



UNIVERSITAT<sup>DE</sup>  
BARCELONA

# Sepsis associated Acute Kidney Injury: incidence, risk factors and continuous renal replacement therapies

Xose Luis Pérez Fernández



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# UNIVERSITAT DE BARCELONA

## DOCTORAL THESIS

### **Sepsis associated Acute Kidney Injury: incidence, risk factors and continuous renal replacement therapies**

Xosé Luis Pérez Fernández

Universitat de Barcelona, 2019



Thesis title: **“Sepsis associated Acute Kidney Injury: incidence, risk factors and continuous renal replacement therapies”**

Memory presented by Xosé Luis Pérez Fernández to obtain de degree of European Doctor in Medicine.

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“Eventually, all things merge into one, and a river runs through it. The river was cut by the world's great flood and runs over rocks from the basement of time. On some of the rocks are timeless raindrops. Under the rocks are the words, and some of the words are theirs. I am haunted by waters.”

**N Maclean, A River Runs Through it and Other Stories.**

“Desde alí, vendo ao fondo os picoutos da raia, ireille escribindo a Vde. das pequenas cousas que vaian constituíndo o meu vivir en Lobosandaus, lugar que eu sinto agora, apenas una hora de pór pé a terra da besta que me trouxera desde Bande, logo da viaxe interminábel en dilixencia, coma un final do mundo coñecido, recoleito en si mesmo aínda que solloso, amábel e hospitalario.”

**XL Méndez Ferrín, Arraianos.**

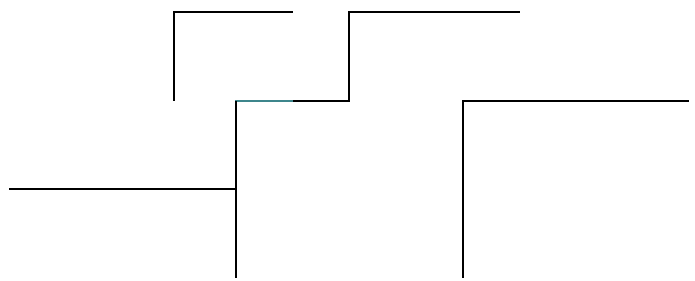
“C'est à ce moment qu'il lut sur la tombe la date de naissance de son père, dont il découvrit à cette occasion qu'il l'ignorait. Puis il lut les deux dates, “1885-1914”, e fit un calcul machinal: vingt-neuf ans. Soudain une idée le frappa qui l'ébranla jusque dans son corps. Il avait quarante ans. L'homme enterré sous cette dalle, et qui avait été son père, était plus jeune que lui.”

**A Camus, Le Premiere Homme.**

“La noche del 23 de junio de 1956, verbena de San Juan, el llamado Pijoaparte surgió de las sombras de su barrio vestido con un flamante traje de verano color canela; bajó caminando por la carretera del Carmelo hasta la plaza Sanllehy, saltó sobre la primera motocicleta que vio estacionada y que ofrecía ciertas garantías de impunidad (no para robarla, esta vez, sino simplemente para servirse de ella y abandonarla cuando ya no la necesitara) y se lanzó a toda velocidad por las calles hacia Montjuich.”

**J Marsé, Últimas Tardes con Teresa.**





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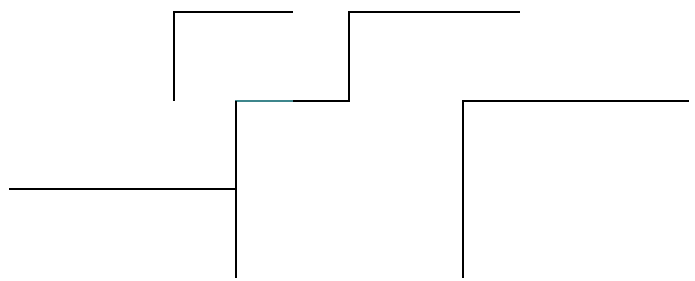
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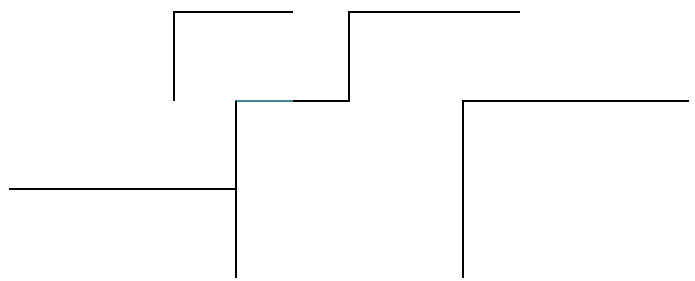
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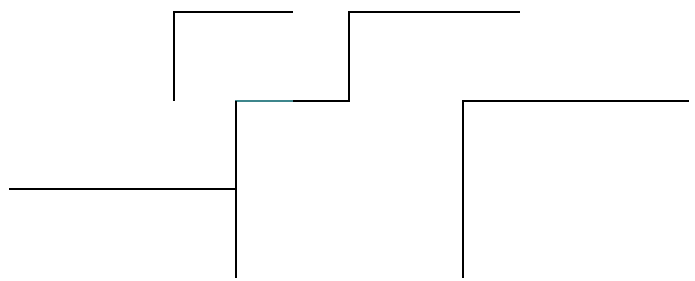
A Monti por ser ella la única compañera de mi vida y traer a este mundo a nuestr@s hij@s Xoán y Aurelia/Bruno que dan sentido a todo.

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*Abbreviations*





## Abbreviations

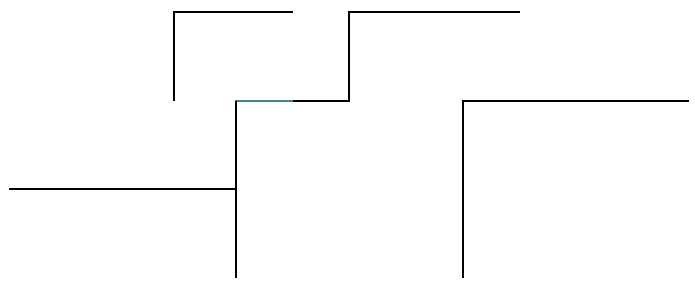
ACE-inhibitor	angiotensin-converting enzyme-inhibitor
ADQI	Acute Dialysis Quality Initiative
aHR	adjusted hazard ratio
AKD	acute kidney disease
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ALI	Acute Lung Injury
ALT	alanine aminotransferase
AN69	Polyacrylonitrile
APACHE2	Acute Physiology and Chronic Health Evaluation score 2
APS-III	acute physiology and chronic health evaluation score 3
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
ARF	acute renal failure
AST	aspartate aminotransferase
AT	Antithrombin
AUC	area under the curve
AUROC	area under the receiver operating characteristic curve
BE	base excess
BP	blood purification
BUN	blood urea nitrogen
CA-AKI	community acquired AKI
CAP	community-acquired pneumonia
CAVH	continuous arteriovenous hemofiltration
CI	confidence interval
CKD	chronic kidney disease
CPB	cardiopulmonary bypass
CPFA	Coupled Plasma Filtration Adsorption
CRRT	continuous renal replacement therapies
CSA-AKI	cardiac surgery associated AKI
CSF2	Colony stimulating factor 2
CVP	central venous pressure
CVVH	continuous venovenous hemofiltration
CVVHD	continuous venovenous hemodialysis
CVVHDF	continuous venovenous hemodiafiltration
d	Days
DAMPs	damage associated molecular patterns
DIC	disseminated intravascular coagulation



DR-5	death receptor
e.g.	for example
EC	extracorporeal circuit
ECMO	extracorporeal membrane oxygenation
ED	emergency department
EGDT	early goal-directed therapy
EIHF	early isovolaemic haemofiltration
EAA	endotoxin activity assay
ESRD	end-stage renal disease
ET	endothelin.
FF	filtration fraction
FO	fluid overload
FST	furosemide stress test
GFR	glomerular filtration ratio
GM-CSF	granulocyte macrophage colony-stimulating factor
h	hours
HA-AKI	hospital acquired AKI
HCO	High cutoff
HD	hemodialysis
HES	hydroxyethyl starch
HF	hemofiltration
HI	hemodynamic index
HMD	Hemodynamic
HR	hazard ratio
HVHF	High Volume hemofiltration
HVT	high tidal volume
IAH	intra-abdominal hypertension
IAP	intra-abdominal pressure
ICU	intensive care unit
IFN- $\gamma$	interferon gamma
IGFBP7	insulin-like growth factor-binding protein 7
IHD	intermittent hemodialysis
IIT	intensive insulin therapy
IL-10	interleukin-10
IL-1ra	interleukin-1 receptor antagonist
IL-1 $\beta$	interleukin-1 $\beta$
IL-4	interleukin-4
IL-6	interleukin-6
IQR	inter-quartile range
ITR	inter-tertile range

IU	international units
IV	intravenous
kDa	kilodaltons
KDIGO	Kidney Disease Improving Global Outcomes
KIM-1	kidney injury molecule-1
L	Litres
LOS	length-of-stay
LPS	lipopolysaccharide
LVHF	Low volume hemofiltration
LVT	low volume tidal
MAP	mean arterial pressure
MCP-1	monocyte chemoattractant protein-1
MD	mean difference
MDRD	modification of diet in renal disease
MIF	macrophage migration inhibitory factor
min	Minutes
MODS	multiorgan dysfunction syndrome
MOF	multi-organ failure
MRI	Magnetic resonance imaging
MRSA	methicillin-resistant Staphylococcus aureus
MV	mechanical ventilation
MW	molecular weight
NETs	neutrophil extracellular traps
NF_κB	nuclear factor_κB
NGAL	neutrophil gelatinase-associated lipocalin
nm	Nanometers
OR	odds ratio
p.m.p	per million population
PA	Polyamide
PAMPs	pathogen associated molecular patterns
PaO <sub>2</sub> /FiO <sub>2</sub>	partial pressure of oxygen arterial blood/inspiratory oxygen supply index
PDHF	pump driven hemofiltration
PE	Plasma exchange therapies
PEEP	end-expiratory pressure
PEI	polyethyleneimine
PG	prostaglandine
PH	proportional hazards
PHVHF	Pulse High Volume hemofiltration
PIRRT	prolonged intermittent RRT
PMX	polymixin

PMX-F	polymixin B cartridges
PMX-HP	Polymyxin B-immobilized hemoperfusion
Ppl	plateau pressure
PRRs	pattern recognition receptors
PS	Polysulphone
PT	prothrombin time
QB	blood flow
qSOFA	quick sequential organ failure assessment
RBC	red blood cell
RCA	regional citrate anticoagulation
RCT	randomized controlled trial
RESP	Respiratory
RIFLE	Risk Injury Failure Loss ESRD
RR	relative risk
RRT	renal replacement therapies
SA-AKI	Sepsis associated acute kidney injury
SBP	systolic blood pressure
SCr	serum creatinine
ScvO <sub>2</sub>	central venous oxygen saturation
SIRS	systemic inflammatory response syndrome
SLED	sustained/slow low-efficiency dialysis
SOFA	sequential organ failure assessment
SSC	Surviving Sepsis Campaign
SURV	Survival
SVR	Systemic vascular resistance
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TGFβ	transforming growth factor-β
TIMP-2	tissue inhibitor of metalloproteinases-2
TMP	transmembrane pressure
TNFR-I	tumor necrosis factor receptor
TNF-α	tumoral necrosis factor-α
TWA	time weighted average
TWA-MAP	time-weighted average mean arterial pressure
UO	urine output
VALI	ventilator associated acute lung injury
VHVHF	Very high volume hemofiltration
vs.	versus
VT	tidal volume
ZBUF	zero-balance ultrafiltration



*Background*





## 1. Background (Supplementary appendix 1)

Sepsis associated acute kidney injury (SA-AKI) in critically ill patients is one of the main issues that critical care professionals must handle in their everyday practice at the intensive care unit (ICU). The appearance of SA-AKI increases mortality<sup>1,2</sup> and all costs associated to these patients (increasing length of stay [LOS], mechanical organ-support requirements, human resources, blood transfusions, etc...).<sup>3,4</sup> Patients with SA-AKI are progressively overloaded with solutes and fluid that health professionals must tightly control and try to decrease when necessary employing pharmacological measures,<sup>5</sup> and renal replacement therapies (RRT).<sup>6</sup>

In 1976 Burton created the term "hemofiltration"<sup>7</sup> and a year later Kramer developed the continuous arteriovenous hemofiltration (CAVH) technique, which used systemic arteriovenous pressure difference in an extracorporeal circuit to continuously produce an ultrafiltrate.<sup>8</sup> In the following decade the limited capacity of this procedure to remove nephrotoxins and the complications related to arterial access led to the development of venovenous pump-driven techniques.<sup>9</sup> The use of venovenous pump-driven techniques became progressively extended and generally referred to as continuous renal replacement therapies (CRRT). This technical innovation was associated with the introduction of biocompatible membranes in the procedures that decreased the generation of inflammatory mediators by the system itself.<sup>10,11</sup>

In 1991 CAVH was measured against pump driven hemofiltration (PDHF), showing a better survival rate in the PDHF group that appeared related to a faster elimination of toxic mediators.<sup>12</sup> These would include nephrotoxins and other toxins as suggested by the improvement in cardiovascular function with hemofiltration observed in animals after endotoxin injection and the impairment of hemodynamics in healthy animals with the infusion of the "septic ultrafiltrate".<sup>13</sup> In this setting, Bellomo et al. suggested that CRRT might remove cytokines from the circulation of septic patients.<sup>14</sup>

Since then, many different strategies and modalities of CRRT have been tested with the aim to improve the outcomes of critically ill patients with SA-AKI, yet none of them (concerning dose,<sup>15,16</sup> timing,<sup>17,18</sup> or adsorption properties<sup>19</sup>) have been clearly successful. On the other hand, from an ICU perspective, all these years of analysis have been critical in the acquisition of knowledge and confidence in the use of CRRT, now

widely extended to all ICUs facilitating the management of critically ill patients with AKI and increasing their survival rate.<sup>6,20</sup> Despite these huge advances, the optimal timing for CRRT, the identification and prevention of risk factors that contribute to the appearance or progression of SA-AKI and the choice of CRRT modality remain all as crucial questions to which sound answers are yet to be found.

### 1.1. AKI definition

Acute kidney injury (AKI), also known as acute renal failure (ARF), is an abrupt decrease in kidney function that occurs over hours to days.<sup>21</sup> This is in contradistinction to chronic kidney disease (CKD), where renal function declines over the course of months to years. In 2004, the Acute Dialysis Quality Initiative (ADQI) published the first AKI consensus definition, with the goal of standardizing disease recognition and endpoints for clinicians as well as for research studies, including clinical trials.<sup>22</sup> The RIFLE criteria (an acronym that stands for risk, injury, failure, loss, and end-stage renal disease [ESRD]) used acute changes in serum creatinine (SCr) and urine output (UO), readily available measurements, to define three progressive levels of renal dysfunction (R, I, and F) and two clinical outcomes (L, E). Subsequent consensus definitions would use the term AKI, a more inclusive term that underscores the importance of the injury and consequent change in the renal function. Through this lens, the 2007 definitions of the Acute Kidney Injury Network (AKIN)<sup>23</sup> focused on the initial injury previously deemed risk, injury, and failure of the RIFLE classification, terming them stage 1, 2, and 3 AKI. Loss and end stage kidney disease in the RIFLE system were removed along with the partial reliance on glomerular filtration rate (GFR). Additionally, the AKIN criteria included small changes in SCr (>26.5  $\mu\text{mol/L}$  increase in 48 hours[h]) in the definition of stage 1 AKI.

Several large observational trials confirmed the validity of the RIFLE and AKIN revised criteria, as increasing severity of AKI was associated with increasing risk of death.<sup>24,25</sup> Despite high incidence and significant effect on outcomes, a concern remained that AKI was underdiagnosed owing to inconsistent screening practices and the tendency for these criteria to miss AKI that occurs before arrival at an acute care setting. The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for AKI present the most recent consensus definitions, which again attempt to refine the sensitivity and specificity of the AKI definitions.<sup>26,27</sup> The KDIGO

definition emphasizes AKI risk assessment and evaluation while extending criteria to include a rise in SCr of 50% or greater over the presumed baseline within seven days of assessment. The association of AKI defined by these criteria with adverse outcomes has now been validated in a large number of clinical studies.<sup>3,28</sup> **Table 1** summarizes the RIFLE, AKIN, and KDIGO criteria for AKI.

**Table 1.** AKI definitions: RIFLE, AKIN, and KDIGO criteria for AKI

Classification	Definition for AKI	Stage	Serum Creatinine criteria for AKI staging	UO criteria
<b>RIFLE</b>	Increase in SCr $\geq 50\%$ within 7 d	Risk	To $\geq 1.5$ times baseline	$< 0.5$ ml/kg/h for $> 6$ h
		Injury	To $\geq 2$ times baseline	$< 0.5$ ml/kg/h for $> 12$ h
		Failure	To $\geq 3$ times baseline or $\geq 44$ mmol/L increase to at least 354 mmol/L	$< 0.3$ ml/kg/h for $> 24$ h or anuria $\geq 12$ h
<b>AKIN</b>	Increase in SCr $\geq 26.5$ mmol/L or $\geq 50\%$ within 48 h	1	Increase of $\geq 26.5$ mmol/L or to 1.5–2 times baseline	$< 0.5$ ml/kg/h for $> 6$ h
		2	To 2–3 times baseline	$< 0.5$ ml/kg/h for $> 12$ h
		3	To $\geq 3$ times baseline or $\geq 26.5$ mmol/L increase to at least 354 mmol/L or initiation of RRT	$< 0.3$ ml/kg/h for $> 24$ h or anuria $\geq 12$ h
<b>KDIGO</b>	Increase in SCr $\geq 26.5$ mmol/L within 48 h or $\geq 50\%$ within 7 d	1	Increase in SCr $\geq 26.5$ mmol/L within 48 h or to 1.5–2 times baseline	$< 0.5$ ml/kg/h for $> 6$ h
		2	To 2–3 times baseline	$< 0.5$ ml/kg/h for $> 12$ h
		3	To $\geq 3$ times baseline or to at least 354 mmol/L or initiation of RRT	$< 0.3$ ml/kg/h for $> 24$ h or anuria $\geq 12$ h

AKI: Acute Kidney Injury; AKIN: Acute Kidney Injury Network; d: days; h: hours; KDIGO: Kidney Disease Global Outcomes; RIFLE: Risk Injury Failure Loss ESRD; RRT: renal replacement therapy; SCr: serum creatinine; UO: urine output.

Consensus definitions for AKI have been critical to move the AKI clinical research field forward, but have significant limitations because they use SCr and UO for the detection of kidney injury. SCr is a marker of GFR and consequently is a late marker of kidney injury (for example [e.g.], by the time SCr rises, injury has long occurred), and it has been suggested that SCr production may be affected by sepsis.<sup>29</sup> UO may reflect a number of states including AKI, such as volume depletion and dehydration.<sup>30</sup> Numerous studies have focused on identifying more sensitive and specific biomarkers of AKI to aid in earlier detection and better prognostication. These include urinary biomarkers of tubular injury such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-



associated lipocalin (NGAL), as well as markers of glomerular filtration, such as cystatin C, which is less dependent on muscle mass than SCr.<sup>31</sup>

A few recent studies have shown that tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) are specific biomarkers of structural renal damage in critically ill patients.<sup>32,33</sup> TIMP-2 and IGFBP7 are protective molecules involved in G1 cell-cycle arrest that moderate apoptotic, angiogenic<sup>34</sup>, inflammatory<sup>35</sup> and ischaemic processes.<sup>36</sup> Since renal cell arrest usually occurs 24–48 h before SCr rises due to a significant fall in the GFR, TIMP-2 and IGFBP7 are thought to be earlier AKI biomarkers than SCr. TIMP-2 and IGFBP7 are detectable in urine. Previous studies in unselected ICU populations have shown that when analysed together as the index [TIMP-2]·[IGFBP7], they perform better than SCr, urine and plasma NGAL, plasma cystatin-C and KIM-1 for early detection of AKI and improved risk stratification for renal and general outcomes.<sup>32,33,37</sup> UO and SCr are increasingly being complemented by these novel biomarkers that can rapidly and specifically recognise AKI. Thus, future definitions of AKI may soon include such biomarkers.

## 1.2. AKI epidemiology

Previous to ADQI definitions, AKI epidemiological studies showed a great variability as these results were based on how AKI was defined and the type of population studied.<sup>38,39</sup> Liaño and colleagues, during a nine month period, from November 1991 to October 1992, designed and conducted a prospective protocol in order to assess all AKI episodes encountered in the 13 tertiary-care hospitals in Madrid, Spain (covering 4.2 million people of over 14 years of age). AKI was considered when a sudden rise in SCr concentration to more than 177  $\mu\text{mol/L}$  was found in patients with normal renal function, or when the sudden rise (50% or more) was observed in patients with previous mild-to-moderate CKD (SCr <264  $\mu\text{mol/L}$ ). The overall incidence of AKI was 209 cases per million population (p.m.p) (95% confidence interval [CI], 195 to 223), mortality (45%) was much higher than that of the other patients admitted and RRT was required in 36% of patients.<sup>38</sup>

Since then, consensus definitions for AKI have greatly facilitated large epidemiological studies examining the incidence and outcomes of AKI. Current incidences of AKI vary between populations, from more than 5000 cases p.m.p per year for non-RRT requiring

AKI, to 295 cases p.m.p per year for RRT requiring disease.<sup>40</sup> The disorder has a frequency of 1-9% in hospital inpatients<sup>41</sup> and is especially common in critically ill patients, in whom the prevalence of AKI is greater than 40% at admission to the ICU if sepsis is present.<sup>42</sup> Occurrence is more than 36% on the day after admission to an ICU,<sup>42</sup> and prevalence is greater than 60% during ICU stay,<sup>43,44,28</sup> although this rate will vary depending on the type of ICU population (medical ICU versus [vs.] neurosurgical ICU, e.g.).<sup>28</sup>

Other studies have found that sepsis contributes in 33% to 50% of all cases of AKI, making sepsis the leading cause of AKI.<sup>45,2</sup> Along the same lines, sepsis studies have found that AKI develops in 40% to 60% of these patients.<sup>46,1,42,47</sup> Not surprisingly, sepsis that is complicated by AKI has a higher mortality rate than sepsis alone, and the severity of sepsis correlates with the severity of AKI.<sup>48</sup> Mortality rates of patients with AKI needing RRT are approximately 35% to 50%, although again will vary based on the population.<sup>15,16</sup> Furthermore, AKI not only complicates the course of sepsis, but it also appears to predispose patients to the development of sepsis.<sup>49</sup> For example, in patients with contrast-induced AKI who subsequently died, 45% developed sepsis as a complication of AKI.<sup>50</sup> In another study, a significantly higher incidence of infections (59 vs. 24%,  $p < 0.001$ ) occurred in patients with AKI compared to patients without AKI after cardiovascular surgery.<sup>51</sup> Similarly, a greater proportion of RRT requiring AKI patients developed blood stream infections when compared to patients without AKI (8.8 vs. 3.5%,  $p < 0.001$ ).<sup>52</sup>

This association between AKI and sepsis along with its clinical impact has led experts to define a specific form of AKI associated to sepsis known as sepsis-associated AKI (SA-AKI) or septic AKI. Implicit in this concept is that dysfunction should be reversible and rescue is possible, but that duration of the insult and underlying renal reserve may limit restoration of renal function. Thus, SA-AKI is a clinical diagnosis based on specific, context-dependent, and imperfect definitions with azotemia and oliguria still its key diagnostic criteria.<sup>26</sup> Similarly, a new global consensus definition of sepsis (Sepsis-3 definitions) has emerged and is likely to be used for epidemiologic and clinical purposes.<sup>53</sup> Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. A major focus of these new definitions was the use of clinical data to develop definitions with prognostic importance (**Figure 1**).

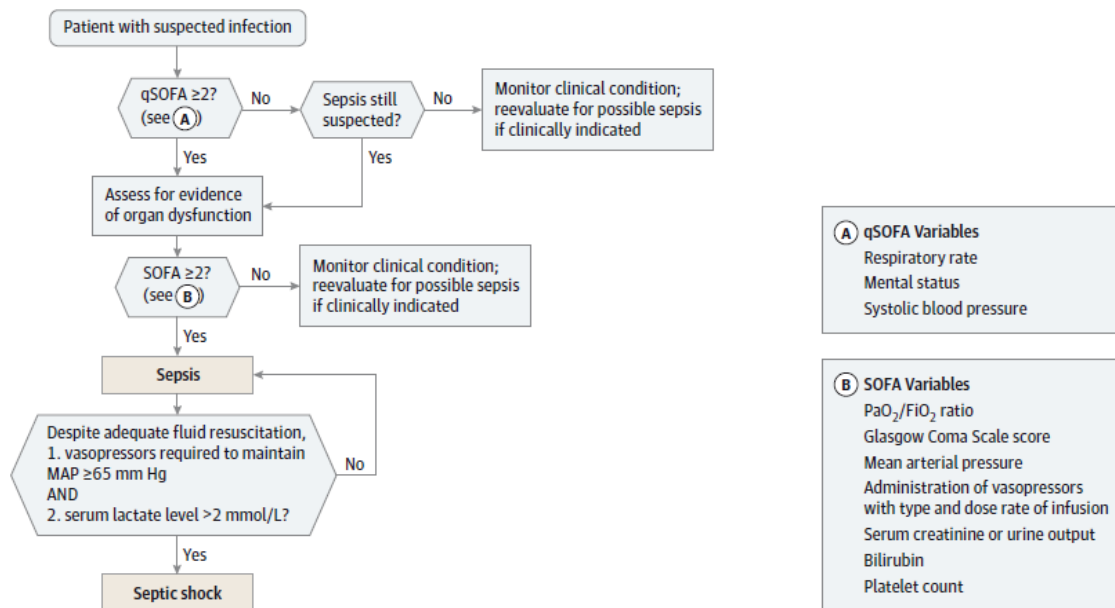


Figure 1. Sepsis-3 definitions

qSOFA, quick sequential organ failure assessment; SOFA, sequential organ failure assessment; MAP, mean arterial pressure; PaO<sub>2</sub>/FIO<sub>2</sub>, partial pressure of oxygen in arterial blood/inspiratory oxygen supply index. Reproduced from JAMA.2016;315(8):801-810.<sup>53</sup>

Logically, SA-AKI should describe a syndrome characterized by the simultaneous presence of both Sepsis-3 and KDIGO criteria. Irrespective of definition, knowledge of baseline renal function remains important and is needed to apply the KDIGO diagnostic criteria. Unfortunately, a baseline SCr may not be available, and a patient with suspected SA-AKI and unknown renal baseline function might have sepsis with CKD, SA-AKI, or both. Ancillary tests and checklists might be helpful to make the correct diagnosis.<sup>54</sup> In the absence of baseline information, however, an estimated GFR using the modification of diet in renal disease (MDRD) equation has been used in patients without a history of CKD.<sup>55</sup> Finally, although urinalysis and urinary biochemistry have limited clinical utility,<sup>56</sup> UO remains important not only for diagnosis but also for risk prediction.<sup>57</sup>

### 1.3. Pathophysiology of SA-AKI

SA-AKI was classically thought to be caused by an ischemic “pre-renal” etiology, attributed to hypoperfusion due to decreased renal blood flow in the setting of leaky

vasculature and systemic vasodilation leading to decreased preload.<sup>58,59</sup> However, several studies have disputed this notion, and research studies are ongoing. For example, arguing against a central role for hypoperfusion per se, a large cohort study found that 25% of hospitalized patients with community-acquired pneumonia (CAP) who never developed shock or required ICU admission developed SA-AKI.<sup>60</sup> A major insight in the pathophysiology of SA-AKI came from an autopsy series of 44 patients who died of sepsis, which found that the degree of renal tubular cell injury in most patients was regional within the kidney, not severe enough to explain the AKI, and most tubular cells appeared relatively normal by electron microscopy.<sup>61</sup>

Furthermore, it is unclear if renal blood flow uniformly decreases during sepsis in humans. A systematic review on this topic concluded that cardiac output is the major determinant of renal blood flow, and because cardiac output is typically increased in sepsis, consequently global renal blood flow may therefore be unchanged or even increased.<sup>62</sup> However, the GFR may still be reduced in the face of normal or supranormal blood flow due to changes in afferent and efferent arteriole vasoconstriction. Thus, it is thought that a large component of SA-AKI is due to functional rather than structural or ischemic injury per se.<sup>63</sup> This is supported by histopathology from large animal models.<sup>64</sup> These effects may be mediated by proinflammatory cytokines and other plasma mediators. For example, plasma from patients with SA-AKI can induce changes in polarity in podocytes and renal tubular epithelial cells in in vitro cell culture.<sup>65</sup>

Gomez and colleagues<sup>66</sup> proposed a “unifying theory” of SA-AKI. In this analysis, the decrease in GFR is in part an adaptive response to inflammatory mediators such as cytokines and lipopolysaccharide (LPS) in which renal tubular cells downregulate metabolic function to use energy toward cell survival. There is also microvascular blood flow dysregulation within the kidneys, which may act to further enhance this adaptive downregulation of cellular metabolism or contribute to regional cellular dysfunction. Furthermore, it has been proposed that both the afferent and efferent arterioles vasodilate, with the efferent arteriole preferentially dilating more.<sup>67</sup> This leads to decreased glomerular capillary pressure and thus decreased GFR.<sup>67</sup> In support of this theory, in animal models of sepsis, use of a selective efferent arteriole vasoconstrictor, angiotensin II, has been shown to increase GFR and UO.<sup>67</sup>

In sum, at this time the exact mechanism of SA-AKI is not fully elucidated. Nonetheless, it seems clear that the primary mechanism is not isolated hypoperfusion. As research in this arena continues, hopefully we will find clinically relevant targets to mitigate the deleterious effects of sepsis on the kidney. As an example, catalytic iron (iron that is not bound to transferrin or protein and is released during tissue injury and during hemolysis) has been proposed to be injurious to the kidney.<sup>68</sup> At least one source of catalytic iron is plasma-free hemoglobin, which can derive from hemolysis or red blood cell (RBC) transfusions. Furthermore, it is thought that plasma-free hemoglobin itself may cause cell damage through oxidation of lipid membranes.

### 1.3.1. Sepsis and organ dysfunction

The “dysregulated” response in sepsis which involves inflammatory and anti-inflammatory events can sometimes lead to homeostasis recovery failure. Main known pathways responsible for this response are some of the following; after activation of immunological innate response, pro-inflammatory cytokines are synthesised, most of them mediated thru nuclear factor\_κB (NF\_κB); complement is activated; coagulation; endothelium dysfunction; and neutrophil extracellular traps (NETs) are generated. All of these associated with immunosuppressive events.<sup>69</sup> Platelets are activated during sepsis and play an important role in organ dysfunction thru thrombotic events such as thrombotic microangiopathy and disseminated intravascular coagulation (DIC). Once activated, platelets modify their shape, hyper express receptors (like P-selectin), and promote degranulation and aggregation. This process enhances platelets adhesion to endothelium, which together with more platelets and leukocytes, leads to the production and liberation of inflammatory and thrombotic mediators and additional leukocytes recruitment; finally interstitial edema appears and NETs are again generated.<sup>70</sup>

Recent theories postulate that identification of pathogenic molecules, known as pathogen associated molecular patterns (PAMPs), and molecules associated to cell injury, known as damage associated molecular patterns (DAMPs), by specific receptors of the innate immunity, known as pattern recognition receptors (PRRs), would trigger a systemic inflammatory response syndrome (SIRS) where the liberation of proinflammatory (interleukin-1β [IL-1β], tumoral necrosis factor-α [TNF-α], interleukin-6 [IL-6], monocyte chemoattractant protein-1 [MCP-1]) and antiinflammatory mediators (interleukin-10 [IL-10], interleukin-4 [IL-4], interleukin-1

receptor antagonist [IL-1ra]), would produce directly or indirectly a multiorgan dysfunction syndrome (MODS).<sup>71,72</sup> Several studies correlate plasmatic concentrations of inflammatory mediators, mainly cytokines (IL-4, IL-1 $\beta$ , MCP-1), with the degree of endothelium dysfunction (hypotension), organ dysfunction, and mortality.<sup>73,74,75</sup>

One of the problems is that sepsis entails multiple disorders in different organs and systems, being unclear the individual contribution of each one, or the dominance of a particular one, in the disease process. Although sepsis is considered as a disorder due to an uncontrolled inflammatory response, clinical interventions directed to the inflammatory elements have not reduce morbidity and mortality associated with the disease.<sup>71</sup> Since inflammation and coagulation are tightly linked, and sepsis-associated coagulopathy is almost universal in patients with sepsis, antithrombotic-targeted therapy has been clinically investigated with an initial apparent success, though controversial and limited<sup>76</sup> and posteriorly refuted by Ranieri et al. in the PROWESS-SHOCK study.<sup>77</sup> Some data also suggests that most deaths from sepsis are due to an extensive death of immune mediator cells.<sup>78</sup> Therefore, in recent years we have moved from immunostimulation to immunosuppression as cause of sepsis, with one stop in coagulation disorders.

The numerous reasons proposed to explain the failure of the different therapies attempted in sepsis probably reflect more a hopeful expectation, such as targeting a single mediator would be enough to modify all events that take place in sepsis, than a real evidence.<sup>79</sup> In the other hand, tailoring the therapy to an individual patient is something desired in medicine for many diseases, and sepsis is not an exception, but so far very difficult to achieve. In the meantime, approaches addressed for non-specific removal of sepsis mediators appear an attractive option to restore organism homeostasis and improve the morbidity and mortality of this disease. The predominant theory for many years considered sepsis an uncontrolled production of inflammatory molecules, as result of data generated in clinical and preclinical studies.<sup>80,81</sup> This prompted several clinical trials with the goal of blocking TNF- $\alpha$  or IL-1 $\beta$ .<sup>82</sup> These trials did not show a significant improvement in patient survival, though a meta-analysis of TNF- $\alpha$  inhibitors suggested a better outcome in treated patients.<sup>83</sup> An often explanation for the failure of these trials was that the anti-inflammatory agents were not administered quickly enough, but there may be others. An inflammatory mediator must be elevated and detectable to be implicated in the pathogenesis of sepsis. The problem is that cytokines

and other inflammatory mediators may have considerable local effects without detectable changes at plasma levels.<sup>84</sup> Thus, a clinical trial<sup>85</sup> in sepsis showed that neonates with sepsis improved after treatment with IL-1ra, even though IL-1 $\beta$  was not detected in plasma, and recovery was associated with a decrease in IL-6 plasma levels.

Other studies have shown that ICU patients have reduced production of both TNF- $\alpha$  and IL-6 in response to endotoxin stimulation,<sup>86,87</sup> whilst IL-10 production was not impaired.<sup>88</sup> These data suggest that instead of a hyper-inflammatory response, septic patients might present an anti-inflammatory or immunosuppressive response, which has been attributed to the apoptosis of cells of the innate and adaptive immune system.<sup>78</sup> Apoptosis causes the deletion of critical effector immune cells and the release of anti-inflammatory cytokines such as IL-10 and transforming growth factor- $\beta$  (TGF $\beta$ ), and suppresses the release of pro-inflammatory cytokines. However, similarly to what happened with anti-inflammatory treatments, use of immunostimulants such as granulocyte macrophage colony-stimulating factor (GMC-SF) or interferon gamma (IFN- $\gamma$ ) did not modify survival in septic patients.<sup>89,90</sup>

Something analogous to what happens with inflammation occurs with the dysfunction of coagulation in sepsis. Activation of the coagulation cascade can be produced by several non-infectious insults, such as thermal injury, pancreatitis and trauma. In this case, the activation of coagulation is associated with an inflammatory response through TNF- $\alpha$  release and complement activation.<sup>91</sup> In sepsis, along with the activation of coagulation through the proinflammatory cascade, there is also a direct activation of coagulation by infectious toxins that upregulate tissue factor (TF) in endothelial cells, leading to the formation thrombin and fibrin clots.<sup>92</sup> However, the procoagulant activity in sepsis it is not only limited to the endothelium since TF is also present in circulating activated monocytes. Thrombin is also generated by these cells, allowing an unlimited supply of TF and a generalized activation of coagulation. This leads to the depletion of natural antithrombotic factors such as protein C, antithrombin (AT) and tissue factor pathway inhibitor (TFPI), turning the hemostatic system into an appropriate target for sepsis intervention. Unfortunately, as happened with the anti o pro-inflammatory treatments, clinical studies have failed to demonstrate a benefit for recombinant TFPI or AT.<sup>93</sup>

### 1.3.2. Risk factors for SA-AKI

Many studies have examined clinical risk factors for AKI; however, relatively few studies have specifically focused on patients presenting with sepsis. In a large prospective cohort study<sup>1</sup> of 390 patients who presented septic shock without preexisting ESRD or AKI, 237 (61%) developed SA-AKI. Delay in antibiotic administration, intraabdominal sepsis, use of blood products, angiotensin-converting enzyme (ACE)-inhibitor/ angiotensin receptor blocker (ARB) use, and elevated body mass index were independently associated with development of SA-AKI.<sup>1</sup> Higher baseline GFR and successful early goal-directed therapy (EGDT) were associated with better renal outcomes.

In a large retrospective study of nearly 1000 patients presenting with sepsis,<sup>47</sup> increasing age, CKD, ACE-inhibitor/ARB use, shock, positive blood cultures, and lower white blood cell or platelet counts were all independently associated with development of SA-AKI. Although studies like these are important to elucidate potential targets for clinical intervention, unfortunately a number of risk factors (age, CKD) are not modifiable, and some targets represent “best clinical practice” for sepsis. For example, early antibiotic administration has been shown to decrease mortality in sepsis<sup>94</sup> representing a cornerstone of sepsis management, and may also help to mitigate SA-AKI.<sup>1</sup>

There may also be genetic susceptibility to AKI in general and to SA-AKI specifically. Polymorphism of cytokine-controlling genes has been associated with sepsis and polymorphism of catechol-O-methyl transferase activity has been associated with AKI risk.<sup>95</sup> More recently a genome-wide association study of patients with AKI (including SA-AKI) found that polymorphism of the likely controller of a transcription factor (on chromosome 4) involved in innate immunity pathways was associated with greater risk of AKI.<sup>96</sup>

### 1.4. Management goals in SA-AKI

As sepsis, if not properly treated will induce SA-AKI in the majority of cases,<sup>97</sup> it is important to achieve those recommended goals for sepsis management<sup>98</sup> in order to prevent SA-AKI from appearing or progressing when it already exists. At present, no specific treatments exist for either the prevention or treatment of SA-AKI, with the exception of supportive care with RRT for established AKI.<sup>26,99</sup> The optimal care of



septic patients at risk for SA-AKI or with established SA-AKI, are general sepsis management recommendations, supportive care of SA-AKI, and avoidance of nephrotoxins.<sup>21</sup>

#### 1.4.1. Global management goals in sepsis

Perhaps the leading cause of ICU admission is sepsis. The widespread application of protocolized resuscitation and management has been extensively promoted for more than 10 years by international societies (the Surviving Sepsis campaign [SSC])<sup>98,100</sup> and has been associated with a marked reduction in sepsis mortality.<sup>101-104</sup> Data from 171 ICUs in Australia and New Zealand demonstrated a decline in mortality in patients with septic shock from 40.3% in 2000 to 22% in 2012; at the same time, mortality from sepsis declined from 30.2% to 14.2%.<sup>105</sup>

Three big randomized controlled trials (RCTs), the Protocolized Care for Early Septic Shock [ProCESS], the Protocolised Management in Sepsis [ProMISe], and the Australasian Resuscitation in Sepsis Evaluation [ARISE], conducted in the United States, United Kingdom, and Australia/New Zealand, respectively,<sup>106,107,108</sup> showed no benefit in terms of survival of EGDT<sup>109</sup> compared to current usual care, which includes early administration of appropriate antibiotics, volume resuscitation, and source control. Early and appropriate antibiotic administration is critical, as observational studies have shown a relationship between survival and time from sepsis onset to antibiotic administration, in particular in patients with septic shock.<sup>110,111</sup> Hypotensive patients who do not receive early resuscitation also have poorer outcomes,<sup>110</sup> along with patients where source control is delayed.<sup>112,113</sup>

With regard to the three large RCTs, what conclusions can be drawn and applied to clinical practice?; first, invasive monitoring and management strategies such as the placement of central venous access should not be routinely applied to all patients with sepsis. It seems reasonable for patients with severe hemodynamic collapse requiring vasopressor support despite volume resuscitation to have a “central line” and potentially central venous pressure (CVP) monitoring although fluid challenges should not be performed based on CVP values alone. Second, along the same lines, therapeutic decisions should not be based on central venous oxygen saturation (ScvO<sub>2</sub>) alone. Third, the use of packed RBC transfusions in septic patients should follow standard

criteria for critically ill patients, as no benefit was observed in patients managed with EGDT, who in aggregate received more transfusions. Along the same lines, the Transfusion Requirements in Septic Shock (TRISS) trial showed no benefit with regard to 90-day mortality (the trial primary outcome) or rates of ischemic events in septic shock patients when a higher hemoglobin threshold for transfusion was used (9 g/dL vs. 7 g/dL).<sup>114</sup>

What should the target blood pressure be in patients with sepsis?; a large RCT conducted in France, the Sepsis and Mean Arterial Pressure (SEPSISPAM) trial,<sup>115</sup> compared blood pressure targets of 65 to 70 mm Hg vs. 80 to 85 mm Hg in patients with septic shock. The overall trial did not show a benefit to higher blood pressure targets, perhaps in part because there was less separation than anticipated of the 2 treatment arms, with those in the standard therapy arm achieving higher blood pressures than expected. However, in a prespecified analysis of patients with chronic hypertension, there was a significant interaction between blood pressure target and renal outcomes. That is, in patients with chronic hypertension, those randomized to the higher blood pressure target had lower rates of doubling SCr (38.9% vs. 50%,  $p=0.009$ ) and need for RRT over the first 7 study days (31.7% vs. 42.2%,  $p=0.04$ ). Patients randomized to the higher target blood pressure arm did require vasopressors for longer periods of time and had more atrial fibrillation.

#### 1.4.2. Fluids

Fluid management in patients with sepsis has been extensively studied over the last years. In patients with established AKI, as discussed earlier, SA-AKI is much more complex than decreased renal perfusion; however, improving renal perfusion in the setting of hypotension may help mitigate some of the harmful effects of SA-AKI. Renal blood flow can be estimated as follows:  $\text{Renal Blood Flow} = (\text{MAP} - \text{Renal Venous Pressure}) / \text{Renal Vascular Resistance}$ .<sup>21</sup> Although this is probably an oversimplification of actual renal blood flow, it conceptualizes the importance of attempting to find the “sweet spot” of “euvolemia” when resuscitating a septic patient; by this, we mean a fluid state in which intravascular volume is optimized with minimal fluid overload. We can see that renal blood flow can be affected by MAP, renal venous pressure, and renal vascular resistance.

It has long been known that hypovolemia produces “pre-renal” ischemic AKI, and the treatment is fluid administration to improve cardiac output and thus oxygen delivery to the kidneys; however, it has become increasingly clear that overzealous fluid administration can cause AKI as well.<sup>116,117,118</sup> If the renal venous pressure increases, as it often does when large amounts of fluid are administered, it can lead to decreased renal blood flow and decreased GFR.<sup>118</sup> The combination of low MAP and intra-abdominal hypertension (IAH) (which increases renal venous pressure), which are often seen in sepsis, may contribute to SA-AKI. In the surgical literature there is some evidence that EGDT, which is a protocol that tries to maximize cardiac output through fluid and inotrope administration, may decrease incidence of SA-AKI.<sup>116</sup> However, the three large sepsis trials previously commented found no benefit with EGDT compared with usual care with regard to mortality or kidney outcomes.<sup>106,107,108</sup>

The ADQI had a consensus conference on fluid therapy.<sup>119</sup> As part of this conference, a conceptual framework for fluid management was proposed (**Fig. 2**) that highlights the importance of individualizing fluid resuscitation and the fact that the goals of fluid therapy may vary over the course of disease.<sup>120</sup> Early on, during the “rescue” phase of resuscitation, fluids are needed to improve circulation, as described previously. This is followed by “optimization” and “stabilization” phases in which fluid therapy is titrated to the individual patients. Finally, during the recovery phase, “deescalation” of fluid therapy, which may include diuretics to enhance fluid mobilization, is needed to avoid the sequelae of volume overload.

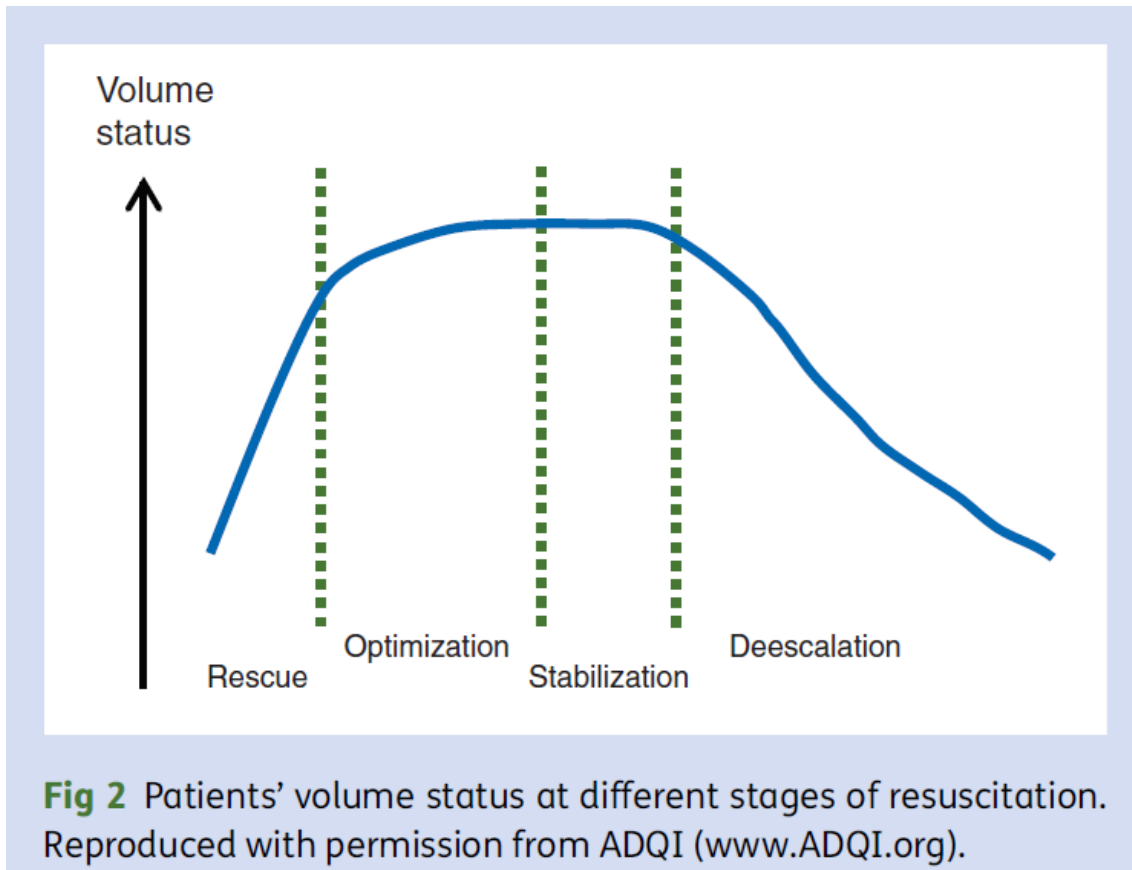


Figure 2. Patient's volume status at different stages of resuscitation

In this context, it should be noted that retrospective studies of clinical trials concerning fluid management have suggested that positive fluid balance, but not diuretic administration, is associated with increased mortality in patients with the acute respiratory distress syndrome (ARDS) and early AKI.<sup>121</sup> Published recently, three different studies with protocols restricting resuscitation fluids successfully reduced volumes of resuscitation fluids compared with a standard care protocol in adult ICU patients with septic shock.<sup>122,123,124</sup>

#### 1.4.3. Mean arterial pressure goals

Autoregulation is the ability of an organ to maintain a relatively constant blood flow across a wide range of MAPs. In a patient who is normotensive, renal autoregulation is intact between MAPs of between approximately 60 to 160 mm Hg. Below 60 mm Hg, renal blood flow decreases and thus GFR decreases. As commented previously Asfar and colleagues<sup>115</sup> looking at blood-pressure targets in patients with septic shock found no mortality benefit of targeting a higher MAP (80–85 mm Hg) vs. a lower MAP (65–

70 mm Hg). However, in patients with chronic hypertension, a decreased incidence of SA-AKI and lower need for RRT was observed in the higher MAP group.

In hypotensive patients with vasodilatory shock refractory to adequate volume resuscitation, judicious use of vasopressors to restore MAP to a level above the lower limit of autoregulation will likely improve renal blood flow and thus GFR.<sup>118</sup> Of course, vasopressors should be used cautiously in cardiogenic shock and only after volume resuscitation in hypovolemic shock. The choice of vasopressor has been the subject of several large trials over the years. In recent years, it has become widely accepted that norepinephrine is the initial vasopressor of choice for septic shock.<sup>125,100</sup>

However, there is growing interest in the use of vasopressin in vasodilatory septic shock. Vasopressin, an endogenous stress hormone, acts via the V1 receptor located on vascular smooth muscle to cause vasoconstriction.<sup>126</sup> Endogenous vasopressin levels, as well as vasopressin receptors, are decreased in septic shock.<sup>126</sup> Importantly for septic shock, the actions of vasopressin include efferent arteriole vasoconstriction (which increases GFR) and improvement in the sensitivity of other vasopressor agents at catecholamine receptors and have been shown in small clinical studies.<sup>127</sup> A much larger study comparing the use of norepinephrine and vasopressin in septic shock found a possible mortality benefit in patients with less severe shock (as defined by norepinephrine infusion rates between 5 and 15 mcg/min) but no mortality difference in patients with severe shock.<sup>128</sup> This has led some to advocate for vasopressin as a second choice vasopressor agent in septic shock when adequate MAP goals cannot be achieved with low-dose norepinephrine.<sup>100,126</sup> Finally, we note that there are no data to support the use of dopamine to improve renal outcomes,<sup>129</sup> and given the increased rate of arrhythmias observed with dopamine compared with norepinephrine in clinical trials, in general, dopamine should be avoided.<sup>130</sup>

#### 1.4.4. Nephrotoxins

Although we have no effective treatments for SA-AKI at present, avoidance of nephrotoxic agents is paramount. The list of agents known to be injurious to the kidneys is extensive; however, there are few agents worth special mention, as they are commonly used in treatment of septic patients. Hydroxyethyl starch (HES) is a colloid that was once commonly used in resuscitation for patients with septic shock. However,

several large studies and systematic reviews have shown use of HES is associated with increased risk of SA-AKI and RRT, and in some cases, with an increased risk of death.<sup>131,132</sup>

A growing body of literature suggests that administration of large volumes of crystalloids with supraphysiologic concentrations of chloride (e.g., normal saline) may be associated with poorer outcomes than more balanced crystalloid solutions (e.g., Ringer Lactate and Plasmalyte).<sup>133,134</sup> Proposed mechanisms include a renal vasoconstrictive effect of high concentrations of chloride, as well as a macula densa-mediated tubuloglomerular feedback mechanism, which triggers afferent arteriolar vasoconstriction, thus lowering the GFR.<sup>133</sup> A large study suggested no benefit to balanced salt solutions over normal saline in a large population of critically ill patients,<sup>135</sup> but recently two single-centre RCTs had positive results in two different populations (emergency department [ED] patients and ICU patients),<sup>136,137</sup> especially in those patients with impaired renal function or high chloride levels. Metabolic acidosis was significantly reduced with the use of balanced solutions, thus more research is clearly needed.

Thus, in patients with sepsis who are at high risk of lactic acidosis, the use of balanced salt solutions may be prudent from a resource utilization perspective as well. Along these lines, a recent multicentre trial<sup>138</sup> randomized critically ill patients with metabolic acidosis to a bicarbonate infusion group or a control group and although no survival differences were found in the global population, a significant better survival was observed in the subgroup of patients with KDIGO AKI stage 2 and 3 assigned to the bicarbonate group. Furthermore, the need for RRT was significantly decreased in those patients receiving bicarbonate.<sup>138</sup>

Several antimicrobial agents have been associated with kidney injury through a variety of mechanisms. Amphotericin, aminoglycosides, and colistin are associated with acute tubular necrosis.<sup>139</sup> Many antibiotics, and in particular the betalactams, can cause interstitial nephritis.<sup>139</sup> Given the high rates of AKI with aminoglycosides and amphotericin, the KDIGO guidelines make special note of these agents.<sup>26</sup> Specifically, the guidelines recommend that aminoglycosides should be used only if no other alternative is available; similarly, amphotericin should be used only when azole or

echinocandins cannot be used, and lipid formulations, which are associated with lower rates of nephrotoxicity, should be used.<sup>26</sup>

One of the most commonly used antibiotics in the ICU, vancomycin, deserves special mention. Originally approved in the 1950s, vancomycin remains one of the antibiotics of choice for methicillin-resistant *Staphylococcus aureus* (MRSA) infection. In the early years of clinical use, vancomycin nephrotoxicity was attributed to impurities from the manufacturing process.<sup>140</sup> Although the manufacturing process has improved, there has been a reported increase in the rate of vancomycin-associated AKI in recent years where a target trough of 15 to 20 mg/dL has been recommended for MRSA infections.<sup>140,141</sup> However, whether or not this is a true condition or whether much of this represents confounding remains controversial.<sup>140</sup> Some studies have suggested that concomitant exposure to other nephrotoxic agents (specifically piperacillin-tazobactam) increases the incidence of vancomycin toxicity.<sup>141</sup> Regardless, close attention should be paid to vancomycin dosing in the setting of AKI, and frequent monitoring of vancomycin levels should be used to guide dosing.

Iodinated contrast agents are perhaps the most widely recognized nephrotoxin used in clinical practice, although newer low-osmolar contrast agents confer a lower risk of nephrotoxicity. Patients with CKD and those with sepsis are at a higher risk of developing AKI from iodinated contrast. Early recognition of AKI using the consensus definitions described previously is also important. In these patient groups (those with AKI or CKD and those with sepsis) it is important to balance the risks and benefits when deciding to obtain these studies. Discussion with a radiologist can help determine if there are alternative means of imaging that can avoid iodinated contrast agents. The use of bicarbonate and N-acetylcysteine to prevent contrast nephropathy is controversial and is the subject of large RCTs.<sup>142</sup> However, there is clear benefit to intravenous fluid administration, so it is critical to ensure patients are volume resuscitated before iodinated contrast administration.<sup>143</sup> Finally, gadolinium, the contrast material used in magnetic resonance imaging (MRI), has been linked to nephrogenic systemic fibrosis in patients with both AKI and CKD.<sup>144</sup> Small studies have suggested an association between gadolinium and AKI in particular in the setting of sepsis, but this association remains controversial.<sup>145</sup>

#### 1.4.5. Pharmacologic strategies for SA-AKI

Despite numerous studies, at present there are no pharmacotherapies to directly prevent or treat SA-AKI. Although an exhaustive review of the literature as it pertains to these medications is beyond the scope of this introduction, many of these studies are reviewed in the KDIGO AKI guidelines.<sup>26</sup> Due to their antiinflammatory properties, there has been significant recent interest in the use of statins (HMG-CoA reductase inhibitors) as a treatment for AKI in multiple settings, including sepsis. In the setting of sepsis, there have been no randomized clinical trials focused on SA-AKI, but in a large prospective cohort study of patients hospitalized with pneumonia, statins were not found to reduce the risk of SA-AKI, and in fact prehospital statin use was associated with a small increased risk of SA-AKI, which was attributed to indication bias.<sup>146</sup>

Diuretics are probably the only pharmacologic strategy that can be recommended when necessary in the management of SA-AKI in order to manage fluid balance or at least minimize the deleterious effects associated with positive fluid balance. A pilot multi-center randomized blinded placebo-controlled trial<sup>5</sup> in adult patients with AKI admitted to three ICUs randomly allocated 73 patients with early AKI to furosemide bolus and infusion or 0.9% saline placebo. Primary endpoint was worsening AKI, defined by the RIFLE criteria. No differences were found in the proportion with worsening AKI ( $p=0.6$ ), kidney recovery ( $p=0.3$ ), or RRT ( $p=0.8$ ). A posthoc analysis<sup>121</sup> in AKI patients of the ARDS net trial showed survival benefits when a conservative fluid strategy (using diuretics) was employed compared to a liberal fluid strategy although this survival effect was related to fluid balance and not to diuretic use.

#### 1.4.6. Non-pharmacologic strategies in SA-AKI

##### 1.4.6.1. Renal Replacement Therapy in SA-AKI

###### a. Epidemiology of SA-AKI requiring RRT

RRT is classically indicated when advanced AKI is present. The great majority of AKI episodes that are admitted to hospital (community acquired AKI [CA-AKI])<sup>147</sup> or appear during hospital admission (hospital acquired AKI [HA-AKI])<sup>148</sup> don't require RRT because either they recover on time, or their severity is not so high as to meet RRT initiation criteria.<sup>149,147</sup> Globally, less than 2% of hospitalized AKI episodes finally



require RRT<sup>148</sup> but these requirements of RRT are much higher when patients require ICU admission<sup>28</sup> and specially in those who present SA-AKI.<sup>3</sup>

In a large United States of America population (n=3,787,410), the community-based incidence of non-RRT requiring AKI (defined using relative changes in SCr levels) and RRT requiring AKI (defined using integrated administrative data) was estimated at 384.1 and 24.4 per 100,000 persons-years, respectively.<sup>40</sup> Between 1996 and 2003, the incidences of non-RRT requiring and RRT requiring AKI in this population increased significantly from 322.7 to 522.4 per 100,000 person-years (38%) and from 19.5 to 29.5 per 100,000 person-years (33%), respectively. The occurrence of AKI was most common among elderly, male and black patients. The same research group studied in the following years the incidence of RRT requiring AKI which increased from 22.2 cases per 100,000 person-years in 2000 to 53.3 in 2009;<sup>150</sup> older age was associated with a higher incidence of RRT requiring AKI.

Critically ill patients with AKI have higher RRT requirements, therefore most of the observational studies reporting RRT requirements in AKI patients have been performed in critical care departments. Clech et al. reported<sup>151</sup> that, among 8,639 critically ill patients, 2,846 (32.9%) had severe AKI, 545 of whom required RRT (6.3%). In Finland, Vaara et al. found that from 24,904 patients admitted to the ICU, 26.6% of patients had AKI (RIFLE R-F), which included 1,686 (6.8%) with RRT requiring AKI (192 p.m.p).<sup>152</sup> Compared with critically ill patients not requiring RRT (n=23,218), those with RRT requiring AKI had higher hospital mortality (RRT/no RRT = 35.0%/15.5%, p<0.001). In Canada, a population-based cohort study found that the annual incidence of RRT requiring AKI in ICUs increased significantly from 0.8% in 1996 to 3.0% in 2010 (p<0.001).<sup>153</sup> Despite this increasing incidence, among RRT requiring AKI patients, 90-day mortality decreased significantly from 49.9% during 1996-2000 to 45.0% during 2006-2010. Globally, the population-based incidence of RRT utilization among critically ill patients with AKI is 11–19 cases per 100,000, which represents 4–8% of all critically ill patients.<sup>45,151,152,28</sup>

AKI is more frequent, more severe, and less likely to resolve once KDIGO stage 3 AKI has been reached and is associated with higher mortality rates in patients with sepsis than in those without.<sup>3,154,2</sup> In a big cohort of critically ill AKI patients, sepsis was associated with a higher proportion of both injury (25.1 vs. 15.8%; p=0.01) and failure

(10.9 vs. 5.9%;  $p=0.05$ ) at ICU admission.<sup>2</sup> In a different and much smaller study comparing SA-AKI with non SA-AKI, a higher need for RRT (33% compared to 10%,  $p<0.001$ ) was reported in the SA-AKI group.<sup>154</sup> Finally, in a recent cohort of critically ill AKI patients, the use of RRT was greater in the septic patients than in the non-septic population (20% vs. 5%,  $p<0.0001$ ).<sup>3</sup> SA-AKI patients who usually require CRRT because of unstable hemodynamics,<sup>155</sup> represent a common and often lethal clinical scenario, with higher mortality of these patients<sup>156,157,158</sup> reflecting organ dysfunction, usually multiple (three or more organs), and not directly related to the use of RRT, although some observational studies have reported controversial results.<sup>159,156</sup>

#### b. Indications for RRT or Timing

A major gap in knowledge exists around timing of initiation in RRT. Understanding which clinical features portend poor outcomes could help guide decisions around timing by suggesting when and in whom to initiate RRT<sup>160-170</sup> Three recent, moderately-sized RCTs reached different conclusions about whether to initiate RRT only when urgent indications develop or prior to their development.<sup>17,171,18</sup>

The classic indications for RRT in SA-AKI are the same as for other critically ill patients with AKI: acidemia, volume overload, electrolyte abnormalities (hyperkalemia), and uremia (pericarditis, encephalopathy). In all cases, the risks of RRT (placement of a large-bore dialysis catheter), as well as blood loss and potential complications of RRT, such as electrolyte disturbances, hemodynamic compromise, air embolism, and worsening kidney injury,<sup>172</sup> must be weighed against potential benefits. Strategies to minimize risks and complications associated with RRT have been proposed and may be of benefit.<sup>173</sup>

Early strategies have been encouraged in the last two decades especially in SA-AKI patients in whom the hypothesis of RRT immunomodulation capacity could potentially modify the clinical course of sepsis. Hypothesis was that removing or reducing the peak of mediators in an early phase of sepsis may avoid MODS instauration.<sup>174</sup> Thus, RRT was tested in patients with early stages of SA-AKI or even in septic patients with no AKI. Special attention must be given to one of these previously referred studies, “impact of continuous venovenous hemofiltration (CVVH) on organ failure during the early phase of severe sepsis: a randomized controlled trial”,<sup>175</sup> which had to be interrupted

because the number and severity of organ failures were significantly higher in the CVVH group respect to the control group (no CRRT).

Two RCTs published at the same time, studied patients with advanced AKI (stages 2 & 3 of AKI KDIGO classification) in two different settings. Gaudry and colleagues<sup>17</sup> conducted a multicenter RCT in France (AKIKI trial), involving 620 patients with KDIGO stage 3 AKI who required mechanical ventilation (MV), vasopressor support, or both but did not present at the time of inclusion, life-threatening complications requiring immediate RRT. AKIKI protocol assigned patients into either an early (RRT initiated immediately after randomization) or a delayed strategy of RRT (RRT initiated if reaching one of the following criteria: severe hyperkalemia, metabolic acidosis, pulmonary edema, blood urea nitrogen [BUN] level higher than 40 mmol/L, or oliguria for more than 72 h after randomization). The primary outcome, survival at day 60, was similar between groups (48.5% in the early-strategy group and 49.7% in the delayed-strategy group,  $p=0.79$ ). Interestingly, about half of the patients in the delayed group did not receive RRT. It is significant that most of the patients included in this trial were critically ill patients with SA-AKI (sepsis was present in 80% of them) and that 56% of the initial RRT supportive treatments were not CRRT but intermittent hemodialysis (IHD).

Two weeks after AKIKI trial was published, Zarbock and colleagues<sup>171</sup> reported findings from their study “Effect of early vs. delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN study”. This was a single-center RCT conducted in Germany, comparing effects of early (when reaching KDIGO stage 2 AKI) to delayed (when reaching stage 3 AKI or earlier if immediate criteria appeared) initiation of RRT in 231 critically ill patients. Patients in the early group had significantly lower 90-day mortality compared with the delayed group. In this trial, RRT was homogeneously performed as continuous venovenous hemodiafiltration (CVVHDF). Noticeably, nearly 50% of the patients included in this study were randomized during cardiovascular postsurgical period and requirements of RRT in the delayed group were incredibly high as 90%. Most of patients assigned to the delayed group were started on CRRT when achieving respiratory failure criteria (78%), revealing a fluid overload scenario that was already present when patients were initially randomized (mean positive fluid balance in both groups was nearly +7 Litres[L]).

Recently published, another large RCT<sup>18</sup> performed in a large multicenter population of critically ill patients with septic shock and “Failure” SA-AKI stage found no differences in survival between an early RRT strategy (within 12 h from Failure stage) and a delayed strategy (> 48 h after Failure stage). Despite these three large RCTs, the timing question remains opened: specifically, “early” vs. “late” have been variably defined; although BUN levels have commonly been used as the cutoff,<sup>167</sup> studies have also used SCr, UO, and RIFLE criteria.<sup>164-166</sup> Clearly, large, well-executed RCTs are needed, although the design of such studies is complex, as some patients may recover from AKI with supportive care alone. More recently, a posthoc analysis of the AKIKI trial in ARDS patients<sup>176</sup> showed no benefits of early RRT on mortality and renal recovery. Finally, although a pilot RCT trial of accelerated vs. standard initiation of RRT<sup>170</sup> demonstrated that this approach was feasible, in the standard arm 13 (25%) of 51 subjects never required RRT and had renal recovery; a large RCT based on this pilot study is actually recruiting patients (STARRT-AKI: Principal Trial).

c. Modality of RRT: intermittent vs. continuous

Replacement of the renal function may be performed through IHD or CRRT. IHD is achieved by diffusive clearance along with a concentration gradient from blood to a dialysate through a semi-permeable membrane. Small molecules (urea, SCr, potassium) diffuse rapidly and are efficiently removed, whereas larger solutes that diffuse poorly are cleared slowly. Classically, IHD is performed intermittently for the treatment of patients with advanced CKD or AKI without hemodynamic compromise to restore metabolic and/or fluid balance.

The use of CRRT vs. intermittent modalities (including conventional IHD and prolonged intermittent RRT [PIRRT]) remains a subject of interest. Several RCTs and systematic reviews have found no differences in mortality or recovery of kidney function.<sup>172</sup> However, the entry criteria for many of the RCTs in this field required that a MAP greater than 70 mm Hg could be maintained (with or without vasopressors), which may not be possible in the setting of septic shock. Thus, the KDIGO guidelines, which recommend that use of CRRT and IHD be complementary, and that CRRT be considered in hemodynamically unstable patients, seem measured and reasonable.<sup>177</sup>

Because hypotension has been associated with prolonged renal recovery in animal models and because there are more episodes of hypotension (on average) with IHD than CRRT, there has been tremendous interest in the impact of modality on renal recovery. A retrospective cohort study of more than 4000 patients with AKI requiring some form of RRT found that CRRT was associated with a decreased risk of long-term dialysis.<sup>178</sup> This effect was more prominent in the patients with CKD. It should be noted that the costs of CRRT are considerably more than IHD.<sup>179</sup>

Finally, PIRRT (originally named sustained/slow low-efficiency dialysis or SLED), is an alternative for hemodynamically unstable patients in particular in centers without CRRT capability.<sup>180</sup> This modality of therapy is typically performed over 6 to 12 h per day to allow for more gentle fluid removal and solute clearance than IHD. However, a particular concern for this modality is antibiotic dosing, because there is an extended period with increased clearance, followed by a long period of reduced clearance, by design.<sup>181</sup>

d. Dose of RRT: high volume vs. normal volume

The dose of dialysis has been the subject of a number of large RCTs. In CRRT, the dose is the sum of the ultrafiltrate plus dialysate (“the effluent”) normalized to body weight (mL/kg/h).<sup>172</sup> For IHD, dialysis adequacy is standardly measured as the Kt/V or urea reduction ratio. In chronic hemodialysis patients, hemodialysis dose might affect morbidity and mortality.<sup>182</sup> A similar correlation between outcome (survival) and dose of treatment with CRRT (volume of ultrafiltrate) was also suggested in ischemic or SA-AKI.<sup>12</sup> Subsequently, animal studies confirmed this link between dose of ultrafiltrate and cytokine removal, specially in sepsis (**Table 2**).<sup>183,184</sup>

**Table 2.** Inflammatory mediators clearance with CRRT

Author	Study	Modality	Membrane	Ultrafiltrate dose	Ultrafiltrate analysis	Plasma reduction
Rogiers <sup>183</sup>	Dogs	HVHF	PS	6 l/h	TNF	No
Rimmele <sup>185</sup>	Pigs	HVHF	AN69	35 ml/kg/h		Endotoxin, IL1B
Bellomo <sup>14</sup>	Humans	CVVHD	AN69	-	TNF, IL1	no
Kelluim <sup>186</sup>	Humans	CVVH	AN69	2l/h	TNF alpha , IL-10, and sL-selectin	TNF
Sanchez Izdo <sup>187</sup>	Humans	CVVH	AN69	300 ml/h	TNF, IL6	no
Hoffmann <sup>188</sup>	Humans	CVVH	PA	2 l/h	TNF, IL-2, IL-6	C3a
Journois <sup>189</sup>	Humans (pediatric)	HVHF	AN69	5 l/m <sup>2</sup>	TNF, IL-10	IL-1, IL-6, IL8
Heering <sup>190</sup>	Humans	CVVH	PS	1 l/h	TNF, IL-1, IL-2R, IL-8	No
Klouche <sup>191</sup>	Humans	CVVH	AN69	1,65 l/h		IL-6
Sander <sup>192</sup>	Humans	CVVH	AN69	1 l/h	TNF, IL-6	no
DeVriese <sup>193</sup>	Humans	CVVH	AN69	1,5-2.7 l/h	TNF, IL-6, IL-1	no
Kamijo <sup>194</sup>	Humans	CVVH	AN69	500-1000 ml/h	IL-6	no
Cole <sup>195</sup>	Humans	CVVH	AN69	2l/h	C3a, C5a IL-6, IL-8, IL-10, TNF	no
Cole <sup>196</sup>	Humans	HVHF	AN69	80 ml/kg/h	C3, C5, IL-10	Transitory changes
Ghani <sup>197</sup>	Humans	HVHF	PS	100 ml/kg/h	IL-6	IL-6
Jiang <sup>198</sup>	Humans	HVHF	AN69	4000 ml/h		IL-6, IL1, TNF
Chen <sup>199</sup>	Humans	HDVVC	AN69	35 ml/kg/h	IL-1, IL-1RA, IL-6, IL-10, TNF	no

AN69: polyacrylonitrile, PA: polyamide, PS: polysulphone, ET:endothelin, PG: Prostaglandin

In 2000 Ronco et al.<sup>200</sup> published the results of their clinical trial evaluating the impact of different ultrafiltration doses in critically ill patients with AKI, either septic or not, randomizing patients to ultrafiltration rates of 20 mL/kg/h (group 1), 35 mL/kg/h (group 2), and 45 mL/kg/h (group 3). The survival rate was significantly lower in group 1 (41%) compared with groups 2 (57%) and 3 (58%), suggesting that a minimal renal dose of 35 mL/kg/h was required to replace renal function in critically ill patients with AKI. In the subgroup of patients with sepsis (SA-AKI), survival was 47% in group 3 compared with 18% in group 2 and 25% in group 1. Though the differences did not reach statistical significance, the authors postulated that sepsis patients might benefit from an ultrafiltrate dose >35 mL/kg/h (*sepsis dose*).

At that time, Bouman et al. summarized the different doses of ultrafiltration in three groups.<sup>201</sup>

- Low volume hemofiltration (LVHF): <30 mL/kg/h
- High Volume hemofiltration (HVHF): 30–50 mL/kg/h
- Very high volume hemofiltration (VHVHF): >50 mL/kg/h

Other following studies investigated different doses of ultrafiltration (some of them even 85, 80 or 70 mL/kg/h during 6–12 h),<sup>196,202,203,198</sup> suggesting all of them an improvement in hemodynamics and short term patient survival compared to the conventional doses used in CRRT for AKI (**Table 3**).

**Table 3.** Clinical response to CRRT

Author	Study	Modality	Ultrafiltrate dose	Clinical improvement
Grootendorst <sup>13</sup>	Pigs	HVHF	150 ml/kg/h	HMD, RESP
Lee <sup>204</sup>	Pigs	HVHF	50-75 ml/kg/h	RESP, SURV
Rogiers <sup>183</sup>	Dogs	HVHF	200 ml/kg/h	HMD
Yekebas <sup>184</sup>	Pigs	HVHF	100 ml/kg/h	HMD, SURV
Rimmele <sup>185</sup>	Pigs	HVHF	35ml/kg/h	HMD
Hoffmann <sup>188</sup>	Humans	CVVH	2 l/h	HMD
Journois <sup>189</sup>	Humans (pediatric)	HVHF	5 l/m2	RESP
Sander <sup>192</sup>	Humans	CVVH	1 l/h	No improvement
Heering <sup>190</sup>	Humans	CVVH	1 l/h	HMD
Oudemans <sup>205</sup>	Humans	HVHF	3,8 l/h	HMD, SURV
Kamijo <sup>194</sup>	Humans	HVVC	500-1000 ml/h	HMD
Ronco <sup>200</sup>	Humans	HVHF	45 ml/kg/h	SURV
Honore <sup>206</sup>	Humans	HVHF	116 ml/Kg/h	HMD, SURV
Klouche <sup>191</sup>	Humans	CVVH	1,65 l/h	HMD
Cole <sup>195</sup>	Humans	CVVH	2l/h	No improvement
Cole <sup>196</sup>	Humans	HVHF	80 ml/kg/h	HMD
Cornejo <sup>203</sup>	Humans	HVHF	100 ml/kg/h	HMD, SURV
Ratanarat <sup>202</sup>	Humans	PHVHF	85 ml/kg/h (6-8 h)+ 35 ml/kg/h (16-18 h)	HMD, SURV
Ghani <sup>197</sup>	Humans	PHVHF	100 ml/kg/h (6h) + 35 ml/kg/h (18 h)	HMD
Jiang <sup>198</sup>	Humans	HVHF	4000 ml/h	HMD, SURV

HMD: Hemodynamic, RESP: Respiratory, SURV: survival, PHVHF: Pulse HVHF

It should be noted that the concentration of mediators in the ultrafiltrate of these studies with HVHF and VHVHF showed inconsistent results (**Table 2**). Some studies found an increase for removal of several cytokines, along with a drop in their plasma levels, in HVHF or VHVHF compared to LVHF for CRRT.<sup>189,197</sup> This fall in cytokines was not always associated with better hemodynamic effects in HVHF or VHVHF compared to LVHF.<sup>193</sup> In contrast, other studies found a level of cytokines in the ultrafiltrate of HVHF negligible, and suggested adsorption as the major mechanism for mediator removal with these techniques.<sup>196</sup> These variations may reflect particular differences with the hemofiltration methods or the technical difficulties involving the analysis of cytokines.

Different theories try to explain why plasmatic levels of inflammatory mediators are so difficult to reduce in SA-AKI patients. The rationale for the application of a blood purification (BP) technique that unselectively removes both types of mediators would therefore be that of cutting the peaks of inflammatory mediators (thus reducing the endothelial effects of permeabilization and vasoparalysis), and at the same time cutting the peaks of the anti-inflammatory response (thus maintaining a certain cell responsiveness to endotoxaemia and bacteraemia, leading to a certain preservation of the immunological response).<sup>174</sup> This theory, however, fails to account for eventual variations in interstitial and tissue concentrations of mediators and cytokines that may be clinically relevant. Therefore, a model was developed coupling mediator removal from the blood compartment to changes in interstitial and tissue mediator levels.

This "*threshold immunomodulation*" hypothesis, initially elaborated by Honoré and Matson,<sup>207</sup> fosters a much more dynamic viewpoint. Following removal from the blood compartment, (pro)mediators are progressively extracted from interstitium and tissues until a threshold level is reached at which particular inflammatory pathways and cascades are brought to a complete standstill, annihilating any further harm to the organism. However, correct determination of this threshold point is difficult in clinical practice because the applied BP technique (e.g. HVHF) might cause significant changes in mediators at interstitial and tissue level that are not mirrored by alterations in the blood compartment. It can thus be assumed that the biological effect of BP does not depend on a dramatic fall in plasma cytokine levels but rather relies on neutralizing harmful mediator effects at tissue level. Still, it remains to be determined how BP



promotes and manages mediator and cytokine flow from tissue and interstitium to the blood compartment.

The "*mediator delivery*" hypothesis, suggested by Alexander and co-workers<sup>208</sup>, emphasizes the use of high replacement volumes (e.g. 3 to 5 L/hour) during BP. Some studies have demonstrated a 20 to 40-fold increase in lymphatic flow displacing a substantial amount of mediators and cytokines to the blood compartment from where they are subsequently eliminated.<sup>209</sup> Thus, the use of high volumes of replacement fluid might be of great importance for extracting mediators but also for enhancing lymphatic transport between the interstitium/tissue and blood compartments. Taken together, all afore mentioned cytotoxic hypotheses indicated that elimination of cytokines at tissue rather than at plasma level was mandatory for a beneficial biological and clinical effect of BP.

The ill-explained relationship between compartments incited Honoré and Joannes-Boyau<sup>210</sup> to develop a fourth cytotoxic hypothesis based upon active transportation between two asymmetric compartments. This theoretical model assumed that effective removal of tissue-damaging mediators and transporting them to the central circulation must have a positive effect. Finally, a new theory proposed by Namas et al.<sup>211</sup> can be considered complementary to the existing cytotoxic hypotheses by coupling reduced endothelial damage at the interstitial level (cytotoxic approach) with the concept of reprogramming leucocytes and mediators towards infected tissue, thus emptying the bloodstream of important promoters of remote organ damages (cytokinetic approach).

HV- or VHVHF are not innocuous to the patients and may be associated with problems related to the vascular access and others such as hypothermia or ionic disorders (dialytrauma).<sup>173</sup> In addition, it requires a rapid change in drug dosing to compensate all the drugs that will undergo an extracorporeal clearance. On the other hand, when the filtration fraction (FF; the ratio between ultrafiltration and plasma flow) exceeds 30% with these techniques, transmembrane pressure (TMP) gradient progressively increases and membrane fouling occurs. This complication might be avoided by using the replacement solution before passage through the filter (predilution), though it might reduce efficiency compared with dilution after passage through the filter (postdilution) at similar ultrafiltration volumes.

Although all these early studies suggested a benefit to higher doses of RRT,<sup>200,212</sup> two well designed large RCTs proved no benefit to higher doses of RRT.<sup>15,16</sup> In the ATN (Acute Renal Failure Trial Network) trial<sup>15</sup>, critically ill patients with AKI receiving the intensive treatment strategy underwent IHD and SLED six times per week and CVVHDF at 35 mL/kg/h; for patients receiving the less-intensive treatment strategy, the corresponding treatments were provided thrice weekly and at 20 mL/kg/h. Intensive renal support did not decrease mortality, improve recovery of kidney function, or reduce the rate of nonrenal organ failure as compared with less-intensive therapy. ATN protocol allowed IHD (nearly 50% of all treatments delivered), SLED, or CRRT to be performed as a great number of recruiting centers did not use CRRT. Sepsis was considered the cause of AKI in 55% of the patients, was present in 63% of patients at randomization, but no differences in mortality were observed after analyzing the effect of the intensity of renal support in this subgroup of patients with SA-AKI. Hypokaliemia and hypophosphatemia were significantly more frequent in the intensive renal support group.

RENAL study (Randomized Evaluation of Normal vs. Augmented Level replacement Therapy Study Group)<sup>16</sup> randomized critically ill adults with AKI to CRRT in the form of postdilution CVVHDF with an effluent flow of either 40 mL/kg/h (higher intensity) or 25 mL/kg/h (lower intensity). Treatment with higher-intensity CRRT did not reduce mortality at 90 days. Sepsis was present in 50% of patients at randomization but once again no differences in mortality were observed after analyzing the effect of the intensity of renal support in this subgroup of septic patients. Hypophosphatemia was detected in 461 patients (65.1%) in the higher-intensity group and in 396 patients (54.0%) in the lower-intensity group ( $p < 0.001$ ).

A smaller trial<sup>213</sup> randomized a total of 140 critically ill patients with septic shock and SA-AKI for less than 24 h to either VHVHF at 70 mL/kg/h or to what authors considered a standard-volume haemofiltration at 35 mL/kg/h, for a 96-h period. No differences were observed between groups in 28-day mortality or early improvements in haemodynamic profile or organ function. All these results have led KDIGO guidelines<sup>26</sup> to recommend an initial dose of 20-25 mL/kg/h when initiating CRRT in critically ill patients (no matter how septic or unstable patients are); furthermore, recent reports are suggesting that this dose could be even lower<sup>214</sup> specially in those patients with no emergent electrolytic disorders such as hyperkalemia or acidosis. However, it is crucial

to quantify dose of dialysis for patients with RRT requiring AKI, as IHD treatments in particular may need to be optimized to achieve the target dose.<sup>15,16</sup>

e. CRRT modality in SA-AKI patients: convection vs. diffusion

Hemofiltration is based on convective mass transport. A transmembrane pressure (TMP) drives both fluid and solutes through a membrane selected for its high hydraulic permeability, allowing removal of larger solutes than hemodialysis. Convective removal of a solute (sieving coefficient) depends on TMP, on molecular weight (MW) and structure of the solute, as well as on the cutoff point of the membrane. Hemofiltration may be performed intermittently but it is usually executed as CRRT, namely CVVH. CRRT include also other techniques such as the continuous veno-venous hemodialysis (CVVHD), which uses diffusion as the main mechanism to remove solutes, and CVVHDF that combines both diffusion and convection. In the other hand, some of the filters used in these techniques have an adsorption property, which is defined as the molecular adherence to the surface or interior of a semi-permeable membrane. Thus, CRRT may include three types of depurative mechanisms: convection, diffusion and adsorption.

Different strategies have been investigated for renal replacement in critical care patients turning out CRRT the most extensively used in clinical practice at the ICU. The reason is that many patients in ICU are hemodynamically unstable and cannot tolerate the subtraction of the blood volume required for IHD. CRRT have been proposed for renal replacement in patients with SA-AKI, based on a better control of azotemia.<sup>215,216</sup> Thus, CRRT have become extensively used in patients with SA-AKI because of their apparent ability to remove, along with the small MW solutes, middle MW molecules (between 5 to 30 Kilodaltons [kDa]) that would include cytokines and other sepsis mediators.<sup>186,14,188</sup>

Non-specific elimination of circulating cytokines and other inflammatory mediators by CRRT has been a matter of controversy ever since it was first proposed. Although several studies have shown the presence of inflammatory mediators in the ultrafiltrate fluid from septic patients with CRRT, few have demonstrated a significant decrease in plasma concentrations of these mediators with the ultrafiltrate usually removed for renal replacement (**Table 2**).<sup>190,192,188</sup> This discrepancy between the presence of

inflammatory mediators in ultrafiltrate fluid and their lack of reduction in plasma suggest a constant production of mediators during sepsis. Similarly, hemofiltration has been associated with hemodynamic improvements in critically ill patients and animal models of acute endotoxic shock without a correlation with the decrease in cytokine plasma concentrations.<sup>187,183,217</sup>

Convective techniques of CRRT (CVVH) has been considered more efficacious for cytokine removal than diffusive techniques (CVVHD) in septic patients (**Table 2**).<sup>186</sup> The rationale is that convection might remove higher MW molecules than diffusion. Based on this higher cytokine removal capacity, convective modalities such as CVVH have been recommended for SA-AKI patients, although significant clinical benefits, including better survival outcomes, have not been proved by RCTs comparing them with other modalities.<sup>218</sup> Furthermore, convective techniques employ high TMP gradients to remove fluids and solutes, and this is associated to an increase in the number of adverse effects related to RRT known as “dialytrauma” events among which the most common are a higher blood transfusion requirements (because of filter clotting) and a higher incidence of hypothermia.<sup>219</sup> Even convective techniques employing non intensive replacement doses can present dialytrauma events as both ATN and RENAL trials reflected.

Moreover, several studies performed in critically ill patients have shown benefits in metabolism and even in survival when adding a diffusion dose to CVVH (CVVHDF).<sup>216</sup> Furthermore, pure diffusive techniques such as CVVHD could have the advantages of being safer (less dialytrauma events) and less expensive (lower filter consumption and lower transfusion requirements). These potential benefits are based on the diffusion clearance capacity, which presents lower thrombogenicity than convection.<sup>216</sup> However, these theoretical advantages in terms of costs and security could be counteracted by a lower capacity in removing medium MW molecules, specially cytokines. Nevertheless, some observational studies performed in patients with SA-AKI have shown similar removal capacity of low and medium MW molecules with the use of CVVHD when compared with CVVH.<sup>186,215</sup>

## f. Membranes in CRRT for SA-AKI

Both membrane and solute characteristics (geometry, charge, MW, and protein binding) determine the degree of removal by ultrafiltration and adsorption in convection and diffusion. Important membrane-related determinants are pore characteristics (size, distribution, and density), pH, charge, and surface.<sup>220</sup> The low cytokines concentrations measured in the ultrafiltrate (effluent) of SA-AKI patients receiving CRRT led to the discovery of the adsorptive capacity of some membranes that are able to modify cytokines plasmatic concentrations without convection.<sup>193,184,183</sup> For some membranes, in particular, the negatively charged polyacrylonitrile (AN69) membrane, adsorption appeared the main mechanism of mediator removal,<sup>193,221</sup> although some studies have questioned this effect.<sup>215</sup>

AN69<sup>222</sup> (native AN69), originally developed in 1969 as the world's first synthetic polymeric membrane, is a copolymer of hydrophobic acrylonitrile and hydrophilic sodium methallylsulfonate and has a symmetric microporous structure. This is also the sole membrane with a hydrogel structure and possesses extremely high hydrophilicity. As AN69 is negatively charged due to sulfonate groups derived from methallylsulfonate monomers, the AN69 membrane adsorbs cytokines via ionic bonding between its sulfonate group and the amino group on the surface of a cytokine molecule. The AN69 membrane has a hydrogel structure, and adsorption to this membrane is considered to take place not only on the membrane surface but also within the bulk layer, thereby exhibiting a high adsorption capacity. In fact, native AN69 membrane is reported to adsorb a greater amount of humoral mediators such as cytokines compared with polysulfone (PS) membrane.<sup>223</sup>

Partial coating of the surface of the AN69 membrane with a biocompatible cation of polyethyleneimine (PEI)<sup>224</sup> reduced the zeta potential on the contact surface between the membrane and blood, thereby reducing bradykinin production greatly, although not all patients were free from this adverse event. The highly specific adsorptive properties distinguish AN69 from other synthetic high-flux membranes as well as from other so-called adsorptive membranes in the field of dialysis. In fact, some studies have shown that the adsorption capacity of AN69 membranes could improve with the use of diffusion techniques.<sup>225,226</sup> With this knowledge, membranes with selective adsorption

of PAMPs (e.g., endotoxin) have been developed with some contradictory results in different trials performed.<sup>227,228,19</sup>

On the other hand, filter permeability may dramatically influence the removal of plasma mediators. Conventional membranes usually have a pore size of about 5 nanometers (nm), allowing the removal of molecules up to a MW of about 30 kDa. High cutoff (HCO) membranes have pore sizes of about 10 nm, allowing the elimination of molecules with MW up to 50 kDa. The use of HCO membranes to increase cytokine removal has been discussed since it was first proposed. An animal septic model compared 100 kDa to 50 kDa pore size filters for CAVH, showing an increased survival rate in the 100kDa group (8 times higher), though it was associated with an increased protein concentration in the ultrafiltrate.<sup>204</sup>

Clinical and experimental studies show that the use of high effluent flows in a pure diffusive treatment effectively removes serum cytokines with a safe profile in albumin clearance.<sup>229</sup> More recently in a small observational study,<sup>230</sup> sequential organ failure assessment (SOFA) score significantly decreased early after initiation of HCO-CVVHD in patients with SA-AKI. The vast majority of clinical studies have been conducted with small sample sizes and methodological deficiencies.<sup>231</sup> However, a RCT was recently conducted which found no advantages with the use of HCO membranes.<sup>232</sup>

#### g. Anticoagulation strategies during CRRT

CRRT success relies on the maintenance of extracorporeal circuit (EC) for as long as possible; however, premature circuit failure due to clotting may cause blood loss, thereby reducing the therapeutic efficacy, and increasing workload and treatment costs. Heparin has been routinely used as the first line anticoagulation strategy (“the queen heparin”) until regional citrate anticoagulation (RCA) was progressively developed, improved and finally extended to most of ICUs worldwide. RCA offers clear advantages when compared to heparin and other strategies specially in terms of filter life and bleeding risk (blood transfusions).<sup>233,234</sup> Benefits in SA-AKI have also been reported<sup>235</sup> with the use of RCA associated to CRRT although this hypothetical immunomodulation role of citrate in sepsis is controversial<sup>236</sup> with well designed future trials still required. Furthermore, RCA requires a strict protocol and well trained RRT

team<sup>237</sup> in order to avoid life-threatening complications such as hypocalcemia, alkalosis or citrate intoxication.<sup>238</sup>

Although in critically ill patients with AKI requiring RRT, RCA has been progressively implemented, liver failure still represents the most important contraindication for the use of RCA<sup>26</sup> and this situation is not uncommon in patients with SA-AKI (incidence varies from 20 to 50% among series).<sup>239,28</sup> This type of patients with SA-AKI and MODS<sup>45,166</sup> represent a different situation where most of the anticoagulation strategies cannot be employed (liver failure, thrombocytopenia, and coagulopathy are present most of the times) and where the EC and filter life decreases abruptly.<sup>240,241</sup> In this adverse scenario, optimizing CRRT characteristics may allow to extend the medium life of our technique and therefore achieve solute and fluid removal endpoints which are related with short-term outcomes in SA-AKI patients.<sup>242,243,161,244</sup> Therefore, it is crucial to have a good vascular access,<sup>245</sup> to closely monitorize FF, prioritize pre-filter reposition when convective modalities are being used,<sup>241</sup> and decrease TMP gradients. Furthermore, modalities that employ diffusion such as CVVHD or CVVHDF could improve filter patency in patients with SA-AKI that present contraindications for anticoagulation strategies.<sup>246</sup>

#### h. Antibiotic dosing during RRT

A number of small studies have shown that it is not uncommon for patients on CRRT to not achieve adequate serum levels of antibiotics needed to optimally treat infections, a particular problem in the setting of septic AKI.<sup>247,248</sup> Dosing of antimicrobials may be even more problematic for PIRRT, in which an extended period of increased clearance is followed by a period of minimal clearance. Not only are there virtually no data to guide antimicrobial dosing, recommendations from expert pharmacists vary widely.<sup>249</sup> For patients on CRRT where clearance is continuous, one general concept is that dosing of antibiotics that are concentration-dependent (fluoroquinolones, aminoglycosides, daptomycin, and amphotericin), should be adjusted by changing dosing interval, whereas the dosing interval of time-dependent antibiotics (beta-lactams and azoles) is constant, while actual dose is reduced.<sup>250</sup>

Another important point is that in general initial dose of antibiotics should remain the same or slightly higher due to increased volume of distribution in patients with renal

failure.<sup>251</sup> Antibiotics/antifungals that are extremely nephrotoxic, such as aminoglycosides and amphotericin, are best avoided unless there are no other suitable alternatives. Finally, when drug levels can be measured, levels should be used to help guide dose and interval of administration.<sup>251,248</sup>

#### 1.4.6.2. Other extracorporeal therapies for SA-AKI

In an attempt to increase PAMPs and DAMPs removal, new BP strategies have been proposed. Adsorption therapies with special cartridges aim to increase cytokines or endotoxin removal, non-selective extracorporeal therapies like Coupled Plasma Filtration Adsorption (CPFA)<sup>252</sup> combine both adsorption and convection techniques, and total plasma exchange tries to replace “bad molecules” by “good molecules” with plasma transfusion.

##### a. Selective adsorptive devices

Polymyxin B-immobilized hemoperfusion (PMX-HP, Toraymyxin®)<sup>253</sup> effects are based on the specific adsorption of endotoxin, which is the initial trigger of the whole clinic-pathological picture of sepsis caused by gram-negative organisms. This technique utilizes a unit in which polystyrene-based fibers are functionalized with covalently bound polymyxin (PMX). This compound is a potent antibiotic that acts as an avid scavenger of circulating LPS, the major component of bacterial endotoxin. Toraymyxin is indicated for sepsis or septic shock caused by gram-negative bacteria by selectively removing endotoxins from the circulation.<sup>253</sup>

Current evidence supporting its use is conflicting although this device has been the most studied. The Early Use of Polymyxin-B Hemoperfusion in Abdominal Sepsis (EUPHAS) study,<sup>227</sup> was a multicenter RCT which provided the first evidence that PMX could significantly reduce mortality of patients with abdominal septic shock. In the ABDO-MIX trial,<sup>228</sup> 243 patients with peritonitis-induced septic shock from abdominal infections were enrolled. The 28-day mortality rate recorded in both groups was significantly lower than that reported in larger studies. However, the incidence of cartridge clotting (11.4%; 25/220 sessions) was higher than in previous reports (EUPHAS study). This latter issue, along with the lack of completion of the two planned sessions of PMX-B and the lack of clarification of the cause of death led to conflicting results. Therefore, the performance of The EUPHRATES<sup>19</sup> (Evaluating the



Use of Polymyxin B Hemoperfusion in a Randomized Controlled Trial of Adults Treated for Endotoxemia and Septic Shock) study was planned in the U.S.A and Canada from 2010 through 2016. In this recently published study, LPS levels were determined using the endotoxin activity assay (EAA). Patients with septic shock, an EAA level  $\geq 0.6$ , and a multiple organ dysfunction score  $>9$  were chosen as participants. PMX-B hemoperfusion treatment plus conventional medical therapy compared with sham treatment plus conventional medical therapy did not reduce mortality at 28 days. Furthermore, EAA measured at day 2 and 3 after randomization showed no differences between the PMX-B hemoperfusion treatment group and the sham treatment group.

b. Non-selective adsorptive devices

Cytosorb® has adsorptive properties,<sup>254</sup> which are based on hydrophobic interactions and ionic attractions, and allows to “trap” medium MW molecules, since most of the inflammatory mediators are low and medium MW molecules. This device has the capacity to remove hydrophobic molecules up to 60 kDa.<sup>255</sup> However, Cytosorb® has some drawbacks to be considered before its use can be widely extended. This adsorptive device owns a high capacity for cytokine adsorption but it is not provided with any endotoxin adsorptive properties.<sup>256</sup> It is worth noting that it is not possible to obtain any depurative advantage neither. Currently, the high cost of those devices and the lack of evidence available in the literature supporting their use, have led to limited application on daily clinical grounds.<sup>257,258</sup> Particularly in sepsis and cardiac surgery, studies have not yet proven any benefit.<sup>259</sup>

CPFA is a modality of blood purification in which plasma is separated from the whole blood by a plasma filter and circulated in a sorbent cartridge.<sup>252</sup> After the sorbent unit, plasma is returned to the blood circuit and the reconstituted whole blood undergoes hemofiltration or hemodialysis. This technique has the capacity to remove non-selectively mediators of medium MW and perform at the same time renal depuration. Most of the studies reported with CPFA are observational cohorts<sup>260</sup> and there is only one multicenter RCT which was terminated because of futility. In this last study,<sup>261</sup> there was no statistical difference in hospital mortality (47.3% controls, 45.1% CPFA;  $p=0.76$ ), nor in secondary endpoints.

### c. Plasmapheresis

Plasma exchange therapies (PE) separate plasma from whole blood by centrifugation or filtration mechanisms, and replace with human plasma or albumin. Plasma replacement could be a good option in septic patients because of the potential benefits of factor replacement. Experience in septic patients with PE is reduced, though most of the studies showed beneficial effects. Stegmayr et al.<sup>262</sup> used PE as rescue therapy in 76 patients with severe multiorgan failure (MOF) observing an increase in survival (86% vs. 33% Acute Physiology and Chronic Health Evaluation (APACHE) II score expected survival). The largest published trial<sup>263</sup> included 106 septic patients and was associated with a decreased mortality in PE group of 20% (33% vs. 53.8%).

## 1.5. Short- and long-term outcomes in SA-AKI

### 1.5.1. Mortality

SA-AKI is distinct from non-sepsis AKI, with differences in pathogenesis, patient characteristics and clinical outcomes.<sup>264,265,49</sup> SA-AKI presents higher mortality than non septic AKI as several studies have reported.<sup>3,266</sup> Most of this higher mortality is related to the MODS that is present in the majority of patients with SA-AKI. Critically ill patients with SA-AKI who require RRT present the highest mortality of all<sup>24,159</sup> although it is not directly related to the use of RRT as some studies had proposed.<sup>267</sup> It seems obvious that SA-AKI patients requiring RRT would probably present an increased mortality if RRT supportive treatment would not be initiated.<sup>268</sup>

#### *1.5.1.1. Risk factors for mortality*

The incidence of RRT-requiring AKI among critically ill patients has increased by almost 4-fold in the last 20 years<sup>159</sup> This has been also accompanied by a significant decline in mortality.<sup>159,239</sup> 90-day mortality declined from 50% in 1996 to 2000 to 45% in 2006 to 2010 (aHR, 0.83 [95% CI, 0.79-0.87]). Despite this good news, critically ill patients with RRT-requiring SA-AKI still present the highest mortality of all AKI patients.<sup>24,3</sup> These patients constitute one of the major challenges physicians must face in their everyday practice as those mortality risk factors related to either the sepsis management, or the SA-AKI management (including of course all the RRT strategy),

have still not been well identified or at least there are no clear defined strategies (besides avoiding fluid overload [FO])<sup>269</sup> that can clearly modify outcomes.<sup>159,270,239</sup>

Early antibiotics and hemodynamic resuscitation avoiding hypotension are probably the most important measures in order to diminish SA-AKI mortality.<sup>271,94</sup> FO seems directly related with mortality in SA-AKI patients<sup>242</sup> and early resuscitation with vasopressors could be justified in these patients when hypotension is not responsive to initial fluid bolus.<sup>272,273</sup> In patients with SA-AKI and ARDS the use of diuretics in order to avoid FO is also recommended.<sup>274</sup> Following the same idea, patients who initiate RRT with FO present higher mortality than those who are started with less anasarca (FO in these patients could suggest either a late RRT initiation or an insufficient diuretic administration).<sup>243,161</sup> Furthermore, patients who after RRT initiation achieved a negative mean daily fluid balance presented better clinical outcomes.<sup>244</sup> All these are hypothesis based on observational studies and therefore exposed to important biases.

Uchino et al.<sup>45</sup> identified mortality risk factors in a big cohort of critically ill patients with AKI (Beginning, Ending Supportive Therapy for the kidney, BEST study). Of 29,269 critically ill patients admitted during the study period, 1738 (5.7%) had AKI during their ICU stay, including 1260 patients who were treated with RRT. 47.5% of these patients presented septic shock. Overall hospital mortality was 60.3%. Independent risk factors for hospital mortality included use of vasopressors, MV, septic shock, cardiogenic shock, and hepatorenal syndrome. Same authors from the BEST study analyzed those AKI patients who required CRRT (1006 patients).<sup>240,275</sup> They performed a multivariable analysis which showed that no CRRT-related variables (mode, filter material, drug for anticoagulation, and prescribed dose) predicted hospital mortality. SCr, platelet count and UO (it was defined as oliguria yes/no) were protective (the higher value, the lower mortality) for hospital mortality.

When analyzing the timing RRT strategies in the BEST study population (1238 patients), the same authors<sup>160</sup> concluded that timing of RRT, a potentially modifiable factor, exerted an important influence on patient survival. Timing was stratified into “early” and “late” by median serum urea and SCr at the time RRT was started. Timing was also categorized temporally from ICU admission into early (<2 days), delayed (2-5 days), and late (>5 days). RRT timing by urea showed no significant difference in crude or covariate-adjusted mortality. When stratified by SCr, late RRT

was associated with lower crude and covariate-adjusted mortality. However, for timing relative to ICU admission, late RRT was associated with greater crude and covariate-adjusted mortality.

Data from the ATN study identified twenty-one independent predictors of 60-day mortality.<sup>276</sup> The 60-day mortality was 53%. Once again SCr and UO at RRT initiation were both protective for mortality. Ohnuma and Uchino,<sup>270</sup> recently reviewed AKI outcome prediction models and their external validation studies, in order to describe the discrepancy of reported accuracy between the results of internal and external validations, and to identify variables frequently included in the prediction models. There were 10 common non-renal variables that were reported in more than three prediction models: MV, age, gender, hypotension, liver failure, oliguria, sepsis/septic shock, low albumin, consciousness and platelet count.

#### 1.5.2. CKD, RRT dependence, and longterm mortality after SA-AKI

The incidence of RRT-requiring AKI thereby accounts for 4–8% of all AKI patients<sup>45,24</sup> and about 12–25% of these patients remain RRT-dependent.<sup>45,28,277</sup> In total, this represents a heavy burden on health care providers, where RRT is one of the most driving cost factors.<sup>278</sup> In addition, the quality of life of ICU patients treated with RRT is essentially impaired compared to other long-term critically ill survivors.<sup>279</sup>

Depending upon its severity, etiology, recovery phenotype and medical follow-up,<sup>280,281</sup> AKI survivors have a high but a variable risk of long-term renal and non-renal complications, including the development of acute kidney disease (AKD), CKD and dialysis-dependent end-stage renal disease (ESRD), cardiovascular complications and premature mortality.<sup>282</sup> Recovery after AKI becomes the main target in those patients in whom preventive strategies could not be effectively implemented<sup>281</sup> but still possess modifiable risk factors causing secondary damage to the kidney.<sup>283</sup>

Compared with other AKI etiologies, SA-AKI may have specific prognostic implications, as it is associated strongly with adverse outcomes. Observational studies consistently have reported significantly worse outcomes with SA-AKI vs. non-septic AKI or sepsis alone.<sup>284,285,42</sup> For instance, LOS has been observed to be longer in patients with SA-AKI vs. non-septic AKI. In a previous report, SA-AKI patients were found to have twice the duration of ICU stay compared with septic patients without

AKI.<sup>284</sup> Similar findings from a larger cohort<sup>42</sup> found SA-AKI patients to have longer ICU and hospital LOS compared with non-septic AKI or sepsis alone. Furthermore, there was a stepwise increase of LOS according to AKI severity and the median ICU LOS from 3.1 to 4.8 days as SA-AKI patients progressed from RIFLE-Injury to RIFLE-Failure. Similar rates of dependence on chronic RRT were observed for SA-AKI (5.7%) vs. non-septic AKI (7.8%) patients. Both ICU and in-hospital mortality rates were significantly higher for patients with SA-AKI compared with patients with non-septic AKI (ICU mortality rate, 19.8% vs. 13.4%; in-hospital mortality rate, 29.7% vs. 21.6%).

In a subgroup analysis of the BEST Kidney trial,<sup>2</sup> the odds of dying in hospital were 50% higher in SA-AKI compared with non-septic AKI, though the different prognosis between septic and non-septic AKI is largely influenced by the composition of the non-septic group and its proportion of conditions with poor prognosis (such as severe ARDS or cardiogenic shock). In addition, the role of confounding in the association between SA-AKI and mortality needs to be addressed as all studies consistently report higher illness severity at onset and more frequent need for RRT in such patients. Conversely, survivors from SA-AKI have been associated with improved renal recovery rates when compared with others AKI etiologies. In the BEST Kidney trial<sup>2</sup> there was a trend for a lower SCr and RRT dependence (9% vs. 14%,  $p=0.052$ ). Peters et al.<sup>3</sup> reported that patients with sepsis admitted with AKIN stage 1 or 2 were more likely to have complete recovery of AKI, compared to patients without sepsis for the same AKIN stage. However, sepsis patients with AKIN stage 3 were less likely to have recovered to a lower AKIN stage by day 7 than non-septic patients with AKIN stage 3 (21% vs. 32%,  $p<0.0001$ ).

Numerous other factors may play a role in renal recovery such as RRT modality, timing of RRT, and other nephrotoxic or ischemic insults. Renal recovery is also highly influenced by comorbid conditions as illustrated by a French multicentric observational study, in which diabetic patients with SA-AKI surviving to hospital discharge were more likely to require long-term RRT and had higher SCr levels.<sup>286</sup> Regardless of short-term recovery, even a single episode of AKI is associated with a greater risk of subsequent CKD and even ESRD.<sup>287</sup>

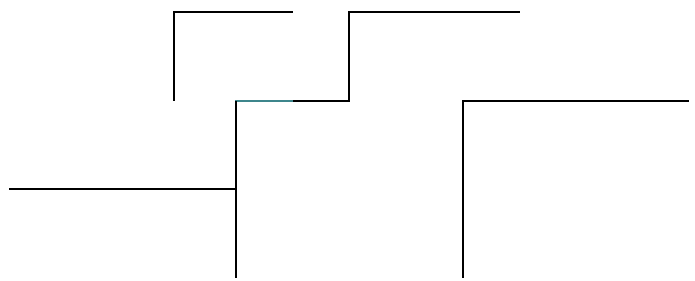
(\*) **Supplementary appendix 1** can be found at the end of this memory in order to complete introduction.

## 1.6. Summary and justification

In summary, despite improving overall outcomes from sepsis, SA-AKI remains associated with significant morbidity and mortality.<sup>3,2</sup> At present, all care for SA-AKI is supportive, and focused on best practices for patients with sepsis<sup>98</sup> (early fluid resuscitation and antibiotics, as well as source control), minimizing FO,<sup>242</sup> considering higher MAP targets in patients with chronic hypertension,<sup>115</sup> and avoiding nephrotoxins. Whether sepsis management recommendations have a significant effect or not in reducing SA-AKI is still a matter of debate.<sup>1,288</sup> Along these lines, for patients who develop severe SA-AKI, RRT may be needed. Whether timing (when) and modality (how) of RRT could modify outcomes of critically ill patients with SA-AKI is still controversial.

For these reasons, during the last years, the purpose of this study was to evaluate the real incidence and mortality of SA-AKI in critically ill patients, the risk factors associated with SA-AKI appearance, the effect of SSC recommendations in preventing from SA-AKI, the clinical variables associated with poor outcome in SA-AKI requiring CRRT together with their relationship with a timing CRRT strategy, and finally through a small randomized pilot study the benefits of a diffusive CRRT strategy (CVVHD) when compared to a convective CRRT strategy (CVVH) both modalities employing the same type of membrane with adsorption capacity.





*Hypothesis*

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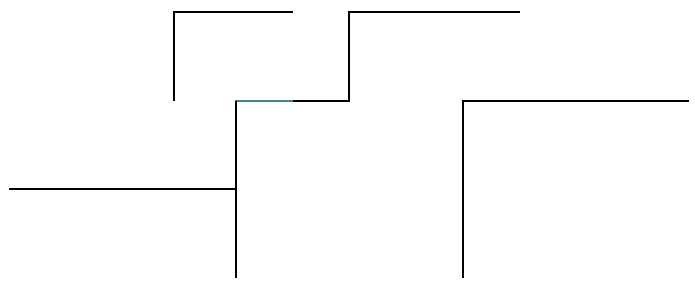




## 2. Hypothesis

1. SA-AKI has a high incidence and mortality in critically ill septic patients. Current recommendations for sepsis management do not prevent SA-AKI incidence.
2. The need for CRRT in septic shock patients with SA-AKI is very high. CRRT timing in these patients should be based on urine output.
3. When CRRT is indicated, CVVHD is superior to CVVH in terms of extracorporeal circuit patency and absence of dialytrauma, without changes in mortality, cytokine or solute plasmatic clearance, and hemodynamic or respiratory variations.





*Objectives*

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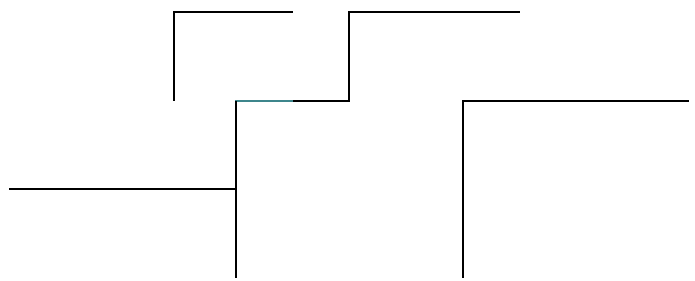


### 3. Objectives

1. To assess the incidence of SA-AKI and its influence in the final outcome of a single center cohort of critically ill patients with sepsis.
2. To identify in a single center cohort of critically ill patients with sepsis, those risk factors for SA-AKI appearance in order to define future therapeutic strategies.
3. To assess the effect that the accomplishment of the SSC management recommendations has on SA-AKI incidence in a single center cohort of critically ill patients with sepsis.
4. To identify through a two-center international retrospective cohort study in a critically ill population with septic shock and SA-AKI requiring CRRT, those factors associated with mortality in order to define future therapeutic strategies.
5. To identify through a two-center international retrospective cohort study in a critically ill population with septic shock and advanced SA-AKI (KDIGO stage 3) requiring CRRT within the first 5 days from ICU admission, those parameters or variables that can be useful to decide CRRT initiation (“timing”) and potentially improve outcome in terms of survival.
6. To evaluate thru a two-center pilot randomized trial in a critically ill population with SA-AKI requiring CRRT, the validity and usefulness of a diffusion CRRT strategy (CVVHD) associated to an adsorption capacity membrane (AN69-ST) compared to a convective CRRT strategy (CVVH) associated to the same membrane. This objective will be assessed registering the mean filter life and the number of dialytrauma events within the first 72 h after randomization and during all the period on CRRT.
7. To evaluate through a two-center pilot randomized trial in a critically ill population with SA-AKI requiring CRRT, the survival outcome of a diffusion CRRT strategy (CVVHD) associated to an adsorption capacity membrane (AN69-ST) compared to a convective CRRT strategy (CVVH) associated to the same membrane. This objective will be assessed registering survival (or mortality) at 28 and 90 days.

8. To evaluate through a two-center pilot randomized trial in a critically ill population with SA-AKI requiring CRRT, the immunomodulation capacity of a diffusion CRRT strategy (CVVHD) associated to an adsorption capacity membrane (AN69-ST) compared to a convective CRRT strategy (CVVH) associated to the same membrane. This objective will be assessed measuring the cytokines plasmatic concentration changes within the first 72 h after randomization.
9. To evaluate through a two-center pilot randomized trial in a critically ill population with SA-AKI requiring CRRT, the solute removal efficacy of a diffusion CRRT strategy (CVVHD) associated to an adsorption capacity membrane (AN69-ST) compared to a convective CRRT strategy (CVVH) associated to the same membrane. This objective will be assessed measuring the solutes plasmatic variations within the first 24 h after randomization.
10. To evaluate through a two-center pilot randomized trial in a critically ill population with SA-AKI requiring CRRT, the clinical efficacy of a diffusion CRRT strategy (CVVHD) associated to an adsorption capacity membrane (AN69-ST) compared to a convective CRRT strategy (CVVH) associated to the same membrane. This objective will be assessed measuring the hemodynamic and respiratory variations within the first 72 h after randomization as well as the number of days in MV and ICU LOS.

**(\*) Methods, results, and discussions are displayed separately for each study.**



*Study 1*

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## 4. Study 1. No impact of surviving sepsis campaign care bundles in reducing sepsis associated acute kidney injury (Supplementary appendix 2)

### 4.1. Objectives

- To assess the incidence of SA-AKI and its influence in the final outcome of a single center cohort of critically ill patients with sepsis.
- To identify in a single center cohort of critically ill patients with sepsis, those risk factors for SA-AKI appearance in order to define future therapeutic strategies.
- To assess the effect that the accomplishment of the SSC management recommendations has on SA-AKI incidence in a single center cohort of critically ill patients with sepsis.

### 4.2. Methods Study 1

Investigators performed a single centre observational study in the critical care department of a tertiary care hospital in order to evaluate the impact of SSC care tasks<sup>289</sup> in SA-AKI incidence. The study was approved by the ethical review board at the research centre and patients remained anonymous. The need for informed consent was waived due to both the anonymous nature of the study and the fact that all interventions had already been tested and published in previous trials.

All ICU patients were actively screened for the presence of sepsis or septic shock at admission and everyday during their ICU stay from November 2005 to June 2007. Eligible patients were those with suspected infection plus any of the following findings: bilateral pulmonary infiltrates with partial pressure of oxygen in arterial blood/inspiratory oxygen supply index ( $\text{PaO}_2/\text{FIO}_2$ ) < 300 mm Hg,  $\text{UO} < 0.5 \text{ mL/kg/hr}$  for at least 2 h or  $\text{SCr} > 177 \text{ } \mu\text{mol/L}$ , coagulation abnormalities (International Normalized Ratio > 1.5 or a partial thromboplastin time > 60 seconds), platelet count  $< 100 \times 10^3/\mu\text{L}$ , total plasma bilirubin  $> 34 \text{ } \mu\text{mol/L}$ , serum lactate  $> 4 \text{ mmol/L}$ , or hypotension (systolic blood pressure [SBP] < 90 mm Hg, MAP < 65 mm Hg, or a

reduction in SBP >40 mm Hg from baseline measurements). Septic shock was defined as hypotension despite adequate volume resuscitation requiring vasopressor support.<sup>290</sup>

We classified AKI according to KDIGO criteria using both SCr and UO.<sup>291</sup> Baseline SCr value was registered from 6 months previous clinical files (90%) or estimated from the MDRD equation when data was not available from clinical records (10%). The stage of AKI was determined daily based on maximum severity by either SCr or UO criteria (until ICU discharge). SA-AKI was defined as AKI appearance or worsening-increase (in AKI stage) within the first week from sepsis onset (stage 3 AKI worsening was defined as RRT requirement).

SSC care tasks<sup>289</sup> goals achievement were specially evaluated within the first 6 h (resuscitation bundle or tasks) and in those patients presenting hypotension EGDT goals such as an adequate fluid challenge >20 mL/Kg, a central venous pressure (CVP) >8 mmHg, and a central venous oxygen saturation (ScvO<sub>2</sub>) >70% were assessed in order to evaluate their impact in SA-AKI incidence. Management tasks (first 24 h) with special attention to steroids use (in those patients requiring vasopressors), blood glucose control, and protective MV (in those patients requiring invasive MV), were also evaluated in order to assess their impact in SA-AKI incidence (**Table 1.1**).

**Table 1.1.** SSC recommendations for sepsis management (2004)<sup>289</sup>

<b>Sepsis Resuscitation Bundle</b> (To be started immediately and completed within 6 hours)	<b>Q1)</b> Serum lactate measured.
	<b>Q2)</b> Blood cultures obtained prior to antibiotic administration.
	<b>Q3)</b> Broad-spectrum antibiotics administered within 3 hours for ED admissions and 1 hour for non-ED ICU admissions.
<b>Hemodynamic measures in the event of hypotension (EGDT)</b>	<b>Q4)</b> Minimum of 20 ml/kg of crystalloid (or 7 ml/kg of colloid) delivered. For hypotension not responding to volume resuscitation, vasopressors employed to maintain mean arterial pressure (MAP) > 65 mm Hg. In the event of persistent arterial hypotension refractory to volume resuscitation (septic shock) and/or initial lactate > 4 mmol/L.
	<b>Q5)</b> Central venous pressure (CVP) of > 8 mm Hg achieved.
	<b>Q6)</b> Central venous oxygen saturation (ScvO <sub>2</sub> ) of > 70% achieved.*
<b>Sepsis Management Bundle</b> (To be started immediately and completed within 24hours)	<b>Q7)</b> Low-dose steroids administered for septic shock in accordance with a standard ICU policy.
	<b>Q8)</b> Glucose control maintained > lower limit of normal, but < 150 mg/dl (8.3 mmol/L).
	<b>Q9)</b> For mechanically ventilated patients inspiratory plateau pressures maintained < 30 cm H <sub>2</sub> O.

## Statistical Analysis

All continuous data are presented as medians (interquartile range [IQR], Q1-Q3) or means (standard deviation, SD), as appropriate for nonparametric or parametric data, respectively. Differences in medians or means between groups were tested with the Mann-Whitney test and the Student *t* test, respectively. Differences in proportions were compared using Fisher's exact test or chi square test where appropriate. A Cox regression model was used to assess the risk factors for the development of SA-AKI within the first 7 days from sepsis onset and variables were included if they had <10% missing data, and the following assumptions: (1) had *p* values <0.1 in the univariate analysis and (2) were clinically plausible. A *p* value <0.05 was considered statistically significant. All analyses were conducted using SPSS version 18.0 (SPSS, Chicago, IL).

### 4.3. Results Study 1

During the study period 650 patients were actively screened for the presence of severe sepsis or septic shock out of which 260 patients (40%) were finally enrolled. From these 260 patients, at sepsis diagnosis 113 patients (43.5%) had KDIGO AKI criteria<sup>26</sup> and 129 patients (49%) had AKI at ICU admission (23% presenting oliguria) (**Figure 1.1**).

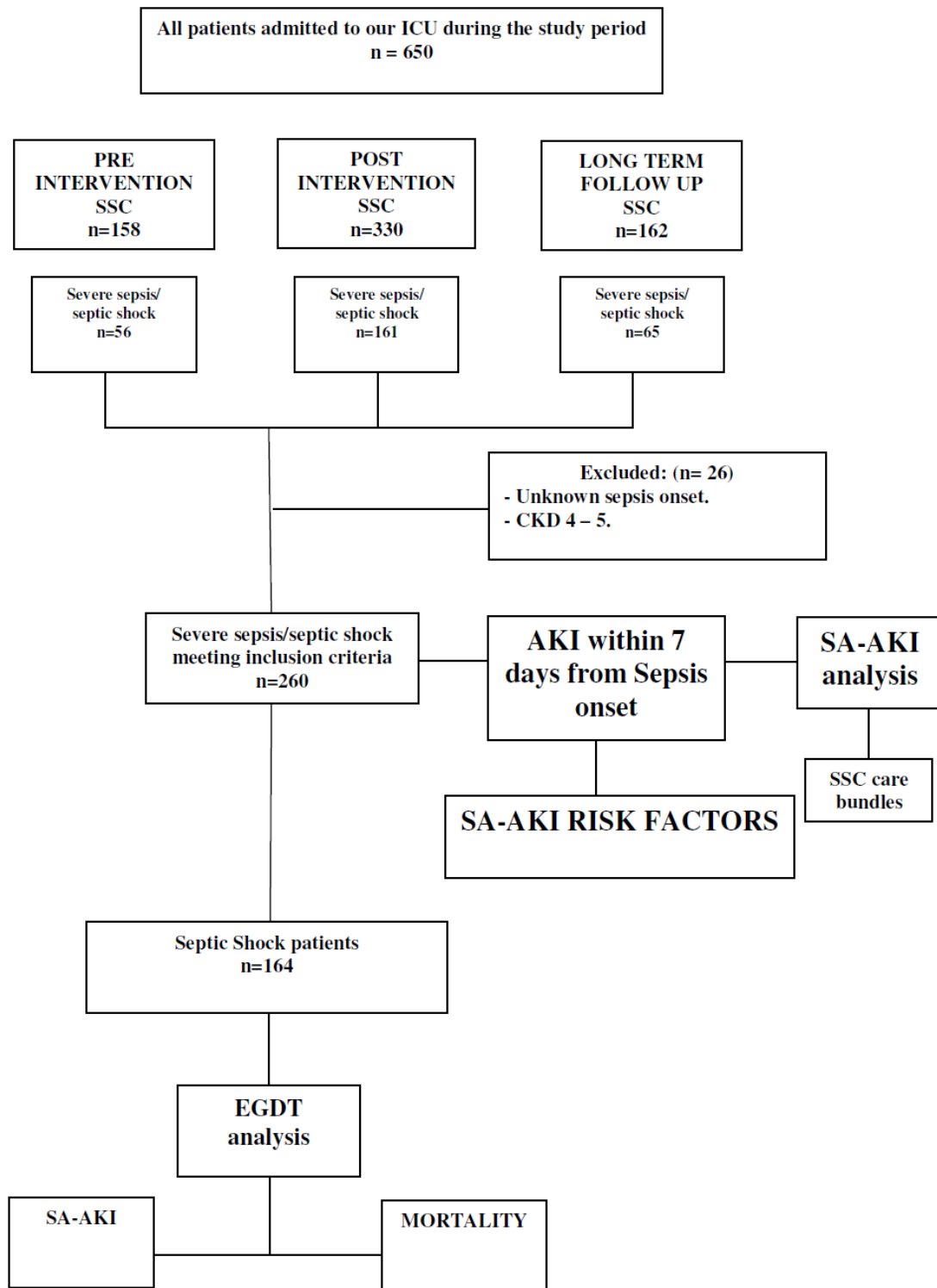


Figure 1.1. Study 1 Flow Chart

Patients were predominantly male (67%), with a mean age of 58.9±15 years. Most patients were admitted to the ICU with severe sepsis from the ED (31%) or ward (29%), but an important part of them developed severe sepsis during ICU admission (40%). At sepsis onset 63.1% of patients presented septic shock and 62.7% were on MV.

82 patients (31.5%) developed SA-AKI at a median of 3 days (IQR 1-5 days) after the onset of severe sepsis or septic shock. When classified according to the KDIGO AKI criteria,<sup>26</sup> 17% developed stage 1 AKI, 16% stage 2 AKI, and 67% stage 3 AKI. From these SA-AKI patients, 37% required RRT during their ICU stay (stage 3 AKI was not synonymous of RRT). **Table 1.2** presents univariate comparisons of demographic characteristics, baseline characteristics, comorbidities, septic characteristics, and SSC bundles accomplishment between patients who developed SA-AKI and those who did not. Patients who developed SA-AKI were older, predominantly male, presented worse baseline renal function, had higher APACHE II score, and were more likely to have positive blood cultures and an abdominal source of infection.

**Table 1.2.** Univariate analysis 7-day SA-AKI risk incidence for patients requiring ICU

	Non-AKI (n=178)	SA-AKI (n=82)	p
<b>Age (years), mean±SD</b>	58.0±16	60.6±14	0.22
<b>Weight (kgs), mean±SD</b>	71.5±13	75.9±16	0.03*
<b>Gender (Male), n (%)</b>	114 (64.0)	61 (74.4)	0.12
<b>Baseline renal function, (mean±SD)</b>			
Creatinine (µmol/L)	78±27	91±35	0.01*
GFR (mL/min/1.73m <sup>2</sup> )	92±45	79.5±32	0.02
<b>Sepsis etiology, n (%)</b>			
Abdominal	36 (20.2)	34 (41.5)	0.01*
Pneumonia	93 (52.2)	35 (42.7)	
Medical miscellanea	27 (15.2)	8 (9.8)	
<b>Sepsis severity, n (%)</b>			
Severe sepsis	78 (43.8)	18 (22.0)	<0.001*
Septic shock	100 (56.2)	64 (78.0)	
<b>Severity Scores, median [Q1-Q3]</b>			
APACHEII score at Sepsis onset	20 [15- 26]	25 [20-30]	<0.001
SOFA score at Sepsis onset	7 [5-10]	9 [6-13]	
<b>Urine Output at ICU admission</b>			
mL/kg/h, mean±SD	1.21±0.7	0.86±0.6	0.0002*
Oliguria (<0.5 mL/kg/h), n (%)	21 (12)	38 (46)	<0.001*
<b>AKI stage at Sepsis onset, n (%)</b>			<b>0.413</b>

	<b>Non-AKI</b> (n=178)	<b>SA-AKI</b> (n=82)	<b>p</b>
<b>No AKI 0</b>	106 (59.6)	41 (50.0)	
<b>Stage 1</b>	30 (16.9)	14 (17.1)	
<b>Stage 2</b>	17 (9.6)	12 (14.6)	
<b>Stage 3</b>	25 (14.0)	15 (18.3)	
<b>KDIGO AKI stage at SA-AKI diagnose, n (%)</b>			
No AKI		0 (0)	
Stage 1		14 (17)	
Stage 2		13 (16)	
Stage 3		55 (67)	
<b>At sepsis diagnosis, mean±SD</b>			
Lactate (mmol/L)	3.3±3.2	5.5±5.3	0.08**
Hemoglobin (g/L)	112±24	111±24	0.89
Bicarbonate (mmol/L)	24.9±6.6	23.5±7.2	0.13
Albumin (g/L), median [Q1-Q3]	26 [21-30]	23 [20-28]	0.04**
<b>Multiorgan dysfunction at sepsis (≥3), n (%)</b>	103 (57.8)	69 (84.2)	<0.001*
<b>Resuscitation bundle (6 hours), n (%)</b>			
Q1 (Lactate)	30 (16.9)	24 (29.3)	0.03
Q2 (Blood cultures)	115 (69.7)	42 (53.2)	0.01
Q3 (Antibiotics < 1-3h)	80 (49.1)	42 (54.5)	0.49
<b>Shock†</b>			
†Q4 (Fluids challenge if hypoTA)	66 (61.7)	39 (58.2)	0.75
†Q5 (CVP>8-12 mmHg)	57 (50.9)	27 (40.3)	0.22
†Q6 (ScvO <sub>2</sub> >70%)	22 (20.6)	13 (19.7)	0.9
<b>Management bundle (24 hours), n (%)</b>			
†Q7 (Steroids)	28 (26.9)	24 (36.4)	0.23
Q8 (Median glycaemia >4 <8.3 mmol/L)	82 (49.7)	29 (36.2)	0.06*
‡Q9 (Median Pplateau<30 cmH <sub>2</sub> O)	74 (73.3)	32 (58.2)	0.07**
<b>SSC Goals measures, median [Q1-Q3]</b>			
Resuscitation bundles compliance (%)	33 [17-33]	33 [17-33]	0.5
Management bundles compliance (%)	66 [33-66]	33 [33-66]	0.3
All SSC bundles compliance (%)	30 [30-40]	30 [20-40]	0.4
Sepsis to antibiotics (minutes)	120 [60-300]	120 [60-270]	0.39
†Sepsis to CVP>8 mmHg (minutes)	292 [60-645]	480 [120-795]	0.45
†Sepsis to ScvO <sub>2</sub> >70% (minutes)	619 [167-1170]	490 [163-1045]	0.9
†Sepsis to steroids (minutes)	522 [210-1020]	780 [180-2640]	0.12
Median Serum glucose (mmol/L)	7.4 [5.7-9.6]	7.9 [5.9-10.6]	0.41
‡Median Plateau pressure (cmH <sub>2</sub> O)	24 [20-30]	28 [24-33]	0.01
<b>Therapy requirements during ICU, n (%)</b>			

	<b>Non-AKI</b> (n=178)	<b>SA-AKI</b> (n=82)	<b>p</b>
RRT	5 (3)	29 (37)	<0.001
MV	103 (57.9)	60 (73.2)	0.02*
Vasopressor use (hypotensive patients)	98 (91.6)	64 (95.5)	0.37
<b>Severity risk factors, n (%)</b>			
Hypoglycaemia (<4 mmol/L)	25 (15.2)	13 (16.2)	0.85
Bacteraemia (positive blood cultures)	58 (40)	36 (54.5)	0.05**
<b>Length of stay among survivors (days), median [IQR]</b>			
ICU	11 [6-23]	15 [8-32]	0.47
Hospital	34 [22-62]	46 [25-74]	0.62
<b>At Hospital discharge among survivors, mean±SD</b>			
Creatinine (µmol/L)	64±27	85±62	0.09
GFR (mL/min/1.73m <sup>2</sup> )	122±59	111±55	0.35
<b>Outcome measures, n (%)</b>			
ICU mortality	60 (33.7)	49 (59.8)	<0.001
Hospital mortality	70 (39.3)	50 (61.0)	<0.001
90-day mortality after sepsis	72 (40.4)	51 (62.2)	<0.001

APACHE II, Acute Physiology and Chronic Health Evaluation scoring system version II; CKD, chronic kidney disease; CVP, central venous pressure; GFR, glomerular filtration rate; ICU, intensive care unit; MV, mechanical ventilation; RRT, renal replacement therapy; SA-AKI, Sepsis-associated Acute Kidney Injury; ScvO<sub>2</sub>, central venous oxygen saturation; SOFA, Sequential Organ Failure Assessment; SSC, sepsis surviving campaign.

(\*) Variables that were included in multivariable logistic regression analysis (p<0.1).

(\*\*) Significant variables (p<0.1) with >10% missing data (therefore, not included in multivariable logistic regression analysis).

(†) Only applies for patients who presented hypotension (Systolic blood pressure <90 mm Hg, mean blood pressure <65 mm Hg, or a reduction in systolic blood pressure >40 mm Hg from baseline measurements).

(‡) Only applies for patients who were on mechanical ventilation (MV).

Hospital deaths occurred in 61% of patients who developed SA-AKI as opposed to 39.3% in the non-AKI septic group (p<0.001) (**Table 1.2**). Kaplan-Meier curves representing 90-day mortality incidence (SA-AKI vs. Non-AKI sepsis) were compared using a log-rank test (**Figure 1.2**).



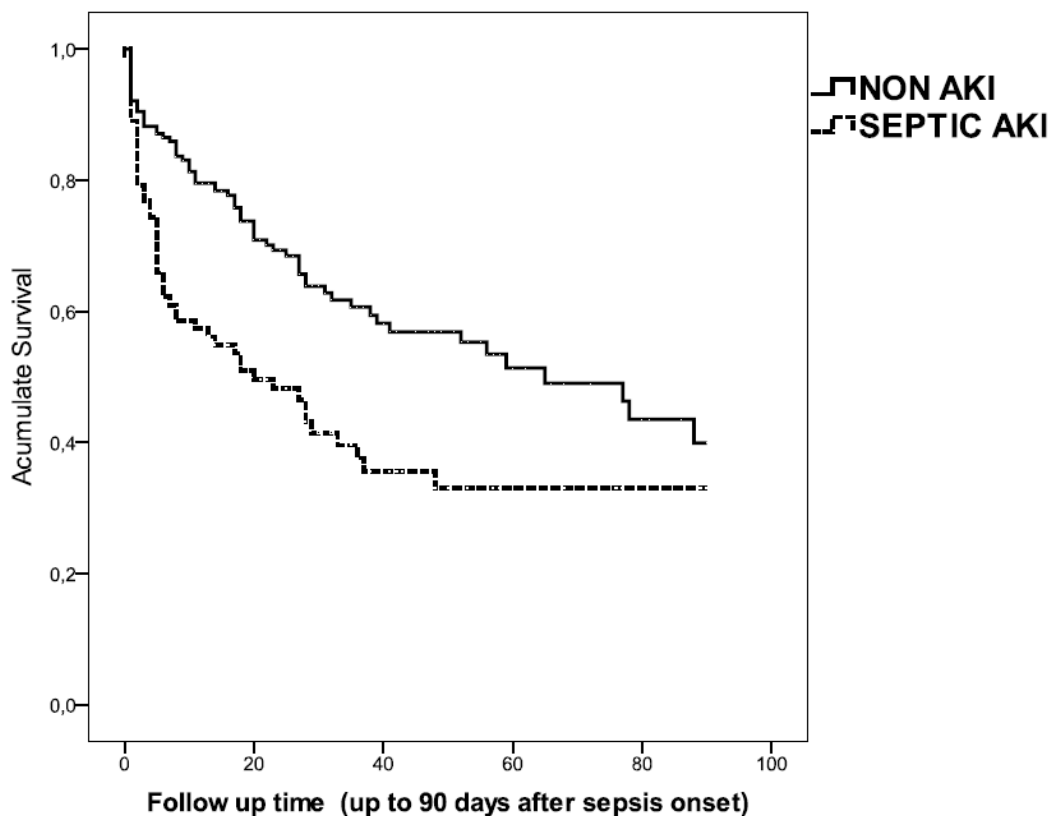


Figure 1.2. SA-AKI vs non-AKI sepsis. Survival at 90 days

AKI, acute kidney injury; SA-AKI, sepsis-associated acute kidney injury; ( $p < 0.001$ )

All SSC tasks<sup>289</sup> were independently analyzed. No differences were observed in task compliance or in terms of time analysis (time from sepsis diagnosis to antibiotic administration). Hypotension was more frequent in SA-AKI patients (83% vs. 62%;  $p < 0.001$ ) as well as MV requirement (73% vs. 58%;  $p < 0.02$ ). In septic shock population, no differences were observed in correct fluid challenge administration, CVP, or ScvO<sub>2</sub> goal achievement between SA-AKI and non-AKI septic patients (**Table 1.2**).

When management tasks<sup>289</sup> (24 h) were analyzed, some differences were found between SA-AKI and non-AKI septic patients (**Table 1.2**). Median glucose level goal (4 to 8.3 mmol/L with no hypoglycemia episodes) was achieved more frequently in the non-AKI septic group compared to the SA-AKI patients (49.7% vs. 36.2%;  $p = 0.06$ ). Among those patients who received MV (63% of the studied population), a higher plateau pressure (Ppl) was observed in SA-AKI patients with a statistically significant difference compared to the non-AKI septic ventilated patients ( $p < 0.01$ ). However,

patients who completed all bundles (resuscitation, management, or both) had no decrease in septic AKI incidence compared to those patients who did not achieve all bundles. After adjustment for confounders, the development of SA-AKI was independently associated with the presence of hypotension (2.3 HR, 95% CI 1.2-4.2,  $p < 0.01$ ) and an abdominal sepsis etiology (1.8 HR, 95% CI 1.1–3.1,  $p < 0.02$ ) (**Table 1.3**).

**Table 1.3.** Multivariate logistic regression of risk factors for 7-day SA-AKI incidence

Factor	Hazard ratio	95% Wald confidence	p
<b>Hypotension<sup>†</sup></b>	2.3	(1.2-4.2)	0.01
<b>Abdominal Sepsis</b>	1.8	(1.1-3.1)	0.02
<b>Q8</b> (Median glycaemia >4 <8.3 mmol/L)	0.7	(0.4-1.2)	0.19
<b>MV</b>	1.4	(0.8-2.4)	0.28
<b>Weight</b> (kgs)	1.006	(0.9-1.0)	0.42
<b>Baseline Creatinine</b> ( $\mu\text{mol/L}$ )	1.19	(0.9-1.5)	0.57

MV, mechanical ventilation; SA-AKI, Sepsis-associated Acute Kidney Injury; SSC, sepsis surviving campaign.

<sup>†</sup>Systolic blood pressure <90 mm Hg, mean blood pressure <65 mm Hg, or a reduction in systolic blood pressure >40 mm Hg from baseline measurements.

## 4.4. Discussion Study 1

### 4.4.1. Highlights

SA-AKI incidence within the first week from sepsis onset was high. In addition, patients who developed SA-AKI had higher hospital mortality. SA-AKI was more likely to develop in patients with hypotension requiring fluid challenge administration and (or) an abdominal sepsis etiology. Finally, none of the SSC tasks significantly reduced the risk for SA-AKI incidence.

### 4.4.2. SA-AKI incidence

We intentionally defined SA-AKI as a renal function worsening (based in SCr and UO changes) only after sepsis onset within the first seven days. Our global incidence was 32% (82 patients from the 260) although in our study we did not differentiate between those who had worsening of SA-AKI and those who developed “new” SA-AKI from

sepsis onset onwards (**Table 1.2**). Most of the previous studies classify as SA-AKI all those patients who already present AKI at sepsis diagnose, extending AKI occurrence sometimes as far as 28 days thus reporting higher rates of SA-AKI.<sup>47,155</sup> This means that our SA-AKI incidence was intentionally underestimated in order to properly evaluate modifiable risk factors and SSC care bundles impact after sepsis onset. This 7-days period seems reasonable in order to evaluate AKI incidence related to sepsis and is reinforced by recent studies evaluating SA-AKI incidence or outcome that used this same 7 days period methodology.<sup>3</sup>

Although our objective was to analyze all those risk factors and management strategies that could modify SA-AKI incidence after sepsis onset we must realize that AKI prevalence at “moment 0” (sepsis identification) was as high as 43.5% in our global septic population (in other words, only 106 patients from the 260 patients had no AKI at sepsis onset), and 50% in those patients whom finally fulfilled our SA-AKI definition (**Table 1.2**). This means that an important part of the patients evaluated already presented some stage of AKI at the beginning of sepsis and this probably increases the difficulty to change renal outcomes for all the risk factors identified and all the resuscitation and management bundles evaluated. It is clear that some of the most important factors that contribute to this “baseline” incidence of SA-AKI are not modifiable from a clinical management point of view (age, CKD, comorbidities such as diabetes mellitus).<sup>292,28</sup> However, we strongly believe that classifying SA-AKI incidence from sepsis onset onwards would permit us to evaluate if those measures initiated at the time of sepsis identification are the ones that can potentially modify renal outcomes.

Kellum et al., (from the ProCESS and ProGRess-AKI investigators)<sup>155</sup> studied 1243 patients with septic shock and classified SA-AKI using SCr and UO. At enrolment, 626 patients (50.4%) had SA-AKI with 399 (32.1%) having stage 2-3 SA-AKI. In our study, 43% had AKI at sepsis onset and 27% had stage 2-3. This means that incidence of SA-AKI at the moment of sepsis identification (or enrolment) in two different studies, but both in critically ill patients with sepsis, was very similar. However, ProCESS investigators defined SA-AKI as the occurrence of AKI within the following 28 days from sepsis onset and that was translated in important differences with our own results. In the ProCESS trial of the 617 patients “without SA-AKI at enrolment”, 233 (37.8%) subsequently manifested SA-AKI within the next 28 days (same methodology as in our

study but more days of follow up) which is translated in a higher incidence than ours. In our own study, from 147 patients “without AKI *at enrolment*” we identified only 41 patients (28%) manifesting SA-AKI within the next 7 days and this explains the difference between the two studies. We strongly believe that extending incidence up to 28 days overestimates the real incidence of SA-AKI as many of the new AKI episodes that occur in an ICU setting after one week will be due to different reasons than the initial process of admission.

#### 4.4.3. SA-AKI mortality

In our study patients who developed SA-AKI had a high severity of illness (APACHE2 and SOFA) and high RRT requirements (37% of our patients classified as SA-AKI finally required RRT). We know from previous studies that in critically ill populations with SA-AKI, RRT requirements are generally high, reflecting a higher severity of AKI respect to non-septic AKI populations.<sup>3,154,2</sup> In our study, all this severity was translated into a significant higher hospital mortality respect to those critically ill septic patients who did not develop SA-AKI ( $p < 0.001$ ), (**Table 1.2**). Plataki et al.<sup>1</sup> described that hospital mortality was significantly greater in patients who developed SA-AKI (49 vs. 34%) in a cohort of critically ill patients with septic shock. Suh et al.<sup>47</sup> also described in their observational study among 992 patients who visited the ED with septic shock that hospital mortality was higher in SA-AKI group and that reduced 30-day survival rate was significantly associated with the severity of SA-AKI.

The ProCESS trial<sup>155</sup> hospital mortality at 60 days was 6.2% for patients without SA-AKI, 16.8% for patients with maximum SA-AKI stage 1 and 27.7% for stage 2-3 SA-AKI ( $p < 0.0001$ ). In our septic cohort nearly 13% of the total patients with sepsis finally required RRT (37% in the SA-AKI group) during their ICU stay compared to only 6% of the ProCESS population revealing important differences in RRT requirements. Same differences can be observed in mortality between the two cohorts probably reflecting differences in the severity of illness as patients included in the ProCESS trial had unexpected low mortalities for an “early” septic shock population (probably patients presented less severe forms of septic shock).

#### 4.4.4. Risk factors for SA-AKI

The presence of hypotension (defined in our study as a SBP<90 mm Hg, MAP<65 mm Hg, or a reduction in SBP>40 mm Hg from baseline measurements) and an abdominal etiology for sepsis (respect to a non-abdominal etiology) were the only two independent risk factors for SA-AKI incidence identified after performing a Cox-regression analysis. Our results are concordant with those of other investigators, who have also reported a relationship between hypotension in critically ill septic patients and renal outcomes (**Table 1.3**).<sup>115,1,97</sup>

Hypotension, when severe and especially when persistent, is clearly associated with organ dysfunction. We know from Kumar et al.<sup>97</sup> that in septic shock patients the duration of hypotension previous to antibiotic administration can increase SA-AKI incidence. Recently Maheshwari et al.<sup>293</sup> reported a strong relationship between ICU hypotension and in-hospital mortality in septic ICU patients. Hypotension exposure was defined by time-weighted average MAP (TWA-MAP) and cumulative time below 55, 65, 75, and 85 mm Hg thresholds. For every one unit increase in TWA-MAP <65 mm Hg, the odds of in-hospital mortality increased 11.4% and the odds of AKI increased 7.0% (p<0.001). For mortality and AKI, odds progressively increased as thresholds decreased from 85 to 55 mmHg. Unfortunately, besides the presence or not of hypotension (clearly related with SA-AKI incidence) and the administration of a correct initial fluid challenge, in our study we did not register more data concerning the severity and the duration of hypotension to make further conclusions. The presence of hypotension in those patients with chronic hypertension and its association with SA-AKI was not evaluated either and we know from the SEPSISPAM study<sup>115</sup> that patients with chronic hypertension may benefit from a MAP target of 80 to 85 mm Hg (high-target group).

The second independent risk factor for SA-AKI identified in our study was the existence of an abdominal sepsis etiology which is also concordant with previous literature,<sup>1</sup> as these patients frequently present increased intra-abdominal pressure (IAP) which can decrease renal flow and promote AKI.<sup>294</sup> Dalfino et al.<sup>295</sup> reported after an observational study in 120 critically ill patients that IAH was an independent predictive factor of AKI at IAP levels as low as 12 mm Hg. Demarchi et al.<sup>294</sup> in 60 consecutive patients admitted in ICU after undergoing abdominal surgery, reported that the first IAP

at the time of admission to the ICU was able to predict the occurrence of AKI (area under the receiver operating characteristic curve [AUROC] was 0.669;  $p=0.029$ ). This phenomenon can be due to an abdominal septic focus which rises IAP. In this cases focus control is priority in terms of surgical or percutaneous drainage besides early antibiotics.<sup>112,113</sup> However, IAP can also be facilitated by FO and edema (abdominal compliance is diminished in these patients), and therefore rises in IAP may inhibit renal venous drainage, further exacerbating the elevation of renal vascular pressure.<sup>118</sup> In our study, IAP was not registered in all patients with abdominal sepsis etiology, thus no correlation could be evaluated between IAP and SA-AKI.

#### 4.4.5. Sepsis resuscitation bundle (6 hours)

In our study EGDT did not reduce the incidence of SA-AKI. Although accomplishment of EGDT bundle was low (only 33% of our patients completed all recommendations within the first 3 or 6 h), no differences were observed in SA-AKI incidence between those patients who had a high compliance and those with a low compliance (**Table 1.2**). Results from the three big multicenter RCTs<sup>106,107,108</sup> (PROCESS, ARISE, and PROMISE) concerning EGDT in septic patients are well-known in terms of outcomes as none of the three trials demonstrated any survival benefit with the use of EGDT protocols when compared to usual care. It has been largely argued that “usual care” in these studies was very similar to the SSC recommendations (EGDT) especially in terms of time to interventions, bundle-completion (items of resuscitation and management have been classically organized in bundles), or volume of fluids administered.

PRISM investigators<sup>296</sup> (who basically analyzed all patients included in the three big previously referred trials) reported that time from ED presentation to first intravenous antimicrobial agents (measured in minutes) was practically the same when comparing all patients in the EGDT groups with all patients in the Usual Care; 75 minutes (min) (IQR 42–120) in the EGDT group and 72 min (IQR 42–119) in the Usual Care group. Thus, probably the only big differences between groups (EGDT vs. usual care) were a higher use of central venous catheters, a higher use of arterial lines, and a higher use of inotropes in the EGDT group. PRISM investigators conclude that EGDT did not result in better outcomes than usual care and was associated with higher hospitalization costs across a broad range of patient and hospital characteristics.

From these 3 big trials, the only one evaluating a new renal failure occurrence within the first week (like in our study) was the PROCESS trial<sup>106</sup>, but in this trial renal failure was defined exclusively as a new need for RRT with no differences observed between the EGDT and the usual care (3.1% and 2.8% respectively). SA-AKI post-hoc evaluation previously commented (28 days criteria) was published two years later under the name of ProGRess-AKI investigators.<sup>288</sup> The PROMISE trial<sup>108</sup> evaluated renal SOFA (based only in SCr changes but not UO) from baseline to 72 h with no differences observed either between EGDT and Usual Care. All 3 trials registered RRT requirements in ICU, with no differences observed between EGDT and Usual care; 11.0% compared to 10.6% (p=0.88). These last percentages are more similar to the ones observed in our cohort (13% of RRT in our whole septic population).

In a recent study,<sup>94</sup> patients with sepsis and septic shock at the ED were evaluated for a sepsis protocol initiated within 6 h after arrival in the ED and all items in a 3-hour bundle of care (blood cultures, broad-spectrum antibiotic agents, and lactate measurement) completed within 12 h. Among patients who had the 3-hour bundle completed within 12 h, a longer time to the completion of the bundle was associated with higher risk-adjusted in-hospital mortality (p<0.001). Once again, outcomes were focused on survival and no data regarding SA-AKI incidence was collected or at least reported. Our own group, in a recent analysis of 295 patients with sepsis at the ED of our tertiary hospital, reported (*Intensive Care Medicine Experimental* 2018, 6(Suppl 2):0355) that among patients who had the 3-hour bundle completed within the first 12 h from ED admission, a longer time to complete the bundle was not associated with higher in-hospital mortality. Septic shock was present in 22.5% of these patients. The complete bundle (3 measures) was completed in 82% of patients (mean time 307±830 min) and was performed in less than 3h in 61.4% of them. A linear association was observed between the delay in lactate determination within the first 12 h and in-hospital mortality (p<0.02), as well as an association between higher amount of crystalloid administered within the first 6 h (p<0.001) and in-hospital mortality (FO was not assessed).

Authors from the ANDROMEDA study<sup>297</sup> recently reported that among patients with septic shock, a resuscitation strategy targeting normalization of capillary refill time, compared with a strategy targeting serum lactate levels, did not reduce all-cause 28-day mortality. In other words, monitoring of hemodynamic resuscitation based on a physical

examination was as useful as lactate monitoring in patients with septic shock in terms of all-cause 28-day mortality. No differences were observed in SOFA at 72 h, new use of RRT, or RRT-free days within 28 days. Interestingly, our own group also evaluated septic patients admitted to ICU from the ED in two different periods (2005-2007 vs. 2015-2017) and reported (Intensive Care Medicine Experimental 2018, 6(Suppl 2):1096) a significant decrease in mortality which could be associated with an improvement in EGDT tasks achievement. The complete bundle (3 measures) was completed in 33% (2005-2007) and 83.5% (2015-2017) ( $p=0.0001$ ) of patients respectively. Hospital mortality during that time decreased from 45.8% (2005-2007) to 29.4% (2015-2017) ( $p=0.04$ ).

#### 4.4.5.1. Antibiotic

Although antibiotic delayed administration had been previously reported as an independent risk factor for SA-AKI particularly in septic shock patients,<sup>1</sup> in our study no relationship was found between time from sepsis to antibiotic and SA-AKI incidence. The percentage of patients with early administration of antibiotics (first hour in those patients with sepsis onset at ICU and 3 h in those initiated at the ED or ward) was similar between the SA-AKI group and the non-AKI group. The same was observed with the median time from sepsis to antibiotics which was similar between those patients who developed SA-AKI and those who did not (**Table 1.2**).

This absence of benefit from an early antibiotherapy in terms of renal outcome (SA-AKI incidence) could be reinforced by the results of a recent meta-analysis<sup>298</sup> evaluating the impact of timing of antibiotics on outcomes in sepsis and septic shock. Authors reported no significant mortality benefit with the administration of antibiotics within 3 h of ED triage or within 1 h of shock recognition. The same results were published by Wasim et al.<sup>299</sup> who observed no differences in SA-AKI incidence and mortality in a contemporary critically ill cohort under the EGDT recommendations (70% of patients received antibiotics within the first 3 h) respect to an historical group where antibiotics (among other measures) were administered much later (only 36% of patients received antibiotics within the first 3 h;  $p=0.0001$ ).

Contrary to our findings, Plataki et al.<sup>1</sup> in their observational cohort study in 390 adults with septic shock admitted to a medical ICU of which 237 (61%) developed SA-AKI, reported that SA-AKI occurrence was independently associated with delay to initiation



of “adequate” antibiotics among others. In this trial the delay to initiation of adequate antibiotics increased the risk of developing SA-AKI but with a very low OR of 1.03 (95% CI, 1.01 to 1.08), per every hour of antibiotic delay, and a “limit” significance of  $p=0.04$ . Authors assessed SA-AKI at the time of diagnosis of shock and hourly thereafter, with patients being classified according to the maximum RIFLE class reached during all their ICU stay. Once again, we understand that some of the SA-AKI events (during all ICU stay) were probably not related with the initial septic shock.

#### 4.4.5.2. Hemodynamic resuscitation (fluids & vasopressors)

In our study, hemodynamic measures were specifically evaluated in patients with hypotension (67% of our study population), but no preventive effects for SA-AKI incidence were identified with the complete accomplishment of the whole hemodynamic bundle or even with the evaluation of each task: a correct fluid challenge in terms of fluid amount (20 mL/kg), a CVP goal achievement ( $>8-12$  mm Hg), a central venous oxygen saturation ( $ScvO_2$ ) goal achievement ( $>70\%$ ), or steroids administration. These recommendations (**Table 1.1**) were those that were active at the time of the study although we nowadays know that some of them are not longer recommended.<sup>98</sup>

Plataki et al.<sup>1</sup> as previously commented, reported in their study a decrease in SA-AKI incidence when a successful early goal directed resuscitation was achieved. They defined an adequate early goal-directed resuscitation as  $ScvO_2 \geq 70\%$  and/or a combination (at least two) of the following clinical factors:  $CVP \geq 8$  mm Hg,  $MAP \geq 65$  mm Hg,  $UO \geq 0.5$  mL/kg/h, and/or improvement in mental state (Glasgow Coma Scale), base excess, or lactate at any point within the first 6 h. Recent trials in septic populations have confirmed that this EGDT based on hemodynamic goals such as CVP and  $ScVO_2$  must only be used after clinical judgement and not as a protocolized practice, reflecting once again that clinical skills and experience are sometimes much more important than invasive monitoring of septic patients.<sup>106,107,108</sup>

Whether recommended fluid challenge (20 mL/Kg at the time of our study and 30 mL/kg nowadays) is related with a better renal outcome or not is still in debate. In our study we did not register the exact amount of fluid administered but just the achievement or not of the 20 mL/kg in those patients who were hypotensive. Some studies<sup>300,301</sup> in very specific settings have suggested a worst outcome of septic patients when fluid

boluses are administered in the wrong scenario (malnourished patients, brain malaria, or even ARDS patients with no ventilation support). Concerning fluid resuscitation and renal outcomes, a recent RCT<sup>272</sup> in septic shock patients reported a decrease in SA-AKI worsening with a fluid restriction management (initiated only after hemodynamic stabilization) compared to a standard care group. In contraposition to these results, a previous and different RCT<sup>302</sup> in patients during major abdominal surgery reported that an excessive fluid restriction increased the level of hypovolemia, leading to an increased incidence of postoperative complications (although no significant differences were observed in renal outcomes). Just published, the RIFTS trial<sup>124</sup> showed that a restrictive fluid resuscitation strategy in septic patients reduced the amount of IV fluid with no adverse effects in mortality or organ failures.

In our study, vasopressor support was mainly performed with norepinephrine as SSC guidelines recommend.<sup>98</sup> 62% of our patients required vasopressors but this percentage was as high as 94% when hypotension was present (**Table 1.2**). We did not register the exact time when vasopressors were administered as some data from different studies<sup>303,304</sup> (related with the previously referred fluid restriction hypothesis) suggests that an early initiation of vasopressor support (or at least not markedly delayed) in patients with septic shock could be beneficial in terms of survival. Latest SSC 2018 update<sup>273</sup> also recommends vasopressors to be initiated within the first hour to achieve MAP of  $\geq 65$  mm Hg when blood pressure is not restored after initial fluid resuscitation. The REFRESH trial<sup>123</sup> recently reported that a regimen of restricted fluids and early vasopressor in ED patients with suspected sepsis and hypotension was feasible with moderate illness severity and low mortality rates. Some ongoing trials<sup>305</sup>, should help us to resolve if early vasopressors can have any impact in final outcome although none of them have renal function as a primary outcome.

The presence of hypotension as previously advanced, was an independent risk factor for SA-AKI incidence within the first 7 days from sepsis onset. Whether the use of norepinephrine could be related to this unfavourable renal outcome cannot be excluded.<sup>306</sup> Recent trials have “opened the door” to other options of vasopressor support that could potentially have an impact in the renal outcome of septic patients although none of them have been clearly successful probably reflecting that SA-AKI incidence in these hypotensive patients is more related to the severity of the disease than to the use of any specific drug for hemodynamic support. The VANISH trial<sup>307</sup>

compared the effect of early vasopressin vs. norepinephrine on kidney failure in patients with septic shock. Authors reported a lower rate of use of RRT in the patients treated with vasopressin. This difference in rates of RRT could reflect the slightly lower SCr values and higher UO seen in the patients treated with vasopressin, particularly on days 3 through 6. Angiotensin II trial<sup>308</sup> was performed in patients with vasodilatory shock (81% of them with sepsis) who were receiving more than 0.2 µg/kg/min of norepinephrine. Authors reported that at 48 h, the mean improvement in the cardiovascular SOFA score was greater in the angiotensin II group than in the placebo group (p=0.01) but no significant differences were observed in other SOFA score components (including renal).

#### *4.4.5.3. Fluid overload and type of fluids*

In our study no daily fluid balance or daily weight were registered. Apart from residual confounding, a second indirect mechanism by which FO may be associated with adverse outcomes is by masking the presence, delaying the recognition, or underestimating the severity of AKI. Since minimal increases in SCr are associated with significant increases in mortality,<sup>39,36</sup> failure to recognize AKI because of FO may lead to a relative increase in mortality in those with FO who (by conventional SCr criteria) do not have AKI, or have mild AKI.

Along these lines, Macedo and colleagues<sup>309</sup> used the PICARD cohort to test the hypothesis that FO would both underestimate the severity of renal dysfunction based on SCr and increase the time to AKI detection. SCr adjusted for fluid balance was significantly higher than the unadjusted SCr at each time point, and RRT was initiated more frequently in patients with late recognition. An adequate assessment of AKI severity could lead to earlier implementation of preventive and therapeutic strategies (for example avoiding contrast, discontinuing nephrotoxic medications, adjusting medication doses) to minimize morbidities associated with AKI. Liu et al.<sup>310</sup> after analyzing 1000 patients from the FACTT trial concluded that fluid management influences SCr and therefore the diagnosis of AKI using SCr-based definitions. Patients with “unrecognized” AKI that were identified after adjusting for positive fluid balance had high mortality rates, and patients who had AKI before but not after adjusting for fluid balance had low mortality rates. Fluid balance in septic patients with AKI is clearly related with mortality as Payen et al.<sup>311</sup> and Bouchard et al.<sup>243</sup> reported in two

different trials performed in critically ill patients with SA-AKI. We also know that a more positive fluid balance both early in resuscitation and cumulatively over 4 days is related with a worst outcome in septic shock patients.<sup>269</sup> FO may have a direct impact on renal function. Direct mechanisms by which FO may have a direct impact on renal function and adverse outcomes include elevations of IAP, which reduces renal plasma flow and decreases the GFR. However, whether AKI has caused FO or viceversa can be difficult to determine. Wang et al.<sup>312</sup> conducted an observational prospective multicenter study among the 2526 critically ill patients. 1172 developed AKI during the first 3 days. FO (defined as as fluid accumulation greater than 10 % of the baseline weight<sup>313</sup>) was an independent risk factor for the incidence of AKI (OR 4.5,  $p < 0.001$ ) and increased the severity of AKI.

Although there is an increasing concern about the impact that colloids or chloride-liberal fluids might have in renal outcome of septic patients and even in survival outcome, the type of fluid was not registered by the time of our study. However, we must point out that balanced crystalloids solutions were not available in our ICUs at the time of this study. The VISEP trial<sup>314</sup> found that HES therapy was associated with higher rates of AKI (22.8% vs. 34.9%,  $p = 0.002$ ) and RRT (18.8% vs. 31.0%,  $p = 0.001$ ) than was Ringer's lactate. Myburgh et al. in another RCT<sup>132</sup> in critically ill patients compared 6% HES to 0.9% sodium chloride (saline) for all fluid resuscitation until ICU discharge. No differences in mortality or significant renal outcomes were observed. Perner et al. in a multicenter RCT<sup>131</sup> compared 6% HES or Ringer's acetate in patients with sepsis. At 90 days after randomization, 51% of patients assigned to HES 130/0.42 had died, as compared with 43% assigned to Ringer's acetate ( $p = 0.03$ ). 22% of patients assigned to HES were treated with RRT vs. 16% assigned to Ringer's acetate ( $p = 0.04$ ).

Some authors propose that administration of traditional chloride-liberal intravenous fluids (saline) may precipitate AKI. Yunos et al.<sup>315</sup> conducted a sequential period pilot study at the ICU comparing a control period (saline) with an intervention period (balanced crystalloids) and reported differences in renal outcomes favouring the use of balanced crystalloids. Contrary to these findings the SPLIT trial<sup>135</sup> reported no differences in renal outcomes when comparing a buffered crystalloid with saline in ICU patients. More recently, two single-center trials were published in the same week and same journal reporting benefits (lower incidence of major adverse kidney events) with the use of balance crystalloids in patients requiring fluids at the ED (SALT-ED trial<sup>316</sup>)

and patients requiring fluids at the ICU (SMART trial<sup>317</sup>). Major adverse kidney event was defined as a composite of death from any cause, new RRT, or persistent renal dysfunction.

#### 4.4.6. Management bundle (24 hours)

In our study, management tasks were analyzed, and some differences were found between SA-AKI and non-AKI septic patients (**Table 1.2**).

##### 4.4.6.1. Steroids administration

In our study, steroids administration (32%) in those patients with septic shock was not associated with a decrease (or an increase) in SA-AKI incidence. This finding of “no renal effect” despite the severity of those patients receiving steroids (most of them presented septic shock) is supported by the majority studies<sup>318</sup> comparing the use or not of steroids in patients with septic shock. However, none of these studies have specifically studied the relationship between steroid administration and SA-AKI incidence.

CORTICUS study<sup>319</sup> did not report renal outcomes. HYPRESS study<sup>320</sup> reported no differences in RRT requirements (12.2% vs. 12.3%) or days free from RRT (7 vs. 6 days). More recently, the ADRENAL trial<sup>321</sup> reported no significant between-group differences with respect to the number of days alive and free from RRT, and the use of RRT (steroid group 31% vs. placebo group 33%,  $p=0.18$ ). In contraposition, the group of Annane et al.<sup>322</sup> recently reported a significantly higher number of organ-failure-free days (14 vs. 12 days,  $p=0.003$ ) in the hydrocortisone-plus-fludrocortisone group than in the placebo group. No differences in the high RRT requirements were observed. Whether this beneficial effect could be related to fludrocortisone administration remains uncertain (in our study no fludrocortisone was administered) as very few studies have evaluated specifically fludrocortisone effect.<sup>323</sup>

##### 4.4.6.2. Median blood glucose

In our study median blood glucose level goal (4 to 8.3 mmol/L with no hypoglycemia episodes) was achieved more frequently in the non-AKI septic group compared to the SA-AKI patients (49.7% vs. 36.2%;  $p=0.06$ ). Although still non-significant from a statistical point of view, this could be concordant with first reports from Van den

Berghe et al.<sup>324</sup> who reported survival and renal benefits (less AKI and less RRT) in a surgical ICU with the use of an intensive insulin therapy (IIT) (maintenance of blood glucose at a level between 4.4 and 6.1 mmol/L). Same authors published 5 years later in the same journal a RCT<sup>325</sup> this time in a medical ICU with a trend for a better renal outcome with the use of an IIT.

WISEP trial<sup>326</sup> previously commented (HES vs. ringer lactate) was a two-by-two factorial trial, that randomly assigned patients with sepsis to receive either IIT to maintain euglycemia or conventional insulin therapy. The trial was stopped early for safety reasons as the rate of severe hypoglycemia (glucose level  $\leq 2.2$  mmol/L) was higher in the IIT group. There were no significant differences in the rate of SA-AKI and the need for RRT. Nice-sugar trial<sup>327</sup> (intensive glucose control or conventional glucose control RCT) did not find differences in renal outcomes either. Finally, Azevedo et al.<sup>328</sup> compared in a critically ill septic population IIT with a carbohydrate-restrictive strategy. Authors reported a significant correlation between blood glucose levels and the incidence of AKI ( $p=0.007$ ) contrary to the results of our study where no correlation was observed between the median blood glucose levels during the first 24 h and the appearance of SA-AKI (7.4 mmol/L non-AKI septic group [IQR 5.7-9.6] vs. 7.9 mmol/L SA-AKI group [IQR 5.9-10.6],  $p=0.41$ ), (**Table 1.2**).

#### 4.4.6.3. Protective ventilation

In our study, in those patients who required invasive MV (63%), a protective ventilation strategy (defined at that time by SSC as a median Ppl  $<30$  cm H<sub>2</sub>O) seemed to protect from developing SA-AKI. This finding gives support to the pulmonary-kidney crosstalk theory in critically ill patients (ventilator-induced AKI).<sup>329</sup> Although differences between non-AKI septic patients and SA-AKI patients in terms of goal achievement (median Ppl  $<30$  cm H<sub>2</sub>O) were not significant (73% in the non-AKI septic group vs. 58% in the SA-AKI group) this was probably due to our small population size. Interestingly, median Ppl was significantly different between those ventilated patients who did not develop SA-AKI and those who did (24 cm H<sub>2</sub>O [IQR 20-30] in the non-AKI group vs. 28 cm H<sub>2</sub>O [IQR 24-33] in the SA-AKI group,  $p=0.01$ ).

The issue of AKI due to MV is an old but still virtually not understood phenomenon and is, however, of major concern.<sup>330</sup> Traditionally, deteriorations in systemic and renal hemodynamics and gas exchange associated with MV have been implicated in this

process.<sup>330</sup> There is an emerging concept that MV exerts a broad spectrum of harmful biological responses with the capacity to affect functions of remote organs,<sup>331</sup> including the kidney.<sup>332</sup> An altered inflammatory network, oxidative stress, and apoptosis have been considered the central hubs of this organ crosstalk in response to MV.<sup>333</sup> Lung protective ventilation has become a cornerstone in the management of ARDS.<sup>334</sup> This approach minimizes both the direct mechanical effects of ventilation and the inflammatory response arising from ARDS together with MV. The ARDS network in their RCT<sup>335</sup> performed in patients with ARDS (60% of patients had sepsis) reported a significant increase in the number of days without failure of nonpulmonary organs or systems, with the lower tidal volume (VT) strategy (6 mL/Kg and P<sub>pl</sub>≤30 cm H<sub>2</sub>O).

Despite these data, some studies report that lung-protective mechanical ventilation does not protect against AKI in patients without ARDS at onset of MV. In a secondary analysis<sup>336</sup> of a RCT in 150 critically ill patients without ARDS at the beginning of MV, lung-protective mechanical ventilation (VT, 6 mL/kg) significantly reduced the development of ventilator associated ARDS, but not the development and/or worsening of AKI. The low incidence of sepsis in this trial (<10%) could explain these results as another study<sup>337</sup> showed that injurious MV causes kidney apoptosis and dysfunction during sepsis but not after intra-tracheal acid instillation in an experimental model performed in rats which compared MV with two different VT strategies.

#### 4.4.7. Limitations

Our study is limited by its observational design, which cannot exclude the possibility of our results being confounded by case-mix heterogeneity<sup>338</sup> or secular trends.<sup>339</sup> Moreover, by including only patients admitted to the ICU, we probably selected more severe patients who did not improve with the initial treatment. This selection bias applies to fluid administration but probably also to antibiotic treatment. We must emphasize too that SSC bundles accomplishment was low but not different from other cohorts published at that time.<sup>103,104</sup> This low accomplishment could explain the high incidence of SA-AKI even after sepsis onset although once again we have to point out that no decrease in SA-AKI incidence was observed in those patients who did achieve high percentages of accomplishment (**Table 1.2**).

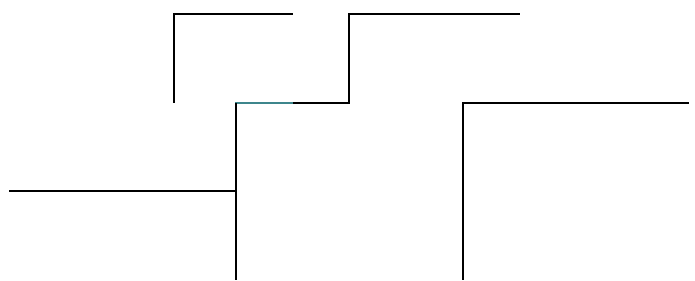
Finally, although 10% of our patients had no baseline SCr registered within the last 6

months (which probably overestimates AKI at sepsis initiation) our SA-AKI definition should avoid this selection bias. However, considering that SCr is a late marker of renal injury, it is likely that a considerable proportion of patients with SA-AKI at sepsis initiation would have SCr within normal levels. In these patients, it would be more difficult to determine if SSC care bundles influenced the development of AKI.

In conclusion, SA-AKI presents a high incidence and worsens prognosis in critically ill septic patients and therefore it should be closely monitored and prevented. None of the SSC bundles seem to have a direct effect in preventing SA-AKI, although avoiding hypotension could be clearly beneficial as well as a protective strategy with Ppl <30 cm H<sub>2</sub>O when MV is required. Septic patients with an abdominal etiology present a higher risk for SA-AKI development, and special measures such as IAP monitoring should be promptly adopted.







*Study 2*

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## 5. Study 2. Clinical variables associated with poor outcome from sepsis associated acute kidney injury and the relationship with timing of initiation of renal replacement therapy (Supplementary appendix 3)

### 5.1. Objectives

- To identify through a two-center international retrospective cohort study in a critically ill population with septic shock and SA-AKI requiring CRRT, those factors associated with mortality in order to define future therapeutic strategies.
- To identify through a two-center international retrospective cohort study in a critically ill population with septic shock and advanced SA-AKI (KDIGO stage 3) requiring CRRT within the first 5 days from ICU admission, those parameters or variables that can be useful to decide CRRT initiation (“timing”) and potentially improve outcome in terms of survival.

### 5.2. Methods Study 2

#### **Design and setting**

We performed a retrospective study using data from two tertiary care hospitals with more than 80 ICU beds each. Patient data were included from 2000-2008 at University Pittsburgh Medical Centre (Pittsburgh, USA), and from 2005-2012 at Hospital Universitari Bellvitge (Barcelona, Spain). The study protocols were approved by each institution’s ethics/investigation review board. Inclusion criteria were the presence of septic shock (defined by international consensus criteria)<sup>98</sup> within the first 24 h from CRRT initiation. CRRT initiation criteria were based on clinical judgement. Exclusion criteria were ESRD, previous RRT in the prior 2 weeks, or less than 24 h of CRRT. For this retrospective, observational, non-interventional study, the research ethics committee of both centres waived the need to obtain informed consent for collection, analysis, and publication of data.

**CRRT**

CRRT was administered with Prisma® or Prismaflex® (Baxter), femoral or jugular vein catheters were used for vascular access, and CVVH, CVVHDF, or CVVHD were prescribed according to individual prescription.

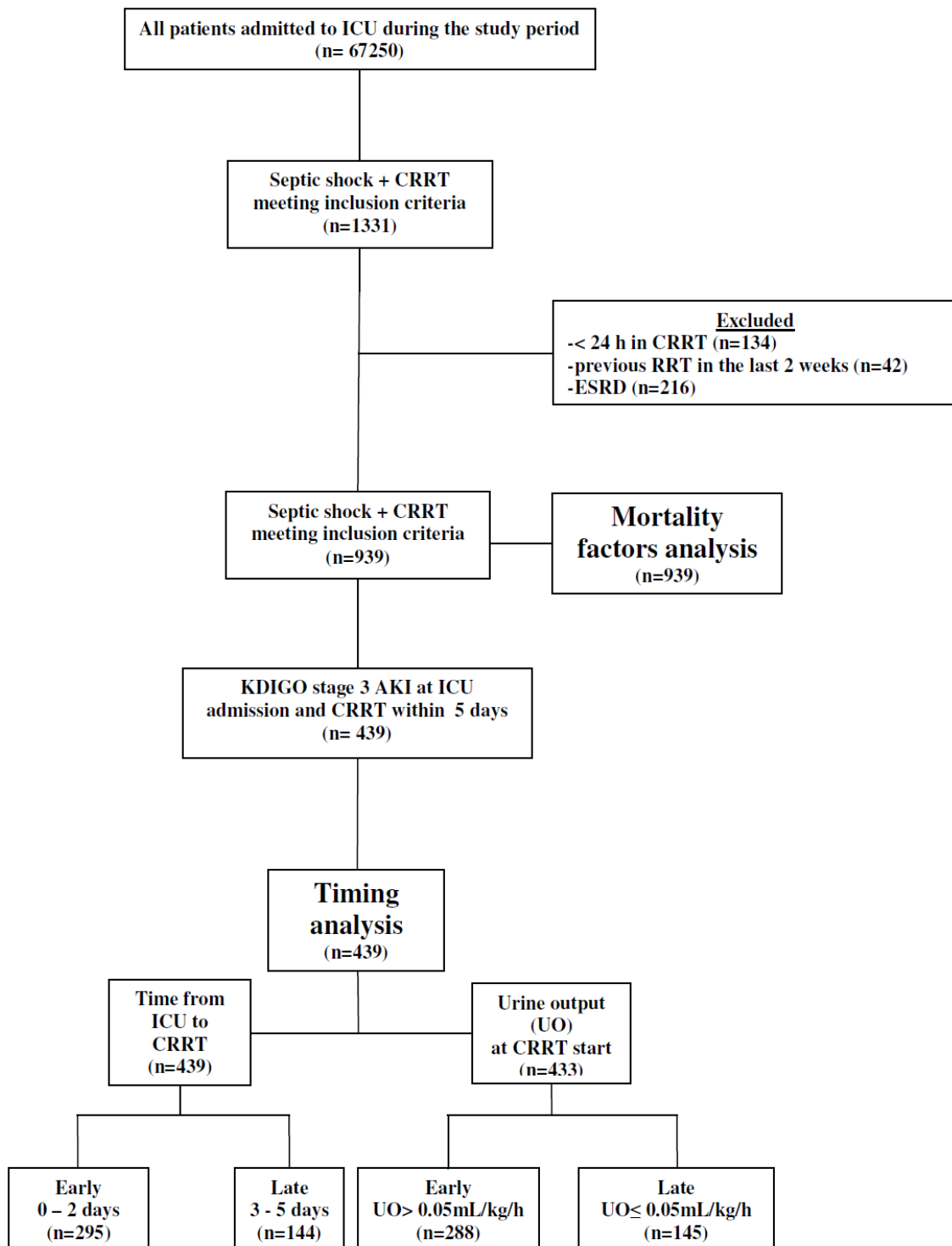
**KDIGO SA-AKI stage**

Demographic, clinical, and CRRT related parameters were abstracted from the electronic medical record. Mean acute physiology and chronic health evaluation score (APS-III) measured at CRRT initiation was internally derived based on available data.<sup>340</sup> Baseline SCr value ( $\mu\text{mol/L}$ ) was either registered from 6 months previous clinical files or estimated, when data was not available from clinical records, by solving the MDRD equation assuming a glomerular filtration rate of  $75 \text{ ml/min/1.73 m}^2$ .<sup>340</sup> KDIGO SA-AKI stage was calculated for every patient at ICU admission and at CRRT initiation based on SCr only, since hourly UO data was not available in the Barcelona data. Patients were followed through hospital discharge and survival status was assessed at 90 days using national databases.

**Timing of Initiation of RRT**

Based on the variables associated with 90-day mortality we decided to separately evaluate “Time from ICU admission to CRRT” and “UO 24 h previous to CRRT” in a subset of our cohort with KDIGO stage 3 SA-AKI at ICU admission and receiving CRRT within the first 5 days from ICU admission. This subset was selected in order to have a more homogenous cohort to analyse. The exclusion criterion of more than 5 days was chosen in order to avoid “late patients” that went on CRRT probably for different reasons than ICU admission besides presenting more comorbidity. Timing based on time (time from ICU admission to CRRT) was compared to timing based on UO (UO during 24 h prior to CRRT initiation) in order to identify which parameter could be more useful to initiate CRRT. Based on previous reports<sup>170</sup> and population’s variable distribution “Time” criteria to start CRRT was defined as “early” when CRRT was started within the first 48 h from ICU admission and as “late” when CRRT was started after 48 h from ICU admission. Based on population’s variable distribution, UO criteria to start CRRT was defined as “early” when UO during the 24 h prior to CRRT was

more than 0.05 mL/kg/h and as “late” when UO was less than 0.05 mL/kg/h during the previous 24 h to CRRT initiation. These criteria are illustrated in **Fig.2.1**.



**Figure 2.1.** Study 2 flow chart

CRRT, continuous renal replacement therapy; ESRD, end stage renal disease; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; mL/kg/h, milliliters/kilogram/hour; SA-AKI, sepsis-associated acute kidney injury; UO, urine output.

## Statistical analysis

Statistical analyses were performed using SPSS software, version 18.0, with statistical significance set at  $p < 0.05$ . Comparisons between groups were performed with Pearson's Chi-Square asymptotic test for categorical variables and using Kruskal-Wallis one-way analysis of variance by ranks for continuous variables. Categorical data is summarized as counts and percent. Continuous data is summarized as medians (25th, 75th percentile or IQR). Risk factors were considered for multivariate cox proportional hazards (PH) regression models if the following assumptions were met: (1) they had  $< 10\%$  missing data, (2) had  $p$  values  $< 0.2$  in univariate analysis, and (3) were clinically plausible. Backward elimination with the likelihood ratio method was used to determine the final models. Results are presented as aHR with 95% CI. Kaplan-Meier survival curves were used to estimate the cumulative mortality rates in all groups studied (timing groups) and differences were calculated using the log-rank test. Cox PH model was used to determine each group's aHR for 90-day mortality.

## 5.3. Results Study 2

### Patients characteristics

In total, 67250 patients were admitted to our ICUs during the study period. Septic shock was present in 18% of these patients during some moment of their ICU stay but only 11% of these patients required CRRT despite a high SA-AKI incidence (92.4%). 939 patients were finally studied, all of them meeting criteria for septic shock within 24 h from CRRT initiation during their ICU stay. Study flow chart is represented in **Fig.2.1**.

Population characteristics at ICU admission and baseline characteristics at CRRT initiation are presented in **Table 2.1**. Median age was 60 years (IQR: 50, 71 years), 62.9% were male, and 57.8% had surgical admission to the ICU. 150 patients (15.9%) had mild CKD. Median time from hospital admission to ICU was 2 days (1, 5 days), median time from hospital admission to CRRT was 7 days (3, 15 days), and median time from ICU admission to CRRT was 4 days (2, 8 days). At CRRT initiation, the median APS-III was 98 (73, 122), 91.7% were on vasopressor support, 88.7% were on MV, serum BUN was  $\geq 100$  mg/dL in 16.5%, serum potassium was  $> 5$  mmol/L in

29.4%, and 96.9% presented SA-AKI based on KDIGO SCr criteria<sup>26</sup> with majority of patients presenting stage 3 SA-AKI (82.6%).

**Table 2.1.** Patient characteristics and outcomes associated with 90-day mortality

Characteristics	Survivors (n = 349)	Non-survivors (n = 590)	All (n = 939)	P
<b>Age, (n=939)</b>	57 (46-67)	63 (53-72)	60(50-71)	<0.001*
<b>Males, n (%)</b>	226 (64.8)	367 (61.9)	591 (62.9)	0.4
<b>Weight (kg), (n=936)</b>	80 (68-96)	79 (70-93)	80 (68-95)	0.5
<b>BMI, (n=841)</b>	28 (24-32)	27(24-32)	28 (24-32)	0.9
<b>SOFA score, (n=939)</b>	11 (8-14)	11 (8-14)	11 (8-14)	0.6
<b>APACHE III score, (n=939)</b>	95 (71-120)	99 (75-123)	98 (73-122)	0.038*
<b>Comorbid condition, n (%)</b>				
Hypertension	138 (39.7)	262 (44.5)	400 (42.7)	0.17
Diabetes	92 (26.4)	146 (24.8)	238 (25.4)	0.6
Cardiac disease	91 (26.1)	146 (24.8)	238 (25.4)	0.3
Chronic liver disease	81 (23.3)	155 (26.3)	236 (25.2)	0.3
Chronic airway obstruction	39 (11.2)	93 (15.8)	132 (14.1)	0.05
Chronic renal disease (includes CKD)	57 (16.3)	93 (15.7)	150 (15.9)	0.9
<b>Charlson comorbidity index</b>	2.2 (0-4)	2.5 (0-4)	2.4 (0-4)	0.007*
<b>Surgical admission, n (%)</b>	227 (66.8)	301 (52.3)	528 (57.8)	<0.001*
<b>Creatinine (umol/L),</b>				
ICU, (n=921)**	211 (132-325)	211 (132-316)	211 (32-317)	0.6
CRRT, (n=938)^^^	308 (238-412)	299 (211-396)	299 (220-403)	0.05*
Baseline, (n=938)	89 (76-114)	91 (72-114)	91 (74-114)	0.9
<b>Weight adjusted Urine Output (mL/kg), †</b>				
ICU, (n=927)	9.5 (3.5-20.1)	9.4 (3.1-20)	9.5 (3.3-20)	0.3
CRRT, (n=912)	4.3 (1.3-9.5)	3.7 (1.1-8.0)	3.9 (1.2-8.6)	0.14*
<b>Vasopressors at CRRT, n (%)</b>	314 (90.1)	547 (92.7)	861 (91.7)	0.3
<b>Mechanical ventilation at CRRT, n (%)</b>	310 (89.0)	518 (88.4)	828 (88.7)	0.8
<b>Serum BUN ≥ 100 mg/dL at CRRT, n (%)</b>	44 (12.7)	109 (18.7)	153 (16.5)	0.02*
<b>Serum potassium &gt; 5 mEq/L at CRRT, n (%)</b>	100 (28.9)	173 (29.7)	273 (29.4)	0.8
<b>CRRT characteristics, n (%)</b>				0.8
CVVH	68 (19.5)	118 (19.9)	186 (19.8)	
CVVHD	65 (18.6)	99 (16.7)	164 (17.4)	
CVVHDF	216 (61.9)	373 (63.3)	589 (62.8)	
<b>KDIGO based on creatinine at CRRT, n (%)</b>				0.99
No SA-AKI	10 (2.9)	17 (3.2)	27 (3.1)	
Stage 1	14 (4.0)	25 (4.2)	39 (4.1)	



Characteristics	Survivors (n = 349)	Non-survivors (n = 590)	All (n = 939)	P
Stage 2	36 (10.3)	60 (10.1)	96 (10.2)	
Stage 3	289 (82.8)	488 (82.4)	777 (82.6)	
<b>Time to ICU/CRRT (days),</b>				
Hospital admission - ICU admission	1 (1-3)	2 (1-6)	2 (1-5)	0.001
Hospital admission - CRRT initiation	5 (3-12)	8 (4-17)	7 (3-15)	0.001*
ICU admission - CRRT initiation	3 (2-7)	4 (2-9)	4 (2-8)	0.016
<b>Mortality, n (%)</b>				
ICU	5 (1.4)	468 (79.3)	473 (50.4)	<0.001
Hospital	10 (2.8)	486 (94.4)	496 (52.7)	<0.001
90 days <sup>§</sup>	0 (0)	590 (100)	590 (62.8)	<0.001

Variables are represented by median (q1-q3) and absolute numbers or percentages (n (%)). Variables measured at ICU capture the 24 hours after ICU admission. Variables measured at CRRT capture the 24 hours before CRRT initiation.

AKI, Acute Kidney Injury; APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; BUN, blood urea nitrogen; CKD, chronic kidney disease; CVVH, Continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; ICU, Intensive Care Unit; KDIGO, Kidney Disease Improving Global Outcomes; SA-AKI, sepsis-associated acute kidney injury; SOFA, sepsis-related organ failure assessment score

Conversion factors for units: serum creatinine in mg/dL to  $\mu\text{mol/L}$ ,  $\times 88.4$ ; serum blood urea nitrogen in mg/dL to mmol/L,  $\times 2.8$ ; Serum potassium in mEq/L to mmol/L,  $\times 1$ .

^ Fisher's Exact Significance for categorical variables; Kruskal-Wallis test for continuous variables.

\*\*maximum serum creatinine value measured in the 24 hours after ICU admission.

^^maximum serum creatinine value on the day of CRRT initiation or on the previous day.

†The available urine in the 24 hours after ICU or prior to CRRT was summed and divided by the weight.

§From CRRT initiation.

\*Included in final Cox regression analysis for 90-day mortality.

Patients were mostly initiated on CVVHDF (62.8%), whereas CVVH and CVVHD where nearly equally employed (19.8% and 17.4% respectively). ICU mortality was 50.4% and hospital mortality 52.7%. Mortality at 90 days from CRRT initiation was 62.8%. Differences between centres in terms of population characteristics, clinical-CRRT management, and survival outcome are presented in **Table 2.2**.

**Table 2.2.** Population characteristics and outcomes according to recruitment center

Characteristics	UPMC (N = 595)	HUB (N = 344)	All (N = 939)	P Value <sup>^</sup>
<b>Age, mean(SD), (n=939)</b>	57.6 (15.0)	62.3 (13.5)	59.4 (14.6)	<0.001*
<b>Males, n (%)</b>	363(61.0)	228(66.3)	591(62.9)	0.12
<b>Weight (kg), mean(SD), (n=433)</b>	87.7 (29)	77.4 (15)	83.8 (25)	<0.0001*
<b>Comorbid condition, n (%)</b>				
Hypertension	207 (34.8)	190 (55.9)	397 (42.7)	0.001*
Diabetes	138 (23.2)	98 (28.8)	236 (25.4)	0.061
Chronic renal disease (includes CKD)	68 (11.4)	80 (23.3)	148 (15.8)	0.001*
<b>Surgical admission, n (%)</b>	363 (63.8)	165 (48.0)	528 (57.8)	0.001*
<b>APACHE III score at ICU, median (Q1-Q3)</b>	107 (77-129)	86 (69-105)	98 (74-122)	0.0001*
<b>Creatinine, umol/L, mean (SD)</b>				
ICU	323 (146)	356 (201)	334 (167)	0.057
CRRT	358 (137)	404 (182)	373 (155)	0.003*
Reference value	107 (50)	102 (46)	105 (50)	0.158
<b>Weight urine output (mL/kg), mean(SD)<sup>†</sup></b>				
ICU	13.9 (17.6)	14.2 (11.7)	14.0 (15.7)	0.732
CRRT	5.1 (7.1)	9.7 (10.3)	6.7 (8.7)	<0.0001*
<b>Mechanical ventilation at CRRT</b>	536 (90.1)	292 (86.4)	828 (88.7)	0.1
<b>Serum BUN ≥100 mgs/dL at CRRT, n (%)</b>	107 (18.2)	46 (13.6)	153 (16.5)	0.08
<b>Serum potassium &gt;5 mEq/L at CRRT, n (%)</b>	188 (31.8)	85 (25.1)	273 (29.4)	0,036*
<b>Arterial pH &lt;7.2 at CRRT, n (%)</b>	13 (2.6)	57 (16.9)	70 (8.4)	0.001*
<b>KDIGO at CRRT, n (%)</b>				0.001*
No SA-AKI	13 (2.2)	14 (4.7)	27 (3.1)	
Stage 1	23 (3.9)	16 (4.7)	39 (4.1)	
Stage 2	31 (5.2)	65 (18.9)	96 (10.2)	
Stage 3	528 (88.7)	247 (71.8)	777 (82.6)	
<b>CRRT characteristics, n (%)</b>				0.001*
CVVH	10 (1.7)	176 (50.9)	186 (19.8)	
CVVHD	153 (25.7)	11 (3.2)	164 (17.4)	
CVVHDF	432 (72.6)	157 (45.9)	589 (62.8)	
<b>Time to ICU/CRRT (days), median (Q1-Q3)</b>				
Hospital admission - ICU admission	1 (1-3)	2 (1-9)	2 (1-5)	0.001*
ICU admission - CRRT initiation	4 (2-10)	3 (2-5)	4 (2-8)	0.001*
<b>Mortality, n (%)</b>				
90 days <sup>§</sup>	376 (63.2)	214 (62.2)	590 (62.8)	0.78

Variables measured at ICU capture the 24 hours after ICU admission. Variables measured at CRRT capture the 24 hours before CRRT initiation.

AKI, Acute Kidney Injury; APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; BUN, blood urea nitrogen; CKD, chronic kidney disease; HUB, hospital universitari de Bellvitge; ICU, Intensive Care Unit; KDIGO, Kidney Disease Improving Global Outcomes; UPMC, university Pittsburgh medical center. Conversion factors for units: serum creatinine in mg/dL to  $\mu\text{mol/L}$ ,  $\times 88.4$ ; serum blood urea nitrogen in mg/dL to mmol/L,  $\times 2.8$ ; Serum potassium in mEq/L to mmol/L,  $\times 1$ ; Serum bicarbonate in mEq/L to mmol/L,  $\times 1$ .

<sup>^</sup> Fisher's Exact Significance for categorical variables; Kruskal-Wallis test for continuous variables.

\*\*maximum serum creatinine value measured in the 24 hours after ICU admission.

^^maximum serum creatinine value on the day of CRRT initiation or on the previous day.

†The available urine in the 24 hours after ICU or prior to CRRT was summed and divided by the weight from CRRT initiation. \* A p-value of  $< 0.05$  was considered to be statistically significant.

## Mortality risk factors

Univariate analysis for 90-day mortality identified variables presented in **Table 2.1**. Mortality differences between years were analyzed in order to identify confounding effects of treatment advances and better CRRT applications but no relevant differences were identified.

Risk factors associated with 90-day mortality were determined by multivariate cox regression and presented in **Table 2.3**. Significant variables associated with increased 90-day mortality included age (aHR 1.01, 95%CI 1.01-1.02,  $p < 0.0001$ ), APS-III score at CRRT (1.01, 1.0-1.0,  $p < 0.048$ ), days from hospital admission to CRRT initiation (1.01, 1.0-1.0,  $p < 0.01$ ), Urea at CRRT (1.01, 1.0-1.0,  $p < 0.04$ ), and medical admission (1.76, 1.5-2.1,  $p < 0.0001$ ) compared to surgical admission. Variables associated with decreased 90-day mortality included SCr at CRRT (0.99, 0.9-1.0,  $p < 0.001$ ) and UO 24 h prior to CRRT (0.77, 0.6-0.9,  $p = 0.049$ ).

**Table 2.3.** Multivariate Cox regression of risk factors for 90-day mortality

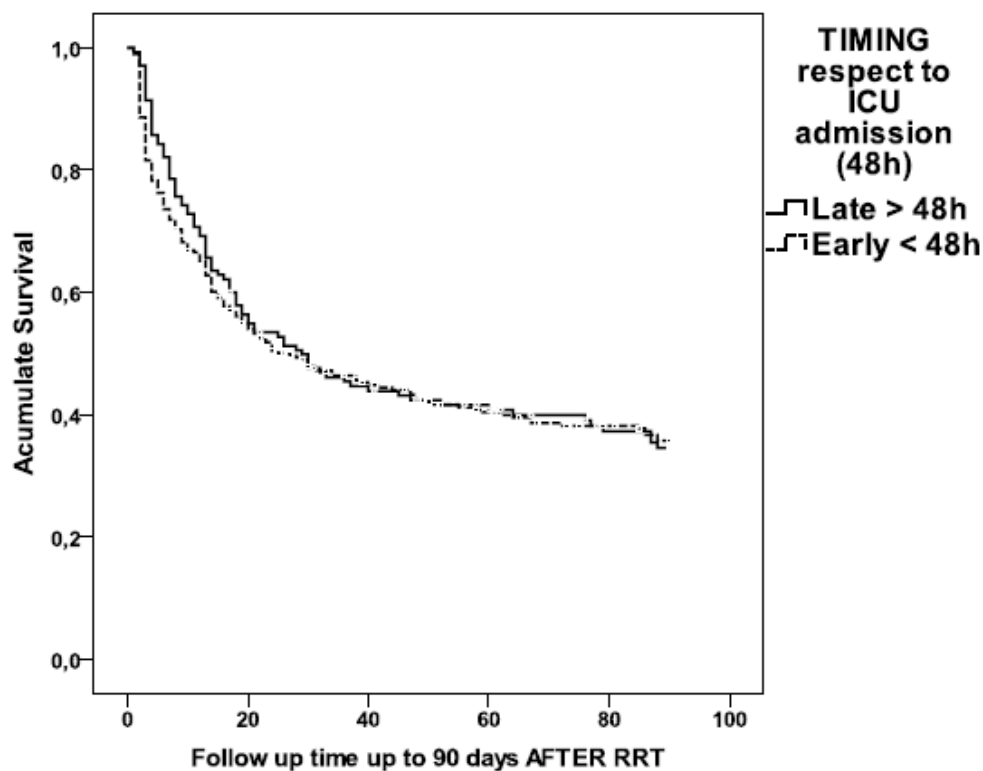
Significant variable	P	aHR	95% CI
Age (years)	$< 0.0001$	1.015	1.009-1.021
APACHE III at CRRT	0.042	1.003	1.000-1.006
Urea at CRRT (mmol/L)	0.036	1.009	1.001-1.017
Creatinine at CRRT ( $\mu\text{mol/L}$ )	0.001	0.999	0.998-0.999
Hospital to CRRT (days)	0.01	1.006	1.001-1.012
Charlson comorbidity index	0.780	0.993	0.948 – 1.041
Urine Output at CRRT (mL/kg/h)	0.032	0.756	0.586-0.976
Medical admission (vs surgical)	0.0001	1.761	1.469-2.111

APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; CI, confidence interval;

CRRT, continuous renal replacement therapy; HR, hazard ratio. All patients presented **septic shock** and required **CRRT** during ICU admission. Patients with baseline creatinine  $> 354 \mu\text{mol/L}$  were excluded. Patients on CRRT for  $< 24$  h were excluded. Maximum serum creatinine value on the day of CRRT initiation or on the previous day. The available urine in the 24 hours after ICU or prior to CRRT was summed and divided by the weight (kilograms) and time (hours). Conversion factors for units: serum creatinine in mg/dL to  $\mu\text{mol/L}$ ,  $\times 88.4$ ; serum blood urea nitrogen in mg/dL to mmol/L,  $\times 2.8$ .

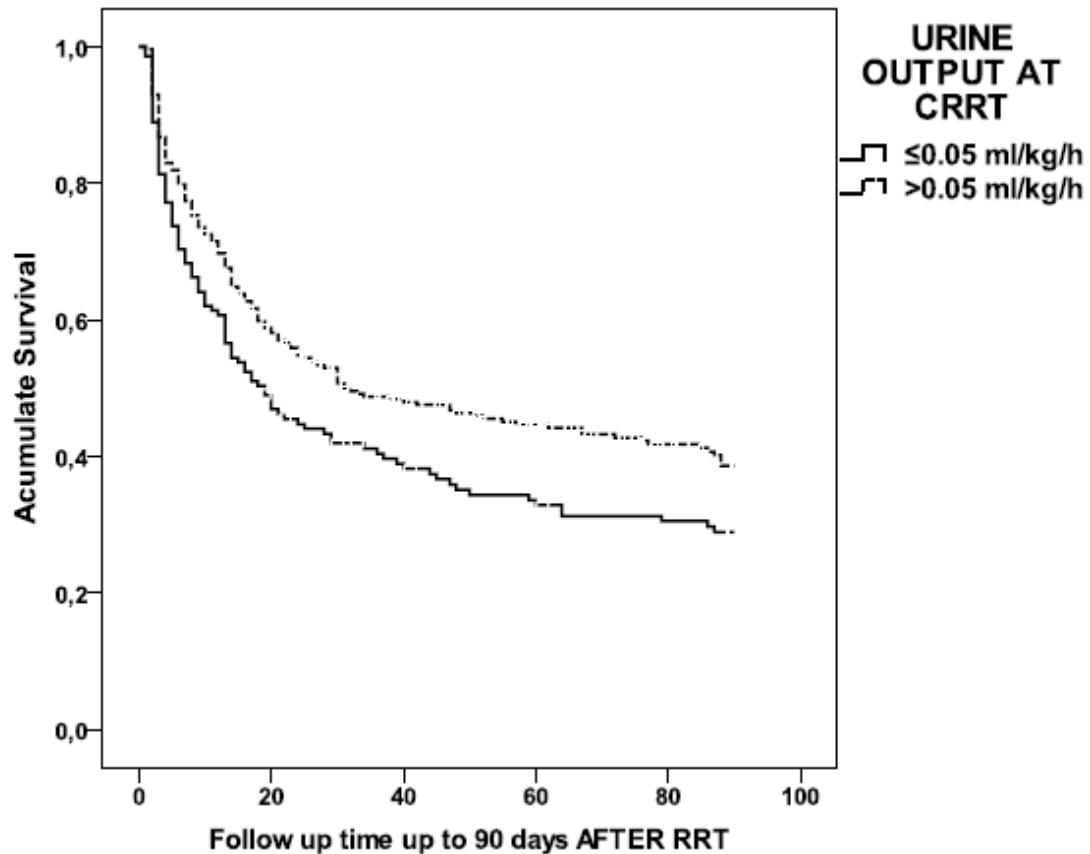
### Patient selection and “timing” of RRT initiation

From the variables associated with mortality we chose two as potential triggers for initiating RRT (days in ICU prior to CRRT, and UO). In order to homogenize groups as much as possible, we confined this analysis to a subgroup of 433 patients with septic shock and stage 3 SA-AKI at ICU admission who received CRRT within the first 5 days from ICU admission. Initiation based on days from ICU to CRRT was compared to initiation based on UO in the 24 h prior to CRRT initiation. Initiation based on days from ICU to CRRT showed no differences between the “early” group (0 to 2 days) and the “late” group (3 to 5 days) ( $p=0.765$ ), whereas initiation based on UO showed important differences in 90-day survival between patients, in whom CRRT was started with  $UO \leq 0.05$  mL/kg/h, and in patients in whom CRRT was started with  $UO > 0.05$  mL/kg/h ( $p=0.019$ ). Kaplan-Meier curves are plotted in **Fig. 2.2** and **Fig. 2.3**.



**Figure 2.2.** Time ICU admission to CRRT in stage 3 SA-AKI patients. Survival at 90 days

No differences in survival were found between patients started within the first 48 h from ICU admission and those started later up to 5 days. Stage 3 AKI is defined by KDIGO creatinine criteria. CRRT, continuous renal replacement therapy; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; SA-AKI, sepsis-associated acute kidney injury; ( $p=0.765$ ).



**Figure 2.3.** UO at CRRT commencement in stage 3 SA-AKI patients. Survival at 90 days

Patients with low UO ( $\leq 0.05$  mL/kg/h) 24 h prior to CRRT presented lower survival compared to those started with higher UO; Stage 3 AKI is defined by KDIGO creatinine criteria; CRRT, continuous renal replacement therapy; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; mL/kg/h, milliliters/kilogram/hour; SA-AKI, sepsis-associated acute kidney injury; ( $p=0.019$ ).

The aHR at 90 days showed that oliguria group ( $\leq 0.05$  mL/kg/h) presented an increased risk for mortality (aHR 2.6; 95%CI 1.6–4.3) compared to the non-oliguric group, and this difference was statistically significant ( $p<0.001$ ). This adjusted Cox regression model and differences between the initiation groups are presented in Tables 2.4, 2.5, 2.6, and 2.7.

**Table 2.4.** Patient characteristics and outcomes in patients presenting stage 3 SA-AKI

Characteristics	Survivors (n =175 )	Non-survivors (n =280)	All (n = 455)	P Value <sup>^</sup>
<b>Age, (n=455)</b>	57 (46-68)	62 (53-72)	60(50-71)	<0.001*
<b>Males, n (%)</b>	106 (60.6)	167 (59.6)	273 (60)	0.46
<b>Weight (kg), (n=453)</b>	80 (68-96)	80 (70-97)	80 (70-97)	0.75
<b>SOFA score, (n=454)</b>	12 (10-15)	12 (10-15)	12 (10-15)	0.32
<b>APACHE III score, (n=454)</b>	108 (88-129)	114 (92-136)	111 (89-132)	0.02*
<b>Charlson comorbidity index, (n=455)</b>	1 (0-3)	2 (0-4)	2 (0-4)	0.001*
<b>UPMC, n (%)</b>	97 (55.4)	178 (63.6)	275 (60.4)	0.09
<b>Surgical admission, n (%)</b>	90 (52.6)	115 (42.3)	205 (46.3)	<0.04*
<b>Creatinine (umol/L),</b>				
ICU, (n=451)**	319 (220-427)	290(209-399)	299 (211-414)	0.08
CRRT, (n=455) <sup>^^</sup>	352 (274-458)	343 (255-448)	346 (259-449)	0.09
Baseline, (n=455)	87 (76-108)	91 (73-114)	89 (75-113)	0.3
<b>Weight adjusted Urine Output (mL/kg/h),<sup>†</sup></b>				
ICU, (n=452)	0.15 (0.08-0.3)	0.14 (0.04-0.26)	0.14 (0.05-0.28)	0.04*
CRRT, (n=449)	0.13 (0.05-0.3)	0.11 (0.03-0.22)	0.12 (0.03-0.25)	0.06
<b>Mechanical ventilation at CRRT, n (%)</b>	149 (86.1)	239 (85.7)	388 (85.8)	1
<b>Serum BUN ≥ 100 mg/dL at CRRT, n (%)</b>	18 (10.3)	39 (14.1)	57 (12.6)	0.25
<b>Serum potassium &gt; 5 mEq/L at CRRT, n (%)</b>	57 (32.6)	91 (32.7)	148 (32.7)	1
<b>CRRT characteristics, n (%)</b>				0.26
CVVH	43 (24.6)	51(18.2)	94 (20.7)	
CVVHD	27 (15.4)	49 (17.5)	76 (16.7)	
CVVHDF	105 (60)	180 (64.3)	285 (62.6)	
<b>Time to ICU/CRRT (days)</b>				
Hospital admission - ICU admission	1 (1-2)	2 (1-8)	2 (1-6)	0.001*
Hospital admission - CRRT initiation	3 (2-5)	4 (2-9)	3 (2-7)	0.0001*
ICU admission - CRRT initiation	2 (2-3)	2 (2-3)	2 (2-3)	0.56
<b>Mortality, n (%)</b>				
ICU	2 (1.1)	231 (82.5)	233 (51.2)	<0.0001
Hospital	19 (10.9)	240 (85.7)	299 (56.9)	<0.0001
90 days <sup>§</sup>	0 (0)	280 (100)	280 (61.5)	<0.0001

Variables measured at ICU capture the 24 hours after ICU admission. Variables measured at CRRT capture the 24 hours before CRRT initiation.

AKI, Acute Kidney Injury; APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; BUN, blood urea nitrogen; CKD, chronic kidney disease; CRRT, continuous renal replacement therapy; CVVH, Continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; HUB, hospital universitari de Bellvitge; ICU, Intensive Care Unit; KDIGO, Kidney Disease Improving Global Outcomes; UPMC, university Pittsburgh medical center.

Conversion factors for units: serum creatinine in mg/dL to  $\mu\text{mol/L}$ ,  $\times 88.4$ ; serum blood urea nitrogen in mg/dL to mmol/L,  $\times 2.8$ ; Serum Potassium in mEq/L to mmol/L,  $\times 1$ ; Serum bicarbonate in mEq/L to mmol/L,  $\times 1$ .

<sup>^</sup> Fisher's Exact Significance for categorical variables; Kruskal-Wallis test for continuous variables.

\*\*maximum serum creatinine value measured in the 24 hours after ICU admission.

^^maximum serum creatinine value on the day of CRRT initiation or on the previous day.

†The available urine in the 24 hours after ICU or prior to CRRT was summed and divided by the weight.

\$ from CRRT initiation.

\* A p-value of < 0.05 was considered to be statistically significant.

**Table 2.5.** Timing in stage 3 SA-AKI patients based on Urine output at CRRT initiation

Characteristics	UO at CRRT > 0.05 ml/kg/h (N = 288)	UO at CRRT ≤ 0.05 ml/kg/h (N = 145)	All (N = 433)	P Value <sup>^</sup>
<b>Age</b> , mean(SD), (n=433)	59.1 (15.4)	59.0 (14.8)	59.0 (15.2)	0.964
<b>Age</b> , n (%)				0.9
<b>Males</b> , n (%)	179 (62.2)	80 (55.2)	259 (59.8)	0.18
<b>BMI</b> , mean(SD), (n=387)	29.0 (8.2)	32.0 (10.2)	30.0 (9.0)	0.002*
<b>Surgical admission</b> , n (%)	130 (45.6)	69 (50.4)	199 (47.2)	0.4
<b>Creatinine, umol/L, mean (SD)</b>				
ICU, (n=429)	236 (143)	259 (175)	244 (156)	0.044*
CRRT, (n=433)	326 (136)	319 (167)	324 (148)	0.486
Reference value, (n=433)	104 (50)	112 (57)	107 (52)	0.092
<b>Weight urine output (mL/kg), mean(SD)<sup>†</sup></b>				
ICU, (n=433)	6.9 (7.7)	1.8 (2.8)	5.2 (6.9)	<0.0001*
CRRT, (n=433)	6.4 (6.8)	0.5 (0.4)	4.4 (6.2)	<0.0001*
<b>Vasopressors at CRRT</b> , n (%)	170 (94.4)	107 (95.5)	277 (94.9)	0.8
<b>Mechanical ventilation at CRRT</b> , n (%)	243 (85.0)	126 (87.5)	369 (85.8)	0.6
<b>Serum BUN ≥100 mgs/dL at CRRT</b> , n (%)	38 (13.2)	18 (12.5)	56 (13.0)	0.88
<b>Serum potassium &gt;5 mEq/L at CRRT</b> , n (%)	97 (33.8)	46 (31.7)	143 (33.1)	0.74
<b>Arterial pH &lt;7.2 at CRRT</b> , n (%)	27 (10.1)	18 (13.8)	45 (11.3)	0.31
<b>Serum bicarbonate &lt;18 mEq/L at CRRT</b> , n %	95 (35.4)	43 (33.1)	138 (34.7)	0.65
<b>KDIGO at CRRT, n (%)</b>				
Stage 1	3 (1.0)	0 (0)	3 (0.7)	
Stage 2	9 (3.1)	0 (0)	9 (2.1)	0.1
Stage 3	276 (95.8)	145 (100)	421 (97.2)	
<b>Time to ICU/CRRT (days), median (Q1-Q3)</b>				
Hospital admission - ICU admission	2 (1-7)	1 (1-4)	2 (1-6)	0,09
ICU admission - CRRT initiation	2 (2-3)	2 (2-3)	2 (2-3)	0,33
<b>Mortality, n (%)</b>				
Hospital	161 (55.9)	97 (66.9)	258 (59.6)	0.03*
90 days <sup>§</sup>	166 (57.6)	100 (69.0)	266 (61.4)	0.028*

Variables measured at ICU capture the 24 hours after ICU admission. Variables measured at CRRT capture the 24 hours before CRRT initiation. AKI, Acute Kidney Injury; APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; BUN, blood urea nitrogen; CKD, chronic kidney disease; HUB, hospital universitari de Bellvitge; ICU, Intensive Care Unit; KDIGO, Kidney Disease Improving Global Outcomes; UPMC, university Pittsburgh medical center. Conversion factors for units: serum creatinine in mg/dL to  $\mu\text{mol/L}$ ,  $\times 88.4$ ; serum blood urea nitrogen in mg/dL to mmol/L,  $\times 2.8$ ; Serum potassium in mEq/L to mmol/L,  $\times 1$ ; Serum bicarbonate in mEq/L to mmol/L,  $\times 1$ .

<sup>^</sup> Fisher's Exact Significance for categorical variables; Kruskal-Wallis test for continuous variables.

\*\*maximum serum creatinine value measured in the 24 hours after ICU admission.

<sup>^^</sup>maximum serum creatinine value on the day of CRRT initiation or on the previous day.

<sup>†</sup>The available urine in the 24 hours after ICU or prior to CRRT was summed and divided by the weight.

<sup>§</sup> from CRRT initiation.

\* A p-value of < 0.05 was considered to be statistically significant.



**Table 2.6.** Timing in stage 3 SA-AKI patients at ICU admission based on days to CRRT

Characteristics	Late CRRT 48 - 240 hrs (N = 144)	Early CRRT ≤ 48 hours (N = 295)	All (N = 439)	P Value <sup>^</sup>
Age, mean(SD),	60.6 (15.6)	53.9 (14.8)	57 (15.5)	0.020
Males, n (%)	34 (59.6)	32 (48.5)	66 (53.7)	0.28
Weight (kg), mean(SD)	88.1 (24.7)	87.3 (30.7)	87.7 (27.9)	0.87
BMI, mean(SD),	88.1 (24.7)	87.3 (30.7)	87.7 (27.9)	0.56
Surgical admission, n (%)	45 (78.9)	28 (43.1)	73 (59.8)	<0.001
<b>Creatinine, umol/L, mean (SD)</b>				
ICU	230 (106)	336 (177)	292 (159)	<0.001
CRRT	354 (106)	354 (168)	354 (141)	0.91
Reference value	115 (62)	133 (124)	124 (97)	0.56
<b>Weight adjusted urine UO (mL/kg), mean(SD)<sup>†</sup></b>				
ICU,	16.3 (27.3)	4.5 (5.8)	10 (19.9)	0.001
CRRT,	4 (5.1)	4.7 (6)	4.3 (5.6)	0.49
Vasopressors at CRRT, n (%)	56 (98.2)	63 (95.5)	119 (96.7)	0.62
Mechanical ventilation at CRRT, n (%)	55 (96.5)	57 (86.4)	112 (91.1)	0.06
Serum BUN ≥100 mgs/dL at CRRT, n (%)	6 (10.5)	5 (7.6)	11 (8.9)	0.75
Serum potassium >5 mEq/L at CRRT, n (%)	19 (33.3)	26 (39.4)	45 (36.6)	0.57
Arterial pH <7.2 at CRRT, n (%)	0 (0)	3 (4.5)	3 (2.4)	0.25
Serum bicarbonate <18 mEq/L at CRRT, n (%)	7 (12.3)	20 (30.3)	27 (22)	0.02
<b>KDIGO at CRRT, n (%)</b>				
Stage 1	1 (1.8)	1 (1.5)	2 (1.6)	
Stage 2	4 (7)	3 (4.5)	7 (5.7)	0.85
Stage 3	52 (91.2)	62 (93.9)	114 (92.7)	
<b>Time from admission to ICU/CRRT (days), median (Q1-Q3)</b>				
Hospital admission - ICU admission	2 (1-5)	1 (1-4)	1 (1-4)	0,26
Hospital admission - CRRT initiation	5 (4-7.5)	2 (2-4.5)	4 (2-6)	<0.001
ICU admission - CRRT initiation	4 (3-5)	2 (2-2)	3 (2-4)	<0.001
<b>Mortality, n (%)</b>				
ICU	71 (49.1)	134 (45.5)	205 (46.7)	0.72
Hospital	81 (56.1)	165 (56.1)	246 (56.1)	>0.99
90 days <sup>§</sup>	92 (63.9)	180 (61.0)	272 (61.9)	0.71

Variables measured at ICU capture the 24 hours after ICU admission. Variables measured at CRRT capture the 24 hours before CRRT initiation.

AKI, Acute Kidney Injury; APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; BUN, blood urea nitrogen; CKD, chronic kidney disease; HUB, hospital universitari de Bellvitge; ICU, Intensive Care Unit; KDIGO, Kidney Disease Improving Global Outcomes; UPMC, university Pittsburgh medical center.

Conversion factors for units: serum creatinine in mg/dL to  $\mu\text{mol/L}$ ,  $\times 88.4$ ; serum blood urea nitrogen in mg/dL to mmol/L,  $\times 2.8$ ; Serum potassium in mEq/L to mmol/L,  $\times 1$ ; Serum bicarbonate in mEq/L to mmol/L,  $\times 1$ .

<sup>^</sup> Fisher's Exact Significance for categorical variables; Kruskal-Wallis test for continuous variables.

\*\*maximum serum creatinine value measured in the 24 hours after ICU admission.

^^maximum serum creatinine value on the day of CRRT initiation or on the previous day.

†The available urine in the 24 hours after ICU or prior to CRRT was summed and divided by the weight.

\$ from CRRT initiation.

\* A p-value of < 0.05 was considered to be statistically significant.

**Table 2.7.** Multivariate logistic regression of timing groups for 90-day mortality

Factors	HR	Adjusted-HR	95% Wald CI	p-Value
Late ICU-CRRT(days)	0.699	0.811	0.480–1.372	0.435
UO $\leq$ 0.05 mL/kg/h	1.383	2.593	1.557–4.321	0.0002*

ICU: intensive care unit. CRRT: continuous renal replacement therapy. mL: milliliters. UO: urine output. KDIGO, Kidney Disease Improving Global Outcomes.

All patients presented KDIGO stage 3 AKI within the first 24 hours from ICU admission and received CRRT within the first 5 days.

\* A p-value of < 0.05 was considered to be statistically significant.

## 5.4. Discussion Study 2

### 5.4.1. Highlights

The main finding of our study is that in patients with SA-AKI, treated with CRRT, numerous factors are associated with decreased survival. A higher age, severity of illness, medical as opposed to surgical admission, a higher BUN at CRRT initiation, a decreased UO at CRRT initiation, a decreased SCr at CRRT initiation, and more days from hospital admission to CRRT initiation, were all associated with worse survival. Among patients with KDIGO stage 3 SA-AKI, survival is lower when CRRT is started in the setting of low UO ( $\leq$ 0.05 mL/kg/h), while timing itself (from ICU admission) is not. These results further inform the debate about when to initiate RRT.

### 5.4.2. Risk factors for mortality

To our knowledge, this is the first study that identifies mortality factors in a cohort of SA-AKI patients all with septic shock within 24 h of CRRT initiation. Most of the variables identified in our cohort are consistent with the ones described in previous observational studies in critically ill patients. Uchino et al.<sup>341</sup> described similar independent mortality predictors (BUN, SCr, age and oliguria) in a subgroup of critically ill AKI patients who received CRRT, whereas Bagshaw et al.<sup>266</sup> compared SA-AKI patients (47.5% of the whole cohort) with non SA-AKI patients although not all septic patients were in shock (78.3%) when initiating RRT (85.4% received CRRT). In another observational study,<sup>239</sup> authors reported predictors of early (7-day) mortality

in patients with SA-AKI who required CRRT. After multivariate adjustment, five variables were associated to early mortality: norepinephrine utilization, liver failure, medical condition, lactate level, and pre-dialysis SCr level.

Our hospital mortality and 90-day mortality is concordant with epidemiological studies that report even higher mortalities in patients with septic shock who need CRRT, not only in local communities<sup>342</sup> but also in international observational studies.<sup>341</sup> Mortality factors which are classically identified in large cohorts of critically ill patients such as age or severity scores don't need further explanation.<sup>341</sup> Older patients present more comorbidities besides more severe forms of organ dysfunction with a worse response to treatment and less capacity to recover.

In our study we could not identify an association between mortality and SA-AKI severity at least in terms of SA-AKI KDIGO stage which was based on SCr variations (UO data was only registered 24 h but not specifically in the 6 or 12 h previous to CRRT). Payen *et al.*<sup>343</sup> described an increased mortality when patients in early phases of severe sepsis were randomized to CRRT compared to a usual care (no CRRT) group and some other studies<sup>344,169</sup> have shown no survival improvement when CRRT is initiated in early AKI stages, especially when those stages are based on SCr variations like in our study.

#### 5.4.2.1. Creatinine at CRRT initiation

In our study high SCr at CRRT seems to be protective which is consistent with the BEST study results<sup>341</sup> and could be explained by a higher muscle mass which represents most of the times a better nutritional status, and a lower dilutional effect on SCr values in those patients with no FO. All observational studies evaluating SCr at RRT initiation are concordant when concluding that SCr is a bad parameter to trigger RRT timing as most of these studies find a higher mortality in those patients that were started on RRT with lower values of SCr traducing as previously mentioned FO and caquexia states as well as severe forms of disease (patients who are started earlier are sometimes sicker than the ones you can permit yourself decide a “wait and see” approach). A recent posthoc analysis<sup>345</sup> of the CASH trial<sup>346</sup> (citrate vs. heparin trial) concluded that low fluid balance-adjusted SCr at CVVH initiation was associated with 28-day mortality, independent of other markers of AKI, organ failure, and surrogates of muscle mass. Data obtained from the ATN study (intensive vs. less intensive renal support) identified

twenty-one independent predictors of 60-day mortality.<sup>276</sup> Sepsis was present in 579 patients (55%). SCr at RRT initiation (mg/dl) (OR 0.834,  $p=0.01$ ), and age (per year) (OR 1.04,  $p=0.01$ ), among others, were strong predictors of mortality.

Oppositely, in our study high BUN and low UO are clearly risk factors for mortality revealing once again that creatinine-based staging is a poor indicator of severity for patients started on RRT<sup>344,168,169</sup>. Both BUN and UO have already been described as severity markers in patients with AKI requiring RRT<sup>341,167</sup> although none of these studies were performed specifically in patients with septic shock. De Corte et al.<sup>347</sup> found no association between serum urea concentration at RRT initiation and mortality in their retrospective single-centre study in ICU patients with AKI. However, Bagshaw et al.<sup>348</sup> found association between the change in urea from admission to RRT initiation ( $>8.9$  mmol/L) and hospital mortality in a prospective study of 234 patients receiving RRT.

#### 5.4.2.2. Urine output at CRRT initiation

It seems clear that in our study, where all patients were “at some point” initiated on CRRT the presence of a low UO at CRRT initiation was associated with a worse prognosis. Oliguria, defined as decreased UO during 24 h ( $<400$  mL/24 h; in our study  $\leq 0.5$  mL/kg/h during 24h), has classically been considered a marker of AKI and is included in all definitions and classifications from RIFLE to KDIGO. We selected  $\leq 0.5$  mL/kg/h cut-off value based on the distribution of the parameter in our study population. Whether oliguria can be a predictive biomarker of AKI in critically ill patients or may have a prognostic utility in patients with AKI requiring RRT has been analysed in several studies. Recently Cho et al.<sup>349</sup> described mortality risk factors after a multivariate logistic regression analysis in patients requiring CRRT. Age, platelet count, APACHE II score, SCr level, and a UO of  $\leq 0.05$  mL/kg/h the first day of CRRT were all prognostic factors for the 28-day all-cause mortality.

Prowle et al.<sup>350</sup> reported that oliguria was significantly associated with the occurrence of new AKI (based on SCr changes). However oliguria occurred frequently compared to the small number of patients (~10%) developing AKI in the ICU, so that most episodes of oliguria were not followed by renal injury. Oh et al.<sup>351</sup> reported a in a cohort of patients with AKI receiving CRRT a decrease in mortality in the nonoliguric group (6-h

UO) compared with the oliguric group. According to all these previous studies, oliguria appearance could be a useful tool to predict optimal RRT initiation. This could be related with a more severe form of AKI although as previously discussed, very few studies have shown worst outcomes when RRT is started in advanced AKI stages specially when AKI is based exclusively on SCr changes and not UO.

Perhaps in our study low UO could be an indicator of FO in patients with AKI but we don't have enough data to confirm this association. FO diagnosis was not registered in our study and the same happens in the majority of the big trials that report oliguria at RRT initiation as an independent factor for mortality. BEST study<sup>341</sup> and ATN study<sup>276</sup> reported oliguria (defined as UO<400 mL/day) at RRT initiation as a mortality predictor but not FO, whereas PICARD study<sup>243</sup> reported FO (defined as a body weight increase>10% respect to baseline) but not oliguria. The FINNAKI study<sup>161</sup> described an association between 90-day mortality and FO in RRT-treated critically ill patients. Furthermore, patients with FO had lower UO (mL/24 hr) on RRT initiation day. Some other studies reporting low UO prognosis when starting RRT, also report fluid balance prognosis. For example, Bagshaw et al.<sup>348</sup> characterized factors associated with start of RRT and reported that mortality at RRT initiation was associated with UO <82 mL/24 h, fluid balance more than 3.0 L/24 h, and percentage of FO more than 5%. In the NEFROINT study<sup>352</sup> mean fluid balance (aHR 1.67 per L/day) and mean UO (aHR 0.47 per L/day) remained independent risk factors for 28-day mortality.

At this point it is important to remark that whether oliguria or low UO is registered with or without the use of diuretics is still a matter of debate as most of the studies that report the prognostic value of UO don't specify if patients were on diuretics or not. We know that the predictive value of UO can be altered by the use of diuretics as reported in the analysis of CRRT weaning obtained from the BEST study.<sup>353</sup> Whether this applies too for AKI diagnosis criteria or oliguria prognostic utility has not been resolved yet. In our study we could not differentiate between those patients who had oliguria with or without the presence of diuretics although common practice suggests that probably nearly all patients were under diuretics previous to CRRT initiation.<sup>354</sup> Posthoc analysis<sup>121</sup> from the FACTT trial reported a relationship between less FO and survival in those patients with ARDS and AKI treated with diuretics. Perhaps patients with AKI unresponsive to diuretics (which seem to present higher mortality related to FO) could constitute an idoneous group in which to evaluate early start of RRT as Lumlertgul et

al.<sup>355</sup> reported in a recent trial that evaluated furosemide stress test (FST) in critically ill patients with AKI at a high risk of requiring RRT.

#### *5.4.2.3. Time from hospital admission to CRRT*

Time from hospital admission to CRRT was identified as an independent mortality predictor as these patients present higher morbidity and mortality due to long hospital stay and sometimes delayed ICU admission.<sup>160</sup> In our study the majority of these patients with longer times from hospital admission to CRRT can be classified as hospital-acquired AKI (HA-AKI) which represents a more severe form of AKI compared to community-acquired AKI (CA-AKI).

Wonnacott et al.<sup>147</sup> reported an observational study where patients with CA-AKI although they were more likely to have stage 3 AKI, had better survival and shorter lengths of hospital stay than patients with HA-AKI. In a retrospective study Hsu et al.<sup>148</sup> examined patients with AKI at discharge whom were classified as either CA- or HA-AKI based on the RIFLE classification criteria. CA-AKI was more common than HA-AKI, but in-hospital mortality and LOS were worse in HA-AKI than CA-AKI.

#### *5.4.2.4. Type of admission*

In our study, medical admission to ICU presented nearly twice risk of 90-day mortality compared to surgical admission and this could be related to a high prevalence of severe community acquired pneumonia (CAP) (nearly 25% of the overall 939 patients). This is interesting because we already reported in our previous study (study 1) that abdominal sepsis was also an independent risk factor for the development of SA-AKI although in that study we did not analyze if those patients with SA-AKI due to abdominal sepsis had lower mortality than those with SA-AKI from other etiologies. In the BEST study,<sup>341</sup> postsurgical AKI was also associated with a lower hospital mortality. In the ATN trial,<sup>276</sup> postsurgical AKI was also related with a nearly significant better outcome (60-day mortality OR 0.64, p=0.08). Whether these differences are related to the well-known “early reversibility” of surgical admissions compared to the “late therapeutic response” in medical patients or to other reasons needs further studies.

### 5.4.3. Timing analysis

In clinical practice, a “wait and see” approach is often used for severe AKI patients who are non-oliguric.<sup>166</sup> Clark et al. reported oligoanuria as the more frequent clinician reported indication for initiation of RRT in a multicenter ICU survey of patients undergoing RRT for AKI. Thus, non-oliguric patients may recover spontaneously and are less likely to develop urgent indications for RRT (FO, hyperkalemia) than oligoanuric patients.<sup>166</sup>

Increasing evidence has been published reporting that the addition of UO criteria to SCr criteria leads to higher AKI incidences with earlier recognition especially in patients with mild to moderate AKI. Macedo et al.<sup>356</sup> showed that the incidence of AKI increased from 24%, based solely on SCr, to 52% by adding the UO as a diagnostic criterion. FINNAKI study<sup>357</sup> reported that episodes of severe oliguria (<0.1 mL/kg/h) for more than 3h were independently associated with the development of SCr-AKI or RRT. Koeze et al.<sup>358</sup> reported that addition of UO criteria detected patients with AKI 11 h earlier than SCr criteria and could double AKI incidences in critically ill patients. However, things are not always so clear. Harris et al.<sup>359</sup> reported that the use of RRT was unlikely with severe oliguria and normal or only moderately raised estimated delta-SCr, despite this being a hotspot for ICU mortality. We know from the FST trials that UO in response to diuretics is a good predictor of renal outcome. Chawla et al.<sup>360</sup> developed the FST in order to predict the severity of AKI. Those patients with AKI who were responsive (>200mL of UO) in the 2 h following a furosemide bolus of 1 – 1.5 mg/Kg had a significant lower risk of progressing to advanced stages of AKI (AKI stage 3). Later Koyner et al.<sup>361</sup> confirmed these results reporting that FST UO was the only biomarker to significantly predict RRT. More recently, the FST trial has proved to be feasible and effective in identifying AKI patients for randomization to different RRT initiation times as Lumlertgul et al.<sup>355</sup> reported.

In our study we sought to understand whether the use of CRRT in patients with different UO patterns would be associated with different outcomes. We compared this analysis to a standard “clock time” from ICU admission variable which is a well-known variable associated with survival outcomes. Patients with longer times from ICU admission to CRRT have been reported to have worst outcomes than those who are “early” initiated. Bagshaw et al.<sup>160</sup> analyzed timing of RRT in the BEST study patients and categorized

temporally from ICU admission into early (<2 days; 64%), delayed (2-5 days; 14%), and late (>5 days; 22%). Late RRT was associated with greater crude and covariate-adjusted mortality. Overall, late RRT was associated with a longer duration of RRT and stay in hospital and greater dialysis dependence. Once again, days from ICU to RRT were not accurately reported with a lack of information for the late group (more than 5 days *but up to?*). Patients in this late RRT group were older, more likely to be a medical admission (worse prognosis) and had more preexisting impaired kidney function. Therefore, we can suggest that the late group were more severe patients with higher comorbidities and some of them initiated on RRT for a different reason not related with the ICU admission process. Other studies<sup>362</sup> have also reported this relation describing a U-curve association between the timing of the RRT initiation after ICU admission and patients in-hospital mortalities. The first peak of the U-curve represents the combined effect of poor clinical conditions (higher APACHE II scores, lower MAP), whereas older age, sepsis with subsequent complications, and maybe an extremely delayed initiation of RRT are responsible for the second peak in the curve. Some observational trials<sup>363,364</sup> in cardiac surgery associated AKI (CSA-AKI) have also described an association between timing in terms of time from post-surgery ICU admission to RRT and mortality, suggesting better outcomes for the early groups although once again patients in the late groups present very different characteristics respect to the patients in the early groups.

In our study, interestingly within the subgroup of patients with septic shock and severe SA-AKI (AKI stage 3), days in ICU prior to CRRT were not predictive of survival while UO was. This suggests that timing of initiation of RRT is a more complex variable than simply time from ICU admission or from SCr-based staging. Indeed a more personalized approach will likely be required as advocated by the ADQI workgroup.<sup>365</sup> Timing of CRRT based on UO seems a more physiological approach and several studies have emphasized the importance of UO as a clinical AKI biomarker.<sup>366</sup> Leite et al.<sup>168</sup> reported survival benefits in a cohort of stage 3 AKI patients treated with early RRT (within 24 h from meeting AKI stage 3 based on UO and SCr) compared to a late group (more than 24 h after AKI stage 3). This methodology defining an advanced AKI stage in order to evaluate “timing” from there onwards is similar to the one we used in our study. Once again the late group was not precisely defined, as number of days to RRT initiation were not reported (late time bias) and this is the most relevant



difference respect to our study (besides population characteristics) as we intentionally selected only those patients that were initiated within the first 5 days.<sup>168</sup> Similarly, Jun et al.<sup>367</sup> in a subgroup of participants of the RENAL study evaluated the impact of RRT timing respect to Injury stage of AKI (RIFLE-I). The median time between RIFLE-I AKI and CRRT commencement was 17.6 h (IQR, 7–46 h). Based on four groups of CRRT commencement, earlier initiation of CRRT was not associated with a significantly lower risk of death at 28 days. Concerning CSA-AKI, the HEROICS trial<sup>368</sup> did not observe benefits in mortality with an early RRT strategy in patients with severe shock and 43% of the patients assigned to the “delayed RRT” strategy did not require RRT.

Park et al.<sup>369</sup> similarly to our study divided patients with AKI into two CRRT groups based on the median 6-hour UO: early ( $\geq 0.24$  mL/kg/h) and late ( $< 0.24$  mL/kg/h). There was no difference in cumulative fluid balance or diuretic use between the two groups. The time from ICU admission to CRRT initiation was unexpectedly short in both groups: 6.8 h in the early CRRT group and 7.9 h in the late CRRT group. The same as in our study, the overall cumulative survival rate was higher in the early CRRT group (log-rank  $p < 0.01$ ). However, although in our study no differences in the median time from ICU admission to CRRT were observed between the early and late groups based on UO (**Table 2.5**), times to CRRT were much longer than those referred by Park et al. probably reflecting a more realistic situation in terms of RRT timing.

Starting CRRT before low UO setting could hypothetically prevent FO which is a well-known mortality predictor in patients with sepsis with or without AKI.<sup>161,350,243</sup> In the ELAIN study<sup>171</sup> mean fluid balance at randomization was 7 litres positive which could explain the better outcome for patients who were assigned to the early CRRT group (KDIGO stage 2 AKI). In this last trial, most of the patients assigned to the delayed group were started on RRT when achieving respiratory failure criteria (78%). A delayed RRT strategy in these patients (87% presented cardiogenic shock at the time of inclusion) with AKI and FO did not seem the best decision. Furthermore, differences in the time from randomization to CRRT were shorter than expected. It is difficult to explain how a difference of only “hours” between both groups (median difference of 19 h) could have such an important clinical impact unless patients at randomization were really in acute lung edema due to cardiogenic shock and unresponsive to diuretics.

Contrary to these findings Gaudry and colleagues reported in their AKIKI trial<sup>17</sup> that no benefit was obtained with an early RRT strategy (KDIGO stage 3 AKI). Interestingly, about half of the patients in the delayed group did not receive RRT and although these patients had lower mortality when compared to the early group (all receiving RRT), after adjusting for severity scores no differences were found. No data of fluid balance at randomization was reported. Contrary to the ELAIN trial, in the AKIKI trial the important differences in terms of time from randomization to RRT (median difference of 53 h between groups) was not translated in significant differences in mortality. Reinforcing this delayed strategy, the IDEAL-ICU study<sup>18</sup> was a large RCT in patients with an early-stage septic shock who had SA-AKI at the failure stage (RIFLE) but without life-threatening complications. No differences in mortality were observed (the trial was stopped early for futility) between an early RRT strategy (Failure stage) and a delayed RRT strategy (after 48 h if renal recovery had not occurred). In the delayed-strategy group, 38% (93 patients) did not receive RRT but this percentage could probably have been even bigger with a 72 h criteria for renal recovery. In the IDEAL-ICU study mean fluid balance at randomization was 3.2 L in both groups and 3.5 L after 2 days from randomization. Differences in terms of time from randomization to RRT were similar to the AKIKI trial (median difference of 44 h). The characteristics of this septic shock population were very similar to our study cohort as well as the times from stage 3 AKI to CRRT. Mortality was also very similar.

It is interesting to point out that both AKIKI and IDEAL-ICU trials had a high percentage of patients (70%) with at least oliguria (defined as  $UO < 0.3 \text{ mL/kg/24h}$ ) at randomization but with no FO situation (at least in terms of fluid balance). Contrary to this situation, the ELAIN trial had also 70% of patients oliguric at randomization (this time defined as  $UO < 0.5 \text{ mL/kg/24h}$ ) but with a probable FO situation (positive fluid balance in cardiovascular disease). In fact, in the ELAIN trial, authors reported significant differences in UO at CRRT initiation probably reflecting the same two different populations we showed in our study (early and late based on UO). Based on our findings we could suggest that an early strategy in terms of UO (*“dont wait for low UO in stage 3 SA-AKI when FO is present”*) could be beneficial in patients with FO and bad clinical tolerance due to cardiovascular failure or leak syndrome (specially from a respiratory point of view). Whether these patients with SA-AKI and lower UO at CRRT initiation had more FO than those patients with higher UO can only be hypothesized but

not demonstrated. Signs of FO such as SCr dilution or respiratory failure were not clearly present in our study although at CRRT initiation in the oliguric group there was a very slight and non-significant trend for a lower SCr level and a higher MV rate compared to the non-oliguric group (**Table 2.5**).

Contrary to our hypothesis, Gaudry et al.<sup>176</sup> in a subgroup analysis of septic shock and ARDS patients from the AKIKI trial (two groups of patients vulnerable to FO) concluded that there were no differences between an early strategy and a delayed strategy in terms of survival and other outcomes. Subgroups were defined according to baseline characteristics: sepsis status (Sepsis-3 definition),<sup>53</sup> ARDS status (Berlin definition).<sup>370</sup> Authors found no significant influence of the baseline sepsis status ( $p=0.28$ ), baseline ARDS status ( $p=0.94$ ) and baseline severity scores ( $p=0.77$  and  $0.46$  respectively) on the comparison of 60 day mortality according to RRT initiation strategy. Furthermore, a delayed RRT initiation strategy allowed 45% of septic shock and 46% of ARDS patients to escape RRT. Time to successful extubation in ARDS patients was not affected by RRT strategy ( $p = 0.43$ ).

#### 5.4.4. Limitations

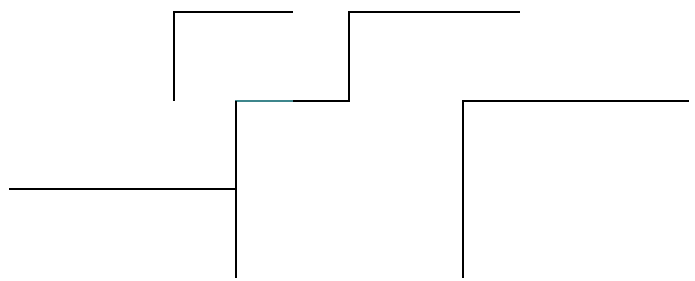
The major limiting factor of our study is to be a retrospective study carried out in different periods and countries where indication to start CRRT was not decided upon a common standardized protocol but was based on clinical decision making. Patients started with CRRT in an oliguric state vs. the others may have other important confounders (such as fluid balance or drug clearance and toxicity) triggering CRRT start and causing mortality. Another limitation is that we focused exclusively on patients who received CRRT and thus we cannot comment on septic shock patients in KDIGO stage 3 SA-AKI who did not receive CRRT as these data were not collected.<sup>244</sup> We know from recent trials that an important percentage of the delayed or late timing patients will not need RRT (as much as 49% in the AKIKI trial, 43% in the HEROICS trial, and 38% in the IDEAL-ICU trial). Furthermore, renal recovery seems to occur earlier in those patients who do not require RRT as AKIKI trial proved (*diuresis, a marker of improved kidney function, occurred earlier in the delayed-strategy group ( $p<0.001$ )*).

Even though we tried to homogenize our population in order to analyze the effect of timing of initiation of CRRT, there may still be residual confounding as patients with

early stages of AKI and those who were started after 5 days from ICU admission were excluded from analysis as both group of patients presented higher severity scores as well as comorbidities. In our study, patients with KDIGO AKI stage 3 started on CRRT after more than 5 days from ICU admission (median time of 14 days) had higher mortality (71.6% at 90 days) with a higher Charlson comorbidity index (probably these more chronic patients were delayed in CRRT initiation decision), and lower SCr values (probably reflecting low nutritional status plus FO). UO was not registered further than 24 h prior to CRRT and this could also represent a study limitation as those patients with longer oliguria state (and probably higher FO) were not properly identified. Finally, fluid balance before and after CRRT initiation was not collected. Positive fluid balance is not only a well-known mortality predictor in AKI patients before and after CRRT initiation,<sup>161,243,244</sup> but it may also dilute SCr underestimating AKI stage.<sup>364</sup>

In conclusion, in patients with septic shock and SA-AKI requiring CRRT, survival is lower as age, severity of illness, BUN and time from ICU admission to CRRT increases. When CRRT is started in the setting of low UO mortality is increased. These results must be considered with caution while big trials are still not completed although we recommend that these variables should be included in studies evaluating timing of RRT initiation in patients with septic shock and SA-AKI.





*Study 3*

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## 6. Study 3. Two different modalities of continuous renal replacement therapy in critically ill patients with sepsis associated acute kidney injury: a pilot randomized study

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(This study has been funded by Instituto de Salud Carlos III through the project PI12/01562 [Co-funded by European Regional Development Fund. ERDF, a way to build Europe])

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### 6.1. Objectives

To evaluate thru a two-center pilot randomized trial in a critically ill population with SA-AKI requiring CRRT:

- The validity and usefulness of a diffusion CRRT strategy (CVVHD) associated to an adsorption capacity membrane (AN69-ST) compared to a convective CRRT strategy (CVVH) associated to the same membrane. This objective will be assessed registering the mean filter life and the number of dialytrauma events within the first 72 h after randomization and during all the period on CRRT.
- The survival outcome of a diffusion CRRT strategy (CVVHD) associated to an adsorption capacity membrane (AN69-ST) compared to a convective CRRT strategy (CVVH) associated to the same membrane. This objective will be assessed registering survival (or mortality) at 28 and 90 days.
- The immunomodulation capacity of a diffusion CRRT strategy (CVVHD) associated to an adsorption capacity membrane (AN69-ST) compared to a convective CRRT strategy (CVVH) associated to the same membrane. This objective will be assessed measuring the cytokines plasmatic concentration changes within the first 72 h after randomization.
- The solute removal efficacy of a diffusion CRRT strategy (CVVHD) associated to an adsorption capacity membrane (AN69-ST) compared to a convective CRRT strategy (CVVH) associated to the same membrane. This objective will be assessed measuring the solutes plasmatic variations within the first 24 h after randomization.



- The clinical efficacy of a diffusion CRRT strategy (CVVHD) associated to an adsorption capacity membrane (AN69-ST) compared to a convective CRRT strategy (CVVH) associated to the same membrane. This objective will be assessed measuring the hemodynamic and respiratory variations within the first 72 h after randomization as well as the number of days in MV and ICU LOS.

## 6.2. Methods Study 3

### Design and Setting

From January 2013 to October 2017 we performed a two-center, parallel-group and randomized single blinded pilot controlled trial in two tertiary care, university hospitals with more than 40 ICU beds available in each one (Hospital Universitari de Bellvitge, Hospital de la Santa Creu i Sant Pau). As a pilot study of at least 50 cases is advisable in many circumstances,<sup>371</sup> and we wanted to compare two treatment options, we aimed to recruit at least 100 patients. Patients fulfilling all inclusion criteria ( $\geq 18$  year-old adult patients, diagnosed with SA-AKI requiring CRRT with written informed consent from patient or legal surrogates) were eligible for randomization within the first 72 h from ICU admission.

Criteria for CRRT initiation were the presence of any of the KDIGO AKI stages, plus one or more of the following immediate initiation criteria: BUN  $> 40$  mmol/L, K<sup>+</sup>  $> 6$  mmol/L, pH  $< 7.15$  in metabolic acidosis, acute pulmonary edema due to fluid overload (FiO<sub>2</sub>  $> 50\%$  in mechanically ventilated patients) and despite diuretic therapy, oliguria / anuria  $> 72$  h. Exclusion criteria included ESRD or previous RRT within the last 2 weeks. Patients with more than 72 h from ICU admission to randomization (CRRT) were excluded as this group of patients commonly present a higher number of comorbidities (such as a longer ICU length of stay), elusive inflammatory responses and, the most of the times, worse outcomes not necessarily related to the acute event when compared to those patients who are admitted to ICU with an acute SA-AKI condition.<sup>160</sup> The Research Ethics Committees of both centers authorized this study for collection, analysis, and publication of data.

### CRRT and study intervention

CRRT was administered using PRISMAFLEX system (Baxter®); jugular or femoral catheters were used for vascular access. The location of the access line tip was confirmed for jugular catheters by chest radiograph. Patients were randomly assigned to one of two interventions: CVVH or CVVHD, both groups employing AN69 surface-treated (AN69ST). AN69ST membrane is a derivative of AN69<sup>372</sup> (native AN69), originally developed in 1969 as the world's first synthetic polymeric membrane, prepared by surface treatment of polyethyleneimine (PEI).<sup>224</sup> For this study we used AN69ST150 which presents a membrane area of 1.5 m<sup>2</sup>.

A sequential randomization (blocks of 10 patients randomized as 1:1) was conducted by a foreign technician who was not involved in data collection, analysis or manipulation. Allocation concealment was warranted by numbered and sealed opaque envelopes that were generated for treatment allocations following the sequential randomization. AN69ST was used as the EC set in both groups from day 1 to CRRT withdrawal day. When no clinical contraindications were present, anticoagulation with unfractionated heparin was initiated, according to the institutional protocol, at a perfusion rate of 5 to 10 units/kg/h with no protamine administration and no circuit TTPa controls. No RCA was used for the study in order to standardize the EC anticoagulation strategy, as RCA was not available in one of the two centers at the time of the study performance; and to avoid information bias. AN69ST was exchanged every 24 h within the first 72 h of CRRT (24 h and 48 h exchanges) and according to individual needs.

Patients were started on CRRT at a fixed dose of 30 mL/kg/h (to ensure a delivered dose of 25 ml/kg/h) with Pristasol®-4 either as dialysate fluid (CVVHD) or as replacement fluid (CVVH) during the first 72 h. Blood flow (Q<sub>b</sub>) of 200-250 mL/min was prescribed in both groups, and plasma flow (Q<sub>plasma</sub>) was adjusted to reach an adequate percentage of pre-filter reposition in the CVVH group to maintain a theoretical filtration fraction (FF) between 18-22%. After the first 72 h, dose could be adjusted according to patient requirements, but the modality (CVVH or CVVHD) and the model of EC set (AN69ST) had to remain unmodified unless patients were transferred to IHD. CRRT protocol is detailed in **Table 3.1**.

**Table 3.1.** Initially prescribed CRRT settings (per-protocol)

	All patients (n=107)	CVVH (n=51)	CVVHD (n=56)	P value
Dose at day 0 (mL/kg/h)	31 ± 10	29 ± 6	32 ± 12	0.7
Dose at day 4 (mL/kg/h)	28 ± 6	27 ± 7	28 ± 6	0.9
Flow (mL/min)	200 (200-220)	220 (200-240)	200 (200-200)	<0.0001
EC exchange lapse	Every 24 h within the first 72 h of CRRT			
FF at day 0 (%)*	17 ± 8	17 ± 8	N/A	
FF at day 4 (%)	15 ± 4	15 ± 4	N/A	
Heparin at day 0	29 (26)	16 (30)	13 (23)	0.4
Heparin at day 4 (n=52)	24 (44)	10 (39)	14 (49)	0.5

Values are presented as n (proportion) or mean (interquartile range). Plus-minus values are means ± SD.

CRRT Denotes continuous renal replacement therapy, CVVH continuous venovenous hemofiltration, CVVHD continuous venovenous hemodialysis, EC Extracorporeal circuit, FF filtration fraction, N/A Not applicable.

\* The filtration fraction is the fraction of plasma which is removed from blood during hemofiltration. The ideal filtration fraction at a hematocrit of 0.30 is around 25%.

## Data collection

Clinical and laboratory data were collected in all patients at baseline, 24 h, 48 h, and 72 h. Cytokines concentrations were only evaluated in 40 patients (20:20) who had all samples collected (that means they were alive after 72 h), measuring to our knowledge, the most relevant cytokines in SA-AKI patients based on previous published research,<sup>256,373</sup> including IL-1 $\beta$ , TNF- $\alpha$ , IL-4, IL-6, and IL-10. Blood samples (pre-affluent and post-effluent), and ultrafiltrate samples were obtained just before the EC exchanges (24 h and 48 h), and after 72 h (no other filter exchanges were mandatory by protocol from 48 h onwards) in order to assess cytokines and solutes clearances (*these calculations are still under analysis*). Pre-affluent samples were obtained from the affluent line just after the catheter in order to avoid mixing with pre-dilution replacement fluid whilst post-effluent samples were obtained just after the membrane in order to avoid mixing with post-dilution replacement fluid. Cytokines plasmatic concentration changes<sup>374</sup> (% of reduction between baseline concentration (pg/mL) and time selected concentration (pg/mL)) were initially assessed from 0 h to 72 h after CRRT initiation.

Registered clinical data included respiratory and hemodynamic variables, comorbidities, sepsis etiology and acute severity scores. Laboratory data included plasma concentration levels of creatinine, urea, potassium, albumin, magnesium, phosphate and

$\beta$ 2-microglobulin, and solute removal was initially assessed by means of measuring plasmatic solute levels differences between baseline and 24 h after CRRT initiation. CRRT prescription parameters, EC patency and CRRT related complications (dialytrauma) were registered from CRRT initiation until the patient was weaned from CRRT or discharged from the ICU. Dialytrauma events during CRRT included the need for packed RBC transfusion due to filter clotting, the presence of hypothermia (defined as rectal temperature  $<35.5^{\circ}\text{C}$ ), the presence of thrombocytopenia ( $<100 \times 10^3/\mu\text{L}$ ), the presence of hypokalemia ( $<3.3 \text{ mmol/L}$ ), and/or the presence of hypophosphatemia ( $<0.7 \text{ mmol/L}$ ). Hours of anticoagulation with heparin were also recorded.

EC patency time, reasons for EC exchanging (clotting or other reasons) and the number of clotted EC were quantified and registered by ICU nurses at bedside. Survival status was assessed at 90 days, using phone call and inter-institutional electronic charts as methods for follow-up.

### **Laboratory quantification**

IL-1, IL-4, IL-6, IL-10, and  $\text{TNF}\alpha$  quantification was performed using Milliplex Map Kits (Merck Millipore, Germany).

### **Statistical analyses**

All continuous data are presented as medians (IQR [Q1 – Q3]) or means (standard deviation, SD), as was appropriate for nonparametric or parametric data. Differences in medians or means between groups were tested with Mann-Whitney test and Student's t-test, respectively. Differences in proportions were compared using Fisher's exact test or  $\chi^2$ -test where appropriate. Intention-to-treat analysis was performed for survival; Kaplan-Meier survival curves were used to estimate the cumulative mortality rates in both groups and significant differences were calculated using the log-rank test. Cox PH model was used to determinate each group aHR for 90-day mortality. Variables were considered for multivariate Cox regression models if they had  $<10\%$  missing data, and the following assumptions: (1) had P values  $<0.1$  in the univariate analysis and (2) were clinically plausible. Backward elimination was performed by the likelihood ratio method. Data are presented as aHRs with 95% CIs. A p-value of  $<0.05$  was considered to be statistically significant. All tests were performed using the statistical software package SPSS 20.0.

### 6.3. Results Study 3

#### Patients characteristics

A total of 6300 patients were admitted to the ICU of recruiting centres during the study period. SA-AKI was present in nearly 40% of these patients during ICU admission (10% of them ultimately required RRT), albeit solely patients requiring CRRT during the first 72 h from ICU admission were screened for the study. 110 SA-AKI patients were included (**Fig. 3.1**).

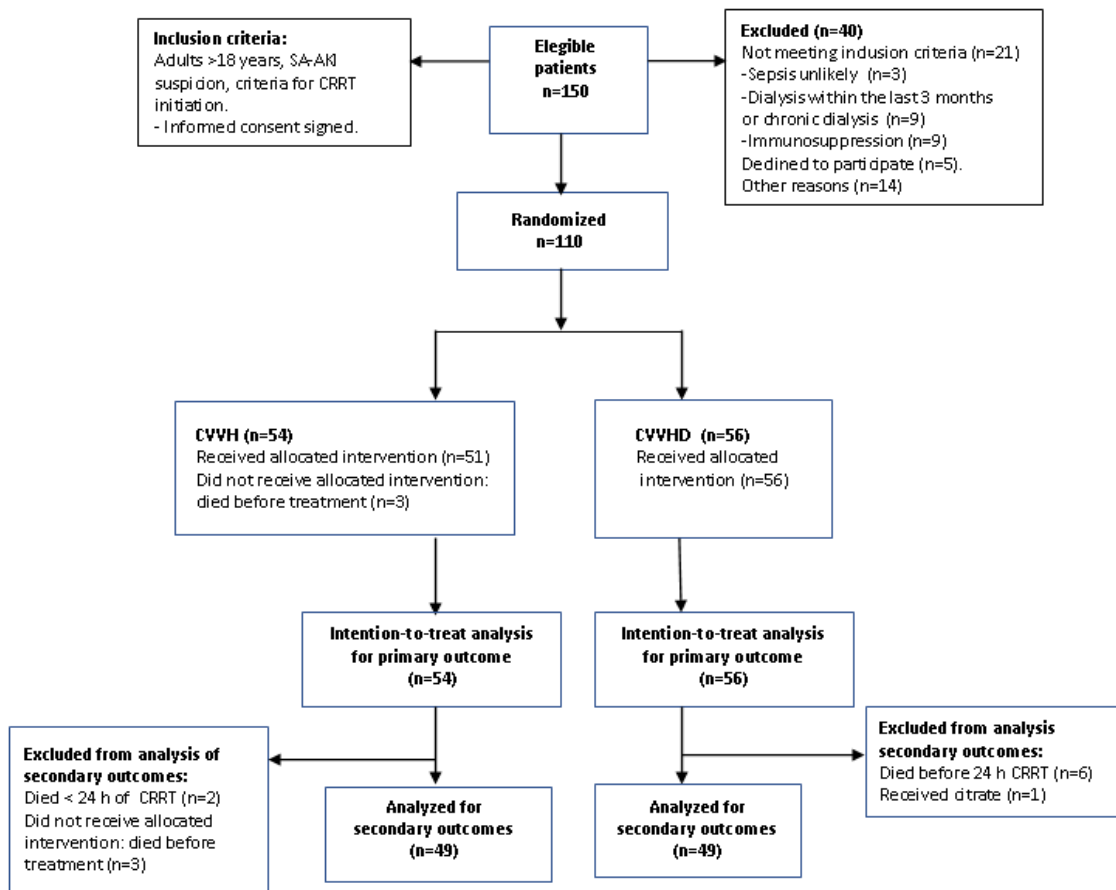


Figure 3.1. Study 3 flow chart

CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; ICU, intensive care unit; SA-AKI, sepsis-associated acute kidney injury.

Mean age was 63±13 years; 60% of patients were male. The most prevalent comorbidities were: hypertension, chronic heart failure and diabetes mellitus (in 53%, 32% and 25%, respectively). The main etiology of sepsis was intrabdominal infection in 38% of patients. Mean SOFA score at ICU admission was 14±2, whereas mean APACHE II score was 25±9. Mean time from hospital admission to CRRT was 95±113. Mean time from ICU admission to CRRT was 17±47 h. Mean time from randomization to CRRT was 1.2±1.1 h. At CRRT initiation (baseline), septic shock was present in 96% of patients, mean norepinephrine dose was 0.50±1.0 µg/kg/min, 81% of patients were on MV, and 74% of patients met criteria for stage 3 AKI as stated by KDIGO guidelines. Baseline characteristics were similar in both groups and are represented in **Table 3.2.**

**Table 3.2.** Baseline characteristics of critically ill SA-AKI patients requiring CRRT

	All patients (N=110)	CVVH (N=54)	CVVHD (N=56)	P value
<b>Male, n (%)</b>	66 (60)	35 (65)	31 (55)	0.8
<b>Age (years) *</b>	63 ± 13	64 ± 14	62 ± 12	0.52
<b>BMI (kg/m<sup>2</sup>)</b>	28 ± 5	29 ± 5	27 ± 5	0.18
<b>Comorbid condition, n(%)</b>				
Hypertension	58 (53)	31 (57)	27 (48)	0.83
Diabetes*	27 (25)	14 (26)	13 (23)	1
CKD	16 (15)	10 (18)	6 (11)	0.6
Chronic heart failure	35 (32)	21 (39)	14 (25)	0.29
<b>Surgical patient, n(%)</b>	50 (46)	29 (53)	21 (38)	0.3
<b>Etiology of sepsis, n(%) †</b>				0.6
Intraabdominal	42 (38)	20 (37)	22 (39)	
Pneumonia	22 (20)	12 (22)	10 (18)	
Urinary Tract Infection	15 (14)	4 (8)	11 (20)	
<b>Bacteriemia, n(%)</b>	45 (41)	24 (45)	21 (38)	0.4
<b>Blood culture isolation (n=43), n(%)</b>				0.4
<i>E. coli</i>	20 (46)	7 (35)	13 (57)	
<i>S. aureus</i>	9 (21)	6 (30)	3 (13)	
<i>E. faecium</i>	6 (14)	2 (10)	4 (17)	
<b>Appropriate antibiotic (n=103), n(%)</b>	84 (82)	43 (88)	41 (76)	0.14
<b>Vasopressors at CRRT, n(%)</b>	106 (96)	53 (98)	53 (95)	0.6
<b>Norepinephrine dose (µg/kg/min)</b>	0.50 ± 1.0	0.50 ± 1.2	0.45 ± 0.7	0.6
<b>MAP (mmHg)*</b>	75 ± 12	74 ± 11	76 ± 12	0.6
<b>SOFA‡</b>	14 ± 2	14 ± 2	14 ± 2	0.35
<b>APACHE II at admission§*</b>	25 ± 9	26 ± 9	24 ± 8	0.24
<b>Baseline Creatinine (µmol/L)</b>	90 (75-108)	90 (75-101)	89 (78-127)	0.23

	All patients (N=110)	CVVH (N=54)	CVVHD (N=56)	P value
<b>Creatinine CRRT initiation (<math>\mu\text{mol/L}</math>)*</b>	312 $\pm$ 175	281 $\pm$ 142	343 $\pm$ 200	0.08
<b>BUN at CRRT initiation (mg/dL)</b>	49 (38-68)	48 (38-65)	55 (37-76)	0.07
<b>Fluid balance 24 h before CRRT (L)</b>	2.9 $\pm$ 1.8	3.1 $\pm$ 1.8	2.7 $\pm$ 1.7	0.3
<b>UO 24 h before CRRT (mL/kg/h)¶</b>	0.29 (0.1-0.6)	0.29 (0.1-0.5)	0.3 (0.1-0.6)	0.9
<b>UO 6 h before CRRT (mL/kg/h)¶</b>	0.20 (0.1-0.4)	0.19 (0.1-0.4)	0.22 (0.1-0.5)	0.1
<b>Time from hospital to CRRT (hours)</b>	95 $\pm$ 133	111 $\pm$ 128	78 $\pm$ 139	0.24
<b>Time from ICU to CRRT (hours)</b>	17.4 $\pm$ 47	19 $\pm$ 46	15.8 $\pm$ 48	0.7
<b>Mechanical ventilation, n(%)</b>	88 (81)	43 (80)	45 (82)	0.4
<b>KDIGO stage at CRRT initiation, n(%)</b>				0.97
stage 1	7 (7)	3 (6)	4 (7)	
stage 2	22 (20)	11 (20)	11 (20)	
stage 3	81 (74)	40 (75)	41 (73)	

Values are presented as *n* (proportion) or median (interquartile range). Plus-minus values are means  $\pm$  SD.

†Sepsis was defined according to the American–European Consensus Conference criteria.

‡ SOFA score ranges from 0 to 24, with higher scores indicating more severe organ failure.

\*Considered for survival multivariable Cox regression model: (1) had *P* values <0.1 in the univariate analysis and (2) were clinically plausible.

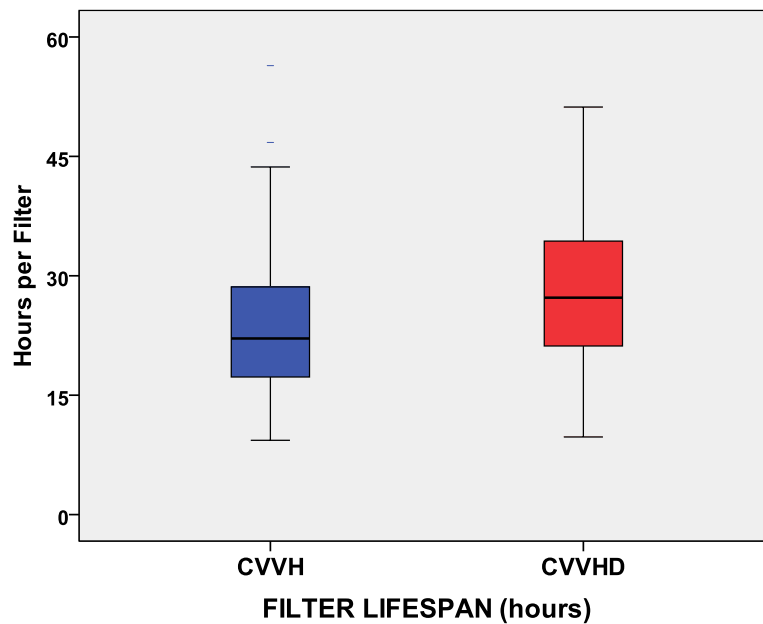
§ The Acute Physiology And Chronic Health Evaluation II score ranges from 0-71, with higher scores indicating more severe acute condition.

¶ The available urine in the 24 hours after ICU or prior to CRRT was summed and divided by the weight.

CVVH continuous venovenous hemofiltration, CVVHD continuous venovenous hemodialysis, BMI Body mass index, CKD chronic kidney disease, MAP mean arterial pressure, SOFA Sequential Organ Failure Assessment, APACHE II Acute Physiology And Chronic Health Evaluation II score, BUN blood urea nitrogen, UO urinary output, ICU intensive care unit, KDIGO Kidney Disease Improving Global Outcomes.

## Study outcomes

Patients randomized to CVVHD received a median of 5 days (IQR 3-8) of therapy compared to 5 days (IQR 3-7) ( $p=0.3$ ) in patients randomized to CVVH. Patients in the CVVHD group presented a mean EC patency of 29 $\pm$ 14 h compared to 25 $\pm$ 10 h ( $p=0.09$ ) in the CVVH group (**Fig 3.2**).



**Figure 3.2.** Filter patency (in hours) in patients who were more than 24 h on CRRT

Patients assigned to CVVHD plus AN69ST150 presented a trend to a higher patency ( $29 \pm 14$  h) respect to those assigned to CVVH plus AN69ST150 ( $25 \pm 10$  h;  $p < 0.09$ ). AN69ST150, adsorption capacity membrane; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis.

At baseline (CRRT initiation), 23% patients in the CVVHD group received heparin (circuit anticoagulation with no protamine administration) compared to 30% of the patients in the CVVH group ( $p = 0.4$ ). Patients in the CVVHD group received heparin for a mean duration of  $130 \pm 65$  h compared to  $94 \pm 70$  h in the CVVH group ( $p = 0.5$ ). No differences in electrolyte disorders, thrombocytopenia, transfusion requirements or other dialytrauma events were observed between CVVHD and CVVH. All these results are represented in **Table 3.3**.



**Table 3.3.** Outcomes according to study group

	All (n=110)	CVVH (n=54)	CVVHD (n=56)	<i>p</i> value
<b>Survival <i>n</i>(%)</b>				
28-day survival	59 (53.6)	25 (46.3)	34 (60.7)	0.19
90-day survival	54 (49.1)	23 (42.6)	31 (55.4)	0.25
Overall survival	49 (44.5)	21 (38.9)	28 (50.0)	0.33
<b>ICU LOS</b>	17 ± 14	17 ± 14	17 ± 15	0.98
<b>Hospital LOS</b>	37 ± 29	42 ± 36	34 ± 23	0.3
<b>MV (days)</b>	11 ± 11	12 ± 11	9 ± 11	0.4
<b>Vasopressors (days)</b>	4.4 ± 5	4.7 ± 5	4.1 ± 5	0.7
<b>Days on CRRT</b>	5 (3-8)	5 (3-7)	5 (3-8)	0.3
<b>EC consumed</b>	5.8 ± 4	5.7 ± 4	5.9 ± 4	0.9
<b>Reason for filter change, <i>n</i> (%)</b>				0.9
Protocol (24h and 48h)	162 (28)	78 (28)	88 (29)	
Clotting	405 (69)	197 (70)	204 (68)	
Other reasons	18 (3)	8 (2)	10 (3)	
<b>EC lifespan (hours)</b>	27 ± 12	25 ± 10	29 ± 14	0.09
≤ 72 h of CRRT	20 ± 5	19 ± 5	20 ± 5	0.25
>72 h	30 ± 29	26 ± 19	34 ± 34	0.26
<b>Heparin at CRRT initiation (<i>n</i>=98), <i>n</i>(%)</b>	29 (26)	16 (30)	13 (23)	0.4
<b>Heparin (hours in heparin during CRRT)</b>	98 ± 67	94 ± 70	130 ± 65	0.5
<b>Dialytrauma (<i>n</i>=98)*</b>				
RBC packages	2.8 ± 2.8	2.4 ± 2	3.1 ± 3	0.3
Hypothermia <sup>Δ</sup>	57 (58)	28 (57)	29 (59)	1
Thrombocytopenia (<103/μL)	67 (68)	31 (63)	36 (74)	0.4
Hypokalemia (<3.3 mmol/L)	16 (16)	6 (12)	10 (20)	0.4
Hypophosphatemia (<0.7mmol/L)	58 (59)	26 (53)	32 (65)	0.3
<b>Total urine output during CRRT (L)</b>	3.0 ± 4.0	2.9 ± 3.8	3.0 ± 4.3	0.9
<b>Negative fluid balance on CRRT (L)**</b>	5.5 ± 6.6	4.6 ± 6.1	6.5 ± 7	0.2
<b>IHD after CRRT <i>n</i>(%)</b>	10 (10)	3 (6)	7 (14)	0.5
<b>RRT at hospital discharge <i>n</i>(%)</b>	4 (4)	0 (0)	4 (8)	0.13

Values are presented as *n* (proportion) or median (interquartile range). Plus-minus values are means ± SD.

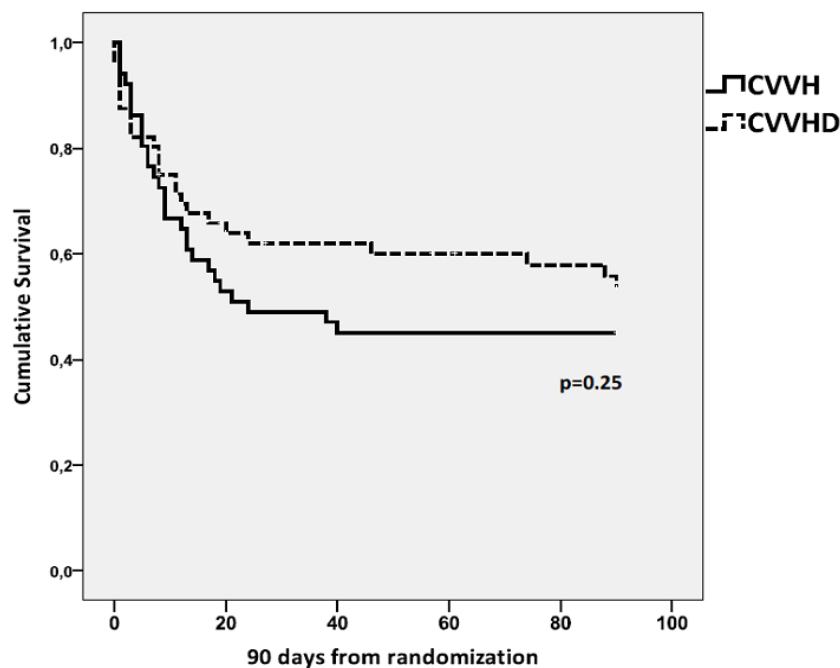
\* Dialytrauma was assessed during the first 72 hours of CRRT.

\*\*Considered for survival multivariable Cox regression model: (1) had *P* values <0.1 in the univariate analysis and (2) were clinically plausible.

Δ Hypothermia was defined as rectal temperature < 35.5°C.

CVVH denotes continuous venovenous hemofiltration, CVVHD continuous venovenous hemodialysis, ICU Intensive Care Unit, ft dosing interval, L Liters, LOS Length-of-stay, MV Mechanical Ventilation, CRRT Continuous renal replacement therapy, EC Extracorporeal circuit, RBC red blood cell, IHD Intermittent hemodialysis, RRT renal replacement therapy.

90-day survival outcome was assessed in all patients (intention-to-treat analysis) but other outcomes were only assessed in those patients who were on CRRT for more than 24 h (n=98). Overall 90-day survival was 55.4% in CVVHD group and 42.6% in CVVH group (risk difference 12.8 percentage points; 95% CI, -5.8 to 31.3; p=0.25). Kaplan-Meier curves obtained using the log-rank test for both groups were plotted and represented in **Figure 3.3**.



**Figure 3.3.** Survival curves at 90 days after randomization

Patients assigned to CVVHD plus AN69ST150 presented non-inferiority respect to those assigned to CVVH plus AN69ST150 (p= 0.25). AN69ST150, adsorption capacity membrane; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis.

No differences in adequate empirical antibiotic administration (88% in the CVVH group vs. 76% in the CVVHD group) were observed between groups. Cox PH model was used to determinate HRs for 90-day mortality and included all variables that were significant for 90-day mortality in the univariate analysis and that were clinically relevant (**Table 3.4**).

**Table 3.4.** Multivariate Cox regression analysis for 90-day mortality

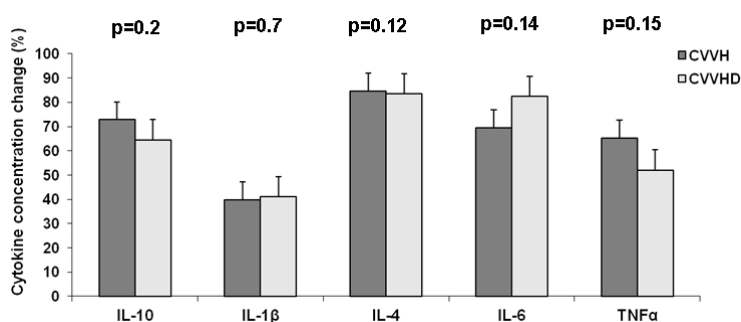
Variable	p value	aHR	95% CI
CVVHD group (vs CVVH)	0.517	0.811	0.431-1.526
Age (years)	0.017	1.041	1.007-1.076
APACHE II at CRRT †	0.068	1.039	0.997-1.082
Diabetes mellitus	0.068	0.468	0.207-1.059
Creatinine at CRRT initiation (umol/L)	0.279	0.999	0.997-1.001
Hospital to CRRT (days)	0.117	1.002	1.000-1.004
Total fluid balance during CRRT (L)	0.003	1.095	1.032-1.161
MAP at CRRT initiation (mmHg)	0.027	0.966	0.936-0.996

Conversion factors for units: serum creatinine in mg/dL to  $\mu\text{mol/L}$ ,  $\times 88.4$ ; serum blood urea nitrogen in mg/dL to mmol/L,  $\times 2.8$ .

† The Acute Physiology And Chronic Health Evaluation II score ranges from 0-71, with higher scores indicating more severe acute condition.

APACHE II denotes Acute Physiology And Chronic Health Evaluation II score, MAP mean arterial pressure, CVVH continuous venovenous hemofiltration, CVVHD continuous venovenous hemodialysis, CRRT Continuous renal replacement therapy.

No differences were observed between CVVHD and CVVH in cytokines plasmatic concentrations changes from baseline to 72 h after randomization. Cytokines plasmatic concentrations changes are represented in **Fig. 3.4**.

**Figure 3.4.** ( $\Delta$ )Total cytokine plasmatic variations (expressed in %) after CRRT initiation

$\Delta$ IL-10 ( $p=0.2$ ),  $\Delta$ IL-1 $\beta$  ( $p=0.7$ ),  $\Delta$ IL-4 ( $p=0.12$ ),  $\Delta$ IL-6 ( $p=0.14$ ),  $\Delta$ TNF- $\alpha$  ( $p=0.15$ ). AN69ST150, adsorption capacity membrane; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; IL-1 $\beta$ , interleukin-1 $\beta$ ; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; IL-4, interleukin-4; IL-6, interleukin-6; IL-10, interleukin-10.

Some solutes concentration differences (from baseline up to 24 h after CRRT initiation) were observed between groups. CVVHD had a trend towards faster clearance for low MW molecules (Urea and SCr) with respect to CVVH ( $p=0.073$  and  $p=0.063$ , respectively), whereas CVVH had a faster clearance of  $\beta$ 2-microglobulin with respect to CVVHD ( $p=0.005$ ). (**Table 3.5**).

**Table 3.5.** Solutes plasmatic concentration differences within first 24 h of CRRT

	TOTAL	CVVH	CVVHD	p value <sup>1</sup>
<b>ΔAlbumin (g/L)</b>				
Mean (SD)	4.3 (5.4)	5.5 (5.3)	3.4 (5.4)	0.0072
95% CI	(3.0 ; 5.6)	(3.6 ; 7.4)	(1.7 ; 5.1)	
Median (P25 ; P75)	3.4 (1.0 ; 8.0)	6.0 (3.0 ; 9.0)	2.0 (0.0 ; 7.0)	
(Min ; Max)	(-16.0 ; 16.0)	(-16.0 ; 14.0)	(-6.0 ; 16.0)	
Valid N	85	41	44	
<b>Δβ2-microglobulin (mg/L)</b>				
Mean (SD)	-3.9 (3.4)	-4.9 (3.6)	-3 (2.9)	<b>0.0051</b>
95% CI	(-4.7 ; -3.0)	(-6.3 ; -3.6)	(-4.0 ; -1.9)	
Median (P25 ; P75)	-3.0 (-5.4 ; -1.4)	-4.4 (-6.6 ; -2.7)	-2.3 (-4.3 ; -1.2)	
(Min ; Max)	(-17.9 ; 1.4)	(-17.9 ; -0.5)	(-14.0 ; 1.4)	
Valid N	85	41	44	
<b>ΔUrea (mmol/L)</b>				
Mean (SD)	-10.4 (8.8)	-8.4 (4.9)	-12.3 (11)	<b>0.0728</b>
95% CI	(-12.3 ; -8.5)	(-9.9 ; -6.8)	(-15.6 ; -8.9)	
Median (P25 ; P75)	-7.9 (-13.6 ; -4.8)	-7.3 (-11.0 ; -4.7)	-9.3 (-14.9 ; -5.9)	
(Min ; Max)	(-52.8 ; 5.3)	(-23.8 ; -2.3)	(-52.8 ; 5.3)	
Valid N	85	41	44	
<b>ΔCreatinine (umol/L)</b>				
Mean (SD)	-161.5 (128.7)	-133.1 (101.3)	-186.8 (145.4)	<b>0.0626</b>
95% CI	(-189.3 ; -133.8)	(-165.5 ; -100.7)	(-230.5 ; -143.1)	
Median (P25 ; P75)	-117.0 (-196.0 ; -85.0)	-105.5 (-173.0 ; -64.5)	-138.0 (-226.0 ; -99.0)	
(Min ; Max)	(-592.0 ; -10.0)	(-498.0 ; -10.0)	(-592.0 ; -12.0)	
Valid N	85	40	45	
<b>ΔUrates (umol/L)</b>				
Mean (SD)	-301.9 (138.05)	-282.8 (138.6)	-319 (137.2)	0.2562
95% CI	(-334.9 ; -269.0)	(-331.9 ; -233.6)	(-364.8 ; -273.3)	
Median (P25 ; P75)	-292.0 (-370.0 ; -191.0)	-286.0 (-352.0 ; -190.0)	-301.0 (-379.0 ; -232.0)	
(Min ; Max)	(-739.0 ; -48.0)	(-739.0 ; -48.0)	(-705.0 ; -68.0)	
Valid N	85	41	44	
<b>ΔGlucose (mmol/L)</b>				
Mean (SD)	-3 (6.6)	-2 (3.6)	-3.9 (8.4)	0.2919
95% CI	(-4.5 ; -1.6)	(-3.2 ; -0.9)	(-6.5 ; -1.3)	
Median (P25 ; P75)	-2.3 (-5.0 ; 0.0)	-2.2 (-5.0 ; 0.5)	-2.6 (-5.0 ; -0.9)	
(Min ; Max)	(-54.3 ; 6.0)	(-10.6 ; 6.0)	(-54.3 ; 4.7)	
Valid N	85	41	44	
<b>ΔSodium (mmol/L)</b>				
Mean (SD)	-3.1 (5.9)	-3.4 (5.5)	-2.8 (6.2)	0.3043

	TOTAL	CVVH	CVVHD	<i>p</i> value <sup>1</sup>
95% CI	(-4.4 ; -1.9)	(-5.1 ; -1.7)	(-4.7 ; -1.0)	
Median (P25 ; P75)	-3.0 (-6.0 ; 0.0)	-3.0 (-6.0 ; -1.0)	-2.0 (-5.0 ; 1.0)	
(Min ; Max)	(-20.0 ; 11.0)	(-16.0 ; 11.0)	(-20.0 ; 10.0)	
Valid N	86	40	46	
<b>ΔPotassium (mmol/L)</b>				
Mean (SD)	-0.2 (1)	-0.1 (1)	-0.3 (1)	0.5589
95% CI	(-0.4 ; -0.0)	(-0.5 ; 0.2)	(-0.6 ; 0.0)	
Median (P25 ; P75)	-0.1 (-0.9 ; 0.3)	-0.2 (-0.6 ; 0.4)	-0.0 (-1.0 ; 0.3)	
(Min ; Max)	(-3.1 ; 2.4)	(-3.1 ; 1.8)	(-2.3 ; 2.4)	
Valid N	86	40	46	
<b>ΔChloride (mmol/L)</b>				
Mean (SD)	-1.7 (6.1)	-1.8 (5.6)	-1.7 (6.6)	0.5522
95% CI	(-3.1 ; -0.4)	(-3.7 ; 0.0)	(-3.7 ; 0.3)	
Median (P25 ; P75)	-2.0 (-4.0 ; 1.0)	-2.0 (-5.0 ; 1.0)	-2.0 (-4.0 ; 2.0)	
(Min ; Max)	(-23.0 ; 19.0)	(-12.0 ; 19.0)	(-23.0 ; 13.0)	
Valid N	86	40	46	
<b>ΔPhosphate (mmol/L)</b>				
Mean (SD)	-21.5 (179.4)	-0.8 (0.6)	-37.7 (239.7)	0.8518
95% CI	(-62.8 ; 19.8)	(-1.0 ; -0.6)	(-112.4 ; 36.9)	
Median (P25 ; P75)	-0.7 (-1.3 ; -0.3)	-0.7 (-1.2 ; -0.5)	-0.7 (-1.3 ; -0.3)	
(Min ; Max)	(-1554.1 ; 1.0)	(-2.9 ; 0.1)	(-1554.1 ; 1.0)	
Valid N	85	41	44	
<b>ΔMagnesium (mmol/L)</b>				
Mean (SD)	-0.09 (0.3)	-0.10 (0.3)	-0.08 (0.3)	0.4177
95% CI	(-0.2 ; -0.0)	(-0.2 ; -0.0)	(-0.2 ; 0.0)	
Median (P25 ; P75)	-0.1 (-0.2 ; 0.1)	-0.1 (-0.2 ; 0.0)	-0.1 (-0.1 ; 0.1)	
(Min ; Max)	(-1.4 ; 0.5)	(-1.1 ; 0.3)	(-1.4 ; 0.5)	
Valid N	85	41	44	
<b>ΔCalcium (mmol/L)</b>				
Mean (SD)	0.4 (0.3)	0.4 (0.2)	0.4 (0.3)	0.3364
95% CI	(0.3 ; 0.5)	(0.3 ; 0.5)	(0.3 ; 0.5)	
Median (P25 ; P75)	0.4 (0.3 ; 0.6)	0.4 (0.3 ; 0.5)	0.4 (0.3 ; 0.6)	
(Min ; Max)	(-0.5 ; 1.0)	(-0.4 ; 0.8)	(-0.5 ; 1.0)	
Valid N	85	41	44	

<sup>1</sup> Student T or Mann-Whitney U test

No hemodynamic and respiratory variations were observed within the first 72 h on CRRT between both groups (**Tables 3.6-3.7**).

**Table 3.6.** Hemodynamic response within the first 72 h of CRRT

	TOTAL	CVVH	CVVHD	p value <sup>1</sup>
<b>ΔSI</b>				
Mean (SD)	0.2 (0.3)	0.2 (0.3)	0.2 (0.3)	0.9228
95% CI	(0.1 ; 0.3)	(0.1 ; 0.3)	(0.1 ; 0.3)	
Median (P25 ; P75)	0.2 (0.0 ; 0.4)	0.2 (0.0 ; 0.4)	0.1 (-0.0 ; 0.5)	
(Min ; Max)	(-1.0 ; 1.1)	(-1.0 ; 0.7)	(-0.7 ; 1.1)	
Valid N	90	43	47	
<b>Cumulative SI</b>				
Mean (SD)	2.4 (0.8)	2.5 (1)	2.3 (0.6)	0.7896
95% CI	(2.2 ; 2.6)	(2.2 ; 2.8)	(2.2 ; 2.5)	
Median (P25 ; P75)	2.2 (1.9 ; 2.7)	2.2 (1.8 ; 2.9)	2.2 (1.9 ; 2.7)	
(Min ; Max)	(1.3 ; 6.9)	(1.3 ; 6.9)	(1.4 ; 4.3)	
Valid N	89	43	46	
<b>AUC SI</b>				
Mean (SD)	60.1 (19.5)	61.4 (23.1)	58.9 (15.5)	0.8663
95% CI	(56.0 ; 64.2)	(54.3 ; 68.5)	(54.4 ; 63.6)	
Median (P25 ; P75)	56.2 (49.5 ; 64.6)	55.0 (49.8 ; 68.3)	58.1 (46.7 ; 63.5)	
(Min ; Max)	(33.1 ; 167.4)	(33.1 ; 167.4)	(33.8 ; 111.0)	
Valid N	89	43	46	
<b>ΔNE</b>				
Mean (SD)	-0.28 (0.56)	-0.23 (0.28)	-0.33 (0.73)	0.3403
95% CI	(-0.4 ; -0.2)	(-0.3 ; -0.1)	(-0.5 ; -0.1)	
Median (P25 ; P75)	-0.2 (-0.4 ; -0.0)	-0.2 (-0.4 ; -0.1)	-0.1 (-0.4 ; 0.0)	
(Min ; Max)	(-4.3 ; 0.7)	(-0.8 ; 0.7)	(-4.3 ; 0.5)	
Valid N	89	42	47	
<b>Cumulative NE</b>				
Mean (SD)	0.56 (0.68)	0.53 (0.50)	0.58 (0.81)	0.3618
95% CI	(0.4 ; 0.7)	(0.4 ; 0.7)	(0.3 ; 0.8)	
Median (P25 ; P75)	0.4 (0.1 ; 0.7)	0.4 (0.1 ; 0.8)	0.3 (0.0 ; 0.7)	
(Min ; Max)	(0.0 ; 3.2)	(0.0 ; 2.1)	(0.0 ; 3.2)	
Valid N	89	42	47	
<b>AUC NE</b>				
Mean (SD)	16.80 (17.86)	15.58 (11.99)	17.88 (21.89)	0.4544
95% CI	(13.0 ; 20.6)	(11.8 ; 19.3)	(11.5 ; 24.3)	
Median (P25 ; P75)	13.3 (3.5 ; 21.3)	14.2 (5.5 ; 20.3)	9.5 (1.3 ; 23.8)	
(Min ; Max)	(0.0 ; 91.7)	(0.0 ; 48.6)	(0.0 ; 91.7)	
Valid N	89	42	47	
<b>NE days *</b>				
Mean (SD)	4.1 (4.8)	3.6 (4.2)	4.5 (5.3)	0.7417

	TOTAL	CVVH	CVVHD	<i>p</i> value <sup>1</sup>
95% CI	(2.6 ; 5.6)	(1.5 ; 5.7)	(2.2 ; 6.8)	
Median (P25 ; P75)	2.0 (1.0 ; 6.0)	2.0 (1.0 ; 5.0)	3.5 (1.0 ; 6.0)	
(Min ; Max)	(0.0 ; 21.0)	(0.0 ; 17.0)	(0.0 ; 21.0)	
Valid N	40	18	22	

*Only for survivors*

**1 Student T or Mann-Whitney U test**

**Hemodynamic response** was assessed considering the following formulas for shock index (SI) and Norepinephrine (NA) dose (mcg/kg/min):

$$\Delta SI = ([HeartRate0h]/[PAS0h]) - ([h72_HeartRate]/[h72_PAS])$$

$$SI = ([h24_HeartRate]/[h24_PAS]) + ([h48_HeartRate]/[h48_PAS]) + ([h72_HeartRate]/[h72_PAS])$$

$$\Delta NE = [NE_{0h}] - [h72_{NE}]$$

$$\text{Cumulative NE} = [h24_{NE}] + [h48_{NE}] + [h72_{NE}]$$

$$\text{NE days} = [NE_{EndDate}] - [dateStartNE]$$

Where:

PAS= Systolic pressure (mmHg)

NE\_EndDate= Last day of Norepinephrine requirements

dateStartNE= First day on NE

0h =At CRRT initiation

h24 = at 24 h on CRRT

h48 = at 48 h on CRRT

**Table 3.7.** Respiratory response within the first 72 h of CRRT

	TOTAL	CVVH	CVVHD	p <sup>1</sup>
<b>Δ PaO<sub>2</sub>/FiO<sub>2</sub></b>				
Mean (SD)	29 (171.8)	12.2 (236.5)	43.5 (93.1)	0.9
95% CI	(-15.7 ; 74.6)	(-83.3 ; 107.7)	(9.9 ; 77.0)	
Median (P25 ; P75)	39.9 (-9.3 ; 119.3)	35.0 (-3.3 ; 119.5)	44.8 (-50.4 ; 114.2)	
(Min ; Max)	(-1012.5 ; 256.7)	(-1012.5 ; 256.7)	(-129.5 ; 212.0)	
Valid N	58	26	32	
<b>Cumulative PaO<sub>2</sub>/FiO<sub>2</sub></b>				
Mean (SD)	709.8 (239.8)	691.1 (231.4)	726.1 (249.5)	0.7
95% CI	(647.8 ; 771.7)	(601.4 ; 780.8)	(636.2 ; 816.1)	
Median (P25 ; P75)	701.1 (528.6 ; 872.6)	696.9 (537.0 ; 853.3)	728.5 (510.6 ; 894.4)	
(Min ; Max)	(214.0 ; 1200.0)	(214.0 ; 1133.3)	(308.3 ; 1200.0)	
Valid N	60	28	32	
<b>AUC PaO<sub>2</sub>/FiO<sub>2</sub></b>				
Mean (SD)	16644.8 (5804.9)	16084.5 (5619.4)	17089.2 (6008.6)	0.8
95% CI	(15028.7 ; 18260.9)	(13654.5 ; 18514.5)	(14803.6 ; 19374.7)	
Median (P25 ; P75)	16734.0 (12179.5 ; 20317.7)	17442.3 (12231.0 ; 20280.0)	16578.0 (12128.0 ; 20355.4)	
(Min ; Max)	(4752.0 ; 29180.0)	(4752.0 ; 24120.0)	(6816.0 ; 29180.0)	
Valid N	52	23	29	
<b>MV (days) *</b>				
Mean (SD)	11.2 (11.6)	12.8 (11.5)	10 (11.9)	0.2
95% CI	(7.2 ; 15.2)	(6.4 ; 19.2)	(4.4 ; 15.5)	
Median (P25 ; P75)	6.0 (4.0 ; 11.0)	9.0 (5.0 ; 24.0)	6.0 (3.5 ; 9.5)	
(Min ; Max)	(-1.0 ; 39.0)	(1.0 ; 38.0)	(-1.0 ; 39.0)	
Valid N	35	15	20	

\* Only for survivors

1 Student T or Mann-Whitney U test

Respiratory response was assessed by PaO<sub>2</sub>/FiO<sub>2</sub> changes and mechanical ventilation (MV) days, considering the following formulas:

$$\Delta \text{PaO}_2/\text{FiO}_2 = ([\text{h72\_PaO}_2]/[\text{h72\_FiO}_2]) - ([\text{h0\_PaO}_2]/[\text{h0\_FiO}_2])$$

$$\text{Cumulative PaO}_2/\text{FiO}_2 = ([\text{h24\_PaO}_2]/[\text{h24\_FiO}_2]) + ([\text{h48\_PaO}_2]/[\text{h48\_FiO}_2]) + ([\text{h72\_PaO}_2]/[\text{h72\_FiO}_2])$$

$$\text{MV days} = [\text{DateEndVM}] - [\text{DateStartMV}] \text{ (survivors)}$$

Units: PaO<sub>2</sub> (mmHg) FiO<sub>2</sub> (0.21 to 1)

No differences in mean days on MV were observed between CVVHD and CVVH groups (9±11 vs. 12±11 days; p=0.4) nor in mean days on vasopressors (4.1±5 vs. 4.7±5 days; p=0.7), respectively. No differences were observed between CVVHD and CVVH groups in mean ICU LOS 17±14 days vs. 17±15 days (p= 0.9), nor in mean hospital LOS 34±23 days vs. 42±36 days (p=0.3), respectively (**Table 3.3**). No differences were observed between CVVHD and CVVH groups in total UO (L) during CRRT (3.0±4.3 L



vs.  $2.9\pm 3.8$  L;  $p=0.9$ ) nor in total negative fluid balance during CRRT ( $6.5\pm 7$  L vs.  $4.6\pm 6.1$  L;  $p=0.2$ ), respectively.

## 6.4. Discussion Study 3

### 6.4.1. Highlights

The present study is the first RCT to demonstrate that CVVHD with an adsorption capacity membrane is as safe and efficient as CVVH in critically ill SA-AKI patients requiring CRRT. Positive effects related to the addition of a diffusion dose to CRRT had already been described but no RCT had previously proved that CVVHD is at least as good as CVVH in SA-AKI patients.

### 6.4.2. Methods

We included a study sample of critically ill patients with severe disease state backgrounds, a wide range of comorbidities and whose main sepsis source was intraabdominal. Nevertheless, study patients accurately represent the regular case-mix population admitted to health care institutions located in our geographic area.<sup>342</sup> Our study was focused on the management of critically ill patients with sepsis, contrary to other studies that have included a mixed population of patients.<sup>375</sup> In around 80% of patients, an appropriate empirical antimicrobial coverage was documented, according to definitive microbiological isolations. No significant differences were observed regarding distribution of this variable between groups.

Noteworthy, patients included in the present study received one of two CVVH- or CVVHD-only modalities in order to better understand the clinical impact each one has on patient outcomes, albeit per-protocol CRRT setting prescriptions were based on the current best practice recommendations at time of patient allocation. A previous study aimed to evaluate the feasibility of comparing the two modes in a randomized trial, the “Optimal Mode of clearance in critically ill patients with Acute Kidney Injury” (OMAKI) study,<sup>375</sup> concluded that there was a non-significant trend towards decreasing vasopressor requirements early after the initiation of RRT in patients who received CVVH. A meta-analysis and systematic review conducted by Friedrich et al.,<sup>218</sup> which included the OMAKI study, did not suggest better clinical outcomes from CVVH, although pooled studies were conducted in different historic periods not being

comparable with current management strategies (regarding dose, timing and technological development of depurative devices).

#### 6.4.3. EC patency

In our study, patients assigned to CVVHD had a trend towards longer EC patency with respect to CVVH, although this difference was not statistically significant. Longer EC viability was not related to the use of heparin as no differences were observed between groups, neither with regards to the percentage of patients in whom heparin was used nor the mean number of hours that heparin was administered. Previous studies had reported longer filter life with the use of diffusive modalities (up to 33% higher than convective modalities), subsequently saving economic costs while decreasing adverse effects related to convective clearance and blood transfusions.<sup>376</sup> Ricci et al.<sup>215</sup> demonstrated a significantly longer median filter lifespan during CVVHD compared to CVVH in a prospective crossover study in a small cohort of critically ill patients. Davies et al.<sup>376</sup> reported a significant increase in circuit life in favor of CVVHDF compared with CVVH. OMAKI trial<sup>375</sup> showed no differences in unscheduled circuit changes per day of therapy between both groups,  $0.2 \pm 0.3$  changes in the CVVH group vs.  $0.2 \pm 0.2$  changes in the CVVHD group ( $p=0.36$ ). Friedrich et al.<sup>218</sup> reported that hemofiltration appeared to shorten time to filter failure. Brain et al.<sup>246</sup> recently published another meta-analysis concerning non anti-coagulant factors associated with filter life in CRRT in which CVVHDF was associated with a 44% lower filter failure rate compared to CVVH.

Differences in EC patency may have been even stronger if our protocol had not included a protocolized filter exchange every 24 h during the first 72 h to ensure adsorption capacity. The adsorption capacity of the filter employed in our study could potentially be saturated after 24 h or even earlier according to previous reports.<sup>193</sup> De Vriese et al. performed AN69-CVVH in 15 patients with SA-AKI and reported a rapid decrease in blood cytokine levels. However, cytokine levels, once reduced, subsequently increased again during CVVH and the AN69 hemofilter had to be replaced once every 3 h. Adsorption to the AN69 membrane appeared to be the main clearance mechanism, being most pronounced immediately after installation of a new membrane and decreasing steadily thereafter, indicating rapid saturation of the membrane.

#### 6.4.4. Diallytrauma

In our study at a fixed dose of 30 mL/kg/h (to achieve a theoretical dose of 20-25 mL/kg/h) during the first 72 h, no differences in diallytrauma events were observed between CVVHD and CVVH. Thrombocytopenia ( $<100 \times 10^3/\mu\text{L}$  after CRRT initiation) was the most common complication (68%), followed by hypophosphatemia ( $<0.7\text{mmol/L}$ ) (59%) and hypothermia (rectal temperature  $<35.5^\circ\text{C}$ ) (58%). Adverse effects related to CRRT modality (diallytrauma) had been previously described in large trials evaluating dose therapy, most of them employing high percentages of convection.<sup>16,15</sup>

ATN trial<sup>15</sup> reported that hypophosphatemia occurred in 17.6 % of patients in the intensive group (CVVHDF 36 mL/kg/h) compared to 10% in the less intensive group (CVVHDF 22 mL/kg/h) ( $p=0.001$ ), and hypokalemia developed in 7.5% and 4.5%, respectively ( $p=0.03$ ). In this last trial definitions of hypophosphatemia and hypokalemia were not described. RENAL trial<sup>16</sup> reported higher rates of diallytrauma (again electrolytic disorders were not defined), with hypophosphatemia appearing in 65% of the patients in the higher intensity CRRT group (CVVHDF 33 mL/kg/h) compared to 54.0% of patients assigned to the lower intensity CRRT group (CVVHDF 22 mL/kg/h) ( $p < 0.0001$ ), and hypokalemia in 23.4% and 24.4% , respectively ( $p=0.34$ ).

The rates of diallytrauma in our study are very high, yet similar to those reported in previous studies.<sup>377,378</sup> Despite these high rates of complications or adverse events, in our study, no differences in diallytrauma were observed between CVVHD and CVVH. As in our study, in the OMAKI trial<sup>375</sup> there were no differences in the RBC transfusion rate between CVVH and CVVHD. However, in our study there was a trend to a longer EC patency with the use of CVVHD but this was not followed by a lower RBC transfusion rate.

#### 6.4.5. Survival

We need to underscore that this study was conceived as an exploratory, proof of concept trial. The sample size was too small to detect significant differences in mortality between both arms. However, although our study was underpowered for detecting small differences between both interventions, it suggests that CVVHD could present survival differences in patients with SA-AKI, when compared to CVVH therapy. This

hypothetical survival advantage associated with the use of CVVHD could be explained by the faster solute removal rate observed in low MW molecules and therefore faster acidosis correction although no strong conclusions can be made beyond this hypothesis.

We have calculated that a sample size of 488 patients (244 per group) would be needed in order to demonstrate this hypothesis, assuming a difference of 13% in the survival rate between trial arms (55% vs. 42%), with an alpha of 0.05 and 80% of statistical power. In the OMAKI trial,<sup>375</sup> mortality (54% CVVH; 55% CVVHD) and dialysis dependence in survivors (24% CVVH; 19% CVVHD) at 60 days were similar. Friedrich et al.<sup>218</sup> found no effect of hemofiltration on mortality or other clinical outcomes (RRT dependence in survivors, vasopressor use, organ dysfunction) compared to hemodialysis.

#### 6.4.6. Cytokines circulatory variations

We must emphasize before analyzing results that cytokines plasmatic concentrations are correlated with prognosis in septic patients<sup>379</sup> and this includes also patients with SA-AKI requiring RRT.<sup>380,381</sup> Observational studies demonstrate that those patients whom present higher plasmatic levels of cytokines do the worst no matter how they are resuscitated in terms of sepsis management.<sup>379</sup> This correlation is not only observed with cytokines levels at baseline but also with cytokines concentrations after days of follow-up, thus those patients whom still present high cytokines levels after several days have worse prognosis respect to those in which cytokines levels have decreased.<sup>382,380</sup> However, whether RRT can be effectively employed to remove cytokines and whether this intervention has a clinical impact in SA-AKI patients outcome has still not been demonstrated.<sup>380</sup>

To our knowledge, our trial is the first study that demonstrates an equal immunomodulatory capacity (or at least cytokines circulatory variations)<sup>374</sup> of CVVHD and CVVH in SA-AKI patients. A small randomized crossover study with 13 patients with SIRS and AKI receiving CRRT, found that CVVH was associated with a 13% decrease in plasma TNF- $\alpha$  concentrations compared with a 23% increase while on CVVHD ( $p < 0.05$ ).<sup>186</sup> Friedrich et al.<sup>218</sup> from crossover RCTs suggested that hemofiltration increased clearance of medium to larger MW molecules, including inflammatory cytokines, compared to hemodialysis, although almost none of the studies

measured changes in serum concentrations. This higher inflammatory mediator clearance with CVVH has been systematically encountered in the majority of studies.<sup>383</sup>

HICORES study<sup>373</sup> was a prospective, randomized, controlled, open-label trial performed in critically ill patients with SA-AKI receiving CVVHDF. Conventional (40 mL/kg/h) and high (80 mL/kg/h) doses of CVVHDF for the duration of CRRT were evaluated. High-dose CVVHDF, but not the conventional dose, significantly reduced IL-6, IL-8 and IL-10 levels. Despite this effect in cytokine levels, there were no differences in 28-day mortality between groups. In many studies although cytokine removal rate was achieved, plasmatic levels of cytokines remained unaltered.<sup>192,195</sup> There are also very few studies that have been able to correlate reduction of cytokines with CRRT and better outcomes. Quinto et al.<sup>384</sup> in a small observational study in 64 critically ill patients requiring CVVHDF determined at the beginning of CVVHDF and after 24 h (outlet) the plasmatic levels of C3a, TNF- $\alpha$ , IL-10, IL-6, and IL-1 $\beta$ . According to the inter-tertile range (ITR) of TNF- $\alpha$  clearance (ITR1 (<0.54); ITR2 (0.54–2.93); ITR3 (>2.93)) authors found that those patients with higher TNF- $\alpha$  removal by RRT (ITR3) had a better survival. Furthermore, in some studies the improvement in organ function and survival obtained with the use of the extracorporeal BP was not necessarily related with cytokine removal. Peng et al.<sup>385</sup> treated rats that had a cecal ligation followed by puncture (a standard model of sepsis) with a modest dose of extracorporeal BP that did not result in acute changes in cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-10). The overall survival to 7 days, however, was significantly better in animals that received extracorporeal BP compared to those with a sham procedure. Thus, the effects of this procedure on organ function and survival do not appear to be due solely to immediate changes in the measured circulating cytokines.

It is important to point out that contrary to our results very few studies have reported a significative cytokine removal with the use of diffusive principles (CVVHD).<sup>199</sup> Messer et al.<sup>225</sup> in an animal model using a 2 x 2 factorial design, examined the impact of prescription (postdilution CVVH vs. CVVHD) and membrane area (0.4 m<sup>2</sup> vs. 2.0 m<sup>2</sup>) on blood-side and dialysate-side middle-molecule clearance. In large dialysers, convective and diffusive prescriptions resulted in nearly identical middle molecule clearance from 10 to 100 kDa MW. In the smaller dialyser, middle molecule clearance was higher when a diffusive therapy (CVVHD) was prescribed vs. a convective therapy (postdilution CVVH).

#### 6.4.7. Solutes concentrations

Similar solutes circulatory changes were observed with both techniques although CVVHD had a bigger circulatory variation of low MW molecules with respect to CVVH during the first 24 h. This finding supports the use of CVVHD when emergent electrolyte or acid base disturbances are present in hemodynamically unstable patients. Ricci et al.<sup>215</sup> reported that median urea and SCr TWA clearances were not significantly different during CVVH and CVVHD. The same as in our study, median  $\beta$ 2microglobulin TWA clearance was higher during convective than diffusive therapy. Friedrich et al.<sup>218</sup> reported in their meta-analysis that few molecules were examined in more than one study, and analyses included few patients. In general, small molecule clearance (for example, urea, phosphate and SCr) was similar between hemofiltration and hemodialysis, whereas hemofiltration achieved higher clearance of larger molecules (up to around 20 kDa).

In our study there was a significative bigger circulatory variation of  $\beta$ 2microglobulin with CVVH compared to CVVHD (**Table 3.5**) which is concordant with the elimination of middle MW molecules with convection. However, it is interesting to point out that no differences were found between CVVH and CVVHD in the circulatory variations of other theoretical medium MW molecules such as cytokines. These last molecules could have more facility to get adsorpted inside the membrane bulk than  $\beta$ 2microglobulin although this is only a possible explanation that needs to be proved with further analysis.

#### 6.4.8. Hemodynamics

Although CVVH had been previously reported as the most adequate modality for severe shock patients, in our study, in which patients included presented a a high rate of shock, no differences were observed between both groups in all hemodynamic variables within the first 72 h. OMAKI study<sup>375</sup> reported that SOFA tended to decline more over the first week in CVVH recipients driven by a reduction in vasopressor requirements compared to CVVHD recipients. Previous studies<sup>187,206</sup> had reported hemodynamic improvements with the use of CVVH in SA-AKI patients specially with high convective doses. This clinical response in septic shock patients in whom norepinephrine doses seemed to decrease when CVVH was initiated gave during many years “reasons” to recommend

and extend the use of HVHF (CVVH >35 mL/kg/h) in hemodynamically unstable septic patients. The publication of the two big RCT “dose trials” (ATN and RENAL),<sup>15,16</sup> reported no survival benefits with the use of high intensity RRT. A post-hoc analysis<sup>386</sup> from the RENAL study in a very small cohort of acidotic patients (115 patients with metabolic acidosis) treated with lower intensity (LI) or higher intensity (HI) CRRT, showed a greater decrease in norepinephrine dose in the HI group.

The majority of these studies reporting hemodynamic improvement during CVVH are not able to correlate hemodynamic changes with cytokine removal. Some studies indicate that the disparity in vascular reactivity between ultrafiltration plus hemodialysis and hemofiltration is primarily related to differences in the extracorporeal blood temperature. Thus, whether this hemodynamic improvement could be due to the effect of CRRT in body temperature is still a matter of controversy. Rokyta et al.<sup>387</sup> reported that CVVH-induced cooling was associated with significant decreases in heart rate, cardiac output, systemic oxygen delivery and consumption. Pestaña et al.<sup>388</sup> reported an association between temperature and hemodynamic changes and the outcome of 19 consecutive hyperthermic septic shock patients with MODS treated with CVVH.

#### 6.4.9. Respiratory changes

In our study, in which a high rate of patients on MV were included, no differences were observed between both groups in all respiratory variables within the first 72 h. Sánchez et al.<sup>187</sup> reported a significant improvement in PaO<sub>2</sub>/FiO<sub>2</sub> in the intervention group (CVVH) in thirty consecutive critically ill, mechanically ventilated, trauma patients with MODS. Piccini et al.<sup>389</sup> reported PaO<sub>2</sub>/FiO<sub>2</sub> improvement and successful weaning from the ventilator with the use of early isovolaemic haemofiltration (EIHf) in patients with septic shock.

#### 6.4.10. Limitations

Limitations of our study are related to its methodology which was conceived as an exploratory, proof of concept trial. Cytokines (only 5 specific cytokines were quantified from the 39 identified so far) were only measured in 40 randomized patients who survived at least 72 h from randomization which means that all presumptions related with cytokine RR should be cautiously interpreted. Furthermore, it is important to point

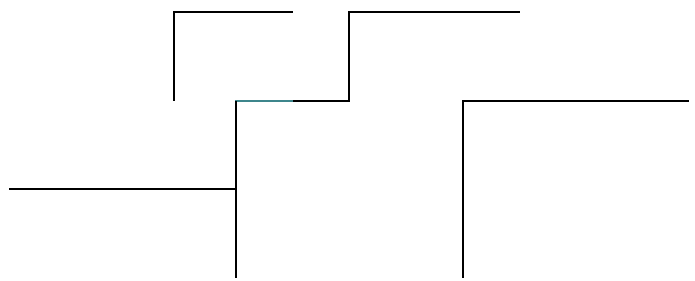
out that bloodstream cytokines "typical" course in SA-AKI is far from being elucidated and that this could be significantly different from one patient to another.

We are also aware of the increasing use of CVVHDF<sup>342</sup> among critically ill patients, which offers advantages related to both convection and diffusion properties. In spite of this latter issue, we think that this study will contribute to increase the diffusive dose when CVVHDF is employed. Furthermore, the use of RCA offers better EC patency than heparin<sup>234</sup> and any observed benefit in filter patency duration that may be attributed to CVVHD should be interpreted cautiously since the anticoagulation options in this trial were limited to heparin. However, there is still a significant percentage of patients with SA-AKI requiring CRRT that present contraindications for the use of RCA.<sup>27</sup>

In conclusion, in patients with SA-AKI, the use of CVVHD associated to a membrane with adsorptive properties presented a trend to an increase in EC patency respect to CVVH. No differences were observed in terms of dialytrauma, survival, cytokines plasmatic concentrations, solutes variations and hemodynamic-respiratory responses. Further multicentre trials with a larger sample size are needed to confirm the hypothesis that CVVHD could be a useful CRRT modality in SA-AKI patients.







*Summary discussion*

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## 7. Summary discussion

SA-AKI is clearly related with clinical outcomes in critically ill septic patients.<sup>3,266</sup> An important percentage of patients with sepsis who are admitted to ICU already present SA-AKI at the time when sepsis is identified but another important group of patients will develop SA-AKI after sepsis management is initiated.<sup>155</sup> Furthermore, even in those septic patients whom initially present with SA-AKI, a worsening of renal function is frequently observed during the following days or even weeks.<sup>3,155</sup> In our study, independently from the renal function at the moment of sepsis identification, the worsening of SA-AKI stage or the appearance of SA-AKI during the following 7 days (from sepsis onset) was clearly associated with a worst outcome in terms of survival (90-day survival). Noticeably, despite restricting the criteria for SA-AKI inclusion (those patients who did not present worsening of SA-AKI stage after sepsis onset were not classified as SA-AKI), the incidence of SA-AKI was very high in this single center cohort of critically ill patients with sepsis although similar to other previous reports.<sup>266,42,3</sup>

In our initial study an important percentage of septic patients presented hypotension and this was clearly associated with SA-AKI incidence as well as the presence of an abdominal etiology which is a well-known risk factor for SA-AKI development.<sup>2,294</sup> It is important to point out that the requirements of RRT in those patients who developed SA-AKI was as high as 37% which translates the severity and importance of SA-AKI appearance in critically ill patients with sepsis.<sup>391</sup> Along these lines, those septic patients with hypotension are clearly in risk of presenting severe forms of SA-AKI<sup>97</sup> frequently requiring CRRT<sup>28,45,354</sup> as their hemodynamic situation will not permit other forms of RRT although well trained teams can achieve good results with the use of SLED<sup>392</sup> or even IHD in patients with septic shock as the IDEAL-ICU trial recently reported.<sup>18</sup>

SSC recommendations or tasks<sup>289</sup> were evaluated in our single center critically ill population in order to measure the effect in SA-AKI incidence. Although the accomplishment of the SSC tasks in our study population was globally low, contrary to other studies<sup>1</sup> we did not observe a decrease of SA-AKI incidence in those patients who had high levels of accomplishment. When SSC tasks were separately analyzed, early

antibiotic administration was not related with a lower incidence of SA-AKI either. In those patients who were hypotensive, EGDT measures achievement did not decrease SA-AKI incidence. Only some of the recommended management tasks seemed to diminish SA-AKI occurrence specially glycemic control and protective ventilation. Thus, in our study recommended measures for sepsis treatment seem to not prevent from SA-AKI incidence which in critically ill patients is closely related to the presence of hypotension, sometimes vasopressor support, and therefore septic shock.<sup>97,293</sup> These patients with septic shock and SA-AKI have high requirements of RRT which most of the times is delivered as CRRT due to hemodynamically instability.<sup>342</sup> Mortality in this population of septic shock patients with SA-AKI requiring CRRT is high and clearly related to severity scores as part of MODS.<sup>47,1</sup>

In a two-center international observational study, we analyzed all those patients with SA-AKI whom required CRRT due to a septic shock condition within the first 24 h from CRRT initiation. A higher age, severity of illness, medical as opposed to surgical admission, a higher BUN at CRRT initiation, a decreased UO and SCr at CRRT initiation, and more days from hospital admission to CRRT initiation were all associated with worse survival.

No association between SA-AKI stage at CRRT initiation and 90-day mortality was observed, the same as the majority of previous studies reported.<sup>344,169</sup> SCr is a bad parameter to decide RRT initiation (timing) as most of the studies<sup>345,276,341</sup> including ours, found a higher mortality in those patients that were started on RRT with lower values of SCr traducing as previously mentioned FO and caquexia states as well as severe forms of disease (patients who are started earlier are sometimes sicker than the ones you can permit yourself decide a “wait and see” approach). However, we did observe a clear relation between BUN or UO, both at CRRT initiation, and mortality. Low UO and high BUN are clearly risk factors for mortality revealing once again that creatinine-based staging is a poor indicator of severity for patients started on RRT.<sup>164,168,169</sup> Both BUN and UO had already been described as severity markers in patients with AKI requiring RRT<sup>341,167</sup> although none of these studies were performed specifically in patients with septic shock and SA-AKI.

Initiation of CRRT should be based in immediate and emergent criteria which we all should know.<sup>26</sup> Whether earlier strategies of CRRT initiation (known as “timing”) could

have an impact in the outcome of patients with SA-AKI was evaluated in a subgroup of homogeneous patients with septic shock all of them presenting advanced SA-AKI stage 3 at ICU admission and initiated on CRRT within the first 5 days from ICU admission. Based on the previous identification of mortality risk factors, UO and time from ICU to CRRT were compared as timing criteria in order to evaluate differences in survival outcomes according to an early or delayed CRRT initiation strategy (timing). This was similar to previous observational studies<sup>167,160</sup> that had reported benefits in early strategies based on different parameters (especially BUN and time from ICU to CRRT) but once again, none of them had been performed in a homogeneous population of patients with the same SA-AKI stage at CRRT initiation. In our study, UO proved to be more useful when deciding CRRT initiation than a standard “clock time” from ICU admission variable. From these results, we could suggest that an “early strategy” in terms of CRRT initiation should probably be restricted to those patients with a decrease in UO and symptomatic FO despite the use of diuretics, but no strong conclusions can be extracted from our observational study as many of the necessary items (fluid balance, diuretic administration, and FO assessment) were missing. Our findings suggest that starting CRRT before low UO setting (in KDIGO stage 3 SA-AKI) could hypothetically prevent FO which is a well-known mortality predictor in patients with SA-AKI.<sup>242</sup> However, this hypothesis should be individually evaluated as each patient tolerance for FO depends on many factors such as cardiovascular function, capillary leak syndrome condition, and nutritional status among others.<sup>393,394,395,396</sup>

Although in our two-center international study mortality risk factors were identified, none of them were directly related to the technique, although some important items such as dose or fluid balance after CRRT initiation were missing. Data from other studies<sup>375</sup> and our own experience obtained during these years of testing and evaluating new extracorporeal devices suggests us that some modalities of RRT can be more efficient in terms of extracorporeal patency and less harmful in terms of adverse events (known as “dialytrauma”)<sup>173</sup> than others.

Convective strategies in SA-AKI patients have been extensively used, especially with CVVH and CVVHDF modalities with the objective of achieving some hypothetically immunomodulating effects that could potentially modify outcomes in patients with sepsis.<sup>200</sup> No clear benefits have been observed<sup>15,16</sup> with the use of convection besides the solutes and fluid removal achieved with other RRT as well. However, EC patency

can be decreased with the use of convection<sup>376,246</sup> especially in those patients where RCA cannot be performed.<sup>27,390</sup> This increase in filter clotting can lead to an increase in the number of dialytrauma events, especially blood transfusions and thrombocytopenia. On the other hand, the development of membranes with adsorption properties<sup>193</sup> could potentially allow to remove cytokines from circulation in patients with SA-AKI requiring CRRT without the use of convection.<sup>225</sup> Therefore, in critically ill patients with SA-AKI meeting CRRT initiation criteria the use of a diffusive strategy such as CVVHD associated to a membrane with adsorption properties could hypothetically lead to an increase in EC patency and less dialytrauma events. To demonstrate this hypothesis we designed and performed a two-center pilot randomized trial in critically ill patients with SA-AKI requiring CRRT.

During a 3-years study in critically ill patients with SA-AKI we compared the use of CVVHD associated to an adsorption capacity membrane with the use of CVVH associated to the same membrane. Patients were initiated on CRRT with a dose of 30 mL/Kg/h which was maintained at least during 3 days. Filters were changed at 24 h and 48 h in order to ensure de adsorption capacity. Similarly to previous reports,<sup>215</sup> we observed a trend to a longer EC patency with the use of CVVHD although this was not translated in a decrease in the number of dialytrauma events (probably due to our small study sample). Survival was evaluated because critically ill patients with SA-AKI requiring CRRT as previously commented are a high mortality risk group where different strategies concerning RRT have historically been tested. Although our pilot trial was underpowered for demonstrating survival differences, we did observe a trend for a better survival outcome with the use of CVVHD although these results need further confirmation with a larger study. This hypothetical survival advantage associated with the use of CVVHD could be explained by the faster solute removal observed in low MW molecules and therefore faster acidosis correction in the CVVHD group compared to the CVVH group.

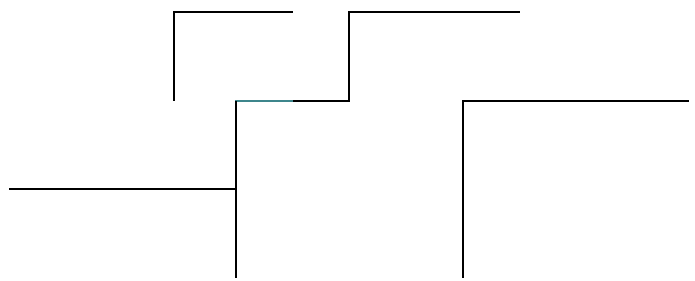
Cytokines concentrations were measured during the first 72 h and no differences were observed between both groups with the use of an adsorption capacity membrane. IL-1, IL-4, IL-6, IL-10, and TNF- $\alpha$  differences in plasmatic concentrations were determined respect to baseline concentrations (at CRRT initiation).<sup>374</sup> Like in previous studies no clear association could be established between cytokines variations and clinical outcomes<sup>373</sup> although these analysis are still under review as well as the adsorption

capacity of the membrane with each modality. However, the fact that no hemodynamic or respiratory differences were observed between both groups suggests that there are probably no differences either in the cytokine removal capacity between groups.

Based on all these previous findings we can conclude that SA-AKI incidence and mortality are high in critically ill patients with sepsis especially in those who present hypotension or septic shock. These last patients due to their severe condition often require CRRT which should be initiated only in advanced AKI stages with immediate initiation criteria together with the help of UO (low UO despite the use of diuretics probably reflects FO but this should be individualized). Finally, CRRT in SA-AKI patients when necessary should be encouraged to a preferential use of diffusive modalities (CVVHD) associated to adsorption capacity membranes which seem to improve EC patency with no clinical outcome differences when compared to convective modalities (CVVH).







*Conclusions*

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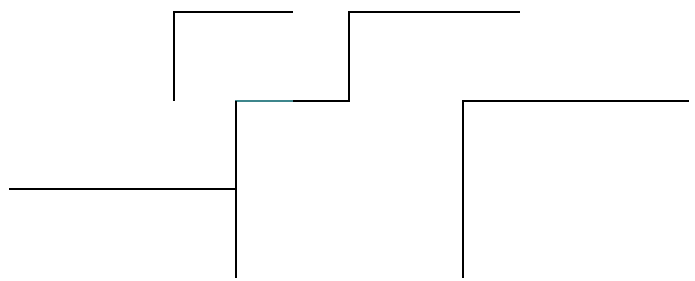


## 8. Conclusions

1. In a single center cohort of critically ill patients with sepsis, the incidence of SA-AKI within the first 7 days from sepsis onset is high and is associated with a higher 90-day mortality.
2. In a single center cohort of critically ill patients with sepsis the presence of hypotension and/or an abdominal etiology was clearly related with the appearance of SA-AKI within the first 7 days from sepsis onset. Septic patients with an abdominal etiology present a higher risk for SA-AKI development and special measures such as IAP monitoring should be promptly adopted.
3. In a single center cohort of critically ill patients with sepsis and a low SSC bundles accomplishment, none of the SSC recommendations seem to have a direct effect in preventing SA-AKI within the first 7 days from sepsis onset.
4. In an international bicenter cohort of critically ill patients with septic shock and SA-AKI, all of them receiving CRRT, 90-day mortality is higher as age, severity of illness, BUN at CRRT and time from hospital admission to CRRT increases. Oppositely, 90-day mortality is lower as SCr and UO at CRRT initiation increases and in patients with abdominal sepsis.
5. In an international bicenter cohort of critically ill patients with septic shock and advanced SA-AKI (KDIGO stage 3), all of them receiving CRRT within the first 5 days from ICU admission, the initiation of CRRT in the setting of oliguria ( $UO \leq 0.5$  ml/kg/h) is associated with a higher 90-day mortality.
6. In a two-center pilot randomized trial in critically ill patients with SA-AKI and CRRT initiation criteria, the use of CVVHD associated to a membrane with adsorptive properties and an effluent dose of 30 mL/kg/h during 72 h, was not associated with an increase in EC patency respect to the use of CVVH associated to the same membrane and the same dose of effluent.
7. In a two-center pilot randomized trial in critically ill patients with SA-AKI and CRRT initiation criteria, the use of CVVHD associated to a membrane with adsorptive properties and an effluent dose of 30 mL/kg/h during 72 h, was not

associated with a decrease in the number of dialytrauma events respect to the use of CVVH associated to the same membrane and the same dose of effluent.

8. In a two-center pilot randomized trial in critically ill patients with SA-AKI and CRRT initiation criteria, the use of CVVHD associated to a membrane with adsorptive properties and an effluent dose of 30 mL/kg/h during 72 h, was not associated with differences in 90-day survival respect to the use of CVVH associated to the same membrane and the same dose of effluent.
9. In a two-center pilot randomized trial in critically ill patients with SA-AKI and CRRT initiation criteria, the use of CVVHD associated to a membrane with adsorptive properties and an effluent dose of 30 mL/kg/h during 72 h, was not associated with differences in cytokines circulatory levels respect to the use of CVVH associated to the same membrane and the same dose of effluent.
10. In a two-center pilot randomized trial in critically ill patients with SA-AKI and CRRT initiation criteria, the use of CVVHD associated to a membrane with adsorptive properties and an effluent dose of 30 mL/kg/h during 24 h, was not associated with significant differences in the solutes circulatory variations respect to the use of CVVH associated to the same membrane and the same dose of effluent.
11. In a two-center pilot randomized trial in critically ill patients with SA-AKI and CRRT initiation criteria, the use of CVVHD associated to a membrane with adsorptive properties and an effluent dose of 30 mL/kg/h during 72 h, was not associated with differences in the hemodynamic and respiratory variations respect to the use of CVVH associated to the same membrane and the same dose of effluent.
12. The use of a diffusive strategy (CVVHD) in critically ill patients with SA-AKI meeting CRRT initiation criteria is safe and feasible. Whether it is associated with longer EC patency and therefore lower dialytrauma rates still requires further and larger studies.



*Future directions*

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## 9. Future directions

### 9.1. Protective RRT

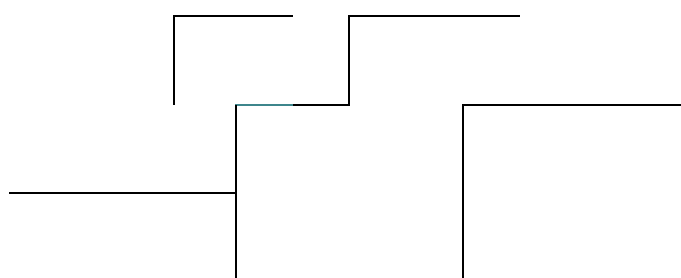
Less is more should be one of the most important “axiomas” in critical care medicine based on the last 20 years experience and results from different studies.<sup>397,16,242</sup> It seems reasonable to only initiate RRT in those patients who are going to benefit from renal support. RRT should be performed in the safer modality and with the most appropriate characteristics depending on the patient’s situation. As critically ill patients are extremely dynamic, RRT should also be modified in accordance to patient’s status. RRT should not be started in patients with refractory shock (futility) or in patients with therapeutic limitation orders. We are actually working in different strategies of protective RRT; checking adsorption results in our CVVHD vs. CVVH study before publication (a strong recommendation for diffusion instead of convection), and performing a new RCT with the use of an adsorption membrane connected to the CPB during cardiac surgery in order to decrease CSA-AKI in high risk patients. These two studies have both obtained public grants from the health ministry (Instituto de Salud Carlos III; PI12/01562 and PI15/00905).

### 9.2. SA-AKI with fluid overload

Besides the classical emergent RRT indications (hyperkaliemia and symptomatic uremia), oliguria despite diuretics is probably the most common reason to initiate RRT in critically ill patients with SA-AKI.<sup>166</sup> This oliguria is usually accompanied by FO which most of the times is followed by respiratory failure.<sup>121</sup> Thus, patients with SA-AKI and oliguria not responsive to diuretics who develop FO and therefore respiratory failure are probably the most common scenario for RRT initiation.<sup>171</sup> However, not all critically ill patients with FO and SA-AKI will require RRT as fluid overload tolerance is closely related to cardiovascular function and endothelial integrity. Those patients with impaired cardiac function are in a high risk of presenting lung edema when SA-AKI and oliguria are progressing. The same happens with SA-AKI when endothelial dysfunction is present (capillary leak syndrome),<sup>395</sup> promoting multi-organ edema earlier than expected. FO should be closely monitored in patients with SA-AKI as oliguria can sometimes be a “late” sign for RRT initiation. Unfortunately, there are no current accurate methods to monitorize FO status in critically ill patients. Devices that



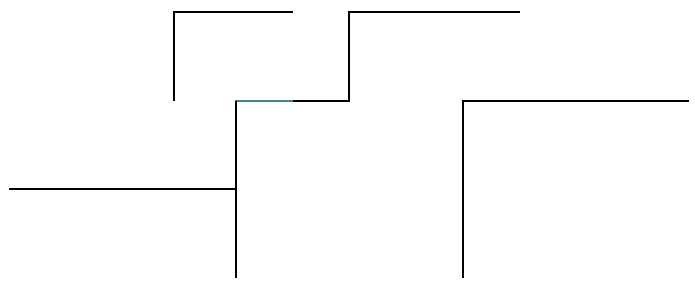
measure or evaluate intravascular volumes are still not sufficiently developed although technology is fastly improving.<sup>394</sup> Hopefully, in a near future, RRT initiation in patients with SA-AKI will be many times based in accurate volume status or FO “numbers” supported by clinical judgement.



*Resumen en castellano*

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*Abreviaturas*

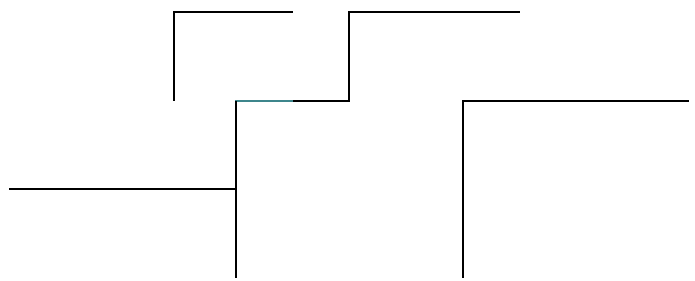
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## Abreviaturas

FRA	fracaso renal agudo
APS-III	Acute Physiology and Chronic Health Evaluation score 3
FRA-NS	FRA de origen no séptico
FRA-OC	FRA de origen comunitario
FRA-OH	FRA de origen hospitalario
FRA-S	FRA de origen séptico
h	horas
HDFVVC	hemodiafiltración venovenosa continua
HDVVC	hemodiálisis venovenosa continua
HVVC	Hemofiltración Venovenosa Continua
IRC	insuficiencia renal crónica
L	litros
LPA	lesión pulmonar aguda
PAM	presión arterial media
PAS	presión arterial sistólica
Pm	peso molecular
Ppl	presión plateau
SDMO	síndrome de disfunción multiorgánica
SDRA	síndrome de distrés respiratorio agudo
SRIS	síndrome de respuesta inflamatoria sistémica
SvcO <sub>2</sub>	saturación venosa central de oxígeno
TCRR	técnicas continuas de reemplazo renal
TRR	técnicas de reemplazo renal
TSF	Test de stress de la furosemida
UCI	unidad de cuidados intensivos
VM	ventilación mecánica





*Introducción*

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## 10.1. Introducción (apéndice 1)

El fracaso renal agudo (FRA) es un empeoramiento abrupto de la función renal en horas o días en contraposición con la insuficiencia renal crónica (IRC) donde el empeoramiento de la función renal ocurre durante el transcurso de meses o años.<sup>21</sup> La introducción de la escala RIFLE<sup>22</sup> mejorada posteriormente con las escalas AKIN<sup>23</sup> y KDIGO,<sup>26</sup> ha permitido la estratificación clínica y pronóstica del FRA, así estadios iniciales de la escala RIFLE se asocian a un mejor pronóstico, mientras que estadios más avanzados representan no sólo un peor pronóstico<sup>398</sup> si no un mayor requerimiento de técnicas de reemplazo renal (TRR),<sup>45,24</sup> que se iniciarán según criterios hasta la fecha mal definidos.<sup>26</sup> Como TRR entendemos aquellos dispositivos extracorpóreos que sustituyen la función renal, mediante técnicas difusivas (hemodiálisis) o convectivas (hemofiltración), que a su vez se pueden realizar de forma intermitente o continua.

La causa más frecuente de FRA es la sepsis, entendiendo como sepsis todas aquellas infecciones que presentan disfunción orgánica.<sup>53</sup> La incidencia de sepsis es creciente estimándose que en España se producen unos 104 casos de sepsis por cada 100.000 habitantes adultos-año con una mortalidad hospitalaria del 20,7%, y unos 31 casos de shock séptico por 100.000 habitantes adultos-año con una mortalidad hospitalaria del 45,7%.<sup>399</sup> Varios estudios publicados en la última década, demuestran que diferentes tratamientos o intervenciones pueden disminuir la mortalidad de la sepsis.<sup>109,110</sup>

Estos y otros avances terapéuticos han llevado al desarrollo de guías terapéuticas internacionales (Surviving Sepsis Campaign [SSC])<sup>98</sup> cuyo cumplimiento se asocia a una mejoría pronóstica,<sup>101,102,103,104</sup> siendo sus pilares básicos una adecuada antibioterapia precoz, el control del foco infeccioso, y una resucitación hemodinámica precoz guiada por objetivos (presión arterial media [PAM] >65 mmHg). A pesar de estos avances, la mortalidad de la sepsis sigue siendo elevada, y sobre todo cuando se asocia a disfunción aguda de múltiples órganos, definida como síndrome de disfunción multiorgánica (SDMO).<sup>72,53</sup> En estos pacientes, la elevada incidencia de FRA, casi un 80% según las series, constituye un factor de riesgo independiente de mortalidad.<sup>104</sup>

El FRA de origen séptico (FRA-S) respecto al FRA de origen no séptico (FRA-NS) presenta importantes diferencias no sólo en cuanto a su patogénesis,<sup>66</sup> sino también en las características clínicas y en el pronóstico final.<sup>3,266</sup> Numerosos autores han descrito

que el FRA-S presenta una mayor morbimortalidad respecto al FRA-NS, cursando con estadios más avanzados de FRA según las diferentes escalas descritas, mayores requerimientos de TRR, mayor necesidad de ingresos en UCI (con mayores requerimientos de soporte hemodinámico y ventilatorio), mayores estancias hospitalarias, y finalmente una mayor mortalidad.<sup>3,266</sup> Los factores de riesgo que contribuyen al desarrollo del FRA-S en el paciente séptico no están bien definidos como tampoco lo están el impacto que tienen sobre la incidencia de FRA-S el cumplimiento de las medidas terapéuticas aconsejadas por la SSC.<sup>1,47,288</sup> Así mismo, el impacto que tiene a nivel de supervivencia la aparición de FRA-S en el paciente con sepsis tampoco está suficientemente definido o al menos no a nivel de paciente crítico con sepsis.<sup>288</sup>

En este contexto clínico del paciente con FRA-S que precisa de ingreso en UCI, es frecuente la necesidad de TRR,<sup>6</sup> que muchas veces por la presencia de inestabilidad hemodinámica, serán mayoritariamente técnicas continuas de reemplazo renal (TCRR),<sup>45</sup> es decir mantenidas en el tiempo para asegurar un equilibrio homeostático y un correcto balance hídrico. Así se calcula que hasta un 60% de todos los pacientes críticos presentarán FRA,<sup>28</sup> de estos alrededor del 50% serán FRA-S, globalmente hasta un 8% requerirán de TRR, pero este porcentaje aumenta hasta un 20% cuando se trata de FRA-S.<sup>3,266</sup>

La mortalidad de estos pacientes con FRA-S que precisan de TCRR es muy elevada traduciendo muchas veces un escenario de SDMO.<sup>354</sup> Los factores de riesgo asociados a esta elevada mortalidad han sido descritos en numerosas series de pacientes críticos en su gran mayoría poco homogéneas en cuanto a sus características clínicas y al grado de FRA-S.<sup>47</sup> Como consecuencia de esta heterogeneidad, es difícil identificar qué factores de riesgo relacionados con el manejo clínico o con el uso de las TCRR podrían tener un impacto en la supervivencia de estos pacientes.

Especialmente controvertido en el paciente con FRA-S es el momento de iniciar las TRR, también llamado “timing”, que durante muchos años se aconsejaba que fuese precoz respecto al estadio del FRA-S,<sup>160</sup> y que en los últimos años ha evolucionado hacia una estrategia más conservadora (estadios 2 y 3 de la escala KDIGO)<sup>17,171,18</sup> basada en diversos estudios aleatorizados pero en torno a la cual todavía siguen existiendo grandes interrogantes sobre que parámetros han de guiar el “timing”. Los parámetros analíticos como la urea y la creatinina no han demostrado ser útiles en

diversos estudios donde se analizaba la idoneidad del “timing” de las TRR en pacientes críticos con FRA.<sup>167,344</sup> Los parámetros basados en medidas de tiempo (“tiempo desde el ingreso hasta la TRR” o “tiempo desde el inicio de la sepsis hasta la TRR”) también han demostrado resultados poco concluyentes.<sup>160,351</sup> La disminución de la diuresis como marcador de FRA podría ser un parámetro útil para decidir el inicio de la TRR como así lo parecen indicar algunos estudios.<sup>168,355</sup> Sin embargo se trata de estudios con muestras poblacionales muy pequeñas y excesivamente heterogéneas en cuanto a su condición clínica.

Por otra parte, en los últimos años un mejor conocimiento fisiopatológico de la sepsis ha permitido establecer diferentes teorías que explican la evolución a SDMO.<sup>72</sup> El reconocimiento de moléculas patogénicas (Pathogen Associated Molecular Patterns, PAMPs), y de moléculas asociadas a daño celular (Damage Associated Molecular Patterns, DAMPs) por parte de receptores específicos del sistema inmunológico innato (Pattern Recognition Receptors, PRRs), desencadenaría un síndrome de respuesta inflamatoria sistémica (SRIS) donde la liberación de mediadores proinflamatorios (IL-1 $\beta$ , TNF- $\alpha$ , IL-6, MCP-1) y antiinflamatorios (IL-10, IL-4, IL-1ra), produciría directa o indirectamente un SDMO.<sup>71</sup> Numerosos estudios correlacionan la concentración plasmática de lipopolisacárido y de mediadores inflamatorios, mayoritariamente citoquinas (IL-4, IL-1 $\beta$ , MCP-1), con el grado de disfunción endotelial (hipotensión), disfunción orgánica, y mortalidad.<sup>74,75</sup> No obstante la multitud de tratamientos ensayados para neutralizar estas citoquinas, o su efecto, de forma selectiva han fracasado repetidamente.<sup>400,401</sup>

En esta línea argumental, las TCRR sí han demostrado desde sus inicios una capacidad de eliminación de mediadores inflamatorios, no específica, y basada fundamentalmente en la capacidad a través de técnicas convectivas (Hemofiltración Venovenosa Continua, HVVC), por gradiente de presión, para filtrar moléculas de mediano peso molecular (Pm), entre 5 y 30 KDa.<sup>14,188</sup> En estudios experimentales con modelos de sepsis se evidencia una correlación entre la dosis de convección, medida en mL/kg/h de ultrafiltrado, y la capacidad de eliminación de citoquinas.<sup>79</sup> En estos estudios se observa una mejoría hemodinámica con dosis altas de convección y en algunos de ellos mejorías significativas en la supervivencia.<sup>197,193</sup>

La teoría inmunomoduladora no específica, a partir de la cual la HVVC es capaz de minimizar los picos de citoquinas, trata de explicar la mejoría hemodinámica y el impacto sobre la supervivencia.<sup>174</sup> No obstante, la ausencia de variación en las concentraciones plasmáticas de citoquinas en algunos de estos estudios<sup>192,195</sup> ha obligado a plantear otras posibles teorías que justifiquen los cambios bioquímicos y hemodinámicos observados.<sup>207,210</sup>

La mayoría de estudios que evalúan el uso de HVVC con dosis convectivas altas (>35 mL/kg/h) a pesar de obtener mejorías hemodinámicas en situaciones de shock séptico no han demostrado mejoría en términos de supervivencia.<sup>205,196,202,203,198</sup> Además, por su dificultad técnica el uso dosis convectivas altas está asociado a la aparición de efectos adversos conocidos genéricamente como *dialytrauma* entre los cuales los más importantes son, un mayor consumo de hemoderivados (por coagulación del filtro), una mayor incidencia de trombocitopenia, episodios frecuentes de hipotermia, y trastornos iónicos.<sup>173</sup> Por este motivo, por su elevado coste económico (mayor consumo de filtros por coagulación frecuente), y por la ausencia de datos concluyentes, la HVVC con dosis >35 mL/kg/h se reservaría únicamente como alternativa con bajo nivel de evidencia para pacientes con shock séptico refractario, estableciéndose la hemodiafiltración venovenosa continua (HDFVVC) con dosis de entre 20-25 mL/kg/h como la técnica de elección en el paciente con FRA-S.<sup>26,27</sup> Estas dosis (con un componente convectivo alto de al menos un 50%) tampoco están exentas de episodios de *dialytrauma*, como así lo reflejan los dos grandes estudios randomizados publicados hasta la fecha.<sup>15,16</sup>

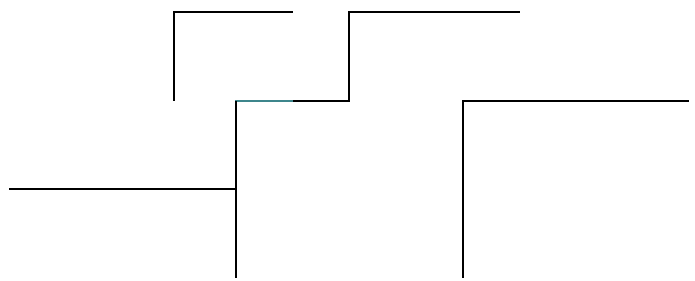
Por otra parte, diversos estudios realizados en pacientes críticos han demostrado un efecto beneficioso a nivel metabólico e incluso en términos de supervivencia cuando se realizan técnicas mixtas (HDFVVC), convección y difusión (por gradiente de concentración).<sup>216</sup> Además, las técnicas difusivas puras como la hemodiálisis venovenosa continua (HDVVC), ofrecen la potencial ventaja de ser más seguras (menor *dialytrauma*) y menos costosas (menor consumo de filtros y hemoderivados). Sin embargo, estas ventajas en términos de coste y seguridad podrían verse contrarrestadas por una menor capacidad para la eliminación de moléculas de mediano Pm, sobre todo citoquinas, convirtiendo a la HDVVC en una TCRR *a priori* poco apropiada para el paciente con FRA-S. No obstante, estudios observacionales realizados en pacientes sépticos cuestionan este planteamiento observándose una similar capacidad de eliminación de moléculas de pequeño y mediano Pm con el uso de HDVVC.<sup>186,215</sup>

El diseño de nuevas membranas con capacidad de adsorción podría ofrecer un beneficio sobreañadido a la HDVVC. La presencia de valores bajos de citoquinas al analizar el ultrafiltrado de algunos pacientes con FRA-S sometidos a TCRR ha puesto en evidencia la capacidad de adsorción de ciertas membranas que sí son capaces de producir variaciones en las concentraciones plasmáticas de citoquinas sin fenómenos convectivos.<sup>193</sup> Esta propiedad física de adsorción, basada en interacciones hidrofóbicas y atracciones iónicas, permite “atrapar” moléculas de mediano Pm. Además, diversos estudios han demostrado que la capacidad de adsorción de estas membranas mejora con el empleo de técnicas difusivas.<sup>225</sup> Por consiguiente, el uso de HDVVC podría ser el más adecuado, aportando sus ya conocidas ventajas de coste y seguridad, a una mejoría de la capacidad de adsorción de la membrana.

El análisis bioquímico de citoquinas (fundamentalmente IL-1 $\beta$ , TNF- $\alpha$ , MCP-1, IL-4, e IL-10) medidas a nivel plasmático y de ultrafiltrado durante las primeras 72 horas (las más importantes a nivel fisiopatológico), pueden ayudarnos a entender como actúa la HDVVC asociada a membranas de adsorción en pacientes con FRA-S. No obstante, es importante señalar que a pesar de que en los pacientes con FRA-S existe una clara correlación entre los niveles de citoquinas y el pronóstico tanto de supervivencia como de recuperación de la función renal,<sup>379,381</sup> no existen hasta la fecha estudios concluyentes que demuestren que la disminución en las concentraciones plasmáticas de estas citoquinas se pueda lograr de una forma eficaz a través del uso de TCRR.<sup>384,373</sup>

En resumen, necesitamos estudios que evalúen la incidencia y mortalidad del FRA-S en las poblaciones de pacientes críticos así como los factores de riesgo potencialmente modificables y las estrategias terapéuticas que puedan modificar su curso o aparición. Así mismo el uso de las TCRR en esta población de pacientes críticos es muy frecuente y conlleva un importante coste socioeconómico y una elevada mortalidad hospitalaria.<sup>20</sup> Conocer los factores pronósticos en este tipo de pacientes, y evaluar las estrategias más adecuadas sobre cuando (timing) y cómo (modalidad) utilizar las TCRR es uno de los retos más importantes de la medicina intensiva en lo que al FRA-S se refiere.





*Hipótesis*

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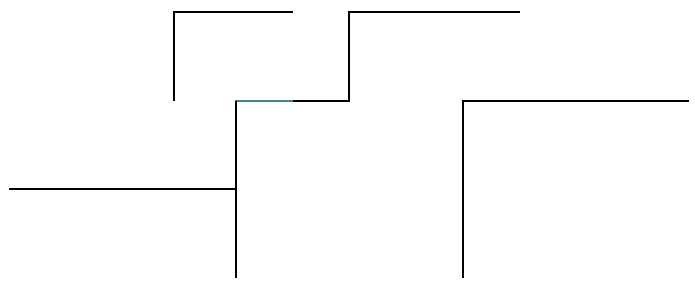




## 10.2. Hipótesis

1. El FRA-S tiene una incidencia y mortalidad muy elevadas en el paciente crítico con sepsis. Las recomendaciones actuales de la SSC no son efectivas para prevenir la aparición de FRA-S.
2. La necesidad de TCRR en los pacientes con shock séptico y FRA-S es muy elevada. El inicio de las TCRR en estos pacientes debería estar guiado por los cambios en la diuresis.
3. En el FRA-S cuando las TCRR están indicadas, la HDVVC es superior a la HVVC en términos de vida media del circuito y ausencia de *dialytrauma* sin cambios en la mortalidad, en el aclaramiento plasmático de citoquinas y solutos, o en la respuesta hemodinámica y respiratoria.





*Objetivos*

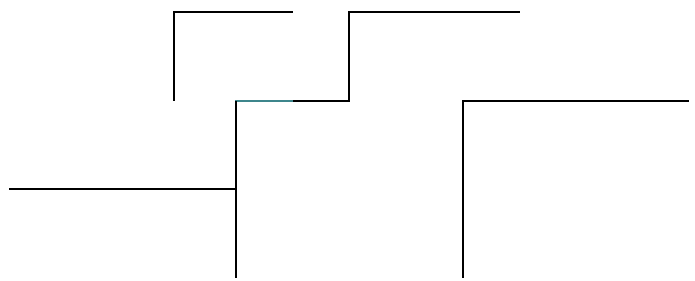
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### 10.3. Objetivos

1. Evaluar la incidencia y el impacto pronóstico que tiene el FRA-S en una cohorte unicéntrica de pacientes críticos con sepsis.
2. Identificar los factores de riesgo para la aparición de FRA-S en una cohorte unicéntrica de pacientes críticos con sepsis con el objetivo de diseñar futuras estrategias preventivas.
3. Evaluar el impacto que tiene el cumplimiento de las medidas terapéuticas recomendadas por la SSC en la incidencia de FRA-S en una cohorte unicéntrica de pacientes críticos con sepsis.
4. Identificar en una cohorte bicéntrica de pacientes críticos con shock séptico y FRA-S que requieren TCRR, los factores de riesgo de mortalidad con el objetivo de definir futuras estrategias terapéuticas.
5. Identificar en una cohorte bicéntrica de pacientes críticos con shock séptico y FRA-S avanzado (estadío 3 KDIGO) que requieren TCRR dentro de los primeros 5 días de ingreso en UCI, las variables o parámetros que pueden ser útiles para decidir el inicio de la TCRR (“timing”) y potencialmente mejorar el pronóstico de este tipo de enfermos.
6. Evaluar a través de un ensayo piloto aleatorizado y bicéntrico en una población de pacientes críticos con FRA-S e indicación de TCRR, la validez y utilidad de una técnica difusiva (HDVVC) asociada a una membrana con capacidad de adsorción en comparación a una técnica convectiva (HVVC) asociada a la misma membrana. Este objetivo se evaluará a través del registro de la duración de los filtros y la incidencia de dialytrauma en las primeras 72 horas después de la aleatorización y durante toda la duración de la TCRR.
7. Evaluar a través de un ensayo piloto aleatorizado y bicéntrico en una población de pacientes críticos con FRA-S e indicación de TCRR, la supervivencia clínica de los pacientes que reciben una técnica difusiva (HDVVC) asociada a una membrana con capacidad de adsorción en comparación a una técnica convectiva (HVVC) asociada a la misma membrana. Este objetivo se evaluará a través del registro de la supervivencia al alta hospitalaria, a los 28 días y a los 90 días.

8. Evaluar a través de un ensayo piloto aleatorizado y bicéntrico en una población de pacientes críticos con FRA-S e indicación de TCRR, la eficacia inmunomoduladora de una técnica difusiva (HDVVC) asociada a una membrana con capacidad de adsorción en comparación a una técnica convectiva (HVVC) asociada a la misma membrana. Este objetivo se evaluará a través del registro del porcentaje de reducción de la concentración plasmática de las diferentes citoquinas durante las primeras 72 horas de TCRR.
9. Evaluar a través de un ensayo piloto aleatorizado y bicéntrico en una población de pacientes críticos con FRA-S e indicación de TCRR, la eficacia depuradora de una técnica difusiva (HDVVC) asociada a una membrana con capacidad de adsorción en comparación a una técnica convectiva (HVVC) asociada a la misma membrana. Este objetivo se evaluará a través del registro de la variación en las concentraciones plasmáticas de los diferentes solutos en las primeras 24 horas de TCRR.
10. Evaluar a través de un ensayo piloto aleatorizado y bicéntrico en una población de pacientes críticos con FRA-S e indicación de TCRR, la eficacia clínica de una técnica difusiva (HDVVC) asociada a una membrana con capacidad de adsorción en comparación a una técnica convectiva (HVVC) asociada a la misma membrana. Este objetivo se evaluará a través del registro de los cambios hemodinámicos y respiratorios en las primeras 72 horas así como de los días en ventilación mecánica (VM) y la estancia en UCI.



*Estudio 1*

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## 10.4. Estudio 1. Ausencia de impacto de las recomendaciones de la “surviving sepsis campaign” en la incidencia de fracaso renal agudo de origen séptico (apéndice 2)

### 10.4.1. Objetivos

- Evaluar la incidencia y el impacto pronóstico que tiene el FRA-S en una cohorte unicéntrica de pacientes críticos con sepsis.
- Identificar los factores de riesgo para la aparición de FRA-S en una cohorte unicéntrica de pacientes críticos con sepsis con el objetivo de diseñar futuras estrategias preventivas.
- Evaluar el impacto que tiene el cumplimiento de las medidas terapéuticas recomendadas por la SSC en la incidencia de FRA-S en una cohorte unicéntrica de pacientes críticos con sepsis.

### 10.4.2. Resultados Estudio 1

Durante el período de estudio 650 pacientes fueron evaluados para objetivar la presencia de sepsis o shock séptico, de los cuales 260 pacientes (40%) fueron finalmente incluidos. De estos 260 pacientes, en el momento de diagnosticarse la sepsis, 113 (43.5%) ya presentaban criterios de FRA-S por la clasificación KDIGO y 129 (49%) FRA-S al ingreso en UCI (23% de ellos presentaban oliguria).

Los pacientes eran predominantemente varones (67%) con una edad media de  $58.9 \pm 15$  años. La mayoría de los pacientes incluidos en el estudio iniciaron la sepsis dentro de la UCI (40%) mientras que el 31% lo hizo en urgencias y el 29% restante en las unidades de hospitalización. Al inicio de la sepsis el 63.1% presentaban shock séptico y el 62.7% requerían VM.

82 pacientes (31.5%) desarrollaron FRA-S con una mediana de 3 días (IQR 1-5 días) después del inicio de la sepsis. Clasificándolos por estadios KDIGO el 17% presentaron estadio 1, el 16% estadio 2, y el 67% estadio 3. De estos 82 pacientes el 37% requirió TRR durante su estancia en UCI (KDIGO 3 no necesariamente comportaba necesidad de TRR).

La **Tabla 1.2** representa las características demográficas, características basales, las comorbilidades, características sépticas, y el grado de cumplimiento de las recomendaciones de la SSC en el grupo de FRA-S y en el grupo de pacientes sépticos sin FRA. Los pacientes que desarrollaron FRA-S eran mayores, predominantemente varones, presentaban una función renal basal disminuida, tenían un score de gravedad APACHE2 más alto, mayor prevalencia de bacteriemia y un mayor porcentaje de sepsis de origen abdominal.

Todas las medidas de resucitación de la SSC (6 primeras horas) fueron individualmente analizadas. No se observaron diferencias en el porcentaje de cumplimiento o en los tiempos analizados (por ejemplo, tiempo desde la sepsis hasta el antibiótico). La presencia de hipotensión fue más frecuente en el grupo de FRA-S (83% versus 62%;  $p < 0.001$ ), así como el porcentaje de pacientes que requirieron VM (73% versus 58%;  $p < 0.02$ ). En los pacientes con shock séptico no se objetivaron diferencias en el cumplimiento de los objetivos de administración de líquidos, presión venosa central, o saturación venosa central de oxígeno (SvcO<sub>2</sub>) entre el grupo de FRA-S y el de no-FRA (**Tabla 1.2**).

En el análisis de las medidas de mantenimiento (24 horas) recomendadas por la SSC, se encontraron algunas diferencias entre los pacientes con FRA-S y los pacientes con no-FRA (**Tabla 1.2**). El objetivo de mediana de glucemia (entre 4 y 8.3 mmol/L sin episodios de hipoglucemia) fue logrado con mayor frecuencia en el grupo de no-FRA que en el grupo de FRA-S (49.7% versus 36.2%;  $p = 0.06$ ). Entre los pacientes que requirieron VM (63% del total), se observaron presiones Plateau (Ppl) más elevadas en el grupo de FRA-S respecto al grupo de no-FRA ( $p < 0.01$ ). Sin embargo, en los pacientes en los que se completaron todas las medidas recomendadas por la SSC (resucitación, mantenimiento, o ambas) no se observó ninguna disminución en la incidencia de FRA-S respecto a los pacientes que no completaron todas las medidas.

Tras realizar un análisis multivariable ajustando el modelo por aquellos posibles factores de confusión, se identificaron la presencia de hipotensión (2.3 HR, 95% CI 1.2-4.2,  $p < 0.01$ ) y la sepsis de origen abdominal (1.8 HR, 95% CI 1.1-3.1,  $p < 0.02$ ) (**Tabla 1.3**), como los dos únicos factores de riesgo independientes para la aparición de FRA-S en una población de pacientes sépticos que requieren ingreso en UCI.

La mortalidad hospitalaria en el grupo que desarrolló FRA-S fue del 61% en contraposición al 39.3% en el grupo de no-FRA ( $p < 0.001$ ) (**Tabla 1.2**). Se representaron y compararon las curvas de supervivencia a 90 días (Kaplan-Meier) entre el grupo con FRA-S y el grupo de no-FRA, utilizando un log-rank test (**Figura 1.2**).

#### 10.4.3. Discusión estudio 1

Definimos el FRA-S como el empeoramiento de la función renal (nueva aparición de FRA o aumento del estadio KDIGO  $\geq 1$ ) dentro de los primeros 7 días desde el diagnóstico de sepsis. Hay que destacar que el propósito de nuestra definición de FRA-S fue el de identificar los factores de riesgo potencialmente modificables (después del inicio de la sepsis) y el de valorar el impacto “real” que las medidas de resucitación y mantenimiento recomendadas por la SSC<sup>289</sup> tenían sobre la función renal del paciente.

Un porcentaje no despreciable de los pacientes de nuestra cohorte ya presentaban FRA en el momento del diagnóstico de sepsis (43.5%) así como en el momento de ingreso en críticos (49%), pero era nuestra intención valorar si las medidas recomendadas desde ese momento por la SSC podían tener algún impacto en la aparición o progresión del FRA-S. Es por ello que definimos el FRA-S como la progresión o nueva aparición de FRA en los primeros 7 días desde el diagnóstico de sepsis y esta definición ha sido avalada por otras publicaciones de impacto internacional, algunas de ellas muy recientes.<sup>3</sup> La incidencia (32%) de FRA-S en nuestra población de pacientes críticos con sepsis fue muy elevada a pesar de los criterios restrictivos de nuestra definición. Hay que tener en cuenta, que no se clasificaron como FRA-S aquellos pacientes que a pesar de tener FRA en el momento del diagnóstico de sepsis no presentaron un empeoramiento de la función renal en los siguientes 7 días después del inicio de la sepsis, los cuales representan casi un 28% del total de la muestra. Esta elevada incidencia refleja la dimensión real del problema.

La aparición de FRA-S en nuestra cohorte de pacientes críticos con sepsis tuvo un claro impacto pronóstico aumentando la mortalidad a los 90 días. El paciente séptico que desarrolla FRA-S se encuentra generalmente englobado dentro de un SDMO<sup>402</sup> como así lo representan los mayores scores de gravedad (SOFA y APACHE2) de nuestra serie, y es por ello que no todo el aumento de la mortalidad se debe al FRA-S. No obstante, existe abundante bibliografía que señala que la FRA-S tiene un mayor impacto

en la morbimortalidad del paciente crítico respecto a la FRA-NS.<sup>266,42</sup> Los pacientes críticos con FRA-S tienen peor pronóstico a corto plazo y un mayor requerimiento de TRR.<sup>3</sup>

Se identificaron dos variables como factores de riesgo independientes para la aparición de FRA-S que fueron por un lado la presencia de hipotensión arterial (definida como PAS < 90 mmHg y/o PAM < 65 mmHg) al inicio de la resucitación y por otro lado la sepsis de origen abdominal en comparación con la sepsis de origen médico (mayoritariamente neumonías comunitarias o asociadas a VM). La presencia de hipotensión arterial siempre se ha correlacionado con la presencia de disfunción orgánica y es bien conocido el estudio de Kumar et al.<sup>97</sup> donde relacionaba el tiempo que el paciente estaba hipotenso antes de recibir el antibiótico con la incidencia de FRA-S. La presencia de un foco abdominal es un conocido factor de riesgo para la aparición de FRA-S en el contexto de elevación de la presión intraabdominal<sup>295</sup>, peor tolerancia al balance positivo (aumenta la presión venosa renal por alteración de la compliance abdominal)<sup>403</sup>, o drenaje tardío del foco séptico.<sup>112</sup> En nuestro estudio no se recogió el tiempo que los pacientes permanecieron hipotensos y esto es importante como recientemente ha publicado el grupo de Maheshwari et al.<sup>293</sup> donde en una muestra de pacientes críticos con sepsis el riesgo de presentar IRA-S estaba claramente relacionado con la cantidad de tiempo durante el cual el paciente permanecía hipotenso.

La confirmación de la importancia pronóstica de la FRA-S en nuestra cohorte de pacientes críticos con sepsis hace necesaria la evaluación de las medidas de manejo terapéutico promovidas por la SSC<sup>289</sup> en cuanto a su impacto sobre la incidencia de FRA-S. Se ha de destacar que en nuestra cohorte histórica el cumplimiento de las medidas de resucitación inicial (primeras 6 horas) y de mantenimiento (24 horas) ha sido bajo. Es decir, nos encontramos ante una cohorte de pacientes sépticos donde el impacto de las medidas promovidas por la SSC no fue el deseado. Sin embargo, sí que hubo un porcentaje destacado de pacientes donde las medidas recomendadas se cumplieron, y es en este grupo de pacientes donde en principio se evaluó si ese cumplimiento estaba acompañado de una disminución en la incidencia de FRA-S respecto al grupo donde el cumplimiento era menor. En nuestro estudio, de todas las medidas de resucitación inicial evaluadas (determinación de lactato, obtención de hemocultivos antes del antibiótico, antibioterapia precoz (3 horas), resucitación adecuada con fluidos en presencia de hipotensión arterial, y resucitación guiada por

objetivos en presencia de hipotensión arterial; no se pudo asociar de forma estadísticamente significativa el cumplimiento de ninguna de ellas a una disminución en la incidencia de FRA-S.

En nuestro estudio no encontramos asociación entre una antibioterapia precoz (dentro de las primeras 3 horas en los pacientes de urgencias o planta, y 1 hora en los pacientes de UCI) y una menor incidencia de FRA-S. A diferencia de otros estudios donde sí se evidenció esta asociación,<sup>1</sup> en nuestra cohorte de pacientes críticos el análisis de la variable “tiempo desde sepsis hasta antibiótico” no demostró ninguna asociación con la función renal. Algunos artículos recientes apoyan nuestros hallazgos, entre ellos los tres grandes estudios multicéntricos donde se evaluaron las medidas de resucitación inicial (EGDT) y donde no se evidenció ninguna diferencia en todos los “outcomes” analizados (entre ellos el renal) respecto al manejo clínico habitual (“usual care”).<sup>106,107,108</sup> No obstante, se ha de señalar que en estos tres grandes estudios, las diferencias en cuanto a los “tiempos” de actuación entre el grupo EGDT y el “usual care” fueron mínimos<sup>296</sup> (gran parte de las “no diferencias” en la mortalidad se atribuyen a este hecho) y por este motivo aún existiendo diferencias (que no las hay) en la incidencia de FRA-S, estas no se podrían atribuir a una administración precoz de la antibioterapia o a cualquier otra de las medidas terapéuticas analizadas. En nuestro estudio una administración correcta de fluidos según las guías (20 mL/kg en aquel momento) en los pacientes con hipotensión arterial (presión arterial sistólica [PAS] <90 mmHg o PAM <65 mmHg) no se asoció a una menor incidencia de FRA-S. Esto es contrario a estudios observacionales previos donde se sí se evidenciaba una menor incidencia de FRA-S en los pacientes resucitados con una dosis correcta de fluidoterapia.<sup>1</sup> No obstante, estudios recientes en pacientes sépticos podrían ir a favor de una estrategia de fluidos un poco más restrictiva (que la actualmente recomendada por la SSC) aún en presencia de hipotensión arterial especialmente cuando se analiza el impacto sobre la función renal.<sup>272,123,124</sup> No hay que olvidar que dos grandes estudios aleatorizados realizados en un área geográfica determinada (África) con escaso acceso a sistemas de soporte orgánico (entre ellos VM) encontraron una mayor mortalidad en el grupo de pacientes sépticos e hipotensos que recibieron una estrategia más liberal de fluidos.<sup>300,301</sup>

En cuanto a las medidas de mantenimiento evaluadas destacaremos que el uso de corticoides en los pacientes con hipotensión arterial no se asoció a una menor incidencia de FRA-S lo cual concuerda con la mayoría de artículos publicados con anterioridad

donde el uso de corticoesteroides en los pacientes con shock séptico (al margen de una retirada más rápida del soporte vasopresor) no se pudo correlacionar con una disminución en la mortalidad ni en los días con TRR.<sup>319,321</sup> Únicamente dos estudios<sup>318,322</sup> donde se añadía fludrocortisona de forma oral a la hidrocortisona endovenosa informaron de mejorías significativas en la supervivencia y en el número de días sin disfunción orgánica (sin especificar más en cuanto a la función renal), aunque estos resultados deben de interpretarse con cautela debido a la metodología de ambos estudios. Un mejor control de glucemia en las primeras 24 horas, definido como una mediana entre 4 y 8.3 mmol/L sin episodios de hipoglucemia, se asoció a una menor incidencia de FRA-S aunque esta diferencia no fue estadísticamente significativa (sólo el 36.7% de los pacientes con FRA-S tuvieron un buen control de glucemia respecto al 49.7% en los pacientes sin FRA-S;  $p=0.06$ ). Nuestro hallazgo concuerda con los dos estudios de Van der Berghe<sup>324,325</sup> donde se evidenció una asociación entre un buen control de la glucemia y una menor incidencia de FRA-S. No obstante, en nuestro estudio no se evidenciaron diferencias en la mediana de la glucemia entre los pacientes sépticos que desarrollaron FRA-S y los que no la desarrollaron.

En nuestro estudio, en el subgrupo de pacientes que requirieron VM invasiva (63%) la ventilación protectora, definida como una mediana de Ppl <30 cm H<sub>2</sub>O en las primeras 24 horas, se asoció a una menor incidencia de FRA-S ( $p=0.07$ ) y la mediana de Ppl durante las primeras 24 horas en los pacientes con VM que desarrollaron FRA-S fue significativamente superior (28 (24-33) vs. 24 (20-30) cm H<sub>2</sub>O;  $p=0.01$ ) respecto a los pacientes con VM que finalmente no desarrollaron FRA-S. Estos hallazgos ponen de manifiesto la importante conexión bidireccional que existe entre la función respiratoria y la función renal, y que estudios previos ya habían señalado no sólo en relación al impacto que la sobrecarga de fluidos en los pacientes con FRA tiene en la función respiratoria,<sup>121</sup> sino también en el efecto que tiene la ventilación no protectora en los pacientes con síndrome de distrés respiratorio agudo (SDRA) sobre la incidencia de FRA-S.<sup>335</sup> El mecanismo fisiopatológico por el cual la ventilación no protectora en los pacientes con SDRA produce FRA no está claramente definido pero podría tratarse de una lesión orgánica a distancia en el contexto de una respuesta inflamatoria secundaria. Esta teoría explicaría por qué este último efecto beneficioso de la ventilación protectora (sobre la incidencia de FRA) es más marcado en el SDRA de origen séptico.<sup>337</sup>

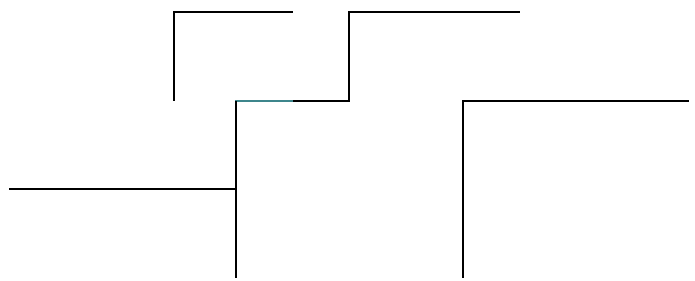
Nuestro estudio tiene las limitaciones inherentes a su diseño unicéntrico y observacional por lo que es susceptible de verse afectado por sesgos de selección. Sólo se incluyeron pacientes que requirieron ingreso en unidades de críticos por lo que es posible que se hayan “perdido” aquellos pacientes que inicialmente sí respondieron a las medidas de resucitación y por ello evitaron su ingreso en UCI (e hipotéticamente la aparición de FRA-S). Además, durante el estudio no se recogieron una serie de variables que podrían comportarse como modificadores de efecto a la hora de valorar la incidencia de FRA-S. Entre estas variables destaca la ausencia de información respecto al tipo de fluido utilizado en la resucitación hemodinámica inicial que es un factor de riesgo conocido en la aparición de FRA-S. Los coloides y en especial los almidones han demostrado una mayor incidencia de FRA-S (además de una mayor mortalidad), y debe señalarse que eran soluciones frecuentemente utilizadas tanto en la época como en el ámbito en el que se realizó el estudio.<sup>131</sup> La resucitación hemodinámica inicial con soluciones salinas también podría tener un potencial impacto en la incidencia o progresión de la FRA-S (especialmente en los pacientes con FRA-S ya presente al inicio de la resucitación).<sup>317</sup>

Por último hay que destacar que una variable tan importante como el balance de fluidos tampoco fue registrada dada la complejidad que requería contabilizar tanto la diuresis como la cantidad de fluidos administrada en cada paciente antes de su ingreso en UCI. Es por ello que hay que tener en cuenta que algunos de los pacientes incluidos en el estudio podrían tener valores falsamente bajos de creatinina por este efecto “dilucional” del balance positivo. Las fórmulas de corrección de la creatinina según el balance de fluidos<sup>310</sup> no se han podido aplicar en este estudio con el consiguiente riesgo de haber infradiagnosticado la existencia de FRA-S. No obstante, creemos que la utilización de la disminución de la diuresis como criterio diagnóstico además de los cambios en la creatinina minimizan este riesgo de infradiagnóstico. Por otra parte, el efecto que la propia anasarca (o balance positivo acumulado) haya podido tener sobre la aparición de la FRA-S tampoco habría sido controlado en este estudio.<sup>242,116</sup>

Por lo tanto, destacaremos que la aparición de FRA-S aumenta la mortalidad de los pacientes críticos con sepsis. Además, observamos en nuestro estudio una alta incidencia de FRA-S que aparece incluso después del inicio de las medidas de resucitación inicial y mantenimiento posterior. Estas medidas en nuestro estudio demostraron ser poco efectivas a la hora de reducir la incidencia de FRA-S que en nuestra población a estudio se asoció de forma significativa a la presencia de



hipotensión, así como al origen abdominal de la sepsis. Es por ello que parece importante evitar la hipotensión arterial persistente además de monitorizar la función renal (y posiblemente la presión intraabdominal, balance de líquidos, y control precoz del foco en la sepsis abdominal) para evitar la aparición de FRA-S.



*Estudio 2*

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## 10.5. Estudio 2: Variables clínicas asociadas al pronóstico del fracaso renal agudo de origen séptico y su relación con el momento de inicio de las terapias continuas de reemplazo renal (apéndice 3)

### 10.5.1. Objetivos

- Identificar en una cohorte bicéntrica de pacientes críticos con shock séptico y FRA-S que requieren TCRR, los factores de riesgo de mortalidad con el objetivo de definir futuras estrategias terapéuticas.
- Identificar en una cohorte bicéntrica de pacientes críticos con shock séptico y FRA-S avanzado (estadío 3 KDIGO) que requieren TCRR dentro de los primeros 5 días de ingreso en UCI, las variables o parámetros que pueden ser útiles para decidir el inicio de la TCRR (“timing”) y potencialmente mejorar el pronóstico de este tipo de enfermos.

### 10.5.2. Resultados Estudio 2

#### 10.5.2.1. Características de la población

En total 67250 pacientes requirieron ingreso en las UCIs de ambos centros durante el período de estudio. El 18% de estos pacientes presentaron shock séptico en algún momento de su ingreso en UCI con una alta incidencia de FRA-S (92.4% de todos los pacientes con shock séptico), pero tan sólo el 11% de estos pacientes con shock séptico requirieron finalmente TCRR. Se incluyeron finalmente 939 pacientes ingresados en UCI que cumplían criterios de shock séptico durante las primeras 24 horas de TCRR. El diagrama de flujos del estudio está representado en la **Figura 2.1**.

Las características de la población del estudio en el momento de ingreso en UCI y en el momento de inicio de la TCRR (basal) están representadas en la **Tabla 2.1**. La edad mediana fue 60 años (Q1 y Q3: 50, 71 años), 62.9% eran varones, y el 57.8% eran pacientes quirúrgicos. 150 pacientes (15.9%) presentaban IRC moderada. La mediana de tiempo desde el ingreso hospitalario hasta la admisión en UCI fue de 2 días (1, 5 días), mediana de tiempo desde el ingreso hospitalario hasta el inicio de las TCRR fue de 7 días (3, 15 días), y la mediana de tiempo desde la admisión en UCI y el inicio de las TCRR fue de 4 días (2, 8 días). Al inicio de la TCRR, la mediana de APS-III era de

98 (73, 122), 91.7% requerían soporte vasopresor, 88.7% requerían VM, el BUN era  $\geq$  100 mg/dL en el 16.5%, el potasio  $>5$  mEq/L en el 29.4%, y el 96.9% presentaba FRA-S basado en la escala KDIGO con una gran mayoría de los pacientes presentando estadio 3 (82.6%).

Los pacientes en su mayoría recibieron HDFVVC (62.8%) como modalidad inicial, mientras que tanto HVVC como HDVVC fueron empleadas como modalidades iniciales en la misma proporción (19.8% y 17.4% respectivamente). La mortalidad en UCI fue del 50.4% y la mortalidad hospitalaria del 52.7%. La mortalidad a los 90 días del inicio de la TCRR fue del 62.8%. Las diferencias que se evidenciaron entre centros a nivel de características poblacionales, manejo clínico-TCRR, y de supervivencia están expuestas en la **tabla 2.2**.

#### *10.5.2.2. Factores de riesgo para mortalidad*

El análisis univariante para mortalidad a 90 días identificó las variables representadas en la **Tabla 2.1**. Se analizaron las diferencias en la mortalidad entre los diferentes años para identificar modificadores de efecto debido a los avances en el tratamiento o a la mejoría en la aplicación de las TCRR, pero no se evidenciaron diferencias relevantes. Los factores de riesgo asociados a la mortalidad a 90 días fueron identificados mediante una regresión multivariable de Cox y están representados en la **Tabla 2.3**. Las variables significativas asociadas a una mayor mortalidad (factores de riesgo) a los 90 días que se identificaron fueron la edad (aHR 1.01, 95%CI 1.01-1.02,  $p<0.0001$ ), el Acute Physiology and Chronic Health Evaluation score 3 (APS-III) al inicio de la TCRR (1.01, 1.0-1.0,  $p<0.048$ ), los días desde el ingreso hospitalario hasta el inicio de la TCRR (1.01, 1.0-1.0,  $p<0.01$ ), el BUN al inicio de la TCRR (1.01, 1.0-1.0,  $p<0.04$ ), y los pacientes médicos (1.76, 1.5-2.1,  $p<0.0001$ ) respecto a los quirúrgicos. Las variables significativas asociadas a una menor mortalidad (factores protectores) a los 90 días que se identificaron fueron la creatinina al inicio de la TCRR (0.99, 0.9-1.0,  $p<0.001$ ) y la diuresis las 24 horas previas al inicio de la TCRR (0.77, 0.6-0.9,  $p=0.049$ ).

#### *10.5.2.3. Criterios de selección para el análisis del "timing" de inicio de las TCRR*

De las variables asociadas con la mortalidad se seleccionaron dos como potencialmente útiles para decidir el inicio de las TRR (estancia en UCI hasta el inicio de TCRR y diuresis durante las 24 horas previas al inicio de la TCRR). Con la intención de homogeneizar los grupos se restringió este análisis a un subgrupo de 433 pacientes con

shock séptico y estadio 3 al ingreso en UCI que recibieron TCRR dentro de los primeros 5 días de ingreso en UCI. El inicio de las TCRR basado en días desde UCI hasta TCRR fue comparado con el inicio de las TCRR basado en la diuresis de las 24 horas previas (UO). El inicio de las TCRR basado en días de UCI a TCRR no demostró diferencias a nivel de supervivencia entre el grupo precoz (0 a 2 días) y el grupo tardío (3 a 5 días) ( $p=0.765$ ), mientras que el inicio de las TCRR basado en la diuresis previa sí mostró importantes diferencias a nivel de supervivencia a los 90 días entre el grupo en el que se iniciaron las TCRR con  $UO \leq 0.05$  mL/kg/h, y los pacientes en los que se iniciaron las TCRR con  $UO > 0.05$  mL/kg/h ( $p=0.019$ ). Las curvas de Kaplan-Meier de ambas clasificaciones de timing están representadas en las **Fig. 2.2** y **Fig. 2.3**. La Hazard ratio ajustada para la mortalidad a los 90 días demostró que el grupo con oliguria al inicio de las TCRR presentaba un aumento del riesgo de muerte (aHR 2.6; 95%CI 1.6–4.3) en comparación con el grupo sin oliguria, y esta diferencia era estadísticamente significativa ( $p<0.001$ ). El modelo final de regresión de Cox ajustado y las diferencias entre los grupos de “timing” están representados en las **Tablas 2.4-2.7**.

### 10.5.3. Discusión estudio 2

Analizados los factores asociados a una mayor mortalidad a los 90 días en una población multicéntrica de pacientes críticos con presencia de shock séptico y FRA-S que requirió TCRR, se identificaron como estadísticamente significativos la edad, los scores de severidad, la urea al inicio de la TCRR, la diuresis al inicio de la TCRR, la creatinina al inicio de la TCRR, los días desde el ingreso hospitalario hasta el inicio de la TCRR, y los pacientes con sepsis médica. Además en el subgrupo de pacientes con FRA-S avanzado (estadio 3 de la clasificación KDIGO) que recibieron TCRR en los primeros 5 días de ingreso en UCI, el inicio de la TCRR en presencia de oliguria se asoció a una mayor mortalidad respecto al grupo de pacientes en los que se inició la TCRR con una diuresis  $>0.5$  mL/kg/h (en las 24 horas previas).

La edad y los “scores” pronósticos están claramente relacionados con la mortalidad en todas las poblaciones publicadas de pacientes críticos.<sup>240</sup> Los pacientes críticos de nuestro estudio que presentaron shock séptico y FRA-S con necesidad de TCRR son una población de pacientes con una elevada mortalidad que la mayoría de las veces refleja un SDMO.<sup>402</sup> A nuestro entender se trata de una de las muestras más grandes publicadas hasta la fecha de pacientes con estas características (shock séptico y TCRR)

y es por ello que los resultados obtenidos deberían servir para establecer estrategias de prevención y tratamiento que reduzcan la mortalidad de este grupo de pacientes.

En nuestra cohorte de pacientes con FRA-S en situación de shock séptico se identificaron (a través de una regresión múltiple) una serie de variables relacionadas con la función renal al inicio de la TCRR con significación pronóstica en cuanto a la mortalidad a los 90 días. La diuresis en las 24 horas previas al inicio TCRR y la creatinina al inicio de la TCRR se identificaron como variables protectoras mientras la que la urea al inicio de la TCRR se identificó como una variable de mal pronóstico. Los valores altos de urea al inicio de la TRR se han asociado tradicionalmente a un peor pronóstico en los grandes estudios observacionales traduciendo en la mayoría de los casos un estadio más avanzado de FRA (en el contexto de un SDMO) y en muchos casos la presencia de un insulto agudo sobre una IRC (“acute on chronic”).<sup>240,167</sup> Sin embargo, esta asociación no ha podido ser demostrada en otros muchos estudios observacionales donde se han evaluado a la urea y a la creatinina como “malos marcadores” de la severidad del FRA o al menos como malos indicadores del inicio de las TRR.<sup>347,240</sup>

Los pacientes con presencia de menor diuresis al inicio de la TCRR presentaron en nuestra cohorte de pacientes críticos una mayor mortalidad. Este fenómeno podría representar un estadio más avanzado de FRA-S al inicio de la TCRR que en algunas series de pacientes se ha asociado a un peor pronóstico.<sup>168</sup> Sin embargo, esta severidad de la FRA-S basada en la diuresis no se correlaciona en nuestro estudio con las cifras de creatinina al inicio de la TCRR que tienen un efecto protector en relación a la mortalidad; es decir cuanto más alta era la creatinina al inicio de la TCRR menor era la mortalidad a los 90 días. Este último fenómeno también se observa en la mayoría de estudios observacionales donde la creatinina al inicio de la TRR tiene este efecto protector.<sup>276,345</sup> Se han descrito fundamentalmente dos teorías para explicar este efecto protector de la creatinina, que serían por un lado la expresión de un buen estado nutricional o muscular en los pacientes con valores altos (valores bajos en este caso podrían ser reflejo de un estado de caquexia),<sup>404</sup> y por otro lado la expresión de un estado de anasarca o balance positivo acumulado importante en los pacientes con valores bajos (valores altos en este caso representarían una menor anasarca).<sup>309</sup> Diversos estudios han descrito fórmulas que ajustan los valores de creatinina al balance positivo acumulado minimizando así este efecto “dilucional” y aumentando la capacidad

predictiva de la creatinina a la hora de valorar el riesgo de requerir TRR o incluso de mortalidad.<sup>310,345</sup> Una tercera teoría explicaría el peor pronóstico de los pacientes que se depuran con valores bajos de creatinina por el hecho de que en muchos de estos pacientes la TRR se inicia de forma urgente (sin dar tiempo a que aumenten las cifras de creatinina – marcador lento de FRA-S) en situación de oligoanuria y SDMO.<sup>341</sup> Los valores bajos de creatinina en estos casos serían un reflejo de la celeridad con la que se inicia la TRR que a su vez es reflejo de la agudeza y severidad del contexto clínico.

La presencia de oliguria al inicio de la TCRR como marcador pronóstico ya había sido identificada en estudios previos donde incluso parece aumentar el valor predictivo del estadio del FRA-S a la hora de evaluar la supervivencia de los pacientes que requieren TRR.<sup>168</sup> En relación a este papel diagnóstico y pronóstico de la diuresis en relación al FRA es importante destacar que ni las propias definiciones (RIFLE, AKIN, KDIGO) ni la mayoría de los estudios discriminan o hacen relación a si la cuantificación de la diuresis se debe hacer con o sin el uso de diuréticos. Sabemos por estudios observacionales que el papel predictivo de la diuresis en la recuperación del FRA disminuye de forma clara con el uso de diuréticos.<sup>353</sup> Por otra parte, también sabemos que en los estadios iniciales del FRA la respuesta a los diuréticos cuantificada en las dos horas siguientes (Test de stress de la furosemida [TSF]) a su administración, tiene un claro valor pronóstico en cuanto a la necesidad de TRR y a la supervivencia final.<sup>360</sup> Además, la mayoría de los pacientes con FRA-S y oliguria presentan una situación de hipervolemia que como ya es sabido es un marcador de mal pronóstico en los pacientes críticos<sup>269,242</sup> y especialmente en aquellos que requieren TRR.<sup>161</sup> Cuánto del papel pronóstico de la oliguria es debido a una situación de hipervolemia y cuánto es debido a que representa un estadio más avanzado de FRA (y probablemente de SDMO) es difícil de diferenciar. Muchos de estos estudios observacionales<sup>276</sup> que identifican a la hipervolemia o la oliguria como factores de mal pronóstico en la población de pacientes críticos con FRA no informan de la posible relación que existe entre uno y otro. No obstante, sí existen estudios donde el valor pronóstico de la hipervolemia “coincide” con el valor pronóstico de la oliguria.<sup>357,352</sup> El análisis “posthoc” del FACTT trial estableció que la menor mortalidad con el uso de diuréticos en los pacientes con SDRA y FRA venía determinada por el efecto en el balance de fluidos y no por el uso del diurético “per se”.<sup>274</sup>



Probablemente es en este subgrupo de pacientes con FRA-S y oliguria a pesar de tratamiento diurético, donde se podría plantear un estudio prospectivo para valorar el timing de las TRR como recientemente se ha publicado en un estudio de factibilidad.<sup>355</sup> Aquellos pacientes con hipervolemia en el contexto de FRA-S y oliguria podrían ser a priori los más favorecidos por una estrategia precoz aunque faltan herramientas precisas que permitan evaluar la volemia real de los pacientes (la hipervolemia en la mayoría de los estudios se define como un aumento > 10% del peso basal).<sup>243</sup> Sin embargo, Gaudry et al. en un análisis de subgrupos del estudio AKIKI no encontraron diferencias en la evolución clínica de los pacientes con FRA y SDRA cuando se aleatorizaban a una estrategia precoz de TRR respecto a una estrategia diferida.<sup>176</sup>

El tiempo desde el ingreso hospitalario hasta el inicio de la TCRR también resultó ser pronóstico en nuestra serie de pacientes probablemente como reflejo de la mayor morbilidad asociada a una estancia hospitalaria prolongada y en ocasiones a una demora del ingreso en UCI. En nuestro estudio la mayoría de los pacientes con tiempos prolongados desde el ingreso hospitalario hasta el inicio de la TCRR representan lo que se denomina FRA de origen hospitalario (FRA-OH)<sup>405</sup> en contraposición con el FRA de origen comunitario (FRA-OC).<sup>148</sup> Las diferencias clínicas y pronósticas entre un grupo y otro han sido descritas en numerosos estudios que identifican a los pacientes con FRA-OH como un grupo de pacientes con estadios menos avanzados de FRA pero con mayores estancias hospitalarias y mayor mortalidad.<sup>148</sup> En nuestro estudio los pacientes con IRA-S de origen no quirúrgico presentan una mortalidad a los 90 días de casi el doble respecto a la población de FRA-S de origen quirúrgico lo cual podría reflejar una mayor prevalencia de neumonía grave de la comunidad (casi el 25% de los 939 pacientes). Esta menor mortalidad de los pacientes quirúrgicos ya había sido descrita previamente en dos grandes estudios de pacientes críticos con necesidad de TRR.<sup>240,1</sup> La causa de estas diferencias podrían estar en relación a la rápida reversibilidad de las sepsis quirúrgicas en comparación con las sepsis de origen médico o no quirúrgico. No obstante, conviene recordar que la sepsis de origen abdominal (quirúrgicas en su mayoría) es un factor de riesgo para la aparición de FRA-S como se ha comentado en el primero de nuestros estudios.

El análisis del “timing” de la TCRR se realizó en los pacientes con shock séptico y FRA-S en estadio avanzado (KDIGO 3) a su ingreso en UCI y que recibieron la técnica en los primeros 5 días de ingreso. Esta subpoblación de pacientes representa a nuestro

entender una cohorte más homogénea de pacientes críticos con FRA-S en los cuales se evaluaron fundamentalmente dos posibles estrategias de “timing”; una basada en la variable “tiempo desde el ingreso en UCI hasta la TCRR”, y otra basada en la variable “diuresis en las 24 horas previas al inicio de la TCRR”.

Sabemos por estudios observacionales que la presencia de oligoanuria en los pacientes con FRA constituye una de las causas más frecuentes para el inicio de las TRR.<sup>166</sup> Los pacientes con FRA no oligúrica tienen más probabilidad de recuperación espontánea de la función renal y menos riesgo de desarrollar indicaciones emergentes de TRR (hipervolemia e hiperkaliemia fundamentalmente).<sup>406</sup> Además sabemos que el TSF es un buen predictor del riesgo de evolucionar a FRA avanzado y requerir TRR como así lo demuestran los estudios donde la presencia de una diuresis inferior a 200 mL en las dos horas siguientes a la administración del bolus de furosemida se asociaba a un mayor requerimiento de TRR y a una mayor mortalidad.<sup>360</sup> Todos estos datos apoyan la importancia de la diuresis a la hora de definir y por tanto identificar a los pacientes con FRA aumentando la sensibilidad de la creatinina (o quizás deberíamos decir “potenciando”) y permitiendo muchas veces un diagnóstico más precoz o al menos alertando al clínico de una forma más precoz que los cambios en la propia creatinina. Por otra parte, el retraso en el inicio de la TRR (medido con la variable “tiempo en días”) desde el ingreso en UCI se ha asociado en diversos estudios observacionales con un peor pronóstico en términos de supervivencia.<sup>160</sup> Muchos de los pacientes que recibían TRR tardíamente (en estos estudios observacionales pero también en nuestro propio estudio) lo hacían por motivos diferentes al proceso de ingreso en UCI.<sup>362</sup> Para evitar este factor de confusión, en nuestra cohorte de pacientes únicamente se evaluaron los pacientes depurados durante los primeros 5 días y que presentaban un estadio avanzado de FRA-S (estadio 3 de la KDIGO) durante las primeras 24 horas de ingreso en UCI.

Con estos criterios de selección, que permitieron homogeneizar las características basales del grupo precoz y grupo tardío, no se observaron diferencias en la supervivencia a los 90 días después del inicio de la TCRR entre los pacientes que se depuraron durante las primeras 48 horas de ingreso y los que se depuraron en los siguientes 3 días (>48 horas hasta el 5º día). Estos resultados coinciden con el análisis “posthoc”<sup>367</sup> del estudio RENAL donde los pacientes con estadio “Injury” de FRA no presentaban diferencias de mortalidad según el tiempo desde el diagnóstico del estadio y

el inicio de la TCRR. Lo mismo se puede concluir extrapolando resultados de los dos grandes estudios aleatorizados<sup>17,18</sup> en pacientes con shock séptico y estadio KDIGO 3 o “Failure” publicados en la literatura donde el retraso en el inicio de la TRR no se asoció a una mayor mortalidad aunque se ha de puntualizar que estos estudios no fueron concebidos para valorar este resultado en concreto ya que muchos de los pacientes asignados al grupo tardío o diferido no requirieron TRR finalmente (49% en un estudio y 38% en el otro). Por el contrario, el estudio ELAIN<sup>171</sup> sí encontró diferencias de supervivencia con el retraso de la TCRR en un grupo de pacientes críticos con FRA y estadio KDIGO 2 aunque tampoco este estudio se diseñó específicamente para evaluar este resultado (5% no requirieron TRR) y además las diferencias en tiempo desde el estadio KDIGO 2 hasta el inicio de la TCRR fueron inesperadamente pequeñas entre el grupo precoz y el grupo diferido (6 horas vs. 25 horas, respectivamente).

En nuestro estudio analizando este subgrupo de pacientes con FRA-S avanzado depurados todos ellos en los primeros 5 días de ingreso en UCI se evidenció que la presencia de oliguria (definida como una diuresis  $\leq 0.05$  mL/kg/h) en las 24 h previas al inicio de la TCRR era predictora de una mayor mortalidad. Sin embargo, un inicio tardío respecto a la variable “tiempo” (definido como el inicio después de 48 horas de ingreso en UCI) no se relacionaba con una mayor mortalidad respecto al grupo de inicio precoz (primeras 48 horas de ingreso en UCI). Estos hallazgos sugieren que los condicionantes o variables que intervienen en la toma de decisiones sobre el inicio de la TCRR en los pacientes con FRA-S son mucho más complejas que una variable “única” como puede ser el “tiempo” o la “creatinina”. Probablemente, es necesario hacer un enfoque individual y “personalizado” de cada caso como así lo recomiendan el grupo de trabajo de la ADQI.<sup>365</sup>

Nuestros hallazgos coinciden con los de Park et al.<sup>369</sup> que en otro estudio observacional en pacientes críticos observaron diferencias de mortalidad entre el grupo precoz ( $\geq 0.24$  mL/kg/h de diuresis) y el grupo tardío ( $< 0.24$  mL/kg/h de diuresis) a favor del grupo precoz. En este caso la diuresis se contabilizaba en las 6 horas previas al inicio de la TCRR. No se observaron diferencias en cuanto al uso de diuréticos o el balance acumulado de fluídos. El inicio de la TCRR antes de la instauración de oliguria en pacientes con estadio avanzado de FRA-S hipotéticamente podría prevenir la aparición de anasarca en este tipo de pacientes críticos en los que la hipervolemia es un reconocido factor de mal pronóstico.<sup>311</sup> Así en el estudio ELAIN,<sup>171</sup> donde los pacientes

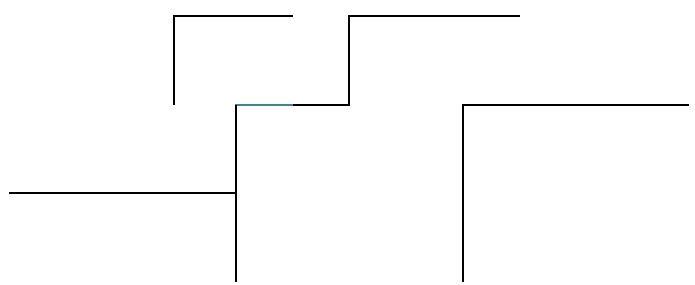
con estadio 2 de la clasificación KDIGO fueron aleatorizados con un balance positivo acumulado medio de 7 litros (el 70% de los pacientes ya estaban oligúricos) a una estrategia precoz o a una estrategia diferida, es posible que el retraso en el inicio de la TCRR en estos pacientes tan sobrecargados de líquido (y con mala tolerancia a la hipervolemia por presencia de cardiopatía) fuese perjudicial como así lo reflejaron las diferencias en la supervivencia encontradas entre un grupo y otro. Además, hay que destacar que en el 80% de los pacientes depurados de forma diferida el criterio de inicio de la TCRR fue la existencia de insuficiencia respiratoria severa a pesar del uso de diuréticos. Por el contrario, en el estudio AKIKI, el análisis de la subpoblación de pacientes con shock séptico, FRA-S y SDRA no evidenció mejorías en la supervivencia con una estrategia precoz de TRR a pesar de la situación respiratoria.<sup>176</sup>

La principal limitación de nuestro estudio viene derivada de su diseño observacional y bicéntrico donde los criterios de inicio de la TCRR no fueron consensuados ni homogeneizados. Los pacientes en los que se inició la TCRR en presencia de oliguria pueden tener otros factores de confusión como la ya mencionada hipervolemia (en nuestro estudio no se recogieron los balances acumulados de fluidos), el uso de diuréticos (tampoco este último parámetro fue recogido en nuestro estudio), el aclaramiento de fármacos o la toxicidad de los mismos. La otra gran limitación de nuestro estudio es que nos centramos exclusivamente en aquellos pacientes que requirieron TCRR y no se analizaron aquellos pacientes que a pesar de desarrollar shock séptico con FRA-S finalmente no requirieron TCRR. Sabemos por estudios recientes que un importante porcentaje de pacientes críticos con shock (la mayoría de ellos séptico) y FRA no requerirán finalmente TRR y que son estos pacientes los que presentan una mejor supervivencia respecto a los pacientes que reciben finalmente TRR.<sup>17,18</sup> Identificar a este tipo de pacientes que finalmente no precisarán TRR (o su contrario) constituye uno de los retos más interesantes en el ámbito de la medicina intensiva.

En el último gran estudio aleatorizado sobre “timing” publicado hasta la fecha (IDEAL-ICU)<sup>18</sup> sigue llamando poderosamente la atención el hecho de que a pesar de que no existen diferencias en la mortalidad entre las dos estrategias evaluadas y de que un elevado porcentaje de pacientes en el grupo diferido no precisan finalmente TRR, la mortalidad en aquellos pacientes del grupo tardío que sí requieren finalmente TRR por causas emergentes dentro de las 48 horas siguientes a la aleatorización (28% de los

pacientes depurados en el grupo tardío) es la mayor de todos los grupos con un 68% de mortalidad respecto al 58 % de mortalidad en los pacientes depurados de forma precoz.

Por lo tanto, en nuestra población a estudio se identificaron claros factores pronósticos con especial interés en la presencia de oliguria al inicio de la TCRR. En esta población de pacientes con shock séptico y estadio 3 de FRA-S la aparición de oliguria nos debería de alertar sobre la conveniencia de iniciar la TCRR sobre todo en aquellos pacientes en los que tengamos signos de hipervolemia.



*Estudio 3*

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## 10.6. Estudio 3: Comparación de dos modalidades de terapia continua de reemplazo renal en pacientes críticos con fracaso renal agudo de origen séptico: ensayo piloto aleatorizado

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### 10.6.1. Objetivos

Evaluar a través de un ensayo piloto aleatorizado y bicéntrico en una población de pacientes críticos con FRA-S e indicación de TCRR:

- La validez y utilidad de una técnica difusiva (HDVVC) asociada a una membrana con capacidad de adsorción en comparación a una técnica convectiva (HVVC) asociada a la misma membrana. Este objetivo se evaluará a través del registro de la duración de los filtros y la incidencia de dialytrauma en las primeras 72 horas después de la aleatorización y durante toda la duración de la TCRR.
- La supervivencia clínica de los pacientes que reciben una técnica difusiva (HDVVC) asociada a una membrana con capacidad de adsorción en comparación a una técnica convectiva (HVVC) asociada a la misma membrana. Este objetivo se evaluará a través del registro de la supervivencia al alta hospitalaria, a los 28 días y a los 90 días.
- La eficacia inmunomoduladora de una técnica difusiva (HDVVC) asociada a una membrana con capacidad de adsorción en comparación a una técnica convectiva (HVVC) asociada a la misma membrana. Este objetivo se evaluará a través del registro del porcentaje de reducción de la concentración plasmática de las diferentes citoquinas durante las primeras 72 horas de TCRR.
- La eficacia depuradora de una técnica difusiva (HDVVC) asociada a una membrana con capacidad de adsorción en comparación a una técnica convectiva (HVVC) asociada a la misma membrana. Este objetivo se evaluará a través del registro de la variación en las concentraciones plasmáticas de los diferentes solutos en las primeras 24 horas de TCRR.



- La eficacia clínica de una técnica difusiva (HDVVC) asociada a una membrana con capacidad de adsorción en comparación a una técnica convectiva (HVVC) asociada a la misma membrana. Este objetivo se evaluará a través del registro de los cambios hemodinámicos y respiratorios en las primeras 72 horas así como de los días en VM y la estancia en UCI.

## 10.6.2. Resultados Estudio 3

### 10.6.2.1. Características de los pacientes

Un total de 6300 pacientes fueron admitidos en las UCIs de los dos centros reclutadores durante el período de estudio. El FRA-S apareció en casi el 40% de estos pacientes durante su ingreso en UCI (un 10% de estos finalmente requirieron TRR) pero únicamente aquellos pacientes con FRA-S que requerían TCRR durante las primeras 72 horas de ingreso en UCI fueron valorados para inclusión en el estudio. Finalmente se incluyeron 110 pacientes con FRA-S (**Fig. 3.1**).

La edad media fue de  $63 \pm 13$  años; 60% de los pacientes eran varones. Las comorbilidades más frecuentes fueron: hipertensión arterial, insuficiencia cardíaca crónica y diabetes mellitus (en el 53%, 32% y 25%, respectivamente). La etiología más frecuente de sepsis fue la infección intrabdominal en el 38% de los pacientes. La media de score SOFA al ingreso en UCI fue de  $14 \pm 2$ , mientras que la media de score APS-II fue de  $25 \pm 9$ . El tiempo medio desde la admisión hospitalaria hasta la TCRR fue de  $95 \pm 113$  h. El tiempo medio desde la admisión en UCI hasta la TCRR fue de  $17 \pm 47$  h. El tiempo medio desde la randomización hasta la TCRR fue de  $1.2 \pm 1.1$  h. Al inicio de la TCRR (basal), el 96% de los pacientes presentaba shock séptico con una dosis media de noradrenalina de  $0.50 \pm 1.0$   $\mu\text{g}/\text{kg}/\text{min}$ , el 81% de los pacientes estaba en VM, y 74% de los pacientes cumplía criterios de FRA avanzado estadio 3 según las guías KDIGO.<sup>26</sup> Las características basales de ambos grupos fueron similares y están representadas en la **Tabla 3.2**.

### 10.6.2.2. Resultados por objetivos

El objetivo de supervivencia a 90 días fue evaluado en todos los pacientes (análisis por intención de tratar) pero el resto de objetivos sólo fueron evaluados en todos aquellos pacientes que estuvieron más de 24 horas (h) con TCRR (n=98). Así mismo, se evaluaron los cambios en las concentraciones plasmáticas de citoquinas de 40 pacientes

(20:20) en los cuales se disponía de la totalidad de las muestras durante las primeras 72 h.

Los pacientes asignados al grupo de HDVVC recibieron  $7\pm 4$  días de TRR en comparación con  $5\pm 3$  días ( $p=0.15$ ) en los pacientes asignados al grupo de HVVC. Los pacientes del grupo de HDVVC presentaron una vida media del circuito de  $29\pm 14$  h en comparación con  $25\pm 10$  h ( $p=0.09$ ) en los pacientes del grupo de HVVC (**Fig 3.2**). En el momento basal (inicio de TCRR), el 23% de los pacientes en el grupo de HDVVC recibieron heparina (anticoagulación sin protamina) en comparación con el 30% de los pacientes del grupo de HVVC ( $p=0.4$ ). Los pacientes del grupo de HDVVC recibieron heparina durante una media de  $130\pm 65$  h en comparación con  $94\pm 70$  h en el grupo de HVVC ( $p=0.5$ ). No se observaron diferencias en la incidencia de trastornos electrolíticos, trombocitopenia, requerimientos transfusionales u otros eventos de dialytrauma entre los pacientes asignados a HDVVC y los pacientes asignados a HVVC. Todos estos resultados están representados en la **Tabla 3.3**.

La supervivencia a los 90 días en el grupo de HDVVC fue del 55.4% y del 42.6% en el grupo de HVVC (diferencia de riesgo 12.8 puntos de porcentaje; 95% CI,  $-5.8$  to  $31.3$ ;  $p=0.25$ ). Las curvas de supervivencia Kaplan-Meier obtenidas a través del log-rank test para ambos grupos han sido representadas en la **Fig. 3.3**. No se observaron diferencias en el porcentaje de tratamiento empírico inicial adecuado (88% en el grupo de HVVC vs 76% en el grupo de HDVVC). El modelo de regresión de Cox fue utilizado para determinar la HRs para la mortalidad a 90 días e incluía todas aquellas variables que habían resultado ser significativas en el análisis univariante y tenían relevancia clínica (**Tabla 3.4**).

No se observaron diferencias en las concentraciones plasmáticas de las citoquinas evaluadas entre el grupo de HDVVC y el grupo de HVVC. La disminución de los niveles plasmáticos de citoquinas expresados en porcentaje de variación respecto a los valores iniciales<sup>374</sup> en ambos grupos está representada en la **Fig. 3.4**.

No se observaron diferencias entre ambos grupos en las variaciones de las concentraciones plasmáticas de solutos durante las primeras 24 h (**Tabla 3.5**) ni en las variaciones hemodinámico-respiratorias en las primeras 72 h de TCRR (**Tablas 3.6 – 3.7**). Los pacientes asignados a HDVVC tuvieron una tendencia a un mayor

aclaramiento de moléculas de pequeño Pm como son la urea y la creatinina, respecto a los pacientes asignados a HVVC ( $p=0.073$  and  $p=0.063$ , respectivamente), mientras que el grupo de HVVC tuvo un aclaramiento más rápido de  $\beta_2$ -microglobulina con respecto al grupo de HDVVC ( $p=0.005$ ). No se observaron diferencias entre grupos (HDVVC y HVVC) en la media de días en VM ( $9\pm 11$  vs.  $12\pm 11$  días;  $p=0.4$ ) ni en la media de días con soporte vasopresor ( $4.1\pm 5$  vs.  $4.7\pm 5$  días;  $p=0.7$ ), respectivamente. No se observaron diferencias entre grupos (HDVVC y HVVC) en la estancia media en UCI ( $17\pm 14$  días vs.  $17\pm 15$  días ( $p=0.9$ ), ni en la estancia media hospitalaria ( $34\pm 23$  días vs.  $42\pm 36$  días ( $p=0.3$ ), respectivamente (**Tabla 3.3**). No se observaron diferencias entre grupos (HDVVC y HVVC) en la diuresis total (Litros, (L)) durante el período de TCRR ( $3.0\pm 4.3$  L vs  $2.9\pm 3.8$  L;  $p=0.9$ ), ni en el balance negativo de fluidos durante el período de TCRR ( $6.5\pm 7$  L vs  $4.6\pm 6.1$  L;  $p=0.2$ ), respectivamente.

### 10.6.3. Discusión estudio 3

Nuestro estudio es el primer ensayo clínico realizado en una población de pacientes críticos exclusivamente con FRA-S y criterios de TCRR que demuestra la factibilidad y seguridad del uso de la HDVVC asociada a una membrana con capacidad de adsorción. Para ello se diseñó un estudio piloto donde los pacientes fueron aleatorizados a recibir HDVVC o HVVC con el mismo tipo de membrana y a la misma dosis durante las primeras 72 horas. A pesar de que los pacientes asignados a HDVVC tuvieron una mayor vida media del circuito esta diferencia no fue estadísticamente significativa y por consiguiente tampoco se observaron diferencias en la incidencia de “dialytrauma” entre un grupo y el otro. No se observaron diferencias significativas en la supervivencia a 90 días entre ambos grupos. Tampoco se observaron diferencias significativas en las variaciones plasmáticas de citoquinas, en las variaciones plasmáticas de solutos, y en la respuesta hemodinámica o respiratoria entre ambos grupos.

Nuestro estudio se diseñó como un ensayo clínico piloto “proof of concept trial” con la idea de demostrar la factibilidad y seguridad de una modalidad en un tipo de paciente específico (FRA-S). En este estudio se analizaron dos estrategias diferentes de TCRR con la idea de describir el funcionamiento de una estrategia puramente difusiva y otra puramente convectiva teniendo en cuenta que las prescripciones de ambas estrategias se hicieron en base a las recomendaciones que existían en el momento del diseño del protocolo. Un estudio previo realizado en una población mixta de pacientes críticos

describió una tendencia (no estadísticamente significativa) a un mayor descenso en los vasopresores con el uso de HVVC respecto a la HDVVC.<sup>375</sup> Un posterior meta-análisis publicado por Friedrich et al.<sup>218</sup> tampoco encontró ventajas con el uso de HVVC respecto a la HDVVC si bien los estudios incluidos en el análisis carecían de la calidad metodológica suficiente como para establecer conclusiones definitivas.

En nuestro estudio, la mayor vida media de las membranas en el grupo de HDVCC coincide con las publicaciones previas donde existía un aumento de casi el 33% en la vida media del circuito con el uso de modalidades difusivas respecto a las convectivas.<sup>215,376,246</sup> Este aumento en la vida media del circuito con el uso de HDVVC en nuestro estudio, aunque no alcanzó la significación estadística, sí se descartó que fuese debido a un mayor consumo de heparina en este grupo. Consideramos que estas diferencias en la vida media de las membranas probablemente podrían haber sido significativas si en nuestro protocolo no se hubiese obligado a hacer un cambio de circuito a las 24 y 48 h con el objetivo de asegurar que la capacidad de adsorción de la membrana estuviese conservada. Basándonos en estudios previos<sup>193</sup> que describían que la saturación del AN69ST podría incluso aparecer antes de las 24 horas de funcionamiento se protocolizaron los cambios comentados y con ello probablemente se disminuyó el impacto que sobre la vida media de la membrana puede tener la difusión en la fase más aguda del proceso séptico (mayor coagulabilidad del circuito en las primeras 72 horas). Además, hay que destacar que en nuestro estudio con el objetivo de no artefactar la dosis difusiva, no se permitió la reposición postfiltro en el grupo de HDVVC a nivel de la cámara “atrapa-burbujas” (como sí se hizo en el estudio OMAKI)<sup>375</sup> con el potencial decremento en la vida media del circuito.

En nuestro estudio con una dosis prescrita de 30 mL/kg/h durante las primeras 72 h de TCRR, no se evidenciaron diferencias en los eventos de dialytrauma evaluados entre la HDVVC y la HVVC. La trombocitopenia ( $<100 \times 10^3/\mu\text{L}$  después del inicio de la TCRR) fue la complicación más frecuente (68%) seguida de la aparición de hipofosfatemia ( $<0.7\text{mmol/L}$ ) en un 59%, e hipotermia (temperatura rectal  $<35.5^\circ\text{C}$ ) en el 58% de los pacientes aleatorizados. La aparición de estos eventos de “dialytrauma” ya habían sido publicados en otros estudios, especialmente en aquellos que evaluaban dosis de TRR más altas, de las cuales el mayor porcentaje era en forma convectiva.<sup>15,16</sup> En nuestro estudio no hubo diferencias en la necesidad de transfusión de hemoderivados entre ambos grupos. El hecho de que las diferencias en la vida media de los circuitos no

fuese suficientemente importante podría también explicar porque no se evidenciaron diferencias en la aparición de trombocitopenia ni tampoco en el consumo de concentrados de hematíes (tanto la trombocitopenia como el consumo de concentrado de hematíes están directamente relacionados con el cambio de membrana o circuito de TCRR).<sup>407</sup>

No se encontraron diferencias estadísticamente significativas entre la supervivencia a los 90 días en un grupo y en el otro, al igual que lo anteriormente publicado en el estudio OMAKI o en el meta-análisis posterior.<sup>375,218</sup> Sin embargo, sí se observó una tendencia a una mayor supervivencia a los 90 días en el grupo de HDVVC que podría justificarse por una posible corrección más rápida de la acidosis y trastornos electrolíticos asociados al FRA-S. A pesar de ello, este resultado precisa ser confirmado con un estudio de mayor muestra poblacional y su explicación es sólo una conjetura. En nuestro estudio no se evidenciaron diferencias en las variaciones plasmáticas de citoquinas (respecto a las concentraciones basales)<sup>374</sup> entre la HDVVC y la HVVC con el uso de una membrana con capacidad de adsorción. Un estudio previo había descrito una mayor capacidad de eliminación de citoquinas con HVVC respecto a la HDVVC, ambas técnicas empleadas con membranas AN69.<sup>186</sup> La mayoría de los estudios que evalúan la capacidad de eliminación de citoquinas se han hecho utilizando dosis altas con técnicas fundamentalmente convectivas (HVVC y HDFVVC) pero no todos ellos han conseguido demostrar una disminución efectiva en los niveles plasmáticos circulantes de citoquinas.<sup>192,195</sup> Diversas teorías<sup>207</sup> han tratado de explicar esta ausencia de efecto a nivel circulatorio a pesar de que en la mayoría de estos estudios sí se constataba una respuesta hemodinámica e incluso respiratoria.<sup>203,187</sup> Además, no existen estudios que hayan conseguido demostrar que la eliminación significativa de citoquinas a través del uso de TCRR tenga un impacto en el pronóstico de los pacientes con FRA-S.<sup>373</sup> Sabemos que los niveles de citoquinas sí se correlacionan con la gravedad del episodio de sepsis<sup>379</sup> e incluso con la supervivencia en aquellos pacientes críticos que finalmente requieren TRR.<sup>381</sup> No obstante, en aquellos pocos estudios que han conseguido demostrar una reducción en los niveles circulantes de citoquinas con el uso de TCRR, esto no se ha correlacionado con una mayor supervivencia.<sup>408</sup> Incluso, existe un estudio experimental<sup>385</sup> que demostraba una mejoría en la supervivencia con el uso de TCRR que no se correlacionaba con una disminución en la concentración de

citoquinas. La eliminación de otras potenciales moléculas dañinas (DAMPs o PAMPs) se ha postulado como una posible explicación.

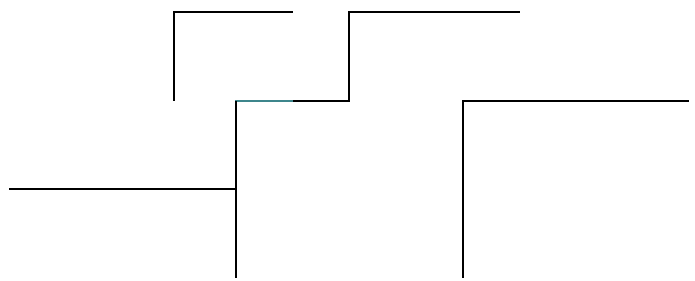
La eliminación de solutos en nuestro estudio fue en líneas generales similar con el uso de HDVVC respecto a la HVVC. Sin embargo, sí se evidenció como ya otros estudios habían reflejado previamente una eliminación más rápida de las moléculas de pequeño Pm con el uso de HDVVC respecto a la HVVC.<sup>215</sup> Este hallazgo apoya el uso de la HDVVC como modalidad de elección en los pacientes con emergencias electrolíticas o del equilibrio ácido-base que presentan inestabilidad hemodinámica motivo por el cual es preferible realizar una TCRR. Por el contrario, la eliminación de  $\beta_2$ -microglobulina en nuestro estudio fue más efectiva con el uso de HVVC que con HDVVC lo cual también es concordante con estudios previos<sup>215</sup> y con el hecho de que las moléculas de mediano Pm son eliminadas con mayor eficacia por convección. Sin embargo, es interesante señalar que no hubo diferencias en la eliminación de otras moléculas de mediano tamaño como uratos o citoquinas entre ambos grupos y esto podría deberse a que estas moléculas quedan atrapadas con mayor facilidad en el espesor de la membrana (“membrane bulk”)<sup>224</sup> respecto a la  $\beta_2$ -microglobulina.

A pesar de que la HVVC se había postulado<sup>203</sup> como una técnica adecuada en los pacientes sépticos con una gran inestabilidad hemodinámica, en nuestro estudio, donde el porcentaje de pacientes con shock y necesidad de VM era superior al 85%, no se evidenciaron diferencias en las variables hemodinámicas y respiratorias evaluadas en las primeras 72 horas de TCRR. Además, hay que señalar que a pesar de que el uso de HVVC con dosis altas se asoció en diversos estudios observacionales a mejorías hemodinámicas y respiratorias,<sup>206,187,386</sup> ninguno de ellos pudo demostrar una correlación entre estas mejorías clínicas y el efecto en la concentración de citoquinas. Algunos estudios incluso señalaban que estas mejorías hemodinámicas se debían al descenso en la temperatura corporal obtenido con las TCRR y no a su efecto sobre los mediadores inflamatorios.<sup>388</sup>

Las limitaciones del estudio están derivadas fundamentalmente de su pequeño tamaño muestral como ya se comentó con anterioridad. Además, es probable que la modalidad de TCRR más utilizada actualmente sea la HDFVVC que ofrece las ventajas de ambas técnicas (difusión y convección).<sup>342</sup> A pesar de esto, creemos que este estudio contribuirá a que en los pacientes con FRA-S e indicación para el inicio de una TCRR

el uso de la dosis de difusión sea preponderante y muy por encima de la hasta ahora recomendada dosis de convección. Por otra parte, somos conscientes del uso cada vez mayor de la anticoagulación regional con citrato que ofrece un alargamiento muy significativo de la vida media del circuito respecto al uso de heparina.<sup>235</sup> Cualquier aumento de la vida media del circuito en este estudio debe de ser interpretado con cautela ya que las opciones de anticoagulación estaban limitadas al uso o no de heparina. Es posible que si la anticoagulación regional con citrato hubiese estado disponible, la cual está recomendada como método de elección para la anticoagulación de las TCRR,<sup>26</sup> los beneficios obtenidos con el uso de la HDVVC a nivel de vida media del circuito hubieran sido inciertos. Sin embargo, existen todavía un grupo importante de pacientes críticos con FRA-S que presentan contraindicaciones para el uso de anticoagulación regional con citrato especialmente en la fase más aguda de la sepsis y en los cuales el uso de HDVVC asociada a una membrana con capacidad de adsorción podría ser una opción aceptable a la hora de iniciar la TCRR.<sup>390,26</sup>

Por lo tanto en nuestro estudio piloto en pacientes críticos con FRA-S demostramos que el uso de una modalidad de HDVVC asociada a una membrana con capacidad de adsorción es tan eficaz y eficiente como la HVVC. Se observó una tendencia a un menor consumo de circuitos con el uso de HDVVC. No se observaron diferencias entre ambas modalidades en la incidencia de efectos adversos relacionados con la técnica (dialytrauma) ni en la supervivencia. Así mismo, tampoco se observaron diferencias entre ambas modalidades en las concentraciones plasmáticas de citoquinas ni de solutos, ni en la respuesta hemodinámica y respiratoria durante las primeras 72 h de TCRR.



*Discusión conjunta*

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## 10.7. Discusión conjunta

La aparición de FRA-S tiene un claro impacto pronóstico de los pacientes con críticos con sepsis.<sup>3,266</sup> Una parte importante de los pacientes con sepsis que ingresan en la UCI ya presentan FRA-S en el momento en que se identifica la sepsis pero otra parte importante de pacientes desarrollarán este FRA-S después de su ingreso en UCI.<sup>155</sup> Además, incluso en los pacientes diagnosticados inicialmente de FRA-S se producirá un empeoramiento de la función renal en los siguientes días o incluso semanas.<sup>3,155</sup> En nuestro estudio, independientemente de la función renal en el momento de la identificación de la sepsis, el empeoramiento en el estadio de FRA-S (según la clasificación KDIGO) o a la nueva aparición de FRA-S durante los siguientes 7 días desde el inicio de la sepsis se asoció a una disminución significativa de la supervivencia a los 90 días. Hay que destacar que a pesar de nuestros criterios restrictivos para clasificar como FRA-S a los pacientes del estudio (no se consideraron como FRA-S aquellos pacientes que a pesar de tener FRA en el momento del inicio de la sepsis no presentaron un empeoramiento del estadio en los siguientes 7 días), la incidencia final en esta cohorte unicéntrica de pacientes críticos con sepsis fue muy alta.<sup>266,42,3</sup>

En nuestro estudio inicial un importante porcentaje de pacientes sépticos presentaban hipotensión arterial y esto estaba claramente asociado con la aparición de FRA-S al igual que la presencia de una etiología abdominal de sepsis que es un factor de riesgo conocido para el desarrollo de FRA-S.<sup>2,294</sup> Es importante destacar que los requerimientos de TRR en estos pacientes que desarrollaron FRA-S fueron elevados (hasta un 37% de los pacientes con FRA-S precisaron de TRR) lo que refleja la severidad e impacto que la aparición del FRA-S tiene en los pacientes críticos con sepsis. Siguiendo esta línea argumental, los pacientes sépticos con hipotensión arterial que presentan un elevado riesgo de desarrollar estadios avanzados de FRA-S,<sup>97</sup> requerirán frecuentemente soporte con TCRR ya que su situación hemodinámica puede limitar el empleo de otras formas de TRR.<sup>28,45,354</sup>

Las recomendaciones de la SSC<sup>289</sup> fueron evaluadas en nuestro estudio unicéntrico de pacientes críticos con el objetivo de medir o evaluar el efecto que la aplicación de las mismas tenía en la incidencia de FRA-S. A pesar de que en nuestra población a estudio el cumplimiento de las recomendaciones (SSC) fue globalmente bajo, en contraposición a otros resultados publicados<sup>1</sup> con anterioridad no encontramos una disminución en la

incidencia de FRA-S en el grupo de pacientes con un alto cumplimiento. Cuando se analizaron las medidas o recomendaciones de forma individualizada tampoco se encontró una correlación entre la administración precoz de antibiótico y una disminución en la incidencia de FRA-S. En los pacientes que presentaban hipotensión arterial la resucitación hemodinámica guiada por objetivos (EGDT) tampoco obtuvo una disminución en la incidencia de FRA-S. Únicamente el cumplimiento de algunas de las medidas de mantenimiento pareció asociarse a una disminución en la incidencia de FRA-S especialmente el control glucémico y la ventilación mecánica protectora (en aquellos pacientes que requirieron VM invasiva). Por consiguiente, en nuestro estudio las medidas recomendadas para el tratamiento de la sepsis (especialmente las medidas de resucitación inicial) no parece que disminuyan la incidencia de FRA-S que en pacientes críticos está a su vez claramente asociada a la presencia de hipotensión arterial,<sup>97,293</sup> en ocasiones soporte vasopresor, y por consiguiente shock séptico. Estos pacientes con shock séptico y FRA-S tienen altos requerimientos de TRR que en la mayoría de ocasiones se tienen que hacer en forma de TCRR por la inestabilidad hemodinámica.<sup>342</sup> La mortalidad en esta población de pacientes con shock séptico y FRA-S que precisan de TCRR es muy elevada y claramente asociada a scores elevados de gravedad como parte en la mayoría de ocasiones de un SDMO.<sup>47,1</sup>

En un estudio de cohortes internacional y bicéntrico analizamos casi 1000 pacientes con FRA-S que requirieron TCRR en el contexto de una situación de shock séptico. Se identificaron como factores de mal pronóstico (mortalidad a los 90 días del inicio de la TCRR) una mayor edad, un mayor score de severidad, un intervalo mayor de tiempo desde el ingreso hospitalario al inicio de la TCRR, un mayor BUN al inicio de la TCRR, una menor diuresis y menor creatinina al inicio de la TCRR, y una causa de admisión médica respecto a la admisión quirúrgica.

No se encontró asociación entre el estadio de FRA-S según la escala KDIGO y la mortalidad a los 90 días de acuerdo con lo publicado en otros estudios también de corte observacional pero con poblaciones más pequeñas y heterogéneas que la nuestra.<sup>344,169</sup> La creatinina sérica es un mal parámetro para decidir el inicio de la TCRR (“timing”) como así lo reflejan la mayoría de los estudios<sup>345,276,341</sup> incluyendo el nuestro en el cual los pacientes con FRA-S en los que se iniciaba la TCRR con valores bajos de creatinina presentaban una mayor mortalidad reflejando como anteriormente se comentó una probable situación de hipervolemia y estadios de caquexia así como formas más severas

de sepsis (los pacientes en los que se inicia la TCRR antes, están en ocasiones más graves que aquellos en los cuales se puede establecer una estrategia de “esperar y ver”). Sin embargo, sí se observó una clara relación entre la urea y la diuresis ambos al inicio de la TCRR y la mortalidad. Una diuresis baja y una urea elevada son claros factores de riesgo para la mortalidad a 90 días revelando una vez más que el estadiaje del FRA-S basado exclusivamente en la creatinina es un mal indicador de la gravedad o severidad de los pacientes que finalmente requerirán TRR.<sup>164,168,169</sup> Tanto la urea como la diuresis ya habían sido descritos previamente como marcadores de severidad del FRA en pacientes con necesidad de TRR aunque ninguno de estos estudios se había llevado a cabo en una población exclusivamente de pacientes con shock séptico.<sup>341,167</sup>

El inicio de las TCRR debe de estar basado en criterios inmediatos y emergentes que son bien conocidos.<sup>26</sup> La hipótesis de que las estrategias más precoces de inicio de la TCRR pudieran mejorar el pronóstico de los pacientes con FRA-S fue evaluado en un subgrupo de pacientes de nuestro estudio todos ellos en situación de shock séptico y FRA-S avanzado (estadío 3 KDIGO) en las primeras 24 horas de ingreso en UCI y todos ellos “iniciados” en TCRR en los 5 primeros días de ingreso. El objetivo de esta selección era el de homogeneizar al máximo la población para poder evaluar, basándonos en la identificación previa de los factores de riesgo para mortalidad, si la “diuresis en las 24 horas previas a TCRR” y el “tiempo desde ingreso en UCI hasta TCRR” podían tener validez como variables para decidir el “timing” de las TCRR con un potencial impacto en la supervivencia. Así se establecieron dos estrategias (precoz y diferida) basándonos en la cantidad de diuresis en las 24 horas previas al inicio de la TCRR (mayor o menor a 0.05 mL/Kg/h) o en el tiempo desde el ingreso en UCI hasta el inicio de la TCRR (mayor o menor a 48 horas). Esta metodología es similar a la de otros estudios observacionales que evidenciaron mejorías en la supervivencia con estrategias precoces de timing basadas en diferentes parámetros (especialmente urea y tiempo desde UCI hasta TCRR).<sup>167,160</sup> Sin embargo ninguno de estos estudios se había realizado en una cohorte homogénea de pacientes con el mismo estadío de FRA-S al inicio de la TCRR.

En nuestro estudio la diuresis resultó ser más útil a la hora de decidir el inicio de la TCRR en comparación con la variable tiempo desde el ingreso en UCI. De los resultados obtenidos podríamos concluir que una estrategia precoz de TCRR debería estar restringida a aquellos pacientes con disminución de la diuresis y signos clínicos de

hipervolemia a pesar del uso de diuréticos pero esto tan sólo es una hipótesis extraída de nuestro estudio observacional donde faltan muchos de los datos necesarios como son el registro del balance de flúidos, las dosis de diuréticos, o el peso del paciente (para definir el estado de hipervolemia). Nuestra hipótesis sería que el uso precoz de la TCRR (dentro del estadio 3 KDIGO del FRA-S) antes de la instauración de una diuresis baja u oliguria (en nuestro estudio la definimos como  $\leq 0.5$  mL/Kg/h en las 24 horas previas al inicio) podría potencialmente prevenir la aparición de hipervolemia que es un reconocido factor de mal pronóstico en los pacientes con FRA-S.<sup>242</sup> No obstante, esta hipótesis debería individualizarse ya que la tolerancia de cada paciente a una situación de hipervolemia depende de diversos factores como son entre otros la reserva cardiovascular, el status nutricional, o el estado de permeabilidad capilar en relación a la sepsis.<sup>393-396</sup>

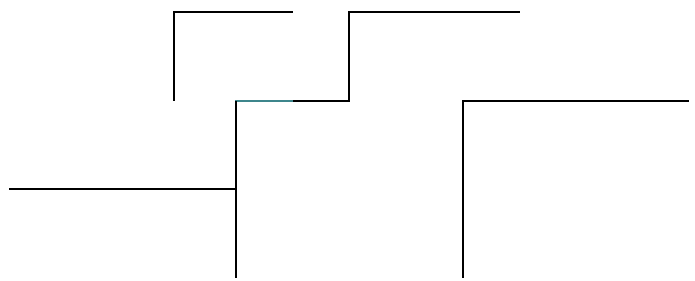
En nuestro estudio internacional y bicéntrico donde se identificaron los diferentes factores asociados a la mortalidad, ninguno de ellos tenía relación específicamente con la TCRR aunque faltaban algunas variables importantes como la dosis renal prescrita o el balance de flúidos después del inicio de la TCRR. Los resultados de otros estudios<sup>375</sup> y nuestra propia experiencia acumulada tras años de ensayar y evaluar diferentes dispositivos de terapia extracorpórea nos sugieren que algunas modalidades de TRR pueden ser más eficientes en relación a la duración del circuito y menos lesivos en relación la aparición de eventos adversos conocidos como “dialytrauma”.<sup>173</sup> Las modalidades convectivas de TCRR (fundamentalmente la HVVC y la HDFVVC) han sido empleadas de forma sistemática en los pacientes críticos con FRA-S con el objetivo de conseguir una hipotética inmunomodulación que pudiera modificar el pronóstico de estos pacientes.<sup>200</sup> Sin embargo, no existen estudios sólidos que demuestren un beneficio con el uso de la convección más allá de la capacidad en la eliminación de solutos y flúidos inherente a prácticamente todas las modalidades de TCRR.<sup>15,16</sup> Además la vida media del circuito (especialmente de la membrana) puede disminuir con el uso de convección<sup>376,246</sup> especialmente en aquellos pacientes en los que no se pueda utilizar anticoagulación regional con citrato.<sup>27,390</sup> Este aumento de la coagulación del filtro o membrana puede dar lugar a un aumento en el número de eventos de dialytrauma especialmente las transfusiones de hemoderivados y la incidencia de trombocitopenia.

Por otra parte, el desarrollo de nuevas membranas con capacidad de adsorción podría permitir la eliminación de citoquinas de la circulación de los pacientes con FRA-S que requieran TCRR sin la necesidad del uso de convección.<sup>225</sup> Así, en pacientes críticos con FRA-S que cumplan criterios para el inicio de TCRR el uso de una estrategia difusiva como la HDVVC asociada a una membrana con capacidad de adsorción podría hipotéticamente aumentar la vida media del circuito y disminuir la incidencia de eventos de dialytrauma. Para demostrar esta hipótesis diseñamos un estudio piloto bicéntrico y aleatorizado en pacientes críticos con FRA-S que requerían TCRR. Durante 3 años se incluyeron y aleatorizaron pacientes críticos con FRA-S con el objetivo de comparar el uso de HDVVC asociada a una membrana con capacidad de adsorción con el uso de HVVC asociada a la misma membrana. Los pacientes fueron “iniciados” en TCRR (según grupo asignado), todos con la misma dosis de 30 mL/kg/h que se mantuvo como mínimo hasta las 72 horas después del inicio de la TCRR. Las membranas se cambiaron por protocolo a las 24 y 48 horas con el objetivo de asegurar la capacidad de adsorción de la membrana. Al igual que en estudios previos,<sup>215</sup> observamos una tendencia al aumento de la vida media del circuito con el uso de HDVVC aunque esto no se acompañó de una disminución en el número de eventos de dialytrauma (probablemente debido al pequeño tamaño muestral).

Este grupo de pacientes críticos con FRA-S que requieren TCRR como previamente se ha comentado presentan una elevada mortalidad y es por ello que históricamente se han ensayado diferentes estrategias de TRR con el objetivo de disminuir dicha mortalidad. Aunque nuestro estudio como ensayo piloto no tiene potencia estadística suficiente para demostrar diferencias en la supervivencia, sí observamos una tendencia a una mayor supervivencia en el grupo de HDVVC aunque estos resultados necesitan ser confirmados con un ensayo clínico mucho mayor. Este hipotético beneficio en la supervivencia podría justificarse por una eliminación más rápida de los solutos de bajo Pm y por consiguiente una corrección más rápida de la acidosis en el grupo de HDVVC respecto al grupo de HVVC. Se midieron las concentraciones plasmáticas de citoquinas durante las primeras 72 horas y no se evidenciaron diferencias en las variaciones plasmáticas entre ambas modalidades (HDVVC y HVVC) con el uso de una membrana con capacidad de adsorción. Las diferencias en las concentraciones plasmáticas de IL-1, IL-4, IL-6, IL-10, y TNF- $\alpha$  se determinaron en relación a las concentraciones plasmáticas basales (momento de inicio de la TCRR).<sup>374</sup> Al igual que en estudios

previos<sup>373</sup> no se evidenció una clara asociación entre las variaciones plasmáticas de citoquinas y la respuesta hemodinámica o respiratoria aunque estos análisis todavía están bajo revisión al igual que la determinación de la capacidad adsorptiva de la propia membrana según la modalidad asignada. Sin embargo, el hecho de que no hubiese diferencias en la respuesta hemodinámica y respiratoria entre ambos grupos nos hace pensar que realmente tampoco existieron diferencias en la capacidad de eliminación de citoquinas entre ambos grupos de tratamiento.

Basándonos en todos estos hallazgos podemos concluir que la incidencia y mortalidad del FRA-S en las poblaciones de pacientes críticos con sepsis son elevadas especialmente en aquellos que presentan hipotensión arterial o shock séptico. Estos últimos, debido a su gravedad a menudo requieren de TCRR que deberían ser iniciadas únicamente en estadios avanzados de FRA-S (estadio 3 KDIGO) con criterios inmediatos de inicio y el apoyo de la diuresis en aquellos pacientes con signos de hipervolemia sin respuesta a diuréticos (aunque esto debe de ser individualizado). Finalmente, el uso de TCRR en pacientes críticos con FRA-S debe de hacerse con modalidades preferentemente difusivas (HDVVC) asociadas a una membrana con capacidad de adsorción lo que parece que aumenta la vida media del circuito sin que existan diferencias clínicas en comparación a las modalidades convectivas (HVVC).



*Conclusiones*

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## 10.8. Conclusiones

1. En una cohorte unicéntrica de pacientes críticos con sepsis y un bajo cumplimiento de las recomendaciones de la SSC, la aparición de FRA-S en la primera semana desde el diagnóstico de sepsis es elevada y empeora el pronóstico en cuanto su supervivencia a los 90 días. *Por lo tanto, en los pacientes críticos con sepsis se deben de establecer protocolos de vigilancia y tratamiento con el objetivo de prevenir la aparición de FRA-S.*
2. En una cohorte unicéntrica de pacientes críticos con sepsis solo se identificaron como factores de riesgo para la aparición de FRA-S dentro de la primera semana desde el diagnóstico de sepsis, la presencia de hipotensión arterial y la presencia de una etiología abdominal. *Por lo tanto, evitar la hipotension arterial y vigilar de forma especial (¿monitorización presión intraabdominal?, control precoz del foco) a los pacientes con sepsis de origen abdominal deberían ser dos medidas fundamentales en el manejo de los pacientes críticos con sepsis.*
3. En una cohorte unicéntrica de pacientes críticos con sepsis y un bajo cumplimiento de las recomendaciones de la SSC, ninguna de las medidas recomendadas obtuvo una disminución significativa de la incidencia de FRA-S en la primera semana después del diagnóstico de sepsis.
4. En una cohorte internacional y bicéntrica de pacientes críticos con shock séptico y FRA-S en la que todos ellos recibieron TCRR, se identificaron como factores pronósticos asociados a una mayor mortalidad a los 90 días del inicio de la TCRR, la edad, la urea plasmática al inicio de la TCRR, y los días desde el ingreso hospitalario hasta la TCRR.
5. En una población internacional y bicéntrica de pacientes críticos con shock séptico y FRA-S en la que todos ellos recibieron TCRR, se identificaron como factores pronósticos asociados a una menor mortalidad a los 90 días del inicio de la TCRR, la creatinina plasmática al inicio de la TCRR, la diuresis previa (24 horas) al inicio de la TCRR, y la sepsis de origen abdominal.
6. En una población internacional y bicéntrica de pacientes críticos con shock séptico y FRA-S avanzado (estadío 3 de la clasificación KDIGO), en la que todos ellos

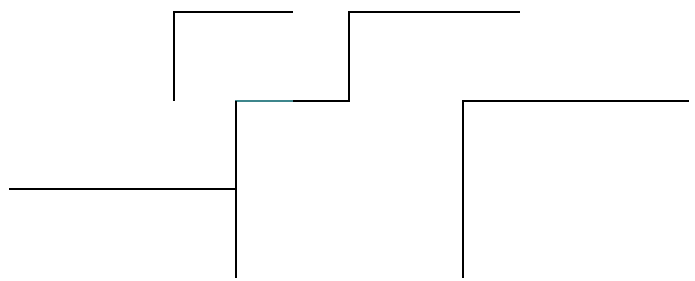
recibieron TCRR dentro de los 5 primeros días de ingreso en UCI, el inicio de la TCRR en presencia de oliguria se asoció a una mayor mortalidad a los 90 días.

7. En un ensayo clínico piloto bicéntrico y aleatorizado en una población de pacientes críticos con FRA-S e indicación de TCRR, el uso de HDVVC con 30 mL/kg/h durante 72 horas asociada a una membrana con capacidad de adsorción, no aumentó la vida media del circuito ni disminuyó la incidencia de “dialytrauma” respecto a un grupo control donde se utilizó HVVC con la misma dosis y asociada a la misma membrana.
8. En un ensayo clínico piloto bicéntrico y aleatorizado en una población de pacientes críticos con FRA-S e indicación de TCRR, el uso de HDVVC con 30 mL/kg/h durante 72 horas asociada a una membrana con capacidad de adsorción, no presentó diferencias significativas en la supervivencia a los 90 días respecto a un grupo control donde se utilizó HVVC con la misma dosis y asociada a la misma membrana.
9. En un ensayo clínico piloto bicéntrico y aleatorizado en una población de pacientes críticos con FRA-S e indicación de TCRR, el uso de HDVVC con 30 mL/kg/h durante 72 horas asociada a una membrana con capacidad de adsorción, no presentó diferencias en las variaciones plasmáticas de citoquinas durante las primeras 72 horas respecto a un grupo control donde se utilizó HVVC con la misma dosis y asociada a la misma membrana.
10. En un ensayo clínico piloto bicéntrico y aleatorizado en una población de pacientes críticos con FRA-S e indicación de TCRR, el uso de HDVVC con 30 mL/kg/h durante 24 horas asociada a una membrana con capacidad de adsorción, no presentó diferencias significativas en las variaciones plasmáticas de solutos respecto a un grupo control donde se utilizó HVVC con la misma dosis y asociada a la misma membrana.
11. En un ensayo clínico piloto bicéntrico y aleatorizado en una población de pacientes críticos con FRA-S e indicación de TCRR, el uso de HDVVC con 30 mL/kg/h durante 72 horas asociada a una membrana con capacidad de adsorción, no presentó diferencias significativas en la respuesta hemodinámica y respiratoria respecto a un

grupo control donde se utilizó HVVC con la misma dosis y asociada a la misma membrana.

12. El uso de HDVVC en pacientes críticos con FRA-S e indicación de TCRR es seguro y eficaz. No obstante, se requiere de la realización de más estudios aleatorizados y de mayor muestra poblacional para confirmar la hipótesis de que el uso de HDVVC asociada a una membrana con capacidad de adsorción en pacientes críticos con FRA-S podría ser superior en términos de eficiencia técnica (menor consumo de membranas, menor dialytrauma) y eficacia clínica (mayor supervivencia), respecto al uso de HVVC.





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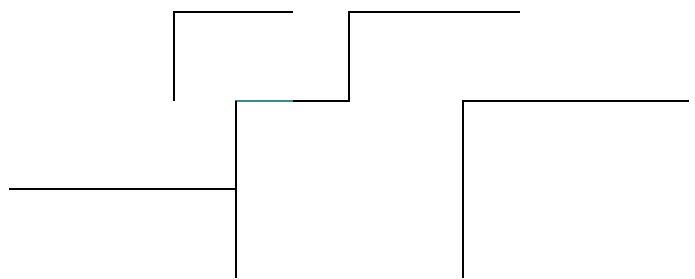
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*Supplementary appendix 1*

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# Management of Acute Kidney Injury and Acid-Base Balance in the Septic Patient

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## KEYWORDS

• Acute kidney injury • Acute renal failure • Sepsis • Acid-base • Biomarkers  
• Renal replacement therapy

## KEY POINTS

- Acute kidney injury (AKI) is an abrupt decrease in kidney function that takes place over hours to days that is associated with increased morbidity and mortality in sepsis.
- Many trials have studied pharmacotherapies to prevent or treat AKI, with disappointing results.
- Management strategies for septic AKI should focus around treatment of underlying sepsis, maintaining adequate intravascular volume and avoiding fluid overload, maintaining adequate mean arterial pressure for renal perfusion, and avoidance of nephrotoxic agents.
- The mainstay of current treatment for septic AKI is renal replacement therapy, which can be delivered either intermittently or continuously.

## INTRODUCTION

### Definitions

Broadly speaking, acute kidney injury (AKI, also known as acute renal failure) is an abrupt decrease in kidney function that occurs over hours to days. This is in contradistinction to chronic kidney disease (CKD), where renal function declines over the course of months to years. In 2004, the Acute Dialysis Quality Initiative (ADQI) published the first AKI consensus definition, with the goal of standardizing disease recognition and endpoints for clinicians as well as for research studies, including clinical trials.<sup>1</sup> The RIFLE criteria (an acronym that stands for risk, injury, failure, loss, and end-stage renal disease [ESRD]) use acute changes in serum

creatinine and urine output, 2 readily available measurements, to define 3 progressive levels of renal dysfunction (R, I, and F) and 2 clinical outcomes (L, E). These criteria were subsequently refined by the Acute Kidney Injury Network (AKIN) and then by the Kidney Disease Improving Global Outcomes (KDIGO) group (Table 1).<sup>2,3</sup> The association of AKI defined by these criteria with adverse outcomes has now been validated in a large number of clinical studies.<sup>4–8</sup>

### Epidemiology

These consensus definitions for AKI have greatly facilitated large epidemiologic studies examining the incidence and outcomes of AKI. Using RIFLE

K.D. Liu adjudicated clinical outcomes for clinical trials by Astute. The other authors have nothing to disclose.

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**Table 1**  
**Comparison of creatinine-based consensus definitions for acute kidney injury**

	RIFLE Criteria	AKIN Criteria	KDIGO Criteria
R(isk)	SCr $\geq$ 150% baseline within 7 d, OR >25% decrease in eGFR	Stage 1 SCr $\geq$ 150% baseline, OR SCr $\geq$ 0.3 mg/L increase within 48 h	SCr $\geq$ 150% baseline within 7 d, OR SCr $\geq$ 0.3 mg/L increase within 48 h
I(njury)	SCr $\geq$ 200% baseline, OR >50% decrease in eGFR	Stage 2 SCr $\geq$ 200% baseline	SCr $\geq$ 200% baseline
F(ailure)	SCr $\geq$ 300% baseline OR SCr >4 mg/dL with acute rise >0.5 mg/dL, OR >75% decrease in eGFR	Stage 3 SCr $\geq$ 300% baseline, OR SCr $\geq$ 4 mg/dL with acute rise of $\geq$ 0.5 mg/dL, OR initiation of RRT	SCr $\geq$ 300% baseline, OR SCr $\geq$ 4 mg/dL, <sup>a</sup> OR Initiation of RRT, OR If <18 y, eGFR <35 mL/min/1.73m <sup>2</sup>
L(oss)	Persistent loss for >4 wk	—	—
E(nd-stage kidney disease)	ESRD >3 mo	—	—

Urine output criteria are the same for all 3 staging systems and are as follows: stage 1: <0.5 ml/kg per hour for 6 to 12 hours; stage 2: <0.5 ml/kg per hour for  $\geq$ 12 hours; stage 3 <0.3 ml/kg per hour for  $\geq$ 24 hours OR anuria  $\geq$ 12 hours.

Abbreviations: AKIN, Acute Kidney Injury Network; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; KDIGO, Kidney Disease Improving Global Outcomes; RRT, renal replacement therapy.

<sup>a</sup> Must meet criteria for stage 1 as well.

criteria to define AKI, numerous large studies have found that the incidence of AKI during an admission to the intensive care unit (ICU) is often greater than 60%, although this rate will vary depending on the ICU population (medical ICU vs neurosurgery ICU, for example).<sup>4,9-11</sup> Other studies have found that sepsis contributes in 33% to 50% of all cases of AKI, making sepsis the leading cause of AKI.<sup>5,12,13</sup> Along the same lines, sepsis studies have found that AKI develops in 40% to 60% of these patients.<sup>14-19</sup> Not surprisingly, sepsis that is complicated by AKI has a higher mortality rate than sepsis alone, and the severity of sepsis correlates with the severity of AKI.<sup>18,20</sup> Mortality rates of patients with AKI needing renal replacement therapy (RRT) are approximately 35% to 50%, although again will vary based on the population.<sup>21,22</sup>

### Pathophysiology

Septic AKI was classically thought to be caused by an ischemic "pre-renal" etiology, attributed to hypoperfusion due to decreased renal blood flow in the setting of leaky vasculature and systemic vasodilation leading to decreased preload. However, several studies have disputed this notion, and research studies are ongoing. For example, arguing against a central role for hypoperfusion per se, a large cohort study found that 25% of hospitalized patients with community-acquired

pneumonia who never developed shock or required ICU admission developed AKI.<sup>23</sup>

A major insight in the pathophysiology of sepsis-induced AKI came from an autopsy series of 44 patients who died of sepsis, which found that the degree of renal tubular cell injury in most patients was regional within the kidney, not severe enough to explain the AKI, and most tubular cells appeared relatively normal by electron microscopy.<sup>24</sup> Furthermore, it is unclear if renal blood flow uniformly decreases during sepsis in humans. A systematic review on this topic concluded that cardiac output is the major determinant of renal blood flow, and because cardiac output is typically increased in sepsis, consequently global renal blood flow may therefore be unchanged or even increased.<sup>25</sup> However, the glomerular filtration rate (GFR) may still be reduced in the face of normal or supranormal blood flow due to changes in afferent and efferent arteriole vasoconstriction.

Thus, it is thought that a large component of septic AKI is due to functional rather than structural or ischemic injury per se.<sup>26</sup> This is supported by histopathology from large animal models.<sup>27</sup> These effects may be mediated by proinflammatory cytokines and other plasma mediators. For example, plasma from patients with septic AKI can induce changes in polarity in podocytes and renal tubular epithelial cells in *in vitro* cell culture.<sup>28</sup> Recently, Gomez and colleagues<sup>29</sup> proposed a "unifying theory" of septic AKI. In this analysis,

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the decrease in GFR is in part an adaptive response to inflammatory mediators such as cytokines and lipopolysaccharide (LPS) in which renal tubular cells downregulate metabolic function to use energy toward cell survival.<sup>29</sup> There is also microvascular blood flow dysregulation within the kidneys, which may act to further enhance this adaptive downregulation of cellular metabolism or contribute to regional cellular dysfunction.<sup>29</sup> Furthermore, it has been proposed that both the afferent and efferent arterioles vasodilate, with the efferent arteriole preferentially dilating more.<sup>30</sup> This leads to decreased glomerular capillary pressure and thus decreased GFR.<sup>30</sup> In support of this theory, in animal models of sepsis, use of a selective efferent arteriole vasoconstrictor, angiotensin II, has been shown to increase GFR and urine output.<sup>30</sup>

In sum, at this time the exact mechanism of septic AKI is not fully elucidated. Nonetheless, it seems clear that the primary mechanism is not isolated hypoperfusion. As research in this arena continues, hopefully we will find clinically relevant targets to mitigate the deleterious effects of sepsis on the kidney. As an example, catalytic iron (iron that is not bound to transferrin or protein and is released during tissue injury and during hemolysis) has been proposed to be injurious to the kidney.<sup>31</sup> At least one source of catalytic iron is plasma-free hemoglobin, which can derive from hemolysis or red blood cell transfusions. Furthermore, it is thought that plasma-free hemoglobin itself may cause cell damage through oxidation of lipid membranes.<sup>32</sup> A small single-center, randomized, double-blind, placebo-controlled trial compared 3 days of enteral acetaminophen with placebo in reducing oxidative injury in patients with severe sepsis and detectable plasma cell-free hemoglobin.<sup>32</sup> The proposed mechanism is the ability of acetaminophen to reduce the ferryl radical in the free hemoglobin and thus prevent lipid peroxidation. In this small study, acetaminophen improved renal function during and after the study.<sup>32</sup> Although there are many limitations to generalizability, this finding warrants further investigation in larger trials and highlights the importance of further studies focused on the pathogenesis of septic AKI.

#### Risk Factors

Many studies have examined clinical risk factors for AKI; however, relatively few studies have specifically focused on patients presenting with sepsis. In a large prospective cohort study of 390 patients who presented in septic shock without preexisting ESRD or AKI, 237 (61%) developed

AKI.<sup>15</sup> Delay in antibiotic administration, intra-abdominal sepsis, use of blood products, angiotensin-converting enzyme (ACE)-inhibitor/angiotensin receptor blocker (ARB) use, and elevated body mass index were independently associated with development of septic AKI.<sup>15</sup> Higher baseline GFR and successful early goal-directed resuscitation were associated with better renal outcomes.<sup>15</sup> In a large retrospective study of nearly 1000 patients presenting with sepsis,<sup>19</sup> increasing age, CKD, ACE-inhibitor/ARB use, shock, positive blood cultures, and lower white blood cell or platelet counts were all independently associated with development of septic AKI.<sup>19</sup> Although studies like these are important to elucidate potential targets for clinical intervention, unfortunately a number of risk factors (age, CKD) are not modifiable, and some targets represent “best clinical practice” for sepsis. For example, early antibiotic administration has been shown to decrease mortality in sepsis and is a cornerstone of sepsis management, and may also help mitigate septic AKI.

#### MANAGEMENT GOALS

At present, no specific treatments exist for either the prevention or treatment of septic AKI, with the exception of supportive care for established AKI with RRT. The optimal care of patients at risk for septic AKI or with established AKI is supportive care and avoidance of nephrotoxins. Fluid management in patients with sepsis is discussed extensively in other sections of this issue, so we focus on issues related specifically to patients with established AKI in this article.

#### “Euvolemia”

As discussed earlier, septic AKI is much more complex than decreased renal perfusion; however, improving renal perfusion in the setting of hypotension may help mitigate some of the harmful effects of septic AKI. Renal blood flow can be estimated as follows:  $\text{Renal Blood Flow} = (\text{Mean Arterial Pressure} - \text{Renal Venous Pressure}) / \text{Renal Vascular Resistance}$ . Although this is probably an oversimplification of actual renal blood flow, it conceptualizes the importance of attempting to find the “sweet spot” of “euvolemia” when resuscitating a septic patient; by this, we mean a fluid state in which intravascular volume is optimized with minimal fluid overload. We can see that renal blood flow can be affected by mean arterial pressure (MAP), renal venous pressure, and renal vascular resistance. It has long been known that hypovolemia produces “pre-renal” ischemic AKI, and the treatment

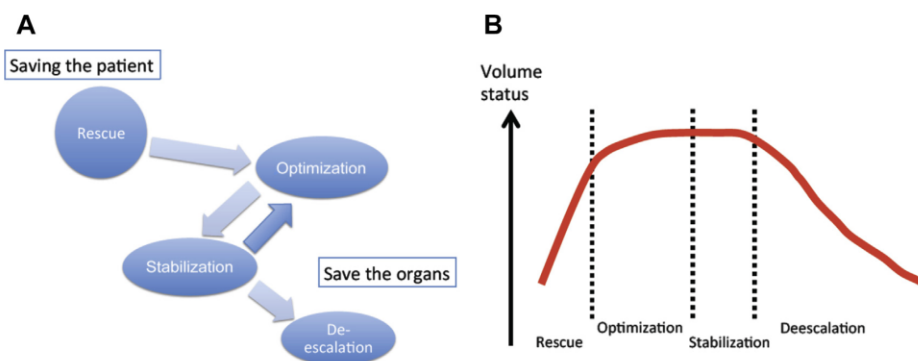
is fluid administration to improve cardiac output and thus oxygen delivery to the kidneys; however, it has become increasingly clear that overzealous fluid administration can cause AKI as well.<sup>33–35</sup> If the renal venous pressure increases, as it often does when large amounts of fluid are administered, it can lead to decreased renal blood flow and decreased GFR.<sup>35</sup> The combination of low MAP and intra-abdominal hypertension (which increases renal venous pressure), which are often seen in sepsis, may contribute to AKI. In the surgical literature there is some evidence that goal-directed therapy, which is a protocol that tries to maximize cardiac output through fluid and inotrope administration, may decrease incidence of AKI.<sup>33</sup> However, 3 recent large sepsis trials found no benefit with early goal-directed therapy compared with usual care with regard to mortality or kidney outcomes.<sup>36–38</sup> A small retrospective study looking specifically at the development of AKI in a cohort of patients treated with early goal-directed therapy versus those treated with usual care found no difference in development of AKI (46% vs 51%, respectively).<sup>17</sup>

The ADQI had a recent consensus conference on fluid therapy.<sup>39</sup> As part of this conference, a conceptual framework for fluid management was proposed (Fig. 1) that highlights the importance of individualizing fluid resuscitation and the fact that the goals of fluid therapy may vary over the course of disease.<sup>40</sup> Early on, during the “rescue” phase of resuscitation, fluids are needed to improve circulation, as described previously. This is followed by “optimization” and “stabilization” phases in which fluid therapy is titrated to the

individual patients. Finally, during the recovery phase, “deescalation” of fluid therapy, which may include diuretics to enhance fluid mobilization, is needed to avoid the sequelae of volume overload. In this context, it should be noted that retrospective studies of clinical trials of fluid management have suggested that positive fluid balance, but not diuretic administration, is associated with increased mortality in patients with the acute respiratory distress syndrome and early AKI.<sup>41</sup>

#### Mean Arterial Pressure Goals

Autoregulation is the ability of an organ to maintain a relatively constant blood flow across a wide range of MAPs. In a patient who is normotensive, renal autoregulation is intact between MAPs of between approximately 60 to 160 mm Hg. Below 60 mm Hg, renal blood flow decreases and thus GFR decreases. A recent study by Asfar and colleagues<sup>42</sup> looking at blood-pressure targets in patients with septic shock found no mortality benefit of targeting a higher MAP (80–85 mm Hg) versus a lower MAP (65–70 mm Hg). However, in patients with chronic hypertension, a decreased incidence of AKI and lower need for RRT was observed in the higher MAP group.<sup>42</sup> In hypotensive patients with vasodilatory shock refractory to adequate volume resuscitation, judicious use of vasopressors to restore MAP to a level above the lower limit of autoregulation will likely improve renal blood flow and thus GFR.<sup>35</sup> Of course, vasopressors should be used cautiously in cardiogenic shock and only after volume resuscitation in hypovolemic shock.



**Fig. 1.** Conceptual model of fluid management proposed by the ADQI. (A) In the critically ill patient, fluid management is proposed to follow 4 stages: rescue, optimization, stabilization and deescalation. (B) Fluid balance during the 4 stages of fluid management. The rescue phase is characterized by positive fluid balance; during the optimization and stabilization phases fluid balance is the most positive and the goal of these phases is to optimize effective circulating volume. Finally, during the deescalation phase, diuretics or RRT may be needed to resolve fluid overload, while maintaining an effective intravascular volume. (Courtesy of Acute Dialysis Quality Initiative. Available at: [www.adqi.org](http://www.adqi.org).)

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The choice of vasopressor has been the subject of several large trials over the years. In recent years, it has become widely accepted that norepinephrine is the initial vasopressor of choice for septic shock.<sup>43–46</sup> However, there is growing interest in the use of vasopressin in vasodilatory septic shock. Vasopressin, an endogenous stress hormone, acts via the V1 receptor located on vascular smooth muscle to cause vasoconstriction.<sup>47</sup> Endogenous vasopressin levels, as well as vasopressin receptors, are decreased in septic shock.<sup>47,48</sup> Importantly for septic shock, the actions of vasopressin include efferent arteriole vasoconstriction (which increases GFR) and improvement in the sensitivity of other vasopressor agents at catecholamine receptors and have been shown in small clinical studies.<sup>48–50</sup> A much larger study comparing the use of norepinephrine and vasopressin in septic shock found possible mortality benefit in patients with less severe shock (as defined by norepinephrine infusion rates between 5 and 15  $\mu\text{g}/\text{min}$ ) but no mortality difference in patients with severe shock.<sup>51</sup> This has led some to advocate for vasopressin as a second choice vasopressor agent in septic shock when adequate MAP goals cannot be achieved with low-dose norepinephrine.<sup>46,47</sup> Finally, for completeness sake, we note that there are no data to support the use of dopamine to improve renal outcomes,<sup>52–54</sup> and given the increased rate of arrhythmias observed with dopamine compared with norepinephrine in clinical trials, in general, dopamine should be avoided.<sup>43</sup>

### Nephrotoxins

Although we have no effective treatments for septic AKI at present, avoidance of nephrotoxic agents is paramount. The list of agents known to be injurious to the kidneys is extensive; however, there are few agents worth special mention, as they are commonly used in treatment of septic patients. Hydroxyethyl starch is a colloid that was once commonly used in resuscitation for patients with septic shock. However, several large studies and systematic reviews have shown use of hydroxyethyl starch is associated with increased risk of AKI and RRT, and in some cases, with an increased risk of death.<sup>55–58</sup> Fluid selection in the setting of septic shock is more globally addressed in other articles in this issue.

A growing body of literature suggests that administration of large volumes of crystalloids with supraphysiologic concentrations of chloride (ie, normal saline) may be associated with poorer outcomes than more balanced crystalloid solutions (ie, Ringer Lactate and Plasmalyte).<sup>59,60</sup>

Proposed mechanisms include a renal vasoconstrictive effect of high concentrations of chloride, as well as a macula densa-mediated tubuloglomerular feedback mechanism, which triggers afferent arteriolar vasoconstriction, thus lowering the GFR.<sup>59,61</sup> A large recent study suggested no benefit to balanced salt solutions over normal saline in a large population of critically ill patients,<sup>62</sup> but more research is clearly needed. For example, only 4% of study subjects had a primary diagnosis of sepsis in this trial. Furthermore, in an observational study comparing normal saline and balanced salt solutions during open abdominal surgery,<sup>63</sup> fewer blood gas and lactate measurements were obtained in subjects who received balanced salt solution. Thus, in patients with sepsis who are at high risk of lactic acidosis, the use of balanced salt solutions may be prudent from a resource utilization perspective as well.

Several antimicrobial agents have been associated with kidney injury through a variety of mechanisms. Amphotericin, aminoglycosides, and colistin are associated with acute tubular necrosis.<sup>64</sup> Many antibiotics, and in particular the beta-lactams, can cause interstitial nephritis.<sup>64</sup> Given the high rates of AKI with aminoglycosides and amphotericin, the KDIGO guidelines make special note of these agents.<sup>3</sup> Specifically, the guidelines recommend that aminoglycosides should be used only if no other alternative is available; similarly, amphotericin should be used only when azole or echinocandins cannot be used, and lipid formulations, which are associated with lower rates of nephrotoxicity, should be used.<sup>3</sup>

One of the most commonly used antibiotics in the ICU, vancomycin, deserves special mention. Originally approved in the 1950s, vancomycin remains the antibiotic of choice for methicillin-resistant *Staphylococcus aureus* (MRSA) infection. In the early years of clinical use, vancomycin nephrotoxicity was attributed to impurities from the manufacturing process.<sup>65</sup> Although the manufacturing process has improved, there has been a reported increase in the rate of vancomycin-associated AKI in recent years where a target trough of 15 to 20 mg/dL has been recommended for MRSA infections.<sup>65–68</sup> However, whether or not this is a true condition or whether much of this represents confounding remains controversial.<sup>65,67</sup> Some studies have suggested that concomitant exposure to other nephrotoxic agents (specifically piperacillin-tazobactam) increases the incidence of vancomycin toxicity.<sup>68</sup> Regardless, close attention should be paid to vancomycin dosing in the setting of AKI, and frequent monitoring of vancomycin levels should be used to guide dosing.

Iodinated contrast agents are perhaps the most widely recognized nephrotoxin used in clinical practice, although newer low-osmolar contrast agents confer a lower risk of nephrotoxicity. Patients with CKD and those with sepsis are at a higher risk of developing AKI from iodinated contrast. Early recognition of AKI using the consensus definitions described previously is also important. In these patient groups (those with AKI or CKD and those with sepsis) it is important to balance the risks and benefits when deciding to obtain these studies. Discussion with a radiologist can help determine if there are alternative means of imaging that can avoid iodinated contrast agents. The use of bicarbonate and N-acetylcysteine to prevent contrast nephropathy is controversial and is the subject of large randomized clinical trials.<sup>69</sup> However, there is clear benefit to intravenous fluid administration, so it is critical to ensure patients are volume resuscitated before iodinated contrast administration.<sup>70,71</sup> Finally, gadolinium, the contrast material used in MRI, has been linked to nephrogenic systemic fibrosis in patients with both AKI and CKD.<sup>72,73</sup> Small studies have suggested an association between gadolinium and AKI in particular in the setting of sepsis, but this association remains controversial.<sup>74</sup>

#### PHARMACOLOGIC STRATEGIES

Despite numerous studies, at present there are no pharmacotherapies to directly prevent or treat AKI. Although an exhaustive review of the literature as it pertains to these medications is beyond the scope of this review, many of these studies are reviewed in the KDIGO AKI guidelines.<sup>3</sup> Due to their anti-inflammatory properties, there has been significant recent interest in the use of statins (HMG-CoA reductase inhibitors) as a treatment for AKI in multiple settings, including sepsis. In the setting of sepsis, there have been no randomized clinical trials focused on AKI, but in a large prospective cohort study of patients hospitalized with pneumonia, statins were not found to reduce the risk of AKI, and in fact prehospital statin use was associated with a small increased risk of AKI, which was attributed to indication bias.<sup>75</sup> Furthermore, a meta-analysis of randomized clinical trials suggested that statins did not improve mortality in patients with sepsis.<sup>76</sup>

#### NONPHARMACOLOGIC STRATEGIES

##### *Renal Replacement Therapy*

The mainstay of treatment for septic AKI is RRT to treat and prevent complications associated with

AKI. Several topics important to the critical care physician are discussed, namely timing of RRT initiation, choice of continuous versus intermittent modality, and dose of RRT.

##### *Indications*

The classic indications for RRT in septic AKI are the same as for other critically ill patients: acidemia, volume overload, electrolyte abnormalities (hyperkalemia), and uremia (pericarditis, encephalopathy). In all cases, the risks of RRT (placement of a large-bore dialysis catheter), as well as blood loss and potential complications of RRT, such as electrolyte disturbances, hemodynamic compromise, air embolism, and worsening kidney injury,<sup>77,78</sup> must be weighed against potential benefits. Strategies to minimize risks and complications associated with RRT have been proposed, and may be of benefit.<sup>79</sup>

##### *Timing (early vs late)*

Optimal timing of RRT initiation continues to be debated in the literature. Although aggregate studies have suggested that earlier initiation of RRT in critically ill patients may improve survival,<sup>80,81</sup> there is significant confounding given the heterogeneity of published studies. Specifically, "early" versus "late" have been variably defined; although blood urea nitrogen levels have most commonly been used as the cutoff, studies have also used serum creatinine, urine output, and RIFLE criteria.<sup>81</sup> Clearly, large, well-executed randomized clinical trials are needed, although the design of such studies is complex, as some patients may recover from AKI with supportive care alone. Although a pilot randomized clinical trial of accelerated versus standard initiation dialysis demonstrated that this approach was feasible, in the standard arm 13 (25%) of 51 subjects never required dialysis and had renal recovery; a large randomized clinical trial based on this pilot study has been initiated.<sup>82</sup>

##### *Modality (intermittent vs continuous)*

The use of continuous RRT (CRRT) versus intermittent modalities (including conventional intermittent hemodialysis [IHD] and prolonged intermittent RRT [PIRRT]) also remains a subject of interest. Several randomized clinical trials and systematic reviews have found no differences in mortality or recovery of kidney function.<sup>77</sup> However, the entry criteria for many of the randomized clinical trials in this field required that an MAP greater than 70 mm Hg could be maintained (with or without vasopressors), which may not be possible in the setting of septic shock. Thus, the KDIGO guidelines, which recommend that use of CRRT and IHD be complementary, and that CRRT be

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considered in hemodynamically unstable patients, seem measured and reasonable.<sup>83</sup> Because hypotension has been associated with prolonged renal recovery in animal models and because there are more episodes of hypotension (on average) with IHD than CRRT, there has been tremendous interest in the impact of modality on renal recovery. A recent retrospective cohort study of more than 4000 patients with AKI requiring some form of RRT found that CRRT was associated with a decreased risk of long-term dialysis.<sup>84</sup> This effect was more prominent in the patients with CKD.<sup>84</sup> It should be noted that the costs of CRRT are considerably more than IHD.<sup>85</sup> Finally, PIRRT (originally named sustained/slow low-efficiency dialysis or SLED), is an alternative for hemodynamically unstable patients in particular in centers without CRRT capability.<sup>86</sup> This modality of therapy is typically performed over 6 to 12 hours per day to allow for more gentle fluid removal and solute clearance than IHD. However, a particular concern for this modality is antibiotic dosing, because there is an extended period with increased clearance, followed by a long period of reduced clearance, by design.<sup>87,88</sup>

#### Dose

The dose of dialysis has been the subject of a number of large randomized clinical trials. In CRRT, the dose is the sum of the ultrafiltrate plus dialysate (the effluent) normalized to body weight.<sup>77</sup> For IHD, dialysis adequacy is standardly measured as the Kt/V or urea reduction ratio. Although early studies suggested a benefit to higher doses of dialysis,<sup>89,90</sup> 2 large randomized clinical trials suggested no benefit to higher doses of RRT.<sup>21,22</sup> However, it is crucial to quantify dose of dialysis for patients with dialysis requiring AKI, as IHD treatments in particular may need to be optimized to achieve the target dose.<sup>21,22</sup>

#### Antibiotic dosing during renal replacement therapy

A number of small studies have shown that it is not uncommon for patients on CRRT to not achieve adequate serum levels of antibiotics needed to optimally treat infections, a particular problem in the setting of septic AKI.<sup>91–93</sup> Dosing of antimicrobials may be even more problematic for PIRRT, in which an extended period of increased clearance is followed by a period of minimal clearance. Not only are there virtually no data to guide antimicrobial dosing, recommendations from expert pharmacists vary widely.<sup>87,88</sup>

For patients on CRRT where clearance is continuous, one general concept is that dosing of antibiotics that are concentration-dependent

(fluoroquinolones, aminoglycosides, daptomycin, and amphotericin), should be adjusted by changing dosing interval, whereas the dosing interval of time-dependent antibiotics (beta-lactams and azoles) is constant, while actual dose is reduced.<sup>94</sup> Another important point is that in general initial dose of antibiotics should remain the same or slightly higher due to increased volume of distribution in patients with renal failure.<sup>94,95</sup> Antibiotics/antifungals that are extremely nephrotoxic, such as aminoglycosides and amphotericin, are best avoided unless there no other suitable alternatives.<sup>3</sup> Finally, when drug levels can be measured, levels should be used to help guide dose and interval of administration.<sup>95</sup>

#### Acid-Base Balance

##### pH goal

The kidneys play a critical role in the maintenance of acid-base homeostasis. Severe sepsis is often associated with lactic acidosis that overwhelms the ability of the pulmonary system to maintain a normal pH through respiratory compensation. Along with the liver, the kidney plays an important role in lactate metabolism.<sup>96</sup> Furthermore, in the setting of AKI, renal acid excretion is impaired. Severe acidosis may have a number of adverse effects, including cardiac dysfunction, arrhythmias, and catecholamine refractory vasodilation. However, the optimal pH goal and management strategies for obtaining that goal are areas of intense debate. Specifically, the use of bicarbonate in lactic acidosis, which is the most commonly encountered acid-base disturbance in sepsis, is intensely debated.<sup>97,98</sup> The current Surviving Sepsis Guidelines do not recommend the use of bicarbonate for lactic acidosis unless the pH is lower than 7.15, and others have advocated for even lower pH targets.<sup>98</sup> However, not all acidosis is treated equal; for example, in the case of lactic acidosis associated with metformin use (which may be precipitated by sepsis), dialysis may be indicated to remove metformin as well as to stabilize pH.<sup>99</sup>

##### Buffers

The treatment of patients with refractory acidemia (pH <7.15) is generally accomplished with either the use of dialysis (which removes metabolic acids and includes a buffer, typically bicarbonate) or a buffer alone. As mentioned previously, severe acidemia is considered an indication for RRT. The use of bicarbonate is quite common, although controversial and with many theoretic harmful effects, such as hypervolemia, hypernatremia, impaired oxygen delivery, and hypocalcemia.<sup>100</sup> An alternative to bicarbonate is tris-hydroxymethyl aminomethane (THAM), a weak base that is able to diffuse



intracellularly, and bind carbon dioxide and metabolic acids.<sup>101</sup> Protonated THAM is then excreted through the kidneys.<sup>101</sup> Adverse effects of THAM include hyperkalemia, hypoglycemia, pseudo-hyponatremia, and increased osmolal gap in patients with renal dysfunction, so its use should be avoided in patients with AKI.<sup>101</sup>

#### **Avoidance of hyperchloremic solutions**

As mentioned previously, the use of high chloride solutions is controversial at present because these solutions have been associated in some studies with increased rates of AKI and morbidity after abdominal surgery.<sup>59,60</sup> However, regardless of these effects, high chloride solutions are associated with a hyperchloremic metabolic acidosis, and in the setting of septic AKI, this acidosis may be exacerbated by concomitant lactic acidosis, respiratory acidosis in the setting of low tidal volume, lung protective ventilation, as well as the impaired ability of the kidney to excrete chloride. Thus, it is prudent to avoid large volume resuscitation with large volumes of 0.9% sodium chloride solution, and instead use balanced salt solutions.

#### **FUTURE DIRECTIONS**

Consensus definitions for AKI have been critical to move the AKI clinical research field forward, but have significant limitations because they use creatinine and urine output for the detection of kidney injury. Creatinine is a marker of glomerular filtration and consequently is a late marker of kidney injury (eg, by the time creatinine rises, injury has long occurred), and it has been suggested that creatinine production may be affected by sepsis.<sup>102</sup> Urine output may reflect a number of states including AKI, such as volume depletion and dehydration.<sup>103</sup> Numerous studies have focused on identifying more sensitive and specific biomarkers of AKI to aid in earlier detection and better prognostication. These include urinary biomarkers of tubular injury such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin, as well as markers of glomerular filtration, such as cystatin C, which is less dependent on muscle mass than creatinine.<sup>104</sup> Recently, a novel biomarker panel has become available to identify patients at increased risk of AKI in the ICU; this test combines insulinlike growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2), inducers of cell cycle arrest.<sup>105,106</sup> However, further studies are needed to determine how to optimally use this test in clinical practice.

#### **SUMMARY**

In summary, despite improving outcomes overall from sepsis, septic AKI remains associated with significant morbidity and mortality. At present, all care for septic AKI is supportive, and focused on best practices for patients with sepsis (early fluid resuscitation and antibiotics, as well as source control), minimizing fluid overload, consideration of higher MAP targets in patients with chronic hypertension, and avoidance of nephrotoxins. For patients with severe AKI, dialysis may be needed. In this context, IHD and PIRRT/CRRT can be considered complementary modalities, although a major concern for PIRRT in septic patients is the lack of data to guide antimicrobial dosing. With regard to acid-base balance, hyperchloremic solutions may exacerbate acidosis and should be avoided; other adverse consequences of these solutions remain controversial. Dialysis is often needed in patients with severe septic AKI for supportive management of acidosis.

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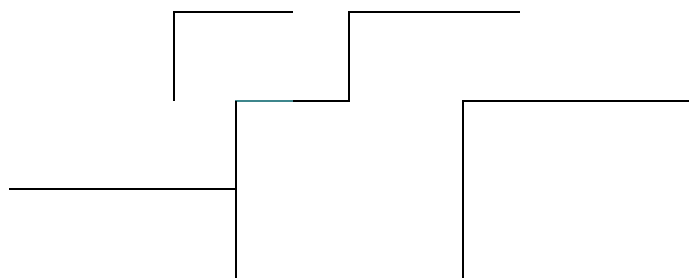
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*Supplementary appendix 2*

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## No impact of surviving sepsis campaign care bundles in reducing sepsis-associated acute kidney injury

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### Key words

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**Abstract.** **Background:** The impact of Surviving Sepsis Campaign (SSC) care bundles in reducing sepsis-associated acute kidney injury (SA-AKI) was evaluated. **Methods:** We conducted an observational single-center cohort study. Accomplishment of SSC care bundles was registered in all patients with severe sepsis admitted to the critical care department of a university hospital during three different periods. The main outcome measured was SA-AKI incidence defined as any worsening of AKI stage within the first 7 days from onset of sepsis. **Results:** Among 260 patients with severe sepsis or septic shock finally meeting inclusion criteria, 82 (31.5%) patients developed SA-AKI. None of the SSC care tasks significantly decreased SA-AKI incidence, although a trend was observed with an initial better blood glucose control as well as with a more protective ventilation strategy. Hypotension requiring fluid challenge (hazard ratio (HR), 2.3; 95% confidence interval (CI), 1.2–4.2) and the presence of an abdominal sepsis etiology (HR, 1.8; 95% CI, 1.1–3.1) were independently associated with SA-AKI. Patients who developed SA-AKI had a higher 90-day mortality rate (62.2 vs. 40.4%). **Conclusion:** In a cohort of septic patients, none of the SSC care tasks significantly decreased SA-AKI incidence within the first week after onset of sepsis.

### Introduction

Sepsis is the leading cause of acute kidney injury (AKI) and has a particularly high morbidity and mortality [1]. Not surprisingly, the severity of sepsis correlates with the sever-

ity of AKI [2]. Sepsis-associated AKI (SA-AKI) significantly increases mortality up to four times compared to critically ill non-AKI septic patients [3, 4, 5]. In recent years, special efforts have been made to decrease sepsis mortality, with positive results based on early hemodynamic resuscitation and early antibiotic administration (Surviving Sepsis Campaign (SSC)) [6]. Although these interventions appear to decrease mortality [7, 8, 9, 10], recent studies seem to show that no further improvement is achieved with SSC bundles accomplishment when protocols are performed by highly qualified and experienced professionals [11, 12, 13].

SA-AKI risk factors have also been studied and those described do not differ considerably from those identified for sepsis mortality, revealing once again that both entities are closely correlated [3, 4, 5]. Furthermore, some studies report different outcomes in SA-AKI incidence when SSC care tasks are achieved [2, 4, 7, 14, 15], although these studies were not specifically designed to evaluate the impact of care tasks on SA-AKI incidence.

This retrospective observational study analyzed all those critically ill patients who presented severe sepsis or septic shock in a tertiary university hospital just before and after an educational program based on SSC care bundles. The primary endpoint of the study was to evaluate the impact of SSC care tasks in SA-AKI incidence, with the secondary endpoint being the identification of SA-AKI risk factors in this septic population.



## Methods

Investigators performed a single-center observational study in the critical care department (ICU) of a tertiary care hospital in order to evaluate the impact of SSC care tasks on SA-AKI incidence. The study was approved by the ethical review board at the research center, and patients remained anonymous. The need for informed consent was waived due to both the anonymous nature of the study and the fact that all interventions had already been tested and published in previous trials.

All ICU patients were actively screened for the presence of severe sepsis or septic shock at admission and every day during their ICU stay from November 2005 to June 2007. Eligible patients were those with suspected infection plus any of the following findings: bilateral pulmonary infiltrates with  $\text{PaO}_2/\text{FIO}_2 < 300$  mmHg, urine output  $< 0.5$  mL/kg/h for at least 2 hours or creatinine  $> 177$   $\mu\text{mol/L}$ , coagulation abnormalities (International Normalized Ratio  $> 1.5$  or a partial thromboplastin time  $> 60$  seconds), platelet count  $< 100 \times 10^3/\mu\text{L}$ , total plasma bilirubin  $> 34$   $\mu\text{mol/L}$ , serum lactate  $> 4$  mmol/L, or hypotension (systolic blood pressure (SBP)  $< 90$  mmHg, mean blood pressure  $< 65$  mmHg, or a reduction in SBP  $> 40$  mmHg from baseline measurements). Septic shock was defined as hypotension despite adequate volume resuscitation requiring vasopressor support [16].

We classified AKI according to Kidney Disease Improving Global Outcomes (KDIGO) criteria using both serum creatinine and urine output [17]. Baseline creatinine value was registered from 6 months previous clinical files (90%) or estimated from the MDRD equation when data was not available from clinical records (10%). The stage of AKI was determined daily based on maximum severity by either creatinine or urine output criteria (until ICU discharge). SA-AKI was defined as AKI appearance or worsening/increase (in AKI stage) within the first week from the onset of sepsis (stage 3 AKI worsening was defined as renal replacement therapy (RRT) requirement).

Achievement of SSC care task goals was specially evaluated within the first 6 hours in those patients presenting hypotension; fluid

challenge  $> 20$  mL/kg, central venous pressure (CVP)  $> 8$  mmHg, and central venous oxygen saturation ( $\text{ScvO}_2$ )  $> 70\%$ .

## Statistical analysis

All continuous data are presented as medians (interquartile range (Q1 – Q3)) or means (standard deviation (SD)), as appropriate for nonparametric or parametric data, respectively. Differences in medians or means between groups were tested with Mann-Whitney test and Student's t-test, respectively. Differences in proportions were compared using Fisher's exact test or  $\chi^2$ -test where appropriate. A Cox regression model was used to assess the risk factors for the development of SA-AKI within the first 7 days from the onset of sepsis, and variables were included if they had  $< 10\%$  missing data, and the following assumptions: (1) had p-values  $< 0.1$  in the univariate analysis and (2) were clinically plausible. A p-value  $< 0.05$  was considered statistically significant. All analyses were conducted using SPSS version 18.0 (SPSS, Chicago, IL, USA).

## Results

During the study period, 650 patients were actively screened for the presence of severe sepsis or septic shock out of which 260 patients (40%) were finally enrolled. Of these 260 patients, at sepsis diagnosis 113 patients (43.5%) had KDIGO AKI criteria and 129 patients (49%) had AKI at ICU admission (23% presenting oliguria).

Patients were predominantly male (67%), with a mean age of  $58.9 \pm 15$  years. Most patients were admitted with severe sepsis to the ICU from the emergency department (31%) or ward (29%), but an important part of them developed severe sepsis during ICU admission (40%). At sepsis onset, 63.1% of patients presented septic shock, and 62.7% were on mechanical ventilation (MV).

82 patients (31.5%) developed SA-AKI at a median of 3 days (IQR 1 – 5 days) after the onset of severe sepsis or septic shock. When classified according to the KDIGO AKI criteria, 17% developed stage 1 AKI, 16% stage 2 AKI, and 67% stage 3 AKI. From these

Table 1. Univariate analysis of 7-day SA-AKI risk incidence for patients requiring ICU admission.

	Non-AKI (n = 178)	SA-AKI (n = 82)	p
<b>Age (years), mean ± SD</b>	58.0 ± 16	60.6 ± 14	0.22
<b>Weight (kg), mean ± SD</b>	71.5 ± 13	75.9 ± 16	0.03*
<b>Gender (male), n (%)</b>	114 (64.0)	61 (74.4)	0.12
<b>Baseline renal function, (mean ± SD)</b>			
Creatinine (µmol/L)	78 ± 27	91 ± 35	0.01*
GFR (mL/min/1.73m <sup>2</sup> )	92 ± 45	79.5 ± 32	0.02
<b>Sepsis etiology, n (%)</b>			
Abdominal	36 (20.2)	34 (41.5)	0.01*
Pneumonia	93 (52.2)	35 (42.7)	
Medical miscellaneous	27 (15.2)	8 (9.8)	
<b>Sepsis severity, n (%)</b>			
Severe sepsis	78 (43.8)	18 (22.0)	< 0.001*
Septic shock	100 (56.2)	64 (78.0)	
<b>Severity scores, median [Q1-Q3]</b>			
APACHEII score at sepsis onset	20 [15 – 26]	25 [20 – 30]	< 0.001
SOFA score at sepsis onset	7 [5 – 10]	9 [6 – 13]	< 0.001
<b>Urine output at ICU admission</b>			
mL/kg/h, mean ± SD	1.21 ± 0.7	0.86 ± 0.6	0.0002*
Oliguria (< 0.5 mL/kg/h), n (%)	21 (12)	38 (46)	< 0.001*
<b>KDIGO AKI stage at SA-AKI diagnosis, n (%)</b>			
No AKI	90 (51)	0 (0)	
Stage 1	24 (13)	14 (17)	
Stage 2	24 (13)	13 (16)	
Stage 3	40 (22)	55 (67)	
<b>At sepsis diagnosis, mean ± SD</b>			
Lactate (mmol/L)	3.3 ± 3.2	5.5 ± 5.3	0.08**
Hemoglobin (g/L)	112 ± 24	111 ± 24	0.89
Bicarbonate (mmol/L)	24.9 ± 6.6	23.5 ± 7.2	0.13
Albumin (g/L), median [Q1-Q3]	26 [21 – 30]	23 [20 – 28]	0.04**
<del>APACHEII score at sepsis onset</del> (%)	103 (57.8)	69 (84.2)	< 0.001*
<b>Resuscitation bundle (6 hours), n (%)</b>			
Q1 (Lactate)	30 (16.9)	24 (29.3)	0.03
Q2 (Blood cultures)	115 (69.7)	42 (53.2)	0.01
Q3 (Antibiotics < 1 – 3 h)	80 (49.1)	42 (54.5) <sup>w</sup>	0.49
<b>Shock<sup>†</sup></b>			
Q4 (Fluid challenge if hypoTA) <sup>†</sup>	66 (61.7)	39 (58.2)	0.75
Q5 (CVP > 8 – 12 mmHg) <sup>†</sup>	57 (50.9)	27 (40.3)	0.22
Q6 (ScvO <sub>2</sub> > 70%) <sup>†</sup>	22 (20.6)	13 (19.7)	0.9
<b>Management bundle (24 hours), n (%)</b>			
Q7 (steroids) <sup>†</sup>	28 (26.9)	24 (36.4)	0.23
Q8 (median glycemia > 4 < 8.3 mmol/L) <sup>†</sup>	82 (49.7)	29 (36.2)	0.06*
Q9 (median plateau < 30 cmH <sub>2</sub> O) <sup>‡</sup>	74 (73.3)	32 (58.2)	0.07**
<b>SSC goal measures, median [Q1 – Q3]</b>			
Resuscitation bundles compliance (%)	33 [17 – 33]	33 [17 – 33]	0.5
Management bundles compliance (%)	66 [33 – 66]	33 [33 – 66]	0.3
All SSC bundles compliance (%)	30 [30 – 40]	30 [20 – 40]	0.4
Sepsis to antibiotics (minutes)	120 [60 – 300]	120 [60 – 270]	0.39
Sepsis to CVP > 8 mmHg (minutes) <sup>†</sup>	292 [60 – 645]	480 [120 – 795]	0.45
Sepsis to ScvO <sub>2</sub> > 70% (minutes) <sup>†</sup>	619 [167 – 1,170]	490 [163 – 1,045]	0.9
Sepsis to steroids (minutes) <sup>†</sup>	522 [210 – 1,020]	780 [180 – 2,640]	0.12
Median serum glucose (mmol/L)	7.4 [5.7 – 9.6]	7.9 [5.9 – 10.6]	0.41
Median plateau pressure (cmH <sub>2</sub> O) <sup>‡</sup>	24 [20 – 30]	28 [24 – 33]	0.01
<b>Therapy requirements during ICU admission, n (%)</b>			
RRT	30 (36.6)		
MV	103 (57.9)	60 (73.2)	0.02*
Vasopressor use (hypotensive patients)	98 (91.6)	64 (95.5)	0.37

Table 1. Continuation.

	Non-AKI (n = 178)	SA-AKI (n = 82)	p
<b>Severity risk factors, n (%)</b>			
Hypoglycemia (< 4 mmol/L)	25 (15.2)	13 (16.2)	0.85
Bacteremia (positive blood cultures)	58 (40)	36 (54.5)	0.05**
<b>Length of stay among survivors (days), median [IQR]</b>			
ICU	11 [6 – 23]	15 [8 – 32]	0.47
Hospital	34 [22 – 62]	46 [25 – 74]	0.62
<b>At hospital discharge among survivors, mean ± SD</b>			
Creatinine (µmol/L)	64 ± 27	85 ± 62	0.09
GFR (mL/min/1.73m <sup>2</sup> )	122 ± 59	111 ± 55	0.35
<b>Outcome measures, n (%)</b>			
ICU mortality	60 (33.7)	49 (59.8)	< 0.001
Hospital mortality	70 (39.3)	50 (61.0)	< 0.001
90-day mortality after sepsis	72 (40.4)	51 (62.2)	< 0.001

APACHE II = acute physiology and chronic health evaluation scoring system version II; CKD = chronic kidney disease; CVP = central venous pressure; GFR = glomerular filtration rate; ICU = intensive care unit; MV = mechanical ventilation; RRT = renal replacement therapy; SA-AKI = sepsis-associated acute kidney injury; ScvO<sub>2</sub> = central venous oxygen saturation; SOFA = sequential organ failure assessment; SSC = sepsis surviving campaign. \*Variables that were included in multivariable logistic regression analysis (p < 0.1). \*\*Significant variables (p < 0.1) with > 10% missing data (therefore not included in multivariable logistic regression analysis). †Only applies to patients who presented hypotension (systolic blood pressure < 90 mmHg, mean blood pressure < 65 mmHg, or a reduction in systolic blood pressure > 40 mmHg from baseline measurements). ‡Only applies to patients who were on mechanical ventilation.

SA-AKI patients, 37% required RRT during their ICU stay (stage 3 AKI was not synonymous of RRT). Table 1 presents univariate comparisons of demographic characteristics, baseline characteristics, comorbidities, septic characteristics, and accomplishment of SSC bundles between patients who developed SA-AKI and those who did not. Patients who developed SA-AKI were older, predominantly male, presented worse baseline renal function, had higher APACHE II score, and were more likely to have positive blood cultures and an abdominal source of infection.

All SSC tasks were independently analyzed. No differences were observed in task compliance or in terms of time analysis (time from sepsis diagnosis to antibiotic administration). Hypotension was more frequent in SA-AKI patients (83 vs. 62%; p < 0.001) as well as MV requirement (73 vs. 58%; p < 0.02). In the septic shock population, no differences were observed with regard to correct fluid challenge administration, CVP, or ScvO<sub>2</sub> goal achievement between SA-AKI and non-AKI patients (Table 1).

When management tasks (24 hours) were analyzed, some differences were found between SA-AKI and non-AKI patients (Table 1). Median glucose level goal (4 – 8.3 mmol/L with no hypoglycemia episodes) was achieved more frequently in the

non-AKI group compared to the SA-AKI patients (49.7% vs. 36.2%; p = 0.06). Among those patients who received MV (63% of the studied population), higher plateau pressure (Ppl) was observed in SA-AKI patients with a statistically significant difference compared to the ventilated septic non-AKI patients (p < 0.01). However, patients who completed all bundles (resuscitation, management, or both) had no decrease in the incidence of septic AKI compared to those patients who did not achieve all bundles.

After adjustment for confounders, the development of SA-AKI was independently associated with the presence of hypotension (2.3 HR, 95% CI 1.2 – 4.2, p < 0.01) and an abdominal sepsis etiology (1.8 HR, 95% CI 1.1 – 3.1, p < 0.02) (Table 2). Hospital deaths occurred in 61% of patients who developed SA-AKI as opposed to 39.3% in the septic non-AKI group (p < 0.001) (Table 1). Kaplan-Meier curves representing 90-day mortality incidence (SA-AKI vs. septic non-AKI) were compared using a log-rank test (Figure 1).

## Discussion

In this cohort of 260 patients with sepsis, none of the SSC tasks significantly reduced

Table 2. Adjusted hazard ratio, 95% confidence interval, and p-values for SSC care tasks determined from multivariable logistic regression analysis of 7-day SA-AKI incidence in severe sepsis and septic shock patients.

Factor	Hazard ratio	95% Wald confidence	p-value
Hypotension <sup>†</sup>	2.3	(1.2 – 4.2)	0.01
Abdominal sepsis	1.8	(1.1 – 3.1)	0.02
Q8 (Median glycemia > 4 < 8.3 mmol/L)	0.7	(0.4 – 1.2)	0.19
MV	1.4	(0.8 – 2.4)	0.28
Weight (kg)	1.006	(0.9 – 1.0)	0.42
Baseline creatinine(μmol/L)	1.19	(0.9 – 1.5)	0.57

MV = mechanical ventilation; SA-AKI = sepsis-associated acute kidney injury; SSC = surviving sepsis campaign. <sup>†</sup>Systolic blood pressure < 90 mmHg, mean blood pressure < 65 mmHg, or a reduction in systolic blood pressure > 40 mmHg from baseline measurements.

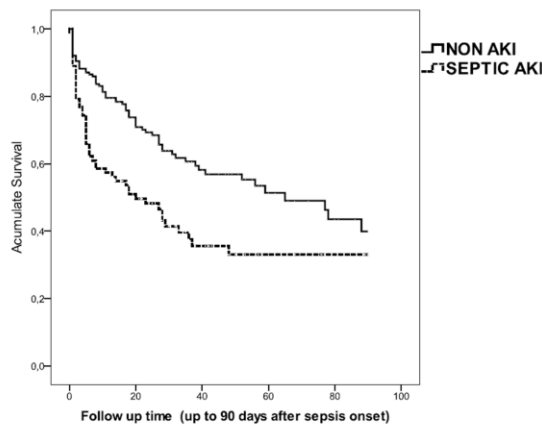


Figure 1. SA-AKI vs. non-AKI sepsis. Impact on survival at 90 days ( $p < 0.001$ ). AKI = acute kidney injury, SA-AKI = sepsis-associated acute kidney injury.

the risk for SA-AKI incidence. SA-AKI was more likely to develop in patients with hypotension requiring fluid challenge administration and (or) an abdominal sepsis etiology. In addition, patients who developed SA-AKI had higher hospital mortality.

SA-AKI was defined as renal function worsening only after onset of sepsis within the first 7 days. Most of the previous studies classify all those patients who already present AKI at sepsis diagnosis as SA-AKI, extending AKI occurrence sometimes as far as 28 days and thus reporting higher rates of SA-AKI [3, 5, 14]. This means that our SA-AKI incidence is intentionally underestimated in order to properly evaluate the impact of SSC care bundles after onset of sepsis.

Although delayed antibiotic administration had been previously reported as an independent risk factor for SA-AKI particularly in septic shock patients [3, 4], no relationship was found in our patients between time from sepsis to antibiotic administration and SA-AKI. Protective ventilation (median Ppl < 30 cm H<sub>2</sub>O) seemed to protect from developing SA-AKI in mechanically ventilated patients which seems to give support to the pulmonary-kidney crosstalk theory in critically ill patients (ventilator-induced AKI). Hemodynamic measures were specifically evaluated in patients with hypotension, but no SA-AKI protective effects were identified for correct fluid challenge, CVP goal, ScvO<sub>2</sub> goal, or steroid administration. Recent trials in septic populations have confirmed that clinical skills and experience are sometimes much more important than invasive monitoring of septic patients [11, 12, 13].

Our results are in accordance with those of other investigators, who have also reported a relationship between illness severity, hypotension in critically ill septic patients, and renal outcome [3, 4]. The etiology of abdominal sepsis has also been described as an independent risk factor for SA-AKI, as these patients frequently present increased intra-abdominal pressure (IAP) that can decrease renal flow and promote AKI [18].

Our study is limited by its observational design, which cannot exclude the possibility of our results being confounded by case-mix heterogeneity or secular trends. Moreover, by including only patients admitted to the ICU, we probably selected more severe patients who did not improve with initial treatment. This selection bias applies to fluid ad-

ministration but probably also to antibiotic treatment. Furthermore, fluid administration was not registered neither in terms of daily balance nor type of fluid employed, which could modify SA-AKI incidence especially with the use of colloids. Although 10% of our patients had no baseline creatinine registered within the last 6 months (which probably overestimates AKI at sepsis initiation), our SA-AKI definition avoids this selection bias. However, considering that serum creatinine is a late marker of renal injury, it is likely that a considerable proportion of patients with AKI at sepsis initiation would have creatinine within normal levels. In these patients, it would be more difficult to determine if SSC care bundles influenced the development of AKI. Even though other biomarkers such as neutrophil gelatinase-associated lipocalin would allow a more accurate identification of AKI, we assume that 1 week of renal function monitoring is enough to evaluate the impact of SSC care bundles.

In conclusion, SA-AKI worsens prognosis in septic patients and should be closely monitored and prevented. None of the SSC bundles seem to have a direct effect in preventing SA-AKI, although avoiding hypotension could be clearly beneficial as well as a protective strategy with Ppl < 30 cm H<sub>2</sub>O when MV is required. Septic patients with an abdominal etiology present a higher risk for SA-AKI development, and special measures such as IAP monitoring should be promptly adopted.

### Conflict of interest

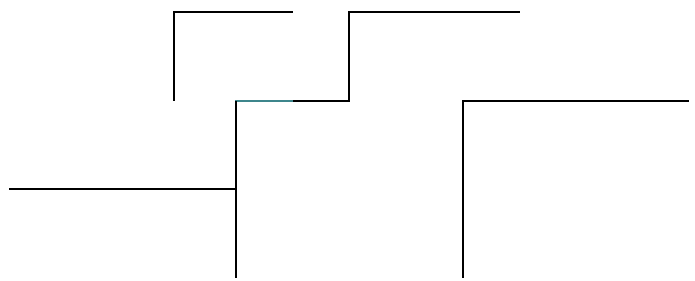
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*Supplementary appendix 3*

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# Supplementary appendix 3

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## Clinical variables associated with poor outcome from sepsis-associated acute kidney injury and the relationship with timing of initiation of renal replacement therapy



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### ABSTRACT

**Purpose:** Identify clinical variables associated with mortality in patients with sepsis-associated acute kidney injury (SA-AKI) receiving continuous renal replacement therapy (CRRT) and examine timing of initiation of CRRT in reference to those variables identified.

**Methods:** Retrospective study conducted at two tertiary care hospitals including 939 septic shock patients with SA-AKI who received CRRT in the intensive care unit (ICU). Cox regression models were used to identify variables associated with 90-day mortality. Timing of CRRT initiation was assessed in relationship to significant clinical variables identified.

**Results:** Overall 90-day mortality was 62.9%. Variables prior to CRRT associated with 90-day mortality included: age (aHR, 1.02; 95%CI, 1.01–1.02,  $p < 0.001$ ), APS-III score (1.01, 1.0–1.0,  $p < 0.048$ ), days from hospital admission to CRRT initiation (1.01, 1.0–1.0,  $p < 0.01$ ), blood urea nitrogen (1.01, 1.0–1.0,  $p < 0.04$ ), medical admission (1.76, 1.5–2.1,  $p < 0.0001$ ), creatinine (0.99, 0.9–1.0,  $p < 0.001$ ), and urine output (0.77, 0.6–0.9,  $p = 0.049$ ). In patients with advanced SA-AKI at ICU admission receiving CRRT within the first 5 days ( $n = 433$ ), urine output during the 24 h prior to CRRT initiation was a strong predictor of survival (2.6, 1.6–4.3,  $p < 0.001$ ).

**Conclusions:** In patients with SA-AKI, survival is lower when CRRT is started in the setting of low urine output.  
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### 1. Introduction

Sepsis is the leading cause of acute kidney injury (AKI) and portends a particularly high morbidity and mortality [1,2]. In order to identify patients with AKI as early as possible, the Acute Kidney Injury Network (AKIN) proposed the AKIN classification, recently updated by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, which stratifies AKI in three different stages according to changes in creatinine and urine output [3,4].

Renal replacement therapies (RRT) are classically indicated when advanced AKI is present. Higher mortality of these patients reflects

organ dysfunction, usually multiple (three or more organs). Patients with septic shock (SS) are particularly susceptible to AKI [5] and those who receive continuous renal replacement therapies (CRRT) because of unstable hemodynamics represent a common and often lethal clinical scenario.

Furthermore, a major gap in knowledge exists around timing of initiation of RRT. Two recent, moderately-sized RCTs reached different conclusions about whether to initiate RRT only when urgent indications develop or prior to their development [6,7]. Understanding which clinical features portend poor outcomes could help guide decisions around timing by suggesting when and in whom to initiate RRT [8–20].

Our retrospective study analyzes patients with SS at CRRT commencement. Our primary objective was to identify factors associated with mortality in patients with SS and AKI requiring CRRT in order to design future interventional trials. A secondary goal was to examine timing of initiation of RRT in reference to the clinical variables identified.

**Abbreviations:** SA-AKI, sepsis-associated acute kidney injury; APS-III, acute physiology and chronic health evaluation score 3; aHR, adjusted hazard ratio; CRRT, continuous renal replacement therapy; ICU, intensive care unit.

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## 2. Methods

### 2.1. Design and setting

We performed a retrospective study using data from two tertiary care hospitals with >80 intensive care unit (ICU) beds each. Patient data were included from 2000 to 2008 at University Pittsburgh Medical Centre (Pittsburgh, USA), and from 2005 to 2012 at Hospital Universitari Bellvitge (Barcelona, Spain). The study protocols were approved by each institution's ethics/investigation review board. Inclusion criteria were SS (defined by international consensus criteria) [21] within the first 24 h from CRRT initiation. CRRT initiation criteria were based on clinical judgement. Exclusion criteria were end stage renal disease (ESRD), previous RRT in the prior 2 weeks, or < 24 h of CRRT. For this retrospective, observational, non-interventional study, the research ethics committee of both centres waived the need to obtain informed consent for collection, analysis, and publication of data.

### 2.2. CRRT

CRRT was administered with Prisma® or Prismaflex® (Baxter), femoral or jugular vein catheters were used for vascular access, and continuous venovenous hemofiltration (CVVH), continuous venovenous hemodiafiltration (CVVHDF), or continuous venovenous hemodialysis (CVVHD) were prescribed according to individual prescription.

### 2.3. KDIGO AKI stage

Demographic, clinical, and CRRT related parameters were abstracted from the electronic medical record. Mean acute physiology and chronic health evaluation score (APS-III) measured at CRRT initiation was internally derived based on available data [22]. Baseline creatinine value ( $\mu\text{mol/L}$ ) was either registered from 6 months previous clinical files or estimated, when data was not available from clinical records, by solving the Modification of Diet in Renal Disease (MDRD) equation assuming a glomerular filtration rate of 75 mL/min/1.73 m<sup>2</sup> [22,23]. KDIGO AKI stage was calculated for every patient at ICU admission and at CRRT initiation based on serum creatinine only since hourly urine output data was not available in the Barcelona data. Patients were followed through hospital discharge and survival status was assessed at 90 days using national databases.

### 2.4. Timing of initiation of RRT

Based on the variables associated with 90-day mortality we decided to separately evaluate "Time from ICU admission to CRRT" and "Urine output 24 h previous to CRRT" in a subset of our cohort with AKIN stage 3 at ICU admission and receiving CRRT within the first 5 days from ICU admission. This subset was selected in order to have a more homogenous cohort to analyze. The exclusion criterion of >5 days was chosen in order to avoid "late" patients that went on CRRT probably for different reasons than ICU admission besides presenting more comorbidity. Timing based on time (time from ICU admission to CRRT) was compared to timing based on urine output (urine output during 24 h prior to CRRT initiation) in order to identify which parameter could be more useful to initiate CRRT. Based on previous reports [20] and population's variable distribution "Time" criteria to start CRRT was defined as "early" when CRRT was started within the first 48 h from ICU admission and as "late" when CRRT was started after 48 h from ICU admission. Based on population's variable distribution, urine output (UO) criteria to start CRRT was defined as "early" when UO during the 24 h prior to CRRT was >0.05 mL/kg/h and as "late" when UO was <0.05 mL/kg/h during the previous 24 h to CRRT initiation. These criteria are illustrated in Fig. 1.

### 2.5. Statistical analysis

Statistical analyses were performed using SPSS software, version 18.0, with statistical significance set at  $p < 0.05$ . Comparisons between groups were performed with Pearson's Chi-Square asymptotic test for categorical variables and using Kruskal-Wallis one-way analysis of variance by ranks for continuous variables. Categorical data is summarized as counts and percent. Continuous data is summarized as medians (25th, 75th percentile). Risk factors were considered for multivariable cox proportional hazards (PH) regression models if the following assumptions were met: (1) they had <10% missing data, (2) had  $p$  values < 0.2 in univariate analysis, and (3) were clinically plausible. Backward elimination with the likelihood ratio method was used to determine the final models. Results are presented as adjusted hazard ratios (aHR) with 95% confidence intervals (CI). Kaplan-Meier survival curves were used to estimate the cumulative mortality rates in all groups studied (timing groups) and differences were calculated using the log-rank test. Cox PH model was used to determine each group's aHR for 90-day mortality.

## 3. Results

### 3.1. Patients characteristics

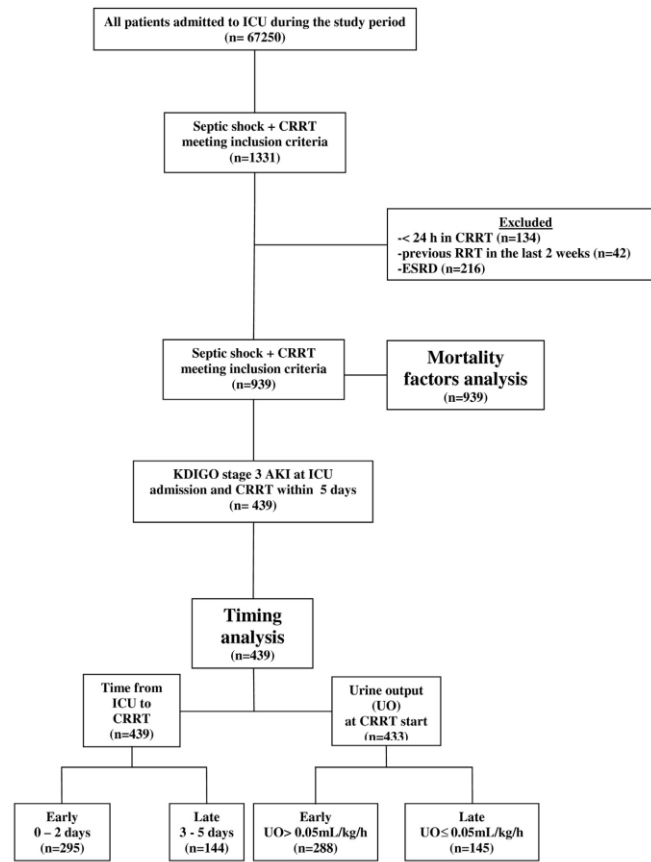
In total, 67,250 patients were admitted to our ICUs during the study period. SS was present in 18% of these patients during some moment of their ICU stay but only 11% of these SS patients required CRRT despite a high AKI incidence (92.4%). 939 SS patients were finally studied, all of them meeting SS criteria within 24 h from CRRT initiation during their ICU stay. Study flow chart is represented in Fig. 1.

Population characteristics at ICU admission and baseline characteristics at CRRT initiation are presented in Table 1. Median age was 60 years (25th and 75th percentile: 50, 71 years), 62.9% were male, and 57.8% had surgical admission to the ICU. 150 patients (15.9%) had mild chronic kidney disease. Median time from hospital admission to ICU was 2 days (1, 5 days), median time from hospital admission to CRRT was 7 days (3, 15 days), and median time from ICU admission to CRRT was 4 days (2, 8 days). At CRRT initiation, the median APS-III was 98 (73, 122), 91.7% were on vasopressor support, 88.7% were on mechanical ventilation (MV), serum blood urea nitrogen (BUN) was  $\geq 100$  mg/dL in 16.5%, serum potassium was  $>5$  mEq/L in 29.4%, and 96.9% presented AKI based on KDIGO creatinine criteria with majority of patients presenting stage 3 AKI (82.6%).

Patients were mostly initiated on CVVHDF (62.8%), whereas CVVH and CVVHD were nearly equally employed (19.8% and 17.4% respectively). ICU mortality was 50.4% and hospital mortality 52.7%. Mortality at 90 days from CRRT initiation was 62.8%. Differences between centres in terms of population characteristics, clinical-CRRT management, and survival outcome are presented in Supplementary appendix.

### 3.2. Mortality risk factors

Univariate analysis for 90-day mortality identified variables presented in Table 1. Mortality differences between years were analyzed in order to identify confounding effects of treatment advances and better CRRT applications but no relevant differences were identified. Risk factors associated with 90-day mortality were determined by multivariable cox regression and presented in Table 2. Significant variables associated with increased 90-day mortality included age (aHR 1.01, 95%CI 1.01–1.02,  $p < 0.0001$ ), APS-III score at CRRT (1.01, 1.0–1.0,  $p < 0.048$ ), days from hospital admission to CRRT initiation (1.01, 1.0–1.0,  $p < 0.01$ ), BUN at CRRT (1.01, 1.0–1.0,  $p < 0.04$ ), and medical admission (1.76, 1.5–2.1,  $p < 0.0001$ ) compared to surgical admission. Variables associated with decreased 90-day mortality included creatinine at CRRT (0.99, 0.9–1.0,  $p < 0.001$ ) and UO 24 h prior to CRRT (0.77, 0.6–0.9,  $p = 0.049$ ).



**Fig. 1.** Study flow chart. CRRT, continuous renal replacement therapy; ESRD, end stage renal disease; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; mL/kg/h, milliliters/kilogram/hour; SA-AKI, sepsis-associated acute kidney injury; UO, urine output.

3.3. Patient selection and “timing” of RRT initiation

From the variables associated with mortality we chose two as potential triggers for initiating RRT (days in ICU prior to CRRT and UO). In order to homogenize groups as much as possible, we confined this analysis to a subgroup of 433 patients with SS and stage 3 AKI at ICU admission who received CRRT within the first 5 days from ICU admission. Initiation based on days from ICU to CRRT was compared to initiation based on UO in the 24 h prior to CRRT initiation. Initiation based on days from ICU to CRRT showed no differences between the “early” group (0 to 2 days) and the “late” group (3 to 5 days) ( $p = 0.765$ ), whereas initiation based on UO showed important differences in 90-day survival between patients, in whom CRRT was started with  $UO \leq 0.05$  mL/kg/h, and in patients in whom CRRT was started with  $UO > 0.05$  mL/kg/h ( $p = 0.019$ ). Kaplan-Meier curves are plotted in Figs. 2 and 3. The aHR at 90 days showed that oliguria group presented an increased risk for mortality (aHR 2.6; 95%CI 1.6–4.3) compared to the non-oliguric group, and this difference was statistically significant ( $p <$

0.001). This adjusted Cox regression model and differences between the initiation groups are presented in Supplementary appendix.

4. Discussion

The main finding of our study is that in patients with SS and advanced AKI, treated with CRRT, numerous factors are associated with decreased survival. Age, severity of illness, medical as opposed to surgical admission, BUN, decreased UO, decreased creatinine and days from hospital admission to CRRT initiation were all associated with worse survival. Among patients with Stage 3 AKI, survival is lower when CRRT is started in the setting of low UO ( $< 0.05$  mL/kg/h), while timing itself (from admission) is not. These results further inform the debate about when to initiate RRT.

To our knowledge, this is the first study that identifies mortality factors in a two centre cohort of SA-AKI patients all with SS within 24 h of CRRT initiation. Most of the variables identified in our cohort are consistent with the ones described in previous observational studies in

**Table 1**  
Patient characteristics and outcomes associated with 90-day mortality from CRRT initiation in septic shock patients.

Characteristics	Survivors (n = 349)	Non survivors (n = 590)	All (n = 939)	p value <sup>a</sup>
Age (n = 939)	57 (46–67)	63 (53–72)	60 (50–71)	<0.001 <sup>f</sup>
Males, n (%)	226 (64.8)	367 (61.9)	591 (62.9)	0.4
Weight (kg), (n = 936)	80 (68–96)	79 (70–93)	80 (68–95)	0.5
BMI, (n = 841)	28 (24–32)	27 (24–32)	28 (24–32)	0.9
SOFA score, (n = 939)	11 (8–14)	11 (8–14)	11 (8–14)	0.6
APACHE III score, (n = 939)	95 (71–120)	99 (75–123)	98 (73–122)	0.038 <sup>f</sup>
Comorbid condition, n (%)				
Hypertension	138 (39.7)	262 (44.5)	400 (42.7)	0.17
Diabetes	92 (26.4)	146 (24.8)	238 (25.4)	0.6
Cardiac disease	91 (26.1)	146 (24.8)	238 (25.4)	0.3
Chronic liver disease	81 (23.3)	155 (26.3)	236 (25.2)	0.3
Chronic airway obstruction	39 (11.2)	93 (15.8)	132 (14.1)	0.05
Chronic renal disease (includes CKD)	57 (16.3)	93 (15.7)	150 (15.9)	0.9
Charlson comorbidity index	2.2 (0–4)	2.5 (0–4)	2.4 (0–4)	0.007 <sup>f</sup>
Surgical admission, n (%)	227 (66.8)	301 (52.3)	528 (57.8)	<0.001 <sup>f</sup>
Creatinine (μmol/L)				
ICU, (n = 921) <sup>b</sup>	211 (132–325)	211 (132–316)	211 (32–317)	0.6
CRRT, (n = 938) <sup>c</sup>	308 (238–412)	299 (211–396)	299 (220–403)	0.05 <sup>f</sup>
Baseline, (n = 938)	89 (76–114)	91 (72–114)	91 (74–114)	0.9
Weight adjusted Urine Output (ml/kg) <sup>d</sup>				
ICU, (n = 927)	9.5 (3.5–20.1)	9.4 (3.1–20)	9.5 (3.3–20)	0.3
CRRT, (n = 912)	4.3 (1.3–9.5)	3.7 (1.1–8.0)	3.9 (1.2–8.6)	0.14 <sup>f</sup>
Vasopressors at CRRT, n (%)	314 (90.1)	547 (92.7)	861 (91.7)	0.3
Mechanical ventilation at CRRT, n (%)	310 (89.0)	518 (88.4)	828 (88.7)	0.8
Serum BUN ≥ 100 mg/dL at CRRT, n (%)	44 (12.7)	109 (18.7)	153 (16.5)	0.02 <sup>f</sup>
Serum potassium > 5 mEq/L at CRRT, n (%)	100 (28.9)	173 (29.7)	273 (29.4)	0.8
CRRT characteristics, n (%)				0.8
CVVH	68 (19.5)	118 (19.9)	186 (19.8)	
CVVHD	65 (18.6)	99 (16.7)	164 (17.4)	
CVVHDF	216 (61.9)	373 (63.3)	589 (62.8)	
KDIGO based on creatinine at CRRT, n (%)				0.99
No AKI	10 (2.9)	17 (3.2)	27 (3.1)	
Stage 1	14 (4.0)	25 (4.2)	39 (4.1)	
Stage 2	36 (10.3)	80 (13.4)	96 (10.2)	
Stage 3	289 (82.8)	488 (82.4)	777 (82.6)	
Time to ICU/CRRT, (days)				
Hospital admission - ICU admission	1 (1–3)	2 (1–6)	2 (1–5)	0.001
Hospital admission - CRRT initiation	5 (3–12)	8 (4–17)	7 (3–15)	0.001 <sup>f</sup>
ICU admission - CRRT initiation	3 (2–7)	4 (2–9)	4 (2–8)	0.016
Mortality, n (%)				
ICU	5 (1.4)	468 (79.3)	473 (50.4)	<0.001
Hospital	10 (2.8)	496 (84.4)	496 (52.7)	<0.001
90 days <sup>e</sup>	0 (0)	590 (100)	590 (62.8)	<0.001

Variables are represented by median (q1–q3) and absolute numbers or percentages (n (%)). Variables measured at ICU capture the 24 h after ICU admission. Variables measured at CRRT capture the 24 h before CRRT initiation.

AKI, Acute Kidney Injury; APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; BUN, blood urea nitrogen; CKD, chronic kidney disease; CVVH, Continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; ICU, Intensive Care Unit; KDIGO, Kidney Disease Improving Global Outcomes; SOFA, sepsis-related organ failure assessment score.

Conversion factors for units: serum creatinine in mg/dL to μmol/L, × 88.4; serum blood urea nitrogen in mg/dL to mmol/L, × 2.8; Serum potassium in mEq/L to mmol/L, × 1.

<sup>a</sup> Fisher's Exact Significance for categorical variables; Kruskal-Wallis test for continuous variables.

<sup>b</sup> Maximum serum creatinine value measured in the 24 h after ICU admission.

<sup>c</sup> Maximum serum creatinine value on the day of CRRT initiation or on the previous day.

<sup>d</sup> The available urine in the 24 h after ICU or prior to CRRT was summed and divided by the weight.

<sup>e</sup> From CRRT initiation.

<sup>f</sup> Included in final Cox regression analysis for 90-day mortality.

critically ill patients. Uchino et al. [8] described similar independent mortality predictors (BUN, creatinine, age and oliguria) in a subgroup of critically ill AKI patients who received CRRT, whereas Bagshaw et al. [2] compared SA-AKI patients (47.5% of the whole cohort) with non SA-AKI patients although not all septic patients were in shock (78.3%) when initiating RRT (85.4% received CRRT). One recent study in surgical critically ill patients receiving RRT (29% received intermittent hemodialysis) also described similar mortality factors although only 36% of the patients presented sepsis [24]. Our hospital mortality and 90-day mortality is concordant with epidemiological studies that report higher mortalities in SS patients who need CRRT not only in local communities [25,26] but also in international observational studies [8,27].

Mortality factors which are classically identified in large cohorts of critically ill patients such as age or severity scores don't need further explanation [8,28]. Older patients present more severe forms of organ

dysfunction with a worst response to treatment and less capacity to recover. Although some studies report that advanced AKI stages at CRRT initiation could be associated with worst prognosis in critically ill patients [29,30,2], in our study we could not identify an statistical relationship between mortality and AKI severity at least in terms of AKI KDIGO stage which was based on creatinine variations (UO data was only registered 24 h but not specifically in the 6 or 12 h previous to CRRT). Payen et al. [31] described increased mortality when patients in early phases of severe sepsis were randomized to CRRT compared to a usual care (no CRRT) group and some [13,19,32] but not all [6] other studies have shown no survival improvement when CRRT is initiated in early AKI stages, especially when those stages are based on creatinine variations like in our study.

In our study high creatinine at CRRT seems to be protective which is consistent with the BEST study results [8] and can be explained by a

**Table 2**  
Adjusted hazard ratio (aHR), 95% CI, and p values for factors determined from multivariable Cox regression analysis of risk factors for 90-day mortality.

Significant variable	p	aHR	95% CI
Age (years)	<0.0001	1.015	1.009–1.021
APACHE III at CRRT	0.042	1.003	1.000–1.006
Urea at CRRT (mmol/L)	0.036	1.009	1.001–1.017
Creatinine at CRRT (μmol/L)	0.001	0.999	0.988–0.989
Hospital to CRRT (days)	0.01	1.006	1.001–1.012
Charlson comorbidity index	0.780	0.993	0.948–1.041
Urine Output at CRRT (mL/kg/h)	0.032	0.756	0.588–0.976
Medical admission (vs surgical)	0.0001	1.761	1.469–2.111

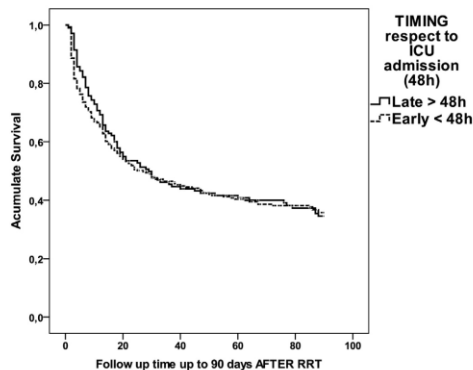
APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; CI, confidence interval; CRRT, continuous renal replacement therapy; HR, hazard ratio.

All patients presented septic shock and required CRRT during ICU admission. Patients with baseline creatinine >354 μmol/L were excluded. Patients on CRRT for >24 h were excluded. Maximum serum creatinine value on the day of CRRT initiation or on the previous day. The available urine in the 24 h after ICU or prior to CRRT was summed and divided by the weight (kilograms) and time (hours).

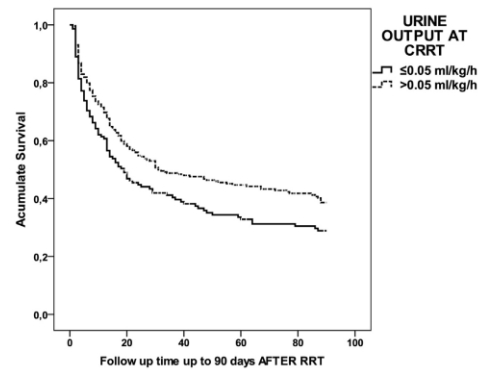
Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; serum blood urea nitrogen in mg/dL to mmol/L, ×2.8.

higher muscle mass which represents most of the times a better nutritional status, and a lower dilutional effect on creatinine values in those patients with no fluid overload. Oppositely, high BUN and low UO are clearly risk factors for mortality revealing once again that creatinine-based staging is a poor indicator of severity for patients started on RRT [3,13,18,19]. Both BUN and UO have already been described as severity markers in patients with AKI requiring RRT [8,17,33,34] although no studies have been performed specifically in patients with SS. Time from hospital admission to CRRT was identified as an independent mortality predictor as these patients present higher morbidity and mortality due to long hospital stay and sometimes delayed ICU admission [9,35]. Medical admission to ICU presents nearly twice risk of 90-day mortality in our study compared to surgical admission and this could be related to a high prevalence of severe community acquired pneumonia (nearly 25% of 939 patients).

In clinical practice, a “wait and see” approach is often used for severe AKI patients who are non-oliguric [16]. These patients may recover spontaneously and are less likely to develop urgent indications for RRT (fluid overload, hyperkalemia) than oligoanuric patients. We thus



**Fig. 2.** Time from ICU admission to CRRT in KDIGO stage 3 SA-AKI patients. Survival curves at 90 days ( $p = 0.765$ ). No differences in survival were found between patients started within the first 48 h from ICU admission and those started later up to 5 days. Stage 3 AKI is defined by KDIGO creatinine criteria. CRRT, continuous renal replacement therapy; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; SA-AKI, sepsis-associated acute kidney injury.



**Fig. 3.** Urine output at CRRT commencement in KDIGO stage 3 SA-AKI patients. Survival curves at 90 days ( $p = 0.019$ ). Patients with low urine output ( $\leq 0.05$  ml/kg/h) 24 h prior to CRRT presented lower survival compared to those started with higher urine output. Stage 3 AKI is defined by KDIGO creatinine criteria. CRRT, continuous renal replacement therapy; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; ml/kg/h, milliliters/kilogram/hour; SA-AKI, sepsis-associated acute kidney injury.

sought to understand whether use of CRRT in patients with different UO patterns would be associated with different outcomes. We compared this analysis to a standard “clock time” from ICU admission variable. Interestingly within this subgroup of severe (stage 3) AKI patients with SS, days in ICU prior to CRRT were not predictive of survival while UO was. This suggests that timing of initiation of RRT is a more complex variable than simply time from ICU admission or from creatinine-based staging. Indeed a more personalized approach will likely be required as recently advocated by the Acute Disease Quality Initiative workgroup [36].

Timing of CRRT based on UO seems a more physiological approach and recent studies have emphasized the importance of UO as a clinical AKI biomarker [3,37]. Leite et al. reported survival benefits in a cohort of patients treated with early RRT based on UO although the late group was not precisely defined, as number of days to RRT initiation were not reported [18]. Starting CRRT before low UO setting could hypothetically prevent volume overload which is a well-known mortality predictor in patients with sepsis with or without AKI [10,38,39]. In the recently reported ELAIN study [6] mean fluid balance at randomization was 7 litres positive which could explain the worse outcome for patients who were in the delayed initiated group.

The limiting factor is to be a retrospective study carried out in different periods and countries where indication to start CRRT was not decided upon a common standardized protocol but was based on clinical decision making. Patients started with CRRT in an oliguric state vs the others may have other important confounders (such as fluid balance or drug clearance and toxicity) triggering CRRT start and causing mortality. Another limitation is that we focused exclusively on patients who received CRRT and thus we cannot comment on SS patients in stage 3 AKI who did not receive CRRT as these data were not collected [40]. Even though we tried to homogenize our population in order to analyze the effect of timing of initiation of CRRT, there may still be residual confounding as patients with early stages of AKI and those who were started after 5 days from ICU admission were excluded from analysis as both group of patients presented higher severity scores as well as comorbidities. AKI stage 3 group started on CRRT after >5 days from ICU admission (median time of 14 days) had higher mortality (71.6% at 90 days) with a higher Charlson comorbidity index (probably these more chronic patients were delayed in CRRT initiation decision), and

lower creatinine values (probably reflecting low nutritional status plus fluid overload).

Duration of oliguria was not registered further than 24 h prior to CRRT and this could also represent a study limitation as those patients with longer oliguria state (and probably higher fluid overload) were not properly identified. Finally, fluid balance before and after CRRT initiation was not collected. Positive fluid balance is not only a well-known mortality predictor in AKI patients before and after CRRT initiation, [3,10,38,39] but it may also dilute creatinine underestimating AKI stage [41].

## 5. Conclusions

In patients with SS and advanced AKI (KDIGO stage 3), survival is lower as age, severity of illness, BUN and time from ICU admission to RRT increases. When CRRT is started in the setting of low UO mortality is increased. These results must be considered with caution while big trials are still not completed although we recommend that these variables should be included in studies evaluating timing of RRT initiation in patients with SS.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.jccr.2017.03.022>.

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***“Esto no es nada. Siga el fuego...”***

Cosme D. Churruca.

*“...que la angustia es un mal pasajero, que hay un orden secreto que rige las cosas y que el mundo pertenece y pertenecerá siempre a los optimistas.”*

J. Goytisoló (Campos de Nijar)