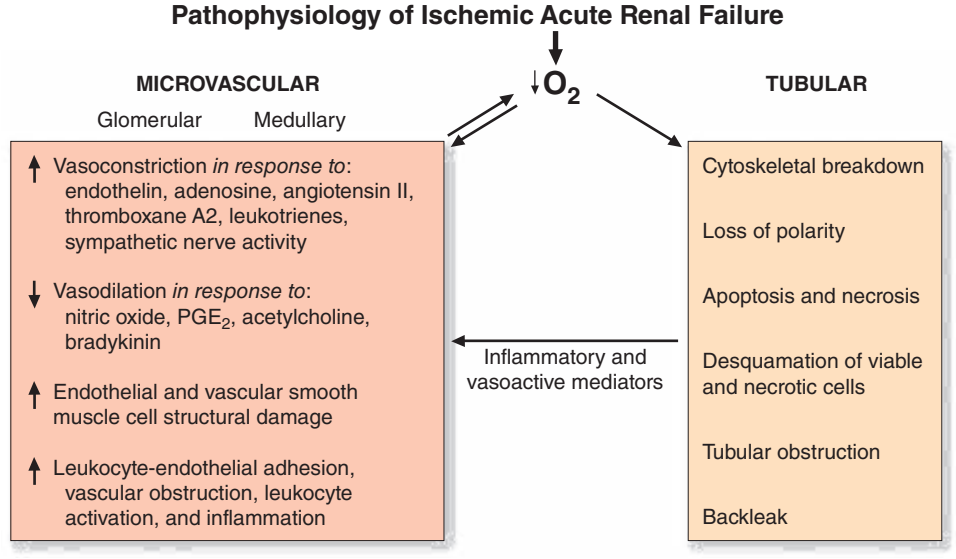

FIGURE 334-4 Interacting microvascular and tubular events contributing to the pathophysiology of ischemic acute kidney injury. PGE_2, prostaglandin E_2. *(From JV Bonventre, JM Weinberg: J Am Soc Nephrol 14:2199, 2003.)*

injury from sustained hypoperfusion, cardiopulmonary bypass may cause AKI through a number of mechanisms including extracorporeal circuit activation of leukocytes and inflammatory processes, hemolysis with resultant pigment nephropathy (see below), and aortic injury with resultant atheroemboli. AKI from atheroembolic disease, which can also occur following percutaneous catheterization of the aorta, or spontaneously, is due to cholesterol crystal embolization resulting in partial or total occlusion of multiple small arteries within the kidney. Over time, a foreign body reaction can result in intimal proliferation, giant cell formation, and further narrowing of the vascular lumen, accounting for the generally subacute (over a period of weeks rather than days) decline in renal function.

Burns and Acute Pancreatitis Extensive fluid losses into the extravascular compartments of the body frequently accompany severe burns and acute pancreatitis. AKI is an ominous complication of burns, affecting 25% of individuals with more than 10% total body surface area involvement. In addition to severe hypovolemia resulting in decreased cardiac output and increased neurohormonal activation, burns and acute pancreatitis both lead to dysregulated inflammation and an increased risk of sepsis and acute lung injury, all of which may facilitate the development and progression of AKI. Individuals undergoing massive fluid resuscitation for trauma, burns, and acute pancreatitis can also develop the abdominal compartment syndrome, where markedly elevated intraabdominal pressures, usually higher than 20 mmHg, lead to renal vein compression and reduced GFR.

Diseases of the Microvasculature Leading to Ischemia Microvascular causes of AKI include the thrombotic microangiopathies (antiphospholipid antibody syndrome, radiation nephritis, malignant nephrosclerosis, and thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome [TTP-HUS]), scleroderma, and atheroembolic disease. Large-vessel diseases associated with AKI include renal artery dissection, thromboembolism, thrombosis, and renal vein compression or thrombosis.

NEPHROTOXIN-ASSOCIATED AKI

The kidney has very high susceptibility to nephrotoxicity due to extremely high blood perfusion and concentration of circulating substances along the nephron where water is reabsorbed and in the medullary interstitium; this results in high-concentration exposure of toxins to tubular, interstitial, and endothelial cells. Nephrotoxic injury occurs in response to a number of pharmacologic compounds with diverse structures, endogenous substances, and environmental exposures. All structures of the kidney are vulnerable to toxic injury, including the tubules, interstitium, vasculature, and collecting system. As with other forms of AKI, risk factors for nephrotoxicity include older age, chronic kidney disease (CKD), and prerenal azotemia. Hypoalbuminemia may increase the risk of some forms of nephrotoxin-associated AKI due to increased free circulating drug concentrations.

Contrast Agents Iodinated contrast agents used for cardiovascular and computed tomography (CT) imaging are a leading cause of AKI. The risk of AKI, or "contrast nephropathy," is negligible in those with normal renal function but increases markedly in the setting of CKD, particularly diabetic nephropathy. The most common clinical course of contrast nephropathy is characterized by a rise in SCr beginning 24–48 h following exposure, peaking within 3–5 days, and resolving within 1 week. More severe, dialysis-requiring AKI is uncommon except in the setting of significant preexisting CKD, often in association with congestive heart failure or other coexisting causes for ischemia-associated AKI. Patients with multiple myeloma and renal disease are particularly susceptible. Low fractional excretion of sodium and relatively benign urinary sediment without features of tubular necrosis (see below) are common findings. Contrast nephropathy is thought to occur from a combination of factors, including (1) hypoxia in the renal outer medulla due to perturbations in renal microcirculation and occlusion of small vessels; (2) cytotoxic damage to the tubules directly or via the generation of oxygen free radicals, especially because the concentration of the agent within the tubule is markedly increased; and (3) transient tubule obstruction with precipitated contrast material. Other diagnostic agents implicated as a cause of AKI are high-dose gadolinium used for magnetic resonance imaging (MRI) and oral sodium phosphate solutions used as bowel purgatives.

Antibiotics Several antimicrobial agents are commonly associated with AKI. *Aminoglycosides and amphotericin B* both cause tubular necrosis. Nonoliguric AKI (i.e., without a significant reduction in urine volume) accompanies 10–30% of courses of aminoglycoside antibiotics, even when plasma levels are in the therapeutic range. Aminoglycosides are freely filtered across the glomerulus and then accumulate within the renal cortex, where concentrations can greatly exceed those of the plasma. AKI typically manifests after 5–7 days of therapy and can present even after the drug has been discontinued. Hypomagnesemia is a common finding.

Amphotericin B causes renal vasoconstriction from an increase in tubuloglomerular feedback as well as direct tubular toxicity mediated by reactive oxygen species. Nephrotoxicity from amphotericin B is dose and duration dependent. This drug binds to tubular membrane cholesterol and introduces pores. Clinical features of amphotericin B nephrotoxicity include polyuria, hypomagnesemia, hypocalcemia, and nongap metabolic acidosis.

Vancomycin may be associated with AKI, particularly when trough levels are high, but a causal relationship with AKI has not been definitively