Acute Kidney Injury—Forging Ahead!

Devasmita C. Dev. M.D.

Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center
February 20, 2009

This is to acknowledge that Devasmita Dev, M.D. has not disclosed any financial interests or other relationships with commercial concerns directly related to this program. Dr Dev will not be discussing of-label uses in her presentation.

Devasmita C. Dev, M. D.
Associate Professor Internal Medicine, UTSW
Division of Nephrology
interests: cardiovascular outcomes in ESRD/CKD, hypertension, vascular access, renal replacement therapies

Acute Kidney Injury – Forging Ahead!

Introduction

Acute kidney injury (AKI) - alias acute renal failure -- delineates a sudden loss of renal function over hours, days and weeks as opposed to months and years. The sooner we realize this catastrophic event, the better we are at trying to reverse the process. Categorizing into extrarenal and intrarenal processes helps us navigate the numerous processes that can be causative in decreasing renal function. Reversibility of extrarenal processes – pre renal and or post renal - is frequently more satisfactory than intrarenal etiologies, although prolonged hypovolemia and or obstruction can lead to intrarenal damage.

The intrarenal processes which occur in hospital are often the most challenging and devastating. Of the intrarenal processes, ischemic nephrotoxic acute kidney injury is the most common caused by renal hypoperfusion from sepsis, hemorrhage, surgical processes and tubular toxins such aminoglycosides, contrasts agents, chemotherapy agents, or malignancies such as myeloma, tumor lysis.

While the setting (in hospital versus not in hospital) and type (extrarenal versus intrarenal) affect patient outcome, in-hospital mortality can increase up to 10 fold or higher in comparison to patients without AKI, particularly if dialysis support is necessary[1]. In fact even with changes in serum creatinine of 0.3-0.4 mg/dl, there is a 70% greater multivariate adjusted odds of death compared to patients that have no change in serum creatinine during hospitalization [2].

Definition of Acute Kidney Injury –RIFLE criteria, AKIN criteria

A closer look at acute renal failure suggests that in fact this entity comprises a sudden loss of renal function at various stages and grades of injury which may be reversible. Therefore if early intervention is to be considered then early diagnosis should be entertained. In 2004, a consensus reached amongst experts in acute renal failure with evidence based data proposed that the name be changed from "acute renal failure" to "acute kidney injury." This group established the Acute Dialysis Quality Initiatives (ADQI) which proposed the RIFLE criteria for standardizing and staging acute kidney injury. The RIFLE definition uses the common clinical parameters serum creatinine and urine output to formulate three severity categories (Risk, Injury, Failure) of acute kidney injury and two clinical outcomes categories (Loss, End-stage), Table 1.

The clinical utility of this definition and staging has now been validated in numerous clinical studies evaluating outcomes [3-7]. Changing the name and standardizing staging criteria for this acute entity shifts our understanding of this entity into grades of injury rather than just failure of renal function, in the hopes

that acting earlier in the process of acute kidney injury will ameliorate poor outcome. In addition, standardized criteria allows also for comparing AKI data from various parts of the world.

Table 1: RIFLE classification per Acute Dialysis Quality Initiative (ADQI) 2nd International Consensus Conference Workgroup 1(www.ADQI.net)

RIFLE CLASSIFICATION	GFR CRITERIA	URINE OUTPUT CRITERIA
RISK	Increased serum creatinine X1.5 or GFR decrease >25%	UO <0.5 ml/kg/h for 6 hours
INJURY	Increase serum creatinine X 2 or GFR decrease >50%	UO <0.5 ml/kg/h for 12 hours
FAILURE	Increase in serum creatinine X 3, GFR decrease 75% or serum creatinine >4 mg/dL or acute rise in serum creatinine >0.5 mg/dL	UO <0.3 ml/kg/h for 24 hr or anuria X 12 hours
LOSS	Persistent ARF: complete loss of kidney function > 4 weeks (28 days)	
End Stage Kidney Disease	End stage kidney disease > 3 months	

Table 2: AKIN Classification, modified RIFLE (Mehta RL, Crit Care 2007)

Table 2

Classification/staging system for acute kidney injury[a]

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4 μmol/l) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg per hour for more than 6 hours
2[b]	Increase in serum creatinine to more than 200% to 300% (> 2- to 3-fold) from baseline	Less than 0.5 ml/kg per hour for more than 12 hours
3[c]	Increase in serum creatinine to more than 300% (> 3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl [≥ 354 μmol/l] with an acute increase of at least 0.5 mg/dl [44 μmol/l])	Less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours

The Acute Kidney Injury Network (AKIN) comprised of nephrologists and intensivists from around the world in 2007 suggested refinements to the RIFLE criteria so as to increase the sensitivity by using smaller changes in serum creatinine to identify patients in the stage 1, Risk, category. In addition, a 48 hour time constraint for diagnosing AKI is suggested to reinforce acuity of the process within clinically relevant time period, as well as classifying any patients receiving renal replacement therapy as Stage 3, Table 2 [6, 8].

A recent study comparing the utility of both these criteria looked at large data base of the Australian New Zealand Intensive Care Society Adult Patient

Database (ANZICS –APD) over the course of 5 years to see how the RIFLE and AKIN criteria fared in diagnosis and classification of AKI and in the prediction of hospital mortality. Stage 1 injury (Risk category for RIFLE criteria) classification improved by 2% from 16.2% by RIFLE, and 18.1% by AKIN. However, this decreased the number of patients then classified as Stage 2 AKIN (Injury stage by RIFLE) from 13.6% to 10.1%. The area under the curve (ROC) for hospital mortality was .66 for RIFLE and .67 for AKIN in all patients and .65 for both when only septic patients from the database was considered [6]. Thus the RIFLE/AKIN criteria – relatively easy to remember and utilize seems to be appropriate as a clinical tool in the diagnosis if AKI for the present.

Progress in AKI Pathobiology

Basic studies in various experimental models of AKI have gradually delineated the response of the vasculature, tubules and interstitial renal tissue to acute insult [9]. These models may be imperfect as treatment strategies which prove to be beneficial in animal models of AKI have frequently not translated to beneficial outcomes for patients. In addition, pathologic changes observed in the animal models of ischemia reperfusion do not always translate to similar pathology in human renal tissue [10].

Some have noted the clinical response of a decline in renal function with AKI to be more of "acute renal success," than acute renal failure explaining the phenotypic range that is often seen with ischemic nephrotoxic injury[11, 12]. Thus hypotheses have been generated regarding regional hypoxia with mismatch of tubular oxygen supply and demand. Mismatch alters regional renal blood flow. In addition a decrease in filtration from tubuloglomerular feedback occurs to prevent further injury and promote recovery. These protective processes may thus be responsible for the disconnect in the pathology of AKI in the patient [13-15].

However despite imperfection of these models valuable understanding regarding pathobiology of AKI has and can be gained as research progresses in this area. For example with acute ischemic injury the inciting processes lead to marked vasoconstriction of the microvasculature (ie. increased endothelial angiotensin II, sympathetics, endothelin, adenosine, thromboxane A2, leukotrienes), disrupt response to endothelial counter vasodilatory biologic mediators (acetylcholine, bradykinin, nitric oxide, PGE_2) which can lead to vascular smooth muscle injury and activation of mediators of coagulation and inflammation via leukocyte adhesion. Resultant hypoxia and decreased nutrient delivery to downhill tubular epithelial cells then lead to increases in reactive oxygen species, calcium, and phospholipases causing breakdown of the epithelial cytostructure with loss of cell polarity, signaling of apoptosis, and initiation of cell necrosis with tubular epithelial desquamation, obstruction increasing intratubular pressure and decreasing glomerular transcapillary hydrostatic pressure with backleak of glomerular filtrate [16, 17].

Newer animal models of AKI try to mimic the clinical setting and outcomes that are found in hospital settings. Ischemic acute kidney injury after surviving cardiac arrest is present in nearly one-thrid of hospitalized patients [18]. A recently developed KCL induced mouse cardiac arrest/resuscitation model [19] may more closely resemble the human whole body ischemia allowing for crosstalk between ischemic organs. In addition, a newer mouse sepsis model using cecal ligation to induce polymicrobial sepsis with volume resuscitation and antibiotic treatment is being used to interrogate events of sepsis associated AKI [20]. In addition, hemodynamic monitoring in a live sheep model of continuous E. coli sepsis has simulated the hyperdynamic state of sepsis with onset of oliguric acute renal failure. This model suggests decreased glomerular filter pressure with subsequent mismatch of medullary energy use requiring high needs for oxygen consumption but inadequate oxygen extraction [21]. Probing the microenvironment in AKI has made it feasible to understand the role of inflammation and crosstalk between injured organs [22]. In addition, progress in understanding pathobiology has made possible investigation of markers of early kidney injury.

In the Search for Early Injury Biomarkers of AKI

Blood urea nitrogen and serum creatinine appear to be relatively good markers for progressive kidney injury however may not be specific or sensitive to detect early kidney injury. In the process of early renal injury, various biomolecules including cytokines, inflammatory markers, tubular enzymes or proteins are detected in the urine and serum. Several of these biomolecules are being actively investigated as injury markers for AKI [23], Table 3. The optimal renal biomarker should detect injury as early as possible, but also be clinically useful in grading the severity of the injury as it relates to outcome.

Table 3

Biomarkers Being Investigated in Human AKI

IL-18	Leucine aminopeptidase
Neutrophil gelatinase-associated lipocalin (NGAL)	B-galactosidase
Kidney injury molecule (KIM-1)	α-glutathione S-transferase
Cystatin C	π-glutathione S-trnasferase
N-acetyl-β-D-glucosaminidase (NAG)	γ-glutamyl transpeptidase
Fatty acid binding protein (FABP)	Alkaline phosphatase
NHE-3	Lactate dehydrogenase
Endothelin	Neutral endopeptidase
Adenosine deaminase binding Protein	α-1 microglobulin
Alanine Aminopeptidase	β-2 microglobulin
	Retinol binding protein
	Matrix metalloproteinase-9

List adapted from Waikar SS, Curr Opin Nephrol Hypertens 2007

Urinary Interleukin -18 (IL-18)

Urinary IL-18, a cytokine released after acute ischemic injury, is noted in the urine of mice and humans in high concentration. Urinary concentratrion of IL18 is noted to be highest in those patients with acute tubular necrosis and delayed renal transplant graft function when levels were measured and compared amongst patients with prerenal azotemia, acute tubular necrosis, urinary tract infections, chronic kidney disease, transplant evaluation, as well as healthy controls [24]. Further prospective analysis of urine collected in a nested case control cohort of critically ill patients without evidence for kidney injury by serum creatinine (< 1.2 mg/dl) on admission to ICU of the Acute Respiratory Distress Syndrome Network (ARDS) trial suggested that urinary IL-18 levels were greater in the patients who went on to develop AKI and this was predictive of mortality. The area under the curve AUC-ROC was 0.73 at 24 hours prior to AKI diagnosis [25]. Post pediatric bypass sugery, AUC of ROC increased at 4, 12, and 24 hours from 61%, 75%, 73% respectively. In contrast, detection of AKI occurred at 48-72 hour by serum creatinine. Current evaluation of the urinary IL-18 as a predictive biomarker of AKI suggests low sensitivity by high specificity. Thus while many patients with AKI may not elevations in urinary IL-18 levels, those that have elevation are rarely false positive elevations [26].

Neutrophil gelatinase-associated lipocalin (NGAL)

This iron transporting protein (other names – lipocalin-2, siderocalin) is found in granules of neutrophils. NGAL significantly increases in the urine of children within 2 hours after undergoing cardiopulmonary bypass for congenital heart repair who go on to develop AKI in 24-72 hours. When this protein was measured by ELISA, the AUC- ROC was noted to be .998 with 100% sensitivity and 98% specificity for AKI [27]. Urinary NGAL levels measured by quantitative immunoblotting at various time points post cardiac surgery in adults are also increased in those who develop AKI. However levels seem to overlap to a greater extent with those that do not develop AKI per se. AUC-ROC immediately post surgery was .67 and increased at 18 hours post op to .80 [28]. Whether this is a result of the methodology or because there is less distinction in adults with this biomarker needs further investigation. Though sample size was small, a double blind evaluation of urinary NGAL levels (by ELISA) of living and deaceased kidney donors with prompt graft function in comparison to those with delayed graft function predicted trend in serum creatinine after multivariate adjustment and suggests this as a possible marker in predicting for detecting delayed graft function [29]. This was also noted for urinary IL-18 in this same study. Larger studies confirming these findings are necessary. Serum NGAL levels have not been as useful in predicting AKI however. Serum levels of NGAL in children with hemolytic uremic syndrome could not discriminate between those requiring renal replacement and those not requiring renal replacement [30]. Standardized methodologies to measure plasma and urine NGAL for rapid results are also being investigated [31].

Kidney Injury Molecule-1 (KIM-1)

KIM-1 protein is a type-1 transmembrane glycoprotein involved in cell to cell and cell to matrix interaction that is markedly up-regulated in proximal renal tubular cells in response to ischemic or nepthrotoxic AKI. KIM-1 sheds its ectodomain into the urine after proximal tubular injury [32]. In established AKI patients, urinary KIM-1 levels showed significant association with outcomes of dialysis or death however this association was no longer significant when adjusted for covariates [33]. Prospective evaluation of KIM-1 level normalized to urinary creatinine concentration at 12 hours after cardiopulmonary bypass surgery in a case control study of 20 pediatric patients with and without AKI was noted to have an AUC of 0.83 suggesting usefulness as possible early injury marker. Further investigation continues to combine this and other markers as panels for evaluation of AKI [34].

Cystatin C

Cystatin C is an endogenous cysteine proteinase inhibitor produced at a constant rate and released in the plasma by all nucleated cells in the body. It is freely filtered and not secreted or reabsorbed but nearly completely catabolized by the proximal tubule. When serum Cystatin C was evaluated post op in cardiac bypass surgery patients at various time points, there was a trend for higher composite values in those with AKI noted 24 hours prior the diagnosis of AKI. However plasma cystatin C was not useful in predicting the development of AKI. Urinary Cystatin C post operatively was predictive for those requiring renal replacement therapy however levels were not different for those with AKI not requiring RRT [35], fig 1.

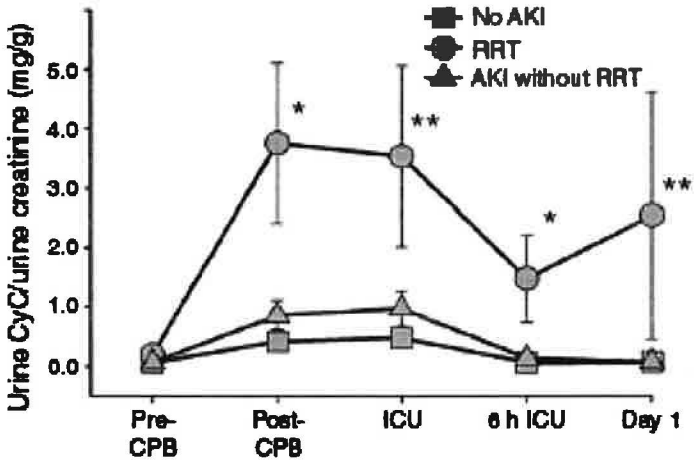


Fig 1: Urine Cystatin C excretion over time (Koyner KL, Kidney Int 2008)

As the search continues, we can expect to see in the near future, these and other markers actively being investigated to determine early kidney injury. It is possible that a combination of markers will be available in the near future to determine early injury and need for intervention. In the interim, therapy changes are being

pursued to prevent, minimize, or support the recovery of renal injury and recovery based on our current definitions.

Therapeutic challenges

Contrast imaging - preventive management

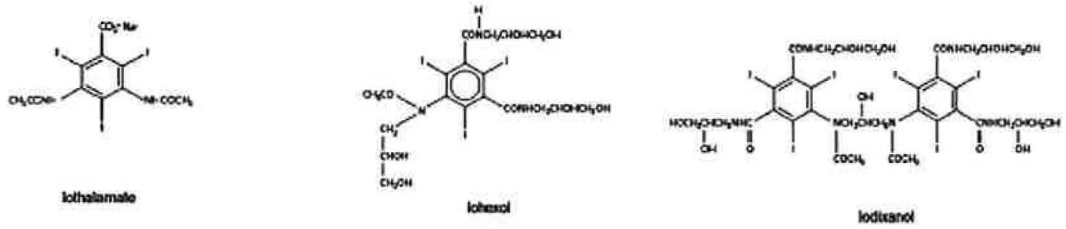
Despite our lack of a magic bullet in reversing AKI, we continue to progress in refining prevention and treatment of AKI. One instance where an improvement can be noted is with contrast induced kidney injury (CIN). The general incidence of contrast induced AKI reported has decreased some over the past decade from approximately 15% to 7% [36, 37], suggesting perhaps better awareness in addition to some therapeutic changes. However given increased numbers of procedures in high risk patient groups, this entity remains 3rd in causing AKI with decreased renal perfusion and nephrotoxic agents, as 1st and 2nd [38]. High risk patient characteristics for AKI include elderly, diabetes, recent kidney injury, recent contrast load, volume depleted state including cardiac or liver failure, concurrent nephrotoxic antibiotics, nonsteroidal, or chemotherapy agents, myeloma, chronic kidney disease. A retrospective review of a large number of patients receiving low osmolar contrast media in Rochester MN from 2004-2006 suggested higher mortality for the group that developed CIN at 30 days ,15.6% versus 5.2% of non CIN group ($p < .001$) with CIN defined as serum creatinine rise of 25% or more or an increase of 0.5% mg/dl within 7 days of exposure [39]. CIN is associated with increased odds of 5.5 for death [40]. While expected renal recovery occurs over days to weeks in 75% of patient, nearly 10% become dialysis dependent [41].

Type of contrast agent

Thus various aspects of CIN including the type of contrast agent and pre and post contrast patient management have and continue to be evaluated. The proposed pathogenesis encompasses an aspect of both renal ischemia and direct tubular toxicity. An initial brief renal vasodilatory response after contrast administration leads to significant vasoconstriction altering blood flow to the renal medulla. Subsequent medullary hypoxia with impaired adaptive response leads to cytotoxic tubular damage with increased oxidant stress and loss of renal function. Cell culture studies also imply direct tubular cell toxicity with loss of cellular proteins and drop in transepithelial resistance, permeability and possible complement activation [42]. Certainly avoidance of iodinated contrast is optimal with risk benefit assessment however often patients in need of specific diagnostic studies propose a therapeutic challenge. While MRI/MRA studies are an option for those without underlying renal dysfunction, MR studies with gadolinium should not be considered in patients AKI or with moderate to severe chronic kidney disease given the risk of nephrogenic systemic fibrosis. Use of low and iso-osmolar iodinated contrast agents, fig 2, is more frequent in the current decade with suggested benefit over 1st generation higher osmolar contrast agents [43-45]. Benefit of isoosmolar agent to that of low osmolar contrast agents

has been suggested but not definitively shown [46]. If contrast must be given, then the most important preventive therapy appears to be avoidance of volume depletion [47-49], and or adequate volume repletion for those that are deemed to be volume depleted [50]. For this reason, diuretics pre and post procedure should be avoided if possible [51].

Fig 2: Molecular structures of iodinated contrast media.



1st gen iothalamate ionic monomer high osmolar, 2nd gen,iohexanol low osmolar non-ionic monomer, 3rd gen iodixanol, iso-osmolar non-ionic dimmer (Efstratiadis G, Hippokratia 2008)

Volume replacement

Subsequent trials addressed the importance isotonic fluid replacement in CIN compared to hypotonic solutions. In addition, fluid administered pre procedure over longer periods of time rather than bolus resulted in better outcome [52 53]. Oral NaCL administration of (1g/10kg) over 2 days (240 mEq in 70kg patient) compared to 6 hrs of IV 0.9% NaCL, suggested no difference between these 2 groups, and was better than NaCL infusion plus furosemide administration [54]. Recent randomized trials have suggested benefit of isotonic bicarbonate infusion over isotonic saline infusion before and after contrast exposure [55, 56] however small patient numbers in these trials cannot rule out the possibility of a type 1 error. Use of bicarbonate solution for volume repletion in the prevention of CIN nephropathy perhaps reinforces the hypothesis that improving the hypoxic renal medullary pH may protect from mitochondrial reactive oxygen species generation and subsequent oxidant injury [55, 57, 58]. Further randomized studies evaluating the benefit of bicarbonate infusion or alkalinization of the urine may be useful to further clarify the use of bicarbonate in CIN. While firm conclusions may not be available from these studies as to what type, how much and when to administer volume, there is little debate for the role of adequate volume repletion prior to contrast administration.

N-acetylcysteine (NAC)

With oxidant injury playing a possible role in contrast induced AKI, the antioxidant with vasodilatory effect, NAC, has also been used and tested for the prevention of CIN. Tepel et al initially suggested that use of 600 mg twice daily of oral NAC on the day prior and day of contrast administration decreased the incidence from 21% in the placebo group to 2 % in the treatment group [59]. Others have subsequently suggested similar benefit with some noting higher dose of 1200 mg NAC twice daily as being more effective [60]. However, again these studies lack

effective sample size to make definitive conclusions. Furthermore meta-analysis of the studies evaluating NAC for CIN has resulted in conflicting results[61, 62].

Therefore, since it is relatively low in cost and with little toxicity, it is being frequently used as prophylaxis by many. There is however no conclusive data to recommend it use routinely at this time.

Peri-procedural blood purification

Since pathogenesis of CIN may be from direct tubular toxicity, a basic inclination to remove contrast from the body may seem appropriate. A single dialysis treatment removes approximately 60-90% of the contrast agent [63]. Therefore several studies have looked at peri-procedural blood purification techniques including hemofiltratin and hemodialysis for decreasing CIN [64-66]. Using change in serum creatinine to define CIN becomes a problem when these techniques are used because creatinine itself is lowered with these blood purification techniques. Lee and colleagues looked a high risk population of CKD stage 5 with eGFR 12.8ml/min/1.73m2 undergoing coronary angiography and did prophylactic hemodialysis after intravenous saline administration post contrast [65]. The level of serum creatinine at day 4 was noted to be higher than the control group and it was noted that the number of patients requiring temporary dialysis was also greater in the saline control group. Again with dialysis there is removal of the very marker that is being used to determine disease. Even after 4 days, it will take time for those having undergone dialysis to reach the same level of serum creatinine as that of the group that did not have serum creatinine removed with dialysis. When added to spontaneous recovery in some patients, improvement in serum creatinine can be misleading. Thus the conclusions of a better renal outcome can be misleading. Recent meta-analysis of 6 randomized studies using hemodialysis suggested that there was no decrease in CIN with periprocedural hemodialysis in comparison to standard medical therapy figure (RR 1.35 for HD, CI 0.93-1.94) [66], fig 3. Gvien these findings, there appears to be no convincing evidence for a clear benefit for peri-procedural hemodialysis in CIN at this time.

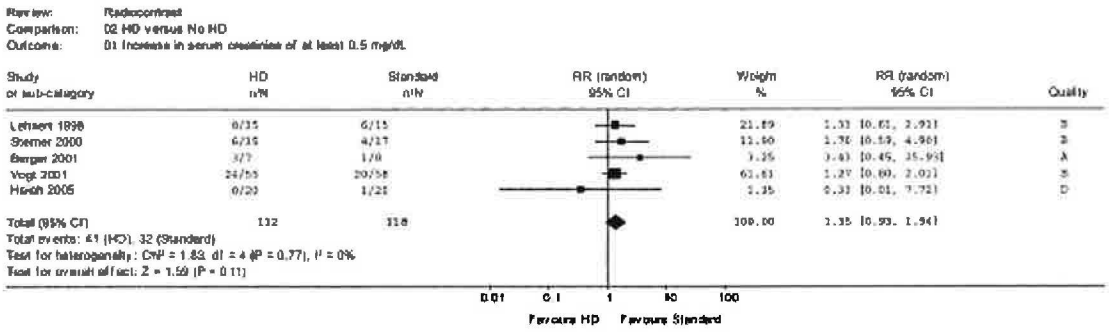


Fig 3: RR for RCIN, analysis of hemodialysis studies only (Cruz DN, Am J Kidney Dis 2006)

Diuretic Dilemma

Diuretic use is relatively common in critically ill patients with AKI. A multinational, multicenter survey of intensivists and nephrologists comprised of academic institutions (77.5%) and other private, regional, and metropolitan hospitals from 16 countries reports use of intravenous furosemide (71.9%) as the most common medication given in bolus dosing. Serum creatinine, urine output, blood pressure, central venous pressure, and risk of toxicity determined dose. Most commonly, diuretics were used just prior to renal replacement therapy or during recovery [67]. Is there benefit or harm with using diuretics in the setting of AKI?

Rationale for diuretic use during AKI is often to "maintain urine flow", "flush out debris", convert from an oliguric to a nonoliguric state, in other words prevention of renal injury. The other rationale is for volume management. Data in both animal and human studies support use of loop diuretics to decrease renal oxygen consumption by decreasing active sodium transport thereby limiting potential ischemic tubular damage [68, 69]. In addition loop diuretic inhibit prostaglandin dehydrogenase which can then prevent breakdown of renal vasodilator prostaglandin PGE2 [70] thereby increasing renal blood flow. Similarly various studies have suggested that nonoliguric AKI patients have better outcomes [71, 72]. However studies evaluating the use of diuretic in AKI have suggested little benefit and one retrospective study suggests increase in mortality. Kleinknecht and colleagues[73] randomized 66 patients with oliguric renal failure to IV furosemide ranging from 1.5to 6.0 mg/kg given every 4 hours in 33 patients and no diuretics in 33 control patients. A persistent diuresis was observed in 5 of the treated group and 2 of the controls. Hemodialysis however was required in most patients with no differences noted in mean time of oliguria, number of dialysis, and mean time with renal insufficiency.

Brown et al[74] conducted a randomized study in 58 established acute renal failure patients assigned to either bolus 1 gm furosemide over 4 hours, or either IV or orally dosing of 3 gm/24 hour to obtain a sustained urine output of 200ml/hr or serum creatinine decreased below 300 umoles/L. Oliguria reveresed in 24/28 patients given sustained furosemide but in only 2 given a single injection. No difference in dialysis treatment number, duration of renal failure, or mortality was found. Deafness was noted in 2 patients, with one becoming permanent.

Ninety-two patients with ARF were studied by Schilliday et al.[75]. Patients were randomized to 3 mg/kg of torsemide (n=30), furosemide (n= 32), or placebo IV (n-= 30) q6h for 21 day or until renal recovery of death. All patients also received 2ug/kg/min dopamine and 20% manitol x3 days priot to randomization. Apache II score for severity of illness was similar in each group, with similar creatinine clearance and urine volumes noted at initiation. Outcomes of renal recovery, need for dialysis, or death were not different between groups although urine flow rates were significantly greater in the loop diuretic groups.

A larger randomized, double blind, placebo controlled study of 388 patients of acute renal failure stratified to severity at presentation 25 mg/kg/d IV or 35 mg/kg/d oral) versus placebo [76]. Patients in the diuretic group had greater renal impairment at baseline and greater serum creatinine at randomization which was not evident at RRT initiation. No differences were noted between the 2 groups for overall mortality, number of dialysis sessions, time on dialysis and time to recovery of renal function although the diuretic group reached urine output of 2L/day over a shorter period of time. (can use data table 2 and 3 –side effects here for illustration). Problems with this study are that all patients received a test dose of furosemide 15mg/kg prior to randomization which may have affected outcome. In addition, increased diuresis of a recovering kidney may have led to slower return to the endpoint of evaluating recovery.

A cohort analysis of the large multicenter PICARD (Project to Improve Acute Renal Disease) data set in critically ill AKI evaluated 552 patients of which 326 patients had used diuretics before renal consultation obtained. The group using diuretics was older, had more patients with congestive heart failure and higher pulmonary capillary wedge pressure, lower cardiac output, and higher vascular resistanceand more cardiorespiratory organ failure. The differences between groups were addressed using propensity scores and the study. Calcuated risk of death was 25% and nonrecovery of renal function 36% with the conclusion that widespread diuretic use should be discouraged [77]. However this was a group of patients in whom renal consultation was requested suggesting perhaps more severe renal failure and nonrecovery of function.

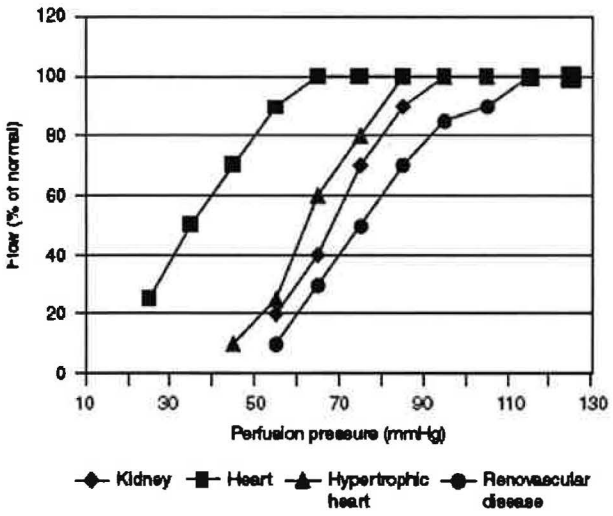
A larger prospective multicenter multination observational study BEST (Beginning and Ending Supportive Therapy for the Kidney) also reviewed this topic and evaluated over 1700 ICU patients using diuretics (furosemide-used in 98% of patients) with groups adjusted for covariates and propensity scores as done in the prior retrospective PICARD cohort. This study found no risk of higher mortality and therefore could not discourage use of diuretics [78].

Despite theoretical benefit in the use of diuretics to decrease AKI, studies in CIN have suggested possible increase of CIN with use of diuretics. Post op cardiac patients have an increase in serum creatinine with increased urine output when loop diuretics are used and therefore avoidance has been suggested when used for protection of renal function after cardiac surgery. These data then suggest that diuretic use to prevent AKI is not useful. Diuretic use in established acute renal failure offer little benefit in changing outcome of mortality or need for renal replacement, particularly in the presence of oliguria. Given current literature, use of diuretic for volume management when necessary in the AKI patient can be considered. However diuretic use to prevent oliguria in the AKI setting is not indicated [79].

Vasopressors in AKI

When renal autoregulatory capacity is compromised, the ability to maintain renal perfusion is lost and blood flow decreases in linear fashion. Loss of blood flow leads to renal ischemia. This can occur at higher than expected mean arterial pressures for patients (usually 80mmhg) with significant vascular disease, fig 4 [80]. Therefore restoring BP becomes critical. Vasopressors that optimize renal perfusion should improve patient outcomes. As such several vasopressors have been under study.

Fig 4: Perfusion pressure and organ flow under pathophysiologic conditions. (Bellomo R, Crit Care 2001)



Dopamine

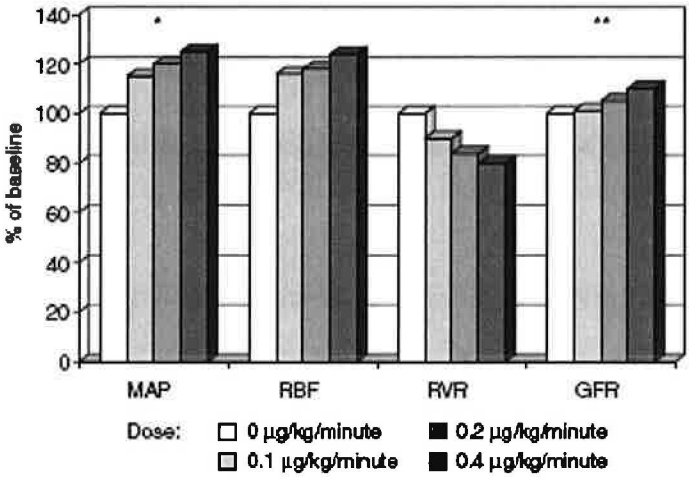
Dopamine, an endogenous catecholamine has dopaminergic effects at low doses of 2-5ug/kg/min whereas at higher doses has β-adrenergic and α adrenergic effects. When used at lower doses in healthy individuals and experimental animals, renal vasodilation with increased renal blood flow and natriuresis is seen [81]. Some studies have also suggested a blunting of endogenous norepinephrine associated vasoconstriction [82]. As a result "low dose dopamine" infusion in AKI has frequently been utilized to maintain renal blood flow. However, review of trials using low dose dopamine in patients with AKI have shown little benefit [83-85].

Norepinephrine

Norepinephrine (NE) via α-adrenergic stimulation acts as a potent vasopressor. Marked splanichnic and renal vasoconstriction can occur in the presence of hypovolemic hypotension, essential hypertension, and with normal circulation. In fact reversible acute kidney injury can be induced when NE is injected into the renal artery [86]. However, under vasodilated states such as sepsis there is significant nitric oxide release, and downregulation of α-adrenergic receptor responsiveness, as well as endothelial damage and loss of vascular smooth

muscle tone the use of intravenous NE may improve renal blood flow [80]. NE used short term in clinically relevant dose so of 0.2-0.4 ug/kg/min in conscious dogs showed improved increased renal blood flow, decreased renal vascular resistance with improvement in MAP, fig 5[87] [80].

Fig 5: Effect of norepinephrine on mean arterial pressure, renal blood flow, renovascular resistance, and glomerulor filtration in dog [87] . (Anderson, WP, J Physiol 1981)



Pretreatment with indomethacin, propranalol, angiotensin did not change this response suggesting that these changes were not attributable to prostaglandins, β receptor stimulation, or angiotensin- mediated but may actually be from restoring systemic blood pressure. NE also did not decrease renal blood flow of dogs during endotoxic shock [88]. More detailed physiologic studies in endotoxemic dogs suggest an increase in both dynamic renal blood flow and perfusion pressure [89]. Other clinical studies have also reported improvement in renal clearance and urine output with NE use in patients with septic shock [90]. Compared to high dose dopamine, NE faired better in restoring MAP and urine output [91].

Vasopressin

Vasopressin is a peptide hormone rapidly released with acute shock, acting via V1 receptors to increase mean arterial pressure and decrease cardiac output. Levels decrease over time with prolonged hypotension [92]. It can potentiate NE effect. In face of marked vasodilation as in septic shock, there may be a relative deficiency and therefore exogenous administration has been considered [93]. Low dose vasopressin infusion in observational studies have suggested improved blood pressure, however given possible decrease in blood flow to other vital organs including kidney, heart, and gut, use has been with caution. When used in conjunction with NE, improved blood pressure allowed for decreasing NE dose in patients with vasodilatory shock [92]. A recent multicenter double blind trial randomized trial compared the use of vasopressin plus low dose NE versus NE

alone in patients with septic shock and found no significant difference in primary outcome of mortality or secondary outcomes including days of free or renal replacement, or ventilator use. There was also no difference in adverse events [93].

Terlipressin

Terlipressin is glycine modified vasopressin which has a longer half life and can be given intermittently. Its use as a vasoconstrictor for marked splanchnic vasodilation of hepatorenal syndrome (HRS) has shown some improvement in renal blood flow and urine output when used with albumin [94, 95]. While it is available for use for HRS type 1 internationally, it is under phase 3 clinical trials in the US.

Renal Replacement in the critically ill and multiorgan failure patient

While presence of AKI already heralds an increase in mortality, prognosis in the critically ill usually with multiorgan failure can be dismal, 50% reported mortality [96]. Therefore supportive management issues need critical analysis in order to make therapy impact. Several studies have therefore evaluated the delivery and dose of renal replacement.

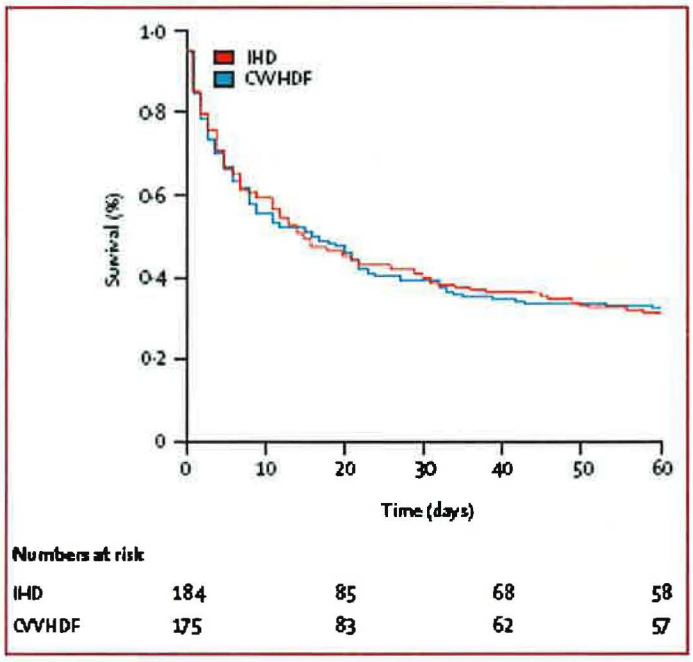
Renal replacement can be offered to the critically in several different forms amongst which the most popular modalities include intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT) or a hybrid of slow continuous dialysis given intermittently with a conventional hemodialysis machine, termed sustained low efficiency dialysis (SLED). CRRT can usually be provided as hemofiltration alone as continuous venovenous hemofiltration, (CVVH), dialysis alone (CVVHD) or with combination of both hemofiltration and dialysis,(CVVHDF). The utility of these modalities and treatment dose is often based on patient need, hemodynamic status and modality availability. However both modality and dose are factors that may affect outcome in the critically ill patient. Therefore both have recently been carefully evaluated to determine the best therapeutic approach in renal replacement.

Modality: Intermittent versus Continuous Renal Replacement Therapy

Single center and multi-center randomized trials evaluating this question suggest that there is little difference in mortality outcome when either intermittent or continuous therapy is used in the critically ill population when similar amounts of dialysis are provided. Uehlinger et al. randomized AKI patients in the ICU to either intermittent hemodialysis (N=55) or CVVHDF (N= 70) and standardized for solute clearance 25ml/min per day and found no difference in patient mortality between groups [97]. Larger multicenter randomized studies by both Vinsonneau

and colleagues (N= 360 patients), fig 6, and Lin and colleagues (n=316) confirmed findings of single center trials [98, 99]. Therefore, modality choice is clinical, done at the bedside and depends on availability.

Fig 6. Estimation of Survival rate according to treatment group. (Vinsonneau C, Lancet 2006)



Dialysis dose

What about dialysis dose? Does dose matter? Dialysis dose in simplified explanation is the amount of urea clearance (small solute clearance) that occurs with each dialysis session. Therefore does increasing the number of treatments from intermittent dosing to daily dosing then improve outcome? A randomized single center study evaluating daily intermittent hemodialysis to alternate day hemodialysis (usual treatment) suggested that there was significant outcome benefit when dialysis was given daily [100]. However a criticism of this study was that baseline dose achieved for each dialysis was low compared to what is expected for a treatment session for even a chronic patient. Therefore when frequency was increased for the same dose, the chances that outcome would improve was obvious. The question then became that if the dose for each treatment was considered to be adequate for treatment or at least as much as the amount of renal replacement that is provided for a chronic dialysis session, then would increasing dose by increasing frequency of treatments be even better for patients with AKI.

What about continuous therapy dose for those requiring CRRT? In CRRT, dose is frequently evaluated by the total ultrafiltration effluent rate. A two center randomized study looked at hemofiltration dose (CVVH). That is the rate of ultrafiltration with convective clearance achieved. A minimum ultrafiltration clearance of 20ml/kg/hr was compared to higher doses of 35ml/kg/hr and 45 ml/kg/hr. Based on this study the higher dose of 35ml/kg/hr was found to improve mortality outcome although the patient group with better survival were significantly younger in age [101]. Yet another single center study suggested that when a dose of dialysis was added to a minimum hemofiltration dose (CVVHDF), there was also improved outcome. However patients in the hemofiltration group were sicker and less hemodynamically stable at baseline [102].

To resolve then issues about dose a multicenter VA/NIH trial, ATN trial comprised of 27 VA and academic medical centers throughout the US was undertaken from 2003-2007 with 1164 patients enrolled evaluating mortality outcome of dialysis dose intensity in critically ill patients [103]. In this study, hemodynamically stable (SOFA score 0-2) patients randomized to conventional intermittent hemodialysis (thrice weekly) with minimum target dose clearance of at least 1.2 KT/V per treatment session or daily hemodialysis with minimum clearance target of at least 1.2 KT/V (urea clearance x time/urea volume of distribution) per treatment. If patients were hemodynamically unstable (SOFA 3-4) they randomized to minimum CVVHDF dose of 20ml/kg/hror 35ml/kg/hr. Thus patients randomized to a standard or high intensity arm. The groups were well matched for severity of illness and other demographics. In addition, the dose prescribed and achieved was monitored during the study with target dose achieved in each group approximately 90% of the treatments. Study results suggested that when a delivered dose of at least 1.2KT/V for intermittent hemodialysis is achieved and or target dose of at least 20 ml/kg/hr total ultrafiltration dose is achieved with CRRT, there is no further mortality benefit in increasing dose intensity in this patient group, [103] fig 7.

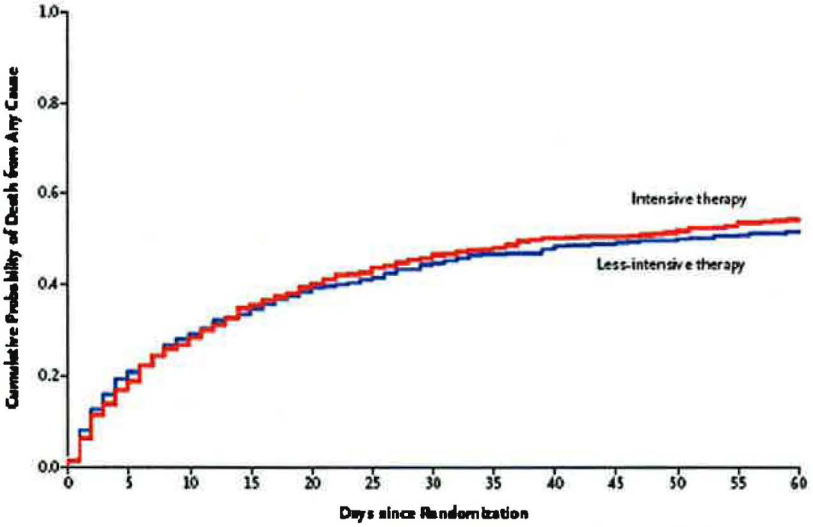


Fig 7: Kaplan-Meier Plot of cumulative probabilities of death. (Palevsky P et al. N Engl J Med 2008)

For those who have difficulty accepting that dose intensity cannot be decided as modality changed during the study, another multicenter study evaluating CRRT dose comparing 20ml/kg/hr and 35 ml/kg/hr, The Randomized Evaluation of Normal versus Augmented Level Replacement Therapy, RENAL, trial is expected to be available this year [104].

Therapies on the Horizon

Bioartificial kidney

A combination of cell therapy and tissue engineering have launched into early clinical testing the bioartificial kidney or renal tubule assist device (RAD). This is composed of a hemodialysis filter and bioreactor containing living renal proximal tubular cells. Renal proximal tubular cells isolated from deceased donor kidneys are cultured for integration into a filtration device. Since these proximal tubular cells have stem cell like characteristics, they are grown in confluent monolayers on the inner surface of hollow fibers of a hemofiltration cartridge [105]. Studies using RAD in acutely uremic dogs with bilateral nephrectomy suggested added metabolic and endocrine and transport replacement to filtration. RAD treated animals actively absorbed K, HCO3-, glucose and excreted NH3 and had appropriate small solute and fluid control [106]. In addition, treated animals were able to reach normal vitamin d levels compared to sham animals. Furthermore septic animals treated with RAD maintained mean arterial pressure and cardiac output for longer time than sham animals [107 108]. Ten AKI patients with expected mortality of 85% were evaluated in a phase I/II study. Six of 10 lived beyond 30 days and the RAD device maintained viability up to 24 hours [109]. A multicenter phase II trial in 58 patient with AKI from multiorgan failure were randomized 2:1 for RAD 72 hours or CRRT alone and suggested some benefit in survival with RAD treatment though not significant; however, the groups may have been unbalanced with greater numbers of African Americans in the RAD treated group and higher APACHE II scores in the CRRT patient group [110]. These preliminary studies suggest that the battle to improve patient outcomes with severe AKI is still on. We look forward to larger clinical studies to bring this technology to the forefront to improve renal replacement [111].

Stem Cell and renal regeneration for acute kidney injury

Hematopoietic stem cells have been shown to locate to the injured kidney when kidney injury is induced in the animal model [112, 113]. In addition resident stem cells have also been located in the kidney as in some other organs and have been shown to undergo dedifferentiation in face of acute kidney injury [114]. Studies have suggested that intrarenal cells are primarily responsible for the regenerative role after ischemic injury [115, 116]. Resident mesenchymal cells may effect injury repair via differentiation into and endothelial lineage with paracrine

effects to prevent micorvascular dropout after renal injury [117]. Furthermore, the possibility of deriving pluripotent embryonic stem like cells from cultured somatic cells is also being actively investigated [118]. The ultimate goal will be to have the therapeutic option and ability to repair renal injury once it occurs.

Summary

AKI remains a significant cause of morbidity and mortality for hospitalized patients. Recent standardized clinical definitions have broadened this entity from failure and loss of function to risk and injury, incorporating a shift in thinking towards early diagnosis and preventive therapies. Critical analyses of current available therapies for supportive management stress the importance of appropriate renal perfusion, and volume management, in addition to adequate dosing with renal replacement therapies. Active investigation towards early diagnoses and more cell based therapies for AKI treatment will hopefully improve patient outcomes.

References

1. Waikar SS, Liu KD, Chertow GM. The incidence and prognostic significance of acute kidney injury. *Curr Opin Nephrol Hypertens.* May 2007;16(3):227-236.
2. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol.* Nov 2005;16(11):3365-3370.
3. Abosaif NY, Tolba YA, Heap M, et al. The outcome of acute renal failure in the intensive care unit according to RIFLE: model application, sensitivity, and predictability. *Am J Kidney Dis.* Dec 2005;46(6):1038-1048.
4. Ali T, Khan I, Simpson W, et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. *J Am Soc Nephrol.* Apr 2007;18(4):1292-1298.
5. Chen YC, Jenq CC, Tian YC, et al. Rifle classification for predicting in-hospital mortality in critically ill sepsis patients. *Shock.* Feb 2009;31(2):139-145.
6. Bagshaw SM, George C, Bellomo R. A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. *Nephrol Dial Transplant.* May 2008;23(5):1569-1574.
7. Kellum JA. Defining and classifying AKI: one set of criteria. *Nephrol Dial Transplant.* May 2008;23(5):1471-1472.
8. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care.* 2007;11(2):R31.
9. Lieberthal W, Nigam SK. Acute renal failure. II. Experimental models of acute renal failure: imperfect but indispensable. *Am J Physiol Renal Physiol.* Jan 2000;278(1):F1-F12.
10. Rosen S, Heyman SN. Difficulties in understanding human "acute tubular necrosis": limited data and flawed animal models. *Kidney Int.* Oct 2001;60(4):1220-1224.
11. Thurau K, Boylan JW. Acute renal success. The unexpected logic of oliguria in acute renal failure. *Am J Med.* Sep 1976;61(3):308-315.
12. Rosen S, Stillman IE. Acute tubular necrosis is a syndrome of physiologic and pathologic dissociation. *J Am Soc Nephrol.* May 2008;19(5):871-875.
13. Brezis M, Rosen S. Hypoxia of the renal medulla--its implications for disease. *N Engl J Med.* Mar 9 1995;332(10):647-655.

14. Rosenberger C, Rosen S, Shina A, et al. Hypoxia-inducible factors and tubular cell survival in isolated perfused kidneys. *Kidney Int.* Jul 2006;70(1):60-70.
15. Rosenberger C, Rosen S, Heyman SN. Normotensive ischemic acute renal failure. *N Engl J Med.* Nov 22 2007;357(21):2204-2205; author reply 2205-2206.
16. Sheridan AM, Bonventre JV. Cell biology and molecular mechanisms of injury in ischemic acute renal failure. *Curr Opin Nephrol Hypertens.* Jul 2000;9(4):427-434.
17. Abuelo JG. Normotensive ischemic acute renal failure. *N Engl J Med.* Aug 23 2007;357(8):797-805.
18. Mattana J, Singhal PC. Prevalence and determinants of acute renal failure following cardiopulmonary resuscitation. *Arch Intern Med.* Jan 25 1993;153(2):235-239.
19. Burne-Taney MJ, Kofler J, Yokota N, et al. Acute renal failure after whole body ischemia is characterized by inflammation and T cell-mediated injury. *Am J Physiol Renal Physiol.* Jul 2003;285(1):F87-94.
20. Dear JW, Yasuda H, Hu X, et al. Sepsis-induced organ failure is mediated by different pathways in the kidney and liver: acute renal failure is dependent on MyD88 but not renal cell apoptosis. *Kidney Int.* Mar 2006;69(5):832-836.
21. Langenberg C, Wan L, Egi M, et al. Renal blood flow in experimental septic acute renal failure. *Kidney Int.* Jun 2006;69(11):1996-2002.
22. Feltes CM, Van Eyk J, Rabb H. Distant-organ changes after acute kidney injury. *Nephron Physiol.* 2008;109(4):p80-84.
23. Waikar SS, Bonventre JV. Biomarkers for the diagnosis of acute kidney injury. *Curr Opin Nephrol Hypertens.* Nov 2007;16(6):557-564.
24. Parikh CR, Jani A, Melnikov VY, et al. Urinary interleukin-18 is a marker of human acute tubular necrosis. *Am J Kidney Dis.* Mar 2004;43(3):405-414.
25. Parikh CR, Abraham E, Ancukiewicz M, et al. Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. *J Am Soc Nephrol.* Oct 2005;16(10):3046-3052.
26. Coca SG, Yalavarthy R, Concato J, et al. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. *Kidney Int.* May 2008;73(9):1008-1016.
27. Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet.* Apr 2-8 2005;365(9466):1231-1238.
28. Wagener G, Jan M, Kim M, et al. Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. *Anesthesiology.* Sep 2006;105(3):485-491.
29. Parikh CR, Jani A, Mishra J, et al. Urine NGAL and IL-18 are predictive biomarkers for delayed graft function following kidney transplantation. *Am J Transplant.* Jul 2006;6(7):1639-1645.
30. Trachtman H, Christen E, Cnaan A, et al. Urinary neutrophil gelatinase-associated lipocalcin in D+HUS: a novel marker of renal injury. *Pediatr Nephrol.* Jul 2006;21(7):989-994.
31. Devarajan P. Neutrophil gelatinase-associated lipocalin (NGAL): a new marker of kidney disease. *Scand J Clin Lab Invest Suppl.* 2008;241:89-94.
32. Han WK, Bailly V, Abichandani R, et al. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. *Kidney Int.* Jul 2002;62(1):237-244.
33. Liangos O, Perianayagam MC, Vaidya VS, et al. Urinary N-acetyl-beta-(D)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. *J Am Soc Nephrol.* Mar 2007;18(3):904-912.
34. Han WK, Waikar SS, Johnson A, et al. Urinary biomarkers in the early diagnosis of acute kidney injury. *Kidney Int.* Apr 2008;73(7):863-869.
35. Koyner JL, Bennett MR, Worcester EM, et al. Urinary cystatin C as an early biomarker of acute kidney injury following adult cardiothoracic surgery. *Kidney Int.* Oct 2008;74(8):1059-1069.

36. Bartholomew BA, Harjai KJ, Dukkipati S, et al. Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. *Am J Cardiol.* Jun 15 2004;93(12):1515-1519.
37. McCullough PA. Contrast-induced acute kidney injury. *J Am Coll Cardiol.* Apr 15 2008;51(15):1419-1428.
38. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis.* May 2002;39(5):930-936.
39. From AM, Bartholmai BJ, Williams AW, et al. Mortality associated with nephropathy after radiographic contrast exposure. *Mayo Clin Proc.* Oct 2008;83(10):1095-1100.
40. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis. *Jama.* May 15 1996;275(19):1489-1494.
41. Scanlon PJ, Faxon DP, Audet AM, et al. ACC/AHA guidelines for coronary angiography. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. *J Am Coll Cardiol.* May 1999;33(6):1756-1824.
42. Efstratiadis G, Pateinakis P, Tambakoudis G, et al. Contrast media-induced nephropathy: case report and review of the literature focusing on pathogenesis. *Hippokratia.* Apr 2008;12(2):87-93.
43. Solomon R. Radiocontrast-induced nephropathy. *Semin Nephrol.* Sep 1998;18(5):551-557.
44. Kolonko A, Kokot F, Wiecek A. Contrast-associated nephropathy--old clinical problem and new therapeutic perspectives. *Nephrol Dial Transplant.* Mar 1998;13(3):803-806.
45. Rudnick MR, Goldfarb S, Wexler L, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. The Iohexol Cooperative Study. *Kidney Int.* Jan 1995;47(1):254-261.
46. ten Dam MA, Wetzels JF. Toxicity of contrast media: an update. *Neth J Med.* Nov 2008;66(10):416-422.
47. Larson TS, Hudson K, Mertz JI, et al. Renal vasoconstrictive response to contrast medium. The role of sodium balance and the renin-angiotensin system. *J Lab Clin Med.* Mar 1983;101(3):385-391.
48. Yoshioka T, Fogo A, Beckman JK. Reduced activity of antioxidant enzymes underlies contrast media-induced renal injury in volume depletion. *Kidney Int.* Apr 1992;41(4):1008-1015.
49. Eisenberg RL, Bank WO, Hedgock MW. Renal failure after major angiography can be avoided with hydration. *AJR Am J Roentgenol.* May 1981;136(5):859-861.
50. Weisbord SD, Palevsky PM. Prevention of contrast-induced nephropathy with volume expansion. *Clin J Am Soc Nephrol.* Jan 2008;3(1):273-280.
51. Solomon R, Werner C, Mann D, et al. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med.* Nov 24 1994;331(21):1416-1420.
52. Krasuski RA, Beard BM, Geoghagan JD, et al. Optimal timing of hydration to erase contrast-associated nephropathy: the OTHER CAN study. *J Invasive Cardiol.* Dec 2003;15(12):699-702.
53. Bader BD, Berger ED, Heede MB, et al. What is the best hydration regimen to prevent contrast media-induced nephrotoxicity? *Clin Nephrol.* Jul 2004;62(1):1-7.
54. Dussol B, Morange S, Loundoun A, et al. A randomized trial of saline hydration to prevent contrast nephropathy in chronic renal failure patients. *Nephrol Dial Transplant.* Aug 2006;21(8):2120-2126.
55. Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *Jama.* May 19 2004;291(19):2328-2334.
56. Briguori C, Airoldi F, D'Andrea D, et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. *Circulation.* Mar 13 2007;115(10):1211-1217.

57. Bakris GL, Lass N, Gaber AO, et al. Radiocontrast medium-induced declines in renal function: a role for oxygen free radicals. *Am J Physiol.* Jan 1990;258(1 Pt 2):F115-120.

58. Katholi RE, Woods WT, Jr., Taylor GJ, et al. Oxygen free radicals and contrast nephropathy. *Am J Kidney Dis.* Jul 1998;32(1):64-71.

59. Tepel M, van der Giet M, Schwarzfeld C, et al. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med.* Jul 20 2000;343(3):180-184.

60. Briguori C, Colombo A, Violante A, et al. Standard vs double dose of N-acetylcysteine to prevent contrast agent associated nephrotoxicity. *Eur Heart J.* Feb 2004;25(3):206-211.

61. Pannu N, Manns B, Lee H, et al. Systematic review of the impact of N-acetylcysteine on contrast nephropathy. *Kidney Int.* Apr 2004;65(4):1366-1374.

62. Nallamothu BK, Shojania KG, Saint S, et al. Is acetylcysteine effective in preventing contrast-related nephropathy? A meta-analysis. *Am J Med.* Dec 15 2004;117(12):938-947.

63. Deray G. Dialysis and iodinated contrast media. *Kidney Int Suppl.* Apr 2006(100):S25-29.

64. Marenzi G, Marana I, Lauri G, et al. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med.* Oct 2 2003;349(14):1333-1340.

65. Lee PT, Chou KJ, Liu CP, et al. Renal protection for coronary angiography in advanced renal failure patients by prophylactic hemodialysis. A randomized controlled trial. *J Am Coll Cardiol.* Sep 11 2007;50(11):1015-1020.

66. Cruz DN, Perazella MA, Bellomo R, et al. Extracorporeal blood purification therapies for prevention of radiocontrast-induced nephropathy: a systematic review. *Am J Kidney Dis.* Sep 2006;48(3):361-371.

67. Bagshaw SM, Delaney A, Jones D, et al. Diuretics in the management of acute kidney injury: a multinational survey. *Contrib Nephrol.* 2007;156:236-249.

68. Heyman SN, Brezis M, Greenfeld Z, et al. Protective role of furosemide and saline in radiocontrast-induced acute renal failure in the rat. *Am J Kidney Dis.* Nov 1989;14(5):377-385.

69. Sward K, Valsson F, Sellgren J, et al. Differential effects of human atrial natriuretic peptide and furosemide on glomerular filtration rate and renal oxygen consumption in humans. *Intensive Care Med.* Jan 2005;31(1):79-85.

70. Ludens JH, Hook JB, Brody MJ, et al. Enhancement of renal blood flow by furosemide. *J Pharmacol Exp Ther.* Oct 1968;163(2):456-460.

71. Anderson RJ, Linas SL, Berns AS, et al. Nonoliguric acute renal failure. *N Engl J Med.* May 19 1977;296(20):1134-1138.

72. Kolhe NV, Stevens PE, Crowe AV, et al. Case mix, outcome and activity for patients with severe acute kidney injury during the first 24 hours after admission to an adult, general critical care unit: application of predictive models from a secondary analysis of the ICNARC Case Mix Programme Database. *Crit Care.* 2008;12 Suppl 1:S2.

73. Kleinknecht D, Ganeval D, Gonzalez-Duque LA, et al. Furosemide in acute oliguric renal failure. A controlled trial. *Nephron.* 1976;17(1):51-58.

74. Brown CB, Ogg CS, Cameron JS. High dose frusemide in acute renal failure: a controlled trial. *Clin Nephrol.* Feb 1981;15(2):90-96.

75. Shilliday IR, Quinn KJ, Allison ME. Loop diuretics in the management of acute renal failure: a prospective, double-blind, placebo-controlled, randomized study. *Nephrol Dial Transplant.* Dec 1997;12(12):2592-2596.

76. Cantarovich F, Rangoonwala B, Lorenz H, et al. High-dose furosemide for established ARF: a prospective, randomized, double-blind, placebo-controlled, multicenter trial. *Am J Kidney Dis.* Sep 2004;44(3):402-409.

77. Mehta RL, Pascual MT, Soroko S, et al. Diuretics, mortality, and nonrecovery of renal function in acute renal failure. *Jama.* Nov 27 2002;288(20):2547-2553.

78. Uchino S, Bellomo R, Morimatsu H, et al. External validation of severity scoring systems for acute renal failure using a multinational database. *Crit Care Med.* Sep 2005;33(9):1961-1967.

79. Karajala V, Mansour W, Kellum JA. Diuretics in acute kidney injury. *Minerva Anestesiol.* Jul 18 2008.

80. Bellomo R, Giantomasso DD. Noradrenaline and the kidney: friends or foes? *Crit Care.* Dec 2001;5(6):294-298.
81. McDonald RH, Jr., Goldberg LI, McNay JL, et al. Effect of Dopamine in Man: Augmentation of Sodium Excretion, Glomerular Filtration Rate, and Renal Plasma Flow. *J Clin Invest.* Jun 1964;43:1116-1124.
82. Hoogenberg K, Smit AJ, Girbes AR. Effects of low-dose dopamine on renal and systemic hemodynamics during incremental norepinephrine infusion in healthy volunteers. *Crit Care Med.* Feb 1998;26(2):260-265.
83. Bellomo R, Chapman M, Finfer S, et al. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet.* Dec 23-30 2000;356(9248):2139-2143.
84. Lauschke A, Teichgraber UK, Frei U, et al. 'Low-dose' dopamine worsens renal perfusion in patients with acute renal failure. *Kidney Int.* May 2006;69(9):1669-1674.
85. Dunning J, Khasati N, Barnard J. Low dose (renal dose) dopamine in the critically ill patient. *Interact Cardiovasc Thorac Surg.* Mar 2004;3(1):114-117.
86. Cronin RE, Erickson AM, de Torrente A, et al. Norepinephrine-induced acute renal failure: a reversible ischemic model of acute renal failure. *Kidney Int.* Aug 1978;14(2):187-190.
87. Anderson WP, Korner PI, Selig SE. Mechanisms involved in the renal responses to intravenous and renal artery infusions of noradrenaline in conscious dogs. *J Physiol.* Dec 1981;321:21-30.
88. Zhang H, Smail N, Cabral A, et al. Effects of norepinephrine on regional blood flow and oxygen extraction capabilities during endotoxic shock. *Am J Respir Crit Care Med.* Jun 1997;155(6):1965-1971.
89. Bellomo R, Kellum JA, Wisniewski SR, et al. Effects of norepinephrine on the renal vasculature in normal and endotoxemic dogs. *Am J Respir Crit Care Med.* Apr 1999;159(4 Pt 1):1186-1192.
90. Redl-Wenzl EM, Armbruster C, Edelmann G, et al. The effects of norepinephrine on hemodynamics and renal function in severe septic shock states. *Intensive Care Med.* 1993;19(3):151-154.
91. Martin C, Papazian L, Perrin G, et al. Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? *Chest.* Jun 1993;103(6):1826-1831.
92. den Ouden DT, Meinders AE. Vasopressin: physiology and clinical use in patients with vasodilatory shock: a review. *Neth J Med.* Jan 2005;63(1):4-13.
93. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med.* Feb 28 2008;358(9):877-887.
94. Bellomo R, Wan L, May C. Vasoactive drugs and acute kidney injury. *Crit Care Med.* Apr 2008;36(4 Suppl):S179-186.
95. Moreau R, Lebrec D. Acute kidney injury: new concepts. Hepatorenal syndrome: the role of vasopressors. *Nephron Physiol.* 2008;109(4):p73-79.
96. Lameire N, Van Biesen W, Vanholder R. The rise of prevalence and the fall of mortality of patients with acute renal failure: what the analysis of two databases does and does not tell us. *J Am Soc Nephrol.* Apr 2006;17(4):923-925.
97. Uehlinger DE, Jakob SM, Ferrari P, et al. Comparison of continuous and intermittent renal replacement therapy for acute renal failure. *Nephrol Dial Transplant.* Aug 2005;20(8):1630-1637.
98. Vinsonneau C, Camus C, Combes A, et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. *Lancet.* Jul 29 2006;368(9533):379-385.
99. Lins RL, Elseviers MM, Van der Niepen P, et al. Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial. *Nephrol Dial Transplant.* Oct 14 2008.
100. Schiffl H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med.* Jan 31 2002;346(5):305-310.

101. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet.* Jul 1 2000;356(9223):26-30.

102. Saudan P, Niederberger M, De Seigneux S, et al. Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. *Kidney Int.* Oct 2006;70(7):1312-1317.

103. Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med.* Jul 3 2008;359(1):7-20.

104. Bellomo R, Cass A, Cole L, et al. Design and challenges of the Randomized Evaluation of Normal versus Augmented Level Replacement Therapy (RENAL) Trial: high-dose versus standard-dose hemofiltration in acute renal failure. *Blood Purif.* 2008;26(5):407-416.

105. Humes HD, Fissell WH, Weitzel WF. The bioartificial kidney in the treatment of acute renal failure. *Kidney Int Suppl.* May 2002(80):121-125.

106. Humes HD, Fissell WH, Weitzel WF, et al. Metabolic replacement of kidney function in uremic animals with a bioartificial kidney containing human cells. *Am J Kidney Dis.* May 2002;39(5):1078-1087.

107. Fissell WH, Lou L, Abrishami S, et al. Bioartificial kidney ameliorates gram-negative bacteria-induced septic shock in uremic animals. *J Am Soc Nephrol.* Feb 2003;14(2):454-461.

108. Fissell WH, Dyke DB, Weitzel WF, et al. Bioartificial kidney alters cytokine response and hemodynamics in endotoxin-challenged uremic animals. *Blood Purif.* 2002;20(1):55-60.

109. Humes HD, Weitzel WF, Bartlett RH, et al. Initial clinical results of the bioartificial kidney containing human cells in ICU patients with acute renal failure. *Kidney Int.* Oct 2004;66(4):1578-1588.

110. Tumlin J, Wali R, Williams W, et al. Efficacy and safety of renal tubule cell therapy for acute renal failure. *J Am Soc Nephrol.* May 2008;19(5):1034-1040.

111. Ding F, Humes HD. The bioartificial kidney and bioengineered membranes in acute kidney injury. *Nephron Exp Nephrol.* 2008;109(4):e118-122.

112. Lin F, Cordes K, Li L, et al. Hematopoietic stem cells contribute to the regeneration of renal tubules after renal ischemia-reperfusion injury in mice. *J Am Soc Nephrol.* May 2003;14(5):1188-1199.

113. Kale S, Karihaloo A, Clark PR, et al. Bone marrow stem cells contribute to repair of the ischemically injured renal tubule. *J Clin Invest.* Jul 2003;112(1):42-49.

114. Chen J, Park HC, Addabbo F, et al. Kidney-derived mesenchymal stem cells contribute to vasculogenesis, angiogenesis and endothelial repair. *Kidney Int.* Oct 2008;74(7):879-889.

115. Lin F, Moran A, Igarashi P. Intrarenal cells, not bone marrow-derived cells, are the major source for regeneration in postischemic kidney. *J Clin Invest.* Jul 2005;115(7):1756-1764.

116. Duffield JS, Park KM, Hsiao LL, et al. Restoration of tubular epithelial cells during repair of the postischemic kidney occurs independently of bone marrow-derived stem cells. *J Clin Invest.* Jul 2005;115(7):1743-1755.

117. Yokoo T, Kawamura T, Kobayashi E. Stem cells for kidney repair: useful tool for acute renal failure? *Kidney Int.* Oct 2008;74(7):847-849.

118. Takahashi K, Tanabe K, Ohnuki M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell.* Nov 30 2007;131(5):861-872.