

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

"Approved"
at the meeting of internal
medicine №1 department
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**GUIDELINES
FOR STUDENTS
INDEPENDENT WORK
IN THE PRACTICAL CLASSES PREPARING**

<i>Academic discipline</i>	Internal medicine
<i>Module</i>	Emergency conditions in clinic of Internal Medicine
<i>Content module</i>	Emergency conditions in clinic of Internal Medicine
<i>Study subject</i>	Curation of the patient with oligouria and anuria
<i>Course</i>	VI
<i>Faculty</i>	of foreign students training

Poltava 2016.

1. Urgency of the theme:

Acute kidney injury (AKI) has now replaced the term acute renal failure and an universal definition and staging system has been proposed to allow earlier detection and management of AKI. The new terminology enables healthcare professionals to consider the disease as a spectrum of injury. This spectrum extends from less severe forms of injury to more advanced injury when acute kidney failure may require renal replacement therapy (RRT). Clinically AKI is characterised by a rapid reduction in kidney function resulting in a failure to maintain fluid, electrolyte and acid-base homeostasis. There have previously been many different definitions of AKI used in the literature which has made it difficult to determine the epidemiology and outcomes of AKI. Over recent years there has been increasing recognition that relatively small rises in serum creatinine in a variety of clinical settings are associated with worse outcomes.

2. The aims of the training course:

To Know:

1. Classification (etiologic and on phases) of acute renal failure.
2. Symptoms and clinical signs of acute renal failure in initiating phase.
3. Symptoms and clinical signs of acute renal failure in oligoanuric phase.
4. Differential diagnosis of acute renal failure and acute anuria.
5. Treatment of prerenal acute renal failure.
6. Treatment of renal acute renal failure.
7. Treatment of postrenal acute renal failure.

To be able to:

1. Detect main clinical signs of acute renal failure using complaints and case history.
2. Define necessary quantity and sequence of patient's examination: physical, laboratory, roentgenological, endovesical.
3. Prove and formulate clinical diagnosis.
4. Make differential diagnosis,
5. Prove conservative treatment and indications for the surgical treatment.
6. To estimate the levels of urea nitrogen, creatinine, potassium and other electrolytes, uric acid, bilirubin protein in patients with different phases of acute renal failure and in the blood of normal people.

The contents of topic:

Background

Acute renal failure (ARF), or acute kidney injury (AKI), as it is now referred to in the literature, is defined as an abrupt or rapid decline in renal filtration function. This condition is usually marked by a rise in serum creatinine concentration or by azotemia (a rise in blood urea nitrogen [BUN] concentration).

However, immediately after a kidney injury, BUN or creatinine levels may be normal, and the only sign of a kidney injury may be decreased urine production. A rise in the creatinine level can result from medications (eg, cimetidine, trimethoprim) that inhibit the kidney's tubular secretion. A rise in the BUN level can occur without renal injury, resulting instead from such sources as GI or mucosal bleeding, steroid use, or protein loading, so a careful inventory must be taken before determining if a kidney injury is present.

Categories of AKI

AKI may be classified into 3 general categories, as follows:

- Prerenal - as an adaptive response to severe volume depletion and hypotension, with structurally intact nephrons
- Intrinsic - in response to cytotoxic, ischemic, or inflammatory insults to the kidney, with structural and functional damage
- Postrenal - from obstruction to the passage of urine

While this classification is useful in establishing a differential diagnosis, many pathophysiologic features are shared among the different categories.

Oliguric and nonoliguric patients with AKI

Patients who develop AKI can be oliguric or nonoliguric, have a rapid or slow rise in creatinine levels, and may have qualitative differences in urine solute concentrations and cellular content. This lack of a uniform clinical presentation reflects the variable nature of the injury.

Classifying AKI as oliguric or nonoliguric based on daily urine excretion has prognostic value.

Oliguria is defined as a daily urine volume of less than 400 mL/d and has a worse prognosis, except in prerenal failure.

Anuria is defined as a urine output of less than 100 mL/d and, if abrupt in onset, suggests bilateral obstruction or catastrophic injury to both kidneys. Stratification of renal failure along these lines helps in diagnosis and decision-making (eg, timing of dialysis) and can be an important criterion for patient response to therapy.

Cardiovascular complications

Cardiovascular complications (eg, congestive heart failure [CHF], myocardial infarction, arrhythmias, cardiac arrest) have been observed in as many as 35% of patients with AKI. Fluid overload secondary to oliguric AKI is a particular risk for elderly patients with little cardiac reserve.

Pericarditis is a relatively rare complication of AKI. When pericarditis complicates AKI, consider additional diagnoses, such as systemic lupus erythematosus (SLE) and hepatorenal syndrome.

Pulmonary complications

Pulmonary complications have been reported in approximately 54% of patients with AKI and are the single most significant risk factor for death in patients with AKI. Several diseases exist that commonly present with simultaneous pulmonary and renal involvement, including pulmonary/renal syndromes (eg, Goodpasture syndrome, Wegener granulomatosis, polyarteritis nodosa, cryoglobulinemia, sarcoidosis). Hypoxia commonly occurs during hemodialysis and can be particularly significant in the patient with pulmonary disease. This dialysis-related hypoxia is thought to occur secondary to white blood cell (WBC) lung sequestration and alveolar hypoventilation.

GI complications

GI symptoms of nausea, vomiting, and anorexia are frequent complications of AKI and represent one of the cardinal signs of uremia. GI bleeding occurs in approximately one third of patients with AKI. Most episodes are mild, but GI bleeding accounts for 3-8% of deaths in patients with AKI.

Mild hyperamylasemia commonly is seen in AKI (2-3 times controls). Elevation of baseline amylase can complicate diagnosis of pancreatitis in patients with AKI. Lipase, which commonly is not elevated in AKI, often is necessary to make the diagnosis of pancreatitis. Pancreatitis has been reported as a concurrent illness with AKI in patients with atheroemboli, vasculitis, and sepsis from ascending cholangitis.

Jaundice has been reported to complicate AKI in approximately 43% of cases. Etiologies of jaundice with AKI include hepatic congestion, blood transfusions, and sepsis.

Hepatitis occurring concurrently with AKI should prompt the differential diagnosis of common bile duct obstruction, fulminant hepatitis B, leptospirosis, acetaminophen toxicity, and *Amanita phalloides* toxin.

Infectious complications

Infections commonly complicate the course of AKI and have been reported to occur in as many as 33% of patients with AKI. Most common sites are pulmonary and urinary tracts. Infections are the leading cause of morbidity and death in patients with AKI. Various studies have reported mortality rates of 11-72% in infections complicating AKI.

Etiology

The driving force for glomerular filtration is the pressure gradient from the glomerulus to the Bowman space. Glomerular pressure is primarily dependent on renal blood flow (RBF) and is controlled by combined resistances of renal afferent and efferent arterioles. Regardless of the

cause of acute kidney injury (AKI), reductions in RBF represent a common pathologic pathway for decreasing GFR. The etiology of AKI consists of 3 main mechanisms.

- Prerenal failure - Defined by conditions with normal tubular and glomerular function; GFR is depressed by compromised renal perfusion
- Intrinsic renal failure - Includes diseases of the kidney itself, predominantly affecting the glomerulus or tubule, which are associated with release of renal afferent vasoconstrictors; ischemic renal injury is the most common cause of intrinsic renal failure.
- Postobstructive renal failure - Initially causes an increase in tubular pressure, decreasing the filtration driving force; this pressure gradient soon equalizes, and maintenance of a depressed GFR is then dependent on renal efferent vasoconstriction

Patients with chronic renal failure may also present with superimposed AKI from any of the aforementioned etiologies.

Depressed RBF eventually leads to ischemia and cell death. This may happen before frank systemic hypotension is present and is referred to as normotensive ischemic AKI. The initial ischemic insult triggers a cascade of events that includes production of oxygen free radicals, cytokines and enzymes, endothelial activation and leukocyte adhesion, activation of coagulation, and initiation of apoptosis. These events continue to cause cell injury even after restoration of RBF.

Tubular cellular damage results in disruption of tight junctions between cells, allowing back leak of glomerular filtrate and further depressing effective GFR. In addition, dying cells slough off into the tubules, forming obstructing casts, which further decrease GFR and lead to oliguria. During this period of depressed RBF, the kidneys are particularly vulnerable to further insults. This is when iatrogenic renal injury is most common. The following are common iatrogenic combinations:

- Preexisting renal disease (elderly, diabetic patients, jaundiced patients) with radiocontrast agents, aminoglycosides, atheroembolism, or cardiovascular surgery
- Angiotensin-converting enzyme (ACE) inhibitors with diuretics, small- or large-vessel renal arterial disease
- Nonsteroidal anti-inflammatory drugs (NSAIDs) with congestive heart failure (CHF), hypertension (HTN), or renal artery stenosis
- Hypovolemia with aminoglycosides, amphotericin, heme pigments, or radiologic contrast agents

Prerenal AKI

Prerenal AKI represents the most common form of kidney injury and often leads to intrinsic AKI if it is not promptly corrected. Volume loss from GI, renal, cutaneous (eg, burns), and internal or external hemorrhage can result in this syndrome. Prerenal AKI can also result from decreased renal perfusion in patients with heart failure or shock (eg, sepsis, anaphylaxis).

Special classes of medications that can induce prerenal AKI in volume-depleted states are angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which are otherwise safely tolerated and beneficial in most patients with chronic kidney disease. Arteriolar vasoconstriction leading to prerenal AKI can occur in hypercalcemic states, with the use of radiocontrast agents, NSAIDs, amphotericin, calcineurin inhibitors, norepinephrine, and other pressor agents.

The hepatorenal syndrome can also be considered a form of prerenal AKI, because functional renal failure develops from diffuse vasoconstriction in vessels supplying the kidney.

To summarize, volume depletion can be caused by the following:

- Renal losses (diuretics, polyuria)
- GI losses (vomiting, diarrhea)
- Cutaneous losses (burns, Stevens-Johnson syndrome)
- Hemorrhage
- Pancreatitis

Decreased cardiac output can be caused by the following:

- Heart failure
- Pulmonary embolus

- Acute myocardial infarction
- Severe valvular disease
- compartment syndrome (tense ascites)
- Abdominal

Systemic vasodilation can be caused by the following:

- Sepsis
- Anaphylaxis
- Anesthetics
- Drug overdose

Afferent arteriolar vasoconstriction can be caused by the following:

- Hypercalcemia
- Drugs (NSAIDs, amphotericin B, calcineurin inhibitors, norepinephrine, radiocontrast agents)
- Hepatorenal syndrome

Diseases that compromise renal perfusion include the following:

- Decreased effective arterial blood volume - Hypovolemia, CHF, liver failure, sepsis
- Renal arterial disease - Renal arterial stenosis (atherosclerotic, fibromuscular dysplasia), embolic disease (septic, cholesterol)

Intrinsic AKI

Structural injury in the kidney is the hallmark of intrinsic AKI, and the most common form is ATN, either ischemic or cytotoxic. Frank necrosis is not prominent in most human cases of ATN and tends to be patchy. Less obvious injury includes loss of brush borders, flattening of the epithelium, detachment of cells, formation of intratubular casts, and dilatation of the lumen (see the images below). Although these changes are observed predominantly in proximal tubules, injury to the distal nephron can also be demonstrated. In addition, the distal nephron may become obstructed by desquamated cells and cellular debris.

To summarize, vascular (large and small vessel) causes of intrinsic AKI include the following:

- Renal artery obstruction (thrombosis, emboli, dissection, vasculitis)
- Renal vein obstruction (thrombosis)
- Microangiopathy (TTP, HUS, disseminated intravascular coagulation [DIC], preeclampsia)
- Malignant hypertension
- Scleroderma renal crisis
- Transplant rejection
- Atheroembolic disease

Glomerular causes include the following:

- Anti-glomerular basement membrane (GBM) disease (Goodpasture syndrome)
- Anti-neutrophil cytoplasmic antibody-associated glomerulonephritis (ANCA-associated GN) (Wegener granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis)
- Immune complex GN (lupus, postinfectious, cryoglobulinemia, primary membranoproliferative glomerulonephritis)

Tubular etiologies may include ischemia or cytotoxicity. Cytotoxic etiologies include the following:

- Heme pigment (rhabdomyolysis, intravascular hemolysis)
- Crystals (tumor lysis syndrome, seizures, ethylene glycol poisoning, megadose vitamin C, acyclovir, indinavir, methotrexate)
- Drugs (aminoglycosides, lithium, amphotericin B, pentamidine, cisplatin, ifosfamide, radiocontrast agents)

Interstitial causes include the following:

- Drugs (penicillins, cephalosporins, NSAIDs, proton-pump inhibitors, allopurinol, rifampin, indinavir, mesalamine, sulfonamides)
- Infection (pyelonephritis, viral nephritides)
- Systemic disease (Sjögren syndrome, sarcoid, lupus, lymphoma, leukemia, tubulonephritis, uveitis)

Postrenal AKI

Mechanical obstruction of the urinary collecting system, including the renal pelvis, ureters, bladder, or urethra, results in obstructive uropathy or postrenal AKI.

If the site of obstruction is unilateral, then a rise in the serum creatinine level may not be apparent due to contralateral renal function. Although the serum creatinine level may remain low with unilateral obstruction, a significant loss of GFR occurs, and patients with partial obstruction may develop progressive loss of GFR if the obstruction is not relieved. Causes of obstruction include stone disease; stricture; and intraluminal, extraluminal, or intramural tumors.

Bilateral obstruction is usually a result of prostate enlargement or tumors in men and urologic or gynecologic tumors in women.

Patients who develop anuria typically have obstruction at the level of the bladder or downstream to it.

To summarize, causes of postrenal AKI include the following:

- Ureteric obstruction (stone disease, tumor, fibrosis, ligation during pelvic surgery)
 - Bladder neck obstruction (benign prostatic hypertrophy [BPH], cancer of the prostate [CA prostate or prostatic CA], neurogenic bladder, tricyclic antidepressants, ganglion blockers, bladder tumor, stone disease, hemorrhage/clot)
 - Urethral obstruction (strictures, tumor, phimosis)
 - Intra-abdominal hypertension (tense ascites)
 - Renal vein thrombosis
- Diseases causing urinary obstruction from the level of the renal tubules to the urethra include the following:
- Tubular obstruction from crystals (eg, uric acid, calcium oxalate, acyclovir, sulfonamide, methotrexate, myeloma light chains)
 - Ureteral obstruction - Retroperitoneal tumor, retroperitoneal fibrosis (methysergide, propranolol, hydralazine), urolithiasis, or papillary necrosis
 - Urethral obstruction - Benign prostatic hypertrophy; prostate, cervical, bladder, colorectal carcinoma; bladder hematoma; bladder stone; obstructed Foley catheter; neurogenic bladder; or stricture

The patient's age has significant implications for the differential diagnosis of AKI.

Newborns and infants

In newborns and infants, causes of prerenal AKI include the following:

- Perinatal hemorrhage - Twin-twin transfusion, complications of amniocentesis, abruptio placenta, birth trauma
- Neonatal hemorrhage - Severe intraventricular hemorrhage, adrenal hemorrhage
- Perinatal asphyxia and hyaline membrane disease (newborn respiratory distress syndrome) - Both may result in preferential blood shunting away from the kidneys (ie, prerenal) to central circulation.

Causes of Intrinsic AKI include the following:

- ATN - Can occur in the setting of perinatal asphyxia; ATN also has been observed secondary to medications (eg, aminoglycosides, NSAIDs) given to the mother perinatally
- ACEIs - Can traverse the placenta, resulting in a hemodynamically mediated form of AKI
- Acute glomerulonephritis - Rare and most commonly the result of maternal-fetal transfer of antibodies against the neonate's glomeruli or transfer of chronic infections (syphilis, cytomegalovirus) associated with acute glomerulonephritis

Congenital malformations of urinary collecting systems should be suspected in cases of postrenal AKI.

Children

Prerenal AKI can be caused by the following:

- Gastroenteritis - The most common cause of hypovolemia in children
- Congenital and acquired heart diseases - Also important causes of decreased renal perfusion in this age group.

Intrinsic AKI

- Acute poststreptococcal glomerulonephritis - Should be considered in any child who presents with HTN, edema, hematuria, and renal failure.
- HUS - Often is cited as the most common cause of AKI in children.

The most common form of HUS is associated with a diarrheal prodrome caused by *Escherichia coli* O157:H7. These children usually present with microangiopathic anemia, thrombocytopenia, colitis, mental status changes, and renal failure.

Patient Education

Educating patients about the nephrotoxic potential of common therapeutic agents is always helpful. A good example is NSAIDs; most patients are unaware of their nephrotoxicity, and their universal availability makes them a constant concern.

History

A detailed and accurate history is crucial to the diagnosis of the type of acute kidney injury (AKI) that a patient has and to determining the disease's subsequent treatment.

Distinguishing AKI from chronic renal failure is important, yet making the distinction can be difficult. A history of chronic symptoms—fatigue, weight loss, anorexia, nocturia, and pruritus—suggests chronic renal failure.

Take note of the following findings during the physical examination:

- Hypotension
- Volume contraction
- Congestive heart failure
- Nephrotoxic drug ingestion
- History of trauma or unaccustomed exertion
- Blood loss or transfusions
- Evidence of connective tissue disorders or autoimmune diseases
- Exposure to toxic substances, such as ethyl alcohol or ethylene glycol
- Exposure to mercury vapors, lead, cadmium, or other heavy metals, which can be encountered in welders and miners

People with the following comorbid conditions are at a higher risk for developing AKI:

- Hypertension
- Congestive cardiac failure
- Diabetes
- Multiple myeloma
- Chronic infection
- Myeloproliferative disorder

Urine output history can be useful. Oliguria generally favors AKI. Abrupt anuria suggests acute urinary obstruction, acute and severe glomerulonephritis, or embolic renal artery occlusion. A gradually diminishing urine output may indicate a urethral stricture or bladder outlet obstruction due to prostate enlargement.

Because of a decrease in functioning nephrons, even a trivial nephrotoxic insult may cause AKI to be superimposed on chronic renal insufficiency.

Acute kidney injury (AKI) has a long differential diagnosis. History can help classify the pathophysiology of AKI as prerenal, intrinsic renal, or postrenal failure, and it may suggest some specific etiologies.

Prerenal failure

Patients commonly present with symptoms related to hypovolemia, including thirst, decreased urine output, dizziness, and orthostatic hypotension.

Elders with vague mental status change are commonly found to have prerenal or normotensive ischemic AKI.

Ask about volume loss from vomiting, diarrhea, sweating, polyuria, or hemorrhage.

Patients with advanced cardiac failure leading to depressed renal perfusion may present with orthopnea and paroxysmal nocturnal dyspnea.

Insensible fluid losses can result in severe hypovolemia in patients with restricted fluid access and should be suspected in elderly patients and in comatose or sedated patients.

Intrinsic renal failure

Patients can be divided into those with glomerular etiologies and those with tubular etiologies of AKI.

Nephritic syndrome of hematuria, edema, and HTN indicates a glomerular etiology of AKI.

Query about prior throat or skin infections.

ATN should be suspected in any patient presenting after a period of hypotension secondary to cardiac arrest, hemorrhage, sepsis, drug overdose, or surgery.

A careful search for exposure to nephrotoxins should include a detailed list of all current medications and any recent radiologic examinations (ie, exposure to radiologic contrast agents). Pigment-induced AKI should be suspected in patients with possible rhabdomyolysis (muscular pain, recent coma, seizure, intoxication, excessive exercise, limb ischemia) or hemolysis (recent blood transfusion).

Allergic interstitial nephritis should be suspected with fevers, rash, arthralgias, and exposure to certain medications, including NSAIDs and antibiotics.

Postrenal failure

Postrenal failure usually occurs in older men with prostatic obstruction and symptoms of urgency, frequency, and hesitancy. Patients may present with asymptomatic, high-grade urinary obstruction because of the chronicity of their symptoms.

A history of prior gynecologic surgery or abdominopelvic malignancy often can be helpful in providing clues to the level of obstruction.

Flank pain and hematuria should raise a concern about renal calculi or papillary necrosis as the source of urinary obstruction.

Use of acyclovir, methotrexate, triamterene, indinavir, or sulfonamides implies the possibility of tubular obstruction by crystals of these medications.

Physical Examination

Obtaining a thorough physical examination is extremely important when collecting evidence about the etiology of acute kidney injury (AKI).

Skin

Skin examination may reveal the following:

- Livido reticularis, digital ischemia, butterfly rash, palpable purpura - Systemic vasculitis
- Maculopapular rash - Allergic interstitial nephritis
- Track marks (ie, intravenous drug abuse) - Endocarditis

Petechiae, purpura, ecchymosis, and livedo reticularis provide clues to inflammatory and vascular causes of AKI.

Infectious diseases, TTP, DIC, and embolic phenomena can produce typical cutaneous changes.

Eyes

Eye examination may reveal the following:

- Keratitis, iritis, uveitis, dry conjunctivae - Autoimmune vasculitis
- Jaundice - Liver diseases
- Band keratopathy (ie, hypercalcemia) - Multiple myeloma
- Signs of diabetes mellitus
- Signs of hypertension
- Atheroemboli (retinopathy)

Evidence of uveitis may indicate interstitial nephritis and necrotizing vasculitis.

Ocular palsy may indicate ethylene glycol poisoning or necrotizing vasculitis.

Findings suggestive of severe hypertension, atheroembolic disease, and endocarditis may be observed on careful examination of the eyes.

Ears

Ear examination may reveal the following:

- Hearing loss - Alport disease and aminoglycoside toxicity
- Mucosal or cartilaginous ulcerations - Wegener granulomatosis

Cardiovascular system

Cardiovascular examination may reveal the following:

- Irregular rhythms (ie, atrial fibrillation) - Thromboemboli
- Murmurs - Endocarditis
- Increased jugulovenous distention, rales, S₃ - CHF

The most important part of the physical examination is the assessment of cardiovascular and volume status.

The physical examination must include pulse rate and blood pressure recordings measured in the supine position and the standing position; close inspection of the jugular venous pulse; careful examination of the heart, lungs, skin turgor, and mucous membranes; and assessment for the presence of peripheral edema.

In hospitalized patients, accurate daily records of fluid intake and urine output and daily measurements of patient weight are important. Hypovolemia leads to hypotension; however, hypotension may not necessarily indicate hypovolemia.

Severe CHF may also cause hypotension. Although patients with CHF may have low blood pressure, volume expansion is present and effective renal perfusion is poor, which can result in AKI.

Severe hypertension with renal failure suggests renovascular disease, glomerulonephritis, vasculitis, or atheroembolic disease.

Abdomen

Abdominal examination may reveal the following:

- Pulsatile mass or bruit - Atheroemboli
- Abdominal or costovertebral angle tenderness - Nephrolithiasis, papillary necrosis, renal artery thrombosis, renal vein thrombosis
- Pelvic, rectal masses; prostatic hypertrophy; distended bladder – Urinary obstruction
- Limb ischemia, edema - Rhabdomyolysis

Abdominal examination findings can be useful to help detect obstruction at the bladder outlet as the cause of renal failure, which may be due to cancer or an enlarged prostate.

The presence of tense ascites can indicate elevated intra-abdominal pressure that can retard renal venous return and result in AKI.

The presence of an epigastric bruit suggests renal vascular hypertension, which may predispose to AKI.

Pulmonary

Pulmonary examination may reveal the following:

- Rales - Goodpasture syndrome, Wegener granulomatosis
- Hemoptysis - Wegener granulomatosis

Diagnostic Considerations

Although acute kidney injury (AKI) potentially is a reversible condition, it can occur in patients with chronic renal failure. Every effort should be made to identify reversibility, even if improvement in renal function is marginal. The best way to identify reversibility is by tracking the rate of deterioration of renal function. If the rate of worsening renal function accelerates, the cause should be sought and treated.

Differentials to consider in AKI include the following:

- | | |
|-------------------------------------|---|
| • Alcoholic Ketoacidosis | • Pediatrics, Inborn Errors of Metabolism |
| • Anemia, Sick Cell | • Pediatrics, Sick Cell Disease |
| • Aneurysm, Abdominal | • Pediatrics, Urinary Tract Infections and Pyelonephritis |
| • CHF and Pulmonary Edema | • Renal Calculi |
| • Diabetic Ketoacidosis | • Renal Failure, Chronic and Dialysis Complications |
| • Obstructive Uropathy | • Toxicity, Alcohols |
| • GI Bleeding | • Urinary Obstruction |
| • Protein Overloading | • Urinary Tract Infection, Female |
| • Steroid Use | • Urinary Tract Infection, Male |
| • Pediatrics, Dehydration | |
| • Pediatrics, Diabetic Ketoacidosis | |

- Metabolic Acidosis

Urine output in differential diagnosis

Changes in urine output generally are poorly correlated with changes in GFR. Approximately 50-60% of all causes of AKI are nonoliguric. However, the identification of anuria, oliguria, and nonoliguria may be useful in the differential diagnosis of AKI, as follows:

- Anuria (< 100 mL/d) - Urinary tract obstruction, renal artery obstruction, rapidly progressive glomerulonephritis, bilateral diffuse renal cortical necrosis
- Oliguria (100-400 mL/d) - Prerenal failure, hepatorenal syndrome
- Nonoliguria (>400 mL/d) - Acute interstitial nephritis, acute glomerulonephritis, partial obstructive nephropathy, nephrotoxic and ischemic ATN, radiocontrast-induced AKI, and rhabdomyolysis

Differential Diagnoses

- | | |
|-----------------------------|----------------------------|
| • Acute Glomerulonephritis | • Henoch-Schonlein Purpura |
| • Acute Tubular Necrosis | • Hyperkalemia |
| • Azotemia | • Hypermagnesemia |
| • Chronic Renal Failure | • Hyponatremia |
| • Hemolytic Uremic Syndrome | • Hypertensive Emergencies |

Approach Considerations

Several laboratory tests are useful for assessing the etiology of AKI, and the findings can aid in proper management. These tests include complete blood count (CBC), serum biochemistries, urine analysis with microscopy, and urine electrolytes.

In some cases, renal imaging is useful, especially if renal failure is secondary to obstruction. The American College of Radiology recommends ultrasonography, preferably with Doppler methods, as the most appropriate imaging method in AKI.

Blood Urea Nitrogen and Serum Creatinine

Although increased levels of BUN and creatinine are the hallmarks of renal failure, the rate of rise is dependent on the degree of renal insult as well as on protein intake with respect to BUN. The ratio of BUN to creatinine is an important finding, because the ratio can exceed 20:1 in conditions in which enhanced reabsorption of urea is favored (eg, in volume contraction); this suggests prerenal acute kidney injury (AKI).

BUN may be elevated in patients with GI or mucosal bleeding, steroid treatment, or protein loading.

Assuming no renal function, the rise in BUN over 24 hours can be roughly predicted using the following formula: 24-hour protein intake in milligrams X 0.16 divided by total body water in mg/dL added to the BUN value.

Assuming no renal function, the rise in creatinine can be predicted using the following formulas:

- For males: weight in kilograms X [28 - 0.2(age)] divided by total body water in mg/dL added to the creatinine value
- For females: weight in kilograms X [23.8 - 0.17(age)] divided by total body water added to the creatinine value

As a general rule, if serum creatinine increases to more than 1.5 mg/dL/d, rhabdomyolysis must be ruled out.

CBC, Peripheral Smear, and Serology

The peripheral smear may show schistocytes in conditions such as HUS or TTP.

A finding of increased rouleaux formation suggests multiple myeloma, and the workup should be directed toward immunoelectrophoresis of serum and urine.

The presence of myoglobin or free hemoglobin (eg, pigment nephropathy), increased serum uric acid level (eg, tumor lysis syndrome), serum lactate dehydrogenase (LDH) (eg, renal infarction), and other related findings may help to further define the etiology of acute kidney injury (AKI).

Serologic tests for antinuclear antibody (ANA), ANCA, anti-GBM antibody, hepatitis, and antistreptolysin (ASO) and complement levels may help to include and exclude glomerular disease.

Although serologic tests can be informative, the costs can be prohibitive if these tests are not ordered judiciously.

Urinalysis

Findings of granular, muddy-brown casts are suggestive of tubular necrosis (see the image below). The presence of tubular cells or tubular cell casts also supports the diagnosis of ATN. Often, oxalate crystals are observed in cases of ATN.

The presence of WBCs or WBC casts suggests pyelonephritis or acute interstitial nephritis. The presence of urine eosinophils is helpful in establishing a diagnosis but is not necessary for allergic interstitial nephritis to be present.

The presence of eosinophils, as visualized with Wright stain or Hansel stain, suggests interstitial nephritis but can also be seen in urinary tract infections, glomerulonephritis, and atheroembolic disease.

The presence of uric acid crystals may represent ATN associated with uric acid nephropathy. Calcium oxalate crystals are usually present in cases of ethylene glycol poisoning.

Bladder Pressure

An intra-abdominal pressure of less than 10 mm Hg is considered normal and suggests that abdominal compartment syndrome is not the cause of AKI. Patients with an intra-abdominal pressure below 15-25 mm Hg are at risk for abdominal compartment syndrome, and those with bladder pressures above 25 mm Hg should be suspected of having AKI as a result of abdominal compartment syndrome.

Emerging Biomarkers

A number of biomarkers are being investigated to risk stratify and predict acute kidney injury (AKI) in patients at risk for the disease. The reason for this is because creatinine is a late marker for renal dysfunction and, once elevated, reflects a severe reduction in GFR. The most promising biomarker to date is urinary neutrophil gelatinase-associated lipocalin (NGAL), which has been shown to predict AKI in children undergoing cardiopulmonary bypass surgery.

Breidhardt et al studied a model that combined the markers plasma B-type natriuretic peptide and NGAL and found it to be a strong predictor of early AKI in patients with lower respiratory tract infection.

Ultrasonography

Renal ultrasonography is useful for evaluating existing renal disease and obstruction of the urinary collecting system. The degree of hydronephrosis does not necessarily correlate with the degree of obstruction. Mild hydronephrosis may be observed with complete obstruction if found early. Obtaining images of the kidneys can be technically difficult in patients who are obese or in those with abdominal distension due to ascites, gas, or retroperitoneal fluid collection.

Ultrasonographic scans or other imaging studies showing small kidneys suggest chronic renal failure.

Doppler ultrasonography

Doppler scans are useful for detecting the presence and nature of renal blood flow.

Because renal blood flow is reduced in prerenal or intrarenal AKI, test findings are of little use in the diagnosis of AKI. However, Doppler scans can be quite useful in the diagnosis of thromboembolic or renovascular disease.

Increased resistive indices can be observed in patients with hepatorenal syndrome.

Nuclear Scanning

Radionuclide imaging with technetium-99m-mercaptoacetyltriglycine ($^{99m}\text{Tc-MAG3}$), ^{99m}Tc -diethylenetriamine penta-acetic acid ($^{99m}\text{Tc-DTPA}$), or iodine-131 (^{131}I)-hippurate can be used to assess renal blood flow and tubular functions. Because of a marked delay in tubular excretion of radionuclide in prerenal disease and intrarenal disease, the value of these scans is limited.

Aortorenal Angiography

This can be helpful in establishing the diagnosis of renal vascular diseases, including renal artery stenosis, renal atheroembolic disease, and atherosclerosis with aortorenal occlusion, and in certain cases of necrotizing vasculitis (eg, polyarteritis nodosa).

Renal Biopsy

A renal biopsy can be useful in establishing the diagnosis of intrarenal causes of acute kidney injury (AKI) and can be justified if it will change management (eg, initiation of immunosuppressive medications). A renal biopsy may also be indicated when renal function does not return for a prolonged period and a prognosis is required to develop long-term management.

In as many as 40% of cases, renal biopsy results reveal an unexpected diagnosis.

Acute cellular or humoral rejection in a transplanted kidney can be definitively diagnosed only by performing a renal biopsy.

Timing of dialysis

Great controversy exists regarding the timing of dialysis. Dialysis, especially hemodialysis, may delay the recovery of patients with AKI. Most authorities prefer using biocompatible membrane dialyzers for hemodialysis.

Indications for dialysis in patients with AKI are as follows:

- Volume expansion that cannot be managed with diuretics
- Hyperkalemia refractory to medical therapy
- Correction of severe acid-base disturbances that are refractory to medical therapy
- Severe azotemia (BUN >80-100)
- Uremia

Maintenance of Volume Homeostasis and Correction of Biochemical Abnormalities

Maintenance of volume homeostasis and correction of biochemical abnormalities remain the primary goals of treatment. Furosemide can be used to correct volume overload when the patients are still responsive; this often requires high intravenous (IV) doses.

Furosemide plays no role in converting an oliguric AKI to a nonoliguric AKI or in increasing urine output when a patient is not hypervolemic.

However, the response to furosemide can be taken as a good prognostic sign. At this stage, the kidneys remain vulnerable to the toxic effects of various chemicals. All nephrotoxic agents (eg, radiocontrast agents, antibiotics with nephrotoxic potential, heavy metal preparations, cancer chemotherapeutic agents, NSAIDs) are either avoided or used with extreme caution. Similarly, all medications cleared by renal excretion should be avoided or their doses should be adjusted appropriately.

Correcting Severe Acidosis

Correcting severe acidosis with bicarbonate administration can be important as a bridge to dialysis. It cannot be overstated that the current treatment of acute kidney injury (AKI) is mainly supportive in nature and no therapeutic modalities to date have shown efficacy in treating the condition. Therapeutic agents, such as dopamine, nesiritide, fenoldopam, and mannitol, are not indicated in the management of AKI and may be harmful for the patient.

Treatment of Hyperkalemia

Hyperkalemia, which can be life-threatening, should be treated by decreasing the intake of potassium in diet or tube feeds, exchanging potassium across the gut lumen using potassium-binding resins, promoting intracellular shifts in potassium with insulin and dextrose solutions, and instituting dialysis.

Correcting Hematologic Abnormalities

Correcting hematologic abnormalities (eg, anemia, uremic platelet dysfunction) warrants appropriate measures, including transfusions and administration of desmopressin or estrogens.

Dietary Modification

Dietary modulation is an important facet of the treatment of acute kidney injury (AKI). Salt and fluid restriction becomes crucial in the management of oliguric renal failure, wherein the kidneys do not adequately excrete either toxins or fluids.

Because potassium and phosphorus are not excreted optimally in patients with AKI, blood levels of these electrolytes tend to be high. Frequent measurements are mandatory to initiate early treatment and avoid complications.

In the polyuric phase of AKI, potassium and phosphorus may be depleted, and patients require dietary supplementation and intravenous replacement.

Calculation of the nitrogen balance can be challenging, especially in the presence of volume contraction, hypercatabolic states, GI bleeding, and diarrheal disease. Critically ill patients should receive at least 1 g/kg/d protein intake but should avoid hyperalimentation, which can lead to an elevated BUN level and water loss resulting in hypernatremia.

Medication Summary

Pharmacologic treatment of AKI has been attempted on an empiric basis with varying success rates. Several promising experimental therapies in animal models are awaiting human trials.

Experimental therapies include growth factors, vasoactive peptides, adhesion molecules, endothelin inhibitors, and bioartificial kidneys. Aminophylline has also been used experimentally for prophylaxis against renal failure.

A prophylactic strategy shown to decrease the incidence of contrast nephropathy is the IV administration of fluids. Although controversy exists regarding the ideal fluid, normal saline and isotonic NaHCO₃ have proven to be effective. Normal saline solution of 1 mL/kg/h administered 12 hours before the procedure and then 12 hours after the procedure is recommended.

In patients who are at high risk for volume overload (congestive heart failure, left ventricular ejection fraction < 40%), isotonic NaHCO₃ solution should be administered before and after the procedure. It can be prepared by mixing 3 ampules of NaHCO₃ in a liter of D5W and can be given at a rate of 3 mL/kg/h for 1 hour prior to the procedure, decreasing the rate to 1 mL/kg/h during the procedure and for 6 hours afterward.

Another prophylactic agent, used with varying success, is *N*-acetylcysteine at a dosage of 1200 mg PO q12h. This is administered to high-risk patients the day before a contrast study is performed and is continued the day of the procedure. Diuretics, NSAIDs, and possibly ACEIs should be withheld near the time of the procedure.

Any protective effect of *N*-acetylcysteine would appear to be limited to patients receiving radiocontrast. A meta-analysis of patients undergoing major surgery found no evidence that *N*-acetylcysteine used perioperatively can alter mortality or renal outcomes when radiocontrast is not used.

Similarly, a review of randomized, controlled trials of other measures used to protect renal function perioperatively (eg, the administration of dopamine, diuretics, calcium-channel blockers, ACEIs, or hydration fluids) found no reliable evidence that these interventions are effective.

I. Objectives for Students' Independent Studies.

You should prepare for the practical class using the existing textbooks and lectures. Special attention should be paid to the following:

1. General clinical symptoms and syndroms of acute renal failure. In the initial phase are present symptoms of the main pathology that's the reason of acute renal failure; as a result of azotemia appear general weakness, anorexia, vomiting, malaise, disorders of consciousness, symptoms of digestive system violation, respiratory disorders, hypoproteinemia, leucocytosis, anemia, oliguria or anuria. Laboratory findings are: specific gravity of urine – is near 1010 within 48 hours of the onset of shock or poisoning; urine chloride concentration fixed between 30-40 mEq/l; serum electrolytes – sodium and: chloride concentrations may be low, normal or high depending on salt and water intake; test of retention – serum creatinine and urea nitrogen tend to rise together at a 1:10 ratio; others.

2. Etiologic classification of acute renal failure and its stages.

There are 3 types of acute renal failure: prerenal, renal and postrenal. Causes of prerenal anuria are: hypovolemia {hemorrhage, gastrointestinal losses, pancreatitis, burns, peritonitis, traumatized tissue, diuretic abuse, impaired cardiac function: congestive heart failure,

myocardial infarction, pericardial tamponade, acute pulmonary embolism, peripheral vasodilatation, bacteriemia, antihypertensive medications, increased renal vascular resistance: anesthesia, surgical operation, hepatorenal syndrome, renal vascular obstruction, bilateral: emboism, thrombosis. Renal azotemia is a result of diseases of glomeruli and small blood vessels: acute poststreptococcal glomerulonephritis, systemic lupus erythematosus, polyarteritis nodosa, serum sickness, and nephrotoxins action -exogenous (heavy metals, carbon tetrachloride, X-ray contrast media) and endogenous (calcium, uric acid, myoglobin, hemoglobin). The causes of postrenal azotemia are: obstruction of ureters, bilateral (extraureteral – tumors: cervix, prostate, endometriosis, priureteral fibrosis, ligation during pelvic operation, and intraureteral – crystals, blood clots, pyogenic debris, stones, edema, papillary necrosis), bladder's neck obstruction (prostatic hypertrophy, bladder carcinoma, bladder infection, functional – neuropathy or ganglionic blocking agents, urethral obstruction).

The clinical course of acute renal failure can be divided into 4 stages: 1) initiating or shock phase, 2) oligo-anuria – diuresis less than 300 ml, 3) normalization of diuresis, 4) recovering phase.

3. Medical tactics in patients of acute renal failure according to etiologic features and phase.

The first principle of therapy of acute renal failure is to exclude potentially reversible causes of deteriorating renal function. Once the diagnosis of acute renal failure has been established, little specific therapy is available. Dialysis for removal of toxins may occasionally be indicated. Even in the presence of acute renal failure any prerenal factors should be corrected to improve the circulation and maximize chances for early recovery of renal function. In the patients who remains oliguric despite correction of prerenal factors, it has become common clinical practice to administer either mannitol or the potent loop diuretic furosemide. The rationale for this therapy is that the combination of correction of prerenal factors and potent diuretic therapy may induce a nonoliguric state and thus attenuate the natural history of acute renal failure. Medical management of acute renal failure includes: be sure all specifically treatable causes of deteriorating renal function have been excluded, correct prerenal factors, attempt to establish a urine output, conservative (nondialytic) treatment: decrease intake of nitrogen, water, and electrolytes to match output, after drug therapy, provide adequate source of calories, clinical monitoring (frequency of vital signs determined by patient status; intake and output, body weight, inspection of wounds and intravenous sites, and physical examinations should be performed daily; biochemical monitoring (frequency of blood urea nitrogen, serum creatinine, electrolytes, and complete blood count determinations will be dictated by patient status; in general, at least daily determination will be needed; calcium, phosphorus, magnesium, and uric acid can often be determined less often; dialytic therapy.

Task 1. Questions for the student:

1. What are the clinical symptoms of urolithiasis?
2. What is the classification of acute renal failure?
3. What are the levels of urea nitrogen, creatinine, potassium and other electrolytes, uric acid, bilirubin, protein in patients with different phases of acute renal failure and in the blood of normal people?

Task 2. Make differential diagnosis of urolithiasis.

Student make differential diagnosis acute renal failure, using complaints, disease and life history, physical examination, laboratory and sonography signs.

Questions for the student:

1. What diseases is it necessary to make differential diagnosis with?

2. What is the medical tactics in the patients with acute renal failure?
3. What are the indications for surgical treatment or acute renal failure?

Multiple Choice.

Choose the correct answer/statement.

1. The cause of prerenal acute renal failure is:
 - A. Stone of the only kidney.
 - B. Haemorrhage.
 - C. Intoxication by heavy metals.
 - D. Nephrectomy of the only kidney.
 - E. Obstruction of the both ureters.
2. In ease of the intoxication by the heavy metals the universal antidote is:
 - A. Natrium tiosulphate.
 - B. Calcium chloride.
 - C. Hydrocortisone.
 - D. Ethylic alcohol.

Real life situations to be solved:

- A. In a patient on the 2nd day after extirpation of the uterus is the anuria, pain in the lumbar region. What diagnostic measures are necessary to be held in this situation to form the diagnosis? What are the surgical tactics?
- B. The patient L., 62 years old, complains of the pain in the right lumbar region, nausea, vomiting, general weakness,-absence of the urine for a 2 days. Biochemistry blood analysis: urea – 41,6 mmol/l, creatinine – 0,46 mmol/l. On general urogram – shadow : of the stone 0,8x0,7 at the proection of the lower part of the right ureter. From the case. history -has the urolithiasis of right kidney. What is the primary diagnosis? What are therapeutic tactics in this case?

Answers to the Self-assessment:

The correct answers to the tests:

- 1- B;
- 2- A.

The correct answers to the real life situations:

A- Yatrogenic defect of the ureters, postrenal anuria, it is necessary to find the organic reason of the obstruction by catheterization of the ureters, if it is impossible the ureterocystoneostomy is indicated;

B-stone of lower part of the right ureter, postrenal anuria, acute renal failure, is indicated the catheterization of the right kidney, to take out the stone is necessary.

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