Chapter 14
Bioartificial Kidneys, Renal Epithelial Cell Systems, and Biomimetic Membrane Devices

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Abbreviations

AKI	Acute kidney injury
ALI	Acute lung injury
AMI	Acute myocardial infarction
ARDS	Acute respiratory distress syndrome
ARF	Acute renal failure
ATN	Acute tubular necrosis
BAK	Bioartificial kidney
BRECS	Bioartificial Renal Epithelial Cell System
CD	Cluster of differentiation
CHF	Chronic heart failure
CKD	Chronic kidney disease
CO	Cardiac output
COVID-19	Coronavirus disease 2019
CPB	Cardiopulmonary bypass
CRRT	Continuous renal replacement therapy
CRS	Cardiorenal syndrome
DAMP	Damage-associated molecular pattern molecules
ECMO	Extracorporeal membrane oxygenation

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G. Bezerra da Silva Junior, M. Nangaku (eds.), *Innovations in Nephrology*,
https://doi.org/10.1007/978-3-031-11570-7_14

ESRD	End stage renal disease
FDA	Food and drug administration
FiO2	Fraction of inspired oxygen
HD	Hemodialysis
HDF	Hemodiafiltration
HF	Hemofiltration
HRS	Hepatorenal syndrome
iCa	Ionized calcium
ICH	Intracerebral hemorrhage/hemorrhagic stroke
ICU	Intensive care unit
IDE	Investigational device exemption
IHC	Immunohistochemistry
IL-	Interleukin
IRB	Institutional review board
LMW	Low molecular weight
LPS	Lipopolysaccharide
MELD	Model for end-stage liver disease
MO	Monocyte
MODS	Multiple organ dysfunction syndrome
MW	Molecular weight
MWCO	Molecular weight cutoff
PAMP	Pathogen-associated molecular pattern molecules
RAD	Renal assist device
RCA	Regional citrate anticoagulation
riCA	Recommended ionized calcium
RRT	Renal replacement therapy
SAE	Serious adverse events
SCD	Selective cytopheretic device
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment
SVR	Systemic vascular resistance
T2D	Type 2 diabetes
TBI	Traumatic brain injury
TNFα	Tumor necrosis factor alpha
US	United States
VFD	Ventilator-free days
WBC	White blood counts

14.1 Introduction

Several etiologies of kidney injuries may result in renal dysfunction including direct or indirect insults to the glomerulus responsible for filtration function, or renal epithelial cells responsible for many of the regulatory and secretory functions of the

kidney. Rabb et al. provides a good primer on inflammatory processes associated with acute kidney injury (AKI), including the initial response, features of acute inflammation, and reparative phases of kidney injury [1]. Other comprehensive, systematic reviews of septic shock-associated AKI discuss pathogen-associated molecular pattern molecules (PAMPs) such as endotoxin, and damage-associated molecular pattern molecules (DAMPs) such as cytokines [2–4]. AKI arising from acute renal tubule cell injury, also referred to acute tubular necrosis (ATN), may be due to direct insult from PAMPs, or through ischemic and/or nephrotoxic processes via DAMPs. Although AKI can arise from hyperinflammation, most commonly resulting from sepsis or tissue trauma, acute tubule cell injury without underlying hyperinflammation has been demonstrated to initiate and promote a systemic hyperinflammatory process that potentiates not only AKI but injury and dysfunction of other organs [5]. The resulting hyperinflammatory process is characterized by excessive activation of innate immune cells, namely neutrophils and monocytes, as well as activation of capillary microvasculature resulting in dysregulated levels of cytokines heavily weighted toward pro-inflammatory mediators. Immune dysregulation and hyperinflammatory, leukocyte-driven processes may lead to tissue damage, organ injury, and consequently, progressive organ dysfunction. Multiple organ dysfunction syndrome (MODS) may result due to inflammatory processes involving both activated leukocytes in circulation and activated endothelial cells in organ microvasculature. Poor tissue perfusion resulting from deleterious interactions of these activated cell populations has ischemic and toxic consequences, including tissue edema, systemic hypovolemia, hypotension, and cardiovascular instability a negative impact on organ function. In the kidney, sequestration and aggregation of activated neutrophils in the peritubular capillaries and tissue infiltration of these cells can lead to necrosis of renal tubule cells, which promotes AKI. Conventional therapies such as hemofiltration strategies have been used to replace the reduced or lost filtration function of the kidney, while some sorbent therapies have focused on the removal of pathogens and secondary immunological mediators such as cytokines thought to be responsible in MODS. This review centers on a review of emerging extracorporeal device treatment interventions using renal epithelial cell-based devices, bioartificial kidneys, and leukocyte processing therapies.

14.2 Overview of Conventional Devices in the Treatment of Kidney Disease: Dialysis, Filtration, and Hemopurification

The most established device-based strategies in the treatment of AKI are filtration technologies including hemodiafiltration and peritoneal dialysis, which attempt to replace lost filtration function of the kidneys. The aim of these filtration-based renal replacement therapies (RRT) is the removal of low molecular weight (LMW) uremic toxins, middle molecular weight cytokines, and other inflammatory molecules through porous membranes via diffusive (dialysis) or convective (filtration)

processes, while retaining beneficial molecules such as albumin through size exclusion. Dialysis is commonly utilized for ESRD to maximize uremic toxin clearance during intermittent treatments. For a thorough, systematic review of peritoneal dialysis in AKI, see Chionh et al. [6]. Extracorporeal blood purification using devices to capture and/or remove inflammatory mediators and both endogenous and exogenous toxins particularly during sepsis and sepsis associated AKI is an evolving area that has been comprehensively reviewed [7]. Extracorporeal cytokine removal using extracorporeal devices is a mature concept focused on the belief that reducing peak cytokine serum levels during the hyperinflammatory period would ameliorate detrimental actions of these molecules [8], potentially also altering tissue cytokine gradients and facilitating restoration of immunologic homeostasis. Many cytokines fall in a molecular weight (MW) range of 8 kDa to 70 kDa (Table 14.1), and endotoxin fragments associated with sepsis are 1 kDa to 15 kDa, which are generally removed by conventional hemodialysis (HD) and hemofiltration (HF) membranes, with a MW-cut off (MWCO) of between 45 and 65 kDa. While measurable cytokine removal is achieved using various modalities including use of high molecular weight cut-off membranes and high volume hemofiltration schemes [8], therapies solely aimed at reducing cytokine load have been largely ineffective in improving clinical outcomes [9–13]. Ineffective filtration treatments may be due to in part, failure to remove blood protein bound toxins, cytokines, and inflammatory molecules [14]. Higher MWCO membranes which

Table 14.1 Molecular weights (MW) of various PAMPs and DAMPs, potential therapeutic targets

Class	Molecule	Molecular weight (kDa) or size range (nm, μm)
PAMPs	Bacteria/LPS fragments	Various, generally 0.2–30 μm/1–15 kDa
	Viruses	Various, generally 5–100 nm
	Fungi	Various, generally 2–25 μm
	Parasites (*T. gondi*)	Various, generally 2–150 μm
DAMPs	Complement (C3a, C4a, C4b, C5a, C5b)	Various, generally 9–190 kDa
	Heat shock proteins	Various, generally 8–100 kDa
	Hyaluronic acid	Various, generally kDa to MDa
	IL-1	17–25 kDa
	IL-1β	17 kDa
	IL-4	30 kDa
	IL-6	21–26 kDa
	IL-8	8 kDa
	IL-10	17 kDa
	IL12p70	70 kDa
	MMPs	Various, generally 50–95 kDa
	Non-proteins: Nucleic acids	Various, generally kDa to MDa
	sIL-6r	55 kDa
	sTNFr-I	60 kDa
	TNF-α	17 kDa
	TNF trimer	51 kDa

may remove protein bound cytokines also result in blood protein loss [15, 16] and require relatively expensive protein administration, entailing albumin supplementation at a minimum. Additional hemopurification strategies using newly developed membranes and alternative techniques such as apheresis or selective plasma exchange have seen some utility for cytokine removal, but still have limited data regarding efficacy in sepsis associated AKI [17]. Devices such as plasma fractionators with precise MWCO along with methods such as double/cascade filtration and coupled plasma filtration adsorption have been used for very precise removal of molecules within a specific MW window [18, 19], but have not seen widespread adoption.

14.3 Introduction to Sorbents and Immunomodulatory Devices for AKI and Multiple Organ Dysfunction Syndrome (MODS)

Citing the difficulty in removing middle molecular weight PAMPs and DAMPs via filtration, the use of sorbents attempts to specifically adhere these molecular targets with high potential therapeutic impact. Use of sorbent materials in conjunction with hemofiltration or as stand-alone devices are relatively mature technologies that attempt to adhere inflammatory molecules to specialized device surfaces through adsorption or through binding via various mechanisms. Sorbent technologies to date have mainly focused on removing specific PAMPs such as endotoxin, or DAMPs including a myriad of cytokines, and are exemplified by devices such as Cytosorb®. Sorbent technologies have been well reviewed by Winchester et al. [20–22]. In brief, sorbent columns or cartridges can be packed with various media in order to adsorb specific molecular targets, many times utilizing immobilized antibodies, functionalized surfaces, or specialized porous resins for molecular interaction and capture. PAMP targets have included endotoxin, also known as lipopolysaccharide (LPS), typified by devices utilizing Polymixin B [23]. Clinical studies involving these devices have been heterogenous, lacking adequate randomization, blinding and incomplete outcomes [23]. Due to the low quality of evidence provided to date, therapeutic use of Polymyxin B-based devices may only be conditionally recommended for very high-risk patients [23]. DAMP molecules have been targeted by sorbent systems such as Cytosorb® [24], finding utility in sepsis, cardiac surgery, organ transplant, and liver failure among other contexts. Specific DAMPs targets of sorbent technologies have included β2-microglobulin, angiogenin, complement factor D, leptin, IL-1, IL-6, IL-8, IL-10, IL-13, IL-18, interferon-α, TGF-β, and TNF-α [22, 24]. However, to date, Sorbent-based blood-purifying technologies have not shown selectivity and durability in lowering blood cytokine levels nor robust efficacy to improve clinical outcomes [2]. Like many technologies in the AKI/sepsis field, additional large, randomized, controlled, clinical trials are still required to provide evidence of clear therapeutic benefit [23].

With the limitations of filtration and sorbent technologies, there is an unmet medical need to develop advanced therapies that address hyperinflammation in kidney disease. Immunomodulatory device treatments in development cover a wide range of approaches to recapitulate the immunologic functions of the kidney from bioartificial kidney and extracorporeal cell bioreactors to leukocyte processing devices. These emerging technologies, which utilize admittedly less well-understood mechanisms of action, attempt to harness the innate characteristics of cells and their cellular feedback mechanisms involved with immune system regulation in order to correct immune dysregulation. Exogenous, extracorporeal bioreactor strategies such as the renal assist device (RAD) and the bioartificial renal epithelial cell system (BRECS) employ metabolically active cells maintained in an extracorporeal circuit in order to process body fluids such as blood or plasma, to both remove inflammatory molecules and supplement beneficial molecules such as secreted factors, leveraging both anabolic and catabolic functions of exogenous renal cells. Leukocyte processing devices, such as the selective cytopheretic device (SCD), attempt to ameliorate immune dysregulation through a multifactorial approach of sequestration of activated leukocyte subpopulations including neutrophils and monocytes, while modulating the circulating leukocyte populations.

14.4 Exogenous Cell-Based Devices: Renal Assist Device (RAD), Bioartificial Kidney (BAK), and Bioartificial Renal Epithelial Cell System (BRECS)

In order to replace renal tubule immunomodulatory activity during AKI, an extracorporeal device containing human renal tubule cells, the RAD, was used in intensive care unit (ICU) patients with AKI requiring continuous RRT (CRRT). Incorporation of the bioreactor into the CRRT circuit was associated with a decrease in the high plasma levels of cytokines in these patients, amelioration of the AKI promoted hyperinflammatory condition and improved survival [25]. This cell-based strategy replaces some of the cellular functions lost or compromised during AKI by supplementing with exogenous renal cells grown in an immuno-isolating device with blood access, which allows for metabolic and secretory support from the applied cells. The premise of the RAD was based upon perceived shortcomings of established renal replacement therapies: HD, HF, HDF, etc., which are centered on small solute and toxin removal of molecules below the MWCO of porous membranes and volume control. However, these therapies fail to replace the many additional aspects of renal function outside of small toxin clearance, including the secretion of hormones: renin, prostaglandins, angiotensin, endothelin, bradykinin, erythropoietin and calcitriol, as well as ignore the important immunomodulatory role held by the kidney, which is still being elucidated. Part of the regulatory strategy in development of a fully implantable bioartificial kidney (BAK), was based on proving the safety and efficacy of extracorporeal cell-based therapy while concurrently working on the miniaturization of required technology and biocompatibility

of components [26, 27]. Different BAK technology approaches, engineering challenges, and related regulatory hurdles are presented in several full-length reviews [28–30].

In the RAD IIa clinical study, safety and initial efficacy was demonstrated in subsets of patients that were treated with a cell containing RAD over a sham device without renal cells [31]. However, in the Phase IIb RAD clinical study, additional cohorts were added, allowing the enrollment of patients being treated with regional citrate anticoagulation (RCA). Surprisingly, improved patient survival rate was demonstrated in the sham device group receiving RCA, in addition to the RAD cell treatment group, in comparison to the sham acellular device during systemic heparin anticoagulation [32]. These cohorts were scrutinized in a retrospective analysis, and the 28-day survival rate in the RCA sham group was observed to be 75% vs. 50% for the heparin anticoagulation sham group (n = 12 for each treatment arm). Similarly, at the 90-day mark, survival rate was 67% for sham device with RCA vs. 25% for sham device with heparin anticoagulation. Demographics for the two patient subsets were comparable, having similar Sequential Organ Failure Assessment (SOFA) scores (12.2 ± 0.9 vs. 13.4 ± 1.1), organ failure number (3.93 ± 0.36 vs. 4.17 ± 0.46), and identical incidence of sepsis (58%) for the heparin versus RCA sham groups, respectively [32]. This unexpected clinical result identified the potential benefit of using an acellular fiber-based device in conjunction with RCA to treat AKI. This approach later became known as selective cytopheretic device (SCD) therapy, which is detailed below.

The halted RAD clinical trial effectively stopped the development and commercialization of the RAD, but led to the development of both the acellular, SCD and a second generation cell-based device called the bioartificial renal epithelial cell system (BRECS), which was designed to be a cryopreservable bioreactor populated with allogenic renal cells for potential "off-the-shelf" use in an extracorporeal therapy for AKI. BRECS cell device recapitulated many aspects of the metabolic support of the RAD in a more practical form factor for on-demand, acute use. Unfortunately, the regulatory hurdles facing the BRECS, including requirement of an extensive Pre-Market Approval (PMA) study and expensive manufacturing requirements led to prioritize the development of the SCD, an acellular device with fewer regulatory hurdles. Review articles of the medical device development process recognize the slow clinical translation process moving from benchtop to bedside, especially so for FDA Class III devices with added regulatory requirements, which tend to take longer to develop [33, 34].

14.5 Leukocyte Processing Strategies: Selective Cytopheretic Device (SCD) in the Treatment of AKI

Mounting evidence for clinical benefit from targeting modulation of the leukocytes themselves to directly modulate hyperinflammation, utilizing innate characteristics of cellular machinery which are effectors of secondary factors (e.g., cytokines), has

arisen from serendipitous discovery of the acellular SCD during the RADIIb trial. The SCD is an extracorporeal, immunomodulatory, device containing hemocompatible fibers enclosed in a housing with inlet and outlet blood flow ports. SCD can be incorporated into a patient's established CRRT circuit (Fig. 14.1), where the blood flow is directed along the outer surface of the fibers where blood cells can interact with membrane surfaces under a low shear stress blood flow and low ionized calcium environment. When SCD were examined microscopically after patient treatment, a significant population of leukocytes were found to be adhered on to the outer membrane surface of the fibers at the interface with the blood flow path [31]. Sequestered leukocytes were dominated by cells of myeloid lineage, namely neutrophils and monocytes. Leukocyte adhesion is not routinely observed in the inner lumen of hollow fiber membranes, the blood flow path for standard hemofilters and dialyzers. This is likely due to the high shear stresses involved at the fiber interface with blood, with blood flowing at high flow rates through small-diameter hollow fibers (on the order of a hundred to hundreds of dynes/cm^2). However, in SCD, with blood flow directed along the outside surfaces of fibers, the shear forces are on the same order as capillary force (<1 dyne/cm^2), favorable dynamics for LE–material interactions such as adhesion are achieved. Some leukocytes are adhered and sequestered over long periods of time in SCD, while some leukocytes may adhere and subsequently release from SCD [35]. Capture and release after potential alteration within the SCD microenvironment and return of these cells to the patient, seems to have biofeedback implications that results in amelioration of many deleterious effects of hyperinflammation during AKI.

The precise mechanism of action of the SCD is becoming better understood and appears to be an immunomodulatory process which inhibits leukocyte activation, a critical component of the systemic inflammatory response syndrome (SIRS) leading to multi-system organ failure. The modulation of the pro-inflammatory state also

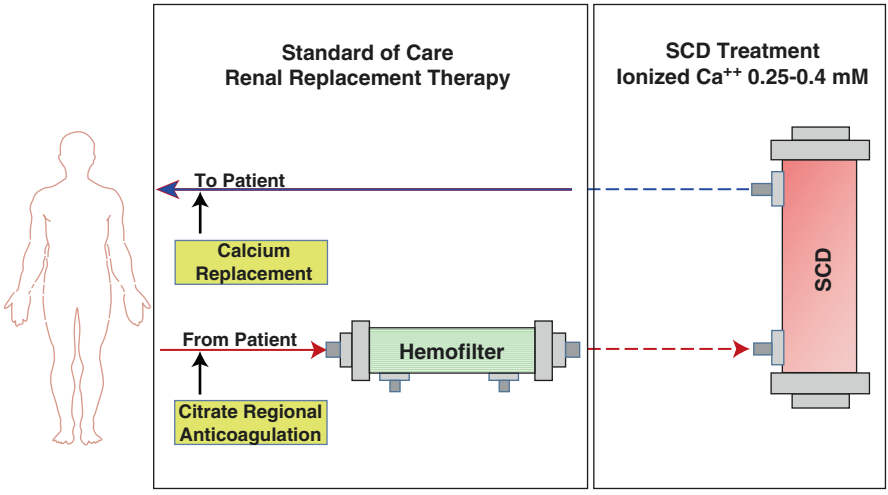

Fig. 14.1 Circuit diagram of SCD therapy incorporated into a standard RRT circuit

allows recovery of renal function in AKI and other associated organ failures. The cartridge in the presence of citrate anticoagulant acts as a selective cytopheretic device to bind and immunomodulate potentially damaging circulating leukocytes. This perspective is based upon evolving data from *in vitro* bench studies, preclinical animal models, and human clinical trials (Tables 14.2 and 14.3) utilizing measurements of biomarkers and leukocyte cell sorting by cytometric analysis.

Table 14.2 SCD clinical trial history for acute indications

Clinical trial	SCD clinical trial description	ClinicalTrials.gov identifier	Key findings
Phase I/II	AKI receiving CRRT, 15 patients (China), SCD treatment arm only [36]		No device-related serious adverse events (SAEs). Reduction in mortality: Case-matched controls was 77.78%, SCD group was 22.22% ($p < 0.027$) [36]
Phase II	FDA/IDE AKI receiving CRRT, 35 patients (USA), SCD treatment arm only [37]	NCT01072682	No device-related SAEs. Expected mortality was >50% based on contemporaneous literature review. At day 60, death from any cause was 31.4%, and all survivors did not require dialysis [37]
Phase III	FDA/IDE protocol SCD-003, AKI receiving CRRT, randomized controlled, multicenter, clinical trial, 134 patients [38]	NCT01400893	Study suspended due to injectable calcium shortage. Ad hoc analysis of SCD group with per protocol circuit recommended ionized calcium (RiCa) levels during RCA demonstrated improved 60-day mortality rate in SCD-treated subjects compared to controls treated with conventional CRRT therapy: 16% (3/19) vs. 41% (11/27). The 60-day dialysis dependency was improved with 0/16 survivors in the SCD-treated group versus 4/16 (25%) in the control non-treated group. A composite endpoint consisting of 60-day mortality or dialysis dependency between the two groups of patients was statistically significant ($p < 0.01$) [38]
Phase I/II	FDA/IDE, pediatric AKI, 16 patients, SCD treatment arm only (SCD-PED-01)	NCT02820350	Case study on the first treated pediatric patient was published [39]. 19 patients enrolled and 16 pediatric patients treated with SCD. Favorable results have been observed with 12 of the 16 SCD-treated patients surviving at 60 days. A favorable reduction compared to historical controls with mortality rates above 50%. All 12 surviving patients were dialysis independent. No SCD-related SAE were recorded [40]

(continued)

Table 14.2 (continued)

Clinical trial	SCD clinical trial description	ClinicalTrials.gov identifier	Key findings
Phase II	Up to 35 COVID-19 patients with AKI and/or ARDS will be treated with SCD, with contemporaneous control group available via CRRT.net	NCT04395911	Recently completed. Outcome measures: 1. (a) mortality at day 60. (b) dialysis dependency at day 60. (c) ventilation free survival at day 28 2. (a) dialysis dependency at day 28. (b) mortality at day 28. (c) urinary output change. (d) pO_2/FiO_2 change. (e) safety assessments including SAEs. (f) device integrity. 3–6 assessed in 10 days of treatment
Phase I/II	FDA/IDE, pediatric AKI, 10 patients, SCD treatment arm only (SCD-PED-02)	NCT04869787	On-going: 1. (a) number of SCD-related AEs. (b) number of unanticipated adverse device effects 2. (a) mortality at day 28 and 60 post treatment. (b) renal recovery: % patients free from chronic dialysis treatments at day 28 and 60. (c) hospital stay from enrollment to day 60. (d) ICU length of stay from enrollment to day 60
Phase III	FDA/IDE, adult AKI, 175 patients, randomized controlled, multicenter clinical trial, supplemental IDE approved		Not yet recruiting, supplemental IDE approved with composite endpoint consisting of 60-day mortality or dialysis dependency

The low ionized calcium (iCa) environment during regional citrate anticoagulation and the low shear stress along the blood pathway within the SCD promotes a selective binding of the most activated neutrophils and monocytes to the membranes of the device [35, 39, 41]. This selectivity is due to the calcium dependency of leukocyte binding processes. It is postulated that once bound, the activated neutrophils are promoted in the low iCa environment to transition from delayed apoptosis to an apoptotic program and released back to the systemic circulation [44–46]. The transition of these neutrophils to apoptosis and release from the SCD results in the clearance of these previously highly activated inflammatory cells via well-described pathways of phagocytosis and digestion within macrophages in the bone marrow and liver [47]. A continuous process of binding, apoptotic conversion, release, and clearance from the circulation of the most activated circulating neutrophils results in immunomodulation of the systemic inflammatory process to a less proinflammatory state [41]. For monocytes, the most activated, proinflammatory circulating monocyte pool is selectively bound to the SCD. The binding and sequestration of this monocyte subset promotes a shift of the circulating pool of the proinflammatory

Table 14.3 SCD preclinical animal disease models and related publications

Acute models		Key findings
SCD ICH	Porcine Model of Intracerebral Hemorrhage [41]	Reduction in edema and leukocyte infiltrate at site of intracerebral injection of thrombin in SCD treatment group [41]
SCD SSMOD	Porcine Model of peritoneal E. coli induced SSMOD [35]	Survival time advantage in SCD treatment group in this severe, non-survival model of sepsis, as well as hemodynamic index improvement [35]
SCD IRI	Canine Model of Ischemia Reperfusion Injury [41]	Reduction in extent of damage, edema and leukocyte infiltrate in peri-infarct zones for SCD treatment group [41]
SCD ALI	Porcine Model of Acute Lung Injury [41]	pO_2/FiO_2 ratio tended to be higher for SCD-treated group, with suggestion of fewer $CD11b^+$ ($CD11R3^+$) leukocytes in lung tissue [41]
SCD CPB(b)	Bovine Model of Cardiopulmonary Bypass [42]	Reduction in immature neutrophil influx, and maintenance of low total leukocytes, neutrophils and monocytes in circulation for the SCD group during the follow up period post-CPB [42]
SCD CPB(p)	Porcine Model of Cardiopulmonary Bypass [43]	Maintenance of low total leukocytes in circulation during the follow up period post-CPB, in the SCD-treated group [43]
SCD ARDS	Porcine Model of Acute Respiratory Distress Syndrome [41]	Reduction in resuscitation fluids and vasopressor requirements for SCD treatment group
Chronic models		
SCD T2D	Ossabaw porcine model of Metabolic Syndrome/Type 2 Diabetes [44]	Improved insulin resistance via HOMA-IR scores up to 2 weeks after SCD therapy [44]
SCD CHF	Canine Model of Chronic Heart Failure [41]	Increase in heart contractility for SCD treatment group assessed by ejection fraction [41]

monocytes to a patrolling, reparative phenotype. This shift thereby promotes immunomodulation of circulating monocytes from a degradative phenotype to a reparative, recovery subset [35, 48], enhancing tissue repair and functional recovery.

Leukocytes that adhere more avidly to the SCD appear to be more highly activated based upon analysis of the expression of the CD11b integrin on the surface of these cells. In an animal model of sepsis associated AKI, an immunomodulatory shift in the leukocyte population to a less inflammatory state is observed with SCD treatment, evidenced by reduced expression of the CD11b integrin marker on the surface of neutrophils in circulation, lower serum levels of myeloperoxidase, lower secretion of proinflammatory cytokines by isolated mononuclear cells and reduced emergence of immature neutrophils in the circulation [35]. Furthermore, in SCD-treated animals, the degree of both cardiovascular and renal dysfunction during sepsis was significantly reduced [35]. SCD therapy aims to treat AKI by ameliorating the degree of renal tubule cell injury through these immunomodulatory processes, whether the damage stems from a non-renal process (e.g., sepsis) or a renal derived hyperinflammatory condition initiated and potentiated from primary ischemic or

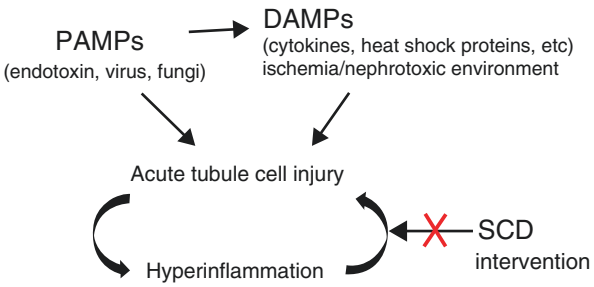

Fig. 14.2 Acute tubule cell injury promoted by any process: hyperinflammation or ischemia/nephrotoxins promote a worsening hyperinflammatory condition. SCD intervention diminishes the feedback cycle of continuing inflammatory injury to the kidney

nephrotoxic insult (Fig. 14.2). SCD intervention diminishes the feedback cycle of continuing inflammatory injury to the kidney, interrupting worsening hyperinflammation. This process elicits a systemic immunomodulatory effect different than simplistic leukocyte trapping and removal achieved by leukoreduction filters.

First in man studies for SCD were unintentionally completed during the acellular cohort testing in the RAD IIb study. However, since then, SCD has been used in several clinical studies in patients undergoing dialytic support for severe AKI as well as other acute indications (Table 14.2), including a Phase I/II study in AKI patients in China [36] and a Phase II multi-center trial in the USA [37]. Once integrated, SCD therapy is administered continuously with sequential replacement of the SCD every 24 h, and generally used for up to 7 consecutive days, but to date, has been used safely as long as 17 consecutive days. This continuous treatment is required to maintain the immunomodulation of circulating neutrophils due to the short half-life of circulating neutrophils, which is less than 24 h [49].

In a Phase III, multi-center, randomized, controlled, pivotal study to assess the safety and efficacy of SCD. In patients with AKI, the study was designed with two-arms: SCD-therapy integrated into CRRT circuits compared to contemporaneous patients being treated with CRRT alone (control). Both groups received RCA. The primary outcome measure was 60-day all-cause mortality. Secondary endpoints included RRT dependency at Day 60, and ventilator free days at Day 28. This trial enrolled 134 patients at 21 U.S centers. Each clinical site used their approved RCA protocol for anticoagulation of the extracorporeal circuit. The per protocol recommended ionized calcium (RiCa) intracircuit levels of 0.25–0.4 mm. Unfortunately, before the study had enrolled only 134 patients which was substantially less than half of the planned target, a national injectable calcium shortage occurred in the United States due to FDA concerns regarding the manufacturing procedures in the major supplier. This shortage resulted in some sites reducing the infusion rate of citrate to minimize calcium solutions to prevent hypocalcemia in patients, thereby resulting in RiCa above per protocol requirements below 0.4 mm and losing efficacy in SCD therapy. The calcium shortage was so severe that nine sites were not able to enroll due to lack of injectable calcium. Accordingly, the clinical trial was

paused, and an interim analysis undertaken on 134 enrolled patients. This analysis demonstrates no significant difference in any of the primary or secondary endpoints between SCD-treated subjects and controls. A post hoc analysis was undertaken to see if the key variable of RiCa had an impact on the endpoints of the study. Those patients whose circuit RiCa below 0.4 mm 90% of the therapy time had a substantially improved 60-day mortality rate in SCD-treated subjects compared to controls treated with conventional CRRT therapy: 16% (3/19) vs. 41% (11/27). The 60-day dialysis dependency was also improved with 0/16 survivors in the SCD-treated group versus 4/16 (25%) in the control non-treated group. A composite endpoint consisting of 60-day mortality or dialysis dependency between the two groups of patients was statistically significant ($p < 0.01$). Dialysis dependency following dialysis requiring AKI is considered a poor outcome due to the high probability of progression to end stage renal disease. In fact, large prospective trials in these types of patients have demonstrated an incidence of greater than 20% of survivors being dialysis dependent after 60 days or more of follow-up [50, 51]. In this regard, a supplemental IDE has been approved by the FDA for a follow-up on pivotal clinical trial with this composite endpoint as the primary outcome.

SCD has also been tested in pediatric patients with AKI (>15 kg, age up to 22 years) in a Phase II clinical trial. A multi-center trial of the SCD therapy to treat children with AKI and MODS receiving CRRT as part of standard of care was initiated under FDA-approved IDE G150179. In pediatric patients, mortality rates have historically approached 50% for those with AKI and MODS requiring CRRT [40, 52, 53].

The first adolescent patient treated with SCD was written up as a case study, which reports on the treatment course for an 11-year-old female with a severe reaction to propofol during an elective surgery that resulted in MODS [39]. After SCD treatment for only 24 h, improvements were seen with regard to the degree of liver injury and hematologic failure. After only 4 days of SCD therapy, lung function improved markedly, allowing for extubation. After SCD therapy for 7 days, kidney function was significantly improved. The patient was later discharged from the hospital with normal renal function [39] and did not require any follow-up dialysis treatments.

In this pediatric clinical trial, 16 pediatric patients have been treated with SCD. Favorable results have been observed with 12 of the 16 SCD treated patients surviving at 60 days. No deaths were associated with device treatment but were due to underlying illness or treatment interventions (post-op complications, extracorporeal membrane oxygenation (ECMO), viral myocarditis). All 12 surviving patients were dialysis independent. Treated patients ranged from 5 to 20 years old; admission diagnoses included: severe rhabdomyolysis (case study presented below), shigatoxin-associated hemolytic-uremic syndrome, community acquired pneumonia, multiple patients with AKI and/or septic shock. Patients generally received 3–7 days of SCD therapy, with one patient withdrawn from care after 11 h of SCD therapy. No SCD-related SAE were recorded [54]. Of importance, the FDA has recently designated the SCD as a Humanitarian Use Device with a pathway for Humanitarian Device Exemption for the treatment of pediatric patients with AKI.

In summary, the SCD has been tested in a number of clinical trials in adult patients with AKI requiring CRRT [32, 36, 37] and pediatric patients [39, 54], demonstrating an excellent safety profile with strong efficacy signals. However, despite promising preclinical data and early clinical data in pilot studies, clinical translation of the SCD has been hampered by the setback encountered during the Phase III multicenter, randomized, controlled, pivotal trial where injectable calcium shortage impacted the intended RCA protocol. This underscores an acknowledgment of the need for better designed clinical trials in the AKI/sepsis field including functional outcome measures that may be decoupled from mortality in heterogenous patient populations, and secondly, the importance of understanding the mechanism of action for proper device function, to ensure the proposed therapy may be beneficial to the sub-group of sepsis patients treated; common issues in clinical trial design in sepsis have been emphasized in reviews by Vincent et al. and Gomez and Kellum [55–57]. In the case of the SCD, maintaining a low iCa environment in the SCD therapy circuit in order to immunomodulate hyperinflammation and achieve efficacious treatment was demonstrated by mortality reduction and elimination of dialysis dependence at 60 days in the subset of patients maintaining RiCa. The combined functional outcome measure including dialysis dependence at 60 days is a more robust clinical measure and is already approved in the SCD-004 IDE protocol as an IDE supplement for Phase III trial. The immunomodulatory effect of the SCD on neutrophils and monocytes appears to have a critical role in reducing acute inflammation resulting in more rapid improvement of cardiovascular, pulmonary, and renal functions in SCD-treated multiorgan failure patients compared to controls. This effect also translates into a regulated repair and recovery of renal function as reflected in the lack of 60-day dialysis dependency in surviving patients after SCD therapy in trials to date. These clinical results, when viewed together with preclinical large animal studies (Table 14.3), reviewed more comprehensively by Pino et al. [41], suggest a beneficial treatment effect in multiple acute inflammatory conditions, as well as chronic inflammatory conditions involved with chronic organ dysfunction, suggesting utility of leukocyte processing in several other inflammatory disease indications.

14.6 Beyond AKI: Potential Impact of Immunomodulatory Devices for Other Kidney-Related Diseases

A focal non-renal inflammatory process, such as acute MI or pneumonia or pulmonary embolism, results in a localized inflammatory response but generally not a systemic inflammatory process with far-reaching sequelae. In contrast, when an AKI insult occurs, it results in loss of tubule immunoregulatory function so that a localized kidney injury develops into a systemic process due to a vicious cycle of incremental worsening inflammation. If a non-renal injury or infectious process is severe or secondary complications occur, such as developing hypotension, AKI often results. The progression to AKI requiring RRT is a reflection of failure of

standard medical care to limit a local inflammatory process such that peripheral organ injury ensues and continues propagating with extension to MODS. An immunomodulatory therapy may then be required for more complete RRT, attempting to halt the downward spiral of progressive inflammation, and worsening renal injury. Despite clinical observations that generally AKI patients have demonstrated a predisposition to go on to develop CKD, clinical trials utilizing the SCD in ICU patients with AKI have demonstrated that all survivors treated with the SCD were dialysis independent 60 days after treatment. In an Investigator-initiated trial of SCD used in ESRD patients for safety and bio-inflammatory assessment, no device-related SAEs were found due to SCD. The bio-inflammatory assay portion of testing showed SCD therapy promoted a shift in circulating monocyte population from predominantly $CD14^{hi}$ expressing MO at baseline/pre-SCD therapy to $CD14^{low}$ expressing MO post-SCD therapy [48].

Treating the hyperinflammatory process with the SCD has been demonstrated in preclinical large animal models (Table 14.3) to reduce the degree of AKI as hyperinflammation develops from various insults, including septic shock and cardiopulmonary bypass (CPB), common disorders associated with AKI [36, 43]. In CPB, leukoreduction filters have been previously utilized to help reduce cell-based hyperinflammation [58]. In SCD preclinical studies, reduction in injury biomarkers during treatment of organ dysfunction including heart and lung failure have been observed [35, 43] and have prompted several investigator initiated pilot clinical trials to assess impact of SCD therapy in patients with various types of organ dysfunction such as cardiorenal syndrome and hepatorenal syndrome. Related chronic indication clinical trials are listed herein (Table 14.4).

Recently, the FDA approved an IDE for SCD treatment of ICU patients with AKI and/or acute respiratory distress syndrome (ARDS)-associated COVID-19 infection. Evidence suggests that hyperinflammation with high concentrations of cytokines plays a critical role in the development of respiratory insufficiency and ARDS in COVID-19. SCD immunomodulatory therapy has been used in emergency/expanded use treatment of patients with refractory COVID-19 ARDS requiring ECMO. Two severely ill patients were selected for treatment based upon their declining clinical criteria and IL-6 levels greater than 100 pg/mL, a biomarker used to assess severity of hyperinflammation. In patient 1, the elevated IL-6 level before treatment was 231 pg/mL, which was reduced to 3.32 pg/mL within 52 h of SCD treatment initiation [59]. For patient 2, cytokine profile was greatly elevated with a pretreatment IL-6 level of 598 pg/mL, which was reduced to 116 pg/mL within 50 h of SCD therapy initiation [59]. Improved IL-6 levels corresponded with improvements in other inflammatory indices in both patients, including procalcitonin, D-dimers, lactate dehydrogenase, ferritin, C-reactive protein, and IL-10 [59]. Pulmonary edema was rapidly reduced, and vasopressors were discontinued within 30 h for both patients, after the start of SCD therapy. Patient 1 received a total of 17 days of SCD therapy and was taken off ECMO 20 days after initiation. Patient 2 was taken off both SCD therapy and ECMO after 16 days of therapy [59]. Both patients were subsequently extubated and discharged alive from the hospital.

Table 14.4 SCD clinical trials in chronic indications of organ failure

Clinical trial	SCD clinical trial description	ClinicalTrials.gov identifier	Key findings/outcome measure(s)
Phase I/II	Safety and bio-inflammatory assay study of SCD treatment in 15 ESRD patients. IRB approved as non-significant risk [48]		No device-related SAEs. Bio-inflammatory assay showed that SCD therapy promoted a shift in circulating monocyte population from predominantly CD14hi expressing MO at baseline/pre-SCD therapy to CD14low expressing MO post-SCD therapy [48]
Phase I/II	Myocardial stunning in ESRD patients requiring chronic hemodialysis with intradialytic hypotension or large intradialytic weight gain, recruiting	NCT03539861	1. Change in regional wall abnormalities identified on echocardiogram 2. (a) number of participants with an adverse event based on iCa measurement. (b) number of participants with an adverse event based on hemoglobin
Phase I/II	SCD treatment of patients with cardio-renal syndrome (CRS). The study will enroll eligible patients in the ICU with acute or chronic systolic heart failure and worsening renal function due to cardiorenal syndrome while awaiting LVAD implantation, recruiting	NCT03836482	1. Percent of patients with reversal of worsening renal function 2. 15 measures including urine production and urine analytes and respective clearances
Phase I/II	SCD treatment of patients with cardio-renal syndrome (CRS), no LVAD, recruiting	NCT04589065	1. Improvement in cardiac function—Left ventricular ejection fraction 2. (a) improvement in renal function by serum creatinine. (b) improvement in renal function by blood urea nitrogen
Phase I/II	SCD treatment of patients with hepatorenal syndrome (HRS), recruiting	NCT04898010	1. To evaluate the safety of daily 24-h SCD treatment in conjunction with CRRT and RCA for up to 7 days in ICU patients with AKI requiring dialysis due to HRS type 1 2. To evaluate the effect of SCD treatment to improve renal function, urine sodium excretion, and net volume removal. Liver function coagulation parameters along with MELD score will also be followed as per standard medical practice. The MELD score will be assessed before, immediately after and periodically after discontinuing therapy

14.7 Summary

Conventional filtration and sorbent therapies will continue to see utility in the management of AKI and MODS, including treating a vast number of cases that arise from sepsis, viral and toxic causes. However, emerging technologies, such as extracorporeal renal cell bioreactor-based bioartificial kidneys, and leukocyte-processing devices such as the SCD may see increased utility as they are developed further and become commercially available. Immunomodulatory therapies aim to treat AKI by reducing the degree of renal tubule cell injury, whether this damage stems from the non-renal hyperinflammation process or a renal derived hyperinflammatory condition, initiated and potentiated from primary ischemic or nephrotoxic renal tubule cell injury. Despite clinical observations that generally AKI patients have demonstrated a predisposition to go on to develop CKD, clinical trials utilizing the SCD in ICU patients with AKI have demonstrated that all survivors treated with the SCD were dialysis independent 60-days after treatment. This is in sharp contrast with the observed 25% incidence of ongoing renal support requirements in survivors receiving intensive dialytic therapy without SCD during these trials. Mechanistic details of immunomodulatory device impact on inflammatory diseases are still being fully elucidated; however, SCD has been demonstrated to impact the activity of neutrophils, which are key cellular players in acute inflammatory processes. Clinical data is mounting and suggests an effect of SCD to diminish ongoing organ injury and speed the recovery of organ function. This effect is most likely related to SCD-induced modulation of the immunologic responses controlling hyperinflammation as well as the regenerative repair processes responsible for functional recovery of organs, and specifically, kidney function. However, like many developing technologies for the treatment of AKI and sepsis, additional large, randomized, controlled, clinical trials with functional outcome measures are still required to provide evidence of clear therapeutic benefit.

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