Acute renal failure in hospitalized patients

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ABSTRACT

Distinguishing among the three categories of acute renal failure is important, as the evaluation and management are tailored to the particular cause. Most cases are due to acute tubular necrosis. To minimize the risk, we should give hospital patients adequate hydration, use potentially nephrotoxic drugs with caution, keep the use of radiographic contrast agents to a minimum, and give patients at risk a nonionic instead of ionic contrast agent when undergoing radiographic procedures.

ACUTE RENAL FAILURE (ARF) is common, with a reported incidence of 2% to 5% of all patients admitted to general medical-surgical hospitals. Furthermore, approximately half of patients who develop ARF die; survivors face marked increases in morbidity and prolonged hospitalization.

The high frequency of occurrence and substantial morbidity and mortality of ARF demand a logical approach to its prevention and early diagnosis, and the prompt recognition and management of its complications.

EARLY RECOGNITION IS CRUCIAL

ARF is characterized by azotemia that progresses rapidly over several hours or days. It may or may not be accompanied by oliguria.

Early recognition is critical. Because renal failure is often asymptomatic, it must be detected by carefully tracking the serum creatinine level. Serum creatinine is more specific than blood urea nitrogen, which may become elevated for a variety of reasons, including catabolic states, fever, and medications.

The earliest manifestations of ARF may be subtle. Losing the function of one half of the nephron mass (1 million glomeruli) will cause creatinine to rise from about 0.7 mg/dL only up to about 1.4 mg/dL. In general, the threshold used to identify ARF is a rise in the serum creatinine level more than or equal to 1.0 mg/dL, but smaller elevations should be taken as early signs of trouble.

THREE TYPES

Once ARF is discovered, it is important to determine the type—prerenal, postrenal, or intrinsic (FIGURE 1)—because the initial evaluation and management are tailored to the particular cause.

Consider small creatinine increases as a possible sign of trouble

Prerenal acute renal failure

Prerenal ARF (due to underperfusion of an otherwise normal kidney) accounted for 21% of cases of ARF in a multicenter study in Madrid.[1]

The hallmark of prerenal failure is that it is quickly reversible with appropriate therapy. Thus, it can be thought of as "a good kidney looking at a bad world."

Prerenal kidney failure can be a result of volume depletion from renal or extrarenal losses, fluid sequestration in liver failure or other edematous states, or inadequate perfusion pressure due to heart failure. The urinalysis is bland, the urinary sodium is low, but urine osmolality is high.

Treatment is imperative, because continued renal hypoperfusion can progress to intrinsic renal failure. Renal perfusion and volume status must be optimized by giving iso-

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TABLE 1

Drugs and other exogenous causes of acute renal failure

Analgesics
- Nonsteroidal anti-inflammatory drugs (NSAIDs)

Anesthetics
- Enflurane
- Methoxyflurane

ACE inhibitors

Antimicrobials
- Acyclovir
- Aminoglycosides
- Amphotericin B
- Bacitracin
- Cephalosporins
- Foscarnet
- Pentamidine
- Polymyxin, colistin
- Sulfonamide, co-trimoxazole
- Tetracyclines
- Vancomycin

Antiulcer agents
- Cimetidine
- Milk-alkali (in excess)

Contrast media
- Bunamiodyl
- Diatrizoate
- Iopanoic acid
- Iothalamate

Diuretics
- Mercurials
- Ticrynafen

Chemotherapy agents and immunosuppressants
- 5-azacitidine
- Carboplatin
- Cisplatin
- Cyclosporine A and tacrolimus
- D-penicillamine
- Ifosfamide
- Interferon alfa or gamma 1B
- Methotrexate
- Mitomycin
- Nitrosourea
- Plicamycin
- Recombinant interleukin 2

HIV protease inhibitors
- Indinavir
- Ritonavir

Recreational drugs
- Amphetamines
- Heroin

Others
- Bacterial toxins
- Chinese herbs
- Dextrans
- EDTA
- Epsilon-amino caproic acid
- Heavy metals
- Industrial chemicals
- Organic solvents
- Pesticides
- Radiation
- Silicone
- Snake or insect venom

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Ultrasound is sensitive and specific for urinary obstruction

tonic fluids. Underlying diseases such as heart failure should be treated.

Postrenal acute renal failure

Postrenal ARF (due to obstruction of the urinary tract) accounted for 10% of cases in the Madrid study.[1]

Urinary tract obstructions may be within the urinary tract (eg, blood clots, stones, sloughed papillae, or fungus balls), or extrinsic (eg, tumors, retroperitoneal fibrosis, or even inadvertent ligation).

Renal ultrasonography, when used to detect obstructions, has a sensitivity and specificity of 90% to 95%. Unfortunately, it is also highly operator-dependent, so it should be performed by a highly experienced radiologist. Ultrasonography can give false-negative results if the obstruction is caused by retroperitoneal fibrosis or by certain malignancies that encase the entire system. It might also fail to detect an obstruction in very volume-depleted patients who do not have enough fluid buildup to show the obstruction.

Treatment should focus on removing the obstruction, with techniques that vary with the type of obstruction.

Intrinsic acute renal failure

Once prerenal and postrenal causes are ruled out, intrinsic renal failure is likely.

Intrinsic ARF (due to disease of the renal parenchyma) accounted for 69% of cases in the Madrid study.[1] Acute tubular necrosis (ATN), the most common type of intrinsic ARF, accounted for 45% of all cases of ARF.[1] Most of the following discussion is therefore focused on ATN; other types of intrinsic ARF are reviewed in detail by Lake and Humes.[2]

ATN is most often caused by renal hypoperfusion and renal ischemia. Other causes include various endogenous nephrotoxic substances (eg, myoglobin and hemoglobin after trauma, cellular products in tumor lysis syndrome, and crystals of uric acid, calcium, and oxalate) and a host of exogenous substances (TABLE 1). If a patient develops ATN while receiving medications, one must review each medication for the possibility of nephrotoxicity.

In oliguric ATN, renal plasma flow declines, but the glomerular filtration rate declines even more. This dichotomy suggests that constriction of the afferent arterioles contributes to the pathophysiologic process. Ischemic injury to epithelial cells can lead to

Types of acute renal failure

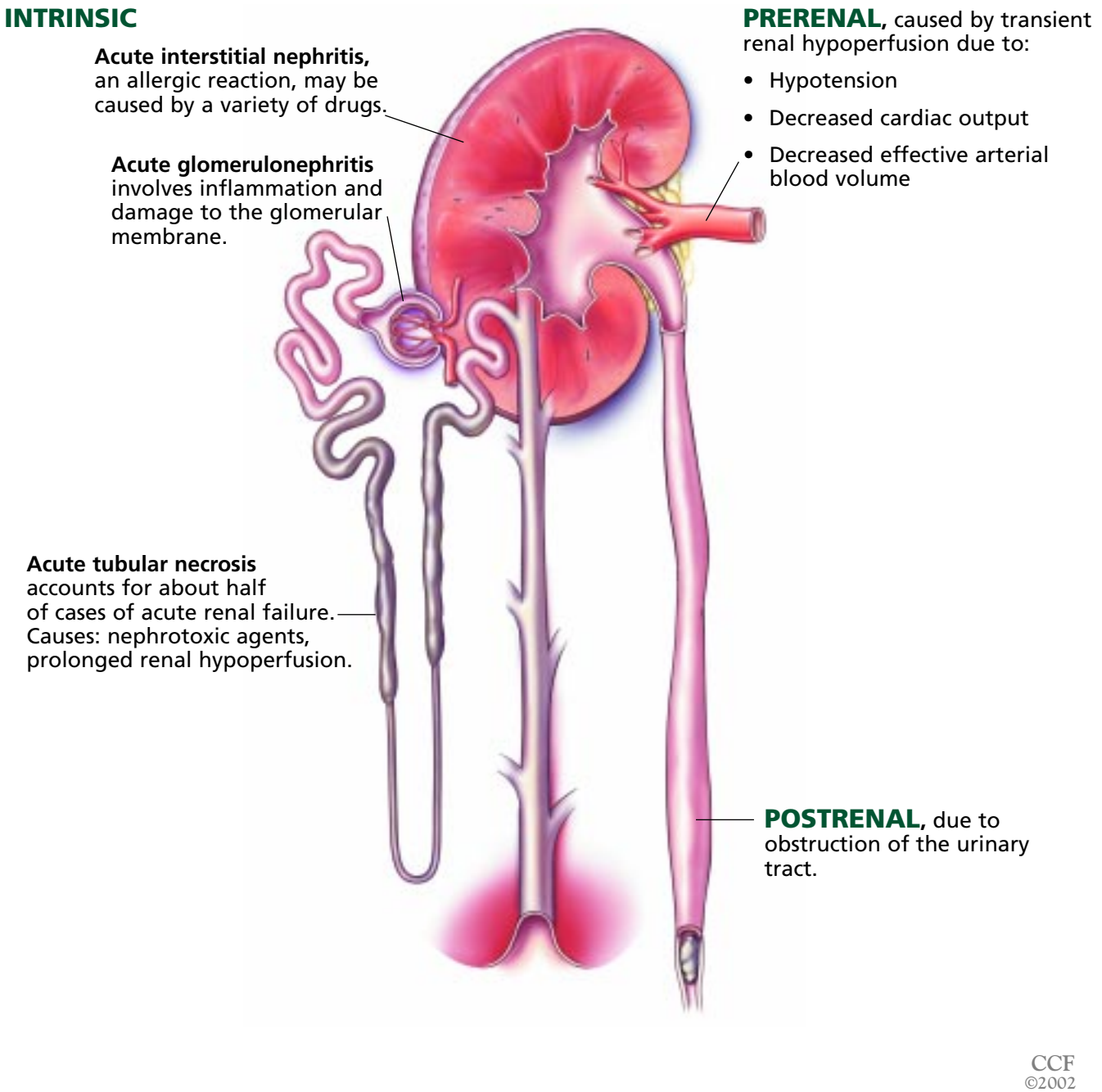

FIGURE 1

tubular backleak, which allows filtrate back into the bloodstream, and tubular obstruction.

The distribution of tubular necrosis within the kidney is patchy, and the degree of necrosis does not correlate with the level of renal dysfunction. This is because the medulla of the kidney, containing the thick ascending limbs of Henle, is less well vascularized and perfused than the cortex and therefore is disproportionately affected by ischemia. The ischemic insult in this region is worsened by reperfusion injury. Persistent vasoconstriction

TABLE 2

How to evaluate patients with ARF

1 Review records, perform history and physical examination

- Findings that suggest prerenal causes
  - Volume depletion
  - Congestive heart failure
  - Severe liver disease or other edematous states
- Findings that suggest postrenal causes
  - Palpable bladder or hydronephrotic kidneys
  - Enlarged prostate
  - Abnormal pelvic examination
  - Large residual bladder urine volume
  - History of renal calculi (perform ultrasound to screen for urinary tract obstruction)
- Findings that suggest intrinsic renal disease
  - Hypotension, exposure to nephrotoxic drugs
  - Recent radiographic procedures with contrast

2 Examine the urine sediment

- If no abnormalities: suspect prerenal or postrenal azotemia
- If eosinophils: suspect acute interstitial nephritis
- If red blood cell casts: suspect glomerulonephritis or vasculitis
- If renal tubular epithelial cells and muddy brown casts: suspect acute tubular necrosis

3 Calculate urinary indices

- Findings that suggest prerenal azotemia or glomerulonephritis
  - Urinary sodium concentration < 20 mEq/L
  - Urine:plasma creatinine ratio > 30
  - Renal failure index < 1
    (Renal failure index = [urinary sodium concentration / urinary creatinine concentration] × plasma creatinine concentration)
  - Urine osmolality > 500
- Findings that suggest acute tubular necrosis or postrenal azotemia
  - Urinary sodium concentration > 40 mEq/L
  - Urine:plasma creatinine ratio < 20
  - Renal failure index > 1
  - Urine osmolality < 400

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Acute tubular necrosis is the most common type of acute renal failure

and congestion from white cells and cell debris lead to ongoing hypoxia and necrosis.

SPECIAL RISK GROUPS

Bone marrow transplant recipients are at increased risk of ARF and have a poor prognosis. Perioperative ATN may result from tumor lysis, sepsis, and nephrotoxins (including antibiotics and contrast agents).

If ARF develops 10 to 16 days after the transplant, the most likely immediate cause is hepatic veno-occlusive disease that mimics acute hepatorenal syndrome.

ARF developing 4 to 12 months after bone marrow transplantation may be due to hemolytic uremic syndrome, perhaps related to cyclosporine or radiation therapy.

HIV patients are also at risk of ARF not only from the usual nephrotoxic insults, but also from potential nephrotoxicity of protease inhibitors. Other agents with similar risks include acyclovir and foscarnet.

A STRATEGY FOR EVALUATING ARF

A patient with ARF requires the physician to play medical detective (TABLE 2).

The medical history should be reviewed for possible nephrotoxic insults such as exposure to contrast materials or medications, or hypotension.

The physical examination should focus on volume status. It is also prudent to screen for signs of systemic diseases that might affect kidney function, such as lupus or Wegener granulomatosis.

Renal ultrasonography should be performed to screen for urinary tract obstruction.

Urine studies. Urinalysis should be performed and urine volume measured. Urine chemistry studies may provide additional information.

Anuria or oliguria is a clue that ARF is caused by one of three causes: urinary tract obstruction; a severe type of ATN called cortical necrosis; or blood vessel blockage by a clot or other obstruction.

Urinalysis, especially examination of the sediment, is fundamental to the evaluation.

Low fractional excretion of sodium in a patient with acute oliguria is a classic sign of prerenal failure, and is also associated with hepatorenal syndrome and acute glomerulonephritis. However, some types of ATN may also have low sodium excretion, specifically, postcontrast ATN, rhabdomyolysis, and multisystem organ failure.

TREATMENT OF INTRINSIC ARF

Treatment for intrinsic ARF is largely supportive, including adjusting medications, providing appropriate nutrition, and correcting volume status, hyperkalemia, and acidosis. The leading indications for dialysis are volume overload and hyperkalemia.

Stop nephrotoxic medications. With any patient with ARF, prescription and nonprescription medications should be reviewed immediately so that any potentially nephrotoxic drugs can be stopped. In addition to contrast media, other nephrotoxic agents include aminoglycosides and amphotericin (TABLE 1). Outside the hospital, the leading nephrotoxic agents are nonsteroidal anti-inflammatory drugs (NSAIDs). Patients can also be put at risk by ACE inhibitors, cisplatin, ifosfamide, and even Chinese herbal remedies.

Manage endogenous nephrotoxic insults. If endogenous nephrotoxicity is diagnosed early enough, it can often be reversed with urinary alkalization, which can prevent kidney failure and the need for dialysis. For example, pigment nephropathy from myoglobin, hemoglobin, or methemoglobin can be treated with urinary alkalization. In many cases, these types of nephrotoxicity result from tumor-specific syndromes such as tumor lysis syndrome or plasma cell dyscrasia (eg, myeloma kidney).[2]

Boost urine output. Renal failure patients who make urine tend to have lower morbidity and mortality rates. They are at less risk of hypervolemia, there is room for bicarbonate and nutrition, and there is less likelihood of hyperkalemia. This observation suggests that increasing urine output should be a priority. Unfortunately, much of the literature on this subject is dated, the studies were poorly designed, and the effect on mortality is not clear.

Mannitol should be avoided in patients with established ARF because it is an osmotic agent which may induce hypervolemia.[3] To increase urine output, hydrate the patient with saline, and then start a loop diuretic.

Dopamine in "renal" doses should probably be used sparingly, if at all, because data on its effectiveness and safety are scant. In normal people, dopamine increases renal blood flow by about 40% and the glomerular filtration rate by about 10%, resulting in increases in salt and water excretion. It is not clear whether these increases are due to a direct effect on the kidney or the result of cardiac effects. Very little information is available about how to apply these results to patients with ARF. Data are not available for routine clinical use, so a trial of dopamine should be for no longer than 24 to 48 hours, followed by a taper.[4,5]

In patients with acute renal failure, avoid mannitol

New directions for therapy. In cells that recover from an ischemic insult, growth factors play a role in recovery. This phenomenon has led to research with epidermal growth factor, insulin-like growth factor, or hepatocyte-type growth factor as therapy for ischemic ATN. Others are investigating endothelium receptor blockers to address the ongoing vasoconstriction, and anti–adhesion-molecule antibodies to prevent vessel congestion by leukocytes.

PROGNOSIS: MORTALITY NEARLY 50%

The mortality rate in ARF is nearly 50%, depending on the type of ARF and comorbidities of the patient. In the Madrid study,[1]

TABLE 3

Measures to prevent acute renal failure in hospitalized patients

- Prevent hypotension, and correct it rapidly when it does occur
- Evaluate renal function before any surgery
- Avoid prescribing nephrotoxic drugs
- Correct volume deficits or electrolyte imbalances, especially before surgery
- Replace traditional contrast agents with nonionic contrast, and use contrast sparingly
- Treat infection quickly
- Treat oliguria quickly

patients with ATN had a mortality rate of 60%, while those with prerenal or postrenal disease had a 35% mortality rate.

Most deaths are not due to the ARF itself but rather to underlying disease or complications. In the Madrid data,[1] 60% of deaths were due to the primary disease, and the remaining 40% were due to cardiopulmonary failure or infection.

Mortality in acute renal failure is about 50%

ARF is not merely a marker of illness. In a follow-up study[6] of 16,000 patients who underwent computed tomography with contrast, 183 of them developed ARF. The mortality rate among those with ARF was 34%, compared with only 7% in a matched cohort from the similarly exposed group.

About half of people who survive ATN recover renal function completely, and another 40% have an incomplete recovery. Only about 5% to 10% require maintenance hemodialysis.

PREVENTING ARF

Because few measures exist to actively treat ARF, clinicians should try to prevent it. Issues to consider are correcting volume status, avoiding exposure to nephrotoxins, and preparing for high-risk procedures such as those using contrast agents (TABLE 3).

Preventing contrast nephropathy

The incidence of contrast nephropathy can be reduced by adequately hydrating patients before the procedure, replacing traditional agents with nonionic contrast, and limiting the quantity of any contrast agent used.

Using nonionic contrast agents can cut the overall risk of contrast nephropathy by half, from about 6% to 3%. In the study by Rudnick et al,[7] risk factors for contrast nephropathy were baseline renal insufficiency (serum creatinine > 1.5 mg/dL) and diabetes; the use of nonionic contrast agents reduced incidence in the highest-risk patients who had both risk factors from 24% to 12%.

The most effective strategy to hydrate patients is to give half-normal saline at 1 mL/kg/hour overnight before the procedure. No benefit is gained by adding mannitol or a loop diuretic.[8] Pretreating with acetylcysteine reduces the rise of creatinine levels slightly but may have minor clinical impact.

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