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Cell Therapy, Advanced Materials, and New Approaches to Acute Kidney Injury

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Abstract

Acute renal failure (ARF) is a common clinical syndrome characterized by an abrupt deterioration in kidney function, resulting in abnormalities in volume-regulatory, metabolic-regulatory, excretory, and endocrine functions. Despite decades of improvements in the provision of intensive care, and specifically in the provision of renal replacement therapy, the morbidity and mortality associated with acute kidney injury (AKI) remain extremely high. This article highlights novel cell therapies, advanced materials, and approaches to AKI with the aim of illuminating a potential path for future basic, translational, and clinical research using these novel modalities.

Keywords

renal failure; renal assist device; acute kidney injury; selective cytopheretic device

Introduction

Acute renal failure (ARF) is a common clinical syndrome characterized by an abrupt deterioration in kidney function resulting in abnormalities in volume-regulatory, metabolic-regulatory, excretory, and endocrine functions. Recently, the Acute Dialysis Quality Initiative (ADQI) group formulated a multilevel classification system—Risk, Injury, Failure, Loss, End-Stage Kidney Disease (RIFLE)—in which a wide range of disease spectra can be included.¹ This group has advocated use of the phrase “acute kidney injury” (AKI) to encompass the entire range of acute abnormalities in renal function. RIFLE defines 3 grades of increasing severity of acute renal disease (ARD) as risk (R), injury (I), and failure (F) and the 2 outcome variables of loss (L) and end-stage kidney disease (E).

A unique feature of the RIFLE classification is that it provides 3 grades of severity of ARD based on urine output or changes in the serum creatinine value from the baseline condition, whichever is more severe (Figure 1). The application of the RIFLE criteria to the assessment of the epidemiology and the prediction of the outcome of ARF has been validated in previous publications.^{2–4} This new classification and other recent contributions have led to an evolution of our understanding of AKI epidemiology and outcomes.

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Conflict of Interest Statement

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Acute kidney injury is not a rare disease. A study from the Nationwide Inpatient Sample (NIS) estimated the incidence of AKI to be 288 per 100 000 in the US population in 2002;⁵ the incidence of AKI requiring dialysis was estimated to be 27 per 100 000 population. Population-based epidemiology studies have estimated rates of AKI requiring dialysis to be 45 per 100 000 in Manchester, United Kingdom, 20 per 100 000 in Scotland, and 8 per 100 000 in Australia. Moreover, the incidence of ARF has continued to rise over the past 2 decades.^{5,6}

Despite decades of improvements in the provision of intensive care, and specifically in the provision of renal replacement therapy (RRT), the morbidity and mortality associated with AKI remain extremely high. The percentage of patients with ARF requiring dialytic intervention ranges from 20% to 60%. Of those requiring dialysis who survive, 12% to 33% require long-term RRT. The mortality in patients with ARF who require dialysis is generally reported to be 50%, while the mortality in those admitted to the hospital with prerenal azotemia is approximately 7%. The overall in-hospital mortality rate in the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) cohort study was 60%.⁷ As with the Program to Improve Care in Acute Renal Disease (PICARD), mortality varied widely across centers. Among countries contributing > 100 patients to the cohort, in-hospital mortality ranged from 51% to 77%.⁸

Thus, AKI is a serious, common, complicated, and costly medical illness, and the outcomes of which have not changed in many years. This article highlights novel cell therapies, advanced materials, and approaches to AKI with the aim of illuminating a potential path for future basic, translational, and clinical research using these novel modalities.

Inflammation as a Pathophysiological Mechanism in AKI

A growing body of evidence indicates that the inflammatory response plays a major role in ischemic AKI.⁹ Indeed, human studies have demonstrated that plasma levels of the proinflammatory cytokines interleukin (IL)-6 and IL-8 predict mortality in patients with AKI. The susceptibility of patients to AKI correlates with polymorphisms of pro- and anti-inflammatory genes, suggesting a role for inflammation. Urinary levels of the proinflammatory cytokine IL-18 are a marker of ischemic kidney injury. Also, autopsy studies and a limited number of biopsies show inflammation after human AKI.

In renal ischemia/reperfusion injury, the inflammatory response results in endothelial activation and injury, enhanced endothelial cell-leukocyte adhesion, leukocyte entrapment, and a compromise in microvascular blood flow. Leukocytes are activated by inflammatory mediators, including cytokines, reactive oxygen species (ROS), and eicosanoids, which upregulate adhesion molecules to engage counter-receptors on the activated endothelium. In addition, leukocytes are recruited by chemokines, which are upregulated by ROS and the proinflammatory cytokines IL-1 and tumor necrosis factor- α (TNF- α). In addition to the contribution of leukocytes and endothelial cells to the inflammatory response following ischemic injury, the renal tubular epithelium also generates mediators that potentiate inflammation. These include proinflammatory cytokines (eg, TNF- α , IL-6, IL-1, and transforming growth factor- β [TGF- β]) and chemotactic cytokines (eg, monocyte chemoattractant protein [MCP]-1, IL-8, and RANTES).⁹ As a result of these observations, many of the new approaches and advanced cellular therapies being developed for the treatment of AKI mediate their effect via modulation of inflammation.

The Limitations of RRT

Traditional indications for initiation of RRT in ARF include volume overload, hyperkalemia, severe metabolic acidosis, uremic complications such as pericarditis and

encephalopathy, or simply treatment of a rapidly rising blood urea nitrogen (BUN) and serum creatinine. There are inadequate data to provide definitive recommendations about the optimal time to initiate RRT. The predominantly retrospective data from the early era of clinical dialysis strongly support the prophylactic initiation of dialysis prior to the onset of advanced uremia. Although these studies support initiation of treatment by the time the BUN reaches 80 to 100 mg/dL, there are limited data addressing the question of earlier initiation of therapy. For example, one randomized study¹⁰ in critically ill patients with oliguric ARF did not find an improvement in 28-day survival and recovery of renal function using high ultrafiltration rates or early initiation of hemofiltration. In another prospective study,¹¹ including 24 trauma patients, “prophylactic” hemofiltration was performed. Despite positive effects on hemodynamic parameters, hemofiltration did not show any benefit with respect to the severity and duration of illness or patient outcome.

For the past 3 decades, intermittent hemodialysis (IHD) has remained the standard replacement therapy for ARF. Intermittent therapy is typically applied daily or on alternate days depending on the catabolic state, usually for 3 to 4 hours. Intermittent hemodialysis is preferable in patients with hemorrhagic diathesis because it can be easily performed without anticoagulation. However, IHD is associated with wide swings in body weight, blood pressure, ventricular filling pressures, and solute concentrations. Hypotension impairs the efficiency of dialysis and can further decrease renal perfusion and exacerbate tubular necrosis.

Because of the more gradual fluid and solute removal of continuous renal replacement therapy (CRRT), the control of volume status is easier and allows administration of medications and nutrition with less concern about volume overload. In addition, because CRRT is a continuous modality, there is less fluctuation of solute concentrations over time and better control of azotemia, electrolytes, and acid-base status. Continuous RRT bears less risk of an increase in intracranial pressure as it does not cause rapid solute shifts. The cumulative solute removal with CRRT is equal to or greater than that of IHD if sufficient ultrafiltration rates are achieved. The main disadvantages of CRRT include access and filter clotting and the consequent need for anticoagulation, the continuous immobilization of the patient, larger clearance of therapeutic drugs and undetermined pharmacodynamic data, and higher cost.¹²

The strength of various forms of RRT is also its essential limitation; although adequate in terms of volume-regulatory and metabolic-regulatory functions (toxin removal), RRT does nothing to mitigate the excretory, endocrine, and immunomodulatory functions lost to AKI. Moreover, RRT may actually promote inflammation via interaction of bioincompatible cellulosic membranes with blood, leading to an activation of complement that is associated with an upregulation of certain leukocyte-adhesion molecules.^{13–15}

The Kidney as an Immunoregulatory Organ

The kidney is regarded as an important endocrine organ, responsible for the secretion of hormones that are critical in maintaining hemodynamics (renin, angiotension II, prostaglandins, nitric oxide, endothelin, and bradykinin), red blood cell production (erythropoietin), and bone metabolism (1,25-[OH]₂-vit D3 or calcitriol).¹⁶ It synthesizes glutathione and free-radical scavenging enzymes and provides gluconeogenic and ammoniagenic capabilities.^{17,18} Catabolism of low-molecular-weight proteins, including peptide hormones, cytokines, and growth factors, is also accomplished by the kidney.¹⁹

The kidney also has a less recognized immunoregulatory function (Figure 2). The mammalian renal proximal tubule cells are immunologically active. They are antigen-presenting cells²⁰ that have costimulatory molecules²¹ that synthesize and process a variety

of inflammatory cytokines.^{21,22} The roles of the renal tubule cells in glutathione metabolism,¹⁷ regulation of vitamin D, and production and catabolism of multiple cytokines¹⁶ are critical to immunoregulation to maintain tissue integrity and host defense under stress conditions.²³

Cell Therapy, Advanced Materials, and New Approaches

The replacement of the functions of renal tubule cells during the episode of AKI in conjunction with hemofiltration provides more complete RRT as compared with the “partial” replacement therapy of current dialysis treatments (Figure 2). Thus, the focus of novel approaches to the treatment of AKI has been to replace the kidney function that RRT alone is not able to address.

The Renal Assist Device

We have developed an extracorporeal device utilizing a standard hemofiltration cartridge seeded with approximately 10^8 renal tubule cells, which grow in confluent monolayers along the inner surface of the fibers.^{24–29} In vitro studies of this renal tubule assist device have demonstrated that the cells retain differentiated active transport properties, differentiated metabolic activities, and important endocrine processes. Additional studies have shown that the RAD, when incorporated in series with a hemofiltration cartridge in an extracorporeal blood perfusion circuit, replaces filtration, transport, metabolic, and endocrine functions of the kidney in acutely uremic dogs.²⁵

Recent studies have demonstrated that renal bioreplacement therapy with the RAD ameliorates endotoxin or bacterial septic shock in acutely uremic animals. Nephrectomized mongrel dogs treated with continuous venovenous hemofiltration (CVVH) and either a RAD or sham cartridge were given endotoxin to simulate gram-negative septic shock.²⁷ Mean peak levels of an anti-inflammatory cytokine, IL-10, and mean arterial pressures (MAP) were found to be significantly higher in cell-treated animals. To further assess the effect in ARF with bacterial sepsis, dogs were nephrectomized and 48 hours later administered intraperitoneally with *Escherichia coli*.²⁸ Immediately after bacteria administration, animals were placed in a CVVH circuit with either a RAD or a sham cartridge. Renal assist device treatment maintained better cardiovascular performance, as determined by MAP and cardiac output, for longer periods than sham RAD therapy. All sham animals died within 2 to 10 hours after bacteria administration, whereas all cell RAD-treated animals survived > 10 hours. Levels of IL-10, an anti-inflammatory cytokine, were significantly elevated in the RAD group, and a significant correlation was observed between the rise in plasma IL-10 levels and the decline in MAP. The RAD maintained renal metabolic activity throughout the septic period. In another study, pigs with normal kidney function were administered *E coli* intraperitoneally.²⁹ One hour later, animals were placed in a CVVH circuit containing either a RAD or a sham cartridge. All animals developed ARF with anuria within 2 to 4 hours after bacteria administration. Renal assist device treatment maintained better cardiovascular performance, as determined by cardiac output and renal blood flow, for longer periods than sham therapy. Consistently, the RAD group survived longer than the controls (10 ± 2 hours vs 5 ± 1 hour, respectively). Renal assist device treatment was associated with significantly lower plasma circulating levels of IL-6, a proinflammatory cytokine, and interferon- γ . These data demonstrate that septic shock results in early ARF and that renal bioreplacement therapy improves cardiovascular performance associated with changes in cytokine profiles and confers a significant survival advantage.

The initial clinical results in the first 10 treated patients demonstrated that the RAD can be delivered safely for up to 24 hours,³⁰ Cardiovascular stability was maintained, and increased native renal function, as determined by elevated urine outputs, temporally correlated with

RAD treatment. The cells demonstrated differentiated metabolic and endocrinologic activity in this ex vivo treatment. Glutathione degradation and endocrinologic conversion of 25-OH-D3 to 1,25-(OH)₂-D3 by the RAD tubule cells were demonstrated. All 10 patients were critically ill with AKI and multiple organ failure, with predicted hospital mortality rates between 80% and 95%. One patient died within 12 hours after RAD treatment following his family's request to withdraw ventilatory life support. Another patient died after a surgical catastrophe (toxic megacolon), which required discontinuation of RAD treatment after only 12 hours. Of the remaining 8 patients, 6 survived > 28 days with renal function recovery. Plasma cytokine levels suggest that RAD therapy produces dynamic and individualized responses in patients depending on their unique pathophysiologic conditions. For the subset of patients who had excessive proinflammatory levels, RAD treatment resulted in significant declines in granulocyte G-colony stimulation factor, IL-6, IL-10, and especially IL-6/IL-10 ratios, suggesting a greater decline in IL-6 relative to IL-10 levels and a less proinflammatory state.

Subsequently, a phase 2, randomized, controlled, open-label trial involving 58 patients who had AKI and required CRRT was performed at 12 clinical sites.³¹ Despite the critical nature and life-threatening illnesses of the patients enrolled in this study, the addition of the RAD to CVVH resulted in a substantive clinical impact on survival compared with a conventional CRRT group. Renal assist device treatment for up to 72 hours promoted a statistically significant survival advantage over 180 days of follow-up in intensive care unit (ICU) patients with AKI and demonstrated an acceptable safety profile.

The Selective Cytopheretic Device

Leukocytes are major contributors to the pathogenesis and progression of many clinical inflammatory disorders, including acute and chronic renal failure. Many therapeutic approaches are under investigation to limit the activation and tissue accumulation of leukocytes at sites of inflammation to minimize tissue destruction and disease progression.^{32–33} A synthetic membrane device, with the ability to bind and inhibit activated leukocytes along a continuous renal replacement extracorporeal circuit, has been developed and is called the SCD. This device incorporates a low-velocity and low-shear force blood path around a bundled collection of dialysis hollow fibers. In conjunction with regional citrate anticoagulation, this coupling of events within the device results in the sequestration of activated leukocytes in conjunction with a low-ionized calcium (iCa) environment due to citrate in the blood circuit to inhibit the release of inflammatory and destructive enzymes and cytokines from the membrane-bound neutrophils and monocytes.^{34–36}

The SCD was evaluated in a porcine model of *E coli*-induced septic shock and demonstrated an ability to lower neutrophil activity (serum myeloperoxidase and CD11b cell-surface expression), diminish neutrophil tissue invasion, decrease systemic capillary leak, preserve cardiac output and mean arterial pressure, and prolong survival time.³⁴

The development of this device arose during the preclinical and clinical evaluation of an RAD^{30–31} containing adult human renal tubule cells. This report presents a subset analysis of a phase 2b clinical study evaluating RAD therapy. Subsets of patients were treated with either systemic heparin or regional citrate anticoagulation and received either a sham non-cell SCD or a cell-containing cartridge. With the compelling data derived from the large-animal studies with the SCD,^{32,33} these subsets of patients were more carefully analyzed to compare the mortality rates in subjects treated with only sham (non-cell) cartridges with systemic heparin anticoagulation or citrate regional anticoagulation. The unanticipated but compelling results are presented below.

Twenty-four patients were randomly assigned to the non-cell cartridge group that received either systemic heparin (n = 12) or regional citrate (n = 12) anticoagulation. Figure 3 displays the survival plot for the 2 subgroups. The mortality rate in the heparin patient group was 50% versus 25% in the citrate-treated group (n = 12 for each treatment arm) at 28 days and 75% versus 33%, respectively, at 90 days (chi-square < 0.05).

In this randomized, blind, multicenter clinical study, the addition of a second hemofiltration cartridge with an altered blood flow path to lower blood velocity and shear rates in a series with a conventional CVVH circuit significantly reduced all-cause mortality at 90 days in ICU patients with AKI. This improved survival was demonstrated in the presence of regional citrate anticoagulation when compared with systemic heparin anticoagulation. The mortality differences between the citrate and heparin treatment groups could not be attributed to the acuity of illness in the 2 groups because the average Sequential Organ Failure Assessment (SOFA) scores were similar for both sets of patients. Treatment with the non-cell cartridge was well tolerated without measurable effects on hematologic parameters, including neutrophil and platelet counts, and with an adverse event profile expected for a seriously ill population in the ICU with AKI.

Alternate New Approaches and Future Directions

Major efforts are underway to identify biomarkers for diagnosing AKI earlier and more accurately so that preventive measures to minimize renal injury may improve patient outcome.³⁷ The use of stem cells to enhance the rate of recovery from AKI is also being investigated by multiple groups,³⁸ anticipating that earlier renal recovery may lessen the morbidity and mortality ARF. Although these directions of inquiry may ultimately prove useful as adjunct approaches to AKI-induced ARF, a more promising direction is to better understand and interrupt the pathophysiologic processes that are activated in AKI, which result in distant-organ dysfunction, multiorgan failure, and eventually death. During the maintenance phase of ARF, while hemodialysis/hemofiltration techniques are being utilized, the patient continues a downhill course into multiorgan failure. Technologies directed to disrupting these multiorgan dysfunctions may well be the next major improvement to enhance the clinical outcome of these critically ill patients.

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Figure 1.
Proposed RIFLE classification scheme for acute renal failure.
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Figure 2. Diagram of inflammatory cascade after acute kidney injury/chronic kidney disease. Reproduced with permission from *Semin Dial.*⁴⁰

Figure 3.
Survival of citrate vs heparin in selective cytopheretic device and continuous renal replacement therapy for acute kidney injury.