unless contraindicated. All adults with CKD who have received pneumococcal vaccination are offered revaccination within 5 years.

For all adults who are at high risk of CKD progression and have GFR < 30 ml/min/1.73 m^2 immunization against hepatitis B is offered and the response must be confirmed by appropriate serological testing.

People with CKD ought to be referred to specialist kidney care services in the following circumstances:

- AKI or abrupt sustained fall in GFR;
- GFR < 30 ml/min/1.73 m2;
- a consistent finding of significant albuminuria (ACR ≥ 300 mg/g [≥ 30 mg/mmol] or AER ≥ 300 mg/24 hours);
- progression of CKD;
- urinary red cell casts, RBC > 20 per high power field sustained and not readily explained;
- CKD and hypertension refractory to treatment with 4 or more antihypertensive agents;
- persistent abnormalities of serum potassium;
- recurrent or extensive nephrolithiasis;
- hereditary kidney disease.

CKD and risk of acute kidney injury. People with CKD are considered to be at increased risk of AKI. This should be kept in mind when deal with CKD patient during intercurrent illnesses, or when undergoing investigation and procedures that are likely to increase the risk of AKI.

Referral for planning renal replacement therapy (RRT) must be done in people with progressive CKD in whom the risk of kidney failure within 1 year is 10–20% or higher.

Timing the initiation of RRT. Dialysis is suggested to be initiated when one or more of the following are present:

- symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus);
- inability to control volume status or blood pressure;
- a progressive deterioration in nutritional status refractory to dietary intervention;
- cognitive impairment.

This often but not invariably occurs in the GFR range between 5 and 10 ml/min/1.73m^2.

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