The kidneys are susceptible to toxic or ischemic injury for several reasons. Thus, it is not surprising that an impressive list of exogenous drugs and chemicals can cause clinical acute renal failure (ARF) [1]. On the contrary, the contribution of environmental toxins to ARF is rather limited. In this chapter, some of the most common drugs and exogenous toxins encountered by the nephrologist in clinical practice are discussed in detail.

The clinical expression of the nephrotoxicity of drugs and chemicals is highly variable and is influenced by several factors. Among these is the direct toxic effect of drugs and chemicals on a particular type of nephron cell, the pharmacologic activity of some substances and their effects on renal function, the high metabolic activity (ie, vulnerability) of particular segments of the nephron, the multiple transport systems, which can result in intracellular accumulation of drugs and chemicals, and the high intratubule concentrations with possible precipitation and crystallization of particular drugs.
11.2 Acute Renal Failure

General Nephrotoxic Factors

FIGURE 11-1
Sites of renal damage, including factors that contribute to the kidney's susceptibility to damage. ACE—angiotensin-converting enzyme; NSAID—nonsteroidal anti-inflammatory drugs; HgCl₂—mercuric chloride.
Renal Injury Due To Environmental Toxins, Drugs, and Contrast Agents

### DRUGS AND CHEMICALS ASSOCIATED WITH ACUTE RENAL FAILURE

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>Cyclosporine, tacrolimus</td>
</tr>
<tr>
<td>M2</td>
<td>Amphotericin B, radiocontrast agents</td>
</tr>
<tr>
<td>M3</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>M4</td>
<td>Angiotensin-converting enzyme inhibitors, interleukin-2†</td>
</tr>
<tr>
<td>M5</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>M6</td>
<td>Aminoglycosides, cisplatin, foscarnet, heavy metals, intravenous immunoglobulin*, organic solvents, pentamidine, Cocaine, Ethanol, lovastatin**</td>
</tr>
<tr>
<td></td>
<td>Sulfonamides</td>
</tr>
<tr>
<td></td>
<td>Acyclovir, Indinavir, chemotherapeutic agents, ethylene glycol***</td>
</tr>
<tr>
<td></td>
<td>Allopurinol, cephalosporins, cimetidine, ciprofloxacin, furosemide, penicillins, phenytoin, rifampin, thiazide diuretics</td>
</tr>
<tr>
<td></td>
<td>Conjugated estrogens, mitomycin, quinine</td>
</tr>
</tbody>
</table>

* Many other drugs in addition to the ones listed can cause renal failure by this mechanism.
† Interleukin-2 produces a capillary leak syndrome with volume contractions.
‡ Uric acid crystals form as a result of tumor lysis.
§ The mechanism of this agent is unclear but may be due to additives.
** Acute renal failure is most likely to occur when lovastatin is given in combination with cyclosporine.
*** Ethylene glycol–induced toxicity can cause calcium oxalate crystals.

---

**FIGURE 11-2**

Drugs and chemicals associated with acute renal failure. (Adapted from Thadhani, et al. [2].)
11.4 Acute Renal Failure

**Aminoglycosides**

1. Filtration
2. Binding
3. Adsorptive pinocytosis
4. Lysosomal trapping and storage

**Nephrotoxicity and ototoxicity remain frequent side effects that seriously limit the use of aminoglycosides, a still important class of antibiotics.** Aminoglycosides are highly charged, polycationic, hydrophilic drugs that cross biologic membranes little, if at all [4,5]. They are not metabolized but are eliminated unchanged almost entirely by the kidneys. Aminoglycosides are filtered by the glomerulus at a rate almost equal to that of water. After entering the luminal fluid of proximal renal tubule, a small but toxicologically important portion of the filtered drug is reabsorbed and stored in the proximal tubule cells. The major transport of aminoglycosides into proximal tubule cells involves interaction with acidic, negatively charged phospholipid-binding sites at the level of the brush border membrane.

After charge-mediated binding, the drug is taken up into the cell in small invaginations of the cell membrane, a process in which megalin seems to play a role [6]. Within 1 hour of injection, the drug is located at the apical cytoplasmic vacuoles, called endocytotic vesicles. These vesicles fuse with lysosomes, sequestering the unchanged aminoglycosides inside those organelles.

Once trapped in the lysosomes of proximal tubule cells, aminoglycosides electrostatically attached to anionic membrane phospholipids interfere with the normal action of some enzymes (i.e., phospholipases and sphingomyelinase). In parallel with enzyme inhibition, undigested phospholipids originating from the turnover of cell membranes accumulate in lysosomes, where they are normally digested. The overall result is lysosomal phospholipidosis due to nonspecific accumulation of polar phospholipids as “myeloid bodies,” so called for their typical electron microscopic appearance. (Adapted from De Broe [3].)

**FIGURE 11-3**
Renal handling of aminoglycosides: 1) glomerular filtration; 2) binding to the brush border membranes of the proximal tubule; 3) pinocytosis; and 4) storage in the lysosomes [3].

**FIGURE 11-4**
Ultrastructural appearance of proximal tubule cells in aminoglycoside-treated patients (4 days of therapeutic doses). Lysosomes (large arrow) contain dense lamellar and concentric structures. Brush border, mitochondria (small arrows) and peroxisomes are unaltered. At higher magnification the structures in lysosomes show a periodic pattern. The bar in A represents 1 µm, in part B, 0.1 µm [7].
Administration of aminoglycosides for days induces progression of lysosomal phospholipidosis. The overloaded lysosomes continue to swell, even if the drug is then withdrawn. In vivo this overload may result in loss of integrity of the membranes of lysosomes and release of large amounts of lysosomal enzymes, phospholipids, and aminoglycosides into the cytosol, but this has not been proven. Thus, these aminoglycosides can gain access to and injure other organelles, such as mitochondria, and disturb their functional integrity, which leads rapidly to cell death. As a consequence of cell necrosis, A, intratubular obstruction by cell debris increased intratubule pressure, a decrease in the glomerular filtration rate and cellular infiltration, B, may ensue. In parallel with these lethal processes in the kidney, a striking regeneration process is observed that is characterized by a dramatic increase in tubule cell turnover and proliferation, C, in the cortical interstitial compartment.

A, Relationship between constant serum levels and concomitant renal cortical accumulation of gentamicin after a 6 hour intravenous infusion in rats. The rate of accumulation is expressed in micrograms of aminoglycoside per gram of wet kidney cortex per hour, due to the linear accumulation in function of time. Each point represents one rat whose aminoglycosides were measured in both kidneys at the end of the infusion and the serum levels assayed twice during the infusion [8].

(Continued on next page)
In rats, nephrotoxicity of gentamicin is more pronounced when the total daily dose is administered by continuous infusion rather than as a single injection. Thus, a given daily drug does not produce the same degree of toxicity when it is given by different routes. Indeed, renal cortical uptake is “less efficient” at high serum concentration than at low ones. A single injection results in high peak serum levels that overcome the saturation limits of the renal uptake mechanism. The high plasma concentrations are followed by fast elimination and, finally, absence of the drug for a while. This contrasts with the continuous low serum levels obtained with more frequent dosing when the uptake at the level of the renal cortex is not only more efficient but remains available throughout the treatment period. $V_{\text{max}}$—maximum velocity.

Two trials in humans found that the dosage schedule had a critical effect on renal uptake of gentamicin, netilmicin [10], amikacin, and tobramycin [11]. Subjects were patients with normal renal function (serum creatinine concentration between 0.9 and 1.2 mg/dL, proteinuria lower than 300 mg/24 h) who had renal cancer and submitted to nephrectomy. Before surgery, patients received gentamicin (4.5 mg/kg/d), netilmicin (5 mg/kg/d), amikacin (15 mg/kg/d), or tobramycin (4.5 mg/kg/d) as a single injection or as a continuous intravenous infusion over 24 hours [10,11].

For tobramycin, no difference in renal accumulation could be found, indicating the linear cortical uptake of this particular aminoglycoside [8]. These data, which supported decreased nephrotoxic potential of single-dose regimens, coincided with new insights in the antibacterial action of aminoglycosides (concentration-dependent killing of gram-negative bacteria and prolonged postantibiotic effect) [12]. N.S.—not significant.
### Risk Factors for Aminoglycoside Nephrotoxicity

<table>
<thead>
<tr>
<th>Patient-Related Factors</th>
<th>Aminoglycoside-Related Factors</th>
<th>Other Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age*</td>
<td>Recent aminoglycoside therapy</td>
<td>Amphotericin B</td>
</tr>
<tr>
<td>Preexisting renal disease</td>
<td>Larger doses*</td>
<td>Cefalosporins</td>
</tr>
<tr>
<td>Female gender</td>
<td>Treatment for 3 days or more*</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Magnesium, potassium, or calcium deficiency*</td>
<td>Dose regimen*</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Intravascular volume depletion*</td>
<td></td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Hypotension*</td>
<td></td>
<td>Foscarnet</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td></td>
<td>Furosemide</td>
</tr>
<tr>
<td>Sepsis syndrome</td>
<td></td>
<td>Piperacillin</td>
</tr>
</tbody>
</table>

* Similar to experimental data.

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### Prevention of Aminoglycoside Nephrotoxicity

- Identify risk factor
  - Patient related
  - Drug related
  - Other drugs
- Give single daily dose of gentamicin, netilmicin, or amikacin
- Reduce the treatment course as much as possible
- Avoid giving nephrotoxic drugs concurrently
- Make interval between aminoglycoside courses as long as possible
- Calculate glomerular filtration rate out of serum creatinine concentration

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**Figure 11-8**
Risk factors for aminoglycoside nephrotoxicity. Several risk factors have been identified and classified as patient related, aminoglycoside related, or related to concurrent administration of certain drugs. The usual recommended aminoglycoside dose may be excessive for older patients because of decreased renal function and decreased regenerative capacity of a damaged kidney. Preexisting renal disease clearly can expose patients to inadvertent overdosing if careful dose adjustment is not performed. Hypomagnesemia, hypokalemia, and calcium deficiency may be predisposing risk factors for consequences of aminoglycoside-induced damage [13]. Liver disease is an important clinical risk factor for aminoglycoside nephrotoxicity, particularly in patients with cholestasis [13]. Acute or chronic endotoxemia amplifies the nephrotoxic potential of the aminoglycosides [14].

**Figure 11-9**
Prevention of aminoglycoside nephrotoxicity. Coadministration of other potentially nephrotoxic drugs enhances or accelerates the nephrotoxicity of aminoglycosides. Comprehension of the pharmacokinetics and renal cell biologic effects of aminoglycosides, allows identification of aminoglycoside-related nephrotoxicity risk factors and makes possible secondary prevention of this important clinical nephrotoxicity.
Amphotericin B

**Proposed partial model for the amphotericin B (AmB)–induced pore in the cell membrane.** AmB is an amphipathic molecule: its structure enhances the drug’s binding to sterols in the cell membranes and induces formation of aqueous pores that result in weakening of barrier function and loss of protons and cations from the cell. The drug acts as a counterfeit phospholipid, with the $C_{15}$ hydroxyl, $C_{16}$ carboxyl, and $C_{19}$ mycosamine groups situated at the membrane-water interface, and the $C_1$ to $C_{14}$ and $C_{20}$ to $C_{33}$ chains aligned in parallel within the membrane. The heptaene chain seeks a hydrophobic environment, and the hydroxyl groups seek a hydrophilic environment. Thus, a cylindrical pore is formed, the inner wall of which consists of the hydroxyl-substituted carbon chains of the AmB molecules and the outer wall of which is formed by the heptaene chains of the molecules and by sterol nuclei [15].
Risk factors for development of amphotericin B (AmB) nephrotoxicity. Nephrotoxicity of AmB is a major problem associated with clinical use of this important drug. Disturbances in both glomerular and tubule function are well described. The nephrotoxic effect of AmB is initially a distal tubule phenomenon, characterized by a loss of urine concentration, distal renal tubule acidosis, and wasting of potassium and magnesium, but it also causes renal vasoconstriction leading to renal ischemia. Initially, the drug binds to membrane sterols in the renal vasculature and epithelial cells, altering its membrane permeability. AmB-induced vasoconstriction and ischemia to very vulnerable sections of the nephron, such as medullary thick ascending limb, enhance the cell death produced by direct toxic action of AmB on those cells. This explains the salutary effect on AmB nephrotoxicity of salt loading, furosemide, theophylline, or calcium channel blockers, all of which improve renal blood flow or inhibit transport in the medullary thick ascending limb.

**FIGURE 11-11**

Proposed approach for management of amphotericin B (AmB) therapy. Several new formulations of amphotericin have been developed either by incorporating amphotericin into liposomes or by forming complexes to phospholipid. In early studies, nephrotoxicity was reduced, allowing an increase of the cumulative dose. Few studies have established a therapeutic index between antifungal and nephrotoxic effects of amphotericin. To date, the only clinically proven intervention that reduces the incidence and severity of nephrotoxicity is salt supplementation, which should probably be given prophylactically to all patients who can tolerate it. (From Bernardo JF, et al. [16]; with permission.)
11.10 Acute Renal Failure

**Cyclosporine**

Intravascular coagulation in a cyclosporine-treated renal transplant recipient. Cyclosporine produces a dose-related decrease in renal function in experimental animals and humans [17] that is attributed to the drug’s hemodynamic action to produce vasoconstriction of the afferent arteriole entering the glomerulus. When severe enough, this can decrease glomerular filtration rate. Although the precise pathogenesis of the renal hemodynamic effects of cyclosporine are unclear, endothelin, inhibition of nitric oxide, release of vasoconstrictor prostaglandins such as thromboxane A₂, and activation of the sympathetic nervous system, are among the candidates for cyclosporine-induced vasoconstriction [18].

The diagnosis of cyclosporine-induced acute renal dysfunction is not difficult when the patient has no other reason for reduced renal function (e.g., psoriasis, rheumatoid arthritis). In renal transplant recipients, however, the situation is completely different. In this clinical setting, the clinician must differentiate between cyclosporine injury and acute rejection. The incidence of this acute cyclosporine renal injury can be enhanced by extended graft preservation, preexisting histologic lesions, donor hypotension, or preoperative complications. The gold standard for this important distinction remains renal biopsy.

In addition, cyclosporine has been associated with hemolytic-uremic syndrome with thrombocytopenia, red blood cell fragmentation, and intravascular (intraglomerular) coagulation. Again, this drug-related intravascular coagulation has to be differentiated from that of acute rejection. The absence of clinical signs and of rejection-related interstitial edema and cellular infiltrates can be helpful. Vanrenterghem and coworkers [19] found a high incidence of venous thromboembolism shortly after (several of them within days) cadaveric kidney transplantation in patients treated with cyclosporine, in contrast to those treated with azathioprine. Recent studies [20] have shown that impaired fibrinolysis, due mainly to excess plasminogen activator inhibitor (PAI-1), may also contribute to this imbalance in coagulation and anticoagulation during cyclosporine treatment.

**Lithium-Induced Acute Renal Failure**

<table>
<thead>
<tr>
<th>Toxic Effect</th>
<th>Plasma Lithium Level</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>1–1.5 mmol/L</td>
<td>Impaired concentration, lethargy, irritability, muscle weakness, tremor, drowsy speech, nausea</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.6–2.5 mmol/L</td>
<td>Disorientation, confusion, drowsiness, restlessness, unsteady gait, coarse tremor, dystartria, muscle fasculation, vomiting</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;2.5 mmol/L</td>
<td>Impaired consciousness (with progression to coma), delirium, ataxia, generalized fasciculations, extrapyramidal symptoms, convulsions, impaired renal function</td>
</tr>
</tbody>
</table>

Symptoms and signs of toxic effects of lithium. Lithium can cause acute functional and histologic (usually reversible) renal injury. Within 24 hours of administration of lithium to humans or animals, sodium diuresis occurs and impairment in the renal concentrating capacity becomes apparent. The defective concentrating capacity is caused by vasopressin-resistant (exogenous and endogenous) diabetes insipidus. This is in part related to lithium’s inhibition of adenylate cyclase and impairment of vasopressin-induced generation of cyclic adenosine monophosphatase.

Lithium-induced impairment of distal urinary acidification has also been defined. A cute lithium intoxication in humans and animals can cause acute renal failure. The clinical picture features nonspecific signs of degenerative changes and necrosis of tubule cells [21]. The most distinctive and specific acute lesions lie at the level of the distal tubule [22]. They consist of swelling and vacuolization of the cytoplasm of the distal nephron cells plus periodic acid-Schiff-positive granular material in the cytoplasm (shown to be glycogen) [23]. Most patients receiving lithium have side effects, reflecting the drug’s narrow therapeutic index.
Renal Injury Due To Environmental Toxins, Drugs, and Contrast Agents

**FIGURE 11-15**

Drug interactions with lithium [24]. Acute renal failure, with or without oliguria, can be associated with lithium treatment, and with severe dehydration. In this case, acute renal failure can be considered a prerenal type; consequently, it resolves rapidly with appropriate fluid therapy. Indeed, the histologic appearance in such cases is remarkable for its lack of significant abnormalities. Conditions that stimulate sodium retention and consequently lithium reabsorption, such as low salt intake and loss of body fluid by way of vomiting, diarrhea, or diuretics, decreasing lithium clearance should be avoided. With any acute illness, particularly one associated with gastrointestinal symptoms such as diarrhea, lithium blood levels should be closely monitored and the dose adjusted when necessary. Indeed, most episodes of acute lithium intoxication are largely predictable, and thus avoidable, provided that precautions are taken [25].

Removing lithium from the body as soon as possible is the mainstay of treating lithium intoxication. With preserved renal function, excretion can be increased by use of furosemide, up to 40 mg/h, obviously under close monitoring for excessive losses of sodium and water induced by this loop diuretic. When renal function is impaired in association with severe toxicity, extracorporeal extraction is the most efficient way to decrease serum lithium levels. One should, however, remember that lithium leaves the cells slowly and that plasma levels rebound after hemodialysis is stopped, so that longer dialysis treatment or treatment at more frequent intervals is required.

**Inhibitors of the Renin-Angiotensin System**

Soon after the release of this useful class of antihypertensive drugs, the syndrome of functional acute renal insufficiency was described as a class effect. This phenomenon was first observed in patients with renal artery stenosis, particularly when the entire renal mass was affected, as in bilateral renal artery stenosis or in renal transplants with stenosis to a solitary kidney [26]. A acute renal dysfunction appears to be related to loss of postglomerular efferent arteriolar vascular tone and in general is reversible after withdrawing the angiotensin-converting enzyme (ACE) inhibitor [27].

Inhibition of the ACE kinase II results in at least two important effects: depletion of angiotensin II and accumulation of bradykinin [28]. The role of the latter effect on renal perfusion pressure is not clear. A. To understand the angiotensin I converting enzyme inhibitor-induced drop in glomerular filtration rate, it is important to understand the physiologic role of the renin-angiotensin system in the regulation of renal hemodynamics, B. When renal perfusion drops, renin is released into the plasma and lymph by the juxtaglomerular cells of the kidneys. Renin cleaves angiotensinogen to form angiotensin I, which is cleaved further by converting enzyme to form angiotensin II, the principal effector molecule in this system. Angiotensin II participates in glomerular filtration rate regulation in at least two ways. First, angiotensin II increases arterial pressure—directly and acutely by causing vasoconstriction and more "chronically" by increasing body fluid volumes through stimulation of renal sodium retention; directly through an effect on the tubules, as well as by stimulating thirst.

(Continued on next page)
and indirectly via aldosterone. Second, angiotensin II preferentially constricts the efferent arteriole, thus helping to preserve glomerular capillary hydrostatic pressure and, consequently, glomerular filtration rate.

When arterial pressure or body fluid volumes are sensed as subnormal, the renin-angiotensin system is activated and plasma renin activity and angiotensin II levels increase. This may occur in the context of clinical settings such as renal artery stenosis, acute renal failure, diuretic therapy, congestive heart failure, cirrhosis, nephrotic syndrome, cirrhosis, sodium restriction depletion, advanced age (age >80).

B1. Normal condition

- Myogenic reflex (Laplace)
- Tubuloglomerular feedback

Autoregulation

Afferent arteriole → Glomerulus → Efferent arteriole

PGE2

B2. Perfusion pressure reduced but still within autoregulatory range (congestive heart failure, renal artery stenosis, diuretic therapy, nephrotic syndrome, cirrhosis, sodium restriction depletion, advanced age [age >80])

- PGE2

B3. Perfusion pressure seriously reduced (prerenal azotemia)

- Local angiotensin II

Sympathetic activity

Angiotensin II

PGE2

Intra-glomerular pressure

Mechanism by which nonsteroidal anti-inflammatory drugs (NSAIDs) disrupt the compensatory vasodilatation response of renal prostaglandins to vasoconstrictor hormones in patients with prerenal conditions. Most of the renal abnormalities encountered clinically as a result of NSAIDs can be attributed to the action of these compounds on prostaglandin production in the kidney [31].

Sodium chloride and water retention are the most common side effects of NSAIDs. This should not be considered drug toxicity because it represents a modification of a physiologic control mechanism without the production of a true functional disorder in the kidney.
### Predisposing Factors for NSAID-Induced Acute Renal Failure

- Severe heart disease (congestive heart failure)
- Severe liver disease (cirrhosis)
- Nephrotic syndrome (low oncotic pressure)
- Chronic renal disease
- Age 80 years or older
- Protracted dehydration (several days)

### Conditions Associated with Risk for NSAID-Induced Acute Renal Failure

NSAIDs can induce acute renal decompensation in patients with various renal and extrarenal clinical conditions that cause a decrease in blood perfusion to the kidney [32]. Renal prostaglandins play an important role in the maintenance of homeostasis in these patients, so disruption of counter-regulatory mechanisms can produce clinically important, and even severe, deterioration in renal function.

![Diagram of Physiologic and Inflammatory Stimuli](image)

**Figure 11-18**

Inhibition by nonsteroidal anti-inflammatory drugs (NSAIDs) on pathways of cyclo-oxygenase (COX) and prostaglandin synthesis [33]. The recent demonstration of the existence of functionally distinct isoforms of the COX enzyme has major clinical significance, as it now appears that one form of COX is operative in the gastric mucosa and kidney for prostaglandin generation (COX-1) whereas an inducible and functionally distinct form of COX is operative in the production of prostaglandins in the sites of inflammation and pain (COX-2) [33]. The clinical therapeutic consequence is that an NSAID with inhibitory effects dominantly or exclusively upon the COX isoenzyme induced at a site of inflammation may produce the desired therapeutic effects without the hazards of deleterious effects on the kidneys or gastrointestinal tract. PG—prostaglandin; TxA₂—thromboxane A₂.
Acute Renal Failure

EFFECTS OF NSAIDS ON RENAL FUNCTION

<table>
<thead>
<tr>
<th>Renal Syndrome</th>
<th>Mechanism</th>
<th>Risk Factors</th>
<th>Prevention/Treatment [34]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium retention and edema</td>
<td>↓ Prostaglandin</td>
<td>NSAID therapy (most common side effect)</td>
<td>Stop NSAID</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>↓ Prostaglandin</td>
<td>Renal disease, Heart failure, Diabetes, Multiple myeloma, Potassium therapy, Potassium-sparring diuretic</td>
<td>Stop NSAID, Avoid use in high-risk patients</td>
</tr>
<tr>
<td></td>
<td>↓ Potassium to distal tubule</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ Aldosterone/rein-angiotensin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute deterioration of renal function</td>
<td>↓ Prostaglandin and disruption of hemodynamic balance</td>
<td>Liver disease, Renal disease, Heart failure, Dehydration, Old age</td>
<td>Stop NSAID, Avoid use in high-risk patients</td>
</tr>
<tr>
<td>Nephrotic syndrome with:</td>
<td>↑ Lymphocyte recruitment and activation</td>
<td>Fenoprofen</td>
<td>Stop NSAID</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td></td>
<td>Combination aspirin and acetaminophen abuse</td>
<td>Avoid long-term analgesic use</td>
</tr>
<tr>
<td>Papillary necrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 11-20
Summary of effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on renal function [31].

All NSAIDs can cause another type of renal dysfunction that is associated with various levels of functional impairment and characterized by the nephrotic syndrome together with interstitial nephritis.

Characteristically, the histology of this form of NSAID-induced nephrotic syndrome consists of minimal-change glomerulonephritis with tubulointerstitial nephritis. This is an unusual combination of findings and in the setting of protracted NSAID use is virtually pathognomonic of NSAID-related nephrotic syndrome.

A focal diffuse inflammatory infiltrate can be found around the proximal and distal tubules. The infiltrate consists primarily of cytotoxic T lymphocytes but also contains other T cells, some B cells, and plasma cells. Changes in the glomeruli are minimal and resemble those of classic minimal-change glomerulonephritis with marked epithelial foot process fusion.

Hyperkalemia, an unusual complication of NSAIDs, is more likely to occur in patients with pre-existing renal impairment, cardiac failure, diabetes, or multiple myeloma or in those taking potassium supplements, potassium-sparring diuretic therapy, or intercurrent use of an angiotensin-converting enzyme inhibitor. The mechanism of NSAID hyperkalemia—suppression of prostaglandin-mediated renin release—leads to a state of hyporeninemic hypaldosteronism. In addition, NSAIDs, particularly indomethacin, may have a direct effect on cellular uptake of potassium.

The renal saline response to loop diuretics is partially a consequence of intrarenal prostaglandin production. This component of the response to loop diuretics is meditated by an increase in renal medullary blood flow and an attendant reduction in renal concentrating capacity. Thus, concurrent use of an NSAID may blunt the diuresis induced by loop diuretics.

Contrast Medium-Associated Nephrotoxicity

RISK FACTORS THAT PREDISPOSE TO CONTRAST-ASSOCIATED NEPHROPATHY

<table>
<thead>
<tr>
<th>Confirmed</th>
<th>Suspected</th>
<th>Disproved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic renal failure</td>
<td>Hypertension</td>
<td>Myeloma</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>Generalized atherosclerosis</td>
<td>Diabetes without nephropathy</td>
</tr>
<tr>
<td>Severe congestive heart failure</td>
<td>Abnormal liver function tests</td>
<td></td>
</tr>
<tr>
<td>Amount and frequency of contrast media</td>
<td>Hyperuricemia</td>
<td></td>
</tr>
<tr>
<td>Volume depletion or hypotension</td>
<td>Proteinuria</td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 11-21
Risk factors that predispose to contrast-associated nephropathy. In random populations undergoing radiocontrast imaging the incidence of contrasts associated nephropathy defined by a change in serum creatinine of more than 0.5 mg/dL or a greater than 50% increase over baseline, is between 2% and 7%. For confirmed high-risk patients (baseline serum creatinine values greater than 1.5 mg/dL) it rises to 10% to 35%. In addition, there are suspected risk factors that should be taken into consideration when considering the value of contrast-enhanced imaging.
Renal Injury Due To Environmental Toxins, Drugs, and Contrast Agents

**FIGURE 11-22**
A proposed model of the mechanisms involved in radiocontrast medium-induced renal dysfunction. Based on experimental models, a consensus is developing to the effect that contrast-associated nephropathy involves combined toxic and hypoxic insults to the kidney [35]. The initial glomerular vasoconstriction that follows the injection of radiocontrast medium induces the liberation of both vasoconstrictor (endothelin, vasopressin) and vasodilator (prostaglandin $E_2$ [PGE$_2$], adenosine, atrionatriuretic factor (ANP)) substances. The net effect is reduced oxygen delivery to tubule cells, especially those in the thick ascending limb of Henle. Because of the systemic hypoxemia, raised blood viscosity, inhibition of sodium-potassium–activated ATPase and the increased osmotic load to the distal tubule at a time of reduced oxygen delivery, the demand for oxygen increases, resulting in cellular hypoxia and, eventually, cell death. Additional factors that contribute to the acute renal dysfunction of contrast-associated nephropathy are the tubule obstruction that results from increased secretion of Tamm-Horsfall proteins and the liberation of reactive oxygen species and lipid peroxidation that accompany cell death. As noted in the figure, calcium antagonists and theophylline (adenosine receptor antagonist) are thought to act to diminish the degree of vasoconstriction induced by contrast medium.

**FIGURE 11-23**
Prevention of contrast-associated nephropathy. The goal of management is the prevention of contrast-associated nephropathy.

Thus it is important to select the least invasive diagnostic procedure that provides the most information, so that the patient can make an informed choice from the available clinical alternatives. Since radiographic contrast imaging is frequently performed for diabetic nephropathy, congestive heart failure, or chronic renal failure, concurrent administration of renoprotective agents has become an important aspect of imaging. A list of maneuvers that minimize the risk of contrast-associated nephropathy is contained in this table. The correction of pre-study volume depletion and the use of active hydration before and during the procedure are crucial to minimizing the risk of contrast-associated nephropathy. Limiting the total volume of contrast medium and using nonionic, iso-osmolar media have proven to be protective for high-risk patients. Pretreatment with calcium antagonists is an intriguing but unsubstantiated approach.
11.16
Acute Renal Failure

References


