Lecture

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MANAGEMENT OF PATIENTS WITH ACUTE KIDNEY INJURY

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Presented lecture is about management of a serious condition – acute kidney injury (AKI). It is intended for students, general practitioners, family physicians, therapists and those who may face with manifestations of AKI, and on which depends its timely diagnosis and the success of therapy. Definition, epidemiology, risk factors, causes, pathogenesis, classification, symptoms, diagnosis and differential diagnosis, treatment, complications, prognosis and prevention of AKI are described.

KEY WORDS: acute kidney injury, management, nephrology

МЕНЕДЖМЕНТ ПАЦІЄНТІВ ІЗ ГОСТРОЮ НИРКОВОЮ НЕДОСТАТНІСТЮ

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Представлена лекція про ведення пацієнтів із важким захворюванням – гострою нирковою недостатністю (ГНН). Вона призначена для студентів, лікарів загальної практики, сімейних лікарів, терапевтів та тих, хто може зіткнутися з проявами ГНН і від яких залежить її своєчасна діагностика та успішність терапії. Зазначені визначення, епідеміологія, фактори ризику, причини, патогенез, класифікація, симптоми, ускладнення, діагностика та диференціальна діагностика, лікування, прогноз і профілактика ГНН.

КЛЮЧОВІ СЛОВА: гостра ниркова недостатність, ведення, нефрологія

МЕНЕДЖМЕНТ ПАЦИЕНТОВ С ОСТРОЙ ПОЧЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

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Представлена лекция о ведении пациентов с тяжелым заболеванием – острой почечной недостаточностью (ОПН). Она предназначена для студентов, врачей общей практики, семейных врачей, терапевтов и тех, кто может столкнуться с проявлениями ОПН и от которых зависит ее своевременная диагностика и успешное лечение. Обсуждаются определение, эпидемиология, факторы риска, причины, патогенез, симптомы, осложнения, диагностика и дифференциальная диагностика, лечение, прогноз и профилактика ОПН.

КЛЮЧЕВЫЕ СЛОВА: острая почечная недостаточность, ведения, нефрология

DEFINITION

Acute kidney injury (AKI), also known as acute renal failure, is defined as a sudden decrease in kidney function, resulting in an inability to maintain acid-base, fluid and electrolyte balance and to excrete nitrogenous wastes [1]. AKI is a designation for a heterogeneous group of conditions that share common diagnostic features: an increase in the blood urea nitrogen concentration; an increase in the plasma or serum creatinine (SCr) concentration, often associated with a reduction in urine output (UO) [1].

EPIDEMIOLOGY

There is lack of studies which evaluating AKI in the community setting, as well as a lack of comparisons between intensive care unit (ICU) patients and non-ICU patients.

According to a recently published meta-analysis the pooled incidence and mortality of AKI in patients is circa 30 % worldwide [2]. The incidence of AKI in critically ill patients

has increased over the years, mostly because of dialysis-requiring AKI, especially among the elderly, the male gender, and the black population.

The incidence of AKI in hospitalized patients has also increased from 4,9 % to 20 % during last 10 years [3]. This may partly be due to the definitions of AKI becoming more time sensitive and may reflect an increase in detection rather than an overall increase in incidence in disease.

RISK FACTORS [4]

Patient-related risk factors: advanced age, arterial hypertension, atherosclerosis, biliary surgery/jaundice, cardiogenic shock, chronic obstructive pulmonary disease, chronic renal disease, cirrhosis of the liver, congestive heart failure, diabetes, female gender, left main coronary disease, left ventricular ejection fraction < 35 %, major vascular surgery, myeloma, nephrotoxic drugs, peripheral vascular disease, pre-eclampsia/eclampsia, renal insufficiency, sepsis.

Procedure-related risk factors: blood loss, cross-clamp time, diarrhea/bowel preparation, diuretic therapy, gastric aspiration/vomiting, hemodilution, hemolysis, hypovolemia (oliguria), hypoxia, ileus obstruction, inflamemation, length of cardiopulmonary bypass, major burns, massive blood transfusions and transfusion reactions, muscle breakdown, nonpulsatile flow, off-pump versus on-pump coronary artery bypass graft surgery, pancreatitis, peritonitis, polytrauma, preoperative starvation, prolonged tissue exposure, surgical edema.

CAUSES

Causes of AKI due to decreased kidney perfusion (prerenal) [5]:

Decreased intravascular fluid volume: extracellular fluid loss (burns, diarrhea, vomiting, diuretics, salt-wasting renal disease, primary adrenal insufficiency, gastrointestinal hemorrhage), extracellular fluid sequestration (pancreatitis, burns, crush, injury, nephrotic syndrome, malnutrition, advanced liver disease).

Decreased cardiac output: myocardial dysfunction (myocardial infarction, arrhythmias, ischemic heart disease, cardiomyopathies, valvular disease, hypertensive disease, severe cor pulmonale, etc.).

Peripheral vasodilation: drugs (antihypertensive agents), sepsis, miscellaneous (adrenal cortical insufficiency, hypomagnesemia, hypercapnia, hypoxia, etc.).

Severe renal vasoconstriction: sepsis, drugs (nonsteroidal anti-inflammatory agents, ß-adrenergic agonists), hepatorenal syndrome.

Mechanical occlusion of renal arteries: thrombotic occlusion, miscellaneous (emboli, trauma, etc.).

Causes of AKI due to parenchymal or vascular diseases (renal) [5]:

Renal vascular disorders: vasculitis, malignant hypertension, scleroderma, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, mechanical renal artery occlusion (surgery, emboli, thrombotic occlusion), renal vein thrombosis.

Glomerulonephritis: postinfectious, membranoproliferative, rapidly progressive glomerulonephritis (idiopathic, polyarteritis nodosa, systemic lupus erythematosus, Wegener's syndrome, microscopic polyarteritis, Goodpasture's syndrome, Henoch-Schonlein purpura, drugs.

Interstitial nephritis: drugs (penicillin, sulfonamide, rifampin, ciprofloxacin, phenindiones, cimetidine, proton pump inhibitors, azathioprine, phenytoin, captopril, thiazides, furosemide, bumetanide, allopurinol, nonsteroidal anti-inflammatory drugs including selective cyclooxygenase-2 inhibitors, 5-aminosalicylates), hypercalcemia.

Infections: nonspecific due to frank septicemia or systemic anti-inflammatory response syndrome, specific organisms (legionella, leptospira, rickettsia, Hantavirus, candida, malaria), specific organ involvement (bacterial endocarditis, visceral abscess, pyelonephritis).

Infiltration: sarcoid, lymphoma, leukemia.

Connective-tissue disease.

Tubular necrosis: renal ischemia (prolonged prerenal), nephrotoxins (aminoglycosides, radiocontrast agents, heavy metals, organic solvents, other antimicrobials), pigmenturia, (myoglobinuria, hemoglobinuria), miscellaneous.

Intratubular: crystal deposition (uric acid, oxalic acid), methotrexate, acyclovir, triamterene, sulfonamides, indinavir, tenofovtransplant rejection, protein deposition (light chains, myoglobin, hemoglobin).

Causes of AKI due to urinary tract obstruction (postrenal) [6-7]:

Extrarenal: ureteral/pelvic intrinsic obstruction (tumor, stone, clot, pus, fungal ball, papilla), extrinsic obstruction (retroperitoneal and pelvic malignancy, fibrosis, ligation, abdominal aortic aneurysm).

Bladder: prostate hypertrophy/malignancy, stones, clots, tumor, neurogenic, medication.

Urethral: stricture, phimosis.

PATHOGENESIS

Renal blood flow is 25 % of cardiac output but some areas are particularly sensitive to ischemic damage. Most of the blood flow supplies the cortex, which contains the glomeruli and convoluted tubules, areas that require good perfusion to achieve filtration and reabsorption, the latter with high energy demands. The outer medulla is comparatively starved of oxygen, its blood supply first traversing the glomerular capillary bed, and losing hydrostatic pressure (in essence, a portal circulation), and then on entering the medulla, losing oxygen by countercurrent exchange with the venous vasa recta. These features are essential to maintain the osmotic gradients within the medulla and thus generate concentrated urine, but render the outer medulla very susceptible to variations in blood flow. This area contains the thick ascending limb of the loop of Henle and S3 segment of the proximal tubule, both with high oxygen requirements. Impaired tubular sodium reabsorption attributable to reduced perfusion causes constriction of the afferent arteriole and a further reduction in glomerular filtration rate (GFR). This compensatory mechanism (tubuloglomerular feedback), designed to protect the downstream nephron, may cause injury if prolonged, or if normal regulation of the arterial tone is blocked (for example, by non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs)). Reduced blood flow in the peritubular capillaries produces ischemic damage in vascular endothelial cells, resulting in cell swelling and the expression of cell adhesion molecules – reducing flow further and leading to leucocyte activation. Adherent leucocytes further impede blood flow and produce cytokines and reactive oxygen species that damage endothelial and tubular epithelial cells. Tubular cells swell, lose their brush border, and develop cytoskeletal abnormalities with abnormal localization of cell membrane components (for example, Na+/K+−ATPase), changes in cellular polarity, and loss of cell-cell and cell-basement membrane attachment. These swollen, detached cells obstruct the tubular lumen, and back leak of filtrate occurs through the damaged basement membrane. In the classic histological appearance of acute tubular necrosis (ATN), tubules are surrounded by flattened, denuded epithelium, and the lumen filled by cell debris, with congested peritubular capillaries and an extensive inflammatory cell infiltrate. Cell death occurs predominantly by necrosis, although apoptosis also contributes – especially in the thick ascending limb and late in the process (Fig.).

A remarkable feature of the kidney is its ability to regain normal structure and function after such injury. Once renal perfusion and oxygen supply are normalized, viable cells still adherent to the tubular basement membrane can spread to cover denuded areas, and then differentiate to reproduce normal tubular architecture, and function. The return of glomerular filtration aids clearance of tubular debris and relief of obstruction. A period may exist where glomerular filtration has normalized, but tubular function remains deranged, hence the polyuric phase of ATN, where urine output is often excessive without normal homoeostasis.

The anuric phase of ATN classically lasts 7–21 days, and recovery to pre-insult levels of renal function can be expected, although some impairment of function may persist, particularly if there is a background of chronic renal insufficiency [8].

CLASSIFICATION

The RIFLE classification is presented in table 1 [9]. The Acute Dialysis Quality Initiative (ADQI) group for the study of AKI was published in May 2004 the consensual RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification. It accomplished the following criteria: easy clinical applicability, sensitivity and specificity, consider baseline SCr variations and also consider the «acute-on-chronic» phenomenon (which means the occurrence of an acute insult over a chronically injured renal function causing its deterioration). This definition classify AKI according to its severity (mild versus severe) and its timing of

occurrence (precocious versus late AKI). By fulfilling these criteria, this classification allow to detect of patients whose kidney function was slightly affected (high sensitivity but low specificity) as well as patients with severe kidney function deterioration (high specificity with diminishing sensitivity).

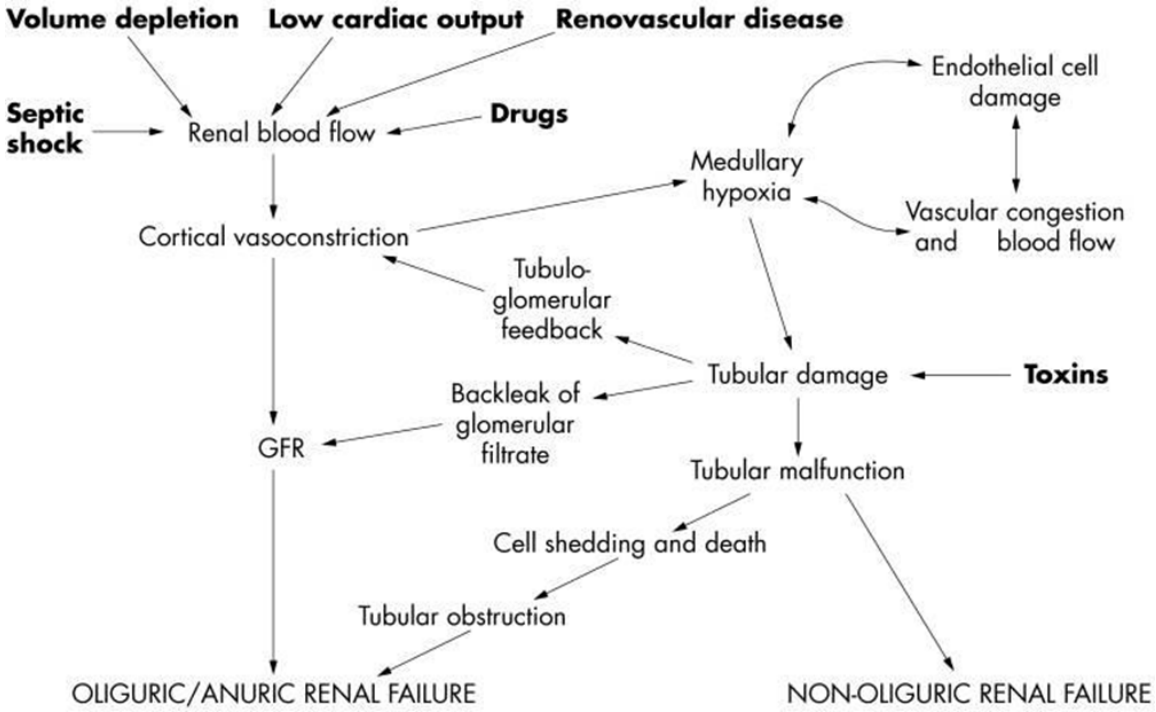

Fig. Mechanisms of acute tubular necrosis by A. Fry and K. Farrington [2]

Table 1

The RIFLE classification of AKI

Class	Glomerular filtration rate	UO
Risk	↑ SCr 1,5 times or ↓ GFR for more than 25 %	less than 0,5 mL/kg/h during 6 hours
Injury	↑ SCr 2 times or↓ GFR for more than 50 %	less than 0,5 mL/kg/h during 12 hours
Failure	↑ SCr 3 times or ↓ GFR for more than 75 % or if baseline SCr ≥353,6 mmol/L (4 mg/dL), ↑ SCr for more than 44,2 mmol/L (0,5 mg/dL)	less than 0,3 mL/kg/h during 24 hours or anuria during 12 hours
Loss of kidney function	Complete loss of kidney function > 4 weeks	
End-stage kidney disease	Complete loss of kidney function > 3 months	

If baseline SCr is unknown and if there is no history of chronic kidney disease (CKD), baseline SCr should be calculated using the Modification of Diet in Renal Disease (MDRD) equation, assuming a baseline GFR of 75 mL/min/1,73m^2.

Limitations of the RIFLE classification [9]. Determination of renal function using RIFLE classification has several limitations: the endogenous production and serum release of Cr are variable, and it is influenced by multiple factors, namely age, gender, diet, and muscle mass; from 10 to 40 % of Cr elimination is performed by tubular secretion and this mechanism is amplified as the GFR diminishes, thus, overestimating renal function in AKI patients; many medications inhibit tubular secretion of Cr, causing a temporary increase in SCr; various factors can interfere with SCr determination, causing a false elevation in SCr; Cr is a marker of renal function, and not of renal lesion; sensitivity and specificity of UO can be significantly changed by the use of diuretics and in diabetes insipidus, et al.; UO can only be determined in patients with a bladder catheter in place, which is not frequent in hospitalized patients; it is possible that the predictive ability of UO could be inferior to that of SCr; etiology of AKI are not considered; classification does not provide any information regarding the origin of the renal lesion (i.e. cellular or subcellular levels), as opposed to several biomarkers of AKI recently identified and studied.

The Acute Kidney Injury Network (AKIN) classification is presented in table 2 [9]. In 2007 a new classification of AKI was proposed by the Acute Kidney Injury Network (AKIN) working group. They modify RIFLE classification in some points: the diagnosis of AKI is only considered after achieving an adequate status of hydration and after excluding urinary obstruction; the AKIN classification only relies on SCr and not on GFR changes; baseline SCr is not necessary in the AKIN classification, and it requires at least two values of SCr obtained within a period of 48 h.

Table 2

AKIN classification of AKI

Stage	SCr	UO
1	↑ SCr more than 26,5 mmol/L (0,3 mg/dL) or ↑ SCr for more than 150-200 % (in 1,5-2 times)	less than 0,5 mL/kg/h during more than 6 hours
2	↑ SCr for more than 200-300 % (in 2-3 times)	less than 0,5 mL/kg/h during more than 12 hours
3*	↑ SCr for more than 300 % (in 3 times and more) or if baseline SCr more than 353,6 mmol/L (4 mg/dL), ↑ SCr more than 44,2 mmol/L (0,5 mg/dL)	less than 0,3 mL/kg/h during 24 hours or anuria during 12 hours

** stage 3 also includes patients requiring, initiating or at the moment on renal replacement therapy (RRT).*

Limitations of the AKIN classification [9]. AKIN classification also have some limitations: it does not allow the identification of AKI when SCr elevation occurs in a time frame higher than 48 hours; stage 3 of the AKIN classification includes three diagnostic criteria and the extreme variability in the beginning and cessation of RRT as well as in RRT modality used and in the dose of dialysis among different physicians, hospitals and countries could significantly limit the prognostic acuity of this classification, particularly of stage 3.

SYMPTOMS

Symptoms of acute kidney failure may include any of the following [10–11]: bloody stools, breath odor and metallic taste in the mouth, bruising easily, changes in mental status or mood, decreased appetite, decreased sensation, especially in the hands or feet, fatigue or slow sluggish movements, flank pain between the ribs and hips, hand tremor, heart murmur, high blood pressure, nausea or vomiting, may last for days, nosebleeds, persistent hiccups, prolonged bleeding, seizures, shortness of breath, swelling due to the body keeping in fluid (may be seen in the legs, ankles, and feet), urination changes, such as little or no urine, excessive urination at night, or urination that stops completely.

During physical examination possible to find [10–11] asterixis and myoclonus, pericardial or pleural rub, peripheral edema (if volume overload is present), pulmonary rales (if volume

overload is present), elevated right atrial pressure (if volume overload is present).

COMPLICATIONS

The most common complication of AKI is an infection of the urinary tract with the further development of chronic pyelonephritis and outcome in CKD [12].

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A patient history and physical examination, with an emphasis on assessing the patient's volume status, are crucial for determining the cause of acute kidney injury (table 3, 4) [10, 13–14].

The history should identify use of nephrotoxic medications or systemic illnesses that might cause poor renal perfusion or directly impair renal function. Physical examination should assess intravascular volume status and any skin rashes indicative of systemic illness.

Patients with AKI may suffer from excessive bleeding, because of uremia induced platelet dysfunction and coagulopathies (for example, sepsis associated disseminated intravascular coagulation).

AKI is associated with numerous metabolic disturbances but energy expenditure is not increased significantly.

Table 3

Historical and physical examination findings in patients with different types of AKI [1]

Type of AKI	History findings	Physical examination findings
Prerenal	Volume loss (e.g., history of vomiting, diarrhea, diuretic overuse, hemorrhage, burns)	Weight loss, orthostatic hypotension and tachycardia
	Thirst and reduced fluid intake	Poor skin turgor
	Cardiac disease	Dilated neck veins, S_3 heart sound, pulmonary rales, peripheral edema
	Liver disease	Ascites, caput medusa, spider angiomas
Intrinsic renal		
Acute tubular necrosis	History of receiving nephrotoxic medications (including over-the-counter, illicit, and herbal), hypotension, trauma or myalgias suggesting rhabdomyolysis, recent exposure to radiographic contrast agents	Muscle tenderness, compartment syndrome, assessment of volume status
Glomerular	Lupus, systemic sclerosis, rash, arthritis, uveitis, weight loss, fatigue, hepatitis C virus infection, human immunodeficiency virus infection, hematuria, foamy urine, cough, sinusitis, hemoptysis	Periorbital, sacral, and lower-extremity edema; rash; oral/nasal ulcers
Interstitial	Medication use (e.g., antibiotics, proton pump inhibitors), rash, arthralgias, fever, infectious illness	Fever, drug-related rash
Vascular	Nephrotic syndrome, trauma, flank pain, anticoagulation (atheroembolic disease), vessel catheterization or vascular surgery	Livedo reticularis, funduscopic examination (showing malignant hypertension), abdominal bruits
Postrenal	Urinary urgency or hesitancy, gross hematuria, polyuria, stones, medications, cancer	Bladder distention, pelvic mass, prostate enlargement

Table 4

Probable etiologies of AKI based on the physical examination [1]

Physical examination	Probable causes of acute renal failure
Temperature	Possible infection
Blood pressure	Hypertension: nephrotic syndrome or malignant hypertension
	Hypotension: volume depletion or sepsis
Weight loss or gain	Hypovolemia or hypervolemia
Mouth	Dehydration
Jugular veins and axillae (perspiration)	Hypovolemia or hypervolemia
Pulmonary system	Signs of congestive heart failure
Heart	New murmur of endocarditis or signs of congestive heart failure
Abdomen	Bladder distention suggesting urethral obstruction
Pelvis	Pelvic mass
Rectum	Prostate enlargement
Skin	Rash of interstitial nephritis, purpura of microvascular disease, livedo reticularis suggestive of atheroembolic disease, or splinter hemorrhages or Osler's nodes of endocarditis

The initial laboratory evaluation should include [1–2, 4] urinalysis, complete blood count, and measurement of SCr level and fractional excretion of sodium (FE_{Na}) (table 5). Imaging studies can help rule out obstruction.

SCr level. It is important to compare the patient's current SCr level with previous levels to determine the duration and acuity of the disease. The definition of acute kidney injury indicates that a rise in creatinine has occurred within 48 hours, although in the outpatient setting, it may be hard to ascertain when the rise actually happened. A high SCr level in a patient with a previously normal documented level suggests an acute process, whereas a rise over weeks to months represents a subacute or chronic process.

Urinalysis. Urinalysis is the most important noninvasive test in the initial workup of acute kidney injury. Findings on urinalysis guide the differential diagnosis and direct further workup.

Complete blood count. The presence of acute hemolytic anemia with the peripheral smear showing schistocytes in the setting of acute kidney injury should raise the possibility of hemolytic uremic syndrome or thrombotic thrombocytopenic purpura.

Urine electrolytes. In patients with oliguria, measurement of FE_{Na} is helpful in distinguishing prerenal from intrinsic renal causes of acute kidney injury. FE_{Na} is defined by formula

$$FE_{Na} = 100 \times \frac{urinary\ sodium \times serum\ creatinine}{serum\ sodium \times urinary\ creatinine}.$$

A value less than 1 percent indicates a prerenal cause of acute kidney injury, whereas a value greater than 2 percent indicates an intrinsic renal cause. In patients on diuretic therapy, however, a FE_{Na} higher than 1 percent may be caused by natriuresis induced by the diuretic, and is a less reliable measure of a prerenal state. In such cases, fractional excretion of urea may be helpful, with values less than 35 percent indicating a prerenal cause. FE_{Na} values less than 1 percent are not specific for prerenal causes of acute kidney injury because these values can occur in other conditions, such as contrast nephropathy, rhabdomyolysis, acute glomerulonephritis, and urinary tract obstruction.

Imaging studies. Renal ultrasonography should be performed in most patients with acute kidney injury, particularly in older men, to rule out obstruction (i.e., a postrenal cause). The presence of postvoid residual urine greater than 100 mL (determined by a bladder scan or via urethral catheterization if bladder scan is unavailable) suggests postrenal acute kidney injury and requires renal ultrasonography to detect hydronephrosis or outlet obstruction. To diagnose extrarenal causes of obstruction (e.g., pelvic tumors), other imaging modalities, such as computed tomography or magnetic resonance imaging, may be required.

Renal biopsy. Renal biopsy is reserved for patients in whom prerenal and postrenal causes of acute kidney injury have been excluded and the cause of intrinsic renal injury is unclear. Renal biopsy is particularly important when clinical assessment and laboratory investigations suggest a diagnosis that requires confirmation before disease-specific therapy (e.g., immunosuppressive medications) is instituted. Renal biopsy may need to be performed urgently in patients with oliguria who have rapidly worsening acute kidney injury, hematuria, and red blood cell casts. In this setting, in addition to indicating a diagnosis that requires immunosuppressive therapy, the biopsy may support the initiation of special therapies, such as plasmapheresis if Goodpasture's syndrome is present.

Table 5

Diagnostic test results and corresponding diseases in patients with AKI [1]

Test result	When to order	Associated diseases/conditions
Elevated antineutrophil cytoplasmic antibody, antiglomerular basement membrane antibody	Suspected acute glomerulonephritis, pulmonary renal syndromes	Vasculitis, Goodpasture's syndrome
Elevated antistreptolysin O titer	Recent infection and clinical picture of acute glomerulonephritis	Poststreptococcal glomerulonephritis
Elevated creatine kinase level, elevated myoglobin level, dipstick positive for blood but negative for red blood cells	Recent trauma, muscle injury	Rhabdomyolysis
Elevated prostate-specific antigen level	Older men with symptoms suggestive of urinary obstruction	Prostate hypertrophy, prostate cancer
Elevated uric acid level	History of rapidly proliferating tumors, recent chemotherapy	Malignancy, tumor lysis syndrome
Eosinophiluria	Fever, rash	Allergic interstitial nephritis
Evidence of hemolysis (schistocytes on peripheral smear, decreased haptoglobin level, elevated indirect bilirubin level, elevated lactate dehydrogenase level)	Fever, anemia, thrombocytopenia, neurologic signs	Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, systemic lupus erythematosus, other autoimmune diseases
Hydronephrosis on renal ultrasonography	Suspected obstruction	Malignancy, prostate hypertrophy, uterine fibroids, nephrolithiasis, ureterolithiasis
Increased anion gap with increased osmolar gap*	Suspected poisoning, unresponsive patient	Ethylene glycol or methanol poisoning
Low complement level	Suspected acute glomerulonephritis	Systemic lupus erythematosus, endocarditis, postinfectious glomerulonephritis
Monoclonal spike on serum protein electrophoresis	Anemia, proteinuria, acute kidney injury in older patients	Multiple myeloma
Positive antinuclear antibody, double-stranded DNA antibody	Proteinuria, skin rash, arthritis	Autoimmune diseases, systemic lupus erythematosus
Positive blood cultures	Intravenous drug use, recent infection, new cardiac murmur	Endocarditis
Positive HIV test	Risk factors for HIV infection	HIV nephropathy

Differentials to consider in AKI include abdominal aneurysm, alcohol toxicity, alcoholic ketoacidosis, chronic renal failure, dehydration, diabetic ketoacidosis, gastrointestinal (GI) bleeding, heart failure, metabolic acidosis, obstructive uropathy, protein overloading, renal

calculi, sickle cell anemia, steroid use, urinary obstruction, urinary tract infection.

Changes in UO generally correlate poorly with changes in the GFR. The identification of anuria, oliguria, and nonoliguria may be useful in the differential diagnosis of AKI, as follows:

- anuria (UO less than 100 mL/day) – urinary tract obstruction, renal artery obstruction, rapidly progressive glomerulonephritis, bilateral diffuse renal cortical necrosis;
- oliguria (UO from 100 to 400 mL/day) – prerenal failure, hepatorenal syndrome;
- nonoliguria (UO more than 400 mL/day) – acute interstitial nephritis, acute glomerulonephritis, partial obstructive nephropathy, nephrotoxic and ischemic ATN, radiocontrast-induced AKI, and rhabdomyolysis.

TREATMENT

Lifestyle [1–2]. Patients with acute kidney injury generally should be hospitalized unless the condition is mild and clearly resulting from an easily reversible cause.

All medications that may potentially affect renal function by direct toxicity or by hemodynamic mechanisms should be discontinued, if possible. For example, metformin should not be given to patients with diabetes mellitus who develop acute kidney injury. Dietary intake of potassium should be restricted.

Risk Assessment [1–2]. All patients, both on admission and during their hospital stay should be assessed regularly for their risk of developing AKI.

Patients with CKD [8]. Patients in the community with CKD (eGFR < 60 mL/min/1,73m2) and patients with normal renal function who are treated with ACEi or ARB are at increased risk of AKI if they develop an illness associated with hypovolemia and hypertension. This provides instructions for temporary cessation of certain medications, which may in this setting, induce, exacerbate and complicate AKI (diuretics, ACEi/ARBs, metformin, NSAIDs). Patients with high BP are advised to follow a DASH (Dietary Approaches to Stop Hypertension) diet, which has proven efficacy. Modification of a DASH diet will be required in CKD patients because of its high potassium and phosphate contents.

Medication [15–18]. Optimal management of acute kidney injury requires close collaboration among primary care physicians, nephrologists, hospitalists, and other subspecialists participating in the care of the patient. After acute kidney injury is established, management is primarily supportive.

Optimise intra-vascular fluid volume. Volume status should be carefully assessed and an attempt should be made to categories the patient into one of three states: hypovolemic, euvolaemic or hypervolaemic. Hartmann's solution or 0.9 % sodium chloride solution should be used. Hartmann's solution contains a small amount of potassium (5 mmol/L) and should be avoided in patients with significant hyperkalemia (potassium ≥ 6 mmol/L). Large volumes of 0.9 % sodium chloride can provoke a hyperchloraemic metabolic acidosis.

The physiologic goals are: 1) return of mean arterial blood pressure (MAP) to ≥ 65 mm Hg (MAP is derived from a patient's systolic blood pressure (SBP) and diastolic blood pressure (DBP); since MAP is a product of cardiac output (CO) and systemic vascular resistance (SVR): [MAP = CO × SVR]. Another way to calculate MAP: double the diastolic blood pressure and add the sum to the systolic blood pressure, then divide by 3); 2) central venous pressure between 8–12 mm Hg; 3) improvement in blood lactate levels; 4) central venous oxygen saturation (ScvO2) > 70 %; and 5) a urine output of ≥ 0,5 ml/kg/h.

Failure of the patient to maintain an effective blood pressure following this regime should raise the possibility of underlying sepsis or significant ongoing losses.

Reduction in plasma potassium concentration. Treatment with calcium is a temporizing measure «buying time» while measures are started to reduce the serum potassium through increasing cellular uptake. Various options exist:

Insulin with glucose. Insulin acts rapidly to indirectly activate the cell membrane Na+/K+−ATPase and thus increase cellular potassium uptake, probably via activation of Na+/H+ channels and an increase in intracellular [Na+]. The addition of glucose to the insulin bolus is necessary to prevent hypoglycemia. Ten units of fast acting soluble insulin should be added to 50 ml of 50 % dextrose and infused over 10–20 minutes. A reduction in $[K+]_p$ is seen after 20–30 minutes. Insulin alone can be given to hyperglycemic patients (blood glucose > 14 mmol/l) as the infusion of further glucose can worsen

hyperkalemia secondary to its osmotic effect. This, plus the need for rapidly attained supraphysiological insulin levels to produce a hypokalemic effect, explains the inadequacy of glucose infusion alone as treatment for hyperkalemia in non-diabetic patients. Whether insulin and dextrose, or insulin alone, is used, the blood glucose should be monitored carefully for at least six hours. Hypoglycemia occurred in up to 75 % of patients in some studies, and was generally associated with higher insulin or lower glucose doses.

β_2 adrenergic agonists. Salbutamol binds to β_2 receptors and through cytosolic second messengers activates the Na+/K+−ATPase, thus promoting cellular potassium uptake. Nebulized and intravenous salbutamol produce a similar effect to insulin, but at higher doses than used for bronchospasm (10–20 mg via nebulizer, or 0.5 mg intravenously). Up to 40 % of patients do not respond. Tachycardia is common especially after intravenous administration. The method should not be used in patients taking β blockers or in those with a high risk of cardiac side effects. For these reasons, insulin is the agent of choice to reduce $[K+]_p$, but salbutamol may be preferably in certain circumstances, especially pediatric patients, and combined therapy with insulin and dextrose plus salbutamol may be more effective than either treatment alone.

Sodium bicarbonate. The infusion of sodium bicarbonate has little immediate effect on hyperkalemia, but may be used to correct acidosis (see later).

Dopamine. The use of low dose (1–3 μg/kg/min) dopamine has been advocated to increase renal perfusion in critically ill patients. Recent studies, including a large randomized controlled trial, have shown it to lack efficacy on renal outcome or overall mortality. Use of dopamine may also reduce splanchnic perfusion, depress respiration, suppress anterior pituitary hormone release and function, and worsen renal function in hypovolemic or normovolaemic patients. Its routine use in AKI is not currently justifiable.

Diuretics. There is a theoretical rationale for the use of loop diuretics in AKI – inhibition of the Na+/K+/2Cl − pump in the thick ascending limb of the loop of Henle, with subsequent decrease in Na+/K+−ATPase activity, should reduce the oxygen requirements of these cells, and thus their susceptibility to ischemic damage. There are scarce clinical data to support this, and recent studies have either correlated the use of diuretics with increased mortality, or shown no benefit. It seems reasonable to use diuretics only in adequately resuscitated – but oliguric – patients, at a dose suitable to the degree of renal impairment (250 mg furosemide intravenously over one hour is a standard regimen), and to stop diuretic treatment if oliguria persists. Converting oliguric to no oliguric renal failure may help with fluid and electrolyte management, but does not seem to affect eventual need for dialysis or overall mortality, and should not delay the start of renal replacement therapy when otherwise indicated. There are no data to support the use of mannitol.

Additional supportive therapy due to the cause of AKI. Supportive therapies (e.g., antibiotics, mechanical ventilation, glycemic control, anemia management) should be pursued based on standard management practices. In patients with rapidly progressive glomerulonephritis, treatment with pulse steroids, cytotoxic therapy, or a combination may be considered, often after confirmation of the diagnosis by kidney biopsy. In some patients, the metabolic consequences of acute kidney injury cannot be adequately controlled with conservative management, and renal replacement therapy will be required.

Relief of obstruction. It is important to relieve urinary tract obstruction promptly. Bladder outflow obstruction can be relieved by passage of a urethral catheter – which should be considered in all patients with AKI to accurately measure urine output – but relief of upper tract obstruction may require either antegrade (percutaneous nephrostomy) or retrograde (cystoscopy and retrograde ureteral catheterization) approaches. Urethral catheterization can be performed immediately, but other techniques require planning. Close collaboration between nephrological, urological, and radiological services is required, and in many cases renal replacement therapy may be necessary before relief of obstruction can be achieved.

A significant diuresis can complicate relief of complete urinary tract obstruction, through both appropriate (excretion of retained solute and water) and inappropriate mechanisms (tubular concentrating dysfunction). Severe polyuria is rare and requires careful management to prevent volume depletion and possible pre-renal impairment, or overzealous

fluid resuscitation and a further drive to diuresis.

Complications of treatment [19–20]. The treatment of urinary obstruction is associated with a variety of complications.

Gross hematuria (a large amount of bloody urine) can occur when the catheter is placed in patients who have bladder outlet obstruction. This happens because the sudden decrease in pressure causes the bladder veins to bleed. Unfortunately, slow decompression of the bladder does not prevent hematuria.

Reflex hypotension (low blood pressure) is a rare complication that can occur if a patient experiences sudden stimulation of the vagus nerve during catheter insertion.

Postobstructive diuresis is high urine output that may, initially, exceed 500 to 1000 milliliters per hour. This frequently occurs after an obstruction is removed. The renal tubules typically cannot reabsorb water and electrolytes in a normal manner after having been obstructed for a period of time. Rarely, a person suffers severe dehydration and requires large amounts of intravenous fluids.

Obstruction may result in an impaired distal tubular response to aldosterone, resulting in a paradoxical hyperkalemic acidosis when relieved. This usually resolves spontaneously. A small number will have permanent tubular damage and a persistent salt wasting nephropathy.

Renal replacement therapy (RRT) [21–23]. The initiation of RRT in patients with AKI prevents uremia and immediate death from the adverse complications of renal failure.

Multiple modalities of RRT are currently available. These include intermittent hemodialysis (IHD), continuous renal replacement therapies (CRRT), and hybrid therapies, such as sustained low-efficiency dialysis (SLED).

Indications for dialysis in AKI are refractory fluid overload; hyperkalemia (plasma potassium concentration > 6,5 me/l) or rapidly rising potassium levels; metabolic acidosis (pH less than 7,1); signs of uremia e.g. pericarditis and decline in mental state; certain alcohol and drug intoxications.

Timing of initiation of dialysis. Studies published during the 1960s and 1970s suggested that improved outcomes were associated with the initiation of hemodialysis when bun reached exceeded 150 to 200 mg/dl. More recent studies have evaluated the relationship between the timing of RRT initiation and clinical outcomes. Several non-randomized studies have reported that improved outcomes, including survival, are associated with early versus late initiation of RRT. It has been suggested that initiation of RRT dialysis prior to the development of overt symptoms and signs of renal failure due to AKI improves the outcome.

Discontinuation of RRT therapy. RRT is usually continued until the patient manifests evidence of recovery of kidney function: increase in urine output; a progressive decline in serum creatinine concentration after initial attainment of stable values (assessed daily during CRRT or predialysis in patients managed with IHD) despite a constant dose of renal support; measurement of creatinine clearance e.g. on six-hour timed urine collections obtained when the urine output exceeded 30 ml/hour based on an average serum creatinine at the beginning and end of the timed collection.

PROGNOSIS

Patients with acute kidney injury are more likely to develop chronic kidney disease in the future. They are also at higher risk of end-stage renal disease and premature death. Patients who have an episode of acute kidney injury should be monitored for the development or worsening of chronic kidney disease [1–2].

PREVENTION

Because of the morbidity and mortality associated with AKI, it is important to identify patients who are at high risk of developing this type of injury and to implement preventive strategies (table 6) [1–2]. Those at highest risk include adults older than 75 years; persons with diabetes or preexisting CKD; persons with medical problems such as cardiac failure, liver failure, or sepsis; and those who are exposed to contrast agents or who are undergoing cardiac surgery.

Table 6

Risk factors of AKI and preventive strategies [1]

Risk factors	Preventive strategies
Cancer chemotherapy with risk of tumor lysis syndrome	Hydration and allopurinol administration a few days before chemotherapy initiation in patients at high risk of tumor lysis syndrome to prevent uric acid nephropathy
Exposure to nephrotoxic medications	Avoid nephrotoxic medications if possible
	Measure and follow drug levels if available
	Use appropriate dosing, intervals, and duration of therapy
Exposure to radiographic contrast agents	Avoid use of intravenous contrast media when risks outweigh benefits
	If use of contrast media is essential, use isoosmolar or lowosmolar contrast agent with lowest volume possible
	Optimize volume status before administration of contrast media; use of isotonic normal saline or sodium bicarbonate may be considered in high-risk patients who are not at risk of volume overload
	Use of N-acetylcysteine may be considered
Hemodynamic instability	Optimal fluid resuscitation; although there is no consensus, MAP goal of > 65 mm Hg is widely used; isotonic solutions (e.g., normal saline) are preferred over hyperoncotic solutions (e.g., albumin)
	Vasopressors are recommended for persistent hypotension (MAP < 65 mm Hg) despite fluid resuscitation; choice of vasoactive agent should be tailored to patients' needs
	Dopamine is not recommended
Hepatic failure	Avoid hypotension and gastrointestinal bleeding
	Early recognition and treatment of spontaneous bacterial peritonitis; use albumin, 1,5 g per kg at diagnosis and 1 g per kg at 48 hours
	Early recognition and management of ascites
	Albumin infusion during large volume paracentesis
	Avoid nephrotoxic medications
Rhabdomyolysis	Maintain adequate hydration
	Alkalization of the urine with intravenous sodium bicarbonate in select patients (normal calcium, bicarbonate less than 30 mEq per L or 30 mmol per l, and arterial pH less than 7,5)
Undergoing surgery	Adequate volume resuscitation/prevention of hypotension, sepsis, optimizing cardiac function Consider holding renin-angiotensin system antagonists preoperatively

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