Acute Tubular Necrosis

This accredited continuing educational program is intended for pharmacists and critical-care nurses.

Participants completing this program should be able to:

• Identify the causes and consequences of acute tubular necrosis (ATN).

• Identify the diagnostic criteria for and consequences of radiocontrast-induced nephropathy (RCN).

• Select the specific causes and consequences of ischemic ATN.

• Identify characteristics of the three phases of ischemic ATN.

• Identify the causes and consequences of nephrotoxic ATN.

• Select the risk factors and pathophysiologic mechanisms involved in RCN.

• Identify steps to help prevent RCN.

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Introduction

Acute kidney failure (AKF), also known as acute renal failure (ARF) (Table 1), is a common condition in hospitalized patients. Morbidity and mortality rates are high, and associated costs are considerable (Table 2).

Table 1. Acute Kidney Failure

Sudden deterioration in renal function:

- A decline in creatinine clearance of more than 25% from baseline; or
- An increase in serum creatinine level of at least 0.5 mg/dL (44 µmol/L); or
- An increase in serum creatinine level of at least 25% to 50% over baseline values[1,2,3] (Some clinicians use the following cutoff levels: 25% if the baseline creatinine level is <1.5 mg/dL [133 µmol/L], and 50% if the baseline is >1.5 mg/dL [133 µmol/L])

Table 2. Acute Kidney Failure: Prevalence, Morbidity, Mortality, Costs

Prevalence of acute kidney failure (AKF)

- About 5% in hospitalized patients[4,5]
- 20% to 30% of patients in intensive care units (ICUs)[2,6]

Possible consequences

- Metabolic acidosis, hyperkalemia, arrhythmia, electrolyte imbalance, gastrointestinal bleeding, uremia, respiratory failure due to fluid overload
- Renal replacement therapy initiated in 20% to 60% of patients[5]

Mortality rates from AKF

- About 45% for AKF acquired in the hospital[2]
- About 70% to 80% for ICU cases[2,4]

Estimated median costs in critically ill patients, from start of renal replacement therapy (RRT) to death or discharge[4]

- Direct costs, $42,100
- Hospital readmissions, $38,414

• Outpatient dialysis, $22,985

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AKF comprises three major types: prerenal, intrinsic, and postrenal AKF. Figure 1 reviews these types and their causes.

Intrinsic AKF has four subtypes classified by cause. About 80% to 90% of intrinsic cases are caused by ischemia, nephrotoxins, or both.[4] This type of intrinsic AKF is known as acute tubular necrosis (ATN) and is the focus of this program. ATN is the most common and generally the most serious type of AKF.

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Overview

ATN is characterized by the destruction of tubular epithelial cells. Risk factors include chronic renal insufficiency (often defined as serum creatinine concentration >1.5 mg/dL [133 µmol/L]), diabetes (especially diabetic nephropathy), congestive heart failure, and other conditions linked with decreased renal perfusion; alterations in thermoregulation (eg, burns, hyperthermia, hypothermia, frostbite); and intake of nephrotoxic agents. Angiotensin-converting enzyme (ACE) inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs) are common causes of prerenal AKF, which can progress to ATN.[5,7] Figure 2 shows the mechanisms of ischemic ATN and nephrotoxic ATN.

Ischemic ATN is associated with severe renal hypoperfusion, which can occur after major surgery or as a complication of shock or other conditions, including exposure to nephrotoxic agents.[8] In addition, uncontrolled prerenal azotemia can lead to ischemic ATN. Parenchymal damage is characteristic of ATN, but not of prerenal azotemia.

Nephrotoxic ATN is associated with the use of radiocontrast agents or other nephrotoxic drugs. These agents affect the kidney by two mechanisms: vasoconstriction leading to ischemia, and direct injury to the tubular epithelium.

PRERENAL AZOTEMIA

Prerenal azotemia and ischemic ATN lie on a continuum as manifestations of renal hypoperfusion.

Early recognition and prompt treatment of prerenal azotemia can help prevent ischemic ATN.

It is important to note that although the terms *intrinsic renal failure* and *ATN* are sometimes used interchangeably, they are not synonymous. In some patients with ischemic or nephrotoxic AKF, the tubular epithelium has not undergone substantial

injury; therefore no laboratory evidence of tubular necrosis (eg, granular or tubular cell urinary casts) is seen. These patients are not at the severe end of the AKF spectrum—they have intrinsic AKF but do not have ATN.[8]

Prerenal and postrenal AKF can be treated, but for intrinsic AKF, no specific approved therapy is currently available. Prevention is therefore the therapeutic keystone for intrinsic AKF. For high-risk patients, specific preventive measures include optimizing fluid balance and renal perfusion, and avoiding or minimizing use of nephrotoxic agents. If ATN does develop, these same measures can improve the chances of recovery.

Pathophysiology

In ATN, damage to the renal tubular cells results in a loss of cell polarity and disruption of cellular matrix adhesion. Necrotic cells rupture and are shed into the lumen of the tubule. The shed cells and debris obstruct the lumen, which has a diameter about equal to the width of one to two cells.[7,9] If a substantial number of nephrons are shut down, tubular filtrate returns to the circulation through the damaged tubular basement membrane. This backflow disrupts homeostatic mechanisms and reduces the glomerular filtration rate (GFR).[9]

POST-TEST

Select only one answer for each question.

1. All of the following statements about ATN are correct *except*:

A. It can be caused by exposure to nephrotoxins, resulting in vasoconstriction or direct injury to the tubular epithelium.

B. It can be caused by prolonged renal hypoperfusion, resulting in ischemia.

C. It is always caused by ischemia, regardless of the underlying mechanism.

D. It can develop as a progression of prerenal AKF.

2. All of the following statements about ATN are correct *except*:

A. ATN is associated with parenchymal damage.

B. ATN is associated with the destruction of tubular epithelial cells.

C. ATN can develop from prerenal azotemia.

D. The terms *ATN* and *intrinsic renal failure* are synonymous.

3. In RCN:

A. Creatinine levels usually rise within 48 to 72 hours after exposure, peak in 7 to 10 days, and return to baseline in about two weeks.

B. Oliguria may occur within 24 hours after exposure, and serum creatinine levels may rise above 5 mg/dL (442 µmol/L).

C. 10% to 25% of all RCN patients require dialysis, and the mortality rate is high.

D. All of the above are correct.

4. All of the following statements regarding indications for renal replacement therapy
are correct, *except*:

A. Guidelines from the *Journal of the American Society of Nephrology* are largely based on GFR.

B. Some clinicians use guidelines based on serum creatinine level (eg, a 50% increase, or an increase of at least 1 mg/dL [88 µmol/L], or a level >10 mg/dL [884 µmol/L]).

C. Others use BUN or the presence of oliguria.

D. For still others, the primary guidelines are acidosis or electrolyte disturbances unresponsive to drug therapy.

5. Select the correct statement pertaining to ischemic ATN.

A. The major etiological factor in ischemic ATN is radiocontrast administration.

B. The function of the tubuloglomerular feedback response is to maintain normal fluid balance and blood pressure.

C. Some high-risk patients with ischemic ATN (eg, those with diabetic nephropathy) develop severe, prolonged vasoconstriction, resulting in renal impairment.

D. If renal blood flow drops to less than 40% of normal, damage to the kidney cells cannot be repaired.

6. In the phases of ischemic ATN:

A. The initiation phase begins with a drop in renal blood flow; homeostatic mechanisms eventually are disrupted.

B. GFR does not drop until the maintenance phase.

C. Once the recovery phase has been reached, fluid and electrolyte balance have stabilized.

D. In the recovery phase, marked diuresis no longer occurs.

7. In nephrotoxic ATN:

A. The causative substances are limited to radiocontrast agents and antimicrobial agents.

B. Injury to the kidney occurs a week or two after administration of the nephrotoxic agent.

C. Prophylactic steps may include adjusting dosages of potentially nephrotoxic agents according to circulating drug levels, body size, or GFR; or, for some patients, administering acetylcysteine.

D. Most patients who survive do not recover normal renal function.

8. All of the following answers are correct *except*:

A. Vasoconstriction resulting in renal medullary ischemia is though to be a cause of RCN.

B. Direct toxicity to renal tubular cells appears to be the predominant cause of RCN.

C. Contrast agents cause an initial, brief vasodilation in the kidney, followed by intense vasoconstriction that may last several hours.

D. Substantial shunting of tubular blood flow from the medulla to the cortex appears to occur after contrast administration.

9. Select the correct statement about RCN:

A. The single most important risk factor for RCN is exposure to high doses or multiple doses of contrast medium.

B. The elimination half-life of contrast agents is relatively short.

C. The route of administration of contrast medium (intra-arterial vs. IV) does not seem to be related to development of RCN.

D. Most patients who develop RCN have one or more easily identifiable risk factors.

10. Steps to help prevent RCN include:

A. Monitoring high-risk patients before and at 48 and 72 hours after the procedure.

B. Using oral or IV hydration immediately after the contrast procedure, and for up to 24 hours after.

C. Avoiding certain procedures, especially MRA, in patients with renal insufficiency.

D. Use of nonionic, low-osmolality contrast agents in all patients undergoing contrast procedures.