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Workgroup 3

Physiologic endpoints (efficacy) for acute renal failure studies

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The lack of significant progress in the prevention and management of acute renal failure (ARF) has been commonly attributed, in part, to the failure to identify suitable physiologic surrogate endpoints for use in research studies testing the efficacy of new interventions. For example, the standardized use of serum cardiac enzyme concentrations and electrocardiographic criteria has facilitated rapid progress in the management of coronary insufficiency, markedly decreasing the morbidity and mortality of acute myocardial infarction. By contrast, ARF prevention and therapy studies using variables such as urine output and serum and urine chemistries have not yielded interventions proven to decrease the morbidity (including requirement for dialysis) and mortality associated with acute renal dysfunction. In fact, very few ARF studies have even demonstrated a beneficial effect on the most commonly used physiologic surrogate endpoints, the serum urea nitrogen and creatinine concentrations (1-2). Of those interventions that have been successful in smaller, phase II--level efficacy studies, most prominently exemplified by the experiences with atrial natriuretic peptide (3) and insulin-like growth factor (4), none subsequently decreased the incidence of clinical (effectiveness) endpoints such as dialysis requirement or mortality in larger phase III trials (5-7). Clearly, it must be determined which physiologic endpoints should be used to test the efficacy of new proposed therapies for the prevention and management of ARF. Candidate endpoints for efficacy studies in ARF prevention and management include glomerular filtration rate (GFR) markers, renal blood flow, urine markers, and urine output. Possible endpoints for efficacy studies of renal replacement therapy (RRT) in ARF include serum markers of renal function and a variety of non-renal markers.

Physiologic Endpoint for Studies of ARF

This report presents an approach to the choice of physiologic endpoints to determine the efficacy of interventions in acute renal failure, answering a series of 6 questions with an analysis of the literature, and recommendations for clinical practice and future research.

Which GFR markers are appropriate indices of renal function for efficacy studies for ARF?

Because there are no pharmacotherapies that have been proven to alter clinical endpoints (dialysis, mortality) in patients with ARF, it cannot be discerned definitively what changes in currently available serum GFR markers (urea, creatinine) are predictive in smaller phase II studies of success in subsequent phase III trials with clinical endpoints. In other words, although some interventions were shown to be effective in altering physiologic endpoints (*e.g.*, prevention of serum creatinine increments after radiocontrast administration in high-risk patients)(1-2), none have been validated by a study of sufficient size to detect effectiveness in altering major clinical endpoints such as dialysis and mortality. Of course, there are abundant data suggesting that patients with severe ARF have adverse outcomes, so it follows that advanced azotemia and severe oliguria are at some level indisputable adverse prognostic markers (8). Admittedly, alterations in urea and creatinine levels in the course of phase II studies may be caused by numerous factors other than changes in GFR (*e.g.*, volume status, catabolism, hemorrhage, corticosteroids, rhabdomyolysis, drugs) and are insensitive compared with more sophisticated clearance measurements of GFR. Nevertheless, the currently available GFR markers do satisfy a number of the specific, measurable, achievable, realistic, time-related (SMART) criteria commonly used to evaluate the outcome or objective of an intervention (9). Table 1 presents an analysis of the utility of currently available physiologic markers of renal function to monitor the effects of a therapeutic intervention aimed at the prevention or management of ARF (7,10-14).

Studies validating the prognostic value of efficacy in achieving alterations in these or other biochemical GFR markers in predicting effectiveness in improving clinical outcomes are needed. Such studies should use the same markers selected to define ARF (15)(see workgroup 1). Sample size should be estimated based on variability in the primary biochemical endpoint in the study population from either a preliminary study or a literature review. Studies should be designed to have 90% power to detect a between-group difference of one SD or less, with α error less than 0.05 (16-17). Positive results should be followed by phase III studies with significant clinical endpoints (18). In future studies, promising newer GFR markers should be studied along with traditional, currently used clinical markers. Examples of newer GFR markers include endogenous substances such as cystatin C (19) and clearance of exogenous markers such as iohexol (10) or iothalamate (7).

Summary: It is unproven if efficacy in achieving changes in currently available serum GFR markers (urea, creatinine, exogenous markers) are predictive in smaller phase II studies of effectiveness in subsequent phase III trials with clinical endpoints.

Recommendations for clinical practice: Strategies for ARF prevention and therapy will need to continue to be based upon results from studies (positive and negative) using surrogate endpoints (creatinine, urea) until definitive studies demonstrating effectiveness in altering clinical endpoints are available. However, clinical decisions based on such evidence should be made cautiously and limited to the use of true surrogates (those that correlate with clinical outcomes) (e.g. serum creatinine at steady state) as opposed to those that do not (e.g. urine output) [Grade E].

Recommendations for future research: Future studies should confirm positive results in small studies with biochemical endpoints with adequately powered larger studies with significant clinical endpoints.

Is renal blood flow a relevant physiologic end point for efficacy studies?

Although decreased renal perfusion is a recognized model of renal injury in animals, it has not been documented to be of etiologic significance in the development of ARF in humans. It is thus unclear whether decreased renal perfusion is a relevant physiologic endpoint for efficacy studies in ARF. Clearly, systemic hypotension is a common precursor of ARF in humans, but other documented etiologic factors, including ischemia--reperfusion, circulating nephrotoxins (*e.g.*, drug toxicity, cytokines, pigments), acidosis, and hypoxemia coexist. However, vasoactive therapies have been used in the management of acutely ill patients and may also alter renal blood flow. Importantly, the logic for defending organ perfusion pressure with vasoactive agents presumes both pressure-dependent renal flow and flow-dependent renal function. Clinical trials of patients in septic shock have demonstrated that renal function and urine output increase once mean arterial pressure is increased above 60 mm Hg by the use of vasopressor therapy (20-22). Whether this benefit is caused by increased global renal blood flow, alterations in renal blood flow distribution, or some other pressure-dependent mechanism is unclear.

Of the available techniques to assess renal perfusion, para-amino hippuric acid clearance is not a valid method to assess renal plasma flow because renal para-amino hippuric acid extraction is impaired in critical illness, cardiac surgery, postrenal transplantation, and ARF (13-14). Primary methods to assess renal blood flow include angiography, indicator extraction or dilution via a renal vein catheterization (para-amino hippuric acid and thermodilution)(23), and ultrasonography (12,24). Radiocontrast nephropathy is probably the most studied form of human ARF. The pathogenesis is thought to involve both ischemia (renal vasoconstriction) and dye-nephrotoxicity. However, when global renal blood flow was measured during radiocontrast administration, it was not diminished (25). In animal models, whereas cortical blood flow increases after radiocontrast administration, medullary blood flow is diminished (26-27). Thus, intrarenal blood flow distribution may be altered in humans receiving radiocontrast, but this possibility has not been studied to date. Blood oxygen level--dependent magnetic resonance imaging has been used to measure intrarenal blood flow redistribution in humans (28), but it is impractical for use in many patients developing ARF. Other potential techniques include microbubble contrast ultrasonography (29). We suggest that these techniques be used to assess renal hemodynamic profiles in human ARF, particularly in studies using vasoactive agents (putative renal vasodilators, vasopressors) to prevent or treat ARF, but renal perfusion

alone is not a suitable primary endpoint for phase II studies. Recent studies of the dopaminergic agent fenoldopam continue to demonstrate the failure of renal vasodilators to prevent radiocontrast nephropathy, despite experimental evidence that this agent is a global and medullary renal vasodilator. Tumlin and colleagues found in a 51 subject pilot study that fenoldopam but not placebo preserved PAH clearance one hour post-radiocontrast, with positive trends toward preserving GFR (30), but the incidence of radiocontrast nephropathy was not diminished in a recently presented 300 subject randomized, placebo-controlled trial (31).

Summary: It is unproven if prevention or reversal of renal hypoperfusion prevents or ameliorates ARF in humans. Tools to simply and accurately measure renal blood flow and intrarenal blood flow distribution are lacking for clinical practice and research.

Recommendations for clinical practice: Strategies to optimize systemic perfusion may prevent or treat ARF [Level III]. Renal vasodilators have not proven effective for ARF prevention or therapy [Level II].

Recommendations for future research: Available techniques to measure renal blood flow should be used in ARF studies, particularly in trials of vasoactive drugs.

Which urine markers are appropriate indices of renal function for efficacy studies for ARF?

Electrolytes, chemistries, tubular/glomerular proteins? Potential renal-specific markers?

Although some data suggest the utility of urinary electrolyte or other chemistries in the differential diagnosis of ARF (32), none of these methods has proven reliable in clinical practice (33). Recent data suggest that the fractional excretion of urea may be a more accurate index in diuretic-treated patients (34). Similarly, none has been conclusively demonstrated to be useful in following the course of ARF or in predicting outcome (35-36). Nevertheless, because of the sound physiologic rationale underlying the assessment of renal tubular function with these substances, we recommend their inclusion in phase II protocols studying the effects of new interventions on renal function in patients at risk for or developing ARF.

Microscopic urinalysis of the urinary sediment, which is commonly used to assess patients with ARF, is often qualitatively useful in the differential diagnosis of renal insufficiency and can disclose some pathognomic findings (*e.g.*, erythrocyte casts signaling glomerulonephritis; leukocyte casts with infectious, allergic, or immune interstitial nephritis)(37). However, the reproducibility and predictive value of urinalysis in the differential diagnosis and monitoring of ARF have not been determined.

Emerging data suggest that urinary concentrations of tubular proteins may provide a more sensitive index of renal tubular injury than urine electrolytes, but the clinical relevance of these markers has not been determined at this point (38). Similarly, although proteomics may yield urinary biomarkers of greater sensitivity to detect and monitor acute renal injury, none are available for clinical or widespread research use at this time (39-40).

Summary: It is unproven if urine chemistries or microscopy are appropriate indices of renal function for efficacy studies for ARF prevention or therapy.

Recommendations for clinical practice: Currently available urine chemistries and urine microscopy may be diagnostically useful, but cannot be used to determine the efficacy of interventions to prevent or treat ARF [Level II].

Recommendations for future research: We recommend that a skilled microscopic analysis of the urinary sediment be performed at entry and possibly serially in ARF studies to assess potential utility as a diagnostic marker or index of therapeutic effect [Grade D].

Is urine output a relevant physiologic end point for ARF efficacy studies?

The traditional definition of oliguria used in the ARF literature is less than 400 mL/24 h. This is the minimum urine volume required to excrete the daily metabolic solute load in a healthy adult, assuming maximum urine-concentrating ability; therefore, oliguria below this cutoff value signals inadequate GFR and acute renal insufficiency (41). Of course, the daily metabolic solute load in a catabolic critically ill patient far exceeds that in healthy subjects, and ICU patients developing renal insufficiency lose the ability to concentrate urine maximally (42). Furthermore, this urine volume (400 mL/d) is inadequate to prevent positive fluid balance in the vast majority of critically ill patients, who routinely have obligate fluid intakes of liters. These and other data suggest that the definition of *adequate urine output* versus *oliguria* should be reinterpreted.

To facilitate clinical studies and management, it is important to define nominal ranges of renal function (normal vs grades of abnormality) from measured physiologic variables. As a general principle, the defined ranges for measured markers of renal function and response to therapy should be based on objective criteria that include measures of related severity of illness, physiologic correlates with measured variable, and direct results of derangements in these variables and subsequent outcome (when available). For example, an approach to assessing the impact of specific markers used in the definition of ARF is to ascertain their effect on outcome from large patient data sets, such as the logistic regression data in Table 2. Data from ICU outcome studies show an adverse prognostic significance of oliguria, not only with the traditional 400 mL definition but also with higher urine outputs to 750 mL/d (30 mL/h). Specifically, data from the Logistic Organ Dysfunction ICU outcome study of 13,000 patients from Europe and North America showed an adverse prognostic significance of oliguria both with a traditional definition (<500 mL/d) and with higher urine outputs (<750 mL/d, 30 mL/h) (43). As shown in Table 2, this study also reported that increases in serum creatinine well below most clinical thresholds for initiating RRT are associated with increased mortality. Another international study of 6400 patients found that transient urine output decrements defined by the higher range (<30 mL/h) that was significant in the Logistic Organ Dysfunction study were predictive of renal insufficiency (44). Together, these data suggest that urine output decrements well above the traditional 400 mL/d are associated with increased mortality. Therefore, it is recommended

that investigators monitor urine output hourly in patients at risk for renal failure and that a higher than customary definition of inadequate urine output (<30 mL/h rather than 400 mL/d) be used to define oliguria.

The monitoring of urine output should be coupled with fluid balance. Simple correction of low urine output by fluid administration may result in the development of a positive fluid balance and also reverse prerenal azotemia. However, a persistently positive fluid balance over several days is associated with a poor prognosis (45). Although poor prognosis is probably related more to the underlying disease process than to fluid resuscitation, the relation is unclear.

Although there is evidence that failure to respond to diuretics (*i.e.*, persistent severe oliguria) portends a poor renal prognosis and survival, it is not known whether this reflects the adverse effects of severe underlying renal (and systemic) tissue injury in the persistently oliguric groups or any beneficial effect of increasing urine flow in ARF. However, nonoliguric renal failure has repeatedly been shown to have improved survival compared to oliguric renal failure (8). The mechanisms underlying this difference in outcome are not known. Potential contributory factors include less severe injury, avoidance of volume overload, minimization of hyperkalemia, ability to give intravenous fluids and nutrition, and avoidance of RRT. In any case, because fluid balance is a central aspect of normal renal function, it is important to record fluid management, diuretic therapy, and fluid balance in any clinical study of ARF. These parameters have not routinely been rigorously recorded in past ARF studies.

Summary: Oliguria defined as <400ml/day is associated with adverse outcomes. However, higher urine outputs (up to 750ml/day) also appear to be associated with adverse outcomes too compared to more normal urine output.

Recommendations for clinical practice: Control of fluid balance may simplify management and improve outcomes in ARF, but this is unproven [Level III].

Recommendations for future research: There is no evidence that urine output is reliable surrogate marker for outcome in studies of ARF and thus should not be used [Grade C]. Urine output, fluid management and balance, and diuretic use should be recorded in future clinical studies of ARF.

Which serum markers are appropriate indices of renal function for efficacy studies for RRT in ARF?

The required dialysis dose in ARF may be higher than with other conditions because of alterations in the peripheral circulation, solute and water exchange among tissue and body compartments, and altered metabolism in this population. The concept of a higher dose of RRT in patients with ARF contrasting with patients with end-stage renal disease appears valid for a variety of reasons; for example, the distribution volume for urea is increased in ARF (46) and is increased further in ARF associated with systemic inflammation.

Urea remains the most commonly used solute for quantification of RRT dose in ARF. Although urea is clearly a marker substance rather than a uremic toxin, a superior marker of RRT dose has not yet been identified and validated (47). Dosing of intermittent hemodialysis in chronic renal failure relies on urea kinetic modeling and targeting small solute clearance quantified by Kt/V , with a proven dose--outcome relation in this population (48). For the reasons outlined, this dose is unlikely to be sufficient in critically ill patients with ARF. In addition, intermittent hemodialysis dose delivery is compromised by hemodynamic instability and solute compartmentalization (49). Failure to prescribe an appropriate dose for larger patients may further impair dialysis delivery in this population (50). Although Kt/V has not been validated for the dosing of acute RRT, it seems prudent to prescribe a minimum dose at least consistent with adequate therapy for end-stage renal disease, aiming for a delivered double-pool Kt/V of 1.2 (51-52). Emerging data have begun to examine and define dose requirements specifically in ARF (41).

Retrospective and preliminary prospective data have suggested the impact of delivered dialysis dose (Kt/V) on mortality in critically ill patients with ARF (52-53). In studies of the effect of dialysis dose on mortality in patients with ARF, the issue of delivered versus prescribed dose (by Kt/V or other measures) needs to be addressed carefully. Intermittent therapy dose delivery is negatively influenced by vascular access, clotting, and time on dialysis, routinely leading to a significant shortfall from the prescribed dose (50-51). Although clotting is similarly a major impediment to dose delivery of continuous therapy, continuous RRT seems to deliver a much higher RRT dose at levels that would not be easily obtained even with a daily intermittent hemodialysis schedule (54).

In convective acute RRT (in which the ultrafiltration rate is equal to the clearance for compounds having a sieving coefficient of 1, such as urea), Ronco et al. (55) found that the ultrafiltration dose is correlated with outcome in a large, randomized, controlled study including 425 critically ill patients with ARF. In this pivotal study, an ultrafiltration dose of 35 mL/kg/h increased survival rate from 41% to 57% compared with a dose of 20 mL/kg/h. It may be of further significance that 11 to 14% (per randomization group) of the patients had sepsis; in this subgroup, there appeared to be a direct correlation between treatment dose and survival even above 35 mL/kg/h in contrast to the whole group, in which a survival plateau was reached. If confirmed by prospective studies, this subgroup finding in septic ARF may favor the use of convective RRT, and specifically the use of high hemofiltration volumes, in this population.

Another way to analyze dialysis dose independently of treatment type and schedule is to use the equivalent renal urea clearance, which kinetically quantifies the time-averaged Kt (56). Along with double-pool Kt/V (51), use of the equivalent renal urea clearance should be considered for studies of RRT dose in ARF, particularly in comparisons of intermittent and continuous modalities. Finally, identification of one or more true uremic toxins and their use to dose RRT should lead to optimization of dose and outcome in future studies (47).

Summary: Unlike ESRD, the RRT dose required to optimize outcome in ARF is unproven, and there is better evidence to guide convective rather than diffusive therapy at this time.

Recommendations for clinical practice: Using purely convective CRRT (CVVH), an ultrafiltration dose of 35ml/kg/hour should be delivered [Grade B]. It is not known what dose of diffusive therapy should be prescribed for RRT in ARF, or how it should be measured.

Recommendations for future research: Future studies should establish the relationship of dose to outcome in ARF, using traditional and emerging markers, and diffusive and/or convective RRT modalities.

What other “non-renal” markers are appropriate indices of renal replacement therapy efficacy in ARF?

RRT efficacy in ARF may also be measured by a variety of nonrenal indices. For example, reversal of uremic bleeding diathesis and shortening of prolonged bleeding time are well-recognized RRT efficacy measures (41). Other potential markers include cytokine levels, measures of leukocyte function, and apoptosis. Candidate cytokines include interleukin (IL) 6, a nonspecific marker of severity of the generalized systemic inflammatory response, cleared to some degree by continuous RRT (57). Although clearance of some inflammatory cytokines and other mediators has been demonstrated, this clearance is of unproven clinical relevance at this point.

Methods to assess leukocyte function include measures of *ex vivo* leukocyte responsiveness (spontaneous or stimulus-induced) (58-61) and of leukocyte priming (62-64). Leukocyte hyporesponsiveness *ex vivo* is associated with profound immune dysregulation with reduced surface molecule expression (HLA class II) and inability to respond to infectious stimuli. Recovery from systemic inflammatory response syndrome is paralleled by recovery of the normal leukocyte responsiveness to proinflammatory stimuli and normal hemodynamics. Although many studies have looked at purified cell populations, the most practical approach seems to be the use of whole blood cytokine assay, because it measures cytokine production in the presence of a wide range of modulating factors (*e.g.*, soluble receptors, natural inhibitors, proteases, and so forth). *Leukocyte priming* is defined as the enhanced response to a second stimulus. Priming activity is important in polymorphonuclear leukocyte—mediated antimicrobial action and in the pathogenesis of tissue damage. Several investigators have reported the priming of polymorphonuclear leukocytes in septic and injured patients (62-64). Priming mediators such as IL-8 act on circulating polymorphonuclear leukocytes by stimulating the oxidative burst; by exerting a priming effect to a secondary stimulus, such as bacterial *N*-formyl peptides; or both. Experimental and clinical evidence support a two-hit model for the development of multiorgan dysfunction syndrome (65-66), and leukocyte priming may be important in the pathogenesis of this phenomenon. The priming activity of polymorphonuclear leukocytes as detected by chemiluminescence is reduced by ultrafiltration and is mediated, at least in part, by ultrafiltered IL-8 (67).

Finally, markers of apoptosis (programmed cell death) may be appropriate nonrenal endpoints for RRT efficacy studies in ARF. Apoptosis has been related to membrane biocompatibility, pre-T-cell activation, and CD14 expression in the end-stage renal disease population (68-70). Apoptosis of monocytes has also been found to correlate with the severity of predialysis chronic renal insufficiency (68). In critically ill

patients, accelerated apoptosis is a marker of severity of the septic process. Inhibitors of caspases, regulatory proteins involved in the signal transduction of apoptogenic stimuli, improve survival in sepsis. Furthermore, caspase inhibition prevents cardiac dysfunction and myocardial apoptosis in a rat model of sepsis. Sepsis-associated mediators (hormones, neuropeptides, proinflammatory and anti-inflammatory cytokines, reactive oxygen species) are usually either proapoptogenic or antiapoptogenic. It is presumed that the cellular environment generated during systemic inflammatory response syndrome/multiple organ dysfunction syndrome favors apoptosis rather than survival. Based on such data, it seems rational to study markers of apoptosis as markers of RRT efficacy in critically ill patients with ARF. Suitable approaches might include assays of the expression of the apoptotic receptor Fas and of its ligand to study the upregulation of apoptotic constituents in peripheral blood mononuclear cells (71-72).

Summary: Emerging “non-renal” markers of RRT efficacy may prove useful if validated by future prospective studies.

Recommendations for clinical practice: Currently, the only “non-renal” indices used in clinical practice are readily available clinical indices (bleeding time, encephalopathy, pericarditis).

Recommendations for future research: Future studies should establish the relationship of emerging “non-renal” indices such as cytokine levels, measures of leukocyte function, and markers of apoptosis, to outcome in ARF patients requiring RRT.

Conclusions

We find that the literature on ARF prevention and management has generally lacked the rigorous approach necessary to identify effective therapies successfully. Furthermore, we believe that the use of reliable physiologic endpoints for efficacy studies, which are proven to predict clinical effectiveness, will focus therapeutic trials in high-yield areas. We hope that standardization of this approach will lead to rapid advances in ARF therapy.

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Table 1. Physiological Markers of Renal Function

<u>Specific (for...)</u>	<u>Measurable</u>	<u>Acceptable</u>	<u>Realistic/Time-Related</u>	
<i>GFR</i>	PAH ^{13, 14}	No	No	
	Creatinine	Yes	Yes	
	Creatinine Clearance	2 hour – yes	Yes	Yes
		24 hour – yes	No	No
	BUN	Yes	Yes	
	Inulin Clearance	Yes	No	
	Iohexol/iopromide ¹⁰	Yes	Yes	
	Iothaltrate ⁷	Yes	Yes	
	I ¹³¹ MAG ¹¹	Yes	No	
	Cr ⁵² EDTA	Yes	No	
<i>Renal Blood Flow</i>	Angiography	Yes	No	
	Indicator dilution ²³ (Thermal or PAH)	Yes	No	
	BOLD MRI	Yes	No	
	Ultrasound ^{12, 22}	Yes	Yes	
	<i>Tubular Function</i>	Urine output	Yes	Yes
I:O Balance		Yes	Yes	
Urinalysis		Yes	Yes	
FeNa		Yes	Yes	
Osmolality		Yes	Yes	
Creatinine (U/P)		Yes	Yes	
Tubular proteins		No	No	

Table 2. Impact of Renal Indices on Survival using Logistic Organ Dysfunction Model

Measures	LODS Points						
	5	3	1	0	1	3	5
Urea (mmol/l)	-	-	-	<6	6-9.9	10-19.9	≥20
				<i>and</i>			
Creatinine (μmol/l)	-	-	-	<106	106-140	≥141	-
				<i>and</i>			
Urine output (l/d)	<0.5	0					

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