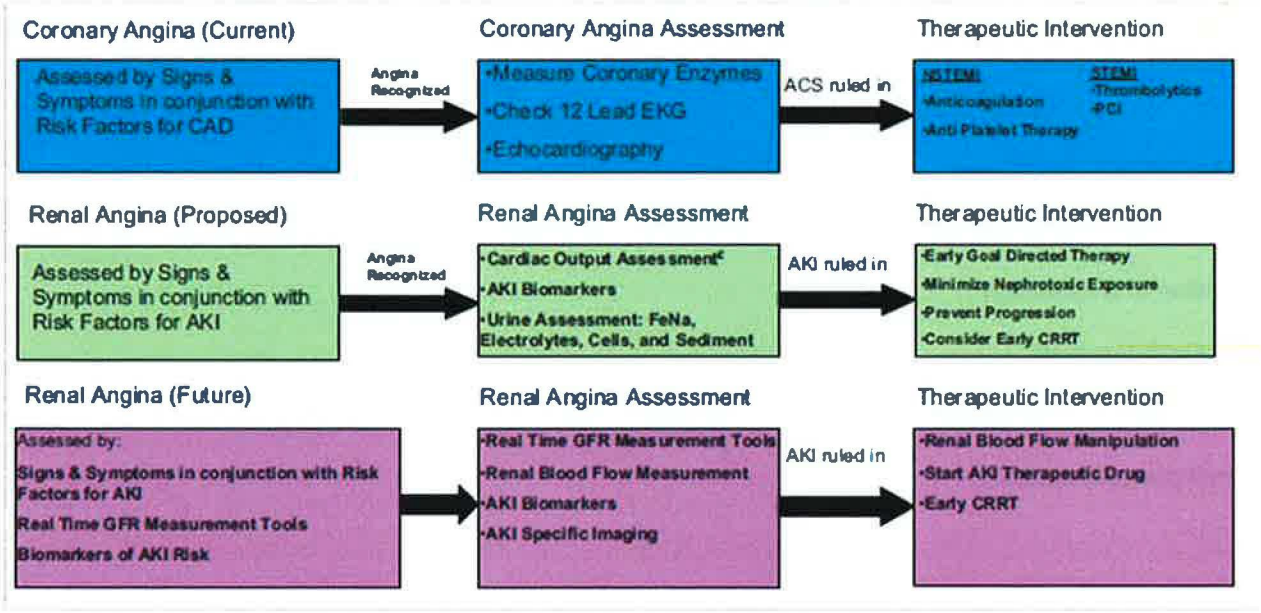

Goldstein. CJASN Apr 2010 in press {41918}

Acute Kidney Injury: the beginning of the end of the dark ages.

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Internal Medicine Grand Rounds

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Research Interests:

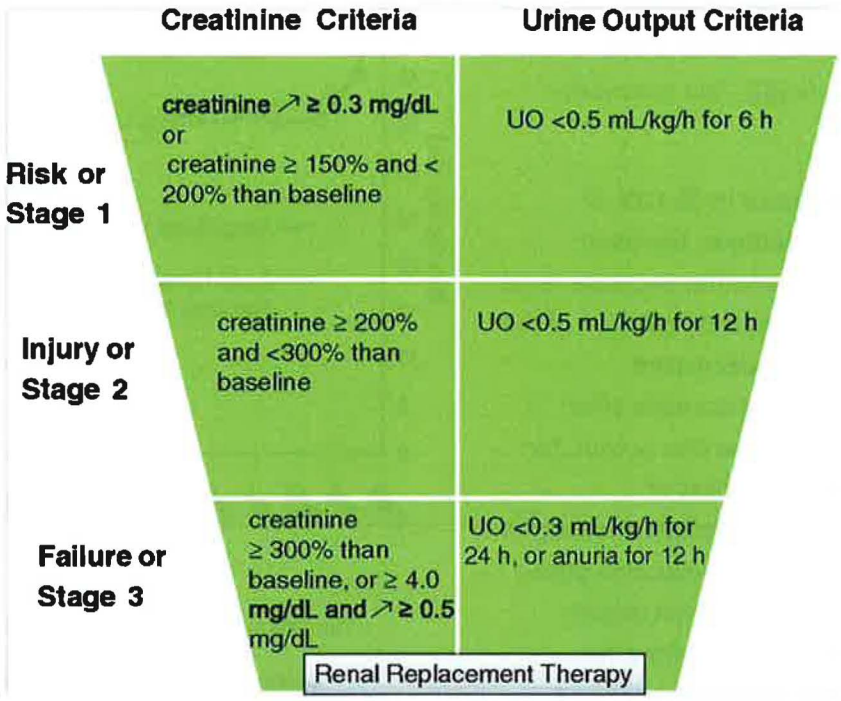
the molecular pathogenesis of ischemic acute kidney injury

renal transplantation

Introduction and definitions.

There has been enormous progress in the understanding of acute kidney injury over the last 5 years. This grand rounds reviews some of the salient new findings, the challenges revealed by these findings, and new insights into the pathogenesis of ischemic AKI.

RIFLE classification for AKI after modifications by the Acute Kidney Injury Network



Hoste, E. A.J. et al. Nephrol. Dial. Transplant. 2010 0:gfq133v1-133; doi:10.1093/ndt/gfq133

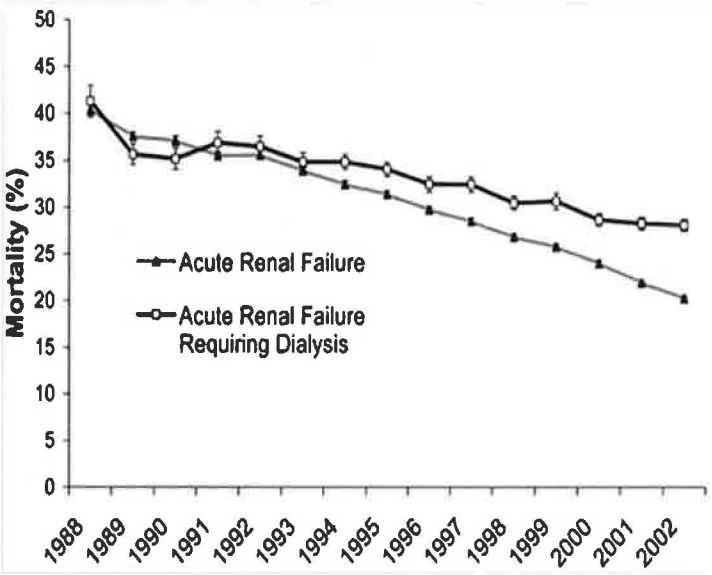
NDT Nephrology Dialysis Transplantation

Early work on "acute renal failure" was compromised by different investigators having different definitions of this disease. Although all agreed on a decrease in renal function over the course of hours to days, there was no agreement on what constituted a decrease in renal function. A major step forward was the formation of the Acute Dialysis Quality Initiative (25) and the Acute Kidney Injury Network (AKIN) (43). In 2005, these consensus groups of nephrologists and intensivists proposed replacing "acute renal failure" with the new strictly defined "acute kidney injury" (AKI). This definition was further refined in 2007. These new definitions are often called RIFLE criteria for "Risk, Injury, Failure, Loss of function, and Endstage renal disease." Only the first three stages, shown in Figure 1 (21), are in wide use. The subtle change of a single word "failure" in the old term acute renal failure to "injury" in the new term acute kidney injury may have profound implications because we now have a deeper understanding of how the kidney is acutely injured and may develop therapies based on this understanding. Furthermore, the concept of structural "injury" clearly is differentiated from the physiologic response of an uninjured kidney to hypoperfusion. Finally, the staging of clinical measures is an early attempt to predict the likelihood of injury if the kidney were biopsied. More about these issues later.

Causes of AKI.

AKI is one major cause of acute renal dysfunction.

One major difficulty in treating ARF is making the diagnosis in time to make a difference in the course of the disease. The problem is differentiating AKI from the other etiologies of acute renal dysfunction. These etiologies have been divided into three broad categories, and have been discussed in many excellent standard textbooks and review articles (for example (5)). We summarize them briefly.



The clinical problem: the mortality of ARF remains high.

Waikar SS J Am Soc Nephrol 2006. 17:1143-1150.

Figure 1: High mortality of AKI

1) Pre-renal causes occur in 55-60% of patients. In these situations, the renal parenchyma is intact, and the decrease renal function is due to decreased perfusion of the kidneys. These include decreased intravascular volume, for example after hemorrhage; decreased cardiac output, for example after excessive doses of antihypertensives; renal vasoconstriction, for example after excessive cyclosporine doses; and administration of drugs that impair autoregulation of renal blood flow, for example angiotensin-converting enzyme inhibitors or inhibitors of prostaglandin synthesis inhibitors.

2) Post renal causes occur in less than 5% of patients but should not be missed because many of these causes may be treated. Again, the renal parenchyma is intact, and the decreased renal function is caused by obstruction of urine flow. Obstruction may occur in the ureters, bladder neck, or urethra.

3) Intra-renal causes occur in the remainder of patients. Unlike pre-renal and post-renal causes of renal dysfunction the initial pathophysiology lies within the kidney and is accompanied by early structural lesions in the parenchyma. Intra-renal causes include diseases of the large renal vessels; glomeruli and renal microvasculature; and tubulointerstitial nephritis , for example associated with allergic responses to drugs.

AKI, the focus of this grand rounds, is a major intra-renal cause of renal dysfunction. In the clinical setting, multiple etiologies are often present at the same time. These include decreased renal perfusion (ischemia) due to hypovolemia, sepsis, or severe myocardial dysfunction; and toxins (either exogenous such as radiocontrast and other drugs, or endogenous such as myoglobin). Indeed a difficulty in treating ARF may be the multiple etiologies, each of which may have a different pathophysiology.

This grand rounds will focus on ischemic AKI, which contributes to most cases of AKI.

Why is AKI important?

– 1) AKI patients have a higher mortality than matched patients without AKI.

The importance of AKI is often not appreciated. In fact, AKI, even mild AKI, has profound detriment implications for mortality and longterm renal failure.

High mortality during AKI has been demonstrated by a variety of techniques. Two multicenter clinical studies, Program to Improve Care in Acue Renal Disease (PICARD) and Beginning and Ending Therapy for the Kidney (BEST Kidney), showed a range of mortality in the participating centers – 24 - 62% (68). The results of these databases were summarized at Medical Grand Rounds by Dr. Dev in Feb 2009 (13).

Epidemiologic studies of administrative data bases show a increasing incidence of AKI and a decreasing mortality (74, 67, 22). Figure 1. Even if the decreasing mortality is true, there is little cause for celebration because it remains unacceptably high, approximately 50% (35). Even after adjustment for comorbidities, the mortality in patients with AKI remains higher that those without AKI (8, 9).

Major point: Even small increases in Scr are associated with increased mortality. An increase in the Scr by as little as 0.5 mg/dl was associated with an increased mortality (8). A landmark study analyzed over 4000 patients who had cardiovascular surgery (36). See Figure 2. This manuscript showed that a 0.5 mg/dL increase in Scr was associated with an increased relative risk of death by 2.77; a >5 mg/dL rise increased the relative risk to 18.64.

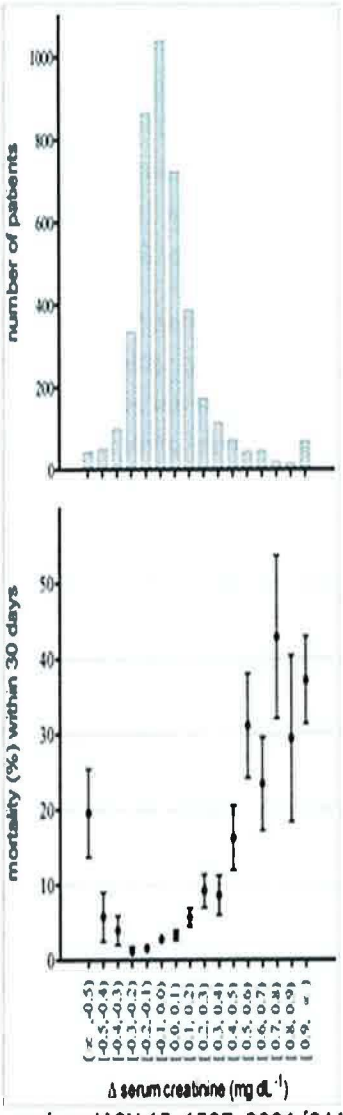


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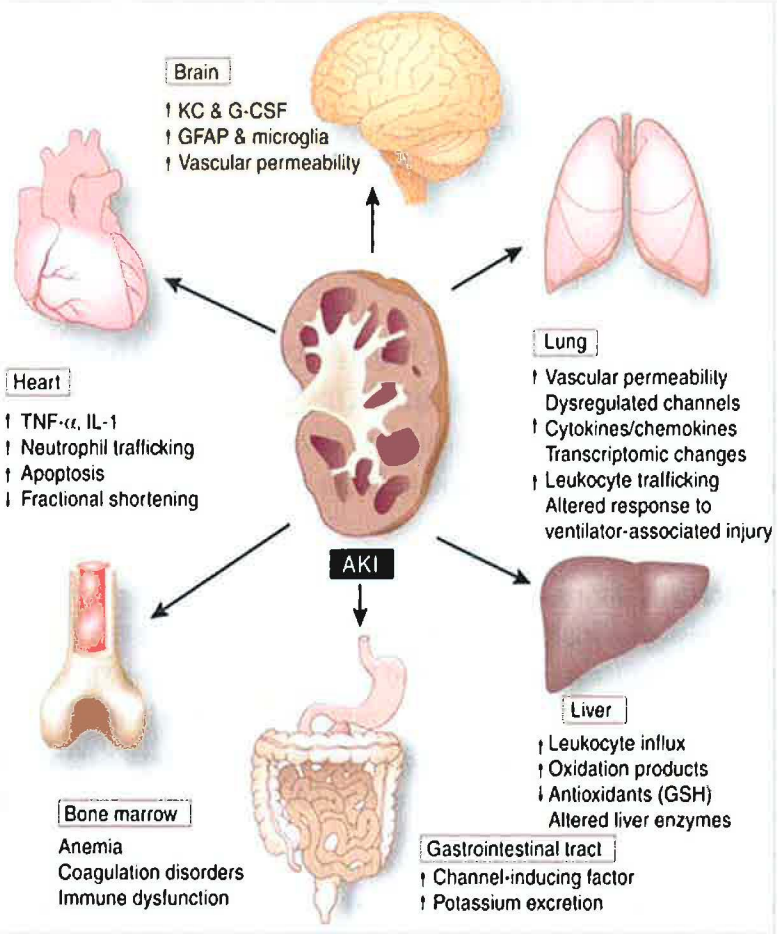
Figure 2: Small increases in Scr increase mortality.

Similar increases in mortality were seen in patients AKI and stroke (64), radiocontrast nephropathy (37), and nonmyeloablative hematopoietic cell transplantation.(51)

Another major point is that small transient rises in Scr are also associated with increased mortality (65). This was an analysis of 2469 pts with a variety of AKI and 16485 pts without kidney injury. As shown in Figure 3, even a transient rise of Scr for a day or two resulted in subsequent mortality. Note that the authors did not differentiate "prerenal" from AKI because they did not think this could be done with confidence. We will discuss the relationship between ischemic AKI and pre-renal azotemia later in this lecture.

Similar results were found in a study of 6,033 patients admitted to a Yale community hospital. 735 of these patients developed an increase of Scr of 0.3 mg/dl or greater. Even if the Scr returned to normal within 48 hr, the patients had a 14.2 % greater mortality rate (62).



Modified. Scheel et al. Kidney Int. 2008 74:849. {41898}

lin an analysis of over 40,000 transplant recipients, transient AKI in the renal allograft immediately after transplantation is associated with increased mortality. This mortality occurs even if the allograft recovers completely from the post-transplant AKI and subsequent renal allograft function is excellent. For example, if the eGFR (MDRD) is 60-69 after full recovery from AKI, the hazard ratio of death was 1.35 (61). The transplant database is useful because of its size and quality. All US transplant centers are required to report longterm results, and the database is managed and analyzed by the National OPTN.

- **1.a) Distant effects of AKI explain the increased mortality: AKI is a multiorgan disease that compromises the function of lungs, heart, and other organs by mechanisms beyond volume overload, and acid-base-electrolyte abnormalities.**

The acute increased mortality after AKI cannot be explained by the fluid, electrolyte, and acid-base abnormalities associated with renal failure. Modern dialysis essentially solves these problems, yet mortality remains high.

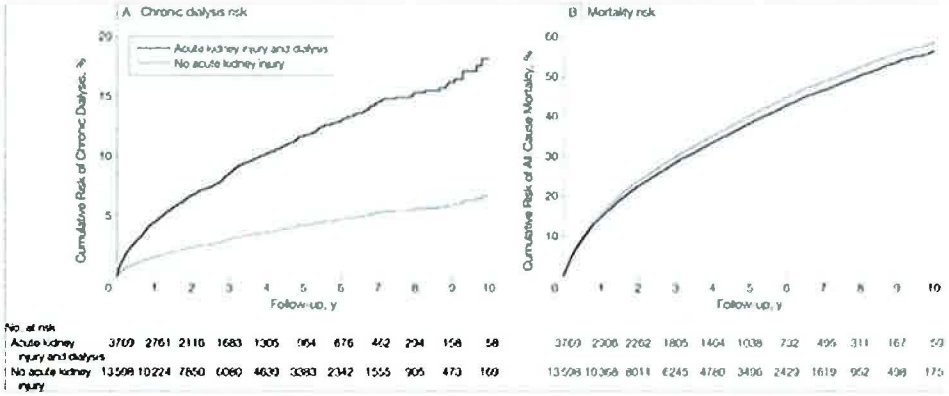
Research from rodents suggest that AKI is much more than renal disease, it is a multi-organ inflammatory disease. This results in dysfunction of non-renal organs, and this may contribute to the increased mortality seen during AKI. These insights arise from rodent work because one can injure the kidneys alone by, for example clamping the renal artery, and then measure inflammation and function in non-renal organs that have not been directly injured **(26, 17).**

Cardiac function is diminished in AKI, not only from volume overload, but also from increased inflammation and cytokine secretion within the heart (26, 7, 63). Similarly, the lung suffers increased permeability, and inflammation during ischemic AKI (33, 12, 38, 32, 18, 31).

The interaction between the kidney and liver during ischemic AKI may be beneficial. Thus, the growth factor HGF may be produced in the liver and lung, and facilitate the repair of the kidney from ischemic injury; similarly interleukin 6 may be produced by the ischemic kidney, stimulate hepatic production of IL10 that returns to the kidney and inhibits maladaptive intrarenal inflammation. (29).

The important message here is that there is crosstalk between the kidney and other organs during ischemic AKI.

Risk of Chronic Dialysis in Association With Acute Kidney Injury and Dialysis During Index Hospitalization



Wald, R. et al. JAMA 2009;302:1179-1185.

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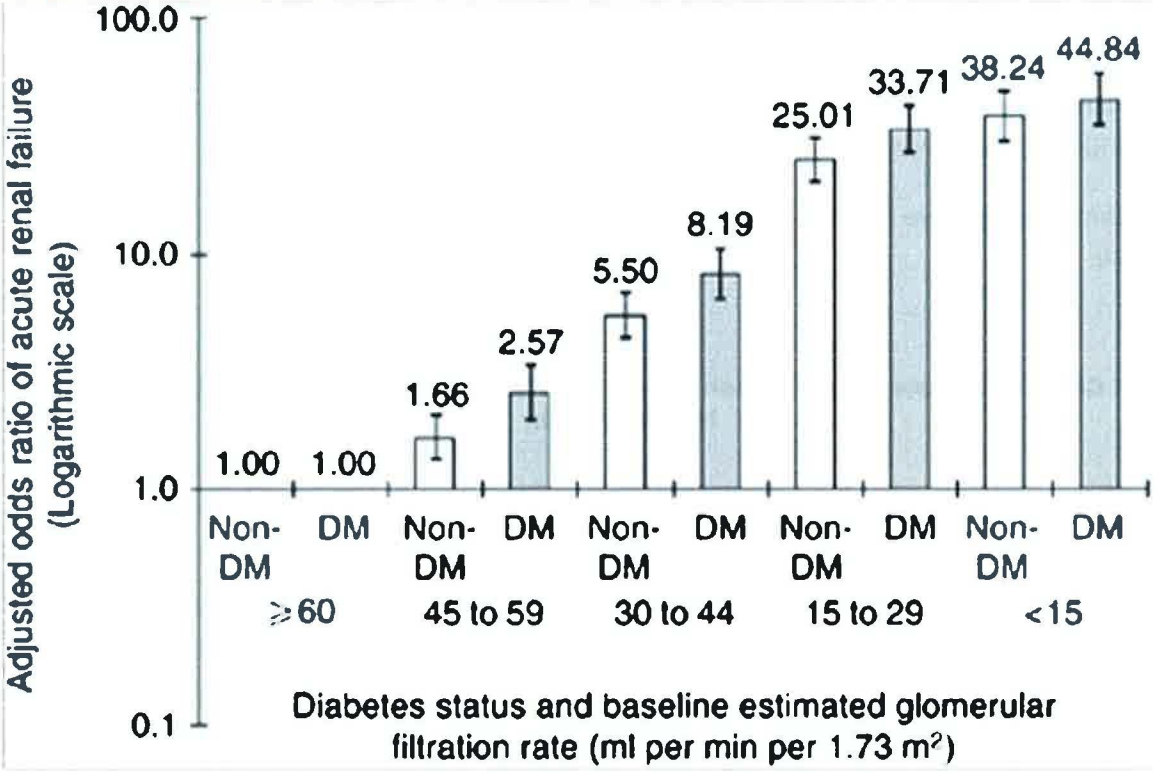
Why is AKI important? 2) AKI has longterm detrimental effects on renal function and contributes to the "epidemic" of chronic kidney disease and end-stage kidney disease.



Hsu. Kidney Int. 2008 74:101. {41905}

Previously, the conventional wisdom was that AKI resulted in temporary injury to the kidney and that after a full recovery, there was no permanent damage to the kidney. However, it is now clear that AKI has a longterm detrimental effect on renal function. In one study of 3769 adults with AKI requiring dialysis, the incidence rate of chronic dialysis over the ensuing 3 years was 2.63 per 100 person years but only 0.91 per 100 person years in the control patients. The control patients were matched for age, propensity score for developing AKI, and mechanical ventilation. Unlike the studies above, there was no difference in mortality in the AKI patient and controls. This was most likely due to the fact that patients were not included in the study unless they survived for at least 30 days after discharge (70). This and similar studies (39) raise the possibility that AKI may be a significant contributor to the growing epidemic of chronic kidney disease and end-stage renal disease (69).

A growing proportion of patients on the medical service have pre-existing chronic kidney disease. These patients have an increased susceptibility to AKI with the associated increased mortality and also the increased risk of progressing to chronic kidney disease or end-stage kidney disease *(28, 23)*.

Treatment of ischemic AKI before dialysis is needed – 2010: The beginning of the end of the dark ages.

TWO OBJECTIVES IN THE RX OF ISCHEMIC AKI BEFORE DIALYSIS

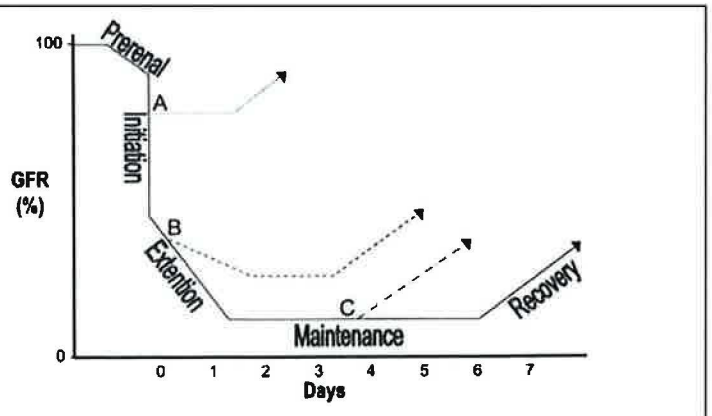
1) Treat the kidney.

2) Treat the patient – the complications of renal dysfunction.

Confusing these objections will result in management errors.

The management of patients with ischemic AKI may be divided into two different objectives: one is the treatment of the kidney, the other is the treatment of the patient. The later treatment is control of the complications of renal dysfunction. Confusing these two different objectives will result in serious errors in management and complications. More later.

Successful management of ischemic AKI must rest on a firm understanding of the pathophysiology discussed below? The clinical course of ischemic AKI may be divided into prerenal, initiation, extension, maintenance, and recovery phases (45). See Figure. For the sake of clarity, the recovery phase is shown as occurring at the end of the clinical course when, in fact, it may begin while the injury is extending. The figure illustrates a well-known striking feature of the clinical course of ischemic AKI. That is the injured kidney does not immediately recover even after renal blood flow is restored. This simple, yet important fact, may result in significant complications if ignored in patient management. More later.



Molitoris. J Am Soc Nephrol 14: 265-267 2003.

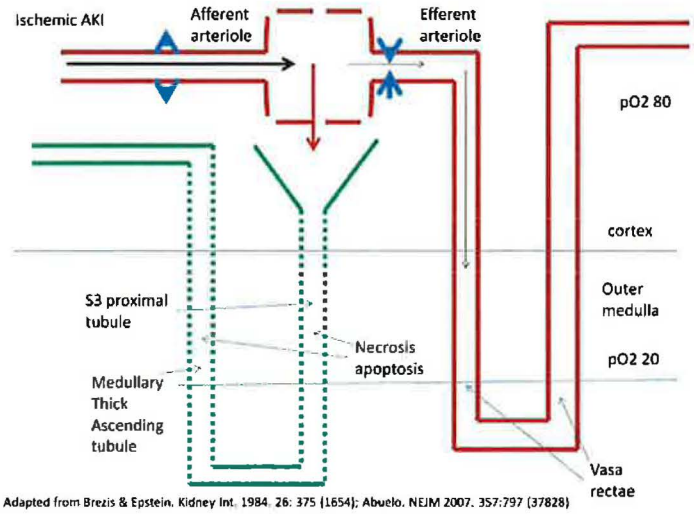
Progression from "pre-renal failure" to structural renal damage: The concept of "renal angina (16)."

To understand how "pre-renal failure", which is a decrease in GFR caused by hypooperfusion without structural injury to the kidney, progresses to outright structural injury, one needs to consider the unique structure and physiology of the kidney. These unique structural and physiologic features also explain those patients where ischemic AKI occurs, yet perfusion to the brain, heart, and other vital organs remains intact.

As shown in the Figure, there are two features of the kidney that make it uniquely susceptible to hypoperfusion. As a result of the counter current mechanism which allows the formation of highly concentrated urine, the oxygen tension in the medulla is approximately 20 torr. Thus tubular cells in the medulla live in an environment which is just barely compatible for survival. Furthermore, the unique blood flow to the kidney has perfusion of the glomerulus followed by perfusion of the tubules in series. If blood flow to the kidney is decreased, then a large fraction is diverted to the urinary space, and less

blood reaches the medulla. There the tubular cells surviving on marginal levels oxygen, die when their oxygen supply is decreased still further (6, 1).

The above explanation of how "pre-renal failure" turns into structural renal damage makes two predictions – both of which are confirmed by data.



The first prediction is that there should be pathology in the renal medulla. This challenges the conventional wisdom that there is no structural injury during what was called acute renal failure. This conventional wisdom is based on the rare renal biopsy of ischemic AKI in the modern era. Such biopsies generally do not interrogate the outer medulla where the injury should occur. However, autopsy studies (58), many from the 1940's (41), confirm the predicted lesions in the human outer medulla. Indeed, the long-forgotten name for AKI was "lower nephron nephrosis" in reference to necrosis of renal tubules seen in the outer medulla. This is the localization of the distal tubules ("lower nephron").

The second prediction forms the basis for the only rationale therapy currently available for preventing the progression of pre-renal azotemia into ischemic AKI. That prediction is that optimization of renal perfusion should prevent progression to AKI (19). In a patient with an intact cardiovascular system, not taking reno-toxic drugs, renal perfusion is increased by optimizing cardiac filling pressures. We discuss this in greater detail below.

Use and misuse of diuretics.

Treatment of the kidney.

Recall our earlier division of the therapy of ischemic AKI into two different objectives: treatment of the kidney and treatment of the patient.

In the treatment of the kidney and in most settings, diuretics should only be used to optimize cardiac output and thus renal perfusion. Thus, if the patient has pulmonary edema, diuretics will improve

cardiac output, renal perfusion, and help prevent the progression of "pre-renal azotemia" to ischemic AKI.

Otherwise, unless given at the time of a single limited ischemic insult, for example in the OR during aortic surgery, or at the creation of vascular anastomoses during transplantation, diuretics are not recommended for treatment of the kidney during AKI (24, 44, 20, 4). This issue was reviewed by Dr. Dev at these Grand Rounds in February of 2009.

Misuse of urine output as a primary goal, instead of as a surrogate for renal perfusion.

In an azotemic patient with a hypoperfused kidney, it may be possible to force a diuresis with high dose combination diuretics. If this treatment exacerbates hypovolumia and thus renal perfusion, then the renal outcome will be worsened after diuretic administration. The goal is renal perfusion, and not urine output. In the absence of diuretics, increased renal perfusion will lead to increase urine output.

Treatment of the patient.

After AKI is established, diminished urine output is common. In the face of obligate fluid intake for nutrition, and medications (such as antibiotics), the goal is maintenance of fluid balance. In this setting diuretics are helpful. This is not for treatment of the kidney, but for treatment of the patient.

Use and misuse of iv fluids – early versus late in the course of ischemic AKI.

Optimization of cardiac filling pressures, and thus, optimizing renal perfusion is the mainstay of treating/ preventing ischemic AKI in 2010. One important maneuver to accomplish this is iv fluid. However, it is increasing apparent that early appropriate administration of iv fluids may be helpful. However, excess fluids, particularly later in the clinical course may actually be harmful. Thus, volume overload is associated with with increase mortality in patients with AKI and sepsis with an odds ratio of 1.1 for each liter increase in volume (42, 52, 72, 11). Early aggressive iv fluids with later conservative fluid administration may be appropriate (55, 59).

Table 3

Mean daily fluid balance among 60-day survivors and non-survivors with acute renal failure (ARF), stratified by time of onset

Mean fluid balance, L/24 hours	Survivors	Non-survivors	*P* value
ARF	0.15 ± 1.06	0.98 ± 1.60	<0.001
Early ARF (occurring within 2 days of ICU admission)	0.14 ± 1.05	1.19 ± 1.48	<0.001
Late ARF (occurring more than 2 days after ICU admission)	0.11 ± 1.03	0.39 ± 1.40	0.06

ICU, intensive care unit.

3,147 patients in ICU c sepsis: 1,120 c AKI, 842 c early AKI, 278 c late AKI.

Payen, D. Crit Care 2008. 12:R74 {41937}

Effects of dialysis on renal recovery.

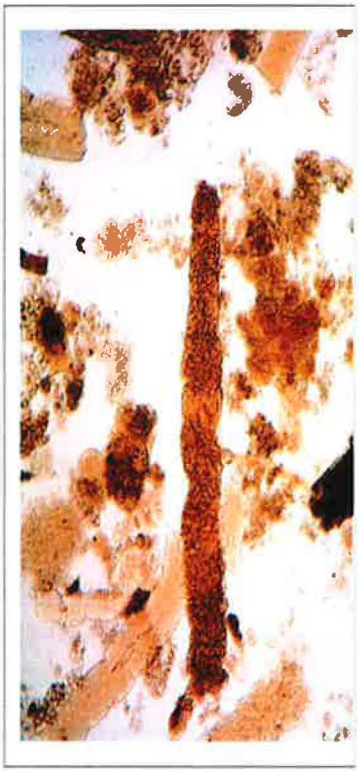
"Conventional wisdom" says that dialysis impairs recovery of the kidney from ischemic AKI. This is thought to occur because of hemodynamic instability during dialysis, vascular catheter-related infection, and/or cytokine release after blood interacts with the dialyzer membrane. Based on these issues, intermittent or CRRT has been proposed to be a better modality for AKI. In fact, there is limited data that any of these has a negative impact on renal recovery (49). Some data suggests that with careful dialysis, and in the absence of catheter-related infections, hemodialysis may not have a negative impact on renal recovery. Thus, hemodialysis before or after renal transplantation does not impact the recovery of renal function in the allograft (30, 2). In this clinical situation, the allograft kidney has ischemic injury that occurs during the trauma or acute illness that causes donor brain death, injury during cold storage, and warm ischemia during creation of the vascular anastomoses between renal allograft and recipient.

Problems in measuring renal function and renal injury.

Because we do not know how to easily and directly measure renal injury, our current diagnosis relies on assaying two major renal functions and assuming that decreased functions are directly correlated with injury. Unfortunately, this may not be true, particularly early after injury (34, 50). One function is the glomerular filtration rate (GFR). Even if we were able to easily and reliably measure the GFR, this would be a poor indicator of injury because, in many patients, the renal mass must be markedly reduced before the GFR decreases. An excellent example is the preserved GFR of normal people who lose half their renal mass. These normal people are living kidney donors who give one of their two kidneys to a loved one with endstage renal disease. Furthermore, we have problems measuring the GFR. We rely on the serum creatinine as surrogate. Unfortunately, it takes time (in many cases, days) for the serum

creatinine to rise after renal injury, the same increment in serum creatinine may have different clinical implications depending the baseline creatine, and, in addition, the serum creatinine depends on the patient's diet, muscle mass, and metabolic state. These issues of measuring the GFR and interpreting the serum creatinine were ably discussed by Dr. Henry Quinones at these Grand Rounds several years ago.

Characteristic microscopic findings from the urine sediment of a patient with acute tubular necrosis.

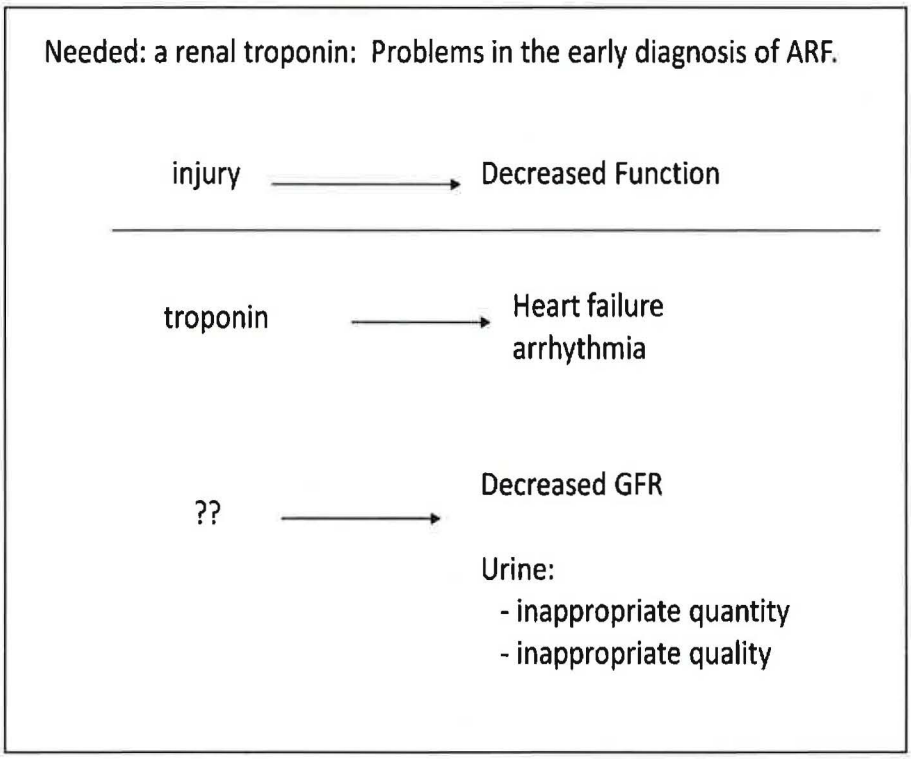


Esson M L , Schrier R W Ann Intern Med 2002;137:744-752

The other major renal function used to diagnose renal injury is the urine output and composition (urine volume, FENa, specific gravity, etc). However, the normal kidney may put out 0.5 to almost 50 liters of urine in a day. The normal urine may be concentrated and contain almost no sodium, or be dilute and rich in sodium depending upon the subject's physiologic state. Interpreting what urine the kidney should be producing in a given patient at a given time may be a formidable challenge, and requires a detailed history and excellent serial physical exams. For example, a high FENa and low urine osmolality may be found in a hypotensive, oliguric patient with ARF, or in a normal person who has just ingested a big MAC combo, super-sized, at MacDonald's. For all of these reasons, the FENa is not used as a criteria for AKI in the recent guidelines. A useful reference for the use and misuse of FENa and other commonly used kidney equations is in the reference list .(47).

An important and easily available test is the urine analysis. If "renal failure casts" are present, the likelihood of ARF is very high (14). Unfortunately, many patients with ARF will not have "renal failure casts", and the urine may not be examined by experienced observers. The urine analysis is an underutilized test. Indeed, some have suggested that the severity of AKI may be predicted by quantitating the number renal failure casts (53).

Needed: a renal troponin.



As shown in the Figure of Page 8, ischemic AKI passes through the phases of pre-renal azotemia to initiation, to extension, to maintenance, to recovery. The diagnosis is often missed until the maintenace phase because, unlike the cardiologists, we do not have a renal "troponin" to make a diagnosis early during the extension phase. An active effort is currently underway to identify molecules in the blood and urine that would alert the clinician that structural damage to the kidney has occurred. A discussion of the current status of these markers is beyond the scope of this lecture, but the interested reader is referred to the literature cited (66).

Needed: therapy to ameliorate the extension phase of ischemic AKI – research at UT Southwestern.

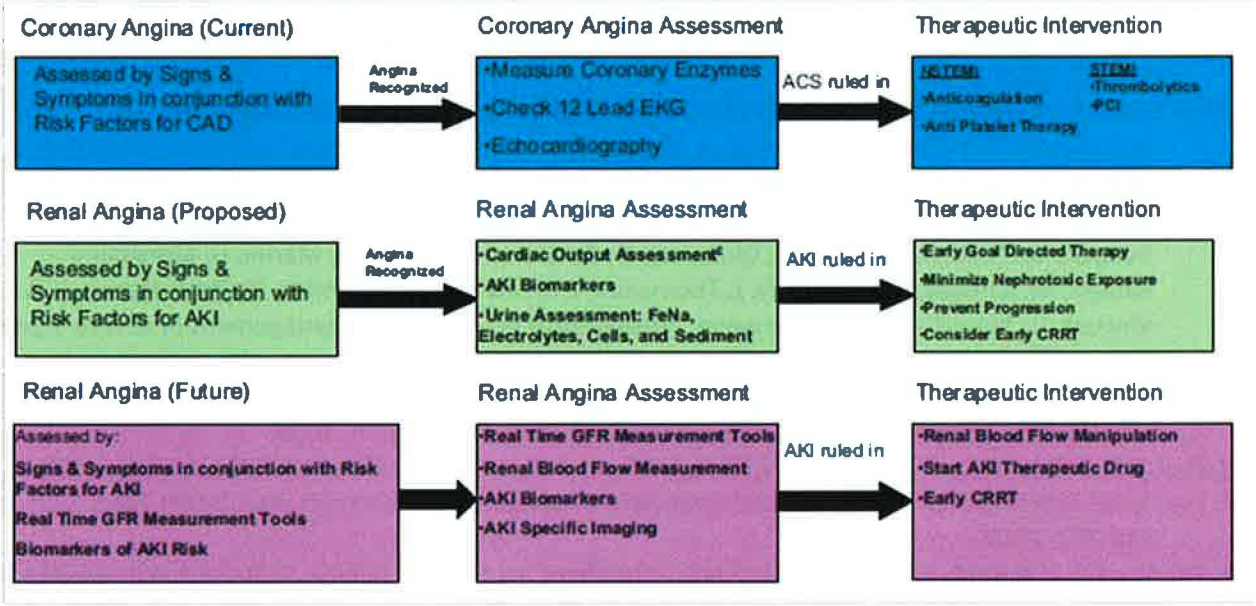
A major contributor to the extension phase of ischemic AKI is the inflammatory response to ischemic injury. injury (60, 46, 27, 10, 15). How the initial ischemic injury is translated into inflammation remains to be fully understood. One hypothesis is that injured cells release "Damage Associated Molecular Pattern molecules" (DAMPs or ALARMINS) that bind to the cell-surface receptor TLR4 and trigger the release of proinflammatory molecules (48, 56, 3, 57, 40). That TLR4 has this maladaptive role in rodent models is suggested by the beneficial effect of transgenic knockout of TLR4 on ischemic acute kidney

injury (AKI) (73, 54). Research from our lab shows that acute ischemic injury results in the release of DAMPs; the DAMPs interact with endothelial TLR4; this activates endothelial cells to express adhesion molecules; these endothelial adhesion molecules allow the maladaptive inflammation that exacerbates ischemic AKI.

We also found that an early critical proinflammatory signal during ischemic AKI is produced in murine S3 proximal tubule cells within 15 minutes of reperfusion in vivo and in vitro. This signal is Interferon Regulatory Factor 1 (IRF-1); IRF-1 is a transcription factor that activates proinflammatory genes (71). Transgenic knockout of IRF-1 also ameliorates ischemic AKI. Analysis of human kidneys with ischemic injury show that this gene is also activated during human ischemic AKI.

Additional data from our laboratory indicates that Bardoxolone methyl (BARD) increases the adaptive genes Nrf2, heme oxygenase 1, and PPAR gamma.

Renal angina – 2010 and in the future (16).



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