APPROACH TO ACUTE KIDNEY INJURY: DIFFERENTIATION OF PRERENAL, POSTRENAL AND INTRINSIC RENAL DISEASE, ACUTE TUBULAR NECROSIS AND RENAL VASCULAR DISEASE

Biff F. Palmer, MD, Office: H5.112; Phone 87848
Email: Biff.Palmer@UTSouthwestern.edu

LEARNING OBJECTIVES

- Given laboratory tests results and radiographic imaging, be able to diagnose a patients with an increased serum creatinine concentration as having post-renal renal disease and list the common clinical etiologies of urinary obstruction
- Given laboratory tests results and radiographic imaging, be able to diagnose a patients with an increased serum creatinine concentration as having pre-renal kidney injury
- Given pertinent aspects of the history, physical examination, serum and urine electrolytes, and urinalysis in any patient, be able to distinguish pre-renal renal failure from intrinsic renal disease
- Given urine and plasma concentrations of sodium and creatinine in any patient, be able to calculate the fractional excretion of sodium (FENa) and interpret the results
- List the renal syndromes associated with use of NSAID's
- List the characteristics of thromboembolic disease of the kidney, multiple choesterol emboli syndrome, renal vein thrombosis, and renal artery stenosis

After determining chronicity and assessing the level of renal function, one should attempt to classify the patient with renal disease into one of several syndromes based on the renal structures most affected: pre-renal, post-renal or intrinsic renal disease. This classification is based on the information obtained in the history, physical examination, laboratory tests and selected imaging studies. It is particularly important to identify prerenal and postrenal disorders because theses disorders are often readily reversible.

I. Post-Renal Renal Failure

Urinary obstruction at any level from the ureters to the urethra may result in acute kidney injury. Urinary obstruction can acutely cause intrarenal vasoconstriction and ischemic tubular injury. Chronic obstruction can lead to interstitial fibrosis and result in chronic kidney disease and even end-stage renal disease if untreated. Although patients with complete obstruction have significantly decreased urine output and even anuria (<100 cc/d), those with partial obstruction may have polyuria secondary to early loss of concentrating ability caused by loss of tubular function.

Acute obstruction of the ureters can be due to stones, sloughed papillae or blood clots. Bladder outlet obstruction is a common cause of acute urinary retention and acute kidney injury especially in elderly male patients with prostate disease. Diabetics are prone to obstruction secondary to a neurogenic bladder. Cervical cancer in women can lead to obstruction as a result of the close proximity of the ureters and cervix. Retroperitoneal fibrosis (as a secondary complication of a prior retroperitoneal bleed or pelvic malignancy) is also a cause of urinary obstruction.

Kidney ultrasound in most patients with obstruction reveals hydronephrosis; however, this finding may be absent in those with retroperitoneal fibrosis, which causes encasement of the collecting system in fibrotic tissue that may prevent dilation of the collecting system. Retroperitoneal fibrosis should be suspected in patients with chronic kidney injury who present with flank pain or abdominal pain in whom prerenal and kidney parenchymal disease have been excluded. Lymphomas or testicular cancer metastatic to the retroperitoneal space may present with post-renal kidney disease. In these settings hydronephrosis may not be present due to encasement of the ureters. Noncontrast CT of the abdomen and pelvis is the preferred imaging modality to establish a diagnosis when the renal sonogram is negative but urinary obstruction is still suspected.

Treatment of post-renal kidney disease involves relief of the obstruction. In many cases, surgical intervention may be required for definitive therapy. In acute obstruction relief of obstruction generally results in full recovery of renal function. In chronic obstruction, residual renal dysfunction leading to chronic kidney disease may ensue even after obstruction is relieved.

II. Pre-Renal Renal Failure

Patients with prerenal azotemia may have a history of fluid loss and decreased fluid intake accompanied by physical examination findings consistent with extracellular fluid volume depletion, such as postural hypotension. Prerenal azotemia may also develop in patients with increased extracellular fluid volume caused by changes in glomerular hemodynamics which accompany disease sates such as congestive heart failure or cirrhosis. A decrease in effective arterial blood volume (EABV) is the cardinal feature of pre-renal azotemia. The concept of EABV provides a meaningful way to explain why congestive heart failure, a condition associated with total body volume overload, and severe vomiting, a condition associated with total blood volume depletion, are both characterized by a decrease in effective arterial blood volume. In both of these conditions blood flow to the kidneys is impaired, renal function may decline and azotemia results. The kidney is structurally normal but is responding to a derangement in the circulation.

Pre-renal azotemia may be a cause of acute or chronic kidney disease. Decreased EABV leads to activation of angiotensin II (AII) and sympathetic nerves which, in turn, cause renal vasoconstriction. If severe enough, renal blood flow (RBF) and glomerular filtration rate (GFR) will be markedly reduced. In addition to a reduction in GFR, renal mechanisms designed to conserve sodium and water become activated. The reduction in glomerular filtration and the enhancement of sodium and water reabsorption act in concert to preserve body fluid volume. It is important to note that in this setting renal tubular function and vascular integrity are normal.

Urine Findings: Pre-renal Azotemia versus Acute Tubular Necrosis (ATN)

	Pre-renal	ATN
Urine Na (mEq/L)	<10	>20
Urine Cl (mEq/L)	<10	>20
FENa	<1%	>1%
U/P Creatinine	>40	<20
U/P Urea	>40	<20
Uosm	100 mOsm > Plasma	Isosmolar
Sediment	Normal, hyaline casts	Granular, cellular casts

Renal sodium and water metabolism

As pointed out above, the renal tubules function normally in pre-renal states so that water and sodium are avidly conserved. The fractional reabsorption of salt and water increases in pre-renal states owing to compensatory mechanisms that promote increased tubular reabsorption of salt and water. These mechanisms include both physical forces, neural and hormonal factors activated during the pathogenesis of the pre-renal state. For example, elevated levels of catecholamines and angiotensin II tend to stimulate proximal tubular sodium reabsorption. In addition, physical factors such as increased peritubular protein concentration and decreased peritubular hydrostatic pressure, owing to the increase in filtration fraction (GFR/RPF), stimulate proximal sodium reabsorption. Also, elevated levels of antidiuretic hormone augment water reabsorption in the collecting duct. These physiologic responses to decreased EABV lead to renal sodium and water retention. Since the kidney operates normally to protect body fluid volume and composition and since its concentrating ability is normal, the electrolyte composition and osmolality of the urine reflect intact function of the tubules. Thus, urinary sodium concentration will be low (usually < 10 mEq/L) and urinary concentration will be high (usually > 500 mOsm/kg).

It is obvious that the clinical presentation of pre-renal azotemia will depend upon the cause for the reduction in EABV. One of the most common causes of pre-renal renal failure is extracellular fluid volume depletion from GI losses. The following case illustrates the features of a patient with severe vomiting who develops volume contraction owing to fluid and electrolyte losses. In patients with vomiting, gastric loss of HCl leads to the generation of metabolic alkalosis. The presence of azotemia, a high plasma bicarbonate concentration and a low plasma chloride concentration in a patient with symptoms and signs of severe volume depletion and a history of vomiting is strong evidence of pre-renal acute kidney injury due to vomiting.

Case presentation

A 45-year-old man with a past history of recurrent chronic intermittent abdominal pain due to peptic ulcer disease presents to the emergency room with a 10-day history of intractable vomiting and abdominal pain. The patient has been unable to keep solid foods down but is able to drink water and keep it down. He has become progressively weak and complains of dizziness upon assuming an upright position.

Physical examination:

General: the patient appears acutely ill and pale. BP 110/60 pulse 100 (supine), BP 80/40 pulse 140 (upright), Vital signs: temperature 37 degree Centigrade; respiratory rate 20 breaths/min;
Remaining examination findings are remarkable for decreased skin turgor, tenting of the skin, sunken eye globes, dry mucous membranes, flat neck veins, and mild epigastric tenderness.
Laboratory data is given in the following table.

Blood Investigations					
Electrolytes:	Sodium Potassium Chloride Total CO2 Glucose	133 mEq/L 2.6 mEq/L 80 mEq/L 40 mEq/L 80 mg/dl	*Renal function:*	BUN Creatinine BUN/Cr ratio Serum osmolality	90 mg/dl 4.5 mg/dl 20/1 304 mOsm
Minerals:	Ca1cium Albumin Pi	8 mg/dl 5.1 g/dl 4.5 mg/dl	*Arterial blood gases:*	pH pCO2 pO2	7.55 51 mmHg 90 mmHg
Hematology:	Hgb Hct WBC	17 g/dl 51% 10,100 /cu.mm.			

Urine Investigations			
Urine chemistry:		*Urinalysis:*	
Sodium	20 mEq/L	S.G.	1.020
Potassium	40 mEq/l	pH	5.0
Chloride	< 10 mEq/L	Protein	Negative
Urea	2200 mg/dl	Glucose	Negative
Creatinine	200 mg/dl	Ketones	+
(U/P) creatinine	44:1	Bilirubin	Negative
Uosm	700 mOsm/kg	Blood	Negative
Fractional excretion of sodium (FENa) = $\frac{\text{U-sodium P-creatinine}}{\text{U-creatinine P-sodium}} \times 100 =$ $\frac{20 \times 4.5}{200 \times 133} \times 100 = 0.34\%$		*Urine microscopy:* Sediment	0-1 WBC/hpf 0-1 RBC/hpf Numerous Hyaline casts, No crystals

To summarize, the patient has a history of ulcer disease, he has prolonged vomiting from gastric outlet obstruction and has only been ingesting water. He is markedly volume depleted as evidenced by severe orthostatic hypotension and other physical signs of volume depletion (tented skin, dry mucous membranes, etc.).

The development of hyponatremia is a result of impaired renal free water excretion. Volume depletion is sensed by baroreceptors distributed throughout the body which send signals to the brain causing the release of antidiuretic hormne (ADH). ADH limits renal water excretion such that water intake can now more easily exceed renal water excretion. The urine is concentrated as reflected by the urine osmolality being much higher than plasma. As free water intake is maintained, but renal water excretion is impaired, dilution of plasma occurs and hyponatremia results.

The BUN and creatinine levels are elevated. The BUN/Cr ratio is also high (20/1) with the normal ratio being approximately 10/1. In pre-renal states, avid proximal tubular reabsorption of filtered urea takes place. The same peritubular forces that augment Na^+ reabsorption in the proximal tubule also increase BUN reabsorption.

The serum creatinine concentration is elevated because of a reduced GFR, which is the main mechanism of renal excretion of creatinine. Unlike urea, creatinine is not reabsorbed avidly by the proximal tubule and in fact is secreted into the proximal tubule lumen from the blood. Urinary levels of urea and creatinine are very high owing to renal reabsorption of water reflecting an intact concentrating mechanism.

Other serum electrolyte abnormalities in this case:

- *Hypokalemia* is observed because of renal K^+ losses. Serum aldosterone levels are increased as a result of low EABV. Distal Na^+ delivery is increased due to the large amount of filtered bicarbonate being delivered to the distal nephron. Bicarbonate in acting as a non-reabsorbable anion in this case. The increase in distal Na^+ delivery combined with the increase in serum aldosterone leads to increased renal potassium excretion. Little if any K^+ is lost from the stomach during vomiting since the K^+ content in gastric secretions is very low.
- *Hypochloremia* can be explained for two reasons. First, there is external loss of chloride due to vomiting (loss of HCl). Second, there is dilution due to free water excess. Note that this second factor is also the major cause for hyponatremia as described above.
- *Total CO2*, which is approximately equal to the plasma bicarbonate concentration, is elevated because of loss of HCl. Consequent to volume depletion and hypokalemia, decreased filtration of bicarbonate as well as elevated renal bicarbonate reabsorption sustain the increase in the plasma level. Notice that the increase in plasma bicarbonate is approximately equal to the decrease in plasma chloride. This primary increase in plasma bicarbonate leads to metabolic alkalosis as reflected by an increase in blood pH and a compensatory increase in pCO_2.

Urine electrolytes and urinalysis in this case:

The urinary sodium and chloride concentrations are reduced because of avid tubular reabsorption. The urine sodium is greater that chloride because it is being dragged into the urine by bicarbonate (non-reabsorbable anion effect) as previously discussed.

The *urinalysis* is also in keeping with normal renal function and anatomy. The specific gravity is elevated at 1.020. A general rule of thumb for estimating urine osmolality from specific gravity can be applied in this setting. By multiplying the digits to the right of the decimal point by 35, one obtains a rough estimate of urine osmolality: 20 x 35 = 700. This rule is only applicable when significant glycosuria or proteinuria is not present. The urinary sediment only shows hyaline casts which represent the concentration of Tamm-Horsfall protein excreted as an acellular cast. When renal damage occurs, the sediment becomes markedly abnormal and cellular elements, tubular debris and casts become prominent.

Case Summary: In pre-renal acute kidney injury, a decrease in EABV triggers the kidney to conserve sodium and water at the expense of retaining excesses of nitrogenous wastes, BUN and creatinine, etc. The kidney is structurally normal and merely responding to an underfilled circulation. This form of renal failure is readily reversible with restoration of effective circulatory volume. Restoration of EABV allows the kidney to regulate volume and electrolytes at normal levels once again.

III. Intrinsic Renal Disease: After excluding pre-renal and post-renal causes of renal failure one needs to consider the various causes of intrinsic renal disease. Intrinsic diseases can be divided into those that primarily affect the glomerulus and those that target non-glomerular structures. In the following paragraphs, acute tubular necrosis and renal vascular disease will be discussed.

A. Acute Tubular Necrosis

Acute tubular necrosis (ATN) is the most common form of intrinsic renal failure. The onset of this condition usually occurs after a period of a sustained ischemia or exposure to nephrotoxic agents. ATN is typically a reversible form of renal failure but can lead to varying degrees of chronic kidney disease depending on the duration and severity of the ischemic or nephrotoxic insult. Ischemic injury is generally the consequence of severe hypoperfusion from cardiogenic shock, sepsis, and hemorrhage. Common causes of nephrotoxic injury include aminoglycoside antibiotics, radiocontrast agents, and myoglobin (as with rhabdomyolysis).

Ischemic or nephrotoxic injury leads to renal tubular cell death. As a consequence, cells slough into the tubular lumen and tubular obstruction occurs. The loss of tubular integrity leads to backleak of filtered solutes into the blood. Renal vasoconstriction also occurs in the setting of ATN. The combined effects of tubular obstruction, renal vasoconstriction, and backleak lead to a reduction in GFR and development of azotemia. Patients with ATN are predisposed to the development of volume overload since salt and water intake now easily exceeds the kidneys excretory capacity. The filtered load of phosphorus is sharply reduced as well. Hyponatremia, metabolic acidosis, hyperkalemia, hyperphosphatemia, hypocalcemia and marked azotemia are typical features.

ATN can be oliguric or non-oliguric. *Oliguric ATN* arbitrarily is said to be present when urine flow is less than 400 ml/day. The degree of renal injury is more severe in oliguric ATN and is typically complicated by a greater degree of azotemia and volume overload. There is a progressive rise in phosphorus, BUN, creatinine, and potassium as muscle breakdown due to hypercatabolism takes place in the absence of renal excretory function. Serum calcium falls in consequence to the rise of serum phosphorus (due to a solubility effect) and a sharp fall in 1,25-$(OH)_2$ vitamin D levels and skeletal resistance to parathyroid hormone (PTH) levels. Life threatening acidosis and hyperkalemia may develop.

In addition, progressive volume overload with weight gain and edema occur unless prompt curtailment of fluid intake is undertaken. Serum magnesium may also rise especially if Mg^{++} containing antacids or cathartics are administered. Gastrointestinal disturbances including hiccups, anorexia, nausea, and vomiting and upper GI hemorrhage are common. Vomiting may become worse as oliguria persists, and mental clouding may ensue with lethargy, confusion, stupor, and coma. At the same time, the patient is predisposed to develop a serious infection, which may be lethal.

The initial sign of renal recovery is an increase in urine flow. Even though urine output continues to increase, the BUN and creatinine continue to rise during the early stages of recovery. Eventually the BUN and creatinine plateau and later begin to fall. While quite variable, the diuretic phase generally lasts 4 - 5 days, however, it may take weeks to months or longer for full recovery of normal function.

Non-oliguric ATN (arbitrarily defined as urine flow >400 ml/d) describes the condition where the BUN and creatinine increase in response to some renal insult but urine flow remains relatively well preserved. This form of ATN occurs when the renal insult is less severe than that which gives rise to oliguric ATN. Non-oliguric ATN typically occurs in the setting of mild ischemic injury or following the administration of toxins such as radiocontrast agents or aminoglycoside antibiotics. Volume overload and hyperkalemia are much less common. The clinical course of nonoliguric ATN is generally milder than oliguric ATN. Dialysis is needed less frequently and morbidity and mortality are significantly less because the underlying cause of the renal failure is typically less severe.

The following case presentation illustrates some of the features of a patient with acute kidney injury due to acute tubular necrosis.

Case presentation

A 62-year-old man presents to the emergency room with a two day history of fever, chills, nausea, vomiting, and right upper quadrant abdominal pain. The patient has become progressively confused and on admission is stuporous. On physical examination, the BP is 80/60, pulse rate 120 beats per min and regular, respiratory rate 32 breaths /min , temperature 38.5 degrees C. The extremities are cool and cyanotic. The sclera is icteric. The JVP is flat at 30 degrees, the lungs are clear, there is tenderness in the RUQ and bowel sounds are decreased.

Laboratory Data:

Serum Electrolytes (mEq/l): Na^+ 128, K^+ 5.5, Cl^- 88, HCO_3 18, creatinine 8.2 mg/dl, BUN 86 mg/dl, arterial pH 7.20, pCO_2 20 mmHg, hematocrit 36%, albumin 3.6 g/dl

Urine electrolytes: (mEq/l): Na^+ 46, K^+ 15, Cl^- 30, creatinine 50 mg/dl, FENa (fractional excretion of Na^+) 5.8%, U/P creatinine 6:1, Uosm 250, SG: 1.008

Urine microscopy: 5-10 WBC/hpf, 10-15 RBC/hpf, muddy brown granular casts and tubular casts present

Interpretation of case

The patient is in shock from biliary tract sepsis. Plasma electrolytes are abnormal as was observed with pre-renal failure, however, in this case, the potassium is elevated and the patient has metabolic acidosis (anion gap 22). Also, note that the BUN/Cr ratio is normal at 10:1 whereas with pre-renal azotemia it was 20:1. Tubular function is grossly impaired thus metabolic acidosis is severe. Injury to the tubules prevents the normal process of bicarbonate regeneration such that daily acid production now exceeds renal acid excretion. Tubular injury leads to impaired renal conservation of sodium and water. Consequently, urine sodium concentration is high and urine osmolality is low (less than plasma). Urinary urea and creatinine concentrations are low as a result of impaired filtration and relatively dilute urine. The presence of large amounts of pigmented (muddy brown) granular casts is characteristic of ATN and is an important distinguishing feature of this disorder. Hence, the examination of the urine is extremely important in the differential diagnosis of acute kidney injury.

As mentioned previously the causes of acute tubular necrosis can generally be traced to either ischemic injury or direct nephrotoxic injury. Radiocontrast injury, rhabdomyolysis, and use of non-steroidal antiinflmmatory drugs (NSAIDs) are some of the more common causes of acute tubular necrosis encountered in clinical practice.

Contrast-Induced Nephropathy

Contrast induced nephropathy is characterized by an increase in the serum creatinine concentration 24 to 48 hours after radiocontrast administration. The acute kidney injury is nonoliguric in the vast majority of patients. In almost all cases, the decline in renal function is mild and transient, with recovery of renal function typically beginning within three to five days.

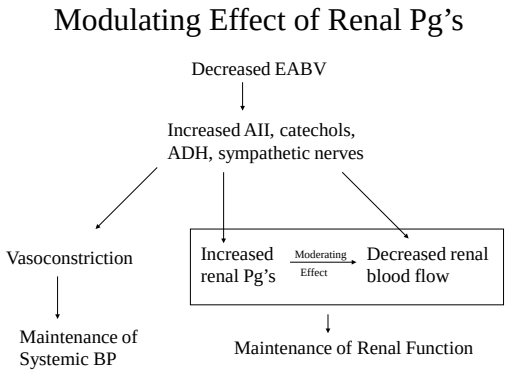
Underlying chronic kidney disease and diabetes mellitus are important risk factors for contrast-induced nephropathy. The most effective intervention to decrease the incidence and severity of this lesion is volume expansion with isotonic saline.

Rhabdomyolysis-induced ATN

Rhabdomyolysis develops when muscle injury leads to release of myoglobin and other intracellular contents into the circulation. Myoglobin is known to cause nephrotoxic injury through a direct toxic effect on the renal tubular cells and cause intratubular obstruction. Muscle breakdown also leads to significant sequestration of fluid such that decreased renal perfusion also plays a contributory role in the development of azotemia. A diagnosis of rhabdomyolysis should be considered in patients with a serum creatine kinase level above 5000 U/L who demonstrate heme positivity on urine dipstick in the absence of hematuria.

Non-steroidal anti-inflammatory Drug (NSAID) Induced ATN

Non-steroidal Anti-inflammatory Drugs (NSAIDs) are some of the most commonly prescribed agents in medicine. In addition, these agents are also available over the counter. In certain settings, these agents can cause an ischemic form of acute tubular necrosis. Because of the widespread use of these agents one should be aware of this complication. Prostaglandins play an important role in the maintenance of renal function primarily in the setting of a systemic or intrarenal circulatory disturbance. The role of prostaglandins is best illustrated when examining renal function under conditions of decreased EABV. In this setting, renal blood flow is decreased while sodium reabsorption and urinary concentrating ability are increased. To a large extent, these findings are mediated by the effects of increased circulating levels of angiotensin II, arginine vasopressin, and catecholamines. At the same time, these hormones stimulate the synthesis of renal prostaglandins, which in turn, act to attenuate these effects. Prostaglandin release under these conditions serves to dampen and counterbalance the physiologic effects of the hormones that elicit their production. As a result, renal function is maintained near normal despite the systemic circulation being clamped down. Predictably, inhibition of prostaglandin synthesis will lead to unopposed activity of these hormonal systems resulting in exaggerated renal vasoconstriction and magnified antinatriuretic and antidiuretic effects.



B. Vascular Renal Disease

This section will discuss 3 different aspects of renal vascular disease: 1) thromboembolic disease of the renal artery, 2) renal vein thrombosis, and 3) renal artery stenosis and acute kidney injury occurring in association with angiotenisn converting enzyme inhibitor or angiotensin receptor blocker therapy.

Thromboembolic Diseases of the Renal Arteries

Arterial thromboemboli or a dissecting aortic aneurysm can cause either ischemic infarction or ischemic atrophy of the kidneys, depending on the extent of vascular occlusion, the rapidity with which occlusion develops, and whether the vascular lesions are a result of clot or atheroemboli. The renal circulation is particularly susceptible to embolic disease because the kidneys normally receive about 20% of the cardiac output.

The primary sources of renal emboli are mural thrombi, which are especially common in patients with atrial arrhythmias or a previous myocardial infarction, and the vegetations associated with bacterial endocarditis. Less often, tumor or fat emboli may be observed. Thrombosis of the renal artery usually is superimposed on an underlying stenotic atheromatous lesion or occurs after a traumatic intimal tear. Rarely, thrombosis occurs as a spontaneous finding.

A wedge-shaped infarct radiating outward from the affected vessel is the classic pathologic change seen in the kidney. The magnitude of the renal injury depends on the extent and duration of the vascular occlusion. Irreversible necrosis usually ensues if the renal artery is totally occluded for 2 hours or longer. Total occlusion for a shorter period may result in acute tubular necrosis rather than infarction.

The clinical findings in renal artery occlusion are variable. Patients may be asymptomatic if the occlusion is incomplete, but nausea, vomiting, flank pain, and fever are common in symptomatic patients. Flank or abdominal tenderness may be detected on physical examination, and a careful search should be undertaken for signs of extrarenal embolization, such as skin lesions and focal neurologic deficits. In addition, an underlying factor that predisposes to arterial embolization, such as atrial fibrillation or a recent myocardial infarction, can often be identified. In many patients, the blood pressure rises shortly after acute infarction as a result of stimulation of the renin-angiotensin system by renal ischemia. The blood pressure usually returns to the baseline level after 2 to 3 weeks.

Most routine laboratory tests are not diagnostic. Gross or microscopic hematuria is observed in only about one third of patients; its frequent absence may reflect the marked reduction in blood supply to the infarcted area, which results in the local cessation of glomerular filtration and urine flow. In the appropriate clinical setting, however, one laboratory finding is highly suggestive of renal infarction: a markedly elevated serum lactate dehydrogenase level (usually greater than five times the upper limit of normal) together with little or no elevation of serum transaminase level.

A radioisotope renogram is the screening procedure of choice for the demonstration of a segmental or generalized decrease in renal perfusion. It is noninvasive and may obviate the need for renal arteriography or contrast-enhanced computed tomography, although these techniques are also useful, particularly if nuclear scanning is unavailable.

Cholesterol Crystal embolization

Cholesterol crystal embolization can be a cause of acute kidney injury in patients with diffuse atherosclerotic disease. This condition can occurr spontanesouly but most often develops after coronary angiography or aortic surgery. Evidence of embolic disease to extrarenal sites can be a clue to the diagnosis. Such sites include the skin (livedo reticularis) and retinal artery emboli (Hollenhorst plaque). Patients present with a rising serum creatinine concentration in association with a bland urine sediment. Some patients develop an increase in the sedimentation rate, peripheral eosinophilia, and hypocomplimentemia.

Renal vein thrombosis

Patients with the nephrotic syndrome have an increased incidence (10 to 40 percent of patients) of arterial and venous thromboemboli, particularly deep vein and renal vein thrombosis (RVT). The tendency to form thrombi at the renal vein in the nephrotic syndrome may be due in part to the loss of fluid across the glomerulus. The ensuing hemoconcentration in the postglomerular circulation may then promote thrombus formation in patients who are already hypercoagulable. RVT may be unilateral or bilateral and may extend into the inferior vena cava.

RVT most often has an insidious onset and produces no symptoms referable to the kidney. In this setting, a pulmonary embolus is usually the only clinical clue to the presence of renal or other deep vein thrombosis. Abnormal ventilation-perfusion scans of the lungs suggestive of pulmonary emboli have been found in as many as 10 to 30 percent of cases with RVT, although most patients are asymptomatic. Infrequently, patients develop acute RVT and present with signs of renal infarction, including flank pain, microscopic or gross hematuria, a marked elevation in plasma lactate dehydrogenase (without change in transaminases), and an increase in renal size on radiographic study. RVT is most common in patients with membranous nephropathy. The gold standards for the diagnosis of RVT are an inferior vena cavagram with selective renal venography, spiral CT scanning, or magnetic resonance imaging using both axial and sagittal views

Renal Artery Stenosis and Angiotensin Converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB)-induced renal dysfunction

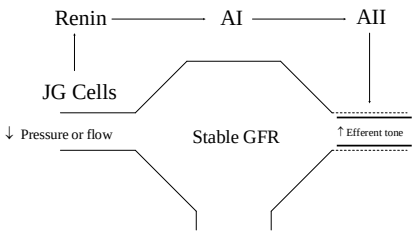
Under conditions of significant (usually >70%) bilateral renal artery obstruction or unilateral renal artery obstruction to a solitary functioning kidney, increased tone of the efferent arteriole acts to attenuate the decline in intraglomerular pressure that results form the arterial obstruction. The trade off is that renal function and glomerular filtration rate become dependent upon sustained constriction of the efferent vessel by AII. A similar physiology can develop in patients with polycystic kidney disease where the renal arteries become extrinsically compressed by large cysts.

ACE inhibitors can also cause an azotemic response under conditions of an absolute (gastroenteritis, aggressive diuresis, poor oral intake) or effective reduction in circulatory volume (moderate to severe congestive heart failure). In these settings angiotensin II-mediated constriction of the efferent arteriole serves to minimize the decline in glomerular filtration rate that would otherwise occur as a result of the fall in renal perfusion pressure. In the volume contracted patient the appropriate response is to hold the ACE inhibitor and restart the drug once the extracellular fluid volume has been replenished.

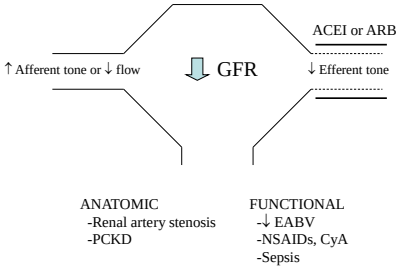
In a patient with congestive heart failure, ACE inhibitors will increase the creatinine when the decrease in intraglomerular pressure resulting from efferent vasodilation is not offset by an increase in renal perfusion. This can occur in patients with severely depressed cardiac function in which afterload reduction can no longer increase cardiac output or in the setting of aggressive diuresis.

A similar mechanism is responsible for renal dysfunction that occurs in patients given ACE inhibitors in the setting of nonsteroidal anti-inflammatory drugs, cyclosporin A (CyA) or early sepsis. In these settings, there is increased vasoconstriction of the renal vasculature. ACE inhibitor-induced efferent vasodilation in the face of decreased perfusion pressure accounts for the fall in glomerular filtration rate.

Maintenance of GFR with Low Flow or Perfusion Pressure



Therapeutic Complications of ACEI or ARB



ANATOMIC
-Renal artery stenosis
-PCKD

FUNCTIONAL
-↓ EABV
-NSAIDs, CyA
-Sepsis