The importance of volume overload, hemodialysis access and duration of time on effective therapy during renal replacement modalities

PhD Thesis

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Abbreviations:

aHR = adjusted hazard ratio

AV = arteriovenous (fistula or graft)

ABPM = ambulatory blood pressure monitoring

AKI = acute kidney injury

AKIN = acute kidney injury network

ANCOVA = analysis of covariance

AN-69 = a type of polyacrylonitrile dialysis membranes

Apache II = "Acute Physiology and Chronic Health Evaluation II": a severity-of-disease scoring system specific for Intensive Care Units

aPTT = activated partial thromboplastin time

ARF = acute renal failure

BIA = bioimpedance analysis (a.k.a. Bioimpedance Spectroscopy, BIS; or Body Composition Monitoring, BCM)

BMI = body mass index

BNP = brain-type natriuretic peptide

BP = blood pressure

BSA = body surface area

BUN = blood nitrogen

CBC = complete blood count

CHF = congestive heart failure

CKD = chronic kidney disease

CKD-EPI = Chronic Kidney Disease Epidemiology (formula to calculate estimated glomerular filtration rate)

CRP = C-reactive protein

CRRT = continuous renal replacement therapy

CV = cardiovascular

DOPPS = Dialysis Outcomes Practice Pattern Study

ED = Emergency Department

EDW = estimated dry weight

ESRD = end-stage renal disease

GI = gastrointestinal

GFR = glomerular filtration rate

HD = hemodialysis

HIV = human immunodeficiency-virus

ICU = Intensive Care Unit

IDWG = interdialytic weight gain

INR = international normalized ratio (of prothrombin time)

IV = intravenous

IQR = 25-75% interquartile range

KDIGO = Kidney Disease Improving Global Outcomes

KDQOI = Kidney Disease Outcomes Quality Initiative

Kt/V = single-pool urea clearance; dimensionless expression of dialysis adequacy

NKF = National Kidney Foundation (of the United States)

OR = Odds Ratio

PT = prothrombin time

RIFLE = risk/injury/failure/loss/end-stage (classification stages of Acute Kidney Injury)

RRF = residual renal function

RRT = renal replacement therapy

TDC = tunneled dialysis catheter

PD = peritoneal dialysis

UF = ultrafiltration

UFR = ultrafiltration rate

UMMC = University of Mississippi Medical Center

US = United States (of America)

VRWG = volume-related weight gain

WBC = white blood cell count

95% CI = 95% confidence intervals

1. Introduction

1.1. Preamble: the burden of end-stage renal disease world-wide

Survival for end-stage renal disease (ESRD) patients remains dismal and much below of their age-adjusted peers. We are far from being able to deliver true cure for chronic renal failure and our technology to replace the functions of the native kidneys is imperfect at best. During the care of these patients many issues remain insufficiently addressed and likely to contribute to adverse outcomes. At a time of increasing burden of chronic kidney disease (CKD) in the aging population and escalating load of prevalent ESRD patients, our specialty is under siege by shrinking reimbursement in the industrialized part of the world, inadequate resources and limitations of trained manpower in most places of the globe. Clinical nephrology training is demanding, requiring excellent cognitive skills and years of dedicated training to deliver optimal care; a competent nephrologist is much more than a "dialysis doctor". Yet, at the same time, interest in nephrology has reached an all-time low, a phenomenon observed world-wide (1, 2). Under such circumstances, we should judiciously re-assess the available resources, both societal and of the health care practitioners', to ensure the best possible care for our patients. Further, we should scrutinize existing knowledge and stimulate interest among trainees, both in research and clinical care, to maintain attraction for the specialty and seek new solutions for our ever-changing clinical problems. There is yet much to be learned about the care of these patients; call for action for all of us.

1.2 Importance of time during renal replacement therapy

Relying predominantly on small solute clearance (3), including single-pool urea clearance (Kt/V) and creatinine removal to define adequacy of renal dialysis constitutes perhaps the "original sin" of clinical nephrology. Historically, an adequate Kt/V was mediated by the combination of filter clearance and time spent on renal replacement therapy. With evolving technology, using larger surface area filters and higher flow rates, identical Kt/Vs have been re-created but within a much shorter time, leading to a potential deterioration of overall well-being and hemodynamical stability. In the largest dialysis trial to date, participants assigned to higher Kt/V with high-flux dialysis were more likely

to experience hypotension (4). Progressive decline of hemodialysis (HD) time was indeed the rule in the U.S. for most of the late 90s and the early 2000s; many limitations of reduced time with such approach were not sufficiently appreciated until the current decade. Among these are that Kt/Vs are not normalized for the body surface area (BSA), may impact smaller subjects differently (including women) (5) and do not account for differences in body compositions (6). It is virtually impossible to deliver identical clearance characteristics during an inherently discontinuous therapy (4 hours, three times a week) to replace the smooth 24-hour function of the native kidneys. The clearance of large-size uremic toxins will be primarily a matter of time spent on renal replacement therapy (RRT) (7-10). Several markers of uremia (phenylacetylglutamine, hippurate, indoxyl sulfate) maintain a markedly elevated level on chronic hemodialysis (x40-120) despite receiving what appears to be an adequate RRT (11, 12). During the care ESRD patients, the last 2 decades have witnessed an evolving shift from purely biochemical determinants of outcome (e.g. urea clearance, hemoglobin, phosphate and parathyroid hormone control) to a broader view emphasizing the use of fistulas, pre-dialysis nephrology care, and maneuvers to preserve residual renal function (13). Additional considerations are the length of effective dialysis received, the presence of inflammation with vascular access catheters and suboptimal compliance with dietary and fluid restrictions (14). As volume removal and ultrafiltration rates are almost impossible to disengage from dialysis duration in chronic outpatient dialysis, excess fluid gains and/or insufficient time on dialysis will result volume overload and worsening blood pressure (BP) control. Since the publication of our original publication on the importance of time during renal hemodialysis (13), significant advancement and new knowledge has accumulated on the subject and will be discussed in this current thesis.

1.3 Blood pressure control in hemodialysis patients

The current approach of excessive reliance on BP measurement at and around the time of the dialysis procedure to assess overall BP control is difficult to support (15). BP monitoring during HD is done primarily to ensure the safety of renal dialysis. Extreme caution should be exercised to extrapolate HD-associated BP to judge the efficacy of BP control in the outpatient setting (16). Optimal BP targets in dialysis patients are subjects

to debate (16) and the link between hypertension and poor cardiovascular outcomes is less clear than in the case of the general population. The assessment of BP for these patients comprises multiple limitations: the functioning arterio-venous (AV) grafts and fistulas in the upper extremities, the presence of peripheral vascular disease (17-19), inappropriately small BP cuffs in the obese (20) and misleadingly high BP immediately after clinic arrival pressure (21). Abrupt changes in fluid volume and plasma ion concentration during HD treatment will frequently predispose patients to erratic BP changes. In the largest controlled trial to date, those assigned to higher Kt/V were more likely to have hypotensive episodes (equilibrated Kt/V of 1.45 vs 1.05, 18.3% versus 16.8%; $p<0.001$) (4). On the other hand, BP stability at and around the time of hemodialysis confers a lower risk of mortality independent of the actual BP values and persisting through a 2-year follow-up period (22). Climatic circumstances may influence blood pressure but so may the interdialytic weight gain (IDWG): e.g., in one study, cooler temperatures were associated with higher systolic blood pressure, IDWG, and serum potassium values across the United States (23). Similarly, in a cohort of 100 ESRD subjects we also observed some influence of "hot and dry" environmental temperatures on IDWG (24).

Ambulatory blood pressure monitoring (ABPM) circumvents many problems of unit-derived BP measurements. It relieves the provider from the burden of making BP management decisions based on HD unit-based measurements, known to be highly inaccurate and heterogeneous across the population (25). It poses minimal inconvenience to the patients (26) and has better long-term reproducibility than casual blood pressure measurement in hemodialysis patients (27, 28). Abbreviated ABPM monitoring or a limited number of BP readings in the outpatient setting convey prognostic information similar to more extensive monitoring (29). Home BP self-recording assesses out-of-unit BP burden well (28), is easy to repeat and represents a simple and low-cost alternative to ABPM (16). Similarly to past studies, we also have demonstrated that the post-dialytic BP had a better association with 48-hour BP burden during ABPM than the predialysis BP (30). A recent paper by Agarwal et al. has explored the clinical utility of intra-dialytic BP recording in estimating the out-of-the-dialysis-unit BP load (31), conferring to the usual clinical practice of nephrologists to review intra-dialytic BP fluctuations when establishing the patients' ideal target weights. Significant practice variation exists across

countries with regard to the nephrologists being present during dialysis, conceivably compromising the practicability of this approach in many places (32).

1.4 Dry weight determination in hemodialysis patients

Defining the ideal volume status and weight continues to be a challenge in clinical practice dialysis (33-35). Elevated BP may or may not equate with hypervolemia. In brief, one needs to find a target or "ideal" weight where both symptomatic fluid overload before dialysis and hypotensive episodes during and after treatments are minimized to as little as possible. There have been many attempts to define such an optimal volume status via scientific, objective and reproducible means (36). The historical practice pattern (37) has been to "challenge" the patients' target weight by gradual escalation of ultrafiltration goals during renal dialysis and, as needed, re-administer IV fluids for hypotensive events and/or symptomatic hypovolemia. As crude as this practice pattern appears, little has changed in clinical practice over the last three decades and the concept of "physician-estimated dry weight" or "physician-declared dry weight" remained well-entrenched in textbooks. These maneuvers, however, can be very distressing to patients and create extra labor and alarm for the dialysis unit care staff (38). Dry weight, probed to a symptomatic threshold (37) causes not only hypotension but also sympathetic activation, potentially triggering acute cardiovascular and vascular access events (39). Repetitive end-dialytic weight below estimated dry weight (EDW) is associated with worsened survival (40). Additional concerns for such an approach are ischemia in the mesenteric (41) or peripheral vascular supply territories (42), both of which could carry a high mortality rate. Further complicating care is the fact that in certain countries (e.g. U.S.), shortage of physicians and the reimbursement paradigm do not provide an incentive for clinicians to be present during RRT and assess intra-dialytic BP changes during the sessions (32). Hence, variation of ultrafiltration goals will be determined by mid-level providers or worse, the dialysis nurse on site. Physicians may have limited time, if some, to review care charts of RRT sessions.

1.5 The interaction between volume status and blood pressure: limitations of physical examination to assess volume status

Establishing the optimal volume status is exceedingly difficult in the multiple co-morbid ESRD cohort. The physical examination may have severe limitations in assessing the necessary or, more importantly, the possible tolerated amount of ultrafiltration (43). Similarly to time on hemodialysis, volume management has not received sufficient attention by decision-maker parties of ESRD-care until very recently (44). Fluid overload is associated with a graded elevation of blood pressure before dialysis (45) and excessive interdialytic fluid gains are associated with worsened survival (46, 47). Clearly, escalating anti-hypertensive therapy alone is insufficient (48-50) without addressing the extracellular fluid space expansion (6, 51, 52), the root cause of hypertension among these subjects. On the other hand, aggressive volume control may accelerate the development of full anuria (53), further compromising downstream management for these patients. At both two extremes, in volume depletion-related hypotension and hypotension induced by excessive ultrafiltration with large IDWGs, physicians may respond by increasing the estimated dry weight; however, in the latter case this would only escalate the volume-overloaded state further (54). Accordingly, it is critical to be able to determine the relative contribution of volume overload to elevated blood pressure in a reproducible, observer independent, standardized manner. The judicious challenge of the target weight remains an important element of blood pressure management in daily practice of nephrology at present time (52, 55). Clearly, a subset of patients have volume-independent hypertension (56) and these subjects need to be identified, as well. Available tools include imaging procedures (chest ultrasonography, inferior vena cava diameter assessment, echocardiography), biomarkers such as atrial and B-natriuretic peptides (38) and, more recently, bioimpedance analysis (BIA) (6, 38, 57, 58) and blood volume monitoring (59, 60).

1.6 Inflammation and C-reactive protein

C-reactive protein (CRP) is an acute phase protein, clinically attractive as an in vivo bioassay to gauge the overall degree of inflammation (61). Elevated CRP has also emerged as a non-traditional risk factor for adverse cardiovascular outcomes in the

general population, potentially adding to conventional vascular risk assessment for non-renal patients (62, 63). The relationship between CRP and hypertension is directional: hypertension is not only associated with elevated CRP in non-renal patients (64), but among normotensive subjects, elevated CRP increases the future risk of hypertension (65). Elevated CRP levels are associated with cardiovascular (CV) disease and mortality (66-68), sudden cardiac death (67) and stroke (69), possibly mediated through an association with preclinical (70) or manifest atherosclerosis (71). The presence of access type has a profound impact on the CRP level in dialysis patients (72). Albumin - historically viewed as a purely "nutritional" marker - is perhaps better viewed as a "negative acute phase" protein and known to correlate inversely with CRP (73, 74). Low albumin is associated with increased mortality (75-77) and serum albumin is low in about half of the hemodialysis patients (78-80) despite what one would consider an "adequate" dialysis by Kt/V-based criteria. A substantial number of these patients have elevated CRP (81). In summary, both serum albumin (82-85) and CRP (86-89) are known to correlate with inflammation and mortality in ESRD patients. Unlike in the case of CRP, the implication of elevated cardiac troponins in this population is not well understood (88). Subtle troponin-I elevation has been associated with worse CV outcomes in ESRD and occasionally has been ascribed to the ESRD status alone. Many of these patients with clinical symptoms (e.g., chest pains, shortness of breath or fever) will also receive measurements of commonly utilized biomarkers looking for myocardial damage and inflammation during Emergency Department (ED) evaluation. To what degree elevated troponin-I may reflect true myocardial damage or being a sign of an underlying infection is not well-defined to date.

1.7 The importance of vascular access catheters

Vascular access dialysis catheters are life-saving during the care of dialysis patients when urgent RRT is needed and an arterio-venous (AV) fistula is not immediately available (90). While regular (non-tunneled) dual-lumen catheters can be used for the hospitalized patients, tunneled (occasionally referred to as "tunneled-cuffed") dialysis catheters (TDC) are preferentially utilized in ambulatory settings (91). These catheters have the advantage of securing themselves into the subcutaneous tissue with a specific

type of polyethylene "cuff," eliciting soft tissue growth and scarring while increasing the exit site's resilience to infections (92). Nonetheless, they represent an inferior access modality (72, 93-96) and are linked to increased mortality (97-100) when compared with traditional AV fistulas or even AV grafts. The Dialysis Outcomes and Practice Patterns Study (DOPPS) II has demonstrated that a 20% increase in the use of a dialysis unit catheter was associated with a 16% increase in mortality risk (101). A later study confirmed that less frequent catheter and graft use is associated with improved patient survival (102). Bacterial colonization of these catheters is in fact common (103) and may adversely impact residual renal function (104) and sooner or later lead to manifest infectious events (105-107). In practical effect, the cumulative duration of the catheter itself represents the largest risk factor for a catheter infection (108, 109) and limiting the catheters' presence to the shortest time possible requires the care provider's vigilance and commitment. Up until now, the literature on long-term dialysis catheters was focused on circumstances of placement (110-112), optimizing patency and function (107, 113, 114), as well as prevention of infections (115-118). On the other hand, circumstances and indications of TDC removal were less well understood or studied. Historically, the removal of these catheters was felt to be a surgical or an interventionalist's task and, up until recently, very little has been published on bedside removal of TDCs by non-interventional nephrologists.

1.8 Adherence

Adherence (compliance) is a critical issue for successful care in dialysis patients. Adherence to dietary salt and water restrictions will influence weight gains and the stability of blood pressure, both during and off renal replacement therapy. Compliance with dietary restrictions would translate into IDWG, determining the ultrafiltration rate and, to large degree, the expected hemodynamic burden of the next hemodialysis session. Major variations exit among dialysis cohorts regarding adherence, perhaps best documented through the DOPPS (119), an international collaboration collecting data on care and practice patterns among Japanese, European and American dialysis patients. The DOPPS collected data on adverse prognostic markers (120), including phosphate control, IDWG and the number of unattended or significantly (≥10 minutes) shortened dialysis

sessions per month (119). In clinical practice, one has to realize that the relationship between mortality, morbidity and behavior is more closely related to shortened and non-attended sessions than to the achieved control of phosphate and potassium (120, 121). Short but repetitive early terminations of HD sessions are not innocent events and can lead to adverse clinical outcomes (120, 122). Of concern are the Southern dialysis networks in the United States, having higher degrees of adverse outcomes despite improvements in overall healthcare delivery. Our own published experience from the Northwestern Louisiana found striking nonadherence the rule, rather than the exception: 85.9% of patients shortened at least one hemodialysis session and 29% skipped at least one hemodialysis session per month (123). Repetitive volume overload will be associated with increased mortality and will lead to large changes in BP during dialysis sessions (124, 125). BP variability is known to be the highest on the first day of the week after the long, three-day period off RRT (126). Dialysis alone may not be the only answer and, perhaps not surprisingly, in the largest controlled trial to date (HEMO trial), those assigned to higher Kt/V (1.45 vs. 1.05) experienced more hypotensive episodes (18.3% versus 16.8%; $p<0.001$) (4). Compliance with the prescribed loop diuretic regimen helps to reduce IDWG between sessions (127, 128), further reducing the expected hemodynamic burden of net ultrafiltration during the following dialysis session. Additional potential maneuvers to decrease hemodynamic fluctuations include decreasing dialysis temperature (129) or, alternatively, increasing session lengths during RRTs (13). We could not gather affirmative evidence for anecdotal claims of excessive fluid intake precipitated by hot or humid weather in a relatively small, single-center study of 100 patients from Central Europe (24). In summary, conclusions from large-scale studies may not be uniformly applicable to select subpopulations of patients (94, 102, 119, 130) and thus, local patterns of suboptimal treatment compliance impact hemodynamic stability and ultrafiltration (UF) burden during dialysis sessions.

1.9 Definition of Acute Kidney Injury: limitations of serum creatinine

The current classification theme of the acute impairment of renal function is heavily dependent on assessment of serum creatinine [Table 1]. However, the practical value of creatinine is much limited in the setting of positive fluid balances and dilutional

effects on creatinine (131-133) and different cut-off values may apply to start renal replacement technologies in critically ill. Volume overload, when massive, may completely mask the rise of serum creatinine and markedly underestimate the degree of renal functional impairment. Chronically ill, wasted patients may have a low muscle mass and creatinine generation rate (134); on the other hand, muscle injury and rhabdomyolysis may lead to disproportionate creatinine elevation in anuric subjects. Accordingly, interpretation of serum creatinine in critically ill may be markedly different from outpatients. As we stated in our recent review paper highlighting limitations of measured serum creatinine in acute kidney injury (AKI), along with calculated glomerular filtration rate (GFR):

> "To some degree, the current thinking is captive to an era, viewing integrity of renal homeostasis as "kidney function percent", a conceptual thought further reinforced by the emergence of automated glomerular filtration calculations (e.g., Modification of Diet in Renal Disease and CKD-EPI formula-based equations). When calculating fractional decline of renal function, only filtration is considered, assuming that decline of all other functions of the human kidney would be parallel to the decline of GFR - an assumption obviously not always taking place in terms of other indices, for instance, volume overload and hemodynamic status. Such thinking, however, applies even less to the setting of AKI in critically ill patients. As reasonable as progressive decline of GFR can be described in gradual CKD progression between the 15-60 mL/min/1.73 m^2 GFR range, clinical experience shows it to be inadequate when trying to define trigger points for clinical uremia in a catabolic state or need for RRT for volume-related indications. Such thinking applies even less to the setting of AKI in volume overloaded or critically ill patients. An observed serum creatinine may have little relevance in a wasted subject with low muscle mass, generalized edema and prolonged respiratory failure with difficulty in weaning (134) Volume overload, when massive, may completely mask the rise of serum creatinine and/or markedly underestimates the degree of renal functional impairment."(135)

1.10 Fluid therapy in critically ill

Since the early 2000s, early goal-directed therapy in sepsis has been the general rule (136), creating a practice pattern of aggressive volume resuscitation in Intensive Care Units (ICU) (137). However, an early study of successful goal-directed therapy to optimize mixed venous O_2 saturation by Rivers et al. (138) was not replicated in

subsequent large, multi-center trials (139, 140). Volume load with isotonic saline promotes a non-anion gap metabolic acidosis, potentially contributing to increased mortality (141). Additionally, neither the use of albumin (142, 143), nor hydroxyethyl starch preparations (144-146) appear to be more effective than isotonic saline expansion alone. If anything, there is a potential for harm, including more RRT needed in hydroxyethyl starch recipients (147, 148). In comparison with historical approaches - which avoided bicarbonate administration - recent trends favor administering bicarbonate-containing fluids (149). Indeed, volume replacement with bicarbonate-containing solutions resulted in a decreased occurrence of elevated creatinine and Risk-Injury-Failure-Loss-End-Stage (RIFLE) staging "injury" or "failure" stage in a prospective, in a prospective, open-label, sequential period pilot study from Australia (149), further supported by a systemic network meta-analysis in 2013 (148). All these studies are raising the possibility that that fluid composition itself is less important than the degree of volume overload developing during a critical illness, especially in those with renal failure.

1.11 Renal replacement therapy in Intensive Care Units

Renal replacement therapy in ICUs continues to represent an ongoing clinical challenge, including the inherent difficulties identifying the "optimal" filling pressures for these patients. They represent an especially vulnerable group of patients with a high mortality rate, where AKI is particularly harmful when occurring as part of multi-organ failure (151, 152). In those with volume-depleted state, early administration of sufficient IV volume replacement is critical to reverse tissue hypoperfusion and impact subsequent prognosis (138). Standard operating practice involves the administration of 20–30 mL/body weight kg IV crystalloids over a 30-minute period, further repeated as necessary. However, over-aggressive volume resuscitation is also harmful and fluid overload has been associated with increased morbidity and mortality in patients with acute respiratory distress syndrome (153, 154), sepsis (155), in surgical ICU patients (156, 157) and those with abdominal compartment syndrome (158, 159). In a large observational clinical trial, persistently negative fluid balance was associated with improved outcomes during critical illness (mean daily fluid balance: -234 mL/day vs +560 mL/day among

non-survivors vs. survivors, p<0.0001) (160). Among children with renal failure, initial pediatric studies established that fluid overload at the initiation of continuous renal replacement therapy (CRRT) was associated with increased mortality (161-163). Among

Table 1. Kidney Disease Improving Global Outcomes (KDIGO) definition and classification of Acute Kidney Injury (AKI)(150)

KDIGO Stage[a]	**Serum Creatinine Increase**	**Urine Output Criteria**[d]
1	1.5–1.9 times baseline[a] or ≥0.3 mg/dl (≥26.5 mmol/L) increase[b]	<0.5 ml/kg per hour for 6–12 h
2	2–2.9 times baseline	≤0.5 ml/kg per hour for ≥12 h
3	3 times baseline or increase in serum creatinine ≥4 mg/dl (≥353.6 mmol/L) or initiation of renal replacement therapy[c] [in patients aged ≤18 years, decrease in estimated glomerular filtration rate to ≤35 mL/min per 1.73 m^2]	≤0.3 ml/kg per hour for ≥24 h or anuria ≥12 h

[a]Serum creatinine increase is known or presumed to have occurred within the prior 7 days.

[b]Serum creatinine to have occurred within any 48-hour period.

[c]For patients reaching stage 3 by serum creatinine >4 mg/dl, rather than require an acute rise ≥0.5 mg/dl over an unspecified time-period, KDIGO requires that the patient first achieve the creatinine-based change specified in the KDIGO AKI definition (either ≥0.3 mg/dl within a 48-hour time window or an increase of ≥1.5 times baseline within 7 days).

[d]Urine output criteria are identical to the corresponding risk/injury/failure/loss/end-stage (RIFLE) and Acute Kidney Injury Network (AKIN) stages.

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children with renal failure, initial pediatric studies established that fluid overload at the initiation of CRRT was associated with increased mortality (161-163). In adult ICU cohorts, AKI non-survivors had a more positive fluid balance than the non-survivors (164, 165). On the other hand, the impact of the RRT in this context was not well studied until recently and it remains uncertain whether CRRT can meaningfully influence prognosis. In our former paper, we observed better outcomes in those with shorter wait-time before CRRT and in those with impaired baseline creatinine (166). Further, the change in creatinine between admission and the initiation of CRRT (but not creatinine at initiation) was statistically different between survivors and non-survivors (1.6 vs. 2.6 mg/dL, p=0.023) (166). Unlike chronic RRT patients, critically ill renal patients are much more heterogeneous with an acute component of renal dysfunction, further complicating the interpretation of serum creatinine. The presence of an indwelling vascular catheter (rather than an AV fistula) is the rule, rather than an exception in these patients. In addition to the importance of time on RRT and hemodialysis access issues, the presence of comorbid fluid overload is another difficult clinical issue to address. Considering the above, there is a critical need to re-assess the impact of volume overload in critically ill patents, especially as it pertains to the trigger point of initiating RRT.

2. Objectives

Certain clinical problems are both unique and pervasive in patients receiving RRT. These include volume overload, a frequent problem in ESRD patients on maintenance dialysis and a potential acute complication of AKI. Time is of the essence both during CRRT (maintaining integrity and patency of extracorporeal circuit) and during maintenance dialysis (prescription of appropriate duration of therapy to provide both uremic control and volume control) to minimize hemodynamic stress in these patients. Catheter use has remained prevalent and in fact escalated in dialysis patients over the last several years. Finally, the patients' willingness to adopt the appropriate lifestyle as well as the dietary and time-commitment limitations remains the ultimate limiting factor for any prescribed medical regimen in ESRD. These clinical concerns are not entirely independent of each other, but rather represent interrelated issues: e.g., dietary non-compliance leads to fluid overload and excessive UF during dialysis; the presence of a catheter leads to elevated inflammatory markers and poses the risk of infection, which in turn may lead to hypotension and excessive fluid resuscitation. My subsequent Ph.D. thesis examines my clinical research on several of these clinical concerns.

2.1 Volume-related weight gain in the Intensive Care Units study

Literature emerging around the middle of the first decade of the 21st century strongly suggested an adverse impact of volume overload in surgical settings for adults and in critically ill children with AKI. On the other hand, the impact of volume overload in adults with AKI was little explored at that time. Since fluid overload is associated with decreased survival in non-renal patients, we hypothesized that larger volume-related weight gain (VRWG) prior to RRT may be associated with higher mortality in critically ill AKI patients treated with CRRT (167).

Specific research goals:

1. To determine the degree of volume overload experienced in a cohort of critically ill patients before being started on CRRT.
2. To examine the association of VRWG with subsequent outcomes in these critically ill patients.

2.2 Dialysis prescription and inflammatory markers on chronic hemodialysis study

Unlike in AKI patients, the source of fluid overload in ESRD patients is not exogenous IV fluid but represents the dietary intake of both salt (sodium-chloride) and water. Time spent on maintenance dialysis, both for the patients and providers' convenience, became progressively reduced in the era of high-flux dialyzers by the early 2000s and time itself turned into a relatively neglected clinical parameter. Large and indiscriminate salt and water intake would lead to large IDWG, especially when time available for treatment is reduced. Under these circumstances, IDWG, hourly UF rate and time spent on renal dialysis represent a triangle of interconnected parameters, further determined by the patients' compliance. Our initial review on the subjects suggested a potential adverse effect of reduced time in ESRD patients receiving maintenance RRT, including an impact on markers of inflammation, such as CRP and albumin (13). Since treatment time and ultrafiltration-rate (UFR) both correlate with patient survival (168), we hypothesized that long treatments with a slow UFR may also influence the control of inflammation on dialysis (169).

Specific research goals:

1. To examine the association of time on chronic hemodialysis on serum CRP and albumin.
2. To examine the association of hourly UF rate on chronic hemodialysis with serum CRP and albumin levels.

2.3 Bedside removal of permanent hemodialysis access catheters studies

Permanent or semi-permanent (long-term) intravascular access catheters became routine from 1990 on and escalated in the last two decades in dialysis patients. These foreign materials create a state of low-degree inflammation and contribute to excess infectious risk and mortality in ESRD patients (97-100). Since prolonged duration of TDCs represent profound risk factors for adverse outcomes, we wished to examine the circumstances, indications and clinical success rate of an emerging nephrology procedure, the bedside removal of these catheters. Our study hypothesis was that bedside removal of TDC by a nephrologist is safe and effective, both for in- and outpatients and when

performed by physicians during graduate medical education training (114, 170). Our secondary objective was to examine the associations between select biomarkers (CRP, troponin-I) and clinical indications for TDC removals in our inpatient cohort (114).

Specific research goals:

1. To determine success rate with bedside removal of TDCs, including the safety and efficacy and complication rates of such procedure in both inpatient and outpatient settings.
2. To examine the impact of vascular access catheters on certain serum biomarkers (CRP, troponin-I) in patients undergoing removal of these semi-permanent vascular access catheters.

3. Methods

My proposed thesis will be supported by my existing publications on the subject (114, 167, 169, 170). Herewith, I would like to review the Materials and Methods of the studies I have utilized to develop this thesis, including one study examining the importance of volume-related weight gain before CRRT (*Volume-Related Weight Gain and Subsequent Mortality in Acute Renal Failure Patients Treated with Continuous Renal Replacement Therapy*. ASAIO Journal 2010 (Jul-Aug); 56(4): 333-7) (167), an another study examining the cross-sectional associations of inflammatory markers with treatment time during conventional hemodialysis (*Correlation of Treatment Time and Ultrafiltration Rate with Serum Albumin and C-reactive Protein Levels in Patients with End Stage Kidney Disease Receiving Chronic Maintenance Hemodialysis: A Cross-Sectional Study*. Blood Purification 2010 (July); 30:8-15) (169) and two studies on TDC removal (*The Safety and Efficacy of Bedside Removal of Tunneled Hemodialysis Catheters by Nephrology Trainees*. Renal Failure 2013 (October); 35 (9): 1264-1268; *Tunneled Hemodialysis Catheter Removals by Non-Interventional Nephrologists: the University of Mississippi Experience.* Seminars in Dialysis 2015 (Sept-Oct); 28(5): E48–E52) (114, 170). The right to re-publish has been obtained from the journals and the publishers. Additionally, several other publications from our research groups will be reviewed or discussed, when appropriate.

3.1 Volume-related weight gain study

3.1.1 ***Study population***

We analyzed demographic, clinical and survival data from an observational, single-center registry of 81 patients treated with CRRT at the University of Mississippi Medical Center (UMMC), Jackson, MS (United States of America) over an 18-month period from January 2003 to June 2004. The study population consisted of all adult patients (age 18 or greater) with AKI admitted to the medical, cardiac, surgical, and cardiothoracic ICU of UMMC and treated with CRRT during the study's period. After obtaining Institutional Review Board approval, the patients were prospectively enrolled into the study during or shortly after an initial nephrology consultation. A written consent

of participation was obtained from the patients or their immediate family. Indications for initiating CRRT included fluid overload and metabolic derangements refractory to conservative management, usually with associated hemodynamic instability. The timing and decision to initiate CRRT as well as the prescribed dose and modality of CRRT were at the discretion of the faculty attending nephrologist and the majority of the subjects received continuous veno-venous hemodiafiltration. All CRRT sessions were performed using Gambro Prisma (Gambro AB, Stockholm, Sweden) CRRT machines using AN-69 polyacrylonitrile dialysis membranes. Patients were excluded if they had preexisting ESRD or if the time from the onset of AKI to the initiation of CRRT was two weeks or greater. The general characteristics of our study cohort and their association with mortality are shown in Table 2. and described in detail in our previous study (166). The principal outcome was mortality on day 30 (167).

3.1.2 ***Definitions and variables of interest***

The patients were considered to have AKI if their serum creatinine increased by 0.5 mg/dL (44.2 μmol/L) or greater from baseline or if they had an abnormal serum creatinine at the presentation with no known baseline value. Data on the patients' creatinine level were collected at the initiation of CRRT. We also recorded the change in creatinine level from hospital admission to the initiation of CRRT and the dose of CRRT. The days waited were the number of days from the diagnosis of AKI to the initiation of CRRT (167). The patients' weights were documented in a variety of settings: ED, regular nursing floors, and the ICUs; in all cases, the first documented weight available on the hospital record was taken as the initial weight; the majority of these was registered only in the ICUs. Standard hospital scales were used for the ambulatory patients and bed scales for the non-ambulatory or ICU patients. Subsequent daily weights in ICUs were monitored with bed scales by the nursing staff of the unit and recorded on daily care charts. In our study, we have defined VRWG as the difference between the initial (first available) weight and the weight at the initiation of CRRT. Weight gain percentage (%) was interpreted as a difference in percentage between the initial weight and weight obtained at the initiation of CRRT. Oliguria was not defined according to the current weight-based Acute Kidney Injury Network (AKIN) standard; instead, by an average urine output of less than 20 mL/hour for at least 12 hours before study enrollment.

Table 2. Baseline Characteristics of the University of Mississippi CRRT Cohort Stratified by Mortality (N = 81) (166)

Baseline Characteristics means (SD) or %	Survivors	Death	*p*
Sample size			
All patients, *n*	40	41	
Baseline creatinine established, *n*	27	33	
Demographics			
Age, *years*	49.4 (16.7)	53.4 (16.6)	0.287
Gender, *female*	12 (30.0%)	12 (29.3%)	0.943
Apache II[a]	26.7 (7.2)	28.4 (6.5)	0.271
Creatinine (mg/dL)			
Baseline	1.4 (0.8)	1.1 (0.3)	0.088
Admission	3.8 (3.5)	2.1 (1.9)	0.011
CRRT initiation (InitCr)	5.3 (2.5)	4.8 (1.8)	0.304
Change in creatinine (mg/dL)			
InitCr – Admission Cr	1.6 (1.9)	2.6 (1.9)	**0.023**
InitCr – Baseline Cr	3.0 (2.0)	3.6 (1.6)	0.207
% change in creatinine[b]			
InitCr – Admission Cr	165% (209)	223% (197)	0.214
InitCr - Baseline Cr	291% (243)	340% (174)	0.379
CRRT dose (mL/kg/hour)[c]	21.1 (10.2)	24.5 (12.6)	0.187
Days waited[d]	3.2 (2.7)	4.2 (3.2)	0.137
Sepsis	25 (61.0%)	23 (56.1%)	0.558
ARF type			
Inpatient ARF	14 (43.8%)	18 (56.3%)	
Outpatient ARF	2 (16.7%)	10 (83.3%)	
ARF on Chronic Kidney Disease	11 (68.8%)	5 (31.3%)	
ICU service type			0.205
Surgical ICU	9 (22.5%)	7 (17.1%)	
Cardiothoracic ICU	10 (25%)	4 (9.8%)	
Cardiology ICU	3 (7.5%)	6 (14.6%)	
Medical ICU	18 (45%)	24 (58.8%)	

The conversion factor for serum creatinine in mg/dL to μmol/L is 88.4. Abbreviations: ARF, acute renal failure; Cr, creatinine; CRRT, continuous renal replacement therapy; ICU, Intensive Care Unit; InitCr, creatinine at CRRT initiation

[a]Apache II scores were calculated at time of renal consult.

[b]Percent change in creatinine was computed by either 100% x (InitCr - AdmCr)/AdmCr or 100% x (InitCr - BLCr)/BLCr.

[c]CRRT was the prescribed CRRT dose in mL/kg/hour. Continuous veno-venous hemofiltration was prescribed pre-filter dosing.

[d]Days waited was the number of days from first 0.5 mg/dL elevation in serum creatinine to initiation of CRRT.

The diagnosis of sepsis was a clinical diagnosis as stated on the medical record and Acute Physiology and Chronic Health Evaluation Apache II scores were calculated at the time of the renal consult was obtained (167).

3.1.3 ***Statistical methods***

Data on patient characteristics are shown as mean ±standard deviation (SD) for continuous variables or percentages for categorical variables. The primary goal of the study was to examine the effect of various cut-off net fluid accumulations, that is VRWG ≥10% or ≥20% and oliguria as variables associated with mortality. VRWG ≥10% patients were compared to those that gained <10%. In a separate analysis, those who gained ≥20% were compared to those gaining < 20%, <10% or between ≥10 and <20%. Additional variables included age, sex, chart diagnosis of sepsis, Apache II scores, CRRT dose, creatinine level at the initiation of CRRT, absolute change form of creatinine, days waited and ICU location. A cross-sectional analysis of selected variables was conducted to identify correlates with mortality. Chi-square tests were used for bivariate analyses of correlations between selected variables and mortality. Independent *t*-tests were performed to assess the correlations of continuous variables with mortality. Multivariate logistic analyses were conducted for more complex correlations. The data were analyzed using SPSS version 16 (SPSS Inc., Chicago, IL) and Minitab (version 13; Minitab Inc., State College, PA) (167).

3.2 Dialysis prescription and inflammatory markers on dialysis study

3.2.1 ***Study population***

We have undertaken a cross-sectional study in a network of 12 hemodialysis centers including all Diaverum Hemodialysis Units in Hungary and the University of

Mississippi Medical Center outpatient hemodialysis unit in Jackson, Mississippi, USA. All patients receiving in-center maintenance hemodialysis three times a week were recruited for the study. Dialysis centers collected data from patient charts and local databases originally established for purposes of quality control. Patient- and dialysis-related characteristics, comorbidity diagnoses, acute events, medication use, and other covariates were extracted in July, 2007. The study was approved by the UMMC Human Research Office and the Office of Scientific Officer of Diaverum, Inc (169).

3.2.2 ***Definitions and variables of interest***

Age was the number of full calendar years completed since birth. Sex was self-reported and either male or female. Ethnicity was either Caucasian or African American. Comorbid conditions, such as diabetes mellitus, coronary artery disease, congestive heart failure (CHF) and human immunodeficiency-virus (HIV) positive state were recorded if listed in the medical records. Medical records were updated within the month of data collection. The dialysis vintage was the number of completed months since starting renal replacement therapy on dialysis. EDW was the physician-prescribed ideal weight. Kt/V was defined as the single-pool urea clearance reported by the dialysis provider health information network. An acute infectious or coronary event was acknowledged based on the medical record during the index month. The presence of residual renal function (RRF) was defined as evidence of at least 200 mL urinary output in a 24-hour urine collection within 3 months of July, 2007. Treatment time was defined as the average length of dialysis sessions in minutes recorded during the index month. The UF rate was defined as the hourly volume removed in mL per kg of body weight (mL/kg/hour) according to the DOPPS (168) and averaged over the index month**.** Serum albumin and CRP were measured as part of the routine care. Albumin was measured by Bromocresol green methods (Diagnosticum Zrt., Hungary; Spectra Laboratories, USA) and reported in gm/L or gm/dL. CRP was measured by immunoturbidimetric assay and reported as either < 5 mg/L, any numerical value above 5 mg/L (Spectra Laboratories, USA) or numerical values both below and above 5 mg/L (APTEC, Belgium) (169).

3.2.3 ***Statistical methods***

Data on patient characteristics are shown as mean ±SD for continuous variables or percentages for categorical variables. Serum albumin and CRP were used as continuous

variables in the analysis of covariance (ANCOVA) models and categorized as bivariate during logistic regression. In our study, we dichotomized *a priori* albumin values at 40 gm/L (approximate mid-normal range value) with albumin > 40 gm/L designated as a favorable outcome for purposes of logistic regression analysis; conversely, albumin ≤ 40 gm/L was designated as low albumin or failure to reach normal albumin levels. Similarly, CRP was dichotomized at 5 mg/L, with CRP ≤ 5 mg/L being designated as a favorable outcome, CRP > 5 mg/L as failure. Potential factors associated with inflammation were tested in Analysis of Covariance (ANCOVA) models. An initial model of 23 variables included age, sex, ethnicity, vascular access, dialysis vintage, RRF, dry weight, comorbidities, medications (statins, aspirin, vitamin-D analogues, phosphate binders, calcimimetic), Kt/V, type of dialyzer, treatment time and UF rate. These parameters are otherwise identical to the ones listed in Table 3. (169). In a subsequent analysis, the initial set has been narrowed down to 15 variables as follows: age, sex, ethnicity, vascular access type, dialysis vintage, dry weight, diabetes mellitus, coronary artery disease, CHF, HIV infection, acute coronary event, acute infectious event, Kt/V, treatment time and UF rate. Logistic regression models were constructed to calculate Odds Ratio (OR) with 95% confidence intervals (CI) predicting favorable outcomes of CRP and albumin. Treatment time was dichotomized at four hours and entered into logistic regression modeling as a categorical variable of > 4 hours for "long" treatment time and ≤ 4 hours for "short" treatment time. The initial logistic regression model operated with the same 15 independent variables as the second ANCOVA model. Stepwise selection was applied in logistic regression modeling to assess the individual contribution of major predictors. As neither of the dependent parameters were found to be normally distributed, the non-parametric Mann-Whitney test was also utilized to establish ranks between longer than 4-hour treatment time and less than 10 mL/kg/h UF rate with favorable outcome in serum albumin and CRP levels. All statistical analyses were performed using SPSS 16 (SPSS Inc., Chicago, IL) (169).

Table 3. Population and treatment characteristics (169)

Demographic characteristics:	
All data/partial missing data:	616 / 103
Age (years):	60.9 ±14.4
Gender (M/F) %	52.1% / 47.9%
Ethnicity (African-American/Caucasian) %	18.2% / 81.8%
Vascular Access (NF/TDC/TC/AVG)* %	67.0% / 19.3% / 7.6% / 6.0%
Dialysis Vintage (months):	46.2 ±44.8
Residual Renal Function (≥ 200 mL) %:	57.6%
Estimated Dry Weight (kg):	72.3 ±17.3
Comorbidities:	
Percent of patients having comorbidity (n=616)	
Diabetes Mellitus	35.2%
Coronary Artery Disease	19.3%
Congestive Heart Failure	43.7%
HIV** Infection	1.3%
Active Smoking	24.5%
Acute Coronary Event	4.7%
Acute Infectious Event	12.9%
Dialysis treatment characteristics:	
Treatment Time (min)	237.3 ±23.8
Ultrafiltration Rate (mL/kg/hour)	7.05 ±4.05
Kt/V:	1.50 ±0.34
Dialyzer***:	F-180NR or F200NR in 1 center vs. Polyflux 17 or Polyflux 21 in 11 centers

***Choice of dialyzer and ethnicity almost completely overlapped

Medications:	
Percent of patients taking medication (n=616):	
Statins (HMG-CoA reductase inhibitors)	26.3%
Aspirin	40.2%
Calcitriol or Vitamin-D analogues	46.8%
Phosphate binders	69.0%
Calcimimetic	5.1%

Table 3. Population and treatment characteristics – continued

Clinical outcomes: serum albumin and CRP:

Mean values:	
Serum albumin (gm/L):	39.8 ±4.6
C-reactive protein (mg/L):	12.7 ±18.2
Favorable outcomes observed (%):	
Serum albumin ≥ 40 gm/L:	57.7%
C-reactive protein ≤ 5 mg/L:	40.9%

*Abbreviations: NF/TDC/TC/AVG=native fistula/tunneled dialysis catheter/temporary catheter/synthetic graft; **HIV=Human immunodeficiency virus.

3.3 Vascular catheter access removal studies

3.3.1 ***Study population***

Our catheter removal experience consisted of two studies, Study A (114) and Study B (170). Study A consisted of a retrospective cohort of a consecutive 3-year bedside TDC removal experience among hospitalized subjects at the University of Mississippi Medical Center performed via the Nephrology Consult Service (January 01, 2007 to December 31, 2009) (114). Study B consisted of a review of mixed inpatient and outpatient bedside TDC removals from January 1, 2010 to June 30, 2013, over a 3 ½ year period at the Nephrology Division of the University of Mississippi Medical Center (170). In study A, patients had been referred to the procedure team by nephrology consulting teams whenever TDC removal became medically necessary in the team's clinical judgment. In Study B, subjects had been referred to the author of the present thesis via nephrology providers from a variety of settings: ED, general inpatient floor, ICUs or ambulatory outpatient sections. In both studies, the decision to remove the TDC was made solely by the patients' nephrology attending physician for a variety of reasons, including proven bacteremia, fever or clinical septic state, catheter malfunction or recovery of renal function. Additionally, in study B, access maturation was also considered as a reason for TDC removal. The basis of data recovery was the procedure teaching and procedure log of the author of the present thesis, which included all inpatient TDC removals by the Nephrology Division for study A and most of the outpatient removal at bedside for study B. In the cases of inpatient TDC removals, these took place in the patients' room on the nursing floor; for outpatient removals, we utilized rooms specifically reserved for

procedures in the outpatient dialysis unit. Some but not all procedures involved renal trainees, as well. For inpatient procedures, the TDC removal always took place on the same day when the decision to remove the catheter was made (114, 170).

3.3.2 ***Definitions and variables of interest***

For study A (114), we reviewed and collected data on multiple patient-related variables: age, ethnicity, sex and highest blood urea nitrogen, creatinine and blood coagulation tests within 24 hours of the procedure. Age was the number of full calendar years completed since birth. Sex was self-reported as either male or female. Ethnicity was either Caucasian or African American. Additionally, we collected data on certain other peri-procedure parameters up to three days before and after the procedure which consisted of peak and nadir white blood cell count (WBC); nadir hemoglobin, nadir platelet count and vital signs (temperature, heart rate, blood pressure). Two additional biochemical parameters associated with inflammation and myocardial stress, CRP and troponin-I were searched for and recovered from medical records, if available within 48 hours of TDC removal. Procedure-related variables, which included the indication for the procedure, the site and location of removal and any complications or difficulties during the procedure were recorded from the teaching log of the author of the present thesis (114). For study B (170), we collected data on similar variables, but within three days before and after the procedure: highest blood urea nitrogen, creatinine, and blood coagulation tests; peak WBC count; nadir hemoglobin and platelet count (when available). Demographic definitions (age, sex and ethnicity) were identical to study A. As a rule, we did not require a complete blood count (CBC) or standard tests of blood coagulation with prothrombin time (PT) and activated partial thromboplastin time (aPTT) before outpatient removals. However, we routinely obtained PT/aPTT among inpatients if not already available within 3 days (170).

Full technical details of the procedure are discussed in the following section as described in our original publications (114, 170, 171), our recent review (172) and can be viewed on YouTube video link (173). Contraindications for the procedure included abnormal coagulation results, including prothrombin time PT International Normalized Ratio (INR) >1.5 and markedly decreased platelet count (<60,000/mm^3), when otherwise correctable. No further selection criteria were applied beyond the above-mentioned

exclusion criteria. All patients provided written consents before the procedure. Both Study A and Study B were reviewed and approved by the UMMC Human Research Office (Institutional Review Board) (114, 170).

3.3.3 ***Statistical methods***

Upon review of both electronic and paper-based medical records, pre-defined information was collected in Microsoft Excel data sheets. Data were analyzed using SPSS Statistics 19 (IBM Corporation, Armonk, NY) and reported with means ±SD or medians 25-75% interquartile range (IQR) for descriptive data; Pearson's correlation and chi-square as well as independent-samples *t*-test were utilized for statistical comparisons (114, 170).

3.3.4 ***Procedure description for Tunneled Dialysis Catheter removal***

"Preparation for the procedure included obtaining informed consent in writing from the patient or next-of-kin and gathering the limited supplies needed in the patient's care room or the dialysis clinic procedure room: suture removal kit, syringes, needles, 1% lidocaine, face mask, sterile gown, sterile gloves, sterile gauze dressing, vascular clamp, chlorhexidine cleaning swabs and dressing tape. Examples of preparation tray are shown in Photo 1. Before starting the procedure, we carefully ascertain the exact location of the retaining subcutaneous "cuff", both by visual inspection and gentle palpation over the subcutaneous tract of the of hardware. If uncertainty about the cuff location persisted, one could also apply a "twist" along the axis of the catheter to identify the retention point of the cuff. Sutures if present were removed after cleaning. Subsequently the catheter exit area, the surrounding skin and the catheter proximal to the hub (including the buried, but mobile portion distal to the Dacron cuff) are carefully cleaned with chlorhexidine-based cleaning solution […] Local anesthesia is achieved with subcutaneous infiltration of 10-15 mL of 1% lidocaine hydrochloride of the surrounding tissues. Afterwards, the cleaned area is draped to create a sterile field for dissection, with additional sterile towel used to wrap around and cover the extracorporeal parts of the catheter. Thereafter, the subcutaneous tissues around the catheter up to the cuff, as well as an additional 2-3 cm proximally are bluntly dissected with a hemostat clamp, to achieve mobilization of the catheter from the surrounding soft tissues. Ideal dissection is achieved by repeatedly inserting the sterile hemostat in all four quadrants around the catheter - that is, above, below, to the right and to the left to it - and opening up the clamp's tip to a width of at least 2 cm. The minimal length of vascular clamp necessary for the procedure would be 15-20 cm, preferentially a straight one. Once the cuff and the catheter are free from all connective tissue, the TDC could be pulled with

a controlled amount of force. During removal, the exit site is covered with sterile gauze and gentle hand pressure is applied to prevent aerosolizing of blood during removal. Hemostasis is obtained by the application of direct pressure on the tract and the exit site with a sterile gauze for 5 minutes or until no bleeding was detectable, whichever is longer; thereafter, a fairly tight dressing is placed until the next morning. […] The total procedure time is usually between 15-20 minutes and we also routinely ask outpatients to stay in the clinic waiting area for at least 30 min after the end of the procedure. For the newly placed catheters (<7-10 days), usually no dissection is needed and most of the catheters can be smoothly pulled after removing of the sutures."(172)

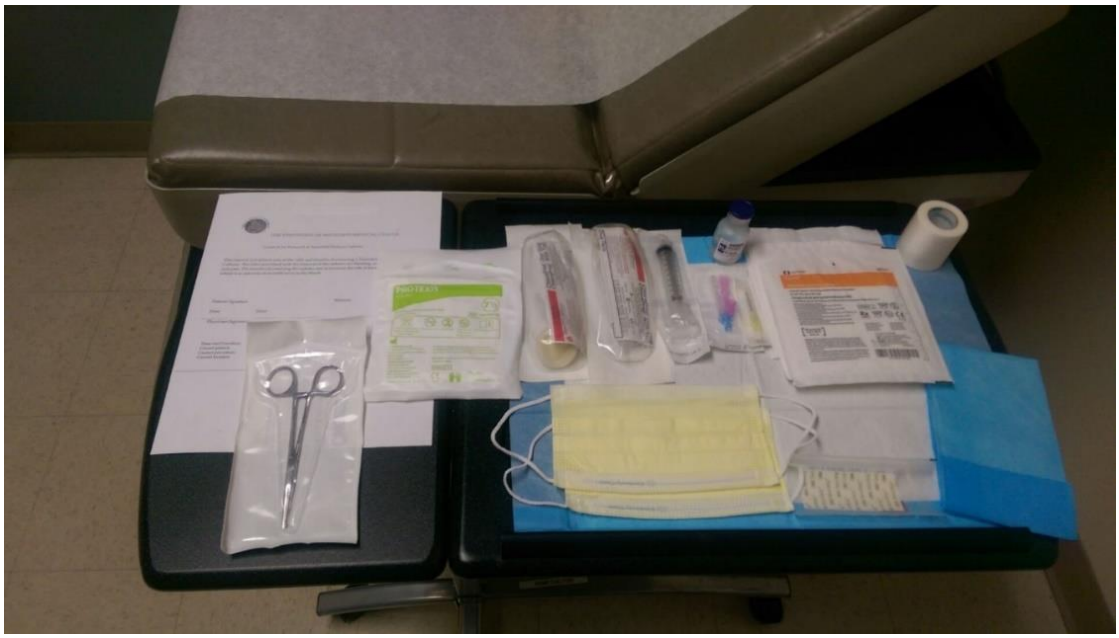

Photo 1.: Sample TDC removal preparation tray at UMMC

4. Results

4.1 Volume-related weight gain in critically ill patients with AKI and subsequent mortality

For our study, the mean age of the 81 patients meeting the inclusion criteria was 51.4 ±16.7 years (range: 23-85), 24 of which were female (30%). The overall raw mortality rate for the cohort was 50.6%. Mean VRWG was 8.3 ±9.6 kg but with a wide range of variation observed in the cohort (range: -10.5 to +45.9 kg). The mean percent weight gain was 10.2 ±13.5% (range: -11 to +81%). Oliguria was present in 53 patients before RRT commenced (65.4%). We have not observed significant associations between Apache II scores and weight changes (p=0.368), chart diagnosis of sepsis and death (p=0.653), or sex and death (p=1.00) in the course of the univariate analysis. Thirty-eight patients (46.9%) had VRWG ≥10% and thirteen patients (16%) had ≥20% VRWG. WRVG ≥10% (p=0.046) and oliguria (p=0.020) were significantly associated with death. The basic cohort demographics stratified by the two major cut-off categories are presented in two separate Tables: VRWG of <10% and ≥10% are presented in Table 4. while VRWG >20% and ≥20% are presented in Table 5. (167). Differences have been observed between the groups with VRWG <10% and ≥10% (creatinine at CRRT initiation, CRRT dose and days waited for CRRT) but these did not persist when the cohort was separated according to VRWG >20% and ≥20%. Female subjects were less likely to experience WRWG ≥20% (167).

We observed that patients with a VRWG ≥10% had a significantly higher risk of dying then the reference group of <10% (OR 2.62, 95% CI: 1.07-6.44; p=0.046) (Figure 1.1). When the patients were stratified using 20% VRWG as the cut-off point, the odds ratio for death in the patients with VRWG ≥20% was even higher, compared with the patients with VRWG <20% (OR 3.98, 95% CI: 1.01-15.75) albeit nominal significance was lost (p=0.067) (Figure 1.2) (167). As shown in Figure 2, separating the cohort into three categories of VRWG (<10%; ≥10 but <20%; ≥20%) was associated with a stepwise progressive increase of mortality: 39.5% (17 of 43), 56% (14 of 25) and 76.9% (10 of 13). Accordingly, against a reference group of VRWG <10%, OR for death was increased to 1.95 (95% CI: 0.72–5.28; p = 0.191) in the group with intermediate weight gains (≥10 but <20%) and to 5.10 (95% CI: 1.22–21.25; p = 0.025) in the group with

Table 4. Clinical Variables and Outcomes in Patients with VRWGs of <10% vs. ≥10% (167)

Clinical Variables	**All**	**VRWG<10%**	**VRWG≥10%**	***p***
Number	81	43	38	N/A
Average weight gain (%)		1.4 ±4.6	20.3 ±13.3	
Age (years)		50.4 ±16.5	52.6 ±17	0.547
Female Sex		27.9%	31.5%	0.718
Apache II scores		27.2 ±6.9	27.9 ±6.8	0.657
Creatinine at CRRT initiation		5.5 ±2.4	4.5 ±1.8	**0.039**
Change in creatinine (mg/dL)		1.8 ±2.2	2.4 ±1.7	0.167
Days elapsed until CRRT		3.1 ±2.9	4.4 ±3	0.061
Sepsis		55.8%	63.1%	0.500
Oliguria		62.8%	68.4%	0.593
ICU Service				0.192
Cardiology ICU (n=9)		16.3%	5.3%	
Cardiac ICU-Surgery (n=14)		11.7%	23.7%	
Medical ICU (n=42)		55.8%	47.4%	
Surgical ICU (n=16)		16.3%	23.7%	
Mortality	**50.6%**	**39.5%**	**63.2%**	**0.029**

Abbreviations: CRRT = continuous renal replacement therapy; ICU = intensive care unit; VRWG = volume-related weight gain

Apache II scores were calculated at time of renal consult. The conversion factor for serum creatinine in mg/dL to μmol/L is 88.4

severe (≥20%) weight gains. Of the forty-one deceased patients 32 had oliguria with an unadjusted OR of death 3.22 (95% CI: 1.23-8.45, p=0.02) for oliguria (167). Finally, we performed a multivariate modeling to assess the correlations of other potential risk factors for death in these patients. When analyzed together, both oliguria (p=0.021) and ≥10 weight gain (p=0.042) maintained independent significance. When sepsis and Apache II scores were included in the modeling, once again, oliguria (OR 3.04, p=0.032) and ≥10% weight gain (OR 2.71, p=0.040) maintained significance in the more complex modeling [Table 6.1-2.].

Table 5. Clinical Variables and Outcomes in Patients

with VRWG of <20% vs. ≥20% (167)

Clinical Variables	**All**	**VRWG<20%**	**VRWG≥20%**	***p***
Number	81	68	13	n/a
Average VRWG (%)		6.0 ±7.4	32.2 ±17.1	
Age (years)		51.9 ±16.7	49.2 ±17	0.61
Female Sex		23.5%	61.5%	**0.00**
Apache II scores		27.3 ±6.8	28.8 ±7.2	0.48
Creatinine at CRRT initiation		5.2 ±2.2	4.2 ±1.6	0.05
Change in creatinine (mg/dL)		2.0 ±2.0	2.5 ±1.5	0.33
Days elapsed until CRRT		3.5 ±2.9	4.7 ±3.1	0.24
Sepsis		57.4%	69.2%	0.40
Oliguria		63.2%	76.9%	0.29
ICU Service				0.54
Cardiology ICU (n=9)		10.3%	15.4%	
Cardiac ICU-Surgery (n=14)		19.1%	7.7%	
Medical ICU (n=42)		52.9%	46.2%	
Surgical ICU (n=16)		17.6%	30.8%	
Mortality	**50.6**	**45.6%**	**76.9%**	**0.01**

Abbreviations: CRRT = continuous renal replacement therapy; ICU = intensive care unit; VRWG = volume-related weight gain

Apache II scores were calculated at time of renal consult. The conversion factor for serum creatinine in mg/dL to mmol/L is 88.4

The effect of sepsis and Apache II scores remained non-significant on multivariate analysis. Altogether, the combined presence of oliguria and ≥10% weight gain explained approximately 12% of the observed mortality. Including into the logistic regression model creatinine level at CRRT initiation, CRRT dose and days waited for CRRT abolished the association of mortality with VRWG ≥10% (p=0.196; OR 0.71-5.29), but not with oliguria (OR 3.94; 95% CI 1.37-11.37; p=0.011), with minimal improvement of the model's overall predictability (R^2 0.16) (167). Analyzing our data through a three-way separation of the cohort (VRWG < 10%; ≥10 but <20%; ≥20%) in logistic regression, the OR of mortality increased 2.17 (95% CI: 1.11-4.26; p=0.024) for each categorical change of VRWG.

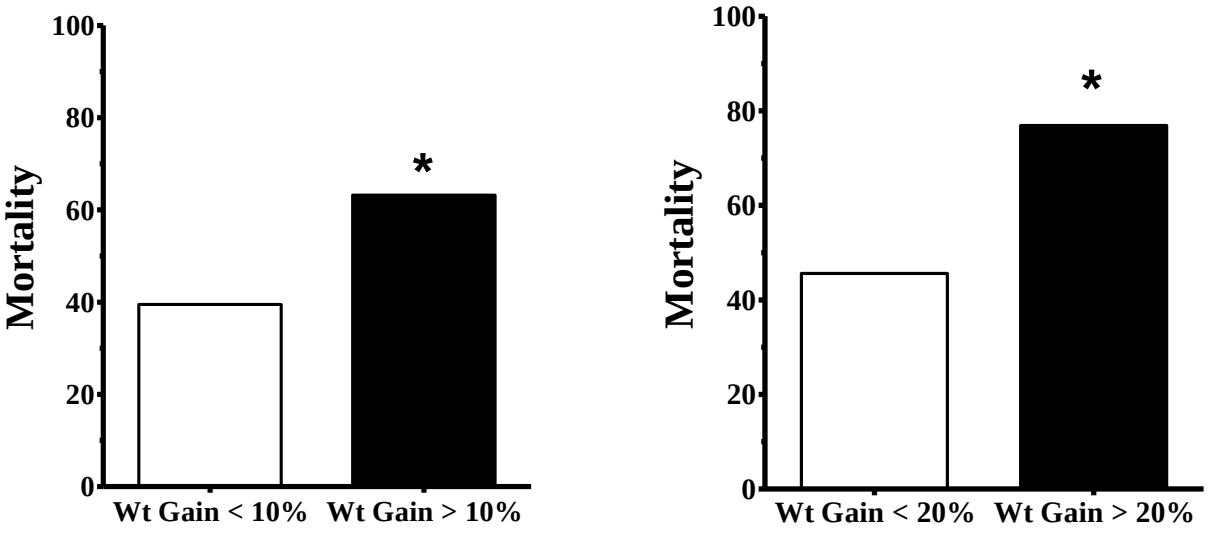

Figure 1.1 and 1.2. Association between VRWG and Mortality at different cut-offs of VRWG

Abbreviations: VRWG = volume-related weight gain; Wt gain: weight gain

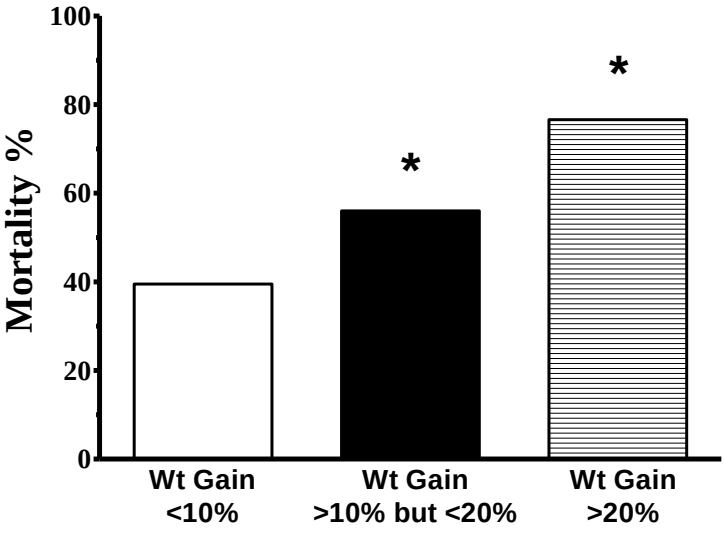

Figure 2. Association between progressive increases in VRWG and Mortality (167)

Asterisk (*) indicating statistical significance (p<0.05)

Abbreviations: VRWG = volume-related weight gain; Wt gain: weight gain

The effect of oliguria also remained significant: OR 2.17 (1.06-8.11; p=0.038); however, Apache II (p=0.239) and sepsis (p=0.352) did not. Including creatinine in the logistic regression model at CRRT initiation, CRRT dose, and days waited did not show an independent association with death for either one (p=0.322, 0.584, 0.163, respectively), but abolished the association of VRWG with death (p=0.125; OR 0.86-3.51), while the association with oliguria persisted (OR 3.80; 95% CI 1.31-11.01; p=0.014) (167). As larger VRWG was also associated with lower serum creatinine (5.5 ±2.4 mg/dL vs. 4.5 ±1.8 mg/dL with lower creatinine in VRWG≥10%; p=0.039), adjusting for creatinine at CRRT start may have resulted in simultaneous adjustment for larger fluid gains, as well, in those with larger fluid gains and dilution of serum creatinine. With the inclusion of multiple covariates (all the above), the results remained virtually unchanged. Finally, we analyzed the OR between the two extreme ends of our cohort: those gaining VRWG <10% vs. those with VRWG ≥20% (a total of 56 subjects) excluding the "intermediate" cohort (VRWG ≥10% but <20%) in multiple logistic regression models. With the inclusion of oliguria, CRRT dose, creatinine at CRRT initiation, and days waited, the OR for death (≥20% vs. <10% VRWG) was 4.34 and now approached significance: p=0.069 (OR 0.89 – 21.16). Further, results with the inclusion of multiple covariate results were similar, as shown in Table 7. (167).

Table 6.1 The Combined Effect of Oliguria and VRWG

During Multivariate Modeling (167)

Clinical Variable	**exp (B) ±95% Confidence Intervals**	**p-value**	**R^2**
Oliguria and ≥10% Volume-Related Weight Gain			
Oliguria	3.23 (1.19-8.73)	0.021	0.12
≥10% VRWG	2.64 (1.04-6.70)	0.042	

Table 6.2. The Effect of Oliguria, VRWG, Sepsis, and Apache II Scores on Mortality During Multivariate Modeling

Oliguria, ≥10% Volume-Related Weight Gain, Sepsis and Apache II scores			
Oliguria	3.04 (1.10-8.36)	0.032	0.13
≥10% VRWG	2.71 (1.05-6.99)	0.040	
Sepsis	0.63 (0.22-1.78)	0.379	
Apache II scores	0.96 (0.89-1.03)	0.219	

Abbreviations: VRWG = volume-related weight gain

Table 7. The Effect of VRWGs (<10% vs. ≥20%) on Mortality During Multivariate Modeling (167)

Clinical Variable	**exp (B) ±95% Confidence Intervals**	**p-value**
Oliguria	1.90 (0.53-6.80)	0.325
VRWGs (<10% vs. ≥20%)	4.03 (0.88-18.38)	**0.072**
Sepsis	0.64 (0.18-2.27)	0.490
Apache II scores	1.02 (0.94-1.12)	0.605
Creatinine at CRRT initiation (mg/dL)	0.92 (0.71-1.20)	0.553
Days elapsed until CRRT	1.10 (0.90-1.36)	0.353

Overall $R^2 = 0.147$.

Abbreviations: VRWG = volume-related weight gain

4.2 Dialysis prescription and inflammatory markers during conventional hemodialysis

Of the 626 reviewed patients, 616 (98.4%) met our inclusion criteria for undergoing maintenance hemodialysis three times a week in the 12 participating centers and having at least one of the critical data (albumin or CRP) obtained during the data collection period available for further analysis. Patient- and treatment-specific characteristics of these 616 participants are summarized in Table 3. (169). Mean age for the cohort was 60.9 ±14.4 years with an overall dialysis vintage of 46.16 ±44.8 months. Racial distribution of patients was 408 (79%) Caucasian and 105 (21%) African American and there was a large burden of diabetes mellitus (35%), congestive heart failure (44%) and coronary artery disease (19%) among the participants. Significant RRF (≥200 mL) was present in over half (58%) of the population. The average treatment time (237.3 ±23.8 minutes) was comparable to the European average at the time the research was taking place and about 16 minutes longer than the US average reported by DOPPS (168). Altogether, 122 (19.8%) patients were dialyzed for longer than 4 hours and 494 (80.2%) for less than or equal to 4 hours; mean treatment time for these was 269.7 ±14 and 229.3 ±18 minutes, respectively. However, mean treatment time did not significantly differ between the European (237.6 ±24 minutes) and the US arm (236.4 ±21.6 minutes) of the cohort**.** Mean UF rate (7.05 ±4.05 mL/kg/h) was the lowest in all DOPPS regions (168). There was no statistically significant univariate association between treatment time and UF rate (Pearson r: -0.042; p=0.222). Both CRP and serum albumin were distributed non-normally. CRP was available for 616 (100%) participants but albumin for only 522 (84.7%). Mean serum albumin was close to 40 gm/L with 301 (57.7 %) patients exceeding this level (169). The distribution of serum albumin values by treatment time and UF rate is shown in Figure 3. and Figure 4., respectively (169).

CRP was highly variable with a wide range (undetectable to 146.8 mg/L) and ≤5 mg/L in 252 (41%) of the cohort. The covariates of the initial ANCOVA model were the same as the patient- and treatment-specific characteristics in Table 3. However, the type of the dialyzer could not be analyzed separately due to an almost complete overlap of the choice of the dialyzer and African American ethnicity. In the initial screening ANCOVA model, only ethnicity (p=0.0036) and acute infection (p=0.0002) were significantly associated with serum albumin, and only vascular access type (p=0.009), acute coronary

event (p=0.0459) and acute infection (p<0.0001) were associated with CRP. Analyzing the set of 15 variables [Table 8.1], serum albumin as a continuous variable was significantly associated with ethnicity, dry weight, HIV status, acute infection and treatment time. In the case of CRP [Table 8.2], a significant association was found with vascular access type, dialysis vintage and acute infection while associations with acute coronary events were no longer significant (169).

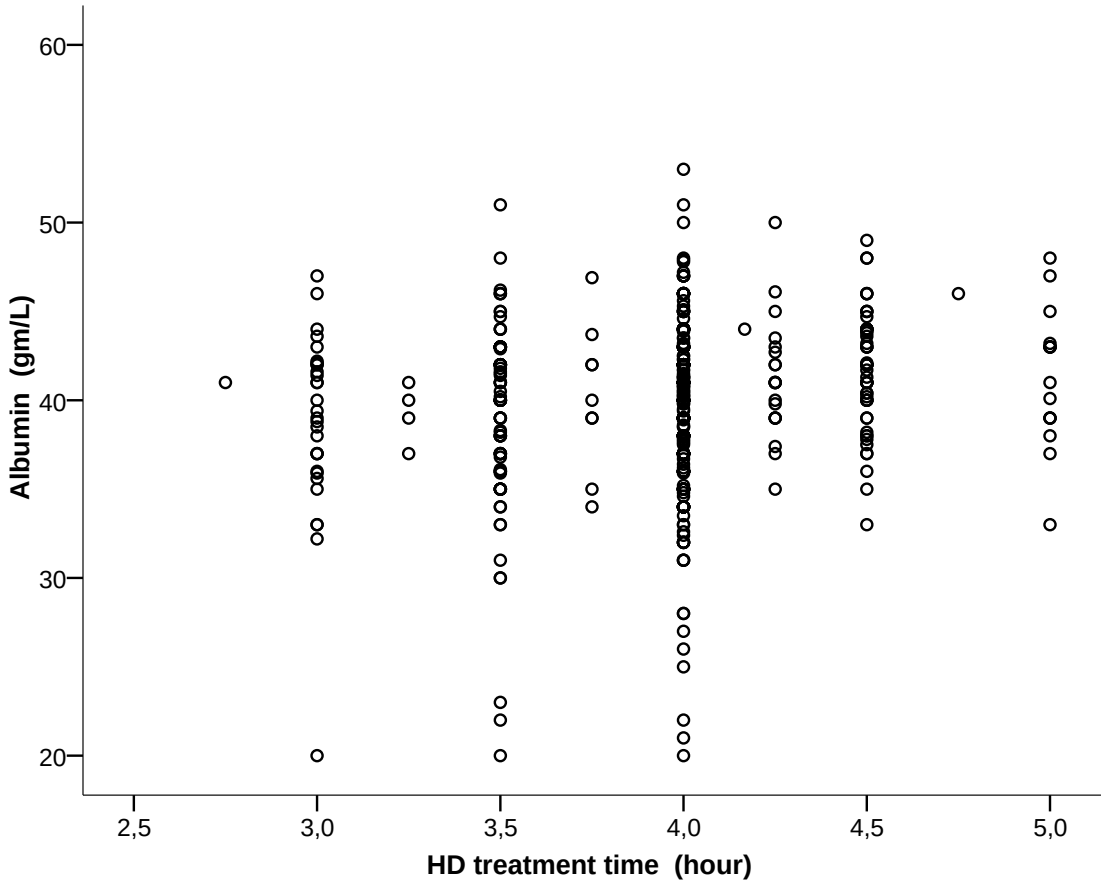

Figure 3. Distribution of serum albumin by treatment time (169)

Abbreviation: HD= hemodialysis

Mean albumin levels were 39.4 ±4.69 g/L among subjects receiving "short" (≤4 hours) treatment and 41.62 ±3.39 gm/L among those receiving "long" treatment (>4 hours). Stepwise selection was applied in logistic regression modeling to assess the individual

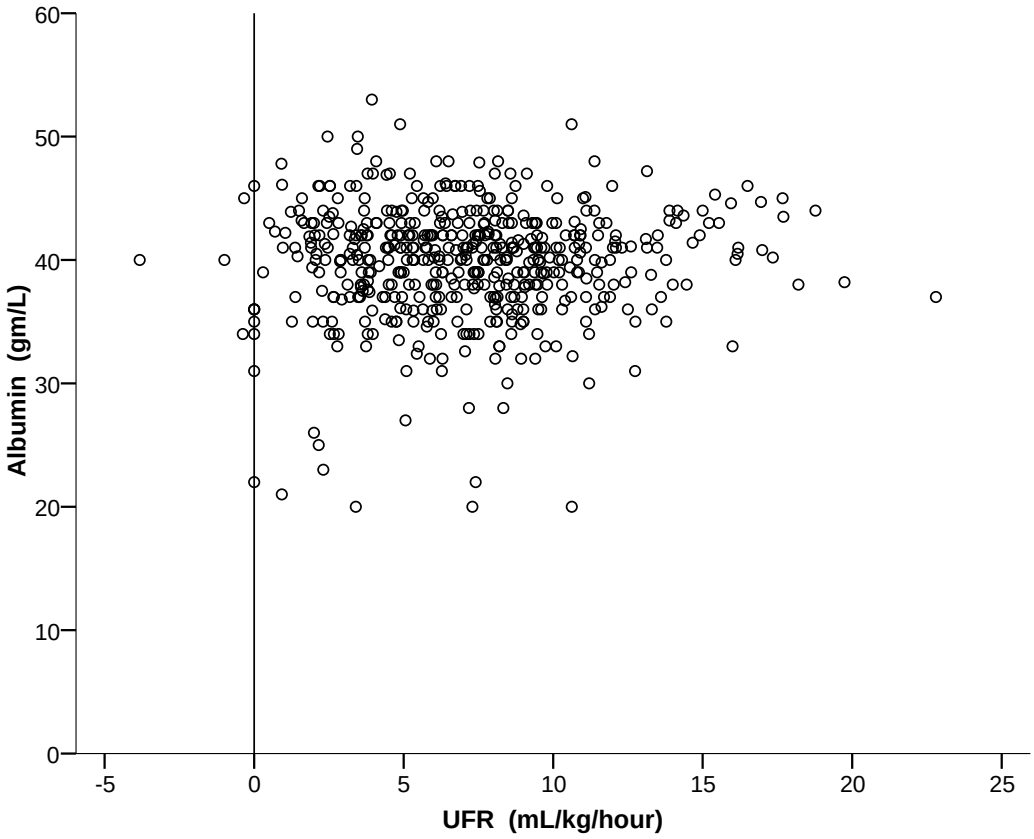

Figure 4. Distribution of serum albumin by ultrafiltration rate (UFR) (169)

Abbreviations: UFR = ultrafiltration rate

contribution of major predictors. For albumin, failure to reach more than 40 g/L in Step 1 correlated with short treatment time, Caucasian ethnicity, lower dry weight and the presence of an acute infection [Table 9.] (169). On the other hand, UF rate was not found to be a significant correlate of failure to reach > 40 gm/L albumin.

After Step 4, a treatment time of longer than 4 hours was associated with decreased odds of low albumin (OR 0.397, 95% CI: 0.235-0.672; p<0.001). Being Caucasian increased the likelihood of failing to reach the albumin target (OR 2.304, 95% CI: 1.462-3.630; p<0.0001), as did acute infection (OR 2.240, 95% CI: 1.327-3.780; p=0.003). Dialysis vintage had only borderline significance (OR 0.995, 95% CI: 0.991-1.000; p=0.041) while dry weight was not significant (169). When additional subcohort analysis was performed according to ethnicity (Caucasian vs. African American), treatment time greater than 4 hours once again reduced the risk of having low albumin (OR 0.385, 95% CI: 0.197-0.683, p=0.002) among the 408 Caucasians. However, the

effect of treatment time among African Americans was no longer significant (p=0.105), likely due to the limited number of these subjects (n=105) (169). Separating CRP according to treatment time, mean CRP in the short-treatment cohort was 12.05 ±18.78 mg/L and 11.23 ±15.62 mg/L in the long-treatment-time subgroup. Logistic regression demonstrated that factors correlating with high CRP were age, congestive heart failure (CHF), lower dry weight and vascular access type [Table 10.] (169). During stepwise selection, only the presence of CHF (OR 1.634, 95% CI: 1.154-2.312; p=0.006) and acute infection (OR 1.799, 95% CI: 1.059-3.056, p=0.03) remained positive correlates of a high CRP level. The significance of age decreased (OR 1.014, 95% CI 1.002-1.026; p=0.02) while dry weight and vascular access type lost significance. UF rate was not found to be a significant correlate of either main outcomes (169).

Table 8.1 – 8.2. (169)

Table 8.1. ANCOVA analysis for serum albumin

Predictor variable	**Significance (*p*)**
Age	0.292
Gender	0.512
Ethnicity	0.001
Vascular Access	0.085
Dialysis Vintage	0.759
Dry Weight	0.034
Diabetes Mellitus	0.108
Coronary Artery Disease	0.266
Congestive Heart Failure	0.169
HIV Infection	0.028
Acute Coronary Event	0.468
Acute Infectious Event	0.000
Kt/V	0.410
Treatment Time	0.016
Ultrafiltration Rate	0.053

$R^2 = 0.122$ (Adjusted $R^2 = 0.092$)

Table 8.2. ANCOVA analysis for C-reactive protein

Predictor variable	**Significance (*p*)**
Age	0.126
Gender	0.215
Ethnicity	0.973
Vascular Access	0.002
Dialysis Vintage	0.017
Dry Weight	0.239
Diabetes Mellitus	0.190
Coronary Artery Disease	0.410
Congestive Heart Failure	0.260
HIV Infection	0.833
Acute Coronary Event	0.059
Acute Infectious Event	0.000
KT/V	0.372
Treatment Time	0.663
Ultrafiltration Rate	0.392

$R^2 = 0.151$ (Adjusted $R^2 = 0.127$)

Abbreviations: HIV = human immunodeficiency virus; ANCOVA = analysis of covariance

Table 9. Results of Logistic Regression for Serum Albumin (169)

Variables entered	Significance (*p*)	Odds ratio (95% CI)
Treatment Time > 4 hours	0.012	0.488 (0.280-0.851)
Ultrafiltration Rate	0.415	0.979 (0.929-1.031)
Age	0.144	1.011 (0.996-1.025)
Female Gender*	0.130	0.731 (0.487-1.097)
Ethnicity (Caucasian)†	0.000	3.386 (1.712-6.697)
Dialysis Vintage	0.078	0.996 (0.991-1.000)
Diabetes Mellitus	0.073	1.466 (0.964-2.229)
Acute Coronary Event	0.467	0.808 (0.455-1.435)
Congestive Heart Failure	0.590	1.119 (0.743-1.684)
HIV Infection	0.340	2.382 (0.401-14.163)
Dry Weight	0.016	0.985 (0.972-0.997)
KT/V	0.136	1.645 (0.855-3.166)
Vascular Access Type‡	0.659	
Tunneled Catheter	0.941	0.981 (0.595-1.619)
Temporary Catheter	0.224	1.640 (0.739-3.637)
Arteriovenous Graft	0.829	1.104 (0.448-2.721)
Acute Coronary Event	0.096	2.082 (0.879-4.932)
Acute Infectious Event	0.007	2.098 (1.219-3.609)

Stepwise Selection for Serum Albumin

	Variables selected	Significance (*p*)	Odds ratio (95% CI)
Step 1	Treatment Time > 4 hour	0.001	0.432 (0.261-0.716)
Step 2	Treatment Time > 4 hour	0.001	0.406 (0.243-0.678)
	Ethnicity (Caucasian) †	0.001	2.113 (1.350-3.307)
Step 3	Treatment Time > 4 hours	0.000	0.380 (0.225-0.641)
	Ethnicity (Caucasian)†	0.000	2.266 (1.440-3.565)
	Acute Infectious Event	0.002	2.322 (1.379-3.910)
Step 4	Treatment Time > 4 hours	0.001	0.397 (0.235-0.672)
	Ethnicity (Caucasian) †	0.000	2.304 (1.462-3.630)
	Acute Infectious Event	0.003	2.240 (1.327-3.780)
	Dialysis Vintage	0.041	0.995 (0.991-1.000)

Symbols: *reference: male; †reference: African American; ‡reference: native AV fistula access

Abbreviations: HIV = human immunodeficiency virus

Table 10. Results of logistic regression for C-reactive protein (169)

Variables entered	Significance (*p*)	Odds ratio (95% CI)
Treatment Time > 4 hours	0.965	1.010 (0.643-1.587)
Ultrafiltration Rate	0.333	1.022 (0.978-1.068)
Age	0.031	1.015 (1.001-1.028)
Gender*	0.085	0.726 (0.504-1.045)
Ethnicity (Caucasian)†	0.045	0.519 (0.274-0.984)
Dialysis Vintage	0.151	1.003 (0.999-1.007)
Diabetes Mellitus	0.465	1.155 (0.785-1.701)
Acute Coronary Event	0.926	1.025 (0.609-1.725)
Congestive Heart Failure	0.032	1.496 (1.035-2.162)
HIV Infection	0.697	1.379 (0.273-6.964)
Dry Weight	0.044	1.012 (1.000-1.024)
KT/V	0.590	1.166 (0.668-2.035)
Vascular Access Type‡	0.078	
Tunneled Catheter	0.059	1.589 (0.982-2.571)
Temporary Catheter	0.044	2.053 (1.018-4.141)
Arteriovenous Graft	0.426	1.427 (0.595-3.420)
Acute Coronary Event	0.735	1.161 (0.490-2.749)
Acute Infectious Event	0.091	1.601 (0.928-2.760)

Stepwise Selection for C-reactive protein

	Variables selected	Significance (*p*)	Odds ratio (95% CI)
Step 1	Congestive Heart Failure	0.000	1.872 (1.341-2.613)
Step 2	Age	0.022	1.014 (1.002-1.026)
	Congestive Heart Failure	0.003	1.693 (1.199-2.390)
Step 3	Age	0.020	1.014 (1.002-1.026)
	Congestive Heart Failure	0.006	1.634 (1.154-2.312)
	Acute Infectious Event	0.030	1.799 (1.059-3.056)

Symbols: *reference: male; †reference: African-American; ‡reference: native AV fistula access

Abbreviations: HIV = human immunodeficiency virus

The Mann-Whitney test demonstrated that treatment time lasting longer than 4 hours was associated with having significantly higher albumin (mean rank 322.63 vs. 248.42, $p<0.0001$), whereas its effect on CRP was not significant ($p=0.85$). UF rate had no significant effect on albumin or CRP levels ($p=0.326$ for albumin, $p=0.931$ for CRP ranks, respectively) (169)

4.3 Tunneled Dialysis Catheter removal success rate and biomarkers

4.3.1 *Results of the Inpatient Cohort*

Our Study A population consisted of 55 hospitalized patients. All TDCs were removed at the bedside and most cases (50/55 or 90.9%) completed by nephrology fellows under attending physician's supervision. The rest of the catheters were removed by the attending physician alone with medical resident(s) observing the procedure. General cohort characteristics are shown in Table 11. (114). Most TDC removals took place in general wards (63.6%), while the rest of the removals were done either in the ED (12.7%) or one of the ICUs (23.6%) with a median time of 3 days [25-75% IQR 1-13] elapsing from admission with TDC in place or TDC placement. Of these, 36 (65.5%) TDCs were removed from the right internal jugular position, 14 (25.5%) from the left internal jugular position, and 5 (9.1%) from femoral veins. Most cases had urgent indication for TDC removal with potential for harm with delays. These included proven (culture-positive) bacteremia in 36.4% of the cases, otherwise unexplained fever in 41.8% of the cases or clinical signs of sepsis with hemodynamic instability or respiratory failure in 20% of the cases. Only three TDCs were removed in patients with recovering renal function, for the reason of being "no longer needed." At the time of TDC removal, four (7.2%) patients were hypothermic, 33 (60%) were febrile or subfebrile (temperature >37 C^{o}) and 7 (12.7%) were on vasoactive supporting agents (norepinephrine or high dose dopamine). All removals were executed successfully without any retention of polyethylene ("Dacron") cuffs or catheter fracture observed. One patient had prolonged local bleeding which was controlled with extended local pressure. None of the cases required interventional radiology or general surgery consultation for assistance (114). Peak CRP (available in 63.6% of the cohort) was 12.9 ±8.4 mg/dL (reference range: <0.49 ml/dL), median troponin-I (34% available) was 0.127 ng/mL [25-75% IQR 0.03-0.9] (reference range: <0.034 ng/mL) and they did not correlate with each other (p=0.848). The associations of CRP and troponin-I with clinical indications for TDC removal and selected clinical parameters are shown in Table 12. (114). We did not observe any association between CRP and clinical indications for TDC removal. Additionally, clinical sepsis (as indication for TDC removal) correlated with systolic BP nadir (p<0.0001), temperature (p=0.002) and the lowest platelet count (p=0.016).

Table 11. Baseline Cohort Characteristics and Indications for Tunneled Dialysis Catheter Removal (N=55) (114)

Age (years)	53.9 (15.4)
Gender *(%, female)*	54.5
Race *(%, African-American)*	90.9
Heart Rate (/min)[c]	95.6 (20.6)
Systolic BP nadir (mmHg)[c]	116.5 (20.7)
Diastolic BP nadir (mmHg)[c]	64.9 (12.3)
Temperature (C^o)[b]	37.6 (1.8)
Blood Urea Nitrogen (mg/dL)[a]	46.8 (23.6)
Creatinine (mg/dL) [a]	6.96 (3.37)
Platelet count, nadir ($x10^3/mm^3$)[c]	189.6 (114.8)
WBC count, peak ($x10^3/mm^3$)[c]	13.6 (8.7)
WBC count, nadir ($x10^3/mm^3$)[c]	7.9 (4.6)
Hemoglobin, nadir (gm/dL[c]	9.4 (1.6)
Biochemical Markers	
CRP (mg/dL)[b] [<0.49 ml/dL]	12.9 (8.4)
Troponin-I (ng/mL)[b] [<0.034 ng/mL]	0.534 (0.708)
Indication for TDC Removal	
Bacteremia	36.4 %
Fever (temperature >38 C^o)	41.8%
Clinical Sepsis	20%
Recovered Renal Function	5.5%

Abbreviations: BP, blood pressure; CRP, C-reactive protein; WBC, white blood cell
Obtained within 72 hours[a], 48 hours[b] or 24 hours[c] of the procedure.
CRP values available for 63.6% of cohort; troponin-I for 34%.

Troponin-I had no association with systolic and diastolic BP or clinical sepsis as indication for TDC removal. However, troponin-I, as a continuous variable showed a trend with confirmed bacteremia (p=0.075); furthermore, the association of troponin-I as a bivariate variable (abnormal/normal) with bacteremia was statistically significant (Pearson's chi-square=0.456, p=0.049) [Table 2.; 3rd column] (114).

4.3.2 ***Results of the Mixed Inpatient-Outpatient Cohort***

For study B, we collected data on 138 subjects, where the mean age was 50 ±15.9 years, 49.3% being female, 88.2% African American and 41% diabetic. General cohort

Table 12. Associations of C-Reactive Protein and Troponin-I with Clinical Indications for TDC Removal and Selected Clinical Parameters (114)

	CRP (mg/dL)[#] *p* value	**Troponin-I** (ng/mL)[#] *p* value	**Troponin-I** (Bivariate: abnormal/normal) *p* value
Indication for TDC Removal			
Bacteremia	0.806	0.075	**0.049**
Fever (temperature >38 C^o)	**0.005**	0.235	**0.018**
Clinical Sepsis	0.977	0.446	0.659
Clinical Parameters			
Systolic BP nadir (mmHg)[c]	0.690	0.561	0.254
Diastolic BP nadir (mmHg)[c]	0.526	0.288	0.945
Temperature (C^o)[b]	**0.031**	0.941	0.256
Platelet count, nadir ($x10^3/mm^3$)[c]	0.292	0.745	0.912
WBC count, peak ($x10^3/mm^3$)[c]	0.225	0.383	0.594

Abbreviations: BP, blood pressure; CRP, C-reactive protein, TDC, tunneled dialysis catheter; WBC, white blood cell.
Obtained within 48 hours[b] or 72 hours[a] of the procedure; #considered as a continuous variable. CRP values available for 63.6% of cohort; troponin-I for 34%.

characteristics are shown in Table 13. The site of removal was the right internal jugular in 76.8% of the cases, the left internal jugular in 15.2% and one of the femoral vein in 8%; 44.9% of the cases took place in an outpatient setting. Main indications at the time of removal were proven bacteremia in 30.4% of the cases, clinical septic or infected state in 15.2%, along with "TDC no longer necessary" in 52.2% due to either recovery of renal function or maturation of permanent dialysis access [Table 13.]. Most of the outpatient removals took place due to access maturation ($p<0.0001$). Like in Study A, all removal procedures were successful and tolerated without tear of the catheter itself but, unlike in study A, we observed Dacron "cuff" separation and subcutaneous retention in 6.5% of cases, all in males. There was a significant association between cuff retention and outpatient removal ($p=0.007$) but not with the operators' training level, or the site of

removal. Once again, similarly to study A, none of the patients required interventional radiology or general surgery consultation for assistance (170).

Table 13. Baseline Cohort Characteristics (N=138) (170)

Age (years)	50 (15.9)
Gender *(%, female)*	49.3
Race *(%, African-American)*	88.2
Co-existing Medical Conditions *(%)*	
Diabetes Mellitus	41
Systemic Lupus Erythematosus	6
Hypertension	85.1
Recent Renal Transplant	6.6
Biochemical Parameters	
Blood Urea Nitrogen, highest (mg/dL)[a] (n=109)	46.4 (18.9)
Creatinine, highest (mg/dL)[a] (n=109)	7.7 (3.9)
Platelet count, nadir ($x10^3/mm^3$)[a] (108)	223.4 (108.5)
PT International Normalized Ratio, highest[a] (n=56)	1.12 (0.31)
PTT, highest (sec)[a] (n=58)	33.1 (8.5)
WBC count, peak ($x10^3/mm^3$)[a] (n=108)	9 (4.7)
Hemoglobin, nadir (gm/dL)[a] (n=108)	10.2 (1.5)

[a]obtained within 72 hours (before or after procedure)

Table 14. Procedure Location and Indications for Tunneled Dialysis Catheter (TDC) Removal (N=138) (170)

Location of TDC removed (%)	
Femoral vein *(left or right)*	8
Right Internal Jugular Vein	76.8
Left Internal Jugular Vein	15.2
Place of TDC Removal *(%, outpatient services)*	44.9
Indication for TDC Removal (%)	
Bacteremia	30.4
Fever (temperature >38 C^o), Sepsis or Clinical Concerns for Infection	15.2
Exit Site Infection (as sole indication)	1.4
TDC "no longer needed" (renal recovery or access maturation)	52.2

5. Discussion

5.1 Volume-related weight gains in critically ill patients with AKI

Volume management is very challenging even for stable, outpatient ESRD patients. Critically ill ICU patients with renal impairment and hemodynamic instability are the most vulnerable to adverse consequences of volume overload. Early publications on adult cohorts have been derived from the non-AKI surgical literature, noting increased morbidity and mortality in volume-overloaded patients with acute respiratory distress syndrome (153, 154), sepsis (155), and surgical ICU patients (156, 157). Quite on the reverse, lesser fluid gains were associated with better outcomes after colon resection (157) or in the case of abdominal compartment syndrome (158, 159). Subsequent studies and meta-analyses further corroborated these findings (174). Fluids are medication, not unlike antibiotics, glucocorticoids or blood pressure medication but an "ideal" fluid management in ICU settings remains insufficiently defined (175). In terms of the clinical significance of pre-CRRT fluid overload, pediatric literature predated material on adults, documenting the graded adverse impact of fluid overload in children (162, 163, 176). As surprisingly this may sound – pediatric cohorts are always smaller than adult ones – children are nonetheless less likely to be confounded by multiple comorbidities of aging and may demonstrate biomedical signals with less ambiguity. To state it differently, both surgical and pediatric cohorts with fluid overload may have represented a relatively "pure model" fluid overload in critical illnesses, leading to an earlier recognition of the phenomenon. Among adults, however, our group(167) was one of the first to describe the progressive risk of death with increasing fluid overload in critically ill renal-failure patients, as discussed earlier in the Results section of the present thesis. Our central finding was that patients with VRWG ≥10% had a markedly higher mortality than those who gained <10% (63% vs. 39%), despite being reasonably similar with regard to demographics, severity of illness, sepsis or oliguria (167). Fluid (volume) overload may dilute the serum creatinine and result in a delay of recognizing AKI and the initiation of appropriate work-up and therapy for it (131-133). In keeping with such speculations, we detected lower creatinine with larger VRWG. We speculate that VRWG and fluid overload were, to a large degree, a surrogate for hypotension, labile hemodynamics or capillary leak, and overall severity of illness in our cohort. The kidneys are encapsulated organs, where a large degree of volume overload, especially in septic patients with

capillary leak may lead to compromised renal perfusion (177, 178). All our patients commenced on CRRT subsequently, further testifying to the severity of the illness of the cohort (166). The predominant local practice of the day of administering large amounts of IV fluids - rather than early vasoactive pressor administration - may have created some of the very large VRWG and may not be uniformly observed in all centers all over the word. If, however, the VRWG was simply a severity of the disease marker, one would have expected the impact on mortality to be diminished when adjusted for the severity of illness (e.g. Apache scores). Our multivariate analysis (which contained Apache II scores, diagnosis of sepsis, oliguria and VRWG) did not support this possibility, although "generic" illness severity scoring systems are known to have a relatively poor performance in similar cohorts (151, 179). Preceding our publication, findings from the Sepsis Occurrence in Acutely ill Patients multi-center database (165), observed larger fluid gains in non-survivors of AKI. The Program to Improve Care in Acute Renal Disease (PICARD) group (180) analyzed data from critically ill adult patients with AKI from multiple ICUs in the U.S. The same group of authors in 2009 observed the association of fluid overload with mortality, irrespective of the modality of RRT(181). Our 2010 study was the first to focus specifically on the impact of VRWG before CRRT in adult cohorts (167).

Oliguria is generally associated with worse outcomes in patients with AKI (151, 165, 182), which is in accordance with our findings as well; mortality was 60.4% in oliguric subjects compared to 39.8% in non-oliguric subjects. Oliguria was not defined based on weight (mL/kg/hour) and our definition of oliguria deviated from the current definition of the AKIN. Our study had several additional limitations evident even at the time of publication: lack of knowledge about weight changes before admission and the uncertainty about baseline creatinine in about one-fourth of the subjects. Additional methodological limitations (modest size, single-center design and lack of randomization) would have made our findings difficult to support without other studies reaching the same conclusion. Delays and individual practice patterns in obtaining renal consults may have influenced the timing of CRRT initiation, further questioning the external validity of our findings. Nevertheless, the subsequent years from 2010 on produced a flurry of supportive investigations on the subject as noted below.

5.1.1 *Literature on the importance of volume overload in critically ill patients with AKI*

Subsequent to our publication, Heung et al. documented that among patients surviving AKI, fluid overload at the beginning of RRT was associated with compromised renal recovery after recovery from critical illnesses (183). Pediatric studies continue to support the importance of VRWG even in very small-sized children (184). Most importantly, a number of other investigations of adult cohorts replicated our findings on the importance of VRWG in AKI. These include a Finnish trial of ICU patients, demonstrating higher 90-day mortality risk after adjusting for disease severity, RRT and sepsis (185); an Italian multicenter trial demonstrating that both fluid overload and oliguria were independent risk factors for 28-day mortality after adjustment for age, sex, diabetes, hypertension, diuretic use, non-renal Sequential Organ Failure Assessment (SOFA) and sepsis (186) (adjusted hazard ratio [aHR] 1.67 per L/day, 95% CI 1.33-2.09 for fluid overload, $p<0.001$); and aHR 0.47 per L/day per L of urine output, 95% CI 0.33-0.67 for oliguria, $p<0.001$ for both). On the other hand, diuretics use was associated with better survival in this population (aHR 0.25, 95% CI 0.12-0.52; $p<0.001$). In 2015 a very large, multicenter trial from Beijing, China once again confirmed that volume overload was an independent risk factor for new-onset AKI with OR 4.508 (95% CI 2.900-7.008; $p<0.001$) and increased the severity of AKI (187). Additionally, non-survivors with AKI had higher cumulative fluid balance during the first 3 days than survivors (2.77 [0.86-5.01] L versus 0.93 [−0.80 to 2.93] L; $p<0.001$). Multivariate analysis revealed that the cumulative fluid balance during the first 3 days was an independent risk factor for 28-day mortality (187). Most recently, the Dose Response Multicentre Investigation on Fluid Assessment (DoReMIFA) study demonstrated that volume overload was more harmful in the presence of AKI and preceded renal dysfunction. Both the severity and rapidity of fluid accumulation development were independent risk factors for ICU-associated mortality (188). A systematic review and meta-analysis also confirmed the associations between fluid overload and mortality in AKI patients but found only a non-significant trend for the association of fluid overload with renal recovery (189). Notwithstanding the limitations - as summed up in our review paper - "…these observations, however, have one major potential major error – confounding by indication, i.e., sicker patients were more likely to be hypotensive and received larger amount of fluids in an attempt to control hypotensive

tendency"(135), sufficient replications of our study findings in multiple settings provide external validity to support our initial findings.

5.1.2 *Fluid composition and AKI*

Attempts at modifying intravenous fluid composition used for volume resuscitation have not been successful so far. Literature emerging over the last decade attempted to support the use of colloid solutions over crystalloid solutions for volume resuscitation; however, concerns emerged about the association between hydroxyethyl starch and increased propensity for AKI in patients with sepsis (145). Similarly, albumin use failed to confer any survival benefits in controlled clinical trials (142, 143) and may have contributed to increased intracranial pressure in select individuals with brain trauma. Preventing metabolic acidosis with bicarbonate-enriched solutions may have an advantage over uncorrected metabolic acidosis (149, 175). In summary, it appears that the degree of net fluid gained (VRWG) is a stronger predictor of outcomes than the type of fluid administered during the early phase of treatment after admission.

5.1.3 *Renal replacement therapy choices – intermittent vs continuous*

The choice between intermittent vs continues RRT remains a difficult one and published literature to date has not demonstrated the superiority of CRRT (190). Similarly, the recent (2012) reiteration of Surviving Sepsis Campaign did not specifically endorse CRRT over intermittent HD (191). The debate about this clinical conundrum continues among nephrologists, as summarized in our recent review:

> "To address hypotension and volume overload in anuric subjects, CRRT is often preferred to intermittent hemodialysis to better control VRWG (190). Historically, the better tolerance of CRRT vs. conventional intermittent HD was attributed exclusively to the prolonged nature of the former enabling more fluid removal over an extended time period (192, 193). Nonetheless, at least clinical experience suggests that the true merit of RRT is not its ability to remove large amounts of fluid but in doing so while provoking less hemodynamic instability. Several mechanisms may contribute to decrease of hypotensive tendency during CRRT (in particular, during veno-venous hemofiltration) to afford net fluid removal (194). Early modalities of continuous therapies without built-in heater circuit likely provoked cooling with subsequent shivering and vasoconstriction, contributing to the improved BP on CRRT. Certainly, in this writer's clinical experience, it appears that the ability of CRRT to decrease hemodynamic

instability is the primary process by which may improve outcomes. With successful source control, such as removing the source of infectious-inflammatory injury (e.g., abscess drained), we have observed many times gradual improvement of BP after 4-6 hours, enabling the clinicians to start net fluid removal. Nonetheless, individual responses are tremendous and calls for astute clinical re-evaluations in these patients. With regard to expected tolerated fluid removal, it appears the most obvious rule appears to be the lack of such. Accordingly, there is no apparent replacement for an astute clinician's daily assessment and judgement to estimate expected tolerance of fluid removal."(135)

Time of initiation (195, 196), modality (193, 197), dose (198, 199), intensity and duration of CRRT (197, 200, 201), all of these remain argued in the literature without a clear preference of one over the other. Nonetheless, securing patency of the CRRT circuit remains a critical challenge in the ICU and multiple modalities, including regular heparin anticoagulation, regional citrate anticoagulation or the combination of both may fail in select patients to maintain circuit patency (202, 203). Our standard protocol of regional citrate anticoagulation at the University of Mississippi resulted in an overall mean filter life of ~45 hours and approximately 70% patency rate at 72 hours (unpublished observation of the author of this thesis).

5.1.4 *Assessment of volume overload*

Multiple technologies are emerging to assist clinicians in this setting, including the assessment of inferior vena cava size, bioimpedance (6, 38, 204), the assessment of lung water content by ultrasound (205, 206) and biochemical markers for volume overload, such as elevated brain-type natriuretic peptide (BNP) (38, 207, 208). With regard to B-type natriuretic peptides, pro-atrial natriuretic peptid, BNP and N-terminal-pro-BNP all correlate independently with age, degree of systolic dysfunction and negatively with residual diuresis and 2-year survival, as well (209). Discordant results between BIA and BNP can be explained by capillary leaks during septic shock (210). Limited investigations explored the use of BIA-based vector analysis in assessing the degree of volume overload in ICU patients and potential associations with subsequent outcomes (208). On the other hand, multi-channel, total-body bioimpedance examinations remain severely underutilized and unexplored in critically ill, volume-overloaded ICU patients with AKI (135).

5.1.5 *Potential role of peritoneal dialysis in volume overloaded subjects*

One of the enigmas of clinical nephrology is the relatively good success rate of acute peritoneal dialysis (PD), practiced in resource-limited environments, comparing favorably to a much more resource-expensive technology, the slow continuous hemodialysis or hemodiafiltration (211-216). Acute abdominal compartment syndrome is an expected complication of over-aggressive volume resuscitation (174). Most importantly, as we pointed out in our recent review paper (135), the use of a temporary acute PD catheter virtually eliminates the possibility of abdominal compartment syndrome in severely volume-overloaded and critically ill medical ICU patients with acute ascites. In these subjects, the clinical success may be partially disconnected from the "clearance" provided by the acute PD and linked to improved perfusion of visceral organs in volume-overloaded subjects with acute ascites.

5.1.6 *Alternatives to serum creatinine to assess renal function; biomarkers in AKI?*

The Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) Consortium has prospectively examined serial biomarker profiles in 1219 adults and 311 children scheduled for cardiac surgery in nine centers. They found that cystatin-C was superior to serum creatinine and serum creatinine-derived eGFR to predict AKI (217). An alternative strategy is to consider volume overload-adjusted changes in serum creatinine. To control for volume overload driven decrease of serum creatinine, literature has been published to predict the value of volume overload-corrected baseline serum creatinine (132, 133): corrected Cr= baseline Cr x correction factor [Correction factor = baseline water space + accumulated fluid balance/ baseline water space (baseline water space: weight (kg) x 0.6)]. However, the practical value of the formula to improve survival predictions is not yet fully defined and understood. Our own results from the ICU cohort of us(167) certainly suggest that dilution of creatinine may have contributed to weakening of the effect of VRWG, but we have not specifically analyzed the data for this possibility. On the other hand, the literature on "biomarkers" of AKI is vast and ever-expanding (218). Our overall concerns with the existing approaches are summarized in our recent review paper, as well:

> "Despite more than a decade of unfulfilled promises and spent efforts, we are yet to see a true disruptive technology to replace conventional markers or a seasoned clinicians' experience.

> Taking a prime example, newer biomarkers of AKI are yet to supersede a very imperfect but much simpler biochemical marker, the serum creatinine in clinical utility (219). The added costs of newer biomarkers for AKI are an additional concern, especially in resource-limited settings. The heterogeneity of clinical etiology for AKI is yet another challenge for biomarker-based diagnostic procedures. In many instances, the underlying etiology of AKI is unclear; in contrast, many biomarker-defined prognostic schemes have been derived from a specific disease cohort of patients. Only few studies used dedicated study adjudicators in attempt to develop rigorous, consensus-based clinical definitions to correlate the markers. Complexity is another problem. In a time-pressured busy environment any recommended prediction model has to be either very simple or it needs to be easily available via the healthcare system computer and bioinformatics network. There is also a major internal limitation for renal biomarkers. While most of the biomarker studies are focused on kidney-derived enzymes or products, AKI is in fact a systemic illness in many instances, being only one feature of multiple organ failure syndrome. Accordingly, there is a major conceptual difference between the so called "renal angina" (220, 221) and, for instance, the classic paradigm of myocardial infarction (MI). In MI, the prime cause of abnormality is the necrosis of myocardial tissues; in renal diseases, most commonly, AKI is a functional consequence of a systemic process." (135)

To further support this viewpoint, in a recent series of limited autopsies by Takasu et al., only a limited degree of renal injury was detected in the examined tissues, markedly disconnected from the profound functional impairment taking place before death (222).

5.1.7 ***Oliguria***

In most clinical contexts, decreases in the urine output (oliguria) implies an acute hemodynamic process or an acute component of renal failure. Oliguria is an excellent independent risk factor predicting adverse renal outcomes (186, 223, 224) as it may be a sign of an overall clinical illness, such as an emerging sepsis. Accurate hourly urine output is difficult to obtain but can add to the assessment of these patients (225). Urine output, however, is not the same as creatinine excretion; only hourly monitoring of creatinine excretion would offer a fair chance of "real-time" monitoring of GFR. A major concern about using oliguria as an independent clinical parameter is, according to the author of the present thesis, the lack of adjustment for volume status. Often, fluid is given without a clear assessment of the underlying disease processes or the volume overload already taking place. Excessive volume resuscitation may be counterproductive in tissue hypoxia

with massive volume overload and in those with pulmonary edema and respiratory failure. As we pointed out in our very recent review:

> "…the presence of low urine output cannot have the same meaning in an approximately euvolemic subject as opposed to one already markedly volume overloaded (>10 or 20% VRWG). In doing so, the scenario would be somewhat analogous for patients on mechanical ventilator support… [to] interpret an arterial blood gas panel and oxygenation without knowing the partial pressure or percent of O_2 on the inhaled gas." (135). And "…before being lost in the plethora of various biomarkers or a myriad of derived hemodynamic parameters, clinical nephrologist should consider using and correctly interpreting basic parameters of critically ill patients with renal failure in ICU. Similar to urine output, VRWG should be considered as "renal vital sign," incorporated into the rounding report and daily consideration of care decisions." (135).

Indexing the urine output for the degree of volume overload is a completely unexplored area of biomedical research and another low-cost technology to potentially assess disease severity (135).

5.2 Time on hemodialysis

To our knowledge, our publication (169) demonstrated for the first time a positive association between treatment time and albumin levels in chronic hemodialysis patients, with a significantly decreased risk (OR 0.397, 95% CI: 0.235-0.672; $p<0.001$) of hypoalbuminemia (<40 gm/L) in those dialyzing longer than 4 hours. Unlike time on dialysis, small solute clearance (Kt/V) was not associated with better albumin values in our study. Past studies of better survival with higher albumin levels (226) may have reflected a better-dialyzed state of patients due to longer treatments, better preserved RRF (227) or both. Longer treatment times achieve a better clearance of larger middle-molecular size substances (79) at a price of lesser hemodynamic fluctuations (228, 229). Volume removal and ultrafiltration rate are, nevertheless, closely integrated features with dialysis duration. Longer treatment time allows for slower fluid removal over a more prolonged period and thus, avoids repetitive episodes of intradialytic hypotension (228, 230), decreases hemodynamic fluctuations (228, 229) and may contribute to preservation of RRF (227). Low albumin is a risk factor for early readmission after hospital discharge

among the elderly (231). As most putative uremic toxins diffuse more slowly than urea (232), their removal will be largely a function of time spent on dialysis. Beside the longer treatment time, we also recorded lower UF rates and longer treatment than reported by the DOPPS from the US at that time (168).

Contrary to our expectations, unlike albumin, CRP showed no significant association with treatment time in our network. Nonetheless, our statistical model explained a remarkably little variation of CRP levels ($R^2 = 0.127$) while several factors thought to influence CRP in a similar population without end-stage renal disease (233) did not appear significant in our cohort. While a statistically significant association has been observed between CRP and the choice of catheter for vascular access (p=0.002), this was not maintained during stepwise regression. Although the hemodialysis procedure itself is known to potentially increase acute phase reactants levels (234, 235), more prolonger treatments may result in better clearance of larger middle-molecular size substances (79). With regard to congestive cardiomyopathy (OR 1.634, 95% CI: 1.154-2.312; p=0.006), there have been reports documenting the association of congestive cardiomyopathy and CRP in non-renal patients (236, 237) and between CRP and volume overloaded state in both pre-dialysis (238) and peritoneal dialysis patients (239). Our study extended this potential association to the hemodialysis population. Anti-hypertensive agent class is known to exert some modest influence on CRP in hypertensive sibships (233), although such relationship is not well explored in ESRD.

In our study, the UF rate did not correlate with either inflammatory marker, which was not what we have expected. Possible explanations for the phenomenon are either a true lack of influence or a balance of competing influences. As most dialysis sessions last very close to the same duration (four hours), the UF rate will become largely a function of IDWG determined by appetite. Healthier patients may be less compliant with salt and water restrictions to accommodate an intact appetite. Accordingly, we speculated that some of the potential long-term harmful effects of increased UFR may be counterbalanced by a better appetite in healthier patients. (169) We also have observed remarkable similar biochemical outcomes (albumin, CRP) between the US and Hungarian arm of the cohort. We believe this observation demonstrates that good outcomes can be reached in disadvantaged and minority populations with attentive medical and dialysis care. (169)

5.2.1 *Recent literature of treatment time, survival and BP control*

Among DOPPS participants between 1996 to 2008, dialysis treatment time increases by 30 minutes was associated with a proportionate decline of all-cause mortality of 6% (130). Further, longer treatment times were associated with higher hemoglobin and albumin and lower WBC count and phosphorus concentrations (130). Shorter dialysis time (session length <240) was also shown to be associated with increased mortality in a large database of Fresenius Medical Care North America (aHR: 1.32, 95% CI: 1.03-1.69) (240). In a post hoc analysis of the 150 participants in the Dry-Weight Reduction in Hypertensive Hemodialysis Patients trial (N=150), fewer hours of dialysis treatment was associated with higher systolic BP, increased need for BP medications and a longer time to achieve a lower BP target (241). Similarly to past studies, in a subsequent study we demonstrated that post-dialytic (post-ultrafiltration) BPs had a better association with 48-hour BP burden during ABPM than predialysis BP (30). Additionally, we also demonstrated that by incorporating both pre- and post-dialysis BP values into linear regression modeling, pre-dialysis systolic BP readings lost significance entirely to predict ABPM-derived systolic BP (30). With the usual practice of three-times-a-week renal dialysis, BP variability is at the peak on the first dialysis of the week, when excess volume is likely to be the largest (126). Further, elevated systolic BP variability (defined as SBP variability above the medium) was associated with increased all-cause mortality (HR 1.51, 95% CI: 1.30-1.76; p<0.001) and cardiovascular mortality (HR 1.32, 95% CI, 1.01-1.71; p=0.04) in a cohort of 6393 prevalent adult HD patients (124). Paradoxical increases of blood pressure during treatments are associated with poor subjective symptoms and are indicative of increased future hospitalization rates, adverse cardiovascular outcomes and a rise of all-cause mortality (242, 243). The lowering of dialysis temperature may be poorly tolerated by patients, but leads to vasoconstriction and a relative rise of BP. Lowered counter-current temperature is associated with improved hemodynamic stability (244) and reduced white matter lesions in the brain (245). Clinical assessment can be incorrect in about 25-40% of patients to identify euvolemia correctly, at least in terms of overall body salt-water content (246). BIA-based assessment leads to less fluid overload (58) and improved left ventricular hypertrophy (53); further, prospective BIA-monitored EDW adjustments may be associated with decreased mortality in ESRD (58), though contrary evidence exists as well.

5.2.2 *Recent literature on interdialytic weight gain*

Greater IDWG has been linked to increased adverse outcomes in multiple studies since (46, 240, 247). In a study by Kalenter-Zadeh et al. in an analysis adjusted for demographics and markers of inflammation, a graded relationship was observed with IDWG: increased risk of CV death for ≥4 kg (aHR 1.25, 95% CI: 1.12-1.39) and decreased risk for <1 kg (aHR 0.67, 95% CI: 0.58-0.76), when compared to the reference group of 1.5-2 kg (46). A study by Flythe et al., from a cohort of over 14,000 prevalent HD patients, noted a 29% increase of mortality risk associated with higher (>3 kg) IDWG relative to lower (≤3 kg) IDWG (240). At the same time, the authors also demonstrated that session length of < 240 minutes had a similar negative impact on survival (aHR 1.32, 95% CI: 1.03-1.69). And, finally, a chronically volume-expanded state with missing EDW by >2 kg and >30% of the time was also associated with adverse CV and all-cause mortality (aHR 1.28, 95% CI: 1.15-1.43) (40). Similarly to the above, Cabrera et al., observed a stronger impact in terms of the relative change of weight; specifically, relative weight gain of >3.5% body weight was independently associated with multiple CV outcomes (CV mortality, myocardial infarction and heart failure) (248). Among other parameters, shorter treatment times with higher hourly UF rates may impact sudden cardiac death rates adversely (249). Some of the published literature debate the independent value of UF rate or volume when adjusting for the presence of volume-overloaded state at the beginning of renal dialysis (60). Dialysate sodium itself exerts an influence on both IDWG and BP control in ESRD. The most recent DOPPS data between phases 2 and 5 (2002 - 2014) indicated a modest decline of IDWG world-wide, probably mediated by a trend to use lower sodium concentrations and the avoidance of sodium-profiling during RRTs (250). For each 1 mEq/L rise of the dialysate sodium concentration, there was an associated rise of 0.13 kg (95% CI: 0.11-0.16) of IDWG. Among the participating regions, drops in IDWG were most evident in North America and Europe. Once again, mortality rate was higher for relative IDWG > 5.7% (aHR: 1.23; 95% CI: 1.08-1.40) compared to the reference category of 2.5 - 3.99% weigh gain (250).

5.2.3 *Dialysis nonadherence*

Historically, restrictions on sodium and water have been advocated to curb IDWG. They are, however, conceptually not equivalent. A weight gain of free water would be

distributed through the entire water space (albeit at the price of decreasing serum sodium); on the other hand, the intake of salt would stimulate thirst and make the drive of fluid intake very hard to avoid (251). The resultant expansion would be effectively limited to the extracellular water space. All dialysis units should carefully consider the local cultural microenvironment to identify causes and patterns of nonadherence and barriers of effective healthcare delivery. Recent data from the Fresenius North America database (2005-2009) detected higher rates of treatment nonadherence among young and non-white subjects, with transportation issues, poor weather conditions, holidays, and non-renal illnesses identified as the underlying reasons (252). Missed treatments were associated with increased risk of ED visits, hospitalization and ICU admissions (252). In another study, non-white patients race and larger dialysis unit size was associated with increased nonadherence (missed and shortened treatments) and further confirmed large geographic variations across the US (253). Race and trust in the health care system may be an additional confounding factor impacting compliance (47, 119). In the U.S., African Americans known to have disproportionate trust towards providers from the same ethnic and cultural background, including physicians (254-256). Urban centers serving minority populations are known to miss various performance targets in general and have higher-than-expected mortality rates (257). As mentioned earlier, our own experiences from the Southeast US documented also remarkable nonadherence: in one cohort from Northern Louisiana 85.9% of patients shortened at least one HD session, and 29% did not attend at least one HD session per month (123). Quality improvement data from the UMMC Jackson Medical Mall Dialysis Unit (>85% of the patients were African American) have shown a similar magnitude of appointment nonadherence: 78.5% of the patients shortened treatment by at least 10 minutes and 31.2% missed at least one HD treatment during the index month (personal communication from Melissa Hubbard, R.D., UMMC Nephrology Unit; October 2009). This latter unit is in the center of the city of Jackson, Mississippi, and is well served by the public transportation system. One very little studied concept is the potential impact of overall climatic conditions on IDWG. The impact of sweating itself is likely to be minimal on IDWG and, in temperate climate at least, environmental conditions presumed not meaningfully impact the net result of session-session variations of fluid intake, sweating and residual urine output (24). Sweat has a relatively little sodium content in healthy subjects, when compared to other body fluids (258). On the

other hand, in a relatively small (N=100) cohort of Hungarian patients we have shown that hot-dry climatic condition resulted in the least weight gain, a difference which was statistically significant, when compared to warm-dry conditions (24).

5.2.4 ***Shortcomings of Kt/V based dialysis clearance***

Body surface area-based adjustment may be a more reliable expression of dialysis dosing than the classical approach which utilizes total body water (5). Examining a prevalent cohort of 7229 patients undergoing thrice-weekly hemodialysis Ramirez and coworkers (5) found that there was no associated survival benefit associated with a single-pool Kt/V >1.7, but the hazard ratio for mortality was progressively lower with higher Kt/Vs if the Kt/V was normalized for the body surface area. Thus, body surface area-based dialysis dose results in dose-mortality relationships are substantially different from those with volume-based dosing. This observation may be particularly relevant to women, who received proportionally smaller dialysis doses, when BSA was considered.

5.2.5 ***Overnight modalities – the future?***

In the future, expanding options of overnight dialysis may well address the time constraints of conventional dialysis and potential shortage of care staff. In one study obtained from the Fresenius North America database, comparing subjects with propensity-matched controls, overnight dialysis resulted in better clearances, improved control of biochemical parameters and an approximately one-fourth reduction of death for over a two-year period (HR 0.75, 95% CI: 0.61-0.91; $p < 0.004$) (259). Enrollee retention was a major issue: in the latter study, after 2 years only 42% of the patients were adherent to the modality. Additionally, further investigation of the Frequent Hemodialysis Network Nocturnal Trial participants showed a yet unexplored paradoxical increase of mortality during the post-trial follow-up period (3.7 years): 3.88 (95% CI, 1.27-11.79; p=0.01) (260). Our own anecdotal experience with the University of Mississippi Nocturnal Shift (n=9) demonstrated good biochemical and BP control, along with excellent Kt/V values for this small cohort of very large or multiple co-morbid chronically ill subjects (unpublished observation of the author of the present thesis).

5.2.6 *The paradigm of pregnancy*

Pregnancy perhaps represents the ultimate model to define what the difference is between "minimum necessary" and an "optimal" dose of renal dialysis. It has been a time-honored observation by now that pregnant patients need more frequent or much longer sessions of renal dialysis, ultimately translating into a longer weekly total time on dialysis. Unlike in the past, when fetal survival was very rare, the more recent era is witnessing a marked improvement in successful pregnancy rate. One recent study has compared pregnancy success rates between the US and Canada, with a notable difference between practice patterns between the two countries. While in the US, the usual practice pattern dictated a daily dialysis of about 4 hours 6 days a week after the first trimester, in Canada, practitioners prescribe HD for 6-8 hours, 6-7 days per week as soon as pregnancy is recognized in a dialysis patients. This registry-based comparison observed a much higher successful live birth rate in Canada relative to that of the United States (86.4% vs 61.4%; p=0.03) (261). Further review of the Canadian nocturnal program also suggests a graded dose-relationship between weekly hours of hemodialysis with live births, improving from 48% in women receiving <20 hours of therapy to 85% in those receiving ≥37 hours (261). Intensified therapy also decreased the number and severity of neonatal and maternal complications (261).

5.3 Transitioning between acute and chronic renal replacement therapy: the importance of access choice

In our series entailing both inpatients (114, 170) and outpatients (170, 171), we have documented an excellent safety profile for bedside TDC removals, presumably contributing to the timely care of these patients. Vascular access catheter utilization remains a profound and escalating problem in the U.S., with >80% patients with no pre-ESRD nephrology care starting RRT with these devices (144), including those seeing a nephrologist in the preceding year (~40%). This situation has visibly worsened since the mid-nineties, when less than 20% of new hemodialysis patients utilized TDCs 60 days after the initiation of renal dialysis (262). It is ironic that the well-intentioned mandate of "Fistula First" initiative led to an escalated utilization of vascular access catheters (263) and replaced AV grafts with a much more morbid technology of TDCs, bringing about

the attendant risk of infection and death (99, 106, 114, 264) Access type (non-AV fistula) and elevated CRP are both risk factors for future infection and both are independently associated with increased infection-related hospitalization, along with other markers of fragility (old age >85, nursing home residence, poor mobility and chronic medical illnesses) (265). The lack of adequate pre-dialysis nephrology care is associated both with higher catheter utilization and mortality within one year after the start of dialysis, observed both in Canada (266) and the US (267). Long-term vascular access catheter use is associated with increased mortality (99, 101, 102) and every attempt should be made to minimize the duration of catheter-dependence. Alternative options to avoid temporary access should be considered, including acute start peritoneal dialysis (268, 269) or the initiation of deferred hemodialysis until chronic AV access have matured.

5.3.1 ***Peritoneal dialysis***

Alternatively, peritoneal dialysis (PD) remains a viable option for effective renal replacement therapy and alleviate the need for indwelling vascular access catheters. PD remains a somewhat enigmatic modality which works clinically well despite the limited small solute clearance it provides. PD is cost-effective (23), avoids the need for temporary vascular access placement and may in fact have a survival advantage over hemodialysis (270), especially during first two or three years of RRT (271). Historically, the "slow but steady" nature of PD has been cited most often as the reason for its clinical efficacy. However, uremic toxins are generated disproportionally in various body compartments. While some tissues (muscles) are more active than others (fat tissue) to generate uremic toxins, in effect the largest generating compartment is the interface of human-bacteria in the gastrointestinal tract. In this regard, it would be perhaps most appropriate to view PD as a "compartment dialysis" (272), a modality delivering a disproportionately large clearance to the gastrointestinal tract, the very compartment generating most uremic toxins. It can be offered upon transition from renal transplantation to maintenance dialysis, a particularly vulnerable period to excess mortality (273). Survival advantages are also likely linked with the better preservation of residual renal function, improved hemodynamic stability, decreased need for human recombinant erythropoietin administration and a lesser risk of acquiring blood borne infections in PD (274-278). Nonetheless, with the exception of Hong Kong and Australia, PD remains severely underutilized all over the world. Obesity, commonly perceived as a

relative contraindication to PD is by itself not a limiting issue and most studies have reported a survival advantage of doing PD in obese patients (274, 279-281). Further, a recent systemic review and meta-analysis of more than 150,000 subjects also confirmed at least a neutrality of large body mass index (BMI) on survival (282). Fat tissue does not participate in urea distribution volume (water space) and relatively inert in terms of production of uremic toxins. Obesity and high BMI, however, do not always equal an excess of total body water space and therefore the feasibility of PD in large subjects without excess fat tissue is a different issue. In a single-center small cohort, we have documented relative success of PD in large subjects weighing >100 kg (Kt/V: 1.96 ± 0.29 vs. 2.22 ± 0.47 in those weighing ≤75 kg) (283).

5.3.2 ***Impact of access choice on morbidity and mortality***

Access-related infection is the single largest reason for admission in ESRD patients and a major cause of or contributor to mortality. The impact of access-related infection is probably under-appreciated in hemodialysis patients for the single reason that the definition is hinging on obtaining blood culture and clinical astuteness to seek infection in the background of confusing clinical presentations. It is critical to recognize infected TDCs and blood cultures should be obtained at a low clinical threshold of suspicion, preferably during dialysis (284, 285). This is highly important as uremia even under treatment and without blood stream access devices confirms an increased risk of bacteremia and fungemia (286). Our inpatient cohort was relatively ill with generally high CRP values. Herewith, the measurement of CRP was unlikely to contribute further to the clinical decision-making.

5.3.3 ***Timely removal of vascular access devices***

An inordinate amount of clinical presentations may be ultimately attributed to access-related infections and patients with indwelling vascular access are at a particulate risk (287). *S. aureus* is a particularly common pathogen (288). Biofilms on the catheter may represent a sanctuary shielding bacteremia from the therapeutic level of antibiotics, making eradication difficult (103). An emerging treatment trend to address the issue of biofilm is the intraluminal antibiotic-enriched catheter “lock” solution which, in addition to systemic antibiosis (289), is cutting the need for catheter removals and recurrent bacteremia in half (289). Whether this strategy results in selecting out resistant bacteria

remains debated (289, 290). While some advocate guidewire-assisted catheter exchange (rather than utilizing a new puncture site), such approach is inevitably challenged by a higher rate of recurrence of infection. Low albumin, anemia or elevated CRP are known risk factors associated with adverse outcomes during TDC exchange (291, 292). As we summarized in our review paper on TDC removals:

> "In our opinion, removal of TDC in the setting of endovascular infection and critical illness is an emergency and mandates immediate action (114, 293). Unlike renal dialysis catheter placement, it is not meaningful to entertain "simulation" training for TDC removal, *in lieu* of real-life, hands-on experience at bedside (294). Furthermore, unless a clear alternative source (e.g., pneumonia, infected decubitus ulcer) is present on presentation, it may be prudent to remove TDCs empirically in hemodynamically unstable patients, while awaiting the blood culture results (114)."(172) … and: "Many of these patients presents with relatively non-specific or perplexing symptoms (e.g., chest pains, shortness of breath or only mild fever) (114, 273) and infection of TDC should be disproportionally high on the differential. Forming the appropriate clinical decision to remove the infected hardware is important part of clinical training. In addition to elevated white blood cell count, otherwise poorly explained rise of troponin-I (114) or CRP (169, 295) may provide useful clues early into the evaluation process."(172)

5.3.4 ***Complications during Tunneled Dialysis Catheter removal***

Bleedings, including major local bleedings do not appear to be a major concern during TDC removals. In a very recent paper by Dossabhoy et al., aspirin or clopidogrel therapy in roughly two-third of the cohort did not seem to increase bleeding risk (1/49 or 2% of the subjects with minor bleeding on these medications) (171). Another study conducted by Martinez et al. also found that anti-platelet therapy or anticoagulation was not associated with an increased risk of bleeding either (296). Checking of coagulation profile such as prothrombin time international normalized ratio (INR) can be generally reserved for patients on vitamin-K antagonist therapy or for those overtly ill and assumed to have consumptive coagulopathy. Only anecdotal experience exists with prolonged INR up until 3 (170, 171) and most of us would favor normalizing INR before catheter removal. Failed removal was generally rare in our experience; e.g., in the personal practice of the author of the present thesis (>400 removal over 15 years) this has happened in less than 1% of the cases. Based on our publications, it is probably expected to occur

no more than 1/50 – 1/200 (172). During graduate medical education training, hands-on assistance was needed from our faculty at a rate 6-10/100 (personal communications from Neville Dossabhoy, M.D., Shreveport, LA and Mihály Tapolyai, M.D., Budapest, Hungary). In our experience, it took approximately 5-8 supervised procedures for our first-year renal trainees to master the ”learning curve” for the procedure and assimilate the skill to competency (172). In our own series, including the one by Dossabhoy et al., we have not encountered catheter body tears. On the other hand, single-lumen twin dialysis catheters (i.e., Tesio, MedComp) are reported to fracture very easily and are not suitable for traction removal (297, 298). Published literature has stated that immediate clamp compression of the proximal catheter fragment is to be executed to prevent air embolism or bleeding for these (297). Subcutaneous tunnels do collapse smoothly with external compression and hemostasis after removal and do not offer routes for air embolisms.

Retained cuffs do not seem to represent a problem. Surgical removal has been routinely offered for the affected patients but all patients deferred. We have not encountered subsequent local infections caused by the retained hardware. As we stated in our review paper:

> “It appears these structures can be left in place, a scenario analogous to the clotted synthetic hemodialysis grafts (297). Alternatively, the retained cuffs can be removed later on, both for cause (e.g., migration) or aesthetic reasons via a direct skin excision above it (297). One unusual complication for retained cuffs is the potential misinterpretation as a mass on mammogram (299). Similar to our results, the published literature appears to quote a rate ≤8% of cuff retention (0-10 %) (126, 297). Additionally, cuff retention may be dependent on the catheter material, much less with polyurethane-based materials (297). In our inpatient series, we also have documented a 0% cuff retention rate (114), but many of those catheters were removed in clinically ill hospitalized patients for suspected or proven infections, had breakdown around the exit site, etc., thus making cuff retention less likely to occur.”(172)

A separate issue is the embedded catheter proximal to the entry point in the internal jugular vein (300). As we summarized in our review paper:

> “If catheter adherence to central veins or right atrium (301) is suspected, the bedside procedure should be aborted and care should be escalated with fluoroscopic guidance and surgical or interventional radiology consultation. Accordingly, it is a key for the operators to recognize the difficult to remove or (“stuck” or “embedded”) catheter. A very large single-center database

spanning nearly a decade suggested this complication in about 1% of long-term dialysis catheters (302). Risk factors for catheter retention include cumulative indwelling time, female gender, small vessel caliber, past episodes of infection creating a prothrombotic state and repeated catheterizations in the same vessel (303). This situation also appears to occur more commonly with catheters implanted into the left internal jugular vein; likely due to the presence of more potential friction points associated with the longer catheters, as well as in those with ipsilateral intracardiac device wires or stents (304) […] Accordingly, retained catheters fixated to the surrounding structures beyond the Dacron cuff may represent a distinct challenge and require endoluminal dilatation (305, 306), transcatheter extractor device (307) or laser sheath liberation (308), depending on institutional experience and are otherwise well summarized in recent reviews (170, 300).”(172)

5.4 Emerging concepts and future directions

5.4.1 ***Optimized start for renal replacement therapy***

Multiple studies argue against a preventive or “early” start of renal dialysis (309-311). In fact, in one of the studies, elderly subjects with early dialysis initiation were associated with greater all–cause mortality, cardiovascular mortality and all-cause hospitalizations (311). Rather, as stated by the National Kidney Foundation (NKF)-KDOQI Hemodialysis Adequacy Work Group, initiation maintenance dialysis therapy should be based on the presence of symptomatic uremia, protein energy wasting, metabolic abnormalities, or volume overload “rather than a specific level of kidney function” (312).

5.4.2 ***Convective clearance.***

Current studies supporting the value of on-line hemodiafiltration represent almost all *post-hoc* analyses (313, 314), but one study (315), with variation of cut-offs representing “sufficient” or “ideal” convective clearance (i.e., the hemofiltration component of RRT): >22 L (313), >17.4 L (314) or >18 L (315) per session. A recent meta-analysis of 35 trials and more than 4000 patients suggested a lower cardiovascular (RR 0.75, 95% CI: 0.58-0.97), albeit not all-cause mortality (RR 0.87, 95% CI: 0.70-1.07) with HDF (316). Perhaps not unrelated, intra-dialytic hypotension was also reduced with HDF (RR 0.72, 95% CI: 0.66-0.80). None of these studies have been adjusted for the

body surface or calculated water space, when calculating the presumed survival effect of an achieved HF rate. Further, cost-effectiveness studies suggested quality-adjusted life year a cost of HDF vs. HD approximately €287,679 (or approximately 300,000 USD in June 2016), above the usually acceptable societal threshold (317). When HD and HDF were compared at different treatment times in a small, single-center trial (2x2 factorial design, HD vs HDF, 4-hour vs 8-hour treatment times), treatment times, but not modality conferred greater hemodynamic stability (9).

5.4.3 *Frequency is not replacing effective time in renal replacement therapy*

Concerns exist with regard to the "stand-alone" frequent dialysis, that is more frequent dialysis (>three times a week) without meaningfully extending the weekly time spent on renal replacement (318). Commitment of time to travel, logistics of more frequent patients' check-in and check-out procedures, increased utilization of medical supplies and increased access complications are additional concerns (319-321). In the pivotal Frequent Hemodialysis Network daily trial a statistically significant increase of "first access events" (repair, loss, and access-related hospitalizations) was observed among frequent dialysis enrollees, compared with a conventional HD group (HR 1.76, 95% CI: 1.11-2.79; p=0.02). To date, no prospective, randomized controlled trials of sufficient power are in existence to report on hard clinical outcomes. On the other hand, home dialysis remains a good choice to optimize weekly time on dialysis. Newer and simpler technologies (e.g., NxStage Home System, NxStage Medical Inc., Lawrence, MA, USA) have simplified the logistics of home dialysis and reduced the time-commitment for preparations. While most of the existing studies are likely to be contaminated by residual confounders, they all suggest survival advantage with more frequent standard 3-4-hour sessions (322, 323) or more prolonged (e.g., nocturnal) sessions of RRT.

5.4.4 *Gradual escalation of treatment time*

According to current DOPPS data, roughly one-quarter of patients in China receive maintenance dialysis only twice a week (26% vs 5%, for the rest of the DOPPS regions) (324). Well-preserved RRF may enable such approach in subjects with well-preserved functional status and less comorbidity. On the other hand, less frequent and incrementally increased hemodialysis may preserve RRF longer (325). In a recent, single-

center Chinese study, independent predictors of RRF loss were thrice-weekly dialyses, larger urea reduction ratios and the presence of intradialytic hypotension (326).

5.4.5 ***Ensuring the lack of constipation and accelerating gastrointestinal transit time.***

Uremic toxins are generated disproportionally in various body compartments. While some tissues (muscles) are more active in that regard than others (fat tissue), the largest generating compartment is in fact the interface of human-bacteria in the GI tract. In this regard, it would be perhaps most appropriate to view PD as a "compartment dialysis" (272), a modality delivering disproportionately large clearance to the gut and liver, the very compartments generating most uremic toxins. Conceptually, this may be the largest contributor to the anti-uremic effect of PD, to explain the somewhat disconnected effectivity from removals of uremia markers, such as creatinine and blood urea nitrogen (BUN). While oral binders of uremic toxins failed to impact renal survival, the much simpler clinical question of frequent/loose bowel movements are in fact not studied in ESRD, including in anuric ESRD patients. Therefore, the scenario is somewhat analogous to end-stage liver disease: to reduce the generation and absorption of uremic toxins by inducing a mild state of diarrhea by laxatives. In a small, single-center trial (N=20), dietary fiber supplements lowered the level of non-dialyzable colon-derived uremic toxin (indoxyl sulfate and p-cresol sulfate) concentrations, presumably by binding in the GI tract (327). Similarly, pre- and probiotic supplements may also have the potential to lower effective uremic toxin generation and absorption (328).

6. Conclusions

In a single-center trial of eighty-one subjects, we found that fluid overload was common (46.9% had VRWG ≥10%) and an important prognostic factor for survival in critically ill AKI patients treated with CRRT. Increasing VRWG had a graded adverse impact on 30-day survival, with mortality increasing by two and half times in those with VRWG ≥10% (OR 2.62, 95% CI: 1.07-6.44; p=0.046) and almost four times with VRWG ≥20% (OR 3.98, 95% CI: 1.01-15.75; p=0.067) in univariate analysis. Oliguria was also a strong predictor of death, with OR for mortality 3.22 (95% CI: 1.23-8.45; p=0.02). Both oliguria (OR 3.04, p=0.032) and VRWG ≥10% (OR 2.71, p=0.040) maintained their statistically significant association with mortality in multivariate models that included sepsis and/or Apache II scoring. Therefore, among the first in adult medicine, we established fluid overload before CRRT to be an important prognostic factor for survival in critically ill patients with AKI. Further studies are needed to elicit mechanisms and develop effective preventive and therapeutic interventions for this very vulnerable group of patients.

We found that treatment time during conventional in-center HD had a significant cross-sectional association with serum albumin but not with CRP. In our study of >600 participants, treatment time longer than four hours was associated with a decreased risk of having low (< 40 gm/L) albumin levels with OR of 0.397 (95% CI: 0.235-0.672; p<0.001). For elevated CRP, significant correlates were congestive heart failure (OR 1.634, 95% CI: 1.154-2.312; p=0.006) and acute infection (OR 1.799, 95% CI: 1.059-3.056; p=0.03). However, we have not observed an association between UFR and either CRP or albumin. To our knowledge, this constituted the first report demonstrating an association between treatment time and albumin levels in hemodialysis patients. A large number of our patients, both from the European and North American cohorts achieved serum albumin and CRP targets, albeit with relatively long treatment times (237.3 ±23.8 minutes; approximately 16 minutes longer than the US average at that time). This study underlines and confirms the critical importance of time in good uremic control.

We have documented an excellent efficacy (100% success rate) and good safety profile during bedside removals of TDC from a combined cohort of two studies and 192 subjects. About one-third of the TDC removals took place urgently due to bacteremia,

and elevated troponin-I had statistically significant associations with catheter-induced bacteremia in inpatients ($p<0.05$). Most (>50%) of the outpatient removals took place due to access maturation or cessation of indication for renal dialysis ($p<0.0001$). During outpatient removals, we observed subcutaneous retainer cuff separation in 6.5% of cases, all in males. There was a significant association between cuff retention and outpatient removal ($p=0.007$) but not with the operators' level of training, or the site of removal. However, we have not observed catheter body tear or frank complications (major vascular damage or air embolism). To our knowledge, these results constituted the first reports demonstrating the feasibility and excellent success rate for bedside removal of tunneled-cuffed permanent hemodialysis catheters by nephrologists. Our results underscore the potential for this procedure to enrich clinical nephrology training and contribute to the clinical competency of practicing nephrologists.

7. Summary

Medicine is an ever-changing science. Not only our knowledge is changing but also the characteristics of the underlying populations. New methods and technology offer not only new avenues to address illnesses but new sources of morbidity and mortality as well. Volume overload is an emerging marker for the severity of illnesses in critically ill patients and a persisting problem in chronic dialysis patients. In critically ill patients with acute renal impairment, volume overload may partially mask the elevation of serum creatinine and appears to be contributing to adverse outcomes independently. Accordingly, volume-related weight gain should be viewed as a prognostic marker on its own during the daily evaluation of these patients and conventional indication of renal replacement therapy (RRT) may not apply in critically ill patients. In dialysis patients, clinical focus is shifting away from a purely biochemical and blood pressure-centered viewpoint to a much more patient-centered one, emphasizing effective volume control, reducing excess fluid gains and promoting hemodialytic stability during RRT. Time on renal replacement therapy is of paramount importance to deliver effective RRT and should not be compromised on the patients' and providers' convenience. Reduced treatment time of less than 4 hours three time a week is associated with likelihood of low albumin. Despite recommendations formed by professional societies, hemodialysis catheter use is still highly prevalent in end-stage renal disease patients and an ongoing source of morbidity and mortality. Every effort should be made to minimize the use and duration of indwelling artificial vascular access devices, including timely removal during catheter sepsis or after access maturation. Bedside removal of tunneled-cuffed hemodialysis catheters is a safe procedure with minimal complication rate, including during graduate medical education by nephrology trainees. New technologies and approaches need to be fostered to optimize the delivery of renal replacement therapy and to address emerging challenges.

8. Összefoglalás

Az orvostudomány folyamatosan változik. Nem csupán ismereteink bővülnek, hanem a vizsgált emberi populációk sajátosságai is változnak. Új módszerek és technológiák mindamellett, hogy a gyógyításnak újabb perspektíváit nyitják meg, komplikációk és halálozások újabb forrásait is jelenthetik. A folyadék-túlterhelés mértéke - mely egy gyakori probléma a krónikus vesepótló terápiára szoruló betegeknél - egy viszonylag újonnan felismert jele lehet az általános állapot súlyosságának az intenzív osztályos kezelés során. Ezen betegeknél az akut vesekárosodás mellett, a folyadékterhelés mértéke részben elfedheti a szérum kreatinin emelkedését, és önmagában is hozzájárulhat a szövődmények kialakulásához. Ennek megfelelően a folyadékmennyiséggel összefüggő súlynövekedésnek kiemelt prognosztikai fontosságot kell tulajdonítani e betegek napi kiértékelése során, ahol a vesepótló terápia (VPT) hagyományos indikációi sem feltétlenül alkalmazhatóak. A krónikusan művese kezelésben részesülő betegeknél a tisztán biokémiai és vérnyomás-értékre koncentráló megközelítés egyre inkább átadja a helyét egy sokkal beteg centrikusabb megközelítésnek, amely a hatékony folyadékmennyiség-kontrollt hangsúlyozza, minimalizálva a felesleges folyadékbevitelt a kezelések között és hangsúlyozza a hemodinamikai stabilitás fontosságát a kezelések alatt. A VPT időtartama kritikus fontossággal bír a kezelés hatékonyságának szempontjából, így nem megengedhető, hogy csupán kényelmi szempontok alapján ezt csökkentsük. A heti háromszor kezelt művese betegek esetében, a négy óránál rövidebb ideig tartó kezelések az albumin szint csökkenésével járnak. A szakmai testületek által javasolt gyakorlat ellenére a hemodialízis katéter használata változatlanul rendkívül gyakori a dialízissel kezelt betegeknél, jóllehet a komplikációk és halálozás esélyét megnöveli. Mindent meg kell tenni hemodialízis kanülök használatának a minimalizására, illetve fertőzés vagy fisztula beérés esetén amilyen hamar csak lehet, eltávolításukra. Az alagutas hemodialízis katéterek betegágy melletti eltávolítása minimális komplikációval terhelt orvosi beavatkozás, amely biztonságosan elvégezhető nefrológus szakorvos jelöltek által is a szakképzés során. Új technológiák és módszerek sikeres beépítése szükséges, hogy optimalizáljuk a meglévő VPT hatékonyságát, és sikerrel nézzünk szembe a reánk váró új kihívásokkal.

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