Possible prevention and therapy of postischemic (ischemic) acute tubular necrosis

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INTRODUCTION — The renal failure phase in patients with postischemic (also called ischemic) acute tubular necrosis (ATN) typically lasts 7 to 21 days [1], with most patients returning to or near their previous baseline level of renal function as the necrotic tubular cells regenerate. Regenerating tubular cells appear to be mostly derived from dedifferentiated cells (kidney-derived stem cells) that have survived the ischemic insult [2-4]. Migrating bone marrow stem cells may contribute to this process, but to a lesser extent.

The following provides an overview of the different phases of ATN due to ischemia (figure 1):

- Initiation phase – Postischemic ATN begins with an early phase of vasomotor nephropathy in which there are associated alterations in vascular reactivity and renal perfusion. These changes lead to cellular adenosine triphosphate (ATP) depletion and oxidative injury.
- Extension phase – The changes in the initiation phase lead to activation of resident cells, such as dendritic cells, macrophages, endothelial cells, and renal epithelial cells, leading to a proinflammatory state. Inflammatory cells adhere to activated endothelium in the peritubular capillaries of the outer medulla; this results in medullary congestion and further hypoxic injury to the S3 segment of the proximal tubule. Elaboration of inflammatory mediators leads to additional cellular injury.
- Maintenance phase – Restoration of tubule cells is accomplished via several potential mechanisms:
  - Adjacent tubule cells redifferentiate and proliferate.
  - Kidney stem cells differentiate into tubule cells.
  - Hematopoietic cells engraft into areas of injury and differentiate into tubule cells or fuse with damaged cells, restoring vital cellular components necessary for cell survival.
- Repair phase – Polarity and function are ultimately reconstituted.

Possible preventive and therapeutic measures for postischemic ATN will be reviewed here, considering experimental animal trials separately from human clinical trials. Pathogenesis and prognosis are discussed separately. (See "Renal and patient outcomes after acute tubular necrosis" and "Pathogenesis and etiology of postischemic (ischemic) acute tubular necrosis".)

EXPERIMENTAL STUDIES — Except for a few isolated studies, the vast majority of animal studies have yet to conclusively demonstrate the benefit of pharmacologic therapy in the prevention or treatment of postischemic ATN. Furthermore, the applicability of animal studies to the prevention of postischemic ATN in humans is unproven. Attempts have been made to preserve renal function through the following general mechanisms: preserving cell viability, preventing or reversing intratubular obstruction, attenuating immunity and inflammation, and enhancing cell-repair processes.

Prevention — The following is a review of the many compounds and/or strategies for prevention that have been evaluated in animal models of ischemic ATN.

- Diuretics – In experimental models of acute kidney injury (AKI), loop diuretics and mannitol minimize the

degree of renal injury and dysfunction if given at the time of the ischemic insult [5-7]. These agents may have a variety of beneficial effects:

- Both can induce a diuresis, potentially washing out obstructing cellular debris and casts.
- Loop diuretics diminish active NaCl transport in the thick ascending limb of the loop of Henle; the ensuing decrease in energy requirement (by as much as 45 percent) protects the cell in the face of a decrease in energy delivery [7]. The terminal (S3) segment of the proximal tubule, which ends in the outer medulla, may also be protected in this setting since the decrease in loop transport increases oxygen availability [8]. This form of tubular protection appears to occur in vivo. In the presence of renal ischemia, the cells of the medullary thick ascending limb release several compounds (nonprostaglandin arachidonic acid metabolites and adenosine, a breakdown product of adenosine triphosphate [ATP]) that inhibit local NaCl reabsorption [9].
- Mannitol may preserve mitochondrial function by osmotically minimizing the degree of postischemic cell swelling or by scavenging free radicals [6,10].

- Dopamine and atrial natriuretic peptide (ANP) – Dopamine or ANP alone appear to be without benefit, despite their ability to increase both renal blood flow and sodium excretion [11,12]. Despite the effect of dopamine to increase outer medullary blood flow in animals by 35 percent, it does not increase medullary pO2, an important measure of tissue oxygen delivery during ischemia-reperfusion injury [13]. This may be one explanation for the lack of effectiveness of dopamine in human ATN (see 'Dopamine' below). In contrast, renal function can be preserved if:
  - ANP or urodilatin (a related peptide apparently produced within the kidney) is given either with dopamine (to prevent hypotension) [14,15] or with mannitol (to wash out obstructing casts) [16].
  - Calcium channel blockers are administered [17].

  ANP and urodilatin act in part by increasing the glomerular filtration rate (GFR; via changes in arteriolar resistance), and they may also be associated with a lesser degree of tubular necrosis and intratubular cast formation [11]. The effects of dopamine in this setting are discussed elsewhere. (See "Renal actions of dopamine", section on 'Clinical utility' and "Natriuretic peptide measurement in heart failure", section on 'Atrial natriuretic peptide'.)

- Fenoldopam mesylate – Fenoldopam is a potent dopaminergic agonist that exerts its pharmacologic effects through dopamine A-1 (DA-1) receptors without alpha- or beta-adrenergic effects [18,19]. The use of fenoldopam is based upon experimental studies that demonstrate the ability of this drug to maintain renal blood flow and kidney tissue oxygenation:
  - In a rat model of ischemia-reperfusion, fenoldopam increased renal blood flow, renal cortical perfusion pressure, and corticomedullary tissue oxygen tension [20].
  - In dogs, fenoldopam maintained renal blood flow, GFR, and natriuresis in response to hypovolemic shock or following aortic cross-clamping [21,22].

  The mechanism by which fenoldopam induces renal vasodilation is through its effect on dilating afferent and efferent arterioles, with no apparent change in GFR [23].

- Amino acids – In vitro studies suggested that the neutral amino acids glycine and, to a lesser degree, alanine (but not other amino acids) protected renal tubular cells against ischemic injury [24]. However, the experimental technique induced the artifact of intracellular glycine depletion, which was corrected by the administration of glycine. No benefit of glycine has been found in in vivo models of postischemic AKI [25].

- Antiapoptotic/necrosis agents – Nonselective and selective caspase inhibitors are effective in attenuating renal injury in ischemia- or endotoxemia-induced AKI [26-28]:

- Minocycline is known to have antiapoptotic and anti-inflammatory effects. It also reduces kidney inflammation and microvascular permeability [29] and has been associated with improved renal function in models of ischemic injury [30].
- Guanosine reduced renal tubular cell apoptosis, an effect associated with inhibition of p53 expression [31].
- Pifithrin-alpha, a novel p53 inhibitor, decreased tubule cell apoptosis and preserved renal function [32]. The importance of p53 in AKI was also suggested by a dose- and time-dependent attenuation of apoptosis and renal injury following the infusion of p53 siRNA [33].
- Poly ADP-ribose polymerase (PARP) is a nuclear enzyme that participates in DNA repair; however, excessive activation of PARP from cellular injury leads to intracellular NAD+ and ATP depletion, ultimately resulting in cell death. A water-soluble and potent PARP inhibitor, 5-aminoisoquinolinone (5-AIQ) may play a role in minimizing ischemia-reperfusion injury to the kidney [34].

- Free radical scavengers – The iron chelator, deferoxamine, is a well-known free radical scavenger. Deferoxamine has demonstrated a marked protective effect in different models of AKI [35-38]. Pyruvate is known as a potent endogenous antioxidant and free radical scavenger. Its derivative, ethyl pyruvate, reduced kidney injury in a cecal ligation puncture model of sepsis [24]. A mitochondrial-targeted tetrapeptide (SS31), which scavenges radical oxygen species and inhibits mitochondrial injury, reduces tubular injury in animal models of renal ischemia [39].

- Growth factors – Exogenously administered erythropoietin (EPO), before or at the time of reperfusion, reduced kidney injury by decreasing tubular necrosis and apoptosis and enhancing tubular proliferation in cisplatin-induced AKI [40-43]. EPO also mediated mobilization and proliferation of endothelial progenitor cells (EPCs) from the bone marrow, which has been shown to participate in tissue repair [44,45].

  Hepatocyte growth factor (*HGF*) can promote cell growth, motility, and morphogenesis of various types of cells [46,47]. Exogenous administration of *HGF* reduced apoptosis and acute renal injury [48]. Similar results have been observed with insulin-like growth factor 1 (*IGF1*) [49].

- Vasodilators – Endothelin-1 (ET-1), a potent vasoconstrictor, has been implicated in animal models of postischemic ATN or radiocontrast nephropathy [50,51]. ET-1 mediates its biological effects by binding to endothelin receptor type A (ETA) or type B (ETB) receptors. Tezosentan, a dual ET-1 receptor antagonist, attenuated renal injury even when administered after ischemia in a rat model [52].

- Heme oxygenases (HOs) catalyze the rate-limiting step in degrading heme to form iron, carbon monoxide, and biliverdin. Biliverdin is converted to bilirubin by biliverdin reductase [53]. There are two major forms of HO, an inducible isoform, HO-1, and a constantly expressed isoform, HO-2. HO activation may provide protection via the enhanced production of carbon monoxide (CO) and the potent antioxidant bilirubin [53,54]. HO may reduce injury through its potent effect to induce vasodilation. The mechanism(s) responsible for HO-induced vasodilation include CO activation of big-conductance KCa (BKCa) channels [55] or other ion channels, and/or nitric oxide-dependent mechanisms [56].

- In ischemia-induced injury, the administration of CO donor compounds decreases the levels of plasma creatinine 24 hours after reperfusion, as compared with vehicle-treated mice [57].

- Bilirubin also reduces kidney reperfusion injury [58].

- In a rat model of renal ischemia, administration of the phosphodiesterase inhibitor, milrinone, was associated with a smaller rise in serum creatinine and less histologic evidence of tubular injury, compared with control animals, possibly as a result of improved renal blood flow [59].

- Anti-inflammatory drugs – A maladaptive immune response or inflammation has been recognized as an early

event in postischemic ATN. Inflammatory cells, including polymorphonuclear cells, monocytes, macrophages, and T cells, have received considerable attention as important contributors to ischemic AKI [60-62]. Several new compounds appear to be effective in reducing injury for ischemia-reperfusion through direct action on leukocytes.

Additional studies suggest that the administration of anti-inflammatory mediators may prove effective in preventing or ameliorating ATN:

- The administration of anti-intercellular adhesion molecule-1 (*ICAM1*) antibodies and synthetic arginine-glycine-aspartic acid (RGD) peptides that inhibit integrins have been found to lessen experimental ATN [63-65]. The RGD peptides are thought to act by diminishing intratubular obstruction via inhibition of cell-cell adhesion in the tubular lumen [63,64].

- The utility of the intravenous (IV) administration of alpha-melanocyte-stimulating hormone (an anti-inflammatory neuropeptide) or its analog (AP214) was evaluated in murine and rat models of ATN [66]. Compared with placebo, active therapy prevented histologic damage and renal dysfunction and remained effective even when administered six hours after induction of ischemia [66] or sepsis [67]. This benefit was associated with inhibition of the induction of interleukin-8 (*IL8*), *ICAM1*, and nitric oxide synthase. Both in vivo and in vitro studies point toward the important role of inducible nitric oxide synthase (iNOS) in mediating injury to proximal tubules, suggesting that iNOS inhibitors may be helpful [68].

- Adenosine binds to members of the G-protein coupled receptor family that includes four subtypes: A1, A2A, A2B, and A3R. Selective A2AR receptor agonists reduce kidney injury by 70 to 80 percent [60,69-71]. Dose-dependent studies in mice indicate that protection is due to reduced neutrophil adherence/recruitment and release of reactive oxygen species, and is independent of any change in systemic hemodynamic parameters [71].

- Sphingosine 1 phosphate (S1P) is a specific ligand for a family of G protein coupled endothelial differentiation gene (Edg) receptors (also referred to as S1PRs 1-5) that evoke diverse cellular signaling responses. An S1P analog, FTY720, leads to sequestration of lymphocytes in secondary lymphatic tissue and to direct epithelial cell cytoprotection to reduce injury from reperfusion injury [72-75].

- Peroxisome proliferator-activated receptors (PPARs) are transcription factors that regulate glucose and lipid metabolism. Pretreatment of animals with fibrates (PPARa ligand) ameliorated cisplatin-induced renal dysfunction. This was accompanied by suppression of nuclear factor kappa B (NF-kB) activation, cytokine/chemokine expression, and neutrophil infiltration, suggesting that the protective effect of fibrates is mediated through its anti-inflammatory effect [76]. Infusion of bardoxolone methyl (BARD) appears to upregulate PPARγ and has been shown to mitigate ischemic tubular injury in animal models [77].

- AKI was ameliorated by statins in a murine model of sepsis. Compared with mice treated with saline, simvastatin-treated mice had significantly less systemic anti-inflammatory effect, lower serum creatinine concentration and tubular damage scores, less tubular hypoxia, and less impaired intrarenal microcirculation [78]. A retrospective study has also suggested a benefit of statins in preventing AKI in patients undergoing elective surgery. (See 'Statins' below.)

- Thrombomodulin and endothelial protein C receptors (EPCRs) activate protein C and promote anticoagulation. Soluble thrombomodulin, independent of its ability to generate activated protein C (APC), reduced kidney ischemia reperfusion injury by improving microvascular flow dynamics, reducing endothelial leukocyte adhesion, and minimizing endothelial permeability [79]. APC has direct anti-inflammatory and antiapoptotic activities and stabilizes endothelial barrier function via EPCRs [80].

- Alkaline phosphatase is expressed abundantly in kidney tissue and in other cells and organs [81,82]. In experimental studies, alkaline phosphatase attenuated inflammation induced by sepsis and reduced mortality [83-87].

- Measures aimed at promoting bone marrow stem cell migration may help limit damage by promoting tubular cell regeneration. As demonstrated in a mouse model, adult bone marrow cells migrate to injured renal tubules and differentiate into renal tubular epithelial cells to repopulate ischemia-damaged renal tubules [88,89]. Experimental ATN has also been attenuated by the infusion of stem cells [88,90].

  However, there is controversy concerning the capacity of these cells to repopulate the renal tubule [91]. Studies demonstrate that tubule repair is through dedifferentiation (differentiation of adjacent cells) [2,3] or through kidney-derived stem cells [4]. In one study that used genetic fate-mapping techniques to label epithelial cells, tubular epithelial cells that survived ischemia-reperfusion injury were shown to proliferate and repopulate the tubule, providing strong evidence that the predominant mechanism of repair after ischemic tubular injury in the adult mammalian kidney is through proliferation of adjacent surviving epithelial cells [92].

  Several studies suggested that the reduction of injury observed with infusion of mesenchymal cells was due to paracrine effects of growth factors and cytokines [93-95]. A more recent study demonstrated that microvesicles derived from bone marrow mesenchymal stem cells accelerated recovery from glycerol-induced AKI by inducing tubule cell proliferation, an effect that was abolished by ribonuclease (RNase).

  Microarray analysis determined that microvesicles shuttle mRNA associated with control of transcription, proliferation, and immunoregulation. These results suggest that mesenchyme stem cells transfer via microvesicles mRNA that activate genes involved in proliferation and cell survival [96].

- Adipose tissue-derived stem cells have been used in the prevention of ischemic ATN. In a rat model of ischemia reperfusion injury, animals receiving stem cells intravenously at the time of reperfusion demonstrated less tubular injury and down-regulated inflammatory-related gene expression, including *CXCL2* and interleukin-6 (*IL6*) [97].

- Antioxidants have been evaluated in postischemic ATN based upon the presumed role of reactive oxygen species in the generation of tubular injury. However, conflicting results have been obtained, perhaps due in part to the antiproliferative effect of these agents, which might slow tubular regeneration and mask any potential beneficial activity [98].

- Glucocorticoid administration during ischemia or with reperfusion reduces injury to proximal tubule cells by a mechanism independent of known anti-inflammatory effects or downstream transcription, appearing to be directly cytoprotective [99].

- Other compounds – Neutrophil gelatinase-associated lipocalin (NGAL), IL-6 and C5a antagonists, interleukin-10 (*IL10*), and ghrelin (a compound with a growth hormone-releasing effect) are other potential compounds that have multiple mechanisms of tissue protection and may be beneficial in human ATN [40-42,48,49,100-103]. (See "Ghrelin".)

- Ischemic preconditioning has been associated with less ischemic injury in the early phase of transplant reperfusion, with improved early function [104,105].

- Blockade of multiple signaling pathways involved in the inflammatory response has been shown to blunt ischemic injury to the kidneys. Fibroblast growth factor-inducible 14 (Fn14), a tumor necrosis factor-like weak inducer of apoptosis (TWEAK) receptor, has been found to be upregulated in ischemic renal tissue. In an animal model of ischemia reperfusion injury, blockade of Fn14 reduced production of proinflammatory cytokines after injury, as well as the accumulation of inflammatory cells, tubular apoptosis, and development of chronic fibrosis [106]. Similarly, blockade of high-mobility group box 1 (*HMGB1*) binding of toll-like receptor 4 (*TLR4*) reduces ischemic tubular injury in rodents [107,108]. Further, small interfering RNA (siRNA) targeting the NF-kB inflammatory pathway prevents ischemia reperfusion injury in rats [109].

Treatment — Experimental studies suggest that it may be possible to accelerate the rate of tubular regeneration and functional recovery in established postischemic ATN. These include the administration of growth factors or the

combination of atrial natriuretic peptide and dopamine.

- Growth factors – Tubular recovery following ischemic injury is associated with the activation of growth response genes and the release of growth factors required for cell regeneration including *IGF1*, epidermal growth factor (*EGF*), and *HGF* [110-113]. The recovery process involves two basic steps: tubular cell regeneration and differentiation into mature, functioning cells [112]. In addition to growth factors, attachment of new cells to the extracellular matrix plays an important role in cell differentiation [112].

  These observations may have potential utility. Although neither *IGF1* nor *EGF* expression appears to be increased in the kidney during the recovery phase from experimental aminoglycoside-induced ATN [114], the exogenous administration of these growth factors can accelerate both tubular regeneration and the recovery of renal function in both postischemic and nephrotoxic AKI [49,115-118]. As an example, rats with postischemic ATN that were treated with *IGF1* had, when compared with a placebo-treated group, a lower peak plasma creatinine concentration (1.8 versus 3.5 mg/dL [158 versus 308 micromol/L]); a lower histologic score of tubular injury at day 7 (0.90 versus 2.35); and more complete recovery of glomerular filtration at day 7 (plasma creatinine concentration 0.6 versus 1.1 mg/dL [53 versus 97 micromol/L]) [49]. *IGF1* also decreases protein breakdown, a potentially important effect in patients with AKI, who are often hypercatabolic [117].

  Although most of the above studies administered the growth factor before or soon after the ischemic episode, treatment delayed for 24 hours (which is more analogous to human disease) is still beneficial [118].

  The administration of thyroid hormone has also appeared to enhance recovery of renal function in a number of animal models of AKI [119,120].

- ANP plus dopamine – In animal models, ANP given with dopamine to prevent systemic hypotension can minimize the degree of renal failure if given concurrently with the ischemic insult [121].

BARRIERS TO SUCCESSFUL CLINICAL TRIALS — The applicability of animal studies to the prevention of postischemic ATN in humans is unproven [122,123]. Several barriers to successful clinical trials persist. These include heterogeneous and complex patient factors (eg, comorbidities and concurrent multi-organ failure in critically ill patients); lack of a standardized definition of and diagnostic criteria for postischemic ATN; and the lack of clear and specific endpoints for clinical trials:

- Acute kidney injury (AKI) is characterized by a changing spectrum of illnesses with significant and extrarenal complications [124,125]. These comorbid conditions are likely contributors to failed treatment regimens, particularly when mortality is used as an endpoint for the clinical trial.

- AKI is a multisystem disease, and, in most studies, renal failure itself is not usually the cause of death [126]. In several studies, either heart failure or noncardiogenic acute respiratory distress syndrome was associated with AKI [127-129]. The potential systemic effects of AKI involve multiple organs, thereby leading to a high mortality.

- The lack of success of clinical trials of AKI is frequently due, in part, to low statistical power, lack of a consensus definition in previous trials, improper endpoints, difficulty in timely administration of the drug, adverse effects of the drug, and patient heterogeneity [130].

- The lack of implementation in clinical trials of appropriate biomarkers to identify patients at an early time point after AKI.

- The lack of clinical studies using imaging modalities to determine in vivo pharmacokinetic and pharmacodynamics properties of drugs for the prevention of AKI. Improved treatment regimens will be informed by a better understanding of the concentration of the drug at the site of action in relation to the on-target biological effect [131]. No activity at the site of action or off-target effects (hypotension) may be related to inappropriate dosing, leading to negative trials [132].

To begin to reduce the morbidity and mortality in AKI, there is a critical need to accurately define AKI; to identify those patients that are at risk for postischemic ATN or have early or established postischemic ATN; and to identify novel biomarkers to diagnose the disorder early in the course. Identification of early versus late postischemic ATN may dictate the type of therapeutic intervention necessary.

Definition of acute kidney injury — To better understand the difficulties associated with studying postischemic ATN, it is important to provide an overview of the evolving definition of AKI, independent of underlying cause. Clinical trials have used widely varying definitions of AKI. This has ranged from a 20 to 30 percent rise in the serum creatinine concentration to the need for renal replacement therapy.

The absence of a consensus on a definition for AKI led to the Acute Dialysis Quality Initiative (ADQI) and the development of the Acute Kidney Injury Network (AKIN), which represents the efforts of workgroups that seek to develop consensus and evidence-based statements in the field of AKI. ADQI used a set of criteria called the RIFLE criteria [133]. A modification of the RIFLE criteria was subsequently proposed by the AKIN [134,135] and further modified by Kidney Disease: Improving Global Outcomes (KDIGO) [136].

A review of the RIFLE criteria and the AKIN and KDIGO modifications is provided elsewhere. (See "Definition of acute kidney injury (acute renal failure)".)

Patients at high risk for postischemic ATN include those with risk factors for AKI, but who have a normal baseline glomerular filtration rate (GFR). They may include patients who have diabetes and hypertension, or are taking medications such as nonsteroidal anti-inflammatory drugs. These individuals represent a population that needs to be identified to modify risk factors, if possible, and initiate preventive strategies when indicated.

Early AKI due to ischemia represents a condition frequently referred to as "prerenal azotemia" and is characterized by a decreased GFR due to renal hypoperfusion. In this setting, the kidney is structurally normal, and the condition is rapidly reversible when the underlying cause is corrected. It is vital to identify such patients as treatment to reverse the renal hypoperfusion may prevent established AKI. During this period, tubule injury may not be detectable or minimal. (See "Etiology and diagnosis of prerenal disease and acute tubular necrosis in acute kidney injury (acute renal failure)".)

Established AKI due to ischemia represents a more severe reduction of GFR and may represent an extension of severe early AKI (prerenal azotemia). In some conditions, AKI may not be preceded by early AKI (eg, sepsis). (See "Etiology and diagnosis of prerenal disease and acute tubular necrosis in acute kidney injury (acute renal failure)".)

An elevation in the serum creatinine concentration is a late marker and will detect AKI only after substantial injury is present [137]. Many factors regulate the generation, volume of distribution, and excretion of creatinine. (See "Assessment of kidney function".)

Thus, it is imperative that new, sensitive biomarkers are employed to detect a group that demonstrates a graded increase in tubular enzymuria (biomarker) and other biomarkers that suggest the earliest evidence of epithelial cell injury yet insufficient to cause frank necrosis and demonstrable rises in serum creatinine. The use and validation of sensitive biomarkers may permit identification of individuals with early tubular injury and identification of a subgroup of patients who might be the target for early intervention. Currently, several urinary biomarkers are being validated, but have not been used clinically [138-141].

PREVENTION — Most of the controlled studies have involved patients with established ATN, not those prior to or early in the ischemic phase. Except for a few isolated studies, the vast majority of clinical studies have yet to conclusively demonstrate the benefit of pharmacologic therapy in the prevention of postischemic ATN.

The best approach to postischemic ATN is to prevent its development. Thus, the first step is to identify persons at high risk for acute kidney injury (AKI). In settings in which patients are subjected to procedures that may induce postischemic ATN (such as surgery), patients at increased risk should be identified and carefully assessed to determine the risk/benefit of such procedures.

Postischemic ATN can result from prolonged hypotension, due most commonly to:

- Major surgery (particularly cardiac surgery, abdominal aortic aneurysm surgery, and surgery to correct obstructive jaundice)
- Sepsis
- Marked hypovolemia
- Severe pancreatitis

Patients with underlying comorbidities, such as chronic kidney disease (CKD), atherosclerosis, diabetes mellitus, advanced malignancy, obesity, and/or poor nutrition, are at particular risk for postischemic ATN [142,143].

Among patients undergoing cardiopulmonary bypass surgery, for example, risk factors for postischemic ATN may be patient related (diabetes, obesity, heart failure) or procedure related (length of cardiopulmonary bypass or nonpulsatile perfusion) [142-144]. Different clinical scoring systems have been developed that help to predict the risk for ATN with cardiopulmonary bypass surgery.

One scoring system analyzed 33,217 patients with a large validation sample [145]. A score was given on the basis of 13 preoperative factors and ranged from 0 to 17 [145]. In the lowest risk group (score 0 to 2), the risk for ATN requiring dialysis was 0.4 percent; whereas, in the highest risk group (score 9 to 13), the risk rose to 21.5 percent. Although this scoring system identifies a subset of high-risk patients, the majority of patients developing severe renal failure actually fell into lower risk categories. This model was validated using an external cohort derived from a database of cardiac surgery performed between 2002 and 2006 at a university hospital in Madrid [146]. Although the model accurately identified patients at risk for ATN, it generally underestimated the risk. Before this scoring system can be used clinically, further validation from other centers will be necessary. Nevertheless, the clinician should recognize factors that increase risk for ischemic ATN and intervene to change modifiable risk factors, such as nephrotoxins and hypovolemia.

In patients at increased risk or early in the ischemic phase, we suggest nonpharmacologic interventions, including optimizing volume status with intravenous (IV) fluids (if necessary), maintenance of adequate hemodynamic status to ensure renal perfusion, and avoidance of further injury by removing or decreasing the effect of any nephrotoxins (eg, avoidance of aminoglycosides, amphotericin, and radiocontrast agents). (See "Treatment of severe hypovolemia or hypovolemic shock in adults".)

Some pharmacologic agents have shown promise in the prevention of postischemic ATN. However, conflicting results have been reported in different studies, or their efficiency is yet to be confirmed. At present, we do **not** administer any pharmacologic agent for the prevention of postischemic ATN.

Issues concerning the prevention of radiocontrast nephropathy and the prevention of nonischemic causes of ATN are presented separately. (See "Prevention of contrast-induced nephropathy".)

Optimizing volume status — Numerous well-designed studies have found that volume expansion or saline loading with IV saline prior to exposure to iodinated radiocontrast agents, cisplatin, amphotericin B, hemoglobin, and myoglobin is effective in lowering the risk of ATN. Details concerning the studies that have examined this issue are available in separate topics. (See "Prevention of contrast-induced nephropathy" and "Prevention and treatment of heme pigment-induced acute kidney injury (acute renal failure)" and "Cisplatin nephrotoxicity" and "Amphotericin B nephrotoxicity".)

By comparison, a paucity of data exists concerning the efficacy of volume expansion with IV fluids to lower the risk of postischemic ATN. A common goal is to optimize volume status in order to maintain cardiac filling, cardiac output, and adequate renal perfusion, thus preventing ischemic kidney injury. These hemodynamic parameters are most often inferred from systolic, diastolic, and mean arterial pressures, or "hemodynamic status." Although this approach has obvious clinical appeal, the impact upon clinical outcomes has not been well described, and the exact regimen will vary based upon patient characteristics and the particular settings in which postischemic ATN is most likely to occur. The three surgical procedures that have the highest risk of postischemic ATN are cardiac

surgery, abdominal aortic aneurysm surgery, and surgery to correct obstructive jaundice.

In general, patients at high risk for postischemic ATN with surgery should be identified, and attention should be given to altering modifiable risk factors (eg, volume status and exposure to nephrotoxins). (See 'Prevention' above.)

A principal goal of the preoperative hydration strategy, as described above, is to optimize volume status, particularly among those at risk for postischemic ATN or early in the ischemic phase. This was best demonstrated by a meta-analysis of 20 randomized controlled trials (RCTs) that investigated the renoprotective effects of perioperative hemodynamic optimization among 4220 surgical patients who were undergoing elective or emergent procedures [147]. Postoperative AKI was reduced by perioperative hemodynamic optimization to achieve normal or supranormal values when compared with the control group, which did not receive similar goal-directed therapy (odds ratios [OR] 0.64, 95% CI 0.50-0.83). This benefit was seen when optimization was initiated preoperatively, as well as intraoperatively and postoperatively, suggesting that ischemic injury can be prevented or effectively treated with prompt reperfusion.

In summary, hemodynamic optimization through volume expansion is a reasonable approach preoperatively, if not contraindicated, for those patients with evidence of hypovolemia (low blood pressure, central venous pressure, or pulmonary capillary wedge pressure). Volume expansion should be avoided in patients with high intra-abdominal pressure, significant difficulties with oxygenation, or considerable peripheral edema that may hinder wound healing. Fluid administration should be assessed at regular intervals intraoperatively and postoperatively (see "Maintenance and replacement fluid therapy in adults"). Inotropes should be reserved for consideration in patients with remarkable hemodynamic instability despite adequate volume repletion by those familiar with their risks.

The preferred choice of IV hydration fluids, such as crystalloid (eg, isotonic saline, lactated ringer's, or bicarbonate solution) or synthetic colloid (eg, hydroxyl ethyl starch), is unclear and depends on the clinical scenario [148-150]. A small, randomized, single-center study examined the effect of perioperative infusion of IV bicarbonate solution versus IV saline on 100 cardiac surgical patients [151]. Compared with those who received saline, fewer patients who received bicarbonate solution developed AKI, defined as a >25 percent increase in creatinine over baseline (26 of 50 versus 16 of 50, respectively; OR 0.43, 95% CI 0.19-0.98). These findings need to be confirmed in larger, multicenter, randomized trials. Until such studies are performed, we continue to administer isotonic saline to achieve and maintain adequate preload.

Numerous colloid products, including various hydroxyethyl starches, have been associated with renal failure in surgical patients [152-154], suggesting they should be avoided for routine volume repletion.

- Sepsis – Issues surrounding measures aimed at restoring major organ perfusion, including the kidney, in patients with sepsis are discussed in detail separately. (See "Evaluation and management of severe sepsis and septic shock in adults".)
- Marked hypovolemia – Rapid volume repletion is indicated in patients with severe hypovolemia or hypovolemic shock. Delayed therapy can lead to ischemic injury and possibly to irreversible shock and multiorgan system failure. Issues that generally need to be considered in this setting include the rate of fluid replacement and the type of fluid infused. (See "Treatment of severe hypovolemia or hypovolemic shock in adults".)
- Severe pancreatitis – Fluid resuscitation is particularly important in severe pancreatitis because patients may accumulate vast amounts of fluid in the injured pancreatic bed. (See "Management of acute pancreatitis", section on 'Initial management'.)

Diuretics — The available evidence suggests that diuretics should **not** be administered as prophylaxis for postischemic ATN [155-157]. Evidence showing that furosemide was ineffective and possibly harmful was shown in a study in which 126 patients with normal renal function were randomly assigned to a continuous infusion of furosemide, low-dose dopamine, or isotonic saline, all initiated at the beginning of elective cardiac surgery and continued for 48 hours [155]. Although the renal outcomes among those given dopamine and isotonic saline were equivalent, furosemide resulted in a significant increase in both the plasma creatinine concentration (an average

maximal change of 0.3 mg/dL versus 0.1 mg/dL [27 versus 9 micromol/L] for both dopamine and saline) and the incidence of AKI (15 versus 2 and 0 percent); the latter was defined as an increase in the plasma creatinine of >0.5 mg/dL (44 micromol/L).

Uncontrolled studies of patients with recent onset of oliguria and renal insufficiency (who may not yet have established AKI) have shown that patients who respond to furosemide and dopamine or mannitol with an increase in urine output have a better outcome than nonresponders [158-160]. However, the responders may simply have had less severe disease, as evidenced by a shorter duration of oliguria (<24 hours), a higher urine output, and a higher urine osmolality (suggesting better preservation of tubular function).

We agree with the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines that diuretics not be given to **prevent** AKI [136].

Dopamine — When infused in low doses (0.5 to 3 mcg/kg per minute), dopamine dilates the interlobular arteries and both the afferent (preglomerular) and efferent (postglomerular) arterioles, leading to a relatively large increase in renal blood flow with a lesser, or no, elevation in glomerular filtration rate (GFR). (See "Renal actions of dopamine".)

This effect led to its use in studies to prevent or ameliorate AKI. However, numerous placebo-controlled studies and meta analyses have found that low-dose dopamine is ineffective in preventing ATN. In addition, there is some evidence that such therapy may cause harm.

Thus, we agree with the 2012 KDIGO guidelines that recommend that "low-dose" dopamine **not** be used to protect patients considered to be at risk for AKI or in those with early and/or established AKI [136].

Overview of studies — An overall lack of efficacy of low-dose dopamine among patients with or at risk for ATN was noted in a 2005 meta-analysis of 61 trials that enrolled 3359 patients [161]. There were no benefits in terms of mortality, requirement for renal replacement therapy, or adverse effects, although there was an increase in urine output on day 1 of therapy.

The following studies also illustrate that low-dose dopamine in early ATN does **not** provide protection from worsening renal dysfunction [162,163]:

- In a double-blind prospective study of early AKI, 328 patients with either oliguria or an increase in serum creatinine concentration and at least two criteria for the systemic inflammatory response syndrome were randomly administered either low-dose dopamine or placebo [163]. Both groups had similar peak serum creatinine concentrations and numbers of individuals who progressed to requiring dialysis.
- In the North American Sepsis Trial (NORASEPT II) study of nearly 400 patients with oliguria and shock due to sepsis, 174 patients nonrandomly received low-dose dopamine (44 percent), high-dose dopamine (32 percent), or no dopamine (24 percent) [162]. The incidence of AKI and the requirement for dialysis were similar among the three patient groups.

A possible contributor to the lack of benefit is that dopamine may actually reduce renal blood flow in patients with early postischemic ATN, in contrast to the typical increase seen in normal subjects [164].

A related issue is whether prophylactic administration of dopamine to patients during or after major surgery might be of benefit. The following examples illustrate the lack of superior efficacy of dopamine, compared with adequate volume expansion, in individuals at risk for ATN in this setting [155,165]:

- One controlled trial performed in patients after elective major abdominal vascular surgery compared the effects of fluid repletion with saline alone versus saline plus low-dose dopamine [165]. No difference in renal function was noted between the two groups. However, AKI was an infrequent occurrence in these well-hydrated patients; as a result, improvement with dopamine would have been difficult to demonstrate.
- In a second study, 126 patients with normal renal function were randomly assigned to a continuous infusion of low-dose dopamine, furosemide, or isotonic saline, all initiated at the beginning of elective cardiac surgery and

continued for 48 hours [155]. The renal outcomes among those given dopamine and isotonic saline were equivalent.

Adverse effects — There are potential risks associated with even low-dose dopamine, including tachycardia, arrhythmias (particularly among cardiac surgery patients), myocardial ischemia, and intestinal ischemia (due to precapillary vasoconstriction), which might promote bacterial translocation from the intestinal lumen into the systemic circulation [159,166,167]. In one study in cardiac surgery patients, for example, low-dose dopamine was independently associated with an increased risk of postoperative atrial fibrillation [166].

Fenoldopam — The dopamine receptor-1 agonist, fenoldopam, has been studied for the prevention of AKI following cardiac surgery and in other patients, including those with sepsis [168-174]. Some studies have shown benefit, while others have not confirmed a clinically relevant benefit. These trials have been limited in part due to small sample size and design.

To better assess the possible prophylactic benefits with fenoldopam, a 2007 meta-analysis was performed of 16 randomized studies with a total of 622 patients administered fenoldopam (at varying doses) and 668 given placebo or other therapy (principally low-dose dopamine) for the prevention or treatment of AKI [172]. Fenoldopam significantly reduced the risk for the following adverse outcomes:

- AKI (OR 0.43, 95% CI 0.32-0.59)
- Need for renal replacement therapy (OR 0.54, 95% CI 0.34-0.84)
- In-hospital death (OR 0.65, 95% CI 0.45-0.91)

Limitations with this analysis included the lack of consistent criteria for initiating renal replacement therapy, heterogeneity of enrolled patients, and inability to independently verify the change in glomerular filtration with infusion of fenoldopam. Thus, confirmation of these benefits is required in a large, multicenter RCT. We agree with the 2012 KDIGO guidelines that suggest **not** giving fenoldopam for the prevention of postischemic ATN [136].

Atrial natriuretic peptide — Natriuretic peptides are a family of peptides that block tubular reabsorption of sodium, vasodilate afferent arterioles, and inhibit the renin-angiotensin system. Its renoprotective effects have been evaluated in multiple trials of patients undergoing surgery [175-177]. Among the best data is a meta-analysis that included 13 RCTs and examined the effects of natriuretic peptides among 934 adult patients with cardiovascular surgery-associated renal dysfunction [175]. A subgroup analysis showed a reduction in AKI requiring dialysis in those receiving natriuretic peptide compared with controls (OR 0.32, 95% CI 0.15-0.66). Interpretation of this meta-analysis is limited by the small size and variable quality of the included trials.

A RCT that was published after the meta-analysis examined the effect of human atrial natriuretic peptide (ANP) on postoperative changes in the serum creatinine and estimated GFR (eGFR), and the need for dialysis one year following surgery among 285 patients with CKD not yet on dialysis who were undergoing on-pump coronary artery bypass grafting (CABG) [178].

Patients who received ANP had a significantly smaller postoperative rise in serum creatinine, compared with control (1.27 versus 1.46 mg/dL). In the early postoperative period, fewer patients in the ANP group required dialysis, compared with control (one versus eight). At one year, only one patient from the ANP group was on dialysis versus five in the placebo group. At the time of publication, the study drug, carperitide, was only available in Japan, although the authors suggest that nesiritide may be equivalent [178]. Pending further RCT data, we do not recommend routine use of ANP for prophylaxis against ATN.

N-acetylcysteine — Several systematic reviews and meta-analysis have examined the efficacy of N-acetylcysteine in the prevention of AKI following surgery [179-181]. A 2009 meta-analysis that included 10 studies involving 1193 patients undergoing surgery found that N-acetylcysteine, compared with placebo, did not provide any beneficial effect in preventing AKI [181]. This includes the prevention of AKI requiring dialysis (OR 1.04, 95% CI 0.45-2.37) and incremental increase in serum creatinine concentration (OR 0.84, 95% CI 0.64-1.11) [181]. We agree with the 2012 KDIGO guidelines that recommend **not** administering N-acetylcysteine to patients at risk for or with early-onset

postischemic ATN [136].

Intensive insulin therapy — Hyperglycemia among critically ill patients appears to be associated with increased mortality, and there is some evidence that stringent glucose control with intensive insulin therapy may be associated with improved outcomes, particularly increased survival. This is discussed separately. (See "Glycemic control and intensive insulin therapy in critical illness".)

A number of studies have also evaluated the efficacy of intensive insulin therapy to prevent the development of ATN among critically ill patients. While some studies suggest a renoprotective effect, renal injury was always a secondary outcome in these trials [182-186].

The largest trial to examine the effects of intensive insulin therapy was the multicenter Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, which randomly assigned 6104 medical and surgical patients to either intensive therapy (target blood glucose level of 81 to 108 mg/dL [4.5 to 6 mmol/L]) or conventional glucose control (target blood glucose of <180 mg/dL [<10 mmol/L]) [186]. There was no difference in the percentage and duration of those requiring renal replacement therapy. Other outcomes of this trial are discussed separately. (See "Glycemic control and intensive insulin therapy in critical illness".)

A 2007 meta-analysis was performed on five studies that evaluated the effect of insulin therapy on outcomes including AKI among critically ill patients [187]. This meta-analysis did not include the NICE-SUGAR trial, and only three of the included trials were RCTs; the other two were nonconcurrent prospective cohort studies. Although not statistically significant, intensive insulin therapy (target glucose of 80 to 100 mg/dL [4.4 to 5.6 mmol/L]) lowered the risk for required dialysis, compared with conventional insulin therapy (target glucose of 180 to 200 mg/dL [10 to 11 mmol/L]) (relative risk [RR] 0.65, 95% CI 0.40-1.05).

We do **not** recommend administering intensive insulin therapy to prevent ATN among critically ill patients.

Remote ischemic preconditioning — Remote ischemic preconditioning (RIPC) is a method by which the deliberate induction of transient nonlethal ischemia of an organ protects against subsequent ischemic injury of another organ. Some [188-191], but not all, studies have suggested that RIPC protects against AKI in various populations [192]. The best data are from a single-blind, randomized trial in which RIPC was induced by three five-minute cycles of thigh ischemia in 120 patients prior to elective cardiac surgery [189]. Postoperative AKI (defined as an elevation of serum creatinine ≥0.3 mg/dL or ≥50 percent within 48 hours of surgery) was reduced among patients randomized to RIPC, compared with controls (20 versus 47 percent, respectively). Post-hoc analysis showed that kidney injury that was sustained for at least two days was also reduced in the RIPC group (17 versus 36 percent). By contrast, in a second randomized study involving 76 patients undergoing "complex" valvular heart surgery, there was no difference in the incidence of AKI, nor of biomarkers of renal injury, between those receiving RIPC and controls [192].

A meta-analysis that included 11 trials (3 involving vascular surgery, 5 cardiac surgery, and 3 percutaneous coronary intervention) with 1216 participants found that, compared with control, RIPC tended to decrease the risk of AKI following surgery and vascular interventions, although the difference was not statistically significant (relative risk [RR] 0.70, 95% CI 0.48-1.02) [193]. Various definitions of AKI were used in individual studies, which limits confidence in the analysis. Confidence is further limited by the inclusion of both surgical and vascular intervention studies, although meta-regression analysis suggested that contrast intervention did not contribute to heterogeneity in the risk estimate for AKI.

The benefit of RIPC on renal outcomes, morbidity, and mortality needs to be studied in larger multicenter trials before it is used clinically [194].

Sodium bicarbonate — Pre-emptive infusion of sodium bicarbonate to prevent contrast-induced nephropathy (CIN) has been the subject of numerous clinical trials and meta-analyses, with mixed results. There is less published experience with this intervention in the prevention of ischemic injury, though results have been similarly mixed, and, ultimately, concerns were raised about the safety of this intervention.

An early positive study suggested that sodium bicarbonate may be a successful preventive therapy. In this pilot double-blinded RCT, researchers examined the perioperative administration of sodium bicarbonate versus sodium chloride solution in patients undergoing cardiopulmonary bypass, requiring cardiac surgery [151]. AKI (defined by a plasma creatinine rise >25 percent from baseline to peak value at any time within the first five days after surgery) occurred less frequently in the sodium bicarbonate group (OR 0.43, 95% CI 0.19-0.98), with an attenuated rise in urinary neutrophil gelatinase-associated lipocalin (NGAL), but without any difference in the requirement for renal replacement therapy.

However, subsequent studies suggested no benefit and, potentially, harm. A phase-IIb, multicenter, double-blinded RCT that compared sodium bicarbonate with sodium chloride solution in patients undergoing cardiac bypass showed no difference in the incidence of AKI (as defined in the study cited above) (47 versus 44 percent, respectively) [195]. Notably, hypertonic infusions were used in this study rather than hypotonic or isotonic solutions, which were used in the first trial [151].

However a larger, double-blinded RCT that included 350 patients and used an identical protocol to that used in the first study cited above [151] demonstrated a **higher** rate of AKI in the sodium bicarbonate compared with sodium chloride group (47.7 versus 36.4 percent) [196]. This difference was not statistically significant in the adjusted analysis, but the authors concluded that the positive results of the earlier pilot trial were likely the result of type-I error and, based upon the result of this larger trial, recommended that perioperative sodium bicarbonate infusion **not** be used to prevent AKI in patients undergoing open heart surgery [196].

Statins — Several cohort studies have examined the prophylactic potential of statins for AKI in high-risk populations. A population-based retrospective study suggested that the use of statins may reduce the risk of AKI following elective surgery [197]. This study identified 213,347 patients age >66 years who underwent surgery in the province of Ontario. Of these patients, 32 percent were taking a statin prior to surgery, and postoperative AKI developed in 4020 patients (1.9 percent). After adjusting for multiple patient and surgical characteristics, the use of statins was associated with a decreased risk of AKI (OR 0.84, 95% CI 0.78-0.90), less acute dialysis (OR 0.83, 95% CI 0.72-0.95), and a decreased 30-day mortality (OR 0.79, 95% CI 0.74-0.85). There was no difference between groups in dialysis requirement 90 to 120 days after surgery. This retrospective analysis is limited by its observational design, and the findings may reflect residual confounding.

A second cohort study examined 78,100 unique adult patients who underwent major abdominal, cardiac, thoracic, or vascular procedures between 2000 and 2010 [198]. The incidence of AKI was compared in matched populations receiving and not receiving statins preoperatively. Matching was based upon propensity scores and examination-relevant patient characteristics, including comorbidities as described by diagnostic codes. Renal function was based upon the most recent preoperative serum creatinine (within 30 days), statin use was based upon medication administration in the hospital prior to surgery, and renal failure was defined by Acute Kidney Injury Network (AKIN) and RIFLE criteria, based upon serum creatinines obtained during the index hospitalization (see "Definition of acute kidney injury (acute renal failure)", section on 'RIFLE criteria' and "Definition of acute kidney injury (acute renal failure)", section on 'AKIN criteria'). Within the limitations of the retrospective design, statin use was associated with decreased risk of postoperative AKI by multiple definitions, with a risk reduction of approximately 20 percent [198].

A third study used insurance billing databases to compare the incidence of AKI post-coronary artery bypass surgery between patients receiving statins prior to surgery and an otherwise matched cohort who was not receiving statins. AKI was defined by billing data, and statin users were matched with non-statin users using propensity scoring and other methods. Patients receiving statins preoperatively had a lower RR of AKI compared with those not receiving statins (RR 0.78, 95% CI 0.63-0.96) [199].

These data need to be corroborated by a randomized trial or follow-up observational studies before being used to guide clinical care [200].

Procedure-related measures — As previously mentioned, the major surgeries most commonly associated with ATN are cardiac surgery, abdominal aortic aneurysm surgery, and surgery to correct obstructive jaundice. Aspects

of these procedures may affect the risk of postischemic ATN.

As an example, patients who undergo cardiopulmonary bypass surgery rely on a heart-lung pump to maintain tissue perfusion [142]. General measures that are used and/or have been evaluated to ameliorate tissue ischemia include cardioplegia, temperature manipulation, administration of agents, use of specific materials to dampen inflammation, and/or pulsatile perfusion via an intra-abdominal balloon pump.

It is unclear if pulsatile perfusion via an intra-abdominal balloon pump protects renal function. Previously, a limitation with this technique was that the pump had to be stopped during cardioplegic arrest. By using the automatic mode, however, the pump can continue to function throughout arrest. The ability of the automatic mode approach to preserve renal function is unclear since studies evaluating its effect are limited, due in part to inaccurate estimates of kidney function.

To evaluate the effectiveness of pulsatile perfusion using the automatic mode versus nonpulsatile perfusion, 100 patients with CKD (grades 1 to 3) were randomly assigned to nonpulsatile perfusion during cardiopulmonary bypass or automatic intra-aortic balloon pump-induced pulsatile perfusion during bypass [144]. Significantly better kidney function was observed with pulsatile perfusion (74 versus 58 mL/min per 1.73 m^2), with a greater difference observed in those with stage 3 CKD. Further studies in a larger number of patients with kidney dysfunction are required before pulsatile intra-aortic balloon pumps can be recommended.

In comparison to on-pump coronary bypass surgery, some [201,202], but not all [203-205], studies have suggested that off-pump surgery reduces the risk of AKI:

- A 2005 meta-analysis evaluating 37 RCTs and 22 risk-adjusted observational studies demonstrated that off-pump CABG was associated with a nonsignificant reduction in AKI in randomized trials (OR 0.61, 95% CI 0.25-1.47), but a significant reduction in observational studies (OR 0.54, 95% CI 0.39-0.77) [206].
- A more recent meta-analysis published in 2010, which included only randomized trials (n = 22, 4819 patients) found that off-pump CABG was associated with a statistically significant 40 percent lower odds of postoperative AKI (variable definitions) and a nonstatistically significant 33 percent lower odds of dialysis requirement, with no discernible mortality benefit [207]. No difference in effect was seen based on preoperative serum creatinine, which had been suggested by an observational study in which off-pump CABG was protective in patients with a baseline serum creatinine <1.5 mg/dL (133 mmol/L), but not in those with higher values [208].
- In a nonrandomized cohort study that was published after the 2010 meta-analysis and included 742,909 nonemergent CABG cases, off-pump surgery, compared with on-pump surgery, was associated with a reduction in a composite outcome of in-hospital death or renal replacement therapy [202]. The greatest reduction in risk was observed among patients with eGFR 15 to 29 mL/min per 1.73 m^2 (with an on-pump minus off-pump risk difference of 3.66 per 100 patients [95% CI 2.14-5.18]) and was almost entirely driven by a reduction in the risk of renal replacement therapy, not death. (See "Off-pump and minimally invasive direct coronary artery bypass graft surgery: Outcomes".)

The CORONARY trial (2012) randomly assigned 4752 patients scheduled to undergo isolated CABG surgery to either an off- or on-pump procedure [209]. The use of off-pump CABG did not reduce the risk of the primary composite outcome, which included dialysis-requiring new-onset renal failure at 30 days, although it did reduce the risk of mild AKI. The CORONARY trial is discussed at length elsewhere. (See "Off-pump and minimally invasive direct coronary artery bypass graft surgery: Outcomes", section on 'Comparison to on-pump CABG'.)

Subgroup analysis of the CORONARY trial showed that the relative risk reduction conferred by off-pump surgery was greater among patients with baseline eGFR <60 mL/min per 1.73 m^2 CKD (RR 0.63), compared with those with eGFR ≥60 mL/min per 1.73 m^2 (RR 0.98) [210]. However, there was no difference between groups in kidney function at one year, even in subgroup analysis of patients with CKD.

Together, these studies suggest that there is a benefit to off-pump CABG in decreasing the risk of mild AKI, but not severe, dialysis-requiring AKI, especially among patients with underlying CKD. However, the long-term benefit in preventing AKI is not clear.

TREATMENT — Established postischemic ATN in humans represents a more severe reduction of glomerular filtration rate (GFR) and may represent an extension of severe early postischemic ATN (prerenal azotemia). In some patients, ATN may not be preceded by early ATN (eg, sepsis).

Overview — At present, early management of patients with established postischemic ATN should include an assessment of the etiology and volume status/systemic hemodynamics and the institution of appropriate therapeutic measures designed to prevent or reduce worsening kidney function. Thus, nonpharmacologic interventions should include maintenance of adequate hemodynamic status, as discussed in the previous section, to ensure renal perfusion and avoidance of further injury by removing or decreasing the effect of any nephrotoxins.

There have been conflicting results concerning the efficacy of other pharmacologic agents in patients with postischemic acute kidney injury (AKI). Their overall efficacy has yet to be determined.

Diuretics — Diuretics, particularly high doses of loop diuretics, are frequently administered to patients with AKI. This is done in part in an attempt to convert oliguric to nonoliguric AKI.

Among patients with established renal failure, a variety of studies, including two randomized trials, have found that diuretics augment urine output, but do not have an effect upon renal and patient survival [65,211-214].

The best designed and largest study found that high-dose furosemide maintained urine output, but had no effect upon renal and patient survival [211]. In this trial, 388 patients with established AKI requiring dialysis were randomly assigned to furosemide or placebo. Furosemide was administered at a dose of 25 mg/kg per day intravenously (IV; maximum of 2 g/day, given over four to six hours) or 35 mg/kg per day orally (maximum of 2.5 g/day). The use of furosemide was significantly associated with a decreased time to a 2 L/day diuresis (5.7 versus 7.8 days), as well as an increased likelihood of obtaining such a diuresis (57 versus 33 percent). Despite the increase in urine output, there were no differences between the two groups in terms of patient survival, renal recovery rates, number of dialysis sessions required, and time on dialysis.

A similar lack of benefit on these hard endpoints with furosemide in established ATN was noted in an earlier trial, in which high-dose diuretic therapy (3 g/day) led, in a few patients, to hearing loss that can be permanent [212].

The dissociation between increasing the urine output and not affecting the course of ATN with diuretic therapy in these trials probably reflects the ability of the diuretic to enhance the urine output in those few nephrons that are still functioning. However, since there is little recruitment of previously nonfunctioning nephrons, there is no effect on the course of the renal failure.

Summary — We agree with the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines that suggest that diuretics **not** be used to treat AKI, except in the management of volume overload [136]. They can be given for a short length of time for volume control, but such use should not postpone the initiation of dialysis (if required) [215]. (See "Renal replacement therapy (dialysis) in acute kidney injury (acute renal failure): Recovery of renal function and effect of hemodialysis membrane", section on 'Supportive management' and "Renal replacement therapy (dialysis) in acute kidney injury (acute renal failure) in adults: Indications, timing, and dialysis dose", section on 'Indications for and timing of initiation of dialysis'.)

Dosing related to loop diuretics is available in a separate topic review. (See "Loop diuretics: Maximum effective dose and major side effects".)

Dopamine — Despite an increase in natriuresis, low-dose dopamine is ineffective in the treatment of established AKI. We therefore do **not** administer low-dose dopamine in this setting.

Well-designed clinical studies have found that dopamine alone is not effective for the treatment of AKI. This was best shown in a meta-analysis of 61 trials that randomly assigned 3359 patients with or at risk for AKI to low-dose

dopamine (≤5 mcg/kg per minute) or either placebo or no therapy [161]. There was no significant effect of low-dose dopamine on mortality, need for renal replacement therapy, or adverse effects, although urine output increased by 24 percent.

As previously mentioned, a possible explanation for this finding is the observation that low-dose dopamine (2 mcg/kg per minute) may actually increase renovascular resistance and reduce renal blood flow among patients with AKI, in contrast to the typical increase in renal blood flow seen in normal subjects [164].

In addition, there are potential risks associated with even low-dose dopamine. These include tachycardia, arrhythmias (particularly among cardiac surgery patients), myocardial ischemia, and intestinal ischemia. (See 'Adverse effects' above.)

Others — A variety of other agents have been tried to reduce the duration or severity of ATN, including thyroid hormone and fenoldopam. To date, however, there has not been convincing evidence for the beneficial effect of either agent in the treatment of established ATN.

Thyroid hormone — The administration of thyroid hormone does not appear to provide benefit in patients with AKI, as shown in a prospective, randomized, placebo-controlled trial of 59 patients with AKI [216]; in addition, active therapy, which suppressed thyroid-stimulating hormone (TSH) levels, was associated with higher mortality rates (43 versus 13 percent for placebo).

Fenoldopam — We agree with the 2012 KDIGO guidelines that fenoldopam not be used to treat AKI [136]. Fenoldopam does not appear to provide any benefit to patients with early AKI [217,218]. The best data are from a multicenter, randomized trial that compared fenoldopam with placebo in 667 patients admitted to an intensive care unit with AKI following cardiac surgery [218]. AKI was defined as greater than 50 percent increase in serum creatinine from baseline or oliguria for more than six hours [218]. Compared with placebo, there was no decrease in the need for renal replacement therapy or in 30-day mortality in patients who received fenoldopam (18 versus 20 percent and 22 versus 23 percent, respectively). Hypotension occurred more frequently in the fenoldopam group, compared with placebo (26 versus 15 percent, respectively).

Atrial natriuretic peptide — The potential efficacy of atrial natriuretic peptide (ANP) alone in established ATN in humans has been evaluated in several major trials [132,219,220]. In a large, multicenter study, 504 critically ill patients with ATN were randomly assigned to a 24-hour infusion of placebo or anaritide (a synthetic form of ANP at a dose of 200 ng/kg per minute) [132]. The major endpoint was dialysis-free survival; the following observations were noted:

- There was no overall difference between the two groups (43 versus 47 percent dialysis-free survival with placebo).
- Patients who were nonoliguric appeared to do worse with anaritide (48 versus 59 percent dialysis-free survival with placebo, $p = 0.03$) while those with oliguric ATN (urine output <400 mL/day) did better (27 versus 8 percent dialysis-free survival with placebo, $p = 0.008$). As in other studies, the outcome was worse in patients with oliguric versus nonoliguric ATN. (See "Nonoliguric versus oliguric acute tubular necrosis".)

Given the last finding that oliguric patients may have had a better outcome than nonoliguric individuals when administered anaritide, a randomized, prospective trial was performed that evaluated the efficacy of this agent in oliguric AKI [220]. Among 222 such patients, a 24-hour infusion of anaritide (200 ng/kg per minute) provided **no** benefit, compared with placebo.

The administration of too high doses of anaritide for only 24 hours may be one reason for the lack of benefit observed in these two trials. This was evaluated in a smaller study of 61 patients with postoperative ATN (defined as a serum creatinine concentration 50 percent above baseline values) who were randomly assigned to human ANP (50 ng/kg per minute) or placebo, which was continued until dialysis was required or the serum creatinine concentration had decreased below the study inclusion value [221]. Prior to or at day 21, active therapy resulted in a significantly decreased frequency of required dialysis (6 versus 14 patients, hazard ratio [HR] 0.28, 95% CI 0.10-

0.73).

Despite these positive results with low-dose ANP, the study was small and underpowered, and a larger randomized prospective study is required to confirm these results and better characterize the role for this agent.

The meta-analysis cited previously [175] that examined the effect of natriuretic peptide use in cardiovascular surgery-associated renal dysfunction included only three trials that assessed the effects of natriuretic peptides in patients with impaired renal function. Of these, only one (cited above) initiated natriuretic peptide after the establishment of AKI. A second meta-analysis and Cochrane Review from the same authors included patients from eight trials who had established ATN following surgery [176,177]. Subgroup analysis suggested that low-dose ANP may reduce dialysis requirements, though study heterogeneity, design weaknesses, and small numbers limit any conclusions that can be drawn regarding the use of natriuretic peptide as a treatment of ATN. KDIGO 2012 guidelines suggest not using ANP to prevent or treat AKI [136].

Erythropoietin — A double-blinded, placebo-controlled trial examined the effect of erythropoietin (EPO) on the prevention of AKI [222]. The study used two biomarkers, gamma-glutamyl transpeptidase and alkaline phosphatase, to identify patients at risk for AKI. One-hundred sixty-two patients with increased biomarkers were assigned to receive either EPO or placebo. There was no difference between groups in the change in the plasma creatinine over four to seven days. However, although this study was negative, we do not believe that EPO should be eliminated as a potential therapeutic option. Potential reasons for failure to show a benefit of EPO included the choice of biomarkers and delayed randomization after entry to the ICU to the first dose of EPO (6.3 hours).

Insulin growth factor-1 — Insulin growth factor-1 (IGF-1) has failed to reduce AKI in clinical trials. One report of a randomized, placebo-controlled, double-blind trial of 72 patients with AKI of less than seven days duration found no benefit in patients treated with IGF-1 [223]. It is possible that delayed therapy, hypotension with IGF-1, and/or the heterogeneity of causes of AKI contributed to the negative results.

Alkaline phosphatase — Alkaline phosphatase is inactivated by reactive oxygen species and peroxynitrite in experimental studies [84] and reduces inflammation and mortality in sepsis [83-87]. A multicenter, randomized, placebo-controlled trial examined the effect of an alkaline phosphatase infusion in 36 critically ill patients [224]. At nearly 24 hours, alkaline phosphatase infusion was associated with reduced excretion of a proximal tubule biomarker, glutathione S-transferase A1-1; reduced nitric oxide (NO) synthase expression; and a decrease in the median plasma creatinine concentration [224].

Renal tubule cell therapy — The renal assist device (RAD) is a conventional hemofilter that is lined with monolayers of renal cells. It is designed to perform the absorptive, metabolic, endocrine, and immunologic functions that are normally performed by a healthy kidney, but are not provided by dialysis. A phase-II, multicenter, randomized, controlled, open-label trial compared mortality and recovery of renal function among 58 patients with established AKI who received either continuous venovenous hemofiltration (CRRT) with the addition of a RAD or traditional CRRT [225]. There was a nonsignificant trend toward decreased all-cause mortality among patients who were treated with the RAD compared with control patients at 28 days. There was a decrease in mortality at 180 days in the RAD-treated group compared with the control group (HR 0.48, 95% CI 0.23-0.99). At day 28, 53 percent in the RAD group had recovered renal function compared with 28 percent of control patients. Serious adverse effects attributed to the RAD were uncommon and included hypoglycemia and thrombocytopenia. A randomized phase-II trial is necessary to evaluate this therapy further.

SUMMARY AND RECOMMENDATIONS

- The vast majority of animal studies have yet to conclusively demonstrate the benefit of pharmacologic therapy in the prevention or treatment of acute tubular necrosis (ATN). A large number of compounds have been evaluated. Attempts have been made to preserve renal function via the following general mechanisms: preserving cell viability, attenuating inflammation, preserving renal blood flow, and preventing or reversing intratubular obstruction. (See 'Experimental studies' above.)

- Several barriers exist for the successful completion of clinical trials in postischemic ATN. These include heterogeneous and complex patient factors, lack of a standardized definition of acute kidney injury (AKI) and diagnostic criteria, and the lack of clear and specific endpoints for clinical trials. (See 'Barriers to successful clinical trials' above.)

- There are widely varying definitions of AKI. The Acute Dialysis Quality Initiative (ADQI) has used a set of criteria called the RIFLE (Risk, Injury, Failure, Loss, and End stage) criteria. High-risk patients include those with risk factors for AKI, but a normal baseline glomerular filtration rate (GFR). This may include patients who have diabetes and hypertension or who are taking medications such as nonsteroidal anti-inflammatory drugs. (See 'Definition of acute kidney injury' above.)

- The first step in preventing postischemic ATN is to identify the patient at increased risk. In patients at risk for postischemic ATN or early in the ischemic phase, we optimize volume status with intravenous (IV) fluids (if necessary), with the goal of optimizing cardiac preload, cardiac output, and, ultimately, renal blood flow. The exact approach may vary based upon patient characteristics and the particular settings in which post-ischemic ATN is most likely to occur. Additional measures should include the avoidance of nephrotoxins and hypotension, a surrogate for reduced renal blood flow (see 'Prevention' above). Inotropes may be considered in clinically significant hypotension refractory to volume optimization.

- A number of pharmacologic agents have been evaluated for the prevention of postischemic ATN. None have been proven effective, and some have proven harmful. We therefore do **not** administer any pharmacologic agents for the prevention of postischemic ATN. (See 'Prevention' above.)

- Among patients with established postischemic ATN, management should include an assessment of the etiology and volume status, and the institution of appropriate therapeutic measures designed to prevent or reduce worsening kidney function. These include maintenance of adequate hemodynamic status to ensure renal perfusion and avoidance of further kidney injury.

- If necessary for volume control, diuretics can be given for a short length of time among patients with established postischemic ATN. We recommend that diuretics **not** be used as prolonged therapy for volume control for established ATN (**Grade 2B**).

- We recommend **not** administering low-dose dopamine among patients with established postischemic ATN (**Grade 1A**).

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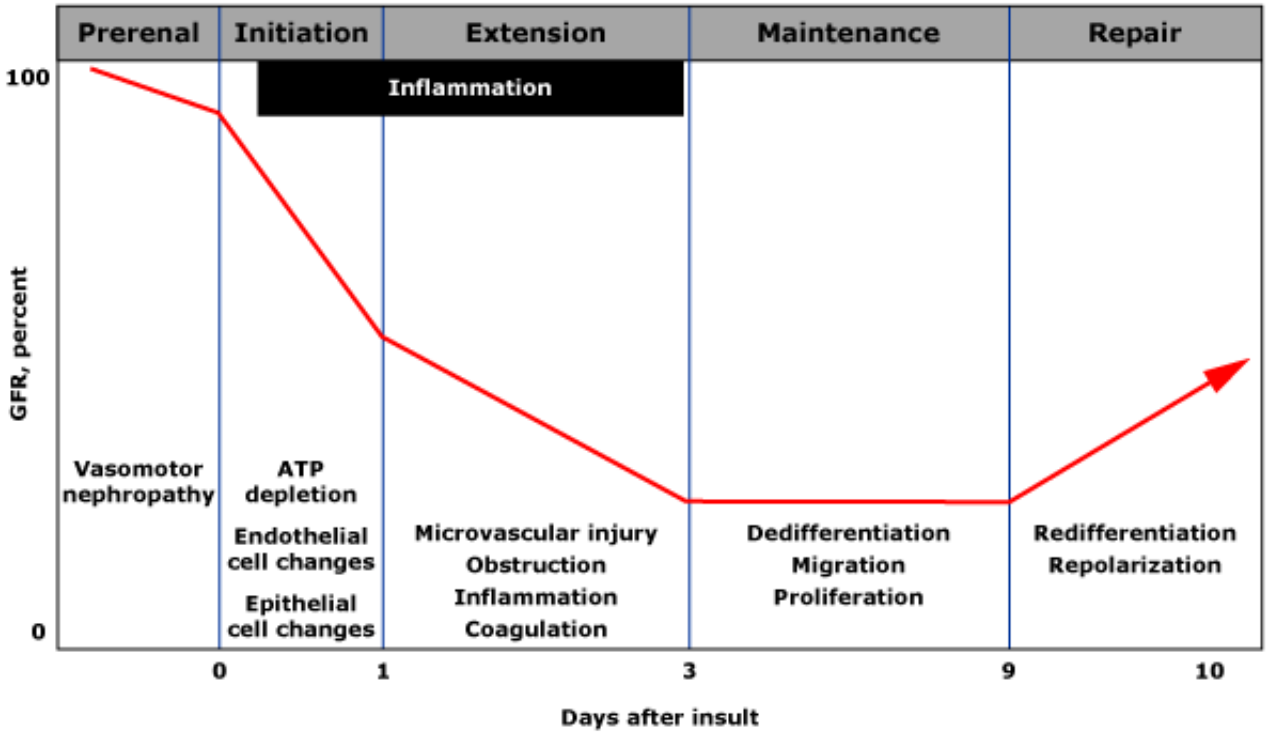
GRAPHICS

Clinical phases of acute kidney injury



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Disclosures

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