Acute renal failure: Ischemia, Inflammation, and Sepsis

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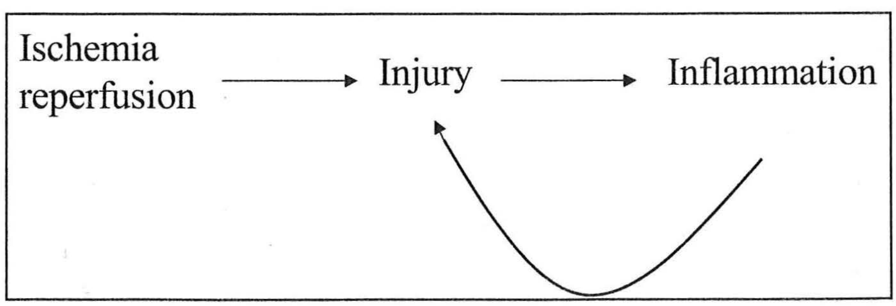


This is to acknowledge that Dr. Lu has disclosed all financial concerns related directly to this program. He has a research grant from Baxter Health Care to investigate the role of natural killer cells in the pathogenesis of renal failure. Dr. Lu will be discussing off-label uses in his presentation.

Research interests: The role of innate immunity in ischemic acute renal failure and transplant rejection. Innate immunity in perinatal listeriosis.

Case presentation - ischemic renal failure in the transplanted kidney.

Introduction

Ischemic acute renal failure (ARF) is important in two clinical settings.

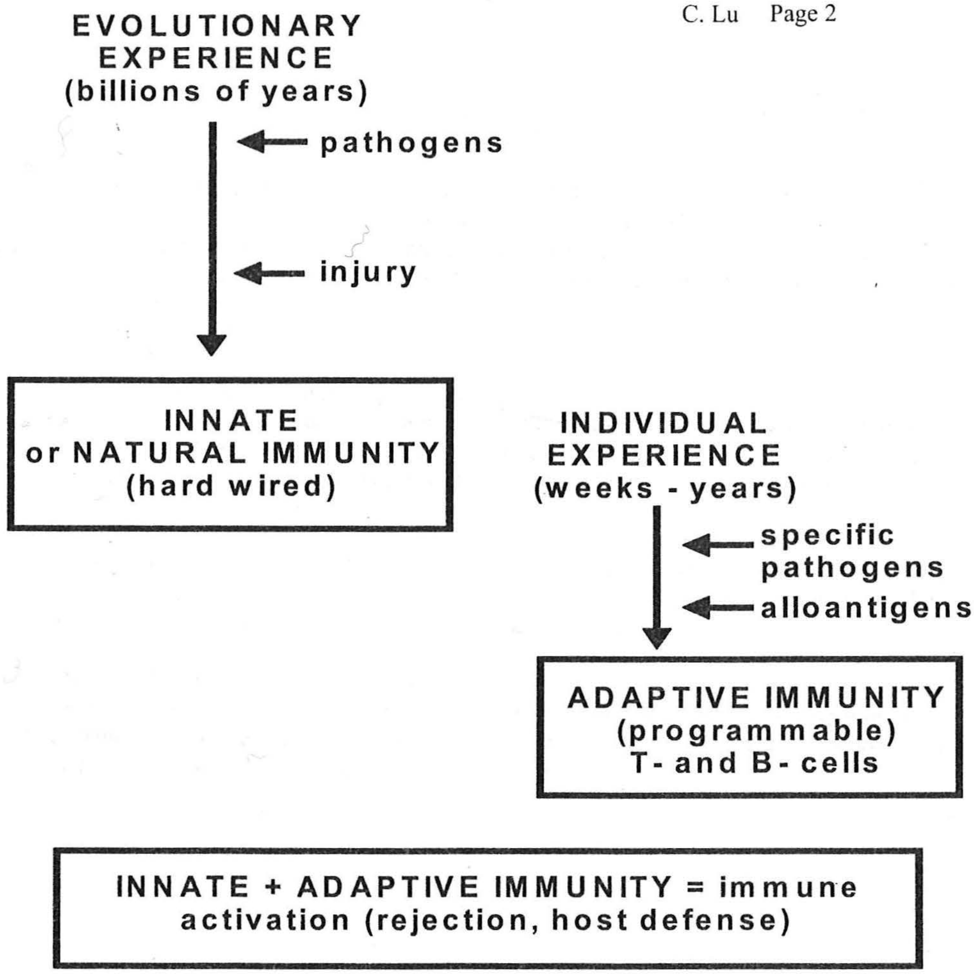
First, ARF in the native kidney is a common condition of hospitalized patients, including patients in intensive care units. It is a serious disorder and has a mortality rate of approximately 30% in the non-ICU patient and 70% in ICU patients. Renal ischemia from hypotension, often in the setting of sepsis, is a frequent cause. This clinical entity was the subject of an excellent UTSWMC Medical Grand rounds by Dr. Robbie Star (1).

Second, all transplanted kidneys suffer ischemic injury during the transplant process. Cadaveric kidneys suffer injury during hypotension associated with the trauma that caused brain death, detrimental effects of brain death on the kidney, and the cold storage required for shipping the kidney to the best HLA match and allowing preparation of the recipient. Both cadaveric and living donor kidneys are injured during the warm ischemia during the time required for creation of vascular anastomosis between the transplant and the recipient. Excessive ischemic ARF during transplantation results in decreased allograft survival, and also to increased allograft rejection

The increased rejection seen in transplanted kidneys with excessive ischemic ARF was initially surprising. However, an abundance of data now indicates that ischemic ARF recruits an inflammatory response; the recruitment of host leukocytes into the allograft should exacerbate any rejection. We will discuss this idea in greater detail later in this lecture.

Despite the dire prognosis of ARF in the native kidney, and the detrimental effect of ARF in the renal allograft, there is no therapy of established acute renal failure except supportive care and dialysis. Furthermore, although optimizing hemodynamic state of the kidney may prevent or ameliorate injury, there is currently no other therapy of impending ARF in the native kidney; mannitol given immediately after completion of the vascular anastomoses and perioperative calcium channel blocker are beneficial in the ARF of renal transplantation but not ARF in native kidneys (2). Possibly the difference between native ARF and transplant ARF reflects therapy at the time of injury in the latter.

Many previous specific therapies, such as IGF-1 (3), developed in rodents to treat ARF have not been successful in human native kidney ARF. This may reflect differences in the physiology of the rodent versus human kidneys (4), or may reflect the "single" hit nature of the experimental models, while human native kidney ARF is complex and involves multiple simultaneous disease processes, for example ischemia, sepsis, and nephrotoxic antibiotics (2) and (5-7). Another possibility, one that this author favors, is that we simply do not yet understand the mechanisms of ischemic renal injury with sufficient sophistication.



The goal of this lecture is to examine our current understanding of the mechanisms of renal injury after ischemia with a particular emphasis on the inflammatory response elicited by such injury. This is not a how-to-treat acute renal failure lecture. That is being discussed by Dr. Toto in the summer lecture series for the House Staff, and is covered in an excellent review by Schrier (2). This lecture is focused on inflammation and the reader is referred to several recent reviews that cover other aspects of the pathophysiology of ischemic ARF (2;5-8).

<u>transplant and acute renal failure</u>: <u>Ischemic injury -> inflammation ("innate immune response") -> transplant rejection ("adaptive immune response"):</u>

All renal allografts suffer unavoidable injury from the transplant process: during surgery to remove the kidney from the donor, when the kidney is transported ex vivo to the recipient, and during the creation of vascular anastomoses between the allograft and recipient. Cadaveric allografts are allografts are further injured by cold storage while in transit from the donor to the recipient and by the hemodynamic instability associated with the trauma or acute illness, which caused bran death of the donor.

As discussed later in this lecture, there is an inflammatory response to this injury. After transplantation, that inflammatory response consists of host leukocytes, including dendritic cells, neutrophils, and lymphocytes, and initiates the process of rejection (9-11). The idea is that the non-specific "innate" inflammatory response to injury recruits the allo-antigen-specific lymphocytes to the transplant.

The importance of this innate inflammatory response is illustrated by experiments where preventing the antigen-nonspecific neutrophilic response to ischemic injury ameliorates the subsequent allo-antigen-specific rejection (for example (12)).

A similar inflammatory response to injury occurs in human transplanted kidneys (13;14). If the inflammatory response to injury recruits an allo-antigen specific T and B cell response to the transplant, then we predict that the greater the ischemic injury, the greater the rejection. That prediction is supported by most of the literature (9;15;16).

<u>Evidence that renal ischemia elicits renal inflammation, and that this inflammation exacerbates renal injury:</u>

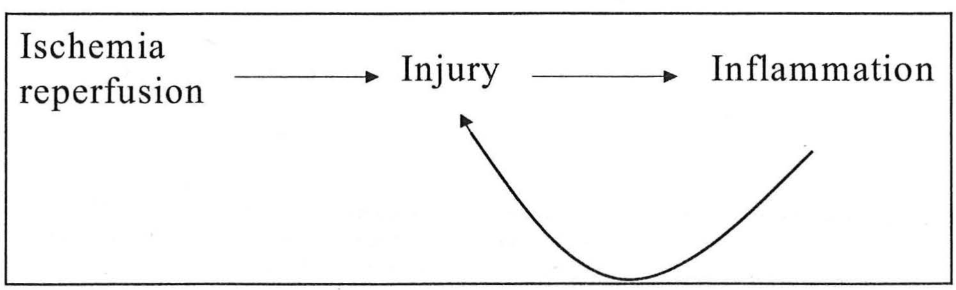
Ischemic acute renal failure elicits an mild interstitial inflammatory infiltrate of lymphocyes, macrophages, and neutrophils. The inflammation is clustered around necrotic and ruptured segments of tubules (17). This inflammatory infiltrate exacerbates injury (18).

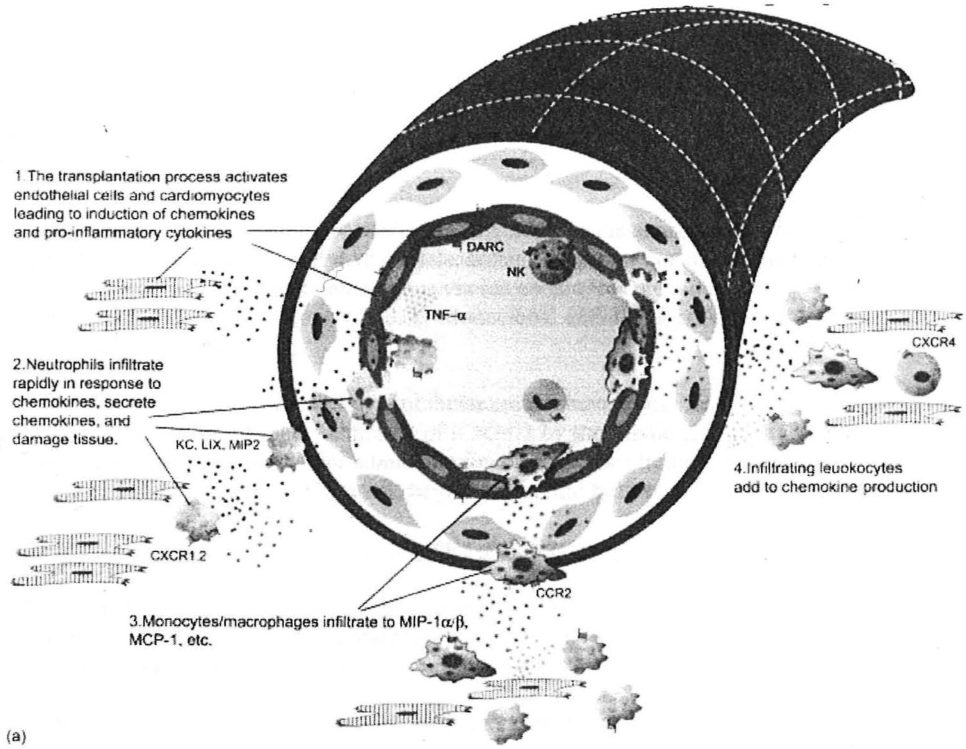
A number of experimental therapies prevent the infiltrate and thus ameliorates renal injury after ischemia . To understand how these work, we must review the five major steps that occur during the translocation of leukocytes from the blood, across the endothelium, and into the interstitium.

First, injured renal tubule cells release inflammatory molecules such as TNF alpha (19;20) and eicosanoids.

Second, in response to these mediators, endothelial cells express adhesion molecules.

Third, leukocytes in the blood adhere by weak, reversible interactions to P and E selectins, vascular cell adhesion molecule-1 (VCAM-1), and hyaluronate on the activated endothelium.





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Fourth, during this weak adherence, the leukocytes receive activation signals, including chemokines such as interleukin 8 and MCP-1 produced by injured renal tubules (21), which change the conformation of their cell-surface beta 2 integrins so that these bind their counterligands on the endothelium. The beta 2 integrins on leukocyte cell surfaces are LFA-1, mac-1, and VLA 4, which bind to counterligands on the endothelium; these include ICAM 1 and 2, and VCAM 1.

Fifth, the leukocyte moves across the endothelium (diapedesis), and migrate to the sites of injury in response to chemotactic molecules. These include chemokines (discussed below), midkine (22), complement, and leukotrienes (23).

Sixth, the leukocytes are activated by their interactions with inflammatory molecules embedded in the extracellular matrix, molecules on the cell surfaces of the renal tubule cells, and cytokines.

Seventh, the activated leukocytes produce molecules such as reactive oxygen species (ROS) and nitric oxide that damage renal cells. See reviews (24-27).

Inhibition of adhesion molecules.

One critical early step in inflammation is binding of leukocytes to selectins on the surfaces of activated endothelial cells. In rodent models, administration of low molecular sugar molecules prevents leukocyte-endothelial interactions via selectins. This prevents diapedesis and thus ameliorates ischemic renal injury (28-31). Monoclonal antibodies against the selectins have a similar inhibitory effect (32).

In response to ischemic renal injury, peritubular epithelium express ICAM-1, the counterligand for LFA 1 on leukocytes (33). Inhibition of ICAM-1 by transgenic mutagenesis (34), monoclonal antibodies (32;35), or administration of antisense oligonucleotides (36;37) all prevent inflammation and ameliorate ischemic acute renal failure.

Inhibition of chemokines, cytokines, and other proinflammatory molecules.

Macrophages are a component of the inflammatory response to renal ischemia (38). Inhibition of chemotactic molecules, MCP 1 and osteopontin, released by renal tubule cells prevents macrophage inflammation of ischemic kidneys (39-41).

Neutrophils are also present in ischemic kidneys. Inhibition of chemokines that specifically attract neutrophils (KC and MIP 2 [the murine analogue of human interluekin 8]) ameliorates ischemic renal injury (42).

T lymphocytes may also contribute to ischemic renal injury. Monoclonal antibodies against CD4 T cells inhibit ischemic injury, as does genetic manipulations that prevent development of these T cells. See review (43). However, the "rag" mouse that has no T cells has the same injury as the wildtype mouse (44;45).

TNFα is one molecule that contributes to ischemic injury. TNFα is produced after renal ischemia (31;34;46-50). Its role in pathogenesis is suggested by data showing that injury is ameliorated by TNFα receptor antagonists (51) or anti-TNFα monoclonal antibodies (52).

Interleukin 1 beta may contribute to late phases of ischemic renal injury (53). Interleukin 18, which shares many activities with interleukin 1 beta, does participate in ischemic renal injury (54;55).

Expression of B7 on endothelium activates lymphocyes and macrophages via the CD28 molecule on their cell surfaces. Inhibiting this molecule ameliorates ischemic acute renal failure (38;56;57) (58-60).

Complement.

A number of experiments indicate that complement activation exacerbates ischemic renal injury. Inhibition of C5 ameliorates ischemic arf (61-63).

How ischemic injury activates complement is not well understood. One possibility is that ischemic injury activates the alternative pathway of complement. This is best described after myocardial ischemia. Ordinarily, there is slow activation of the alternative pathway via "C3 tickover" that is inhibited by complement inhibitory proteins DAF (CD55) and protectin (CD59) which are thought to be present on all cell surfaces (64). Reperfusion injury increases intracellular calcium which activates a phosphosphatidylinositol-specific phosphlipase C. This enzyme cleaves the cell-surface complement inhibitory proteins; as a result the uninhibited alternative pathway produces C3a, and C5a that activates endothelia and recruit an inflammatory infiltrate. The C5-9 membrane attack complex is also produced, and this stimulates other cells to release interleukin 8 and platelet activating factor (PAF) which are chemotactic and activate endothelia (65). The importance of complement in injury after myocardial ischemia is illustrated by the ability of complement inhibitor sCR1 to ameliorate inflammation and also infarct size (66). An alternative possibility is that "natural antibodies" recognize injured tissues and activate complement (67).

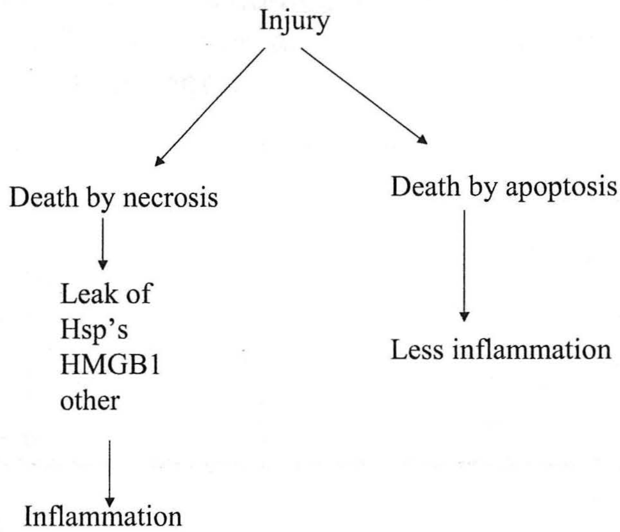
The detrimental effect of complement activation on ischemic renal failure may have important implications for dialysis. In rodent models, contact of blood with non-biocompatible membranes results in complement activation and exacerbates acute renal failure (68). The use of biocompatibile hemodialysis membranes may be appropriate in the clinical treatment of acute renal failure (69;70).

Natural inhibitors of renal inflammation after renal injury.

A number of molecules are produced by the kidney that inhibit inflammation and thus ameliorate injury. These include BMP-1 (osteogenic protein 1) (71-74). (75), interleukin 10 (76), alpha MSH (77), lipoxin A (78), and heme oxygenase 1 (79-81).

Apoptosis and inflammation - how a cell dies makes a difference.

Both necrosis and apoptosis occur in the ischemic kidney (82). Severely injured cells may die a necrotic death; less severely injured cells may have time to active the genetically programmed events that ultimately result in apoptosis (83).



How cells die has major implications for the inflammatory response to ischemia. Apoptosis inhibits inflammation. Necrosis results in the release of intracellular proteins into the extracellular space. Some of these proteins, for example, interleukin 1 alpha, HMGB1, and heat shock proteins increases inflammation (84-87). On the otherhand, apoptosis is cell death where there is no release of proinflammatory intracellular proteins into the extracellular space. Instead the cells are phagocytosed by macrophages and dendritic cells. Such phagocytosis inhibits the production of proinflammatory cytokines and facilitates tolerance induction (84;85;88;89).

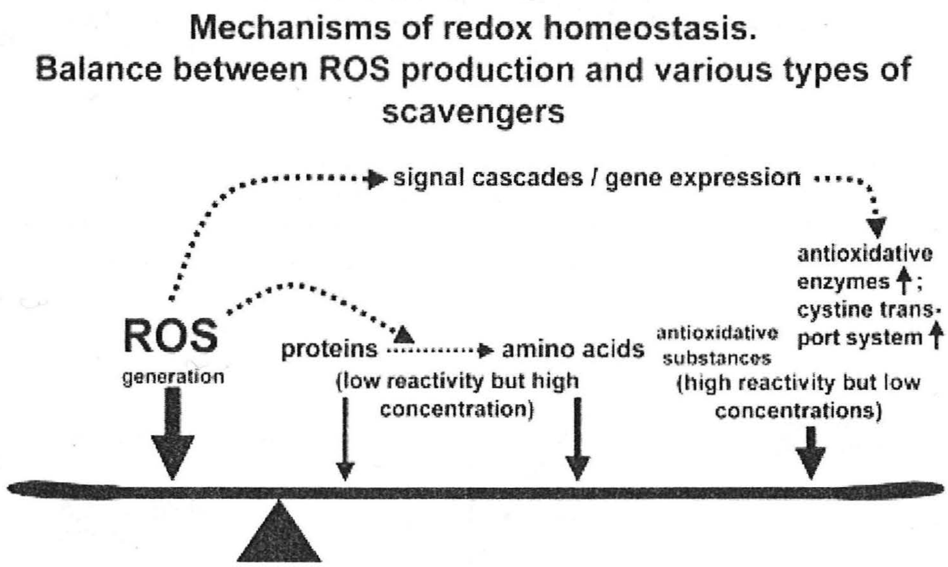
After ischemic injury apoptosis may be triggered in renal tubule cells by a number of signals. These include growth factor depravation, loss of cell-cell or cell-matrix adhesion, hypoxia, oxidant stress that occurs during the reperfusion phase of ischemic renal failure, and stimulation of cell surface receptors fas, TNFR1, and/or angiotensin R2 (90). Apoptosis may also remodel excessive tubular proliferation during the repair phase of acute renal failure (91;92).

The above signals trigger the activation of caspases that in turn trigger apoptosis. In addition to apoptosis, some of these proteases, caspases 1,4, and 5, are proinflammatory (90). Appropriately stimulated cells form a protein complex called an inflammasome that activates these caspases (93). The caspases in turn cleave pro-interleukin 1 and pro-interleukin 18 into their active products. These then recruit inflammatory cells into the ischemic kidney.

The importance of caspases in renal ischemia is supported by rodent experiments where inhibitors of caspases ameliorate injury (94;95). Whether these act by directly inhibiting apoptosis or inflammation remains to be determined (96).

Reactive oxygen and renal injury.

At the high concentrations found after ischemia/ reperfusion, free radicals - nitric oxide, superoxide anions, and related reactive oxygen species - damage the kidney (15;97;98).



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However, at moderate concentrations, these molecules also are regulatory mediators in signaling processes that regulate vascular tone, the control of ventilation, erythropoietin production, and transmission of information from membrane receptors such as the interleukin 1 receptor or the insulin receptor to the nucleus. Indeed, cells may normally change their internal redox potential to regulate gene activation. See reviews (99;100) and recent Medical Grand Rounds by J. Garcia. Thus, in addition to direct toxic effects, these free radicals may also cause the activation of proinflammatory genes and genes that regulate apoptosis.

Free radicals may be generated during ischemic ARF by the inefficient utilization of oxygen by mitochondria injured by ischemia (100) or by inflammatory cells entering the injured tissues.

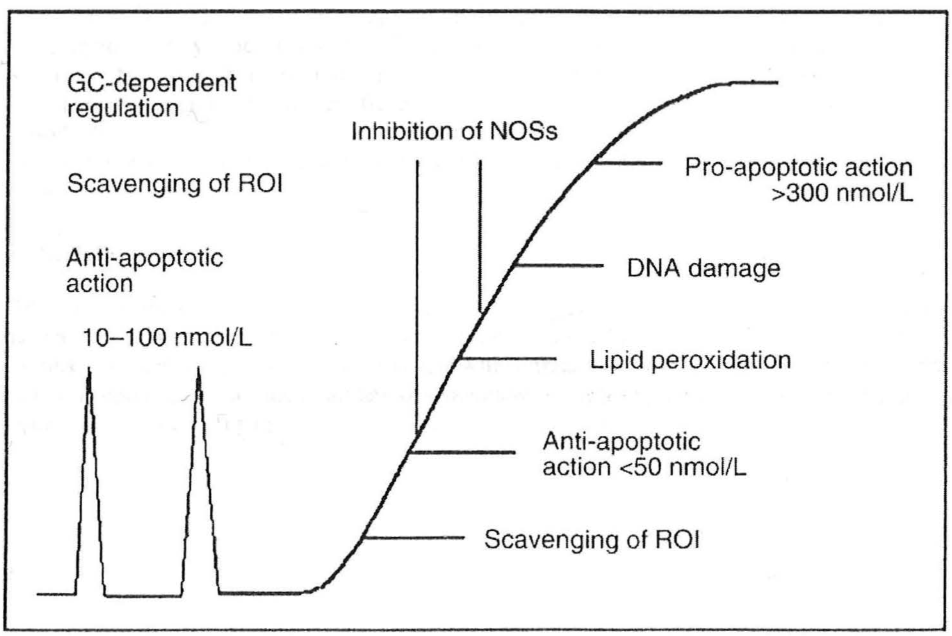
Furthermore, ischemia may deplete intracellular reducing molecules and thus make the cell more vulnerable to oxidative injury during the reperfusion of injured tissues.

Changes in the redox potential induced by ischemia/ reperfusion induce the expression of transcription factors such as NF kappa B and AP-1 (101), HIF 1alpha (102-104), p38 (19), and egr 1 (105;106). These transcription factors then activate genes for pro-inflammatory cytokines and molecules. Inhibition of these transcription factors, for example p38, may ameliorate injury due to ischemia reperfusion in vitro (107).

Whatever the effect of reactive species - toxic versus signaling - antioxidants have reversed ischemic injury in rodent models and have had limited success in very special types of ARF. One is contrast nephropathy (108). The other is the administration of recombinant superoxide dismutase to renal allograft recipients (15) . The effectiveness of the latter is controversial because it has not worked in all trials (109), and thus has not been widely adopted by the transplant community.

Nitric oxide - "NOS vs NOS" (110).

The effects of nitric oxide on ischemic acute renal failure are complex. The low concentrations of nitric oxide produced by endothelial nitric oxide synthase (eNOS) ameliorate acute renal failure by dilating blood vessels and enhancing renal perfusion. The high concentrations of



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nitric oxide produced by inducible nitric oxide (iNOS) are converted by ROS (see above) into peroxynitrite. This is a toxic compound that exacerbates ischemic injury in most studies (see review (110)).

In line with the above formulation, inhibition of eNOS exacerbates ischemic arf (111). On the otherhand, inhibition of iNOS by mycophenolate decreases NO and acute renal failure in mice (112). Antisense iNOS also ameliorates ischemic acute renal failure (113).

Ischemic acute renal failure as a systemic disease.

Ischemic acute renal failure involves extrarenal organs (see review (114)).

The renal inflammatory response to injury is regulated by extrarenal organs. Renal injury is ameliorated by HGF produced by the lung (115), and by acute phase proteins produced by the liver (116). Renal injury is exacerbated by brain death (117-119).

Extrarenal organs are affected by ischemic acute renal failure. There is increased inflammation in the heart (120) and multiple other organs (121).

Sepsis and acute renal failure.

Acute renal failure is a common complication of sepsis. One possibility is that sepsis results in hypotension and hypoperfusion of the kidney; in other words, acute renal failure associated with sepsis is a form of ischemic acute renal failure. However, recent data suggests that endotoxin produced during sepsis has direct effects on the kidney (122). Endotoxin may inhibit renal vasodilatory nitric oxide production (123), increase inflammation in the glomerulus by increasing production of the chemokine MCP 1 (123), and other direct effects on the kidney (124).

Conclusion.

The goal of this lecture has been to examine recent insights into the inflammatory response to ischemic renal injury. Unfortunately, none of the therapies I have discussed is yet ready for clinical use. Therefore, I would like to close with summary slide from Schrier's recent review (2). It is good advice for the treatment of patients with acute renal failure before the nephrologist is consulted. See next page.

Table 3. **Recommendations for Acute Renal Failure***

1. Evaluate patient for acute renal failure when serum creatinine level increases by > 0.5 mg/dL (40 μmol/L).

2. Exclude prerenal causes (e.g., volume depletion, cirrhosis, cardiac failure, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors).

3. Exclude postrenal causes (using renal ultrasonography and measurement of postvoid residual).

4. Review urinary sediment (muddy brown casts: ATN; red blood cell casts: glomerulonephritis or vasculitis; pyuria: acute interstitial nephritis; clear sediment: prerenal or postrenal azotemia).

5. Evaluate urine electrolytes in absence of diuretics (urine osmolality; urine sodium concentration; urine–plasma creatinine ratio; and fractional excretion of sodium).

6. After exclusion of prerenal and postrenal azotemia and confirmation of ATN by measuring urine sediment and urine electrolytes, notify nephrologist when serum creatinine level is ≥ 2.0 mg/dL (≥ 180 μmol/L).

7. Note the projected need for dialysis: oliguric ATN (urine volume < 400 mL/24 hr), 85% of patients; nonoliguric ATN (urine volume > 400 mL/24 hr), 30% to 40% of patients.

8. Avoid excessive fluid "resuscitation" leading to pseudo acute respiratory distress syndrome, ventilator support, and multiorgan complications.

9. Avoid hypotension. Generally, there is no need to treat hypertension aggressively in the absence of a hypertensive crisis (acute end-organ damage).

10. Maintain fluid balance and treat hyperkalemia. Do not use "renal-dose" dopamine.

11. For patients with acute renal failure, review patient's active medications for necessary dose adjustments.

12. When indicated, use enteral rather than parenteral alimentation.

13. Discuss timing for initiation and mode of renal replacement with nephrologists (intermittent vs. continuous hemodialysis; daily dialysis in catabolic patients [e.g., those with sepsis or rhabdomyolysis]); discuss use of biocompatible membrane.

* ATN = acute tubular necrosis.

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