Enabling Innovative Translational Research in Acute Kidney Injury

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Abstract

Acute kidney injury (AKI) is a common, heterogeneous, and detrimental clinical condition that has significant attributable morbidity and mortality. Despite major advances in understanding the epidemiology, pathogenesis, and outcomes of AKI, preventive measures remain inadequate and therapeutic approaches (except for renal replacement therapy) have largely proven futile so far. Critical to the process of designing rational therapies is translational research, which involves the transition between the basic research discoveries and everyday clinical applications to prevent, diagnose, and treat human diseases. Progress in innovative approaches has been hampered due in part to the reliance on functional markers (serum creatinine and blood urea nitrogen) that are neither sensitive nor specific to diagnose AKI. This limitation has created a great deal of interest and intense investigation to identify a "troponin-like marker" that would facilitate recognition of AKI and allow for timely implementation of the precise therapeutic agent. The other major obstacle in this field is the diverse and complex nature of AKI that involves multiple independent and overlapping pathways, making it difficult to cure AKI with a single approach. In this review, we will summarize the advances, ongoing studies, and future perspectives in the field of translational research of AKI. Clin Trans Sci 2012; Volume 5: 93–101

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Introduction

The kidney is a complex organ that has evolved to serve a number of important functions: excretion of the waste products of the metabolism, regulation of body water and salt, maintenance of appropriate acid balance, and secretion of a variety of hormones and autocoids. To accomplish these intricate functions, the kidney is elaborately composed of several cell types that function as a unit (the nephron) and not as individual cells. This exceptional characteristic also implies an intricate process of regeneration and hence requires special attention for early diagnosis and appropriate preventive and therapeutic approaches. This statement has unfortunately proven far more challenging, highlighting the vital need for relevant investigations to enhance the "bench to bedside" transition.[1,2] Even the exact definition of acute kidney injury (AKI) has been the subject of considerable debate and incongruity has long surrounded the term making cross-comparison among studies difficult.[3,4] Recently, a new definition has been proposed for AKI (previously known as acute renal failure) by the AKI network (AKIN) that has been validated and gained broad consensus among clinicians.[5] This proposal defines AKI based on a >0.3 mg/dL rise or a >50% (1.5-fold from baseline) increase in serum creatinine or the development of oliguria as defined by urine output <0.5 mL/kg/h for more than 6 hours.[5] In contrast, the RIFLE classification initially defined several stages of AKI including Risk, Injury, Failure, Loss of function, and End Stage Renal Disease, which have more recently been modified to three main stages of severity of AKI (Risk, Injury, and Failure).[6] The "Risk" criteria is defined by an increase in serum creatinine ≥1.5× baseline or decrease in glomerular filtration rate (GFR) ≥25% or a urine output of <0.5 mL/kg/h for ≥6 hours. The "Injury" is defined by an increase in serum creatinine ≥2.0× baseline or decrease in GFR ≥50% or a urine output of <0.5 mL/kg/h for ≥12 hours. Finally, "Failure" is defined by increase in serum creatinine ≥3.0× baseline or decrease in GFR ≥ 75% or an absolute serum creatinine ≥354 μmol/L with an acute rise of at least 44 μmol/L or a urine output of <0.3 mL/kg/h for ≥24 hours or anuria for ≥12 hours.

AKI is a common clinical condition encountered both in the hospital and outpatient settings and is an important cause of morbidity and mortality regardless of etiology and setting.[7–10] The incidence of AKI is increasing at a disturbing pace[10,11] and is attributed to several factors including shifts in patient demographics (older, more comorbid illness), severity of illness (multiple organ dysfunction syndrome), and AKI associated with expansion of invasive and complex medical and surgical procedures (organ transplantation, cardiac surgery).[7,8] Additionally, as the population continues to age, it is anticipated that there will be an even more substantial rise in the incidence of AKI.[12,13] It is estimated that AKI accounts for 1% of hospital admissions in the United States.[14] In addition, approximately 25% of patients in the intensive care unit (ICU) develop AKI and 5% of the patients in the ICU require renal replacement therapy among whom mortality rates range between 40% and 60%.[15–19] Moreover, AKI is associated with an increased length of hospital stay, which is an obvious and significant burden on the health care system.[20,21] For instance, total hospital cost of patients with creatinine levels of 2.0 mg/dL is increased by approximately $34,000.[21] Furthermore, because of the potential for involvement of multiple organ systems, AKI should be regarded as a systemic disease. The distant organ effects of AKI are increasingly being recognized,[22] and deterioration of renal function has a detrimental consequence on virtually all organ systems and body homeostasis. In addition, numerous primary systemic conditions affect the kidney and can present with AKI. In conjunction with the increasing recognition of clinical AKI, several advances have been made in identifying the mechanisms and pathways of disease and a number of targets have been identified in preclinical models. Despite these advances, trials in humans have not proven successful. These data underscore the urgent need of translational studies in the field of AKI. The purpose of this review is to briefly discuss the current status of translational research in AKI and provide a framework for future studies.

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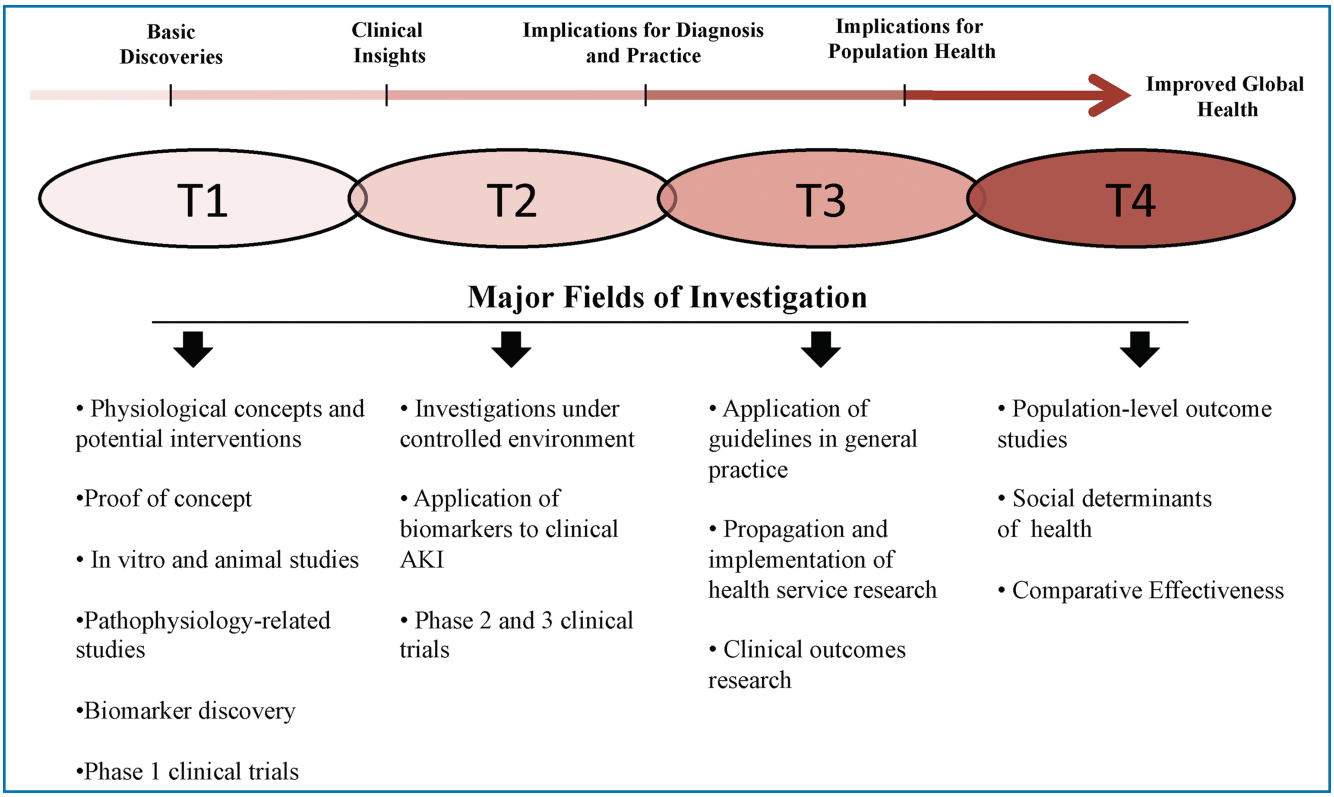

Figure 1. Spectrum of translational research (T1–T4) opportunities in acute kidney injury.

Translational research and AKI

Translational research is an integral part of most, if not all, fields of medicine.[23] Although translational research has been generally considered as "bench to bedside transition," it is now considered to have a much wider scope and encompasses additional domains representing the continuum of preclinical discovery and application to humans.[24–26] These domains overlap in a number of aspects with an ultimate goal of improving global health. The first domain (T1) represents research findings in "basic" research[24–26] encompassing discovery in preclinical models, human physiology, biomarker discovery, proof of concept, and Phase 1 studies in humans. The (T2) domain provides knowledge of the performance of specific interventions in carefully selected populations to test for safety and efficacy in Phase 2 and Phase 3 clinical trials. The application of findings to general practice is encompassed in the (T3) domain and includes Phase 4 trials and health services and outcomes research. The (T4) domain comprises the study of population health and outcomes including factors such as social determinants, for example, economic conditions limiting access to care. The applicability of the spectrum of T1–T4 research to the field of AKI is schematized in *Figure 1*. Although these four domains are somewhat distinct, it is implicit that the findings from each area of translational research can and should inform the design and conduct of future studies. For instance, knowledge from Phase 2 and Phase 3 studies of a new compound may result in a reassessment of the molecule in preclinical studies based on the efficacy of the compound in specific populations. Similarly, T3 research could identify areas of clinical need where new diagnostic and therapeutic molecules would improve management of patients. In this sense, translational research is not just "bench to bedside" but an integrative "bench to bedside and back" approach.

In this review, we utilize this framework to delineate specific elements in AKI and provide information on resources that are currently available in this field.

Diagnostic modalities—the biomarker revolution

It is clear that implementation of any appropriate therapeutic agent first requires accurate diagnosis of the clinical condition. This is why so much effort and investment has been directed at finding a suitable biomarker to diagnose AKI. An ideal biomarker: (1) should be noninvasive and easily performed; (2) should be highly sensitive and specific to ensure timely diagnosis; and (3) must exhibit strong biomarker performance on statistical analysis.[27–30] Remarkable advances in other diagnostic fields of medicine have made it possible for immediate interventions with specific agents to manage life-threatening conditions. One such example is the field of cardiology where translational research has introduced the utilization of cardiac enzymes to facilitate recognition of myocardial cell injury and development of newer therapeutic approaches that has significantly decreased the mortality and morbidity in this group of patients.[31] In contrast, the field of nephrology relies on evidence of renal dysfunction—elevation of serum creatinine and oliguria—to diagnose AKI.[27,30] Serum creatinine is a relatively late indicator of renal injury. This is due in part to multiple factors that can modulate serum levels, including race, gender, protein intake, certain drugs, muscle mass, and total body volume.[32,33] In addition, significant AKI can occur without major increases in serum creatinine levels that could be explained by increased tubular secretion or renal reserve.[34] This implies that significant changes in serum creatinine will only be detected once the kidneys have experienced at least 50% reduction in function. Moreover, the rise in serum creatinine does

Biomarker	Source of sample	Main method of detection	Time of elevation in AKI	References
Tubular enzymes (AP, γ-GT, and others)	Urine	ELISA	Intermediate	94, 95
Cystatin C	Plasma	Nephlometric immunoassay	Intermediate	28, 96
IL-18	Urine	ELISA	Intermediate	28, 95
NGAL	Plasma	Western blot	Early	38, 39,97
L-FABP	Urine	ELISA	Early	98, 99
KIM-1	Urine	ELISA	Intermediate	49, 50
Netrin-1	Urine	ELISA	Early	100, 101

AP: alkaline phosphatase; γ-GT: γ-glutamyl transferase; NGAL: neutrophil gelatinase-associated lipocalin; L-FABP: L-type fatty acid-binding protein; KIM-1: kidney injury molecule-1.

Table 1. A partial list of emerging biomarkers for early detection of AKI.

not by itself distinguish among pre-, intra- and, postrenal causes of AKI. Another dilemma is the determination of baseline renal function in hospitalized patients. Ideally, a baseline creatinine should reflect the level of renal function at steady state prior to the hospitalization. In most studies, a baseline creatinine is not available for most of the patients and, therefore, the first creatinine measured in the hospital is considered as "baseline." The major limitation of this concept is that creatinine level at hospital admission likely reflects the effects of the disease process that occurred before hospital admission, or during the initial phase of hospital care.[35,36] Hence, it is evident that there is an urgent need to introduce sensitive and specific biomarkers that indicate cellular damage and enable physicians to intervene early on and potentially limit the extent of renal injury. In fact, the American Society of Nephrology has designated the development of such biomarkers for early detection of AKI as a top research priority.[37]

Over the past few years, several groups of investigators have identified novel biomarkers in experimental animals as well as humans with AKI (*Table 1*). The utility of such biomarkers could serve multiple imperative functions. These include identification of the exact site of injury within the nephron, recognition of the specific etiologies causing AKI, and could also be a valuable tool to evaluate prognosis and response to treatment. One extensively studied example is the neutrophil gelatinase-associated lipocalin (NGAL), which is a 25-kDa protein that is expressed only at very low levels under physiological condition in several human tissues but its levels are markedly increased following injury in epithelial cells, including the kidney, colon, liver, and lung.[38–40] A growing body of evidence suggests that NGAL is one of the most upregulated genes in the kidney very early after acute injury in animal models of sepsis, ischemia, and nephrotoxic AKI.[38–40] Recently, an NGAL reporter mouse model was generated by inserting a double-fusion reporter gene encoding luciferase-2 and mCherry into the NGAL locus.[41] It was elegantly shown that the NGAL-Luc2-mC reporter accurately illuminates injury *in vivo* in real time. Strikingly, specific cells of the distal nephron were found to be the source of urinary NGAL.[41] These studies were followed with human studies in various settings including sepsis, cardiac surgery, transplant, and nephrotoxicity.[42–45] Another biomarker that has gained increasing interest and provided promising results is kidney injury molecule-1 (KIM-1). KIM-1 is a transmembrane glycoprotein that is released into urine with proximal tubular injury.[46] This feature is intriguing because the bulk of all ischemic and toxic AKI is exerted at the proximal tubules.[47] More importantly, KIM-1 expression is not detectable under normal circumstances, while expression is significantly upregulated in various models of AKI.[48,49] These include cisplatin, cyclosporine, radio contrast, ischemia/reperfusion, folic acid, and even experimental models of autosomal dominant polycystic kidney disease.[49] On the other hand, several functions have been attributed to KIM-1 (such as a role in autophagy) that are under extensive investigation.[50] Nonetheless, KIM-1 has vital diagnostic and predictive properties in the context of AKI. This has been confirmed not only in animal models of AKI but also in human studies.[47–50] Although there is a strong body of evidence that supports the potential of NGAL or KIM-1 to be used as a standard diagnostic tool, it may be more feasible to use a panel of multiple biomarkers for the precise and well-timed diagnosis of AKI.

Recent studies by Endre et al.[51] have utilized a novel approach by using urinary biomarkers to triage intervention in the EARLYARF trial to evaluate the efficacy of erythropoietin versus placebo in incipient AKI. While the results of the intervention with erythropoietin were negative, the experimental design in this study offers a prototype for using biomarkers to trigger randomization.

Current therapeutic approaches and future targets

There has been outstanding progress in the T1 and T2 category related to AKI. Numerous studies have identified different aspects of AKI and complications related to it. This has resulted in an evolution in understanding the pathophysiological nature of AKI.[52] Despite such substantial advances the successful "bench-bedside" transition has remained elusive and almost no meaningful progress has been made to cure or reverse AKI. Hence clinicians rely on conservative measures and renal replacement therapy for the management of AKI. Remarkable technological advances have been made in the field of hemodialysis. However, the optimal time of intervention with dialysis in AKI still remains to be clarified. The current practice prescribes early intervention based on clinical criteria and volume status rather than just biochemical parameters. With regards to the dose of dialysis, two recent large, multicenter, randomized, controlled trials examined the role of intensifying the dosage of dialysis (25–40 mL/kg/h) versus the standard prescribed dose (20 mL/kg/h).[53,54] Both studies concluded that increasing the dosage and frequency of dialysis did not translate to a decrement in mortality rates in critically ill patients with AKI. Nevertheless, it is important to note that the results of these studies indicate that a minimal dosing threshold must be achieved to optimize clinical outcomes.[55] Refinements in dialysis modalities including the advantage of high-flux membranes with higher filtration rates, which are more permissive to "middle

molecules," and enhanced cytokine removal compared to low-flux membranes and convective over pure diffusive strategies are yet to be conclusively validated.[56–59]

The feasibility of a "bioartificial kidney" has been examined in a number of animal studies. Humes and colleagues demonstrated that a "renal assist device" composed of renal proximal tubule progenitor cells can effectively replace all the major functions of the kidney in acutely uremic dogs following bilateral nephrectomy[60,61] as well as animal models of sepsis.[62] These exciting reports led to Phase 1 and 2 clinical trials that tested the applicability, safety, and efficacy of this novel approach in humans.[63] Unfortunately, the pivotal Phase 3 trial was terminated early due to concerns of higher mortality in the treatment group potentially related to some changes in the protocol. These studies highlight the difficulties in transitioning from small Phase 2 to larger Phase 3 studies. Although this approach could be potentially beneficial, larger, randomized, multicenter trials are required to unequivocally confirm its role as a novel therapeutic modality in AKI.

Because of the vast nature of kidney-offending conditions and agents, numerous pathways have been proposed to prevent, minimize, or reverse AKI. For instance, extensive studies targeted different deranged pathways during sepsis-induced AKI. These targets include inhibition of inflammatory mediators, enhancement of renal perfusion by blocking vasoconstrictor mechanisms and intensifying vasodilator mechanisms, attenuation of leukocyte infiltration, inhibition of the coagulation cascade, and administration of growth factors to accelerate renal recovery.[64–66] Most of the mentioned attempts provided solid evidence in animal models of sepsis-induced AKI but unfortunately none could provide beneficial effects in this group of patients. In fact, only activated protein C[67] and steroid replacement therapy[68] have been shown to reduce mortality in patients with sepsis and are now accepted adjunctive treatment options for sepsis in general.[64,66]

Another example is the pharmacological interventions that were designed to prevent renal ischemia or modulate the ensuing inflammatory or hormonal milieu. Low-dose dopamine, long thought to prevent AKI by improving renal perfusion, was shown to have no effect on mortality and renal replacement requirement.[69,70] Another vasoactive hormone, atrial natriuretic peptide that enhances glomerular filtration rate by dilating the afferent and constricting the efferent arteriole (thereby increasing the intraglomerular hydrostatic pressure and subsequently promoting filtration),[71] seemed to be an appropriate therapeutic option. Although there appeared to be a trend toward improvement of AKI, this peptide also promoted hypotension and arrhythmias in high doses and the beneficial potential is still a subject of ongoing debate.[72,73] On the other hand, recombinant human insulin-like growth factor-1 that showed encouraging results at decreasing renal tubular apoptosis and inflammation in mice when administered immediately after renal ischemia[74] failed to show any benefit in a small randomized control trial of 72 critically ill patients with AKI.[75]

In spite of challenges and diverse failures, some exciting results and achievements have also emerged in the recent years. Knowledge gained from preclinical models has led to the initiation of several clinical studies targeting specific pathways. Phase 1 studies (*Table 2*) are most commonly pursued in cardiac surgery patients where the timing and nature of insult can be well defined. In contrast, Phase 2 and 3 studies (*Table 3*) target a broader segment of AKI but the preponderance is in settings where the nature of the insult can be defined, for example, contrast nephropathy.

One promising therapy is the utilization of mesenchymal stem cells (MSC) as a novel therapeutic modality in AKI.[76,77] MSC are unique and versatile multipotent cells that possess antiinflammatory and immunomdulatory properties.[78,79] These characteristics have ignited great interest and extensive study of MSC in different clinical conditions. MSC have proven beneficial in numerous animal models of injury including myocardial ischemia,[80] inflammatory lung diseases,[81] sepsis,[82] and AKI.[76,77] It is now evident that MSC mainly exert their beneficial effects via endocrine and paracrine and differentiation-independent mechanisms.[83,84] These and other findings have led to exciting clinical trials that are evaluating the efficacy and safety of administration of MSC in cardiac surgery-related AKI (http://clinicaltrials.gov, NCT00733876).

Another potential approach is the utilization of endogenous antioxidative enzymes. One such enzyme is HO-1 that is a stress inducible enzyme.[85] HO-1 cleaves the porphyrin ring at the alpha-methene bridge to form equimolar amounts of iron, biliverdin, and carbon monoxide.[86] Biliverdin is then converted to bilirubin by biliverdin reductase.[87] HO-1 has important antiapoptotic and antiinflammatory functions that have been attributed to one (or more) of its byproducts.[88] Induction of HO-1 has been shown to be protective in several forms of injury including AKI.[89] Furthermore, evidence suggests that polymorphism of HO-1 (short GT repeats) in humans is associated with better clinical outcome in various conditions including renal transplantation[90] and arteriovenous fistula patency in hemodialysis patients.[91] There are now ongoing clinical trials that are examining the beneficial effects of HO-1 byproducts including carbon monoxide in kidney transplantation (http://clinicaltrials.gov, NCT00531856) and bilirubin in endotoxemia (http://clinicaltrials.gov, NCT00916448).

As mentioned, many therapeutic agents that showed great potential in animals failed to complete the translational steps. This may have various explanations most likely of which is the fact that these agents were utilized only after AKI was established. This further highlights the urgent need for novel biomarkers to diagnose AKI so that proper treatment can be implemented in a timely and accurate manner.

What is needed to enhance translational research in AKI?

It is evident from the discussion above that progress in the field requires sharing of information across the domains of basic discovery and clinical care. Future clinical and translational research in AKI will require the development of collaborative networks of investigators drawn from various disciplines who are willing to share their expertise and resources. Since AKI is a heterogeneous disorder, like sepsis, it is helpful to consider the scope of activities that are currently required to enhance fundamental knowledge for the diagnosis and treatment of this disorder. Based upon this information, we can develop strategies for facilitating clinical and translational research activities and define the infrastructure that will be needed. *Table 4* describes some of the main elements that need to be considered. An approach is to build a network of centers that will be responsible for developing a databank of AKI patients that are carefully characterized with respect to their clinical course, alterations in renal function, and various markers of renal injury and renal pathology. Given the wide variation in the natural history and management of this disorder globally, it is essential that we develop mechanisms for sharing information and for collaboration among centers. Several key issues will need to be addressed including the infrastructure needed (database, protocols for web-based information transfer,

Clinical trials identifier	Study sponsor	Drug/biologic intervention	Setting	Target
NCT00683553	Quark Pharmaceuticals	15NP (small interfering RNA)	Cardiac surgery	Apoptosis
NCT00733876	AlloCure Inc.	Mesenchymal stem cells	On-pump cardiac surgery	Repair
NCT00821522	Maine Medical Center Research Institute	Remote ischemic preconditioning	Cardiac surgery	Primary prevention in ischemia reperfusion injury
NCT01275612	Mario Negri Institute for Pharmacological Research	*Ex vivo* expanded mesenchymal stem cells	Cisplatin-induced AKI	Repair
NCT00861822	University Health Network, Toronto	RBC transfusion presurgery	Cardiac surgery	Oxygen delivery
NCT00878956	Austin Health	Bicarbonate	Cardiac surgery	Oxidative stress

*http://clinicaltrials.gov.

Table 2. T1 (Phase 1) Drug studies currently underway for AKI*.

Clinical trials identifier	Study sponsor	Drug/biologic intervention	Setting	Target
NCT00878956	Austin Health	Bicarbonate	Cardiac surgery	Oxidative stress
NCT01251029	Assaf-Harofeh Medical Center	N-acetylcysteine	Major surgery under general anesthesia	Oxidative stress
NCT01225094	Lawson Health Research Institute	Curcumin	Elective Abdominal Aortic Aneurysm Repair	Antiinflammatory
NCT01066351	Thammasat University	Beta-erythropoietin	CKD patients cardiac surgery	Antiapoptotic and anti-inflammatory
NCT00982527	Bambino Gesù Hospital and Research Institute	Fenoldopam	Pediatric cardiac surgery	Dopamine D-1 receptor
NCT00557219	Medical University of Gdansk	Fenoldopam and Ketanserin	Cardiac surgery	Dopamine D-1 receptor agonist Adrenergic blocker and platelet aggregation
NCT01072682	CytoPherx, Inc	Selective cytopheretic device (SCD)	ICU AKI	Immunomodulation
NCT01245595	Stanford University	Aminophylline	Pediatric cardiac surgery	Phosphodiesterase inhibitors
NCT01146925	CorMedix	CRMD-001-Deferiprone	Cardiac angio contrast exposure	Oxidative stress
NCT00791648	Vanderbilt University	Atorvastatin	Cardiac surgery	Oxidative stress
NCT00978354	University of Alberta	Furosemide	ICU AKI	Diuresis
NCT01256372	Action Pharma A/S	AP214	Cardiac surgery	Inflammation

*http://clinicaltrials.gov.

Table 3. T2 studies (Phase 2 and 3) in AKI*.

etc.) the requirements for sharing information with regulatory issues, training needs for developing researchers and the resources that are required, and what will be the hurdles to be overcome in establishing such networks. A key aspect of these networks is that the number of centers involved varies for different activities, for example, all centers could participate in the registry function, but only a few in longitudinal data collection and some centers may only participate in clinical trials activity.

One major barrier for clinical trials in AKI is related to the selection of appropriate endpoints for outcome measures. Most clinical trials rely on one or more criteria that relate to (1) changes in serum creatinine (doubling or a 50% increase in creatinine from baseline levels), (2) dialysis initiation, (3) impact on length of stay in the ICU, and (3) overall mortality. Each of these criteria has inherent problems. The criteria involving change from baseline creatinine would vary depending on the selection of actual "baseline" value, which have not been consistent. Studies have used the first admission creatinine, inpatient nadir, or an outpatient creatinine level to define baseline values and depending on which value is used, the end point of doubling or 50% increase in serum creatinine may not be an accurate reflection of the status of AKI in a given patient.[35] The timing of dialysis initiation in AKI is highly variable and influenced by not only comorbidities but also variations in decision-making processes of physicians taking care of these patients.[92] The length of stay in the hospital or ICU and overall mortality are dependent on several factors and not solely on the status of AKI. For example, renal function following a given therapeutic intervention may improve, but the patient

Component	Reason	Proposed tools	Infrastructure required	Examples from other areas
Observational studies				
Cross-sectional	Prevalence of disease in various settings is not well known. Do not have knowledge of key elements, e.g., renal pathology	Develop a registry of patients with AKI	Web-based techniques for minimal data collection, HIPAA and IRB compliant, consent issues. Coordination center for data analysis and reports.	PICARD network, USRDS (registry model), sepsis, and critical care Registries. Pediatric CRRT Registry, Latin America AKI Registry
Longitudinal	Incidence of disease. Establish natural history of ARF; characterize the phenotype and genotype of patients with AKI, establish relationships of various patient and process factors with outcomes. Collect biological samples	Develop a longitudinal dataset that includes biological samples (including renal biopsy material) collected at specific time points in the course of AKI	Web-based techniques for data acquisition, HIPAA compliance, informed consent, Data coordination center, biological sample repository. Data analysis	Diabetes GoKIND study, AIDS collaborative networks, PICARD network, O'Brien AKI Registry*
Intervention studies				
Single/multicenter clinical research	Establish mechanisms of disease	Develop translational research networks linking basic scientists to clinicians to evaluate specific diagnostic interventions and therapeutic targets in limited numbers of patients, e.g., Physiological studies	Link basic scientists working on AKI with clinical centers with patients	PICARD network, Glomerulonephritis network
Single-center clinical trials	Phase 1 and 2 clinical trials	Develop mechanisms to support safety and efficacy and proof of concept trials in well-characterized patients with AKI	CTSA resources, Biological sample processing.	Industry-sponsored studies, AKIN network
Multicenter clinical trials	Phase 2–4 trials	Develop networks of centers with access to large numbers of patients with AKI for efficacy and effectiveness trials.	Clinical trial protocols, resources for trial implementation DCC for CRF design and development data acquisition, and analysis.	VA-NIH clinical trial for dialysis in AKI; Hemo trial ARDS network, AKIN
Health services research				
Evidence-based guidelines	Best practices for management of AKI	Develop evidence-based guidelines	Compilation and analysis and grading of available evidence, recommendations for nondialytic and dialytic management of AKI, treatment algorithms	ADQI, KDIGO
Outcomes research	Health economics and relationship of AKI to development of CKD	Establish benefit-cost and cost effectiveness of various strategies for AKI. Establish links of AKI to CKD	Mechanisms to collect data prospectively on costs and outcomes from AKI	USRDS for CKD, sepsis trials, large database analysis, e.g., Kaiser, Veterans Medical Centers
Comparative effectiveness research	Generation and synthesis of evidence that compares the benefits and harms of alternate methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care eg Dialysis timing, dose modality in AKI	Systematic reviews	AKI Registry for longitudinal observational data	ADHERE heart failure Registry, O'Brien AKI Registry*
		Experimental studies including RCTs	Data coordination for support of multicenter RCTs	
		Observation studies including Registries	Statistical support	
		Retrospective analysis including administrative data	Decision support	
		Decision modeling		

*UAB-UCSD O'Brien Center (www.ObrienAKI.org).

Table 4. Elements for clinical investigation in AKI and requirements for translational research.

could succumb to nonrenal causes (e.g., respiratory or cardiac failure). These barriers need to be carefully considered and better endpoints (possibly through the use of novel biomarkers) would certainly improve clinical trial designs.

Recognizing the need to accelerate research in this field, several resources have been developed to assist with the complexities associated with the pathogenesis and treatment of AKI. The University of Alabama, Birmingham and the University of California, San Diego NIH-NIDDK funded O'Brien Center for AKI research (http://www.obrienaki.org) offers some of the infrastructure described for this purpose and more details are provided in *Table 4*. The center provides multiple interdisciplinary cores that cover all areas of translational research. The prospects provided for the T1 category include development and training in the use of rodent models of AKI, multimodality small animal imaging core for state-of-the-art molecular imaging and a physiology core. The physiology core provides expertise including measurements of GFR, tubular reabsorption, renal hemodynamics, and isolation of primary renal and vascular cells in culture from rodents.

The objective of the Clinical Research Core (O'Brien Core A) is to provide resources to enable interdisciplinary clinical investigation in AKI that will advance our understanding of the natural history and pathophysiology of human AKI, ascertain genetic contributions for susceptibility and prognosis of AKI, enhance our diagnostic specificity, and expand our preventive and therapeutic approaches for this disorder. The core provides a Web-based database for the conduct of a wide range of observational and interventional clinical studies in AKI and is flexible in accommodating the research objectives of individual investigators and collaborating centers. This database has been used to establish a multicenter international registry of AKI that currently has 13 centers participating. Additionally, the core provides a genomics resource to facilitate the investigation of genetic determinants (both risk and outcome) of AKI, and enable investigators to perform systematic genomic analyses to allow correlation with clinical phenotypic information. Furthermore, the core provides access to various biomarker assays and a biological sample repository linked to the clinical database to enable further characterization of patients. Moreover, the center is actively involved in education and training as well as multiple registry projects that cover different areas of T2-T4 categories. Finally, recognizing the need not only for continued bench-type research but also the call for an integrative "bench to bedside and back" approach to AKI, the O'Brien Center also provides a core for Preclinical Studies in AKI (Core B).

Conclusion

AKI remains a serious clinical problem, with an alarming rate of morbidity, mortality, and rising incidence. Although investigators at all levels of translational research related to AKI have made important contributions, most of these have failed to translate into clinical care for patients with AKI. Diverse factors have thwarted progress in developing effective therapeutics for AKI.[93] These include (1) a reliance on traditional diagnostic tools that have major limitations for precise and judicious implementation of therapeutic agents, (2) the complex pathophysiology of AKI with involvement of multiple overlapping and temporal pathways, (3) heterogeneous patient population, and (4) lack of standardized clinical trial designs. The availability of novel biomarkers and improved knowledge of the natural history of AKI will continue to enhance our understanding of this complex disease. We believe that improving outcomes from AKI will require a concerted effort to enhance collaborative research and facilitate translation of knowledge not only from the "bench to bedside" but from the "bedside to the bench and back" (B2B). Several resources are now available through the NIDDK-funded UAB-UCSD O'Brien Center for AKI research to facilitate this process. We hope that this review will stimulate additional interest in the field and spark investigators to leverage these resources.

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