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Impact on Delta SOFA score in Sepsis-Induced Acute Kidney Injury: A Comparative Study of Haemofilter Efficacy in Continuous Renal Replacement Therapy

A MULTICENTRIC CLINICAL TRIAL

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“This is the reality of intensive care: at any point, we are as apt to harm as we are to heal".

Atul Gawande

A la doctora Patricia Ortiz Ballujera, gràcies per la dedicació que m'has mostrat, pel teu suport i per ser un exemple com a professional i com a persona.

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Estic segura que sense vosaltres això no hauria sigut possible.
Moltíssimes gràcies!

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TITLE: Impact on Delta SOFA score in Sepsis-Induced Acute Kidney Injury: A Comparative Study of Haemofilter Efficacy in Continuous Renal Replacement Therapy

BACKGROUND

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated response to infection and is a significant cause of mortality worldwide. In sepsis, acute kidney injury is a major factor contributing to morbidity, resulting from inflammation and microcirculatory dysfunction. It is the most common cause of death from infection, especially if there is a lack of early detection and treatment.

The management of sepsis-induced acute kidney injury is complex and involves measures to eliminate infection sources, targeted antibiotics, and intensive care interventions such as vasopressors, mechanical ventilation, and continuous renal replacement therapy. Despite the availability of various CRRT filters, such as the AN69ST or oXiris® haemofilter, there is a lack of high-quality studies and clinical guidelines that demonstrate their superiority over one another. This knowledge gap has resulted in the absence of a standardized protocol for continuous renal replacement therapy using haemofilter that adsorbs inflammatory mediators in clinical practice.

OBJECTIVE

This study aims to address this critical gap of knowledge by comparing the reduction of the Sequential Organ Failure Assessment (SOFA) scores of conventional filters (AN69ST) and the oXiris® haemofilter during continuous renal replacement therapy in sepsis-acute kidney injury patients. The secondary objectives are to compare the survival, the reduction of inflammatory mediators and lactate levels, and the number of days requiring vasoactive drugs, mechanical ventilation, and renal replacement therapy.

DESIGN AND SETTING

This study is designed as a randomized, triple-blind, prospective, parallel groups and multicentric clinical trial that will be performed at the ICU of Hospital Universitari Doctor Josep Trueta (HUJT) and Hospital Santa Caterina (HSC).

PARTICIPANTS

The target population of this clinical trial are adult patients admitted to the ICU with sepsis-induced acute kidney injury who meet the diagnostic criteria for both sepsis and AKI (KDIGO criteria), and who requires continuous renal replacement therapy.

METHODS

254 participants will be enrolled using a consecutive non-probabilistic sampling method and the time of recruitment will be 2 years. A first SOFA score will be measured and will be set as the SOFA score at admission. Additionally, we will measure the inflammatory mediators and lactate levels. Later, the patients enrolled on the clinical trial will be randomised in a 1:1 ratio into two groups: group A will be treated using conventional haemofilter during the continuous renal replacement therapy, and group B will be treated with oXiris® haemofilter. At 24 and 72 hours we will measure again the SOFA score respectively (SOFA score 24h and 72h), inflammatory mediators and lactate levels. The major outcome variable will be the delta SOFA score (Δ-SOFA).

KEYWORDS

S-AKI, Acute kidney injury, CRRT, oXiris, AN69ST, sepsis, septic shock, ICU, intensive medicine.

2. ABBREVIATIONS AND ACRONYMS

Δ-SOFA	Delta Sequential Organ Failure Assessment	**CVVHD**	Continuous Veno-Venous Haemodialysis
ABG	Arterial Blood Gas	**CVVHDF**	Continuous Veno-Venous Hemodiafiltration
AKD	Acute Kidney Disease	**DAD**	Diffuse Alveolar Damage
AKI	Acute Kidney Injury	**DAMPs**	Damage-Associated Molecular Patterns
APACHE II	Acute Physiology and Chronic Health Disease Classification System II	**DIC**	Disseminated Intravascular Coagulation
APC	Activated Protein C	**DNA**	Deoxyribonucleic Acid
APCs	Antigen-Presenting Cells	**ECG**	Electrocardiogram
aPTT	Activated Partial Thromboplastin Time	**ECMO**	Extracorporeal Membrane Oxygenation
ARDS	Acute Respiratory Distress Syndrome	**EDTA**	Ethylene-Diamine-Tetra-Acetic Acid
BIS	Bispectral Index	**EMS**	Emergency Medical Service
BP	Blood Pressure	**FiO_2**	Fraction Of Inspired Oxygen
CatSalut	Servei Català De La Salut	**GCS**	Glasgow Coma Scale
CCI	Score Charlson Comorbidity Index Score	**GNB**	Gramm Negative Bacteria
CEIC	Comitè Ètic D'investigació Clínica	**GPB**	Gramm Positive Bacteria
CHF	Congestive Heart Failure	**HC**	Hospital Coordinator
CKD	Chronic Kidney Disease	**HCO**	High Cut-Off
CRF	Case Report Form	**HD**	Haemodialysis
CRRT	Continuous Renal Replacement Therapy	**HLA-DR**	Human-Leukocyte Antigen-D Related
CS	Code Sepsis	**HR**	Heart Rate
CVVH	Continuous Veno-Venous Hemofiltration	**HSC**	Hospital de Santa Caterina

HUJT	Hospital Universitari Doctor Josep Trueta
IC	Informed Consent
ICD-10	International Classification Of Diseases-10 Coding
ICU	Intensive Care Unit
ID	Identification
IFNs	Interferons
Ig	Immunoglobulin
IL	Interleukins
INR	International Normalized Ratio
IQR	Interquartile Range
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
LAL	*Limulus Amoebocyte Lysate*
LMWH	Low Molecular Weight Heparin
LPS	Lipopolysaccharide
MAP	Mean Arterial Pressure
MDSCs	Myeloid-Derived Suppressor Cells
MRI	Magnetic Resonance Imaging
MRMs	Multiresistant Microorganisms
MV	Mechanical Ventilation
NETs	Neutrophil Extracellular Traps
NIV	Non-Invasive Ventilation
NMBAs	Neuromuscular Blocking Agents
NOD	Nucleotide-Binding Oligomerization Domain
oHCP	Others Health Care Professionals
PAI-1	Tissue Plasminogen Activator Inhibitor
PAMPs	Pathogen-Derived Molecular Patterns
PaO_2	Partial Pressure Of Oxygen
PC	Protein C
PCR	C-Reactive Protein C
PCT	Procalcitonin
PD-1	Programmed Death Protein 1
PD1-R	Programmed Death Protein 1-Receptor
PEEP	Positive End-Expiratory Pressure
PEI	Polyethyleneimine
PI	Principal Investigator
PRRs	Pattern-Recognition Receptors
PT	Prothrombin Time
qSOFA	Quick Sequential Organ Failure Assessment
RIG	Retinoic Acid-Inducible Gene
RN	Research Nurses
ROS	Reactive Oxygen Species
RR	Respiratory Rate
RRT	Renal Replacement Therapy
S-AKI	Sepsis-Induced Acute Kidney Injury

$SatO_2$	Oxygen Saturation	TECs	Tubular Epithelial Cells
sCR	Serum Creatinine	TFPI	Tissue Factor Pathway Inhibitor
SCUF	Slow Continuous Ultrafiltration	TGF-ß	Transforming Growth Factor ß
SOFA	Sequential Organ Failure Assessment	TLR	Toll-Like Receptors
SP	Study Physicians	TNF-α	Tumor Necrosis Factor Alpha
SPSS	Statistical Package for the Social Sciences	Tº	Temperature
SSC	Surviving Sepsis Campaign	VD	Volume Distribution
t-PA	Tissue Plasminogen Activator	VILI	Ventilator-Induced Lung Injury
TAFI	Thrombin-Activatable Fibrinolysis Inhibitor	VT	Volume Tidal

3. INTRODUCTION

3.1 CONCEPT OF SEPSIS AND SEPTIC SHOCK

3.1.1 Definition and epidemiology

Sepsis is defined as a **life-threatening organ dysfunction caused by a dysregulated host response to infection**. It is the primary cause of death from infection, especially if it is not recognized and treated promptly (1). Sepsis is a global health concern, with rising incidence ranging between 200 and 400 cases per 100.000 people/year (2,3), and a mortality rate around 20% and 30% (4).

Septic shock should be considered a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities contribute to a greater risk of mortality than that posed by sepsis alone. Patients with **septic shock** can be clinically identified by a **vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia**.

3.1.2 Pathophysiology and clinical manifestations

INFLAMMATION

Sepsis is essentially an inflammatory condition caused by the activation of the body's innate immune system.

The first response by the host immune system to any invading pathogen is recognition of pathogen-derived molecular patterns (PAMPs, e.g., endo- and exotoxins, lipids, or DNA sequences) or endogenous host-derived danger signals (DAMPs; damage-associated molecular patterns). PAMPs are molecules that circulate following the destruction of pathogens or can be released by live pathogens, while DAMPs are host cellular components released when cells are lysed (5). The most potent of all the PAMPs is bacterial lipopolysaccharide (LPS), also known as endotoxin, and is primarily found as a component of the outer membrane of Gram-negative bacteria (6).

These molecules are recognized by certain cell-surface receptors and complement proteins, that are found on different types of cells, including immune cells (antigen-presenting cells (APCs) and monocytes), epithelial cells, and endothelial cells.

When PAMPs or DAMPs bind to PRRs (pattern-recognition receptors) such as Toll-like receptors (TLR), nucleotide-binding oligomerization domain (NOD)-like receptors, retinoic acid-inducible gene (RIG)-like receptors, and others, it triggers a complex intracellular signalling system that initiates the transcription of early activation genes, cell metabolism, and the adaptative immunity (7). These genes, includes various pro-inflammatory interleukins (IL), such as IL-1, IL-12, IL-18, tumor necrosis factor alpha (TNF-α), and interferons (IFNs). Subsequently, these pro-inflammatory molecules activate additional cytokines, such as IFN-y, IL-6, IL-8, as well as the complement and coagulation pathways (7,8). Simultaneous to the proinflammatory response, a systemic inhibition of the immune system occurs to restore homeostasis.

The result is that monocytes and macrophages have less capacity to release proinflammatory cytokines, and blood monocytes are reprogrammed with reduced expression of human-leukocyte antigen-D related (HLA-DR). Additionally, there is an increase in T-cell apoptosis and release of anti-inflammatory mediators to counteract continual inflammation (9). This immunosuppression, occurring in the later stages of the disease, often leads to a state known as "immunoparalysis" (8) (Figure 1). Therefore, patients with sepsis become vulnerable to nosocomial infections, opportunistic pathogens, and reactivation of viral infections (10).
As a result of the increased activation of both pro-inflammatory and anti-inflammatory pathways, the inflammation that occurs in sepsis leads to gradual damage to tissues, and finally causing **multi-organ dysfunction**.

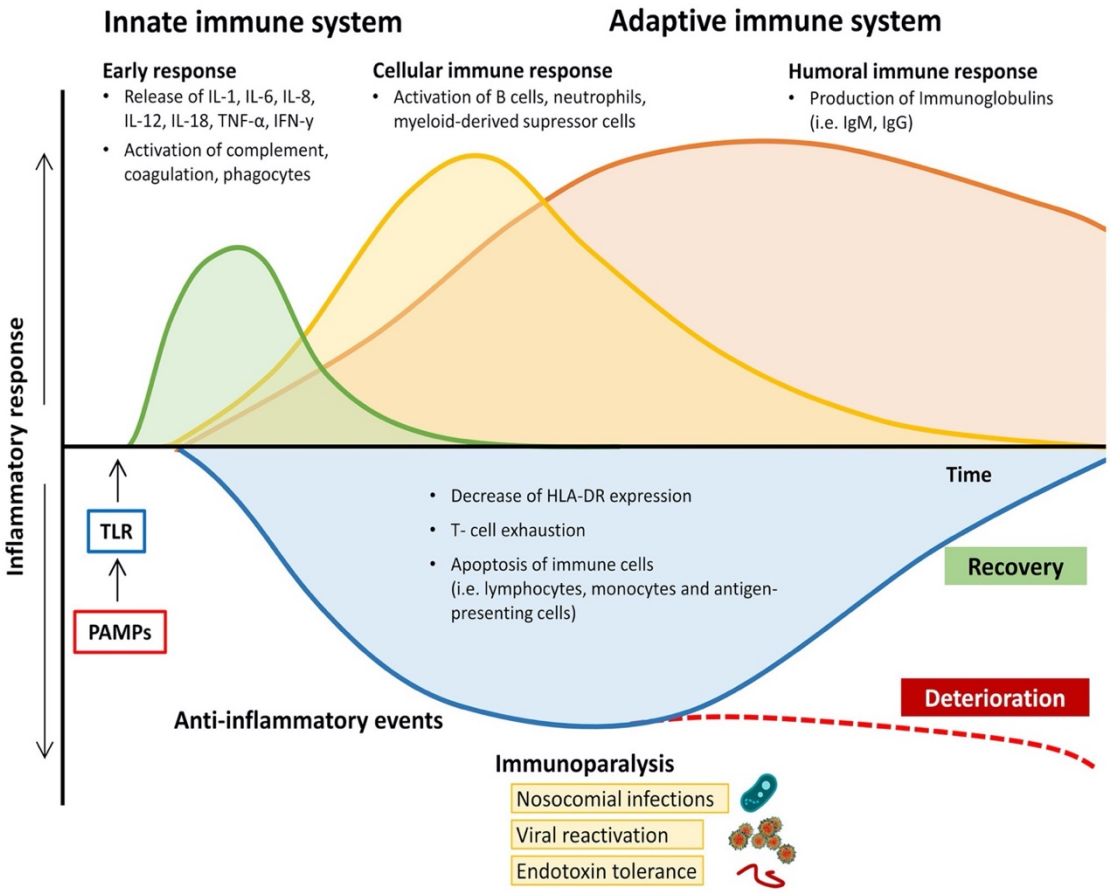


FIGURE 1. **Changes in pro- and anti-inflammatory response of the immune system during the course of sepsis and septic shock**

HLA-DR, human leukocyte antigen-D related; IgM/G, immunoglobulin M/G; IL, interleukin; IFN-γ, Interferon γ; TNF-α, tumor necrosis factor alpha; TLR, toll-like receptor

THE ROLE OF ENFOTHELIUM AND COAGULATION IN SEPSIS

Under normal physiological conditions, blood flows through the blood vessels with a natural anticoagulant state. This is achieved through the interaction of thrombomodulin, thrombin, protein C (PC) and activated protein C (APC). As we can see on Figure 2, adapted from "*Activated protein C for sepsis*" (11), in the normal state, vascular endothelial cells express thrombomodulin, which after binding to thrombin, inhibits thrombin formation by generating APC from soluble PC. APC inhibits Va and VIIIa, key cofactors in the **extrinsic and intrinsic pathways**, respectively, emphasizing anticoagulation to maintain blood flow. Additionally, on the cell surface the plasminogen activator initiates fibrinolysis, contributing to the breakdown of blood clots and helping to prevent excessive clot formation (12).

In sepsis and septic shock, the normal anticoagulative state within the vascular endotelial cells is disrupted. The activation of the innate immune receptors, the complement, and the production of inflammatory cytokines, impacts on coagulation and the vascular endothelium.
Sepsis leads to a state of **hypercoagulability**, characterized by the presence of microvascular blood clots, fibrin deposition, formation of neutrophil extracellular traps (NETs), and endothelial injury. These changes contribute to the prothrombotic environment observed in sepsis, which can further complicate the clinical condition of the patient (7). These patients are susceptible to a prothrombotic state through four primary mechanisms (5):

- Activation of the extrinsic pathway, involved in initiating the clotting process.
- Amplification of coagulation through the effects of cytokines released during inflammation.
- Anticoagulant pathways suppression.
- Impairment of fibrinolysis.

Tissue factor pathway is the initial and main trigger for the activation of the coagulation in sepsis. The tissue factor is located in inflammatory cells, mainly the monocytes and other circulating macrophages. When monocytes and other cells are activated by PAMPs and DAMPs, they release extracellular vesicles that express coagulant tissue factor and phosphatidylserine on their surfaces. Tissue factor is released into circulation and activates the **extrinsic coagulation** pathway. Furthermore, tissue factor is in the vascular endothelium, and its exposure to circulation in case of endothelial damage leads to activation of the **common coagulation pathway.**
Neutrophils also participates on the activation of the coagulation cascade through the expression of the tissue factor and the release of chemical mediators and proteins, and neutrophil extracellular traps (NETs), that are highly prothrombotic. NETs are particles of histones, procoagulant DNA and other DAMPs that are released during the pathogen invasion to contain the infection. The release of inflammatory cytokines and bacterial wall fragments are strong trigger for the activation of coagulation cascade.
As sepsis progresses, the three mechanisms that normally prevents the activation of coagulation, [antithrombin, PC, and tissue factor pathway inhibitor (TFPI)], become disrupted. As we can see on Figure 3, adapted from "*Activated protein C for sepsis*" (11) too, this disruption leads to a state of hypercoagulability. Antithrombin is decreased in sepsis because of reduced synthesis and increased degradation through proteases and neutrophil elastases. Proinflammatory cytokines inhibit the production of PC and protein S, thrombomodulin and antithrombin III. In addition, TFPI is also reduced as a result of the endothelial dysfunction (13).

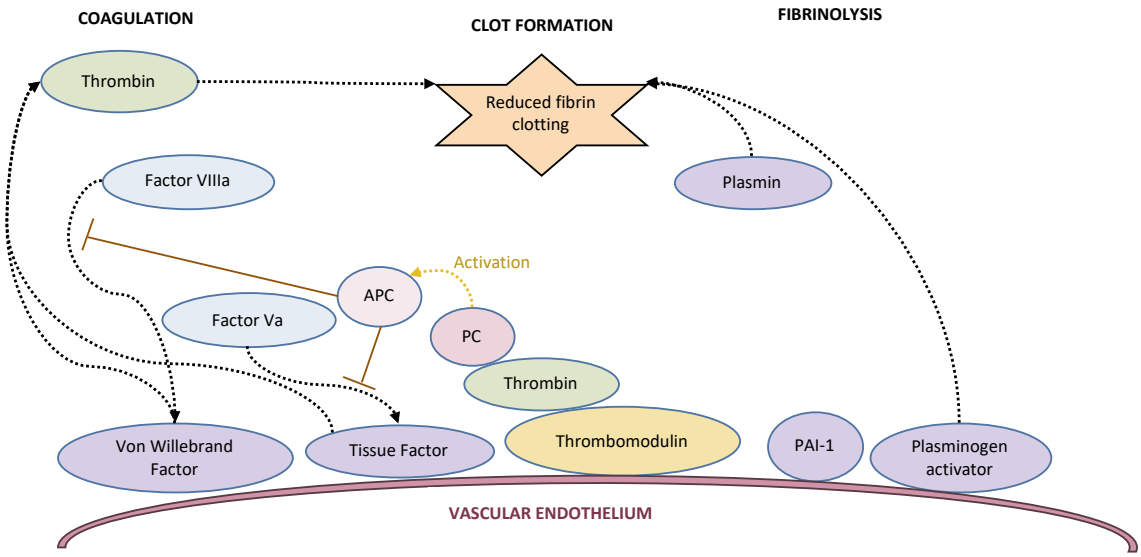


FIGURE 2. **Normal physiology in circulating blood: balancing coagulation and fibrinolysis**

In normal physiology, the thrombin-thromdomodulin complex interacts with protein C (PC) to form APC, that inhibits thrombin formation by preventing factor Va from interacting with tissue factor (extrinsic pathway) and factor VIIIa from interacting with Von Willebrand factor (intrinsic pathway). Plasminogen activator and plasmin also contribute to fibrinolysis to reduce any formed clots.

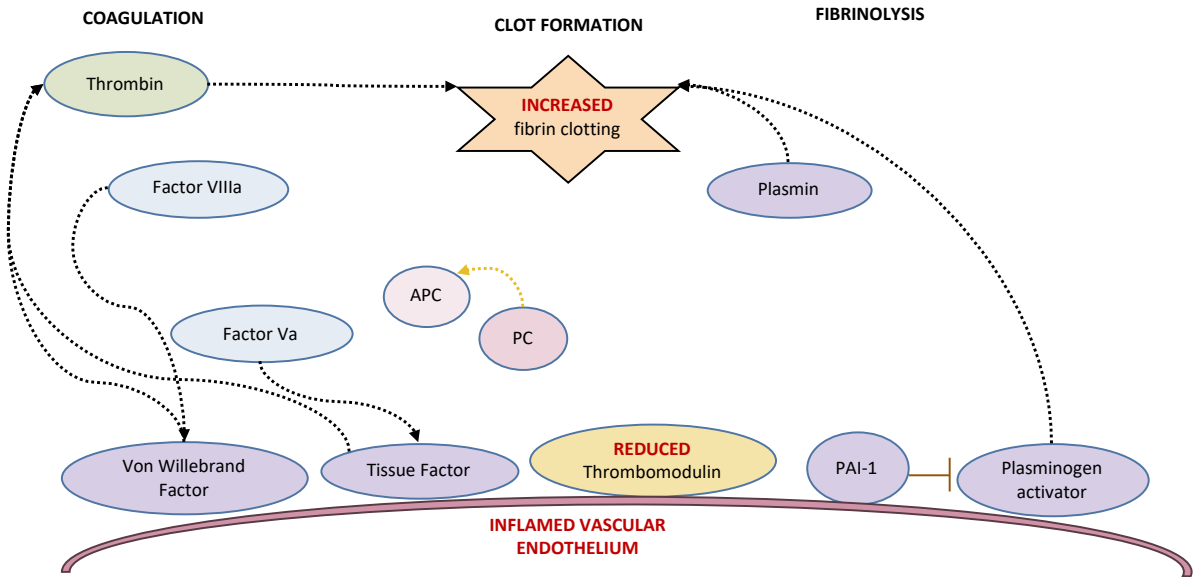


FIGURE 3. **Potential mechanisms responsible for increased coagulation in sepsis**

In sepsis, inflammatory mediators activate endothelial cells. Thrombomodulin expression is reduced, leading APC-dependent anticoagulation inefficient. Fibrinolysis is inhibited by the cytokine-induced expression of plasminogen-activator inhibitor 1 (PAI-1). As a result, the increased expression of TF and von Willebrand factor leads to clot formation and disseminated intravascular coagulation.

In sepsis, fibrinolytic activity depends on the balance between the tissue plasminogen activator (t-PA), tissue plasminogen activator inhibitor (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI).

Impairment of fibrinolysis occurs as a result of increased PAI-1, TAFI levels and plasma levels of nuclear products. PAI-1 and TAFI are both substances involved in regulating the process of fibrinolysis. PAI-1 is a protein that inhibits the action of tPA, responsible for converting plasminogen (an inactive protein) into plasmin (an enzyme that breaks down fibrin). When PAI-1 levels increase, it reduces the activity of tPA, leading to impaired fibrinolysis and making it more difficult for the body to dissolve blood clots. TAFI, on the other hand, is an enzyme that helps to regulate fibrinolysis by inhibiting plasmin from breaking down fibrin. When TAFI levels are elevated, it further slows down the process of fibrinolysis and makes it harder for clots to be dissolved. Both PAI-1 and TAFI play important roles in maintaining the balance between clot formation and clot dissolution, but when their levels are increased, they can contribute to impaired fibrinolysis and a prolonged clotting state (5).

Since coagulation serves as a defense mechanism, bacterial pathogens are confined in a fibrin network at the infection site, limiting the spread to adjacent tissues and systemic circulation. In this context, impairment of fibrinolysis can be useful, but it can also have negative consequences (14).

COMPLEMENT SYSTEM IN SEPSIS

Complement activation products (such as the anaphylatoxins C3a, C4a, and C5a) are elevated in the early stages of sepsis (15).

C5a has been shown to be a small proinflammatory peptide and a potent chemo attractant for neutrophils, monocytes, and macrophages. In neutrophils, the presence of C5a triggers an oxidative burst, leading to the generation of reactive oxygen species (ROS) and the release of granular enzymes, causing tissue damage. Additionally, C5a acts as a stimulant for the synthesis and release of proinflammatory cytokines and chemokines, thereby amplifying the inflammatory response. During inflammation, these mechanisms are considered to contribute to vasodilation, tissue damage, and the development of multiple organ failure.

The potential involvement of C5a in the development of sepsis has been associated with several complications, such as neutrophil dysfunction, apoptosis of lymphoid cells, exacerbation of

systemic inflammation, cardiomyopathy, disseminated intravascular coagulation (DIC), and complications associated with multiple organ failure (16).

IMMUNOSUPRESSION AND PERSISTENT INFLAMMATION

In sepsis there is a significant component of immunosuppression that also occurs in both early and late stages of the disease (7). During the initial phases of sepsis, B and T lymphocytes decreases, and APCs experience a higher rate of apoptosis (17).

The precise mechanisms responsible for sepsis-induced lymphopenia are not fully understood; however, it may involve increased migration into the tissues, increased apoptosis, and reduced production of them, as emergency hematopoiesis prioritizes the release of neutrophils and monocytes (18).
Prolonged lymphopenia and reduced immunoglobulin levels in sepsis have been associated with increased mortality rates (19).

In addition to lymphopenia, an increased rate of apoptosis in APCs and monocytes is often observed, which is accompanied by an increase in granulopoiesis (17). This process involves the migration of immature myeloid cells into the peripheral blood, where they become myeloid-derived suppressor cells (MDSCs) and can release anti-inflammatory cytokines such as IL-10 and transforming growth factor ß (TGF-ß). These cytokines contribute significantly to the exacerbation of immunosuppression (7).

Simultaneously, there is a decrease expression of human leukocyte antigen DR (HLA-DR) on the surface of the remaining monocytes and dendritic cells. This leads to impaired pathogen recognition and a reduction in the opsonization process involving T cell receptor proteins. Consequently, there is a disruption of the Th1 and Th2 response, which is an essential component of the adaptive immune response (20).
The expression of programmed death protein 1 (PD-1) is increased on the surface of T cells, APCs and epithelial cells in patients with sepsis. PD-1 binds to the inhibitory programmed death protein 1-receptor (PD1-R) expressed on B and T lymphocytes, resulting on the apoptosis of immune cells, depletion of T and B cells, and APCs dysfunction (21) (Figure 4).

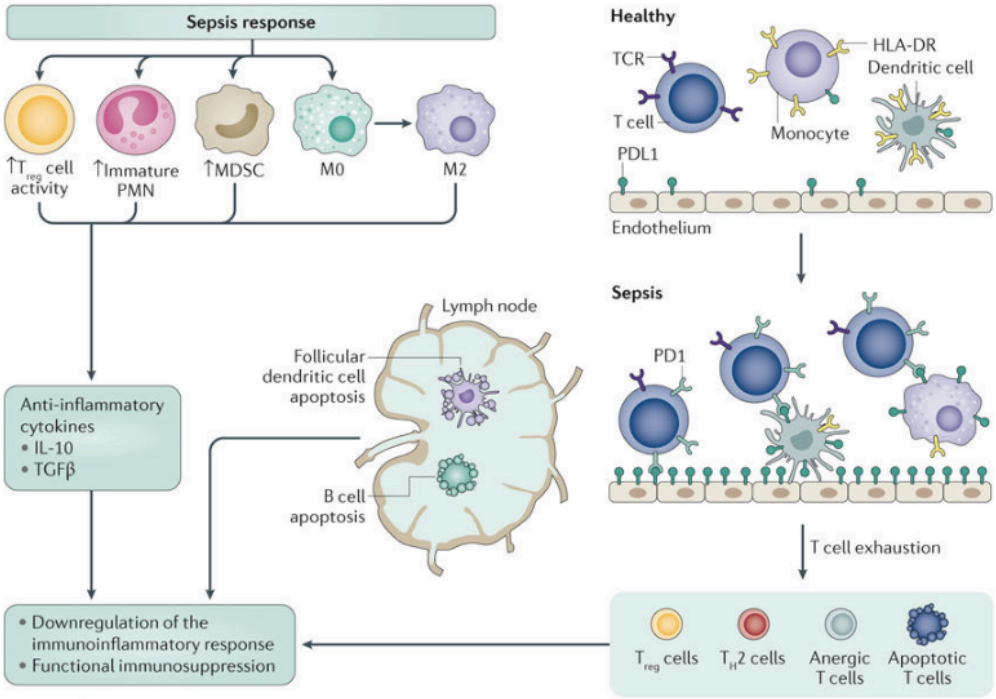


FIGURE 4. **Late immunosuppressive effects of sepsis**

After the transitory acute inflammatory response, chronic immunosuppression occurs. Immature polymorphonuclear leukocytes (PMNs) and myeloid-derived suppressor cells (MDSCs) mobilise from the bone marrow, and monocyte differentiation leads to the production of M2 macrophages. This, in turn, decreases inflammation by producing anti-inflammatory cytokines such as IL-10 and TGF-β. APC reduces the expression of HLA-DR, while T cells and stromal cells upregulate PD1 and PDL1, leading to an increase in apoptosis and abrogation of the immune response. Extracted from "*Sepsis and septic shock*" (7)

The simultaneous downregulation of the inflammatory response in sepsis leads to the extensive loss of immune cells and the **inability of the host to continue to defend itself** against invading pathogens (7) (Figure 5).

It has been observed that septic patients have **low plasma levels of IgA, IgG and IgM**, and that is associated with a reduced survival at the onset or during sepsis or septic shock (22). The cause is not fully understood, but probably is a result of multifactorial events such as endothelial dysfunction and vascular leakage, redistribution to inflamed tissue, complement consumption, excessive catabolism and immunosuppression (23).

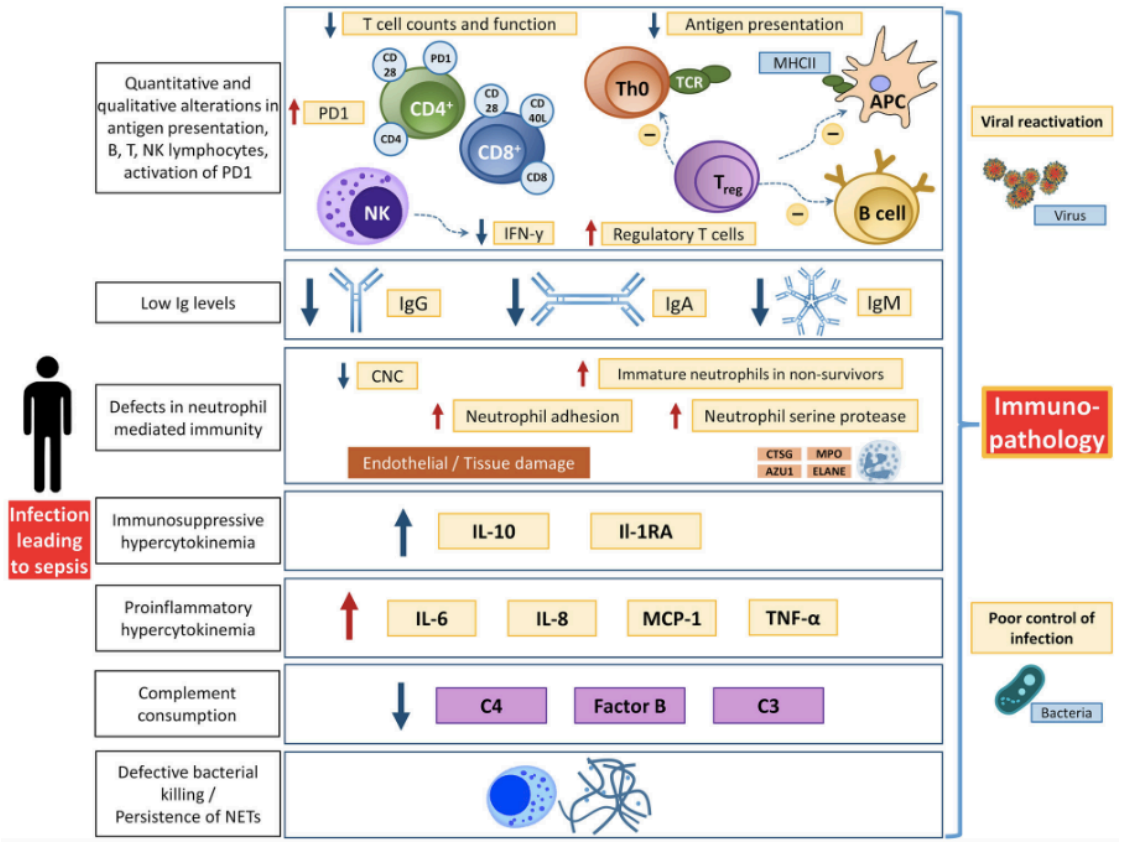


FIGURE 5. **Overview of different aspects of immunological dysfunction**

APC, antigen presenting cell; AZU1, azurocidine 1; CNC, circulating neutrophils count; CTSG, cathepsin G; ELANE, elastase; IFN-γ, interferon γ; Ig, immunoglobulin; MHCII, major histocompatibility complex II; MPO, myeloperoxidase; PD1, programmed death protein 1. Adapted from Bermejo-Martin JF (23)

ACUTE RESPIRATORY DISTRESS SYNDROME

When critically ill patients develop pulmonary dysfunction, there is often an associated primary pulmonary affection (pneumonia, exacerbation of chronic obstructive pulmonary disease, aspiration, pulmonary embolism or pulmonary contusion). In case of sepsis induced acute respiratory distress syndrome (ARDS), a primary pulmonary pathology is absent in many cases (8). The development of sepsis-induced ARDS in the result of an unregulated and complex interaction between inflammatory cytokines and cellular mediators, resulting in damage to the alveocapillary unit. This process can be categorized into three interlacing phases (24), summarized at Figure 6:

EXUDATIVE PHASE	PROLIFERATIVE PHASE	FIBROTIC PHASE
First days: edema and alveolar haemorrhage	**First weeks**: organization and repair	**3-4 weeks after the onset**: collagenous fibrosis

FIGURE 6. **Phases of sepsis-induced Acute Respiratory Distress Syndrome (ARDS)**

The impairment of the pulmonary epithelium and endothelium results in increased alveolar capillary permeability, leading to the formation of protein-rich alveolar fluid exsudate, which progressively accumulates. This exudate not only deactivates surfactant factor but also causes damage to type 2 pneumocytes, leading to an increase in interalveolar surface tension and causing **microatelectasis**.

The local release of inflammatory mediators contributes to widespread endothelial cell damage, leading to the development of diffuse alveolar damage (DAD) in the advanced stage of sepsis-induced ARDS in certain patients (25). DAD is a histological term defined by the American Thoracic Society as the presence of key histological features (diffuse distribution, uniform temporal appearance, alveolar septal thickening due to organizing fibrosis, usually diffuse airspace organization may be patchy or diffuse, hyaline membranes) and pertinent negative findings (lack of granulomas, necrosis, or abscesses, lack of infectious agents, no viral inclusions and negative results with special stains for organisms, lack of prominent eosinophils and neutrophils and negative cultures) (26).

Once pulmonary edema accumulates in the interstitium and air spaces of the lungs, it causes increased respiratory effort and compromised gas exchange. This, in turn, leads to hypoxemia, less carbon dioxide elimination, and finally in acute respiratory failure (12).

If the patient receives treatment at an early stage, lung injury can be reversible. However, if there is an ongoing secretion of protein-rich fluid and continued infiltration of neutrophils, mononuclear cells, fibroblasts, and lymphocytes, respiratory failure progresses and the pulmonary fibrosis completely transforms the lungs. Collagen accumulates, leading to the formation of microcystic honeycomb structures, traction bronchiectasis, and fibrosis of the alveolar ducts. Additionally, there is an abnormal enlargement of air spaces and a disproportionate increase in dead space (volume of a breath that does not participate in carbon dioxide excretion). Increases of pulmonary dead space and a decrease in respiratory compliance are independent predictors of mortality in ARDS (27).

CARDIAC DYSFUNCTION

There are different acute cardiac disorders caused by sepsis, but septic cardiomyopathy has become the focus of a lot of studies in recent decades because it is associated with significantly increased of mortality of up to 50% (28).

Septic cardiomyopathy is a cardiac dysfunction that affects both ventricles and presents all the signs of circulatory failure. It is characterized by endothelial and myocardial dysfunction due to the arterial vasodilatation and microcirculatory maldistribution of blood flow. Proinflammatory mediators produces a downregulation of β-adrenergic receptors and their components, resulting on a decrease in **myocardial adrenergic response** (8).

Another mechanism is the influence of complement system. Activated complement factor C5 (C5a) is a strong proinflammatory mediator that induces the release of granular enzymes, cytokines and ROS, and increases chemotaxis of neutrophils. ROS can inhibit mitochondrial respiration, leading to apoptosis and consequently causing metabolic dysfunction in the myocardium (29) and hypoxia (7).

NEUROLOGICAL MANIFESTATIONS

Sepsis is characterized by an altered mental state, such as lethargy, confusion or delirium. Some patients may develop septic encephalopathy, which is clinically manifested by a disruption of the circadian rhythm, disorientation, agitation and hallucinations (30).

In some patients, it affects them so profoundly that it is mandatory to secure their airway with an intubation. It is important to rule out other causes of neurological symptoms, such as hypoxaemia, hypoglycaemia, drug toxicity or central nervous system infection.

HAEMATOLOGICAL DYSFUNCTION

Some primary haematological manifestations are anaemia, leucocytosis, neutropenia and thrombocytopenia. Anaemia is caused by the inflammation and the shortened red blood cell survival because of the haemolysis in the setting of Disseminated Intravascular Coagulation (DIC) (30).

DIC is one of the manifestations of severe sepsis and can manifest in two clinical patterns: with evident bleeding from numerous sites, or with thrombosis affecting small and medium blood vessels. The divergence in DIC presentation is because of the balance between the clotting and fibrinolytic systems, as mentioned above. In septic patients, if the fibrinolytic system dominates, the patient will experience bleeding from different sites. But if the coagulation system prevails, the patient will present cyanotic fingers and toes and may even develop gangrene in the digits

or upper and lower extremities. It is important to exclude heparin-induced DIC, as it may mimic septic-induced DIC (7).

DIC is diagnosed by thrombocytopenia and prolongation of prothrombin time (PT) or activated partial thromboplastin time (aPTT) (30).

HEPATIC DYSFUNCTION

Liver disfunction is common in sepsis, but sepsis-induced acute liver failure only occurs in less than 2% of patients (31). Septic hepatic dysfunction is diagnosed by an increase >2mg/dL in bilirubin concentration and a coagulopathy with INR >1.5 (32). The liver is implicated in the host response and participates in the clearance of the infectious agents such as endotoxin and bacteria. Also have a function on the detoxification and synthesis of proteins for metabolic, immune and coagulation functions (33).

The aetiology of the hepatic dysfunction in sepsis is unknow, but it has seen that during sepsis process there are a poor hepatic perfusion leading to a centrilobular necrosis of the liver (7). Clinical manifestations are: hypoxic hepatitis, sepsis-induced cholestasis, coagulopathies, hyperammonaemia that leads to an encephalopathy (30).

ENDOCRINE MANIFESTATIONS

Hyperglycemia is common in septic patients as a result of stress-induced increases in glucagon, catecholamines, cortisol and growth hormone. This, combined with insulin resistance because of the cytokine release, contributes to elevated blood glucose levels (34).

Some patients may experience **adrenal insufficiency** or **vasopressin deficiency** as a result of store depletion, increased vasopressinase activity and nitric oxide-mediated inhibition of vasopressin production (35).

3.2 SEPSIS-INDUCED ACUTE KIDNEY INJURY (S-AKI)

The major cause of sepsis-induced morbidity is **renal dysfunction** progressing to **renal failure** (36). AKI affects 25% to 67% of critically ill patients, with a mortality rate ranging from 30% to 60% (37). AKI is characterized by a sudden and persistent decrease in the glomerular filtration rate, leading to the accumulation of nitrogenous waste products and uremic toxins (38).

As separate syndromes, sepsis and AKI make the host vulnerable to each other; while sepsis is the primary factor leading to the onset of AKI, AKI of any cause increases the risk of developing sepsis (39). However, both sepsis and AKI are clinical diagnoses, and usually it is challenging to define the exact onset of these syndromes or determine which one occurs first.

Sepsis-associated acute kidney injury (S-AKI) is a common complication in hospitalized and critically ill patients, which increases the risk of developing chronic comorbidities and is associated with extremely high mortality (40).

As we observe at Figure 7, AKI may present simultaneously with sepsis at hospital admission (**situation a**) or be develop during hospitalization **(situation b)**. S-AKI can undergo early recovery during the first week after detection and is associated with a good prognosis. Some patients may experience one or more episodes of relapse after the initial recovery from AKI during their hospital stay, emphasizing the importance of monitoring and eliminating any nephrotoxic agents administered during hospitalization. If some patients do not achieve full recovery within 7 days, they will be categorize as having acute kidney disease (AKD), which may either recover later or progress to chronic kidney disease (CKD).

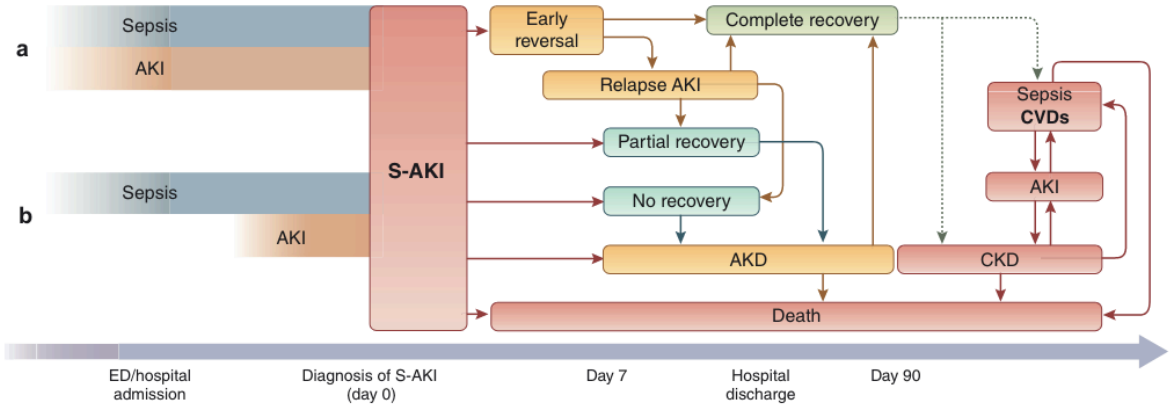


FIGURE 7. **Clinical course outcomes of S-AKI**

CVD, cardiovascular disease; ED, emergency department. Modified from *"Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment"* (40).

Understanding the pathophysiology of S-AKI is limited by several factors. One major limitation is establishing temporality, as over 50% of septic shock patients develop AKI before receiving medical care (41). Therefore, as mentioned early, it is difficult to determine which condition occurred first. Another limitation is that patients with S-AKI are often in critical condition, making it risky to obtain tissue biopsies to establish a pathologic diagnosis (42). Additionally, monitoring techniques to asses renal blood flow are still limited (43).

The precise mechanisms underlying S-AKI remains poorly understood, but an appropriate volume resuscitation is the treatment that can decrease the incidence of severe renal failure in sepsis (7). The prevailing hypothesis attributes S-AKI to hypoperfusion and shock, leading to a decreased renal blood flow that results in tubular epithelial cell necrosis (38). However, ischemia-reperfusion injury is not the only mechanism of S-AKI. In the absence of renal hypoperfusion or hemodynamic instability, and with normal or increased renal blood flow S-AKI can still be diagnosed (43).

As we have mentioned, sepsis is usually accompanied by inflammation, microcirculatory dysfunction and metabolic reprogramming, just like the other organs affected by it.
The renal tubular epithelial cells (TECs) have TLRs that bind with DAMPs and PAMPs filtered through the glomerulus or peritubular capillaries, leading to an increase in oxidative stress and mitochondrial damage. Furthermore, TECs also initiate signals to neighbour cells to deactivate them, in order to minimize cell death at the expense of function.

S-AKI is characterized by changes in microcirculatory flow leaded by endothelial injury, autonomic nervous system response, shedding of the glycocalyx and activation of the coagulation cascade. The glycocalyx is a layer of carbohydrates that covers the surface of endothelial cells in blood vessels and epithelial cells, and have a role on protecting, signalling and interacting with other cells. In the context of sepsis, the shedding of the glycocalyx refers to the loss of this protective layer, resulting in the loss of normal blood vessels function. This leads to the **leakage of fluids and proteins into surrounding tissues** (40). Consequently, capillaires become **occluded by leukocytes and platelets**, causing damage to the endothelium with endothelial leakage and **vasodilation**. These events contribute to **peritubular edema**, reducing oxygen supply to TEC because of the increased diffusion distance (8) (Figure 8).

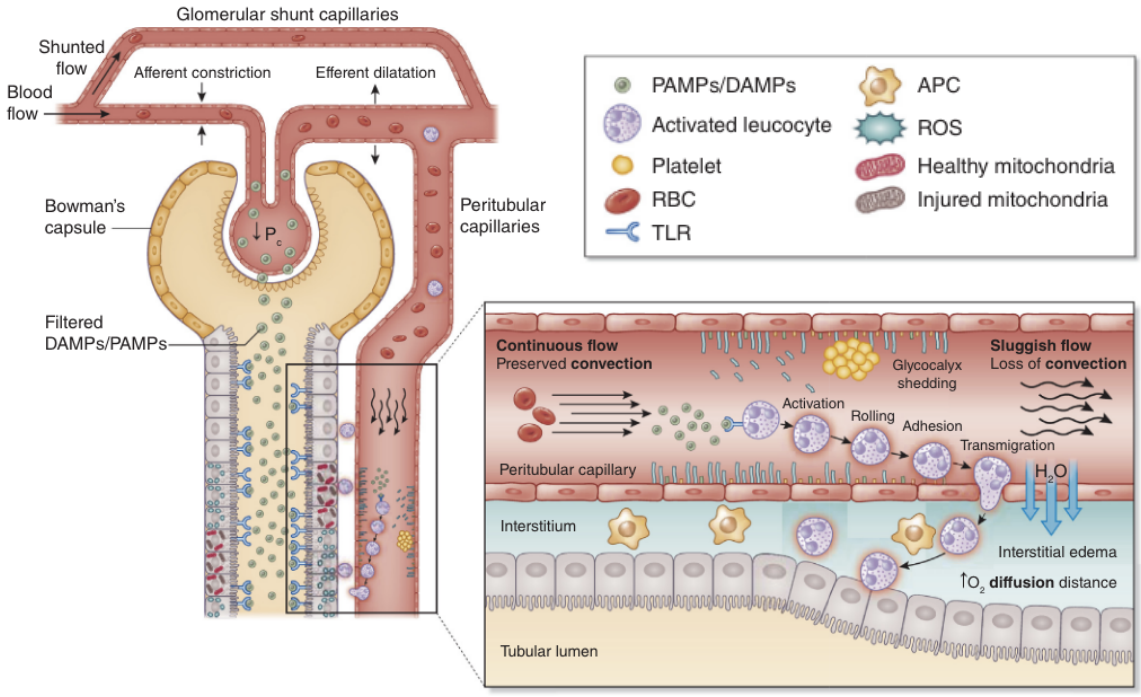


FIGURE 8. **Microcirculatory and inflammatory alterations**

APCs, antigenpresenting cells; RBCs, red blood cells.

Extracted from "*Sepsis-Associated Acute Kidney Injury*" (42)

3.3 DIAGNOSIS OF SEPSIS

Early identification and appropriate management in the initial hours after the development of sepsis improves outcomes (32).

In 2015 the Catalan Health Service (CatSalut) implemented the CODE SEPSIS *(«Codi Sèpsia» in Catalan)* (CS) with the aim to facilitate the early detection, initial treatment, and interhospital coordination to improve the management of patients with sepsis or septic shock as a life-threatening situation (4). The CS is modelled on other codes established in Catalonia, such as the Infarction Code, Polytrauma Code and Stroke Code, and should be activated in a hospital setting, for patients with sepsis or septic shock who are not at the end of their life and have no limitations on the use of life support techniques. The CS uses the anamnesis suggestive of an infectious syndrome plus organ failure (B, C or D) and / or early hyperlactacidemia to clinically identify a septic patient (Figure 9).

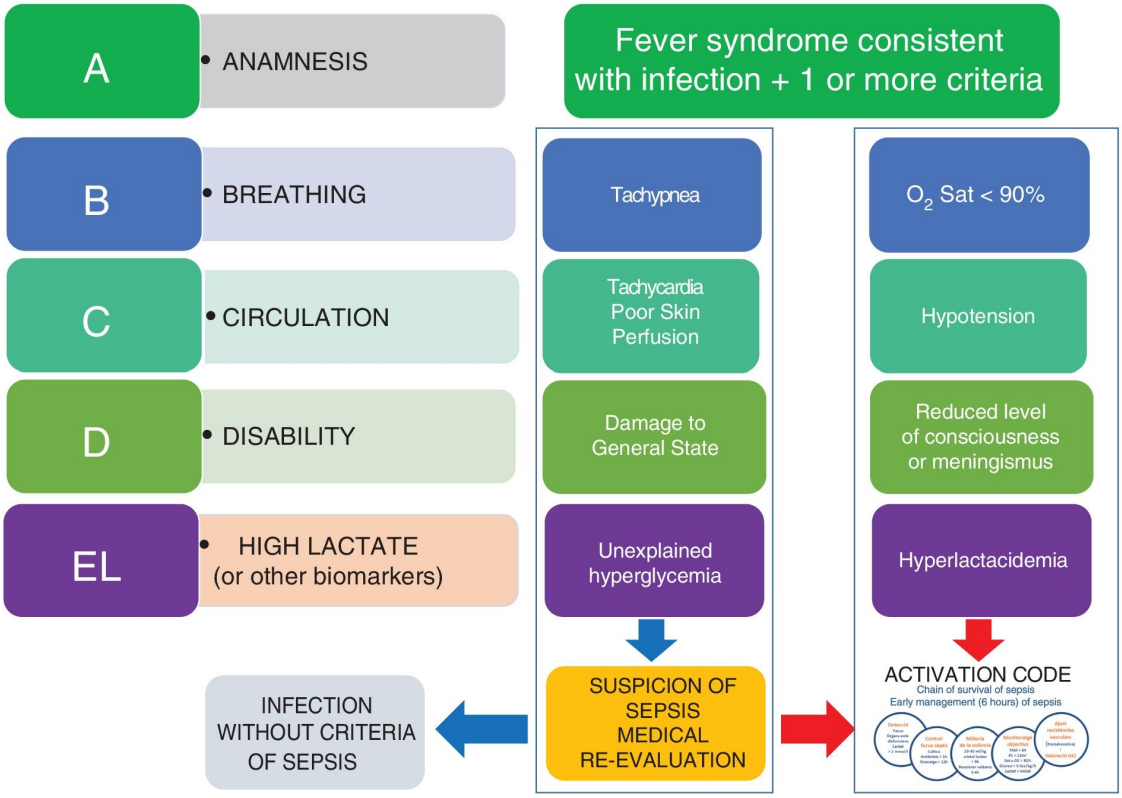


FIGURE 9. **Algorithm of the CS for the detection of the septic patient**

Clinical detection based on cardiovascular, respiratory, and neurological assessment. Tachycardia and Tachypnea are considered adaptative responses that may anticipate the appearance of organ failure. Extracted from *"Interhospital sepsis code in Catalonia (Spain): territorial model for initial care of patients with sepsis"* (4)

An essential aspect of CS is identifying the case, administering empirical antibiotic therapy, and initiating measures to restore tissue perfusion. Hospitals should have a protocol for managing specific empirical antibiotic therapy for septic patients, a protocol for hemodynamic management, and clear criteria for ICU admission.

As we mentioned early in this project, Sepsis-3 (1) defined sepsis as a life-threatening **organ dysfunction** caused by a dysregulated host response to infection. Thus, an organ dysfunction must always be outruled when new infection is suspected, and a new infection needs to be outruled in any case of new onset of organ dysfunction.

DIAGNOSIS OF AN ORGAN DYSFUNCTION

An organ dysfunction can be represented by an increase in the Sequential Organ Failure Assessment (SOFA) (originally the Sepsis-related) score of **2 points or more** (1), as a consequence

of infection. There is a good correlation between increasing score and mortality (44); a SOFA score of two or more points is associated with mortality rate of approximately 10% (45).

SOFA score employs 6 criteria reflecting the function of an organ system (respiratory, cardiovascular, renal, neurological, hepatic and haematological), each one scored from 0 to 4 with an increasing score reflecting worsening organ dysfunction as described on Table 1 (46). If the physiological parameters do not match any row, zero points are awarded. The row giving the highest number of points must be selected if the physiological parameters match more than one row.

Many clinical trials use the SOFA score as an outcome measure. The association between the SOFA score at admission and during ICU stay with long-term outcomes has led some investigators to propose delta SOFA as a valid alternative outcome in clinical trials. **Delta SOFA (Δ-SOFA)** is calculated as the change in the total SOFA score between a defined time point (e.g. the admission SOFA) and a defined study day (45).

TABLE 1. **Criteria for assessment of the Sequential Organ Failure Assessment (SOFA) scores**

CRITERIA		0	1	2	3	4
RESPIRATORY SYSTEM	PaO_2/FiO_2 (mmHg)	>400	<400	<300	<200 [a]	<100 with respiratory support
NERVOUS SYSTEM	Glasgow Coma Scale	15	13-14	10-12	6-9	<6
CARDIOVASCULAR SYSTEM	MAP [b] or Administration of vasopressors required [c]	>70	<70	Dop ≤5 or Dob any dose	Dop >5 or Epi ≤0,1 or Norepi ≤0,1	Dop >15 or Epi >0,1 or Norepi >0,1
LIVER	Bilirubin (mg/dL) [d]	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0

COAGULATION	Platelets x10^3/ml	>150	<150	<100	<50	<20
KIDNEYS	Creatinine (mg/dl)[e] or urine output (mL/d)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or urine output <500 ml/day	>5.0 or urine output <200 ml/day

Norepi indicates norepinephrine; Dop, dopamine; Dob, dobutamine; Epi, epinephrine; PaO_2, partial pressure of oxygen; and FiO_2, fraction of inspired oxygen.

[a] Values are with respiratory support.

[b] MAP indicates Mean Arterial Pressure, expressed in mmHg

[c] Adrenergic agents administrated for at least 1 hour, and doses are in μg/kg/min.

[d] To convert bilirubin from mg/dL to μmol/L, multiply by 17.1.

[e] To convert creatinine from mg/dL to μmol/L, multiply by 88.4.

Sepsis-3 recommend that patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with quick-SOFA (qSOFA) (1). The qSOFA score was invented to facilitate easier identification of patients who were potentially at risk of dying from sepsis and the components of SOFA score were too complex and required multiple laboratory test that might be impractical on that moment. The qSOFA is more simply, consists in only 3 criteria: Glasgow Coma Scale (GCS), systolic blood pressure and respiratory rate (Box 1) (47). A qSOFA of 2 or more points indicates organ dysfunction with a predictive validity similar to that of the full SOFA score outside the ICU. Inside the UCI it is recommended to use the SOFA score, not the qSOFA because it have more predicted validity (48).

BOX 1. **qSOFA (Quick SOFA) Criteria**

- Respiratory rate ≥22 / min
- Altered mentation
- Systolic blood pressure ≤ 100 mmHg

The Figure 10, summarise the recommended diagnostic process according to the new definition of sepsis and septic shock from the Sepsis-3 guidelines. To provide a quick and complete identification of a patient with suspected sepsis outside the ICU, the qSOFA should be used. If the qSOFA is ≥2 points, evidence of organ dysfunction should be considered. The SOFA score should be used to determine the presence of organ dysfunction. If the patients SOFA score is ≥2 points, the diagnosis of sepsis is confirmed. If the patient presents with sepsis associated with

circulatory or metabolic dysfunction requiring vasopressors agents to maintain the mean arterial pressure (MAP) ≥65mmHg and has a lactate level >2 mmol/L, septic shock is diagnosed.

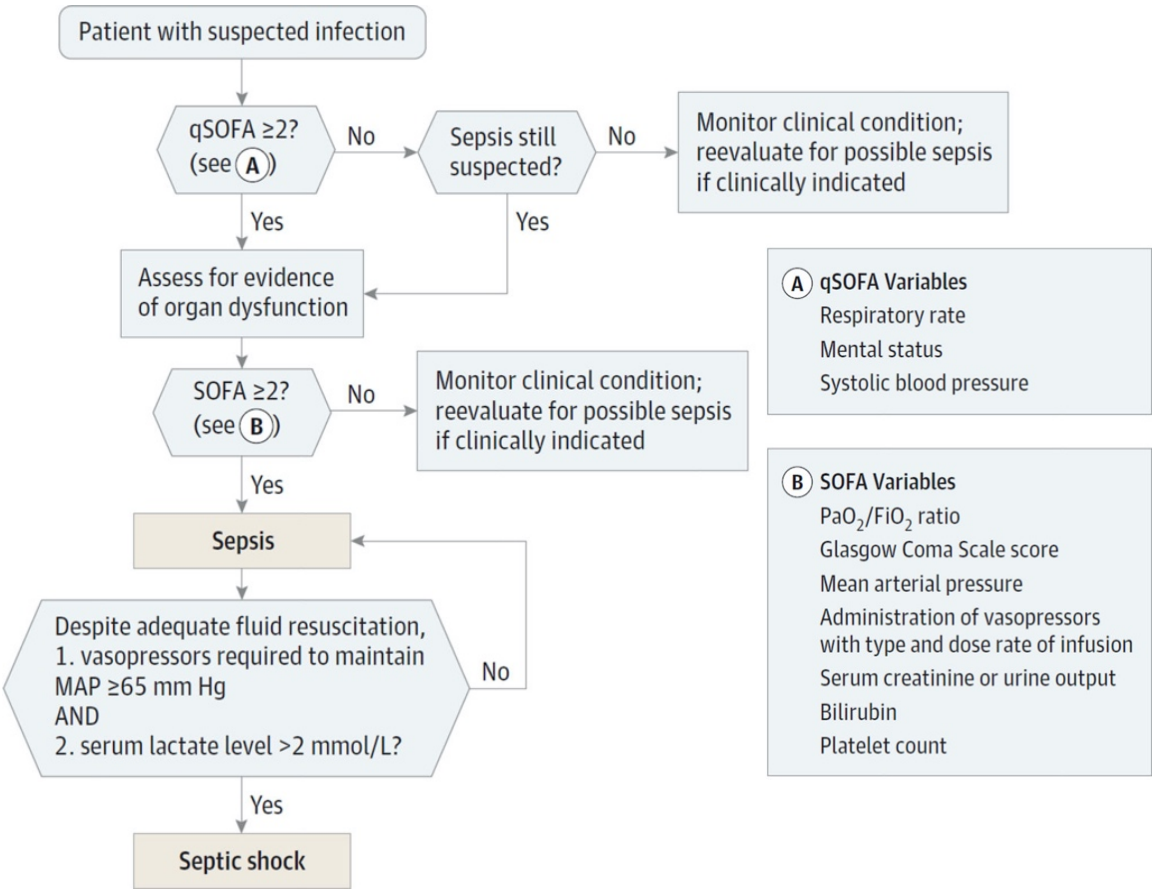


FIGURE 10**. Implementation of Clinical Criteria for Recognizing Patients with Sepsis and Septic Shock**

DIAGNOSIS OF A SUSPCTED NEW INFECTION

Additionally, a new infection can be diagnosed in a patient with suspected sepsis searching for the site of infection and identifying the underlying pathogen.

Sepsis-3 recommend doing all the microbiologic cultures before the starting antimicrobial therapy if it not implies a delay in the start of antimicrobials. Microbiological samples should be taken from the suspected site of infection (49). Table 2 shows the initial microbiological assessment based on the suspected site of infection.

TABLE 2. **Initial evaluation of common sources of sepsis**

SUSPECTED SITE	SYMPTOMS AND SIGNS	INITIAL MICROBIOLOGICAL EVALUATION
UPPER RESPIRATORY TRACT	Pharyngeal inflammation, exudate or swelling and lymphadenopathy	Throat swab

LOWER RESPIRATORY TRACT	Productive cough, pleuritic chest pain, consolidative auscultatory findings	Sputum, rapid influenza testing, urinary antigen testing, culture of protected brush or bronchoalveolar lavage
URINARY TRACT	Urgency, dysuria, loin, back pain	Urine culture and microscopy showing pyuria
VASCULAR CATHETERS	Redness or drainage at insertion site [1]	Culture of blood (from catheter and peripheral site), culture catheter tip
PLEURAL CATHETER	Redness or drainage at insertion site [1]	Culture of pleural fluid
WOUND OR BURN	Inflammation, edema, erythema, discharge of pus	Gram stain and culture of draining pus. NOT wound culture[2]
SKIN OR SOFT TISSUE	Erythema, edema, lymphangitis	Culture draining pus
CENTRAL NERVIOUS SYSTEM	Signs of meningeal irritation	Cerebrospinal fluid cell count, protein, glucose, gram stain and culture
GASTROINTESTINAL	Abdominal pain, distension, diarrhoea, vomiting	Stool culture
INTRA-ABDOMINAL	Specific abdominal signs and symptoms	Aerobic and anaerobic culture of percutaneously or surgically drained abdominal fluid collections
GENITAL TRACT	♀ Low abdominal pain, vaginal discharge ♂ Dysuria, frequency, urgency, urge incontinence, cloudy urine, prostatic tenderness	♀ Endocervical and vaginal swabs ♂ Urine gram stain and culture
BONE	Pain, warmth, swelling, decreased use	Blood cultures, MRI, bone cultures at surgery or by interventional radiology
JOINT	Pain, warmth, swelling, decreased range of motion	Arthrocentesis with cell counts, gram stain and culture

MRI, Magnetic Resonance Imaging. Modified from *"Microbiological Requirements for Studies of Sepsis"* (50)

[1] Not always present.

[2] Wound culture is not reliable.

3.3.1 Diagnosis of S-AKI

The diagnosis of AKI is based on an elevated serum creatinine (sCr) concentration and/or a reduction in diuresis, as serum creatinine is an indicator of renal damage, and oliguria, although not specific to S-AKI, appears to have strong association with AKI (40).

S-AKI is defined as the simultaneous presence of both **sepsis** (following the Sepsis-3 criteria (1)) and AKI [following the **Kidney disease** Improving Global Outcomes (KDIGO) **criteria]** (39) (Annex 2). However, the definition of sepsis is based on SOFA score, which is problematic when evaluating AKI because the SOFA score by itself is insufficient to quantify a kidney dysfunction. It does not distinguish AKI from chronic kidney disease (CKD) nor adequately consider demographic differences in baseline creatinine, so it cannot reliably assess S-AKI and we have to use both SOFA score and KDIGO criteria (40,42). However, even with KDIGO criteria, sCr is problematic because aggressive fluid resuscitation of the septic patient may result in dilution of sCr, leading to underdiagnosis of S-AKI. In addition, sCr may under-represent changes in glomerular filtration and tubular injury due to decreased skeletal muscle perfusion during sepsis, resulting in decreased creatinine production (42). Figure 11, adapted from the work of Carlos L. et all (42), proposes an evaluation of renal function in patients with suspected or documented infection based on KDIGO criteria and SOFA score.

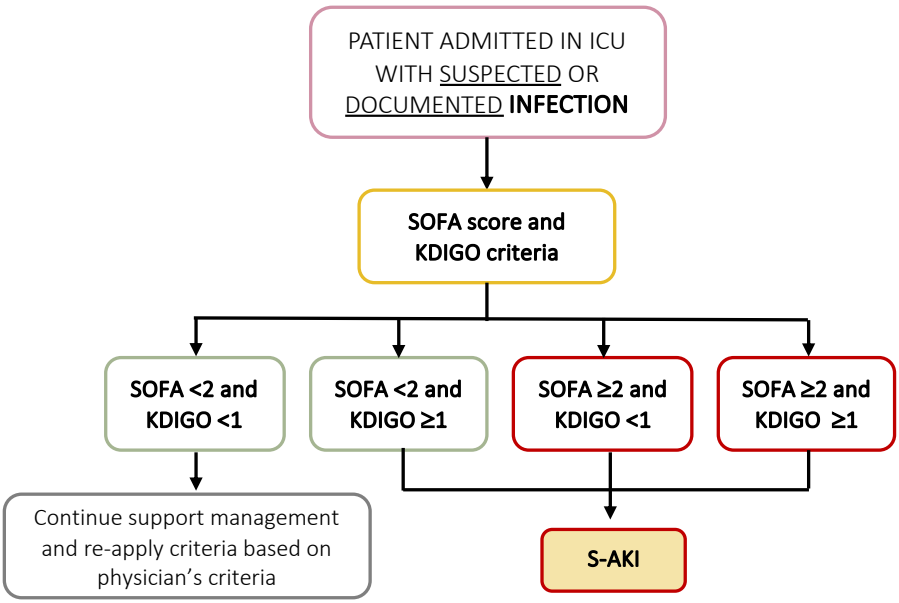


FIGURE 11. **Proposed approach to S-AKI.** *Modified from Carlos L. et all.*

3.4 TREATMENT

In 2004, the Surviving Sepsis Campaign (SSC) was initiated to improve the worldwide treatment of sepsis and increase survival rates (8). The application of a set of procedural measures have reduced the relative risk of mortality up to 25% (51).

The conventional treatment for sepsis involves efforts to eradicate the focus employing interventions such as interventional radiology or surgical procedures, along with promptly administering empirically targeted antibiotics. Further, intensive care measures are implemented to provide individual organ support like vasopressor administration, mechanical ventilation, and renal replacement therapy (8), in order to maintain critical organ function. Apart from these strategies, the removal of cytokines with blood purification therapies has been suggested as one method to improve the organ dysfunction.

3.4.1 Source control

Early source control is key to sepsis management and includes drainage of infected fluids, debridement of infected soft tissue, removal of infected devices or foreign bodies, and correction of anatomical abnormalities that cause microbial contamination. Effectiveness depends on the site of infection, the patient's premorbid condition and available resources (49).

3.4.2 Empirically targeted antibiotics

Early and appropriate initiation of antibiotic treatment and identification of the septic source are crucial to prevent AKI and reduce mortality. Therefore, *International Guidelines for Management of Sepsis and Septic Shock (32)*, recommend that the administration of IV antimicrobials be initiated **as soon as possible** after recognition and within 1 hour for both sepsis and septic shock. However, caution must be exercised when prescribing antibiotics to treat the infection that leads to sepsis, as many of them are also nephrotoxic. This is particularly true for vancomycin when used in combination with other antimicrobials such as piperacillin-tazobactam, aminoglycosides, or amphotericin B, or with other nephrotoxins such as intravenous radiocontrast media (52).

As we mentioned early, hospitals should have a protocol for managing specific empirical antibiotic therapy for septic patients, specially that one’s admitted into ICU.
After responding to therapy, the emphasis should be on controlling the septic focus and de-escalating fluids and antibiotic as needed. There is no consensus on de-escalation criteria,

guidelines recommend a daily assessment, procalcitonin levels and clinical criteria to decide when to discontinue antimicrobials (32).

3.4.3 Resuscitation / Fluid therapy

Fluid resuscitation followed by vasopressor agents is the optimal treatment in septic shock. An early effective fluid resuscitation is crucial for stabilization of sepsis-induced tissue hypoperfusion or septic shock. Guidelines (32) recommended that initial fluid resuscitation begin with **30 mL/Kg** (ideal body weight) of IV **isotonic crystalloid** within the first 3 hours. It has been demonstrated that the use of hydroxyethyl starch and gelatin based solutions, and fluids with high chloride concentrations increases the risk of AKI and mortality (53,54).

Most patients require continued fluid administration after the initial resuscitation. The administration of fluids must be balanced with the risk of fluid accumulation and potential harm associated with fluid overload and renal edema (40). To avoid over and under-resuscitation, fluid administration should be guided by dynamic measures such as passive leg raising combined with cardiac output measurement, fluid challenges against stroke volume, systolic pressure, and increases in stroke volume in response to changes in intrathoracic pressure. For those patients who received large volumes of crystalloids, guidelines recommend using albumin over crystalloids alone.

Serum lactate is an important biomarker of tissue hypoxia and dysfunction. Guidelines recommend using lactate levels as a resuscitation target in the early stages of sepsis and septic shock, always taking into account the clinical context and other causes of elevated lactate.

Guidelines recommend that for adults with septic shock, **norepinephrine** should be the first-line agent over other vasopressors, and that if MAP levels are inadequate, **vasopressin** should be added rather than escalating the dose of norepinephrine.

We have to take into account, that for those patients who have septic shock and cardiac dysfunction with persistent hypoperfusion after adequate fluid resuscitation, guidelines suggest adding dobutamine to norepinephrine or using epinephrine alone (32).

3.4.4 Mechanical ventilation

ARDS caused by pneumonia or non-pulmonary infections can lead to acute respiratory failure. Patients with hypoxia without hypercapnia are treated with high concentrations of inhaled oxygen delivered via nasal prongs, a face mask with reservoir or a Venturi mask.

Some patients with severe hypoxia may need an escalation of oxygen therapy support, including non-invasive ventilation (NIV) or high flow oxygen. Guideliness recommend that for those patients who presents sepsis-induced hypoxemic failure, the use of high flow nasal oxygen over NIV (32).

Ventilator-induced lung injury (VILI) is acute lung injury caused or worsened by non-invasive ventilation (NIV) or mechanical ventilation (MV). The main mechanisms are volutrauma (overdistension of the alveoli), barotrauma, and biotrauma (inflammation). VILI typically occurs in patients with underlying severe conditions such as sepsis, trauma, and major surgeries, which cause dysregulation of the immune system (55).

To prevent VILI, it is crucial to take into account the Volume Tidal (VT), the plateau pressures and the Positive End-Expiratory Pressure (PEEP) level. The VT refers to the volume of air delivered to the lungs with each breath, the plateau pressure is the pressure measured in the lungs during an inspiratory pause (end of an inhalation), and the PEEP is the positive pressure applied at the end of the expiration phase to keep the alveoli open and prevent them from collapsing. The **lung protective ventilation** is a revolutionary method of ventilating critically ill patients that aims to achieve maximum lung recruitment while using limited VT and plateau pressures to prevent overdistension-induced lung damage and to set the appropriate PEEP level to minimize the cyclic opening and closing of airways and lung units (56).

The guidelines recommend using a low VT ventilation strategy (6 mL/kg), an upper plateau pressure target of 30 cm H_2O and higher PEEP in sepsis-induced ARDS. And for those patients who have moderate-severe ARDS induced by sepsis, it is recommended using prone ventilation for more than 12 hours daily (32). Prone ventilation is a strategy to improve oxygenation when more traditional modes of ventilation fail, because it alters the mechanics and physiology of gas exchange by reducing the ventral-dorsal transpulmonary pressure difference, decreasing dorsal lung compression and improving lung perfusion (57). In the Figure 12, we can see the physiological effects of supine and prone positioning.

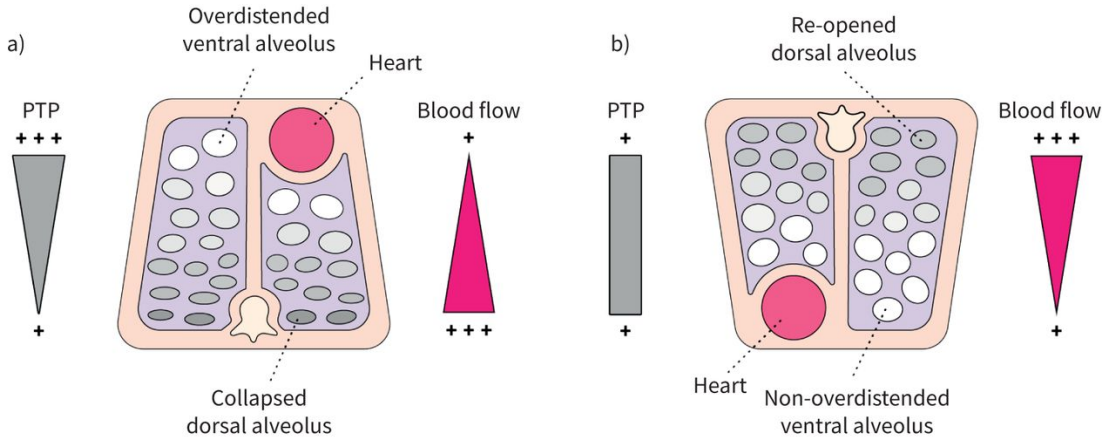


FIGURE 12. **Effects of a) supine positionating and b) prone positionating on lung mechanics**

In the supine position, the weight of the dorsal lung, mediastinum, abdominal compartment and diaphragm compresses the lung. Placing the patient in the prone position reduces the compression of the lung by its weight, as fluids are redistributed in a gravitational manner, the sternum supports the weight of the mediastinum, the diaphragm is displaced caudally, reducing compression of the posterior lung. In addition, the triangular shape of the lung contains more parenchyma in the dorsal half than in the ventral half, resulting in better aeration.

Adapted from the *"Awake prone positioning for hypoxaemic respiratory failure: past, COVID-19 and perspectives"* (56).

To facilitate mechanical ventilation, the guidelines recommend using intermittent neuromuscular blocking agents (NMBAs) boluses.

Extracorporeal membrane oxygenation (ECMO) is indicated in patients with severe acute respiratory failure to facilitate gas exchange in the setting of refractory hypoxaemia or hypercapnic respiratory acidosis (32). ECMO is a life support machine that replaces the function of the heart and lungs.

3.4.5 Renal Replacement Therapy (RRT)

Renal Replacement Therapy (RRT) is frequently required in critically ill patients developing AKI (58). Haemodialysis, hemofiltration and hemodiafiltration are currently the RRT of choice for the treatment of S-AKI. However, there is no consensus on the optimal time to initiate the CRRT in septic patients. Factors such as laboratory tests, hemodynamic instability, and decision-making by the intensivist team determine its initiation (59).

Continuous renal replacement therapy (CRRT) is a slow and constant extracorporeal blood purification that simulates the continuity of kidney function. The principal objective of CRRT is to remove excess fluid and blood solutes retained as a result of reduced or absent glomerular filtration (58). CRRT is as effective as an intermittent renal replacement therapy at removing solutes during a 24-48h period, and is better tolerated by hemodynamically unstable patients (60).

MECHANISM OF SOLUTE AND FLUID TRANSPORT

CRRT is based on four main physiologic principles:

a) **Diffusion:** is the movement of solutes across a semi-permeable membrane, from the side with highest concentration of particles to the side with de lowest concentration until an equilibrium is reached between the two compartments (Figure 13). For CRRT modalities that incorporates diffusion (CVVHD and CVVHDF), diffusion occurs when blood flows on one side of the membrane and dialysate solution flows counter-current on the other side, allowing the removal of small molecules, but not large molecules.

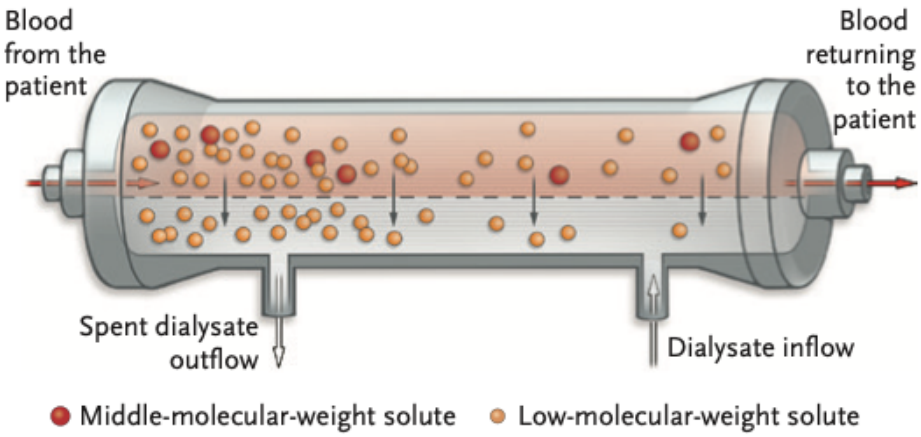


FIGURE 13. **Diffusion mechanism of fluid and solute transport during CRRT**

Low molecular weight solutes difuse across the dialysis membrane, driven by their respective concentration gradient. The dialysate fluid flows counter-current, helping on maintaining the concentration gradient across the length of the haemodialyzer fibers. The rate of diffusion is inversely related to the molecular weight of the solute. Adapted from "*Extracorporeal Kidney-Replacement Therapy for Acute Kidney Injury*" (61)

b) Convection: is the process whereby solutes pass through membrane pores, dragged by fluid movement (ultrafiltration) occurring as a result of hydrostatic and / or osmotic transmembrane pressure (Figure 14). Compared to diffusive transport, convective transport allows for higher removal rates of solutes with higher molecular weights.

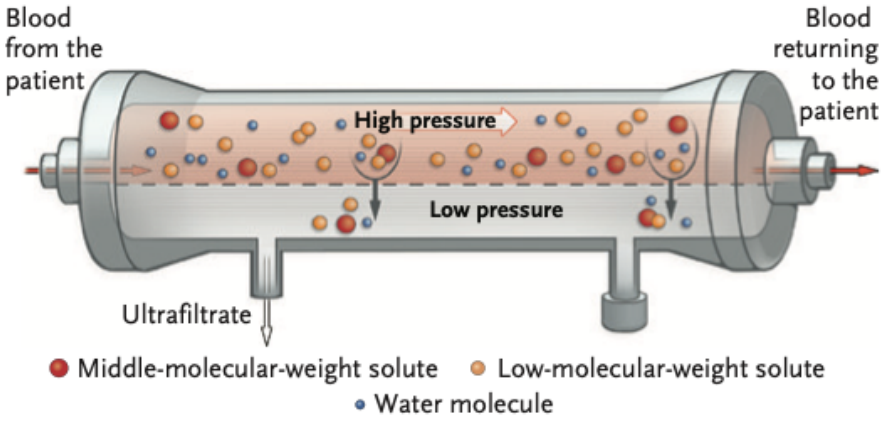


FIGURE 14. **Convection mechanism of fluid and solute transport during CRRT**

Hemofiltration generates a large volume of ultrafiltrate by the hydrostatic gradient across the membrane, and the solute is entrained in the bulk flow plasma water across the membrane. The convective flux is limited by the ratio of the molecular diameter of the solute to the diameter of the membrane pores.

Adapted from "*Extracorporeal Kidney-Replacement Therapy for Acute Kidney Injury*" (61)

c) Adsorption: is the adherence of solutes and biological matter to the surface of a membrane. High levels of adsorption can cause certain filters to clog (membrane fouling), resulting in decreased effective permeability. Some of the proteins found at the highest concentration in plasma (i.e., albumin, immunoglobulins, fibrinogen, etc) are the major contributors of the membrane fouling because of their size, so the plasma concentration of these proteins is not significantly affected. The absorptive surface area depends on the pore structure rather than its surface area. For this reason, adsorption of peptides and low-molecular-weight proteins (e.g., β_2-microglobulin) to low-flux membrane is not clinically significant.

d) Ultrafiltration: it is a mechanism of fluid removal. It involves the movement of plasma water (solvent) across a semi-permeable membrane, facilitated by a pressure gradient between the blood and the dialysate or ultrafiltrate compartments. This process is heavily influenced by the rate of membrane fouling. Ultrafiltration can be used in different CRRT modalities; when only fluid removal is required to control volume overload, slow continuous ultrafiltration (SCUF) can be employed; convective blood cleansing modalities such as continuous veno-venous hemofiltration (CVVHF) and continuous veno-venous

hemodiafiltration (CVVHDF) can be used. Finally, continuous veno-venous haemodialysis (CVVHD) does not involve the use of replacement fluid and thus does not have a convective component, but ultrafiltration is still used to achieve net fluid removal.

GOALS AND INDICATIONS

The principal **objectives** of CRRT are (62):

- Removal of waste products
- Restoration of acid-base balance
- Correction of electrolyte abnormalities
- Hemodynamic stabilization
- Fluid balance
- Nutritional support
- Removal and/or modulation of septic mediators (not all the modalities of CRRT)

There are some accepted **indications** to use the CRRT such as acute renal failure combined with (63):

- Hemodynamic instability
- Severe fluid overload unresponsive to diuretics
- Hypercatabolic states or trauma (rhabdomyolysis)
- High fluid requirements (nutrition, blood products)
- Sepsis, lactic acidosis, ARDS or multiple organ dysfunctions score
- During ECMO for fluid management

CONTINUOUS RENAL REPLACEMENT THERAPY TECHNIQUES

As mentioned earlier, there are various techniques available for CRRT that differ in vascular access, extracorporeal circuit design, treatment frequency and intensity, predominant transport mechanism used, and membrane type (58,62) (Table 3):

- **Slow continuous ultrafiltration (SCUF):** The objective of this procedure is to achieve volume control in patients with severe, diuretic-resistant volume overload. It is very effective for volume reduction, but the low filtration rate and the absence of replacement fluids makes this therapy ineffective as a blood purification modality (Figure 15).

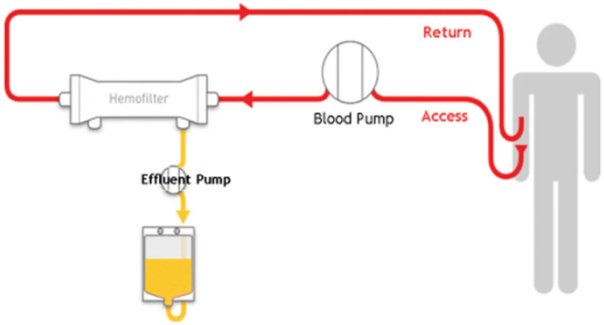


FIGURE **15. Slow continuous ultrafiltration (SCUF)**

- **Continuous veno-venous haemodialysis (CVVHD):** This process is based in diffusion mechanism, where the dialysate is perfused through the haemodialysis filter against the direction of blood flow, creating a concentration gradient. The dialysate has physiologic concentration of sodium, chloride, magnesium, potassium and glucose, and it is buffered with bicarbonate or a bicarbonate precursor (lactate, citrate or acetate). The effluent is composed of the spent dialysate and any ultrafiltration for volume management. There is no need of replacement fluids, and solutes with small molecular weights, such as potassium, urea, and creatinine, can pass through the membrane more easily than higher molecular weight solutes. The ultrafiltration rates are relatively low compared to CVVH (64) (Figure 16).

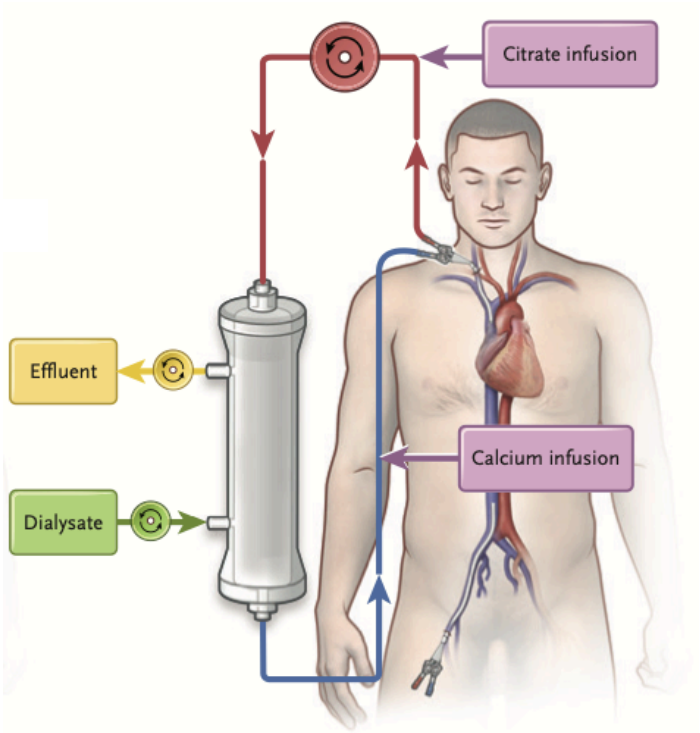


FIGURE 16. **Continuous veno-venous haemodialysis (CVVHD)**

- **Continuous veno-venous hemofiltration (CVVH):** The hemofiltration is based in convection, which the transfer of solutes through ultrafiltered plasma water is known as "solvent drag". During hemofiltration, there is not any dialysate perfused through the hemofillter, and the effluent only consists of ultrafiltrate. Convection sweeps solutes along with the fluid independent of their concentration gradient. The porosity of the membrane determines which solutes are removed. Higher and lower molecular weight solutes are transported with equal efficacy until the molecular radius exceeds the pore size (64), and it is used to remove solutes beyond the small solute range that cannot be eliminated through diffusion alone. After removing a large volume of fluid, it is important to maintain

intravascular volume by using replacement fluid. Based on the patient's serum potassium and acid-base balance, the replacement fluid can be used to correct electrolyte and acid-base abnormalities. Fluid and sodium balance is determined by the difference in volume between the ultrafiltrate generated and reinfused replacement fluids.

Replacement fluids can be introduced into the extracorporeal circuit either before the filter ("pre-dilution") or after the filter ("post-dilution") (64,65). If its pre-dilution mode, blood will be diluted, reducing the risk of clogging but reducing too the effective solute clearance. If its post-dilution mode, may increase the risk of sludging and occlusion with fibres due to haemoconcentration during filtration (Figure 17).

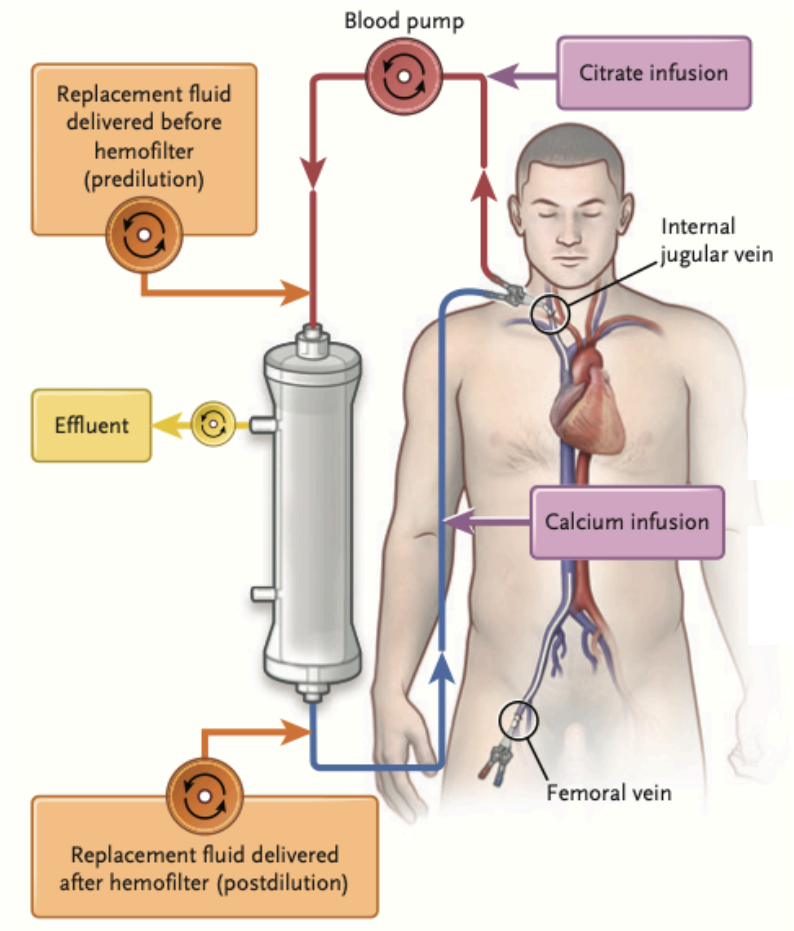


FIGURE 17. **Continuous veno-venous hemofiltration (CVVH)**

- **Continuous veno-venous hemodiafiltration (CVVHDF):** This process combines the principles of haemodialysis and hemofiltration, using both diffusion and convection methods. Dialysate is used along with high ultrafiltration rates, greater than that required for volume balance, and therefore with a replacement fluid to effectively remove small and medium-sized molecules (65). Reinfusion fluid replaces the ultrafiltrate, either in pre-dilution or post-dilution mode (58) (Figure 18).

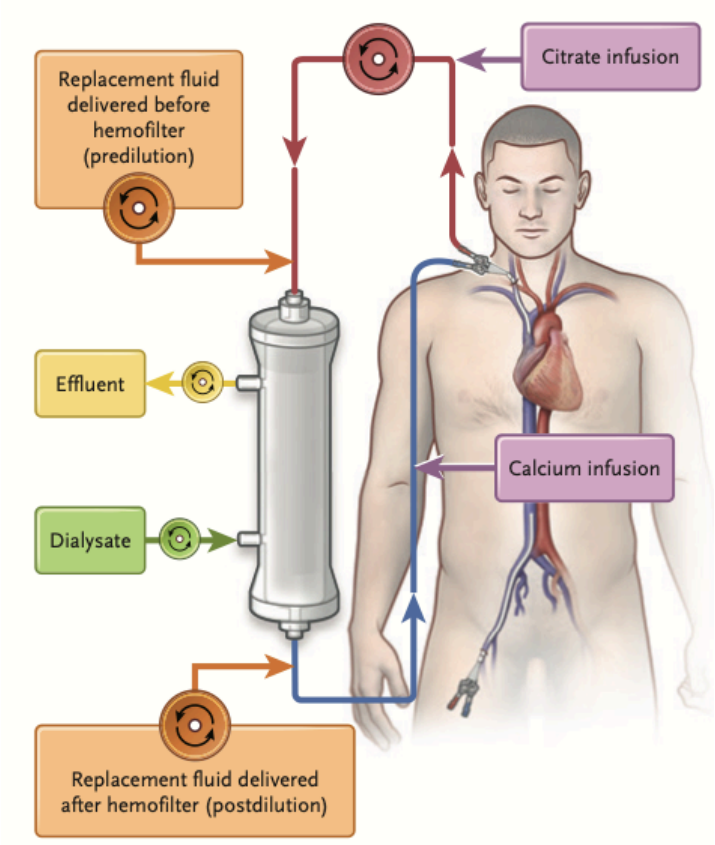


FIGURE 18. **Continuous veno-venous hemodiafiltration (CVVHDF)**

TABLE 3. **Different techniques and their mechanism of solute clearance**

CRRT TECHNIQUES	MECHANISM OF SOLUTE CLEARANCE			MOLECULES REMOVED
	CONVECTION	DIFFUSSION	ABSORPTION	
SCUF	+	-	-	-
CVVHD	+	++++	-	Small molecular weight
CVVH	++++	-	+	Middle molecular weight
CVVHDF	+++	+++	+	Large and middle weight

Abbreviations: —, none; **+**, negligible; **++**, some; **+++**, marked; **++++**, major control system; **SCUF**, slow continuous ultrafiltration. **CVVHD**, continuous veno-venous haemodialysis; **CVVH**, continuous veno-venous hemofiltration; **CVVHDF**, continuous veno-venous hemodiafiltration.

Modified from "*Continuous renal replacement therapy principles*" (58)

The patient's volume status, serum urea, potassium, and acid-base balance determine the choice of CRRT modality. In patients with isolated volume overload, such as cardiac or hepatic failure, malnutrition, capillary leak syndromes, or in patients who have become resistant to diuretics, SCUF may be considered. Haemodialysis (CVVHD) can manage isolated electrolyte abnormalities. Nevertheless, most critically ill patients receive large amounts of intravenous fluids as part of their resuscitation and nutrition. Therefore, those with kidney injuries usually require ongoing management with fluids and electrolytes, that can be accomplished using either hemofiltration (CVVH) with appropriate replacement fluid or with hemodiafiltration (CVVHDF) (66).

REQUIREMENTS FOR CRRT

An efficient vascular access, special designed CRRT machine and high-flux membrane are essential for CRRT efficacy (Figure 19).

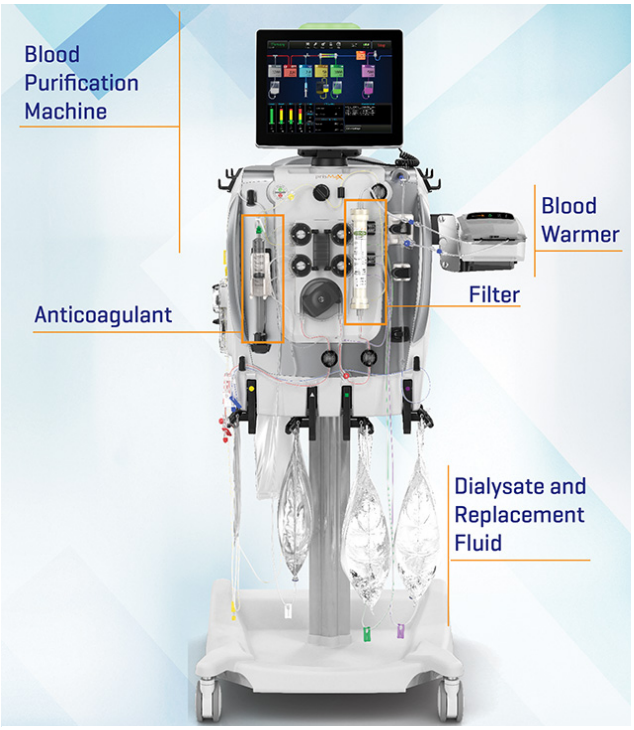


FIGURE 19. **CRRT Machine**

Adapted from: www.baxter.com

The **vascular access** is important to achieve adequate blood flow, which reduces the risk of extracorporeal clot formation and the interruption of CRRT therapy. It is essential to manage catheters correctly to minimize infections, mechanical problems and to achieve an adequate blood flow rate (67). According to the KDIGO guidelines, catheter placement sites should be

prioritized in the following order: right internal jugular vein, femoral vein, left internal jugular vein, subclavian vein (dominant side) and subclavian vein (non-dominant side) (52).
The CRRT machine is an integrated system consisting of blood purification machine, haemofilter, line sets, solutions (replacement fluid and dialysate solution) and other accessories (drainage bags, dual-lumen catheters, anticoagulant, syringes, etc).

In order to avoid hypothermia, a **blood warmer** is needed to maintain an optimal temperature of the blood (37ºC).

To maintain the extracorporeal circuit, an **anticoagulant** is required. Without it, when blood is conducted into the circuit, the non-physiological environment leads to the activation of platelets, leukocytes and the coagulation cascade, resulting in fouling of the membrane and clotting fibers and the entire haemodialyzer. In addition, the blood loss due to clotting can result in anaemia in the patient. KDIGO guidelines recommend the use of regional anticoagulation, such as citrate, for patients with an increased bleeding risk, impaired coagulation, and who are not receiving effective systemic anticoagulation. We have to take into account that the effect of sodium citrate relies on forming complex with ionized calcium, therefore we are removing an essential component of the coagulation cascade. To avoid the loss of calcium, it is recommended to compensate by an exogenous infusion (68).

KDIGO guidelines recommend systemic anticoagulation during CRRT, using agents such as unfractionated heparin or low molecular weight heparin, for patients without an increased bleeding risk, with normal coagulation, and not already receiving systemic anticoagulation.

To maintain a normal acid-base balance, during CRRT is necessarily to correct metabolic acidosis using bicarbonate, acetate or lactate in the **dialysate** or **replacement fluids**.

The **haemodialyzer or haemofilter** are generally made up of semipermeable cellulose or synthetic polymer membranes fabricated as hollow fibers. Blood flows inside of the hollow fibers, and dialysate flows on the outside of the fibers, allowing for a large exchange surface (1 to 2.5m^2) in a compact cartridge (61) (Figure 20). The dialyzer includes the dialysis membrane (hollow fibres) and the canister in which the membrane is housed and has to be efficient in removing waste and at the same time be biocompatible with human blood.

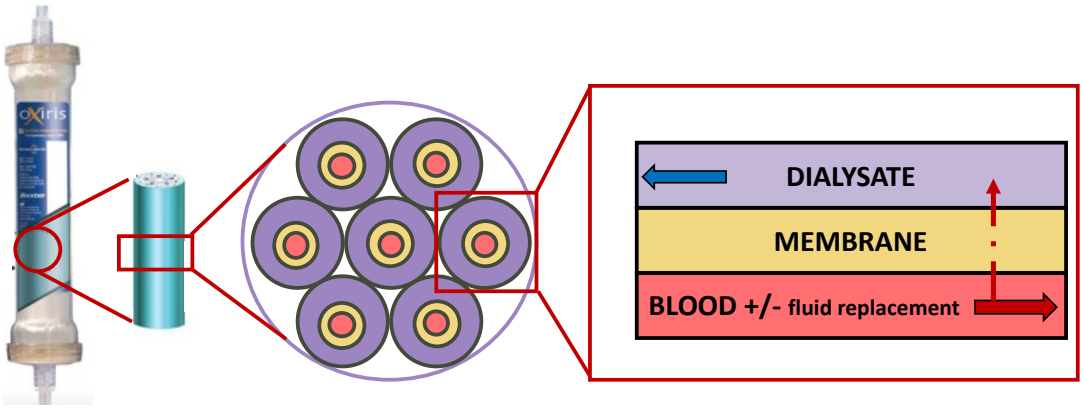


FIGURE 20. **Design of hollow fibers**

Modified from "*Design optimization of hollow fiber dialyzers to enhance internal filtration based on a mathematical model*" (69)

The permeability of the membrane is influenced by the pore size, the number of pores and the thickness of the membrane. A high cut-off (HCO) membrane has wider pores and more uniformity in pore size, generally allowing a greater movement of solutes and ultrafiltrate across it, increasing the rate of clearance and by allowing more ultrafiltrate to flow.

Extracorporeal blood purification therapies have been suggested as supplementary treatments to regulate the dysregulated immune response for critically diseases such as sepsis. The primary goal of these therapies is to eliminate inflammatory mediators (cytokines), PAMPs and DAMPs from blood (70).

There are several haemofilters capable of adsorbing these types of inflammatory mediators, in this project, we will focus on the AN69ST membrane and the oXiris® haemofilter.

AN69 and AN69ST membrane

The **AN69 membrane** is a copolymer of acrylonitrile and sodium methallylsulfonate designed to facilitate solute removal in dialysis through diffusion and convection mechanisms. Additionally, it incorporates the adsorption mechanism to effectively remove medium-sized uremic toxins and protein-bound retention products (71). However, AN69 membranes can interact with blood, causing bradykinin generation and anaphylactic reactions in patients being dialyzed (72). In order to improve hemocompatibility, a **AN69 surfaced-treated (AN69ST)** membrane with a polyethyleneimine (PEI) coating has been developed, which neutralises the negative charges of the conventional AN69 membrane (70).

There are limited reports of basic research on the cytokine adsorption capacity of the AN69ST membrane and clinical trials of this membrane.

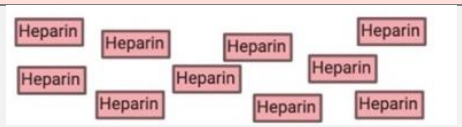
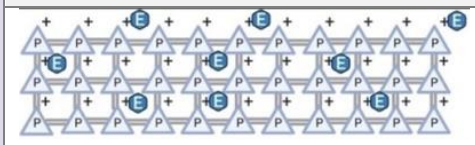
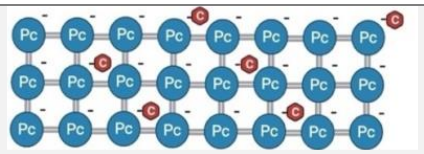
oXiris® haemofilter

Recently, there have been some new haemofilters capable of adsorbing inflammatory mediators that have been attracting attention, such as CytoSorb hemoadsorption device, Toraymyxin hemoperfusion cartridges or the oXiris® haemofilter. Among them, the oXiris® haemofilter is the only one that can provide renal replacement therapy, remove endotoxin and adsorb cytokines simultaneously (73).

The oXiris® haemofilter (Baxter, Meyzieu, France), is a modified AN69ST membrane with high permeability, layered with three components (Table 4):

1) AN69ST core membrane, with a high adsorptive affinity for cytokines
2) Positively-charged PEI, which allows to remove endotoxins and cytokines from blood simultaneously (74). Compared with the AN69ST, the oXiris® haemofilter has more PEI molecules into the AN69ST membrane surface to increase the binding of negatively-charged endotoxins (75)
3) Heparin-grafting, which provides local anti-thrombogenicity.

TABLE 4. oXiris® filter and the role of each layer

		LAYER	STRUCTURE	ROLE
BLOOD				
MEMBRANE		3rd layer	Heparin	Anti-thrombotic role
		2nd layer	Polyethyeneimine (PEI)	It has positive charge, which helps absorbs endotoxins (negatively charged molecule)
		1st layer	Polycrylonitrile copolymer (acrylonitrile and methallyl sulfonate)	It has negative charge, which helps absorbs the cytotoxins (positively charged molecules)
EFFLUENT				

KEY

 HEPARIN;  PEI;  POLYCRYLONITRILE COPOLYMER;  CYTOKINE;  ENDOTOXIN

Modified from *"The Emergency Use of the oXiris® Device with Continuous Kidney Replacement Therapy in COVID-19 Patients with Acute Kidney Injury"* **28**/01/2024 21:40:00

The oXiris® haemofilter is available to use with different CRRT modalities such as hemofiltration (CVVH), haemodialysis (CVVHD) and hemodiafiltration (CVVHDF) (70).

Numerous in vitro studies have shown that the oXiris® membrane has a high capacity for adsorbing cytokines, also improves hemodynamics by reducing fluid requirements and lactate levels compared to AN69ST haemofilter (77). Additionally, it significantly decreases endotoxin levels compared to the Toraymyxin hemofilter (78).

Multiple small-size clinical studies found that CRRT with oXiris® haemofilter could improve hemodynamic and decrease the cytokines, procalcitonin, endotoxins and SOFA scores in septic patients with AKI (79–84). Nevertheless, the absence of high-quality studies and clinical guidelines leads to a variability in clinical practice.

Currently, the delivery of oXiris®-CRRT is mainly based on consensus recommendations from Europe and Asian-Pacific region (74) (Figure 21):

1) In the case of S-AKI patients, oXiris®-CRRT should be initiated based on clinical signs such as hemodynamic instability and microcirculatory dysfunction, as well as laboratory parameters including procalcitonin, IL-6, and lactate.
2) The oXiris® haemofilter is recommended to be changed at 12-24 hours post-initiation if patients have persistently high cytokine levels or if a circuit clotting is anticipated. If patients show improvements in clinical signs and laboratory parameters, the filter can be used up to 72h.
3) At 24h post-initiation a therapeutic effect evaluation should be done to determine clinical and laboratory features
4) For regional anticoagulation it is recommended use citrate, and for systemic anticoagulation, heparin is recommended.
5) An effluent flow of 20-35 mL/Kg/h is the standard care, with a blood flow rate of 150-200 mL/min

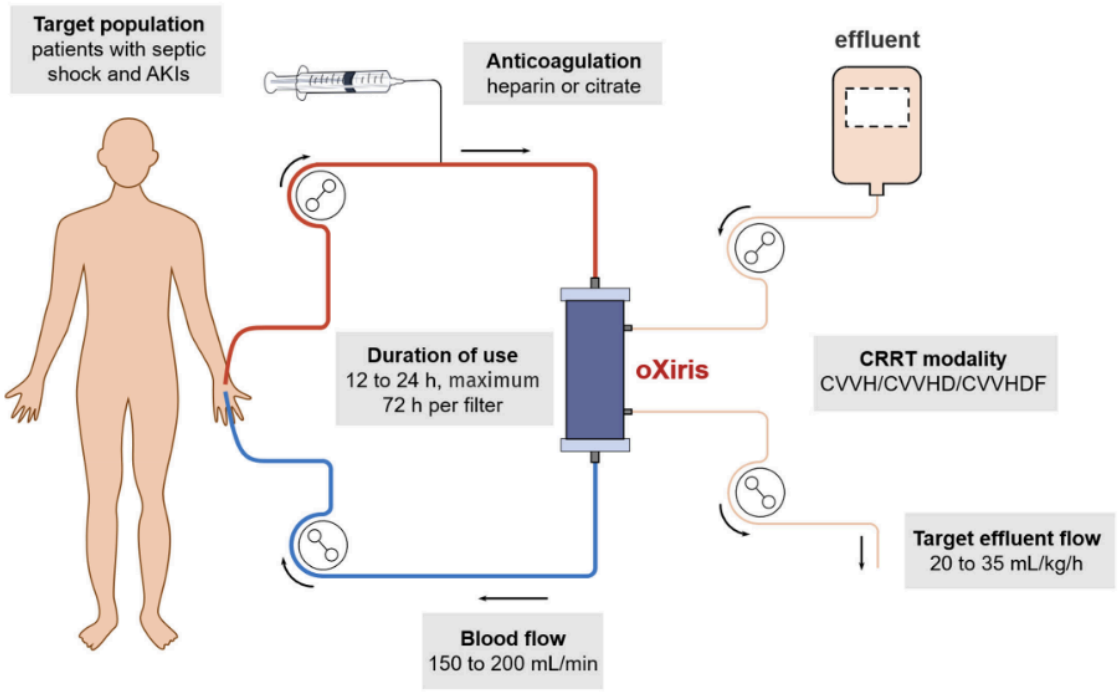


FIGURE 21. **Key recommendations for the delivery of oXiris-CRRT by the Asia-Pacific expert consensus**

ANTIBIOTIC DOSING IN CRRT

Solute removal is particularly relevant to antimicrobial therapy, because many critically ill patients with AKI require treatment with one or more antimicrobial (60). The drug elimination rate during CRRT can be highly variable depending on the method used, the patient's characteristics and drug pharmacokinetics and pharmacodynamics (85). Inappropriate doses of antimicrobial agents may lead to treatment failure, increased adverse drug reactions or drug resistance of pathogens (86).

DOSE OF CONTINUOUS RENAL REPLACEMENT THERAPY

There are several patients and device specific factors that influences CRRT dose in critically ill patients, therefore, it should be evaluated frequently to accommodate timely changes according to specific goals of therapy (87). The total effluent fluid rate is used to determine the dose of CRRT in diffusive, convective and hybrid modalities, reported in ml/kg/h, and determined according the CRRT technique. KDIGO guidelines suggest delivering an average effluent dose of **20 to 25 ml/kg/h**, but it should be adjusted to the specific needs of the patient (68).

COMPLICATIONS OF CRRT

There exist some complications of the CRRT that we have to keep in mind. Table 5 is a summary of the potential complications of CRRT and their management or preventive strategies (88,89).

TABLE 5. **Summary of potential complications of CRRT and their management**

FACTORS	POTENTIAL COMPLICATION	MANAGEMENT
EXTRACORPOREAL CIRCUIT	Filter clogging or clotting	Anticoagulation or filtration fraction <30%
	Air embolism	Preval accidental disconnects, monitor deaeration chamber
VASCULAR ACCESS	Local complications: bleeding, hematoma, AV fistula, thrombus, stenosis	Correction of coagulopathy and ultrasound guidance
	Vascular access disconnection	Vascular access connection should be visible and periodically checked for integrity
	Systemic complications: arrhythmias, hemothorax, pneumothorax	Ultrasound guidance
	Infection of the central line	Strict sterile precautions, regular dressing changes, timely catheter replacement
	Central venous stenosis	Subclavian catheter less preferred
METABOLIC ACIDOSIS	Citrate toxicity	Decrease blood flow and/or increase dialysate flow rate and/or decrease or discontinue citrate
	Citrate deficit	Increase blood flow and/or decrease dialysate flow rate and/or increase buffer concentration in others CRRT solutions
EUGLUCEMIC DIABETIC KETOACIDOSIS	Glucose loss in effluent, no nutrition	Insulin and dextrose supplementation
METABOLIC ALKALOSIS	Citrate excess	Decrease blood flow, and/or increase dialysate flow, and/or decrease buffer concentration in other CRRT solutions
HYPERNATREMIA	Trisodium citrate solution	Hypotonic citrate, low sodium dialysate
HYPOCALCEMIA HYPOPHOSPHATEMIA	Inadequate IV supplementation	Frequent lab-check, adequate IV supplementation

HYPOMAGNESEMIA		
HYPOTHERMIA	Extracorporeal radiant heat loss and use of cold CRRT solutions	Blood warmer
HYPOTENSION	Acetate or lactate buffer	Bicarbonate buffer
	Aggressive ultrafiltration	Slow down ultrafiltration, albumin prime
	Vasopressor removal	Infuse vasopressor away from dialysis catheter tip
	Acute respiratory acidosis	Increase minute ventilation, decrease the concentration of bicarbonate bath
NUTRITION LOSSES	Loss of amino acids, trace elements and water-soluble vitamins in effluent	Increase protein intake to 2.5 g/kg/day, supplement eater-soluble vitamins, periodic monitoring of trace elements and supplements
ALTERED DRUG PHARMACOKINETICS	Loss of antibiotic in effluent	Periodic monitoring of drug levels
INADVERTENT FLUID BALANCE	Excess ultrafiltration, no ultrafiltration rapid fluid removal causing hypotension	Nursing education, accurate hourly in and out calculation and adjust net ultrafiltration to goal
INCORRECT CRRT SOLUTION	Unanticipated electrolyte or acid-base abnormalities	Nursing education, periodic machine, and solution check by dialysis nurse and physicians, periodic laboratories

3.4.6 Additional therapies

For patients with septic shock and an ongoing requirement for vasopressor therapy, guidelines recommend using IV corticosteroids, usually hydrocortisone.

It is also recommended using low molecular weight heparin (LMWH) for the venous thromboembolism prophylaxis (32).

CRRT techniques allow for an unrestricted volume of nutritional support, however nutrients that are water soluble and have low molecular weight are eliminated (65). The KDIGO guideline recommend: 1.7 g/kg/d of protein, 5 to 7 g/kg/d of carbohydrates and lipids at 1.2 to 1.5 g/kg/d (52).

4. JUSTIFICATION

Acute Kidney Injury is an epidemic issue, being sepsis recognized as the main precipitating factor for AKI. S-AKI implies a high burden of morbidity and mortality, and have a significantly increased mortality relative to those with AKI of another aetiology (90). This critical condition often requires intensive medical interventions and specialized medical personnel, equipment, and facilities to manage this critically ill patients, and the associated costs of these interventions contribute to the financial burden on health system.

Blood purification therapies has been suggested for removing cytokines in patients with a septic-shock-induced cytokine storm. This technique uses extracorporeal adsorption of inflammatory mediators through specifically developed filters, adsorption membranes or columns to improve the immune homeostasis in sepsis. However, there are limited outcomes regarding these approaches (91). Currently, there is a lack of randomized controlled studies demonstrating improved prognosis for the use of the oXiris® haemofilter in sepsis and septic shock. The available data on its clinical effects are mainly based on anecdotal findings from case series and retrospective cohorts (92).

Understanding CRRT is important for the health system because it contributes to improved patient outcomes, prevents the progression of renal dysfunction and associated complications, leading to better health outcomes and potential cost savings. Staying up-to-date with the latest evidence-based practices in CRRT ensures that healthcare professionals provide care in line with the best available evidence and avoid unnecessary or less effective procedures. This reduces the costs associated with ineffective interventions.

This clinical trial will be useful to identify the more effective and safer haemofilter for patients with S-AKI that requires CRRT. This would improve clinical outcomes, reduce the burden on healthcare by decreasing the duration of hospitals stays, the need for intensive care and the resource utilization. The trial may provide valuable knowledge about the comparative effectiveness of different haemofilter, which can influence the development of treatment protocols and clinical guidelines, leading to more standardized and effective care.

5. HYPOTHESIS

5.1 MAIN HYPOTHESIS

The CRRT with oXiris® haemofilters **improves the Delta SOFA score** more than CRRT with conventional haemofilters in patients with S-AKI.

5.2 SECONDARY HYPOTHESIS

- The use of CRRT with oXiris® haemofilters provide **higher survival rates** compared to CRRT with conventional haemofilters in patients with S-AKI.
- The oXiris® haemofilters during CRRT **reduce the inflammatory mediators and levels of lactate** more than CRRT with conventional haemofilters in patients with S-AKI.
- With the CRRT using oXiris® haemofilters, patients with S-AKI require **fewer days of vasoactive drugs** compared to CRRT with conventional haemofilters.
- Using oXiris® haemofilters during CRRT, **reduces the duration of mechanical ventilation** in patients with S-AKI compared to CRRT with conventional haemofilters.
- The use of oXiris® haemofilters implies a **reduction in the duration of renal replacement therapy** compared to CRRT with conventional haemofilters in patients with S-AKI.

6. OBJECTIVE

6.1 MAIN OBJECTIVE

Evaluate and compare the **delta Sequential Organ Failure Assessment (SOFA) scores** in patients with sepsis-induced acute kidney injury (S-AKI) when using the CRRT with oXiris® haemofilter versus the conventional haemofilter.

6.2 SECONDARY OBJECTIVES

- Compare the **survival** of the CRRT with oXiris® haemofilters compared to CRRT with conventional haemofilter in patients with S-AKI.
- Asses and quantify the **reduction in inflammatory mediators and lactate** in the blood when using the oXiris® haemofilter during CRRT compared to the conventional haemofilter, in patients with S-AKI.
- Compare the **number of days requiring vasoactive drugs** when using an oXiris® filters during CRRT versus using conventional haemofilters in patients diagnosed with S-AKI.

- Analyze the **number of days requiring mechanical ventilation** when employing the oXiris® haemofilter during CRRT versus the conventional haemofilter in patients diagnosed with S-AKI.
- Compare the **number of days needing renal replacement therapy** when using CRRT with an oXiris® filters versus using a conventional haemofilter in patients diagnosed with S-AKI.

7. MATERIALS AND METHODOLOGY

7.1 STUDY DESIGN

To study the main objective of this project, a randomized, triple-blind, prospective, parallel groups and multicentric clinical trial will be performed at the ICU of Hospital Universitari Doctor Josep Trueta (HUJT) and Hospital Santa Caterina (HSC).

The study is designed to compare, as its main objective, the **delta SOFA score** in patients with S-AKI according to the treatment received (CRRT with oXiris® haemofilter or CRRT with conventional haemofilter such as AN69ST) and, thus, determine the most effective treatment for this type of patients.

All the patients that meet the inclusion criteria and do not meet the exclusion criteria will be treated following the current protocol, and they will be randomised in a ratio of 1:1 in one of the two groups:

- **Group A**: it is the control group, patients will receive the CRRT with conventional haemofilters (AN69ST)
- **Group B**: it is the intervention group, patients will receive CRRT using the oXiris® haemofilter meanwhile the intervention group receive the other treatment.

It is important to clarify that some patients may require additional treatments in addition to renal replacement therapy, to improve the multiorgan failure.

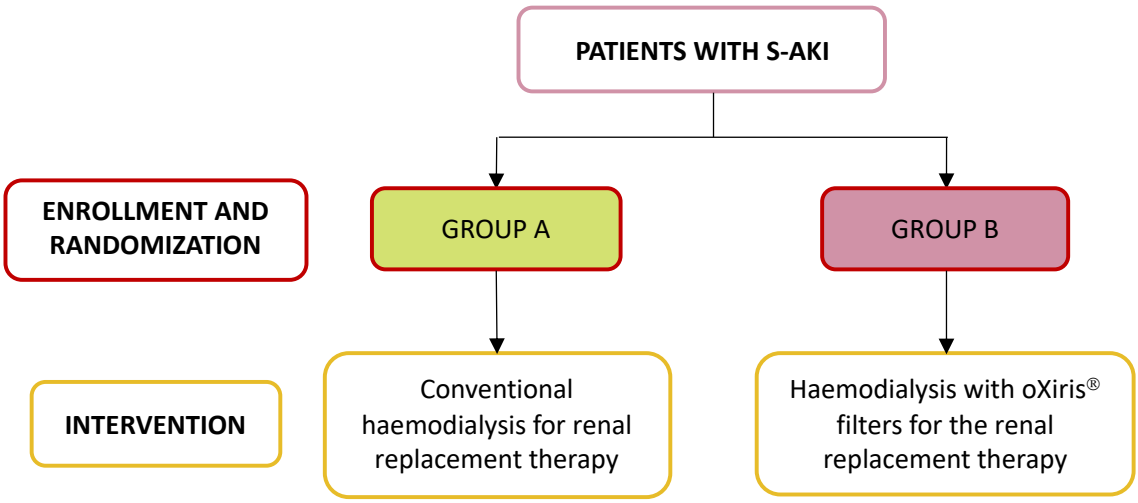


FIGURE 22. **Summary of the different intervention groups**

For the masking method, we will use a triple bind approach. An independent professional from the study research team and the ICU, will cover the brand marks on the front and the bar code on the back using non-transparent tape, and it will assign a code for identification purposes on the front of the filter. Therefore, the treating physician, critical care nurse and ICU staff will be blinded to the type of filter because they won't be able to see the type of haemofilter. The participants will be blinded because of the sedation, and the statistician who will be analyse the data will also be blinded.

The trial will follow an intention-to-treat approach, whereby all randomised participants will be analysed according to the group to which they were initially assigned, regardless of the treatment they received. This principle increases internal and external validity by allowing the benefits of randomised to be maintained. However, it is dependent on the dropout proportion, the higher the dropout rate, the greater the threat to validity.

7.2 STUDY SETTING

This project will be performed at the ICU of **Hospital Universitari Doctor Josep Trueta** (HUJT) and the UCI of **Hospital de Santa Caterina** (HSC).

These hospitals have been chosen because both offers public service and have the human and technological resources required in the UCI, as well as the necessary expertise to attend to critical patients and the training required to use haemodialysis devices. The ICU of HUJT is the reference intensive care unit for the Health Region of Girona, and both ICU provides care for critically ill patients with high complexity.

7.3 SUBJECTS SELECTION

The population of this study will consist of consecutive patients admitted to the ICU of both hospitals with sepsis induced AKI diagnosed according to SOFA score criteria (TABLE 1) and the KDIGO criteria (Annex 2).

In order to participate in the study, patients must meet the inclusion criteria and not meet any of the exclusion criteria. Additionally, they will be required to read and understand an information sheet (Annex 5) about the study and to sign the informed consent form (Annex 6).

7.3.1 Inclusion criteria

Patients who meet all the following criteria may enter the present study:

- Patients ≥18 years.
- Patients with S-AKI who meet the diagnostic criteria for sepsis (Sepsis-3) **and** KDIGO criteria for AKI, as described on the Introduction section.
- Patients where it is decided that the best treatment for S-AKI is CRRT
- Accepted and signed informed consent form (Annex 5 and 6).

7.3.2 Exclusion criteria

Patients will be excluded from the study if they meet any of the following criteria:

- AKI associated with chronic kidney disease.
- Pregnancy.
- Neutropenia <500/μl.
- Pre-existing immune deficiencies or immune-suppressive therapy, especially corticosteroids (prednisone >0.5 mg/kg/day or equivalent).
- Organ transplantation within the last 12 months.
- Terminally ill patients.
- Patients classified as “do not resuscitate” or patients with limitation on the therapeutic efforts.
- Need for extracorporeal membrane oxygenation (ECMO).

7.3.3 Withdrawal of the study

Patients may withdraw from the study if any of the following situations occurs:

- **Voluntary decision of the patient** to leave the clinical trial. Once the patient has regained consciousness after sedation and mechanical ventilation, they will be fully informed again about the study's objectives and asked for consent to use the data collected during the study for statistical analysis. If the patient does not consent, they must fill out the Informed Consent Revocation Form (Annex 8) and notify the research team.
- **Withdrawn request by the family**. They may choose to leave the study at any time by notifying the research team and completing the Informed Consent Revocation Form For Family (Annex 8)
- **Need for extracorporeal membrane oxygenation** (ECMO)
- **Death** of the patient

If a patient withdraws from the clinical trial or passes away, no additional patients will be enrolled as all participants have already been included in the sample size.

7.4 SAMPLING

7.4.1 Sample size

Accepting an alpha risk of 0.05, a statistical power of 0.8, a moderate reduction in SOFA score when using CRRT with oXiris® haemofilter (84,93), in a two-sided test **98** subjects are necessary in each group. Assuming a drop-out rate of 30%, we finally need **127** subjects in each group, that is a total of **254** subjects.

Computations were carried out with Prof. Dr. Marc Saez' software based on 'pwr' of the free statistical environment R (version 4.3.2).

7.4.2 Sample collection

Our sample will be recruited trough a consecutive non-probabilistic sampling method as patients are admitted into the ICUs.

All the patients who meet the inclusion criteria and do not meet the exclusion criteria will be informed about the study. Those patients who are interested in participating will have to receive the information document (Annex 5) and the informed consent (Annex 6) and will have to sing the latter.

If a patient cannot decide because of their critical state, the family or legal guardian will have to be informed instead. They will need to sign the informed consent (Annex 6) if they want the patient to participate in the study.

7.4.3 Sample recruitment time

According to data obtained from the ICUs, the HUJT has approximately 180 patients every year with S-AKI, while the HSC has 93 patients every year. So, to reach the 254 patients for this trial, and taking into account that not all S-AKI patients will require CRRT, **2 years of recruitment will be needed**.

7.5 VARIABLES

7.5.1 Independent variable

The independent variable for this study is "**Treatment with CRRT using oXiris® haemofilters**". It is conceived as a dichotomous nominal qualitative variable expressed as:

- **Use of the oXiris® haemofilters**: patients will be treated with CRRT using the oXiris® haemofilters.
- **Use conventional haemofilters**: patients will be treated with CRRT using the conventional haemofilters.

7.5.2 Dependent variable

DEPENDENT VARIABLE OF THE MAIN OBJECTIVE

The primary dependent variable is the delta SOFA score (Δ-SOFA), that is the difference between the SOFA score at admission time (0h) and the SOFA score at a defined study day.

SOFA score employs 6 criteria to assess the performance of organ systems. These criteria include respiratory, cardiovascular, renal, neurological, hepatic, and haematological functions. Based on the patient's score on these criteria, they will have a different SOFA score (Table 1).

- **Partial pressure of oxygen (PaO_2)** or **Fraction of inspired oxygen (FiO_2):** continuous quantitative variables that represents the respiratory function in the SOFA score.
  - PaO_2 refers to the oxygen pressure in arterial blood, expressed in millimeters of mercury (mmHg) based on an arterial blood sample.
  - FiO_2 is the concentration of oxygen in a gas the mixture, represented in percentage of oxygen.

- **Glasgow Coma Scale (GCS)**: asseses patients according to three aspects of responsiveness: best eye-opening (E), best verbal response (V) and best motor response (M). The levels of response are scored from 1 (no response), up to normal values of 4 (E), 5 (V) or 6 (M); and the total GCS has values between 3 and 15. The score is the sum of the scores (E+V+M) as well as the individual elements (E, V and M). See Annex 1. It is an ordinal qualitative variable, extracted from the medical history or the anamnesis.
- **Mean Arterial Pressure (MAP)** or **requirement of vasopressor drugs**: MAP is a continuous quantitative variable, that represents the cardiovascular function of the patient in the SOFA score. MAP is measured with an arterial catheter. If MAP is <70mmHg we will use the requirement of vasopressor agents as a variable.
- **Bilirubin**: continuous quantitative variable, that represents the liver function in the SOFA score. It is measured in a blood sample and expressed in milligrams per deciliter (mg/dL) or micromoles per liter (μmol/L).
- **Platelets:** continuous quantitative variable, that represents the coagulation function in the SOFA score. It is measured in a blood sample and expressed as the number of platelets multiplied by 10^3 per milliliter (x10^3 /mL).
- **Creatinine** or **Urine output**: continuous quantitative variable, that represents the renal function in the SOFA score. It is measured in a blood sample (creatinine) or urine 24h. Creatinine is expressed as milligrams per deciliter (mg/dL) or micromoles per liter (μmol/L), and the urine output as a milliliters per day (mL/d).

We will calculate the SOFA score at the admission, 24 hours after the treatment and 72 hours after the treatment. In the calculation of the score, the worst values for each parameter in the 24-hour period will be used.

With the SOFA score at admission, the SOFA score at 24 hours and 72 hours post-treatment, we will calculate:

- **Delta SOFA score at 24h post-treatment** (Δ-SOFA score 0-24): is the difference between the admission SOFA score (0 hours) and the 24-hour SOFA score.
- **Delta SOFA score at 72h post-treatment** (Δ-SOFA score 0-72): is the difference between the admission SOFA score (0 hours) and the 72-hour SOFA score.

Δ-SOFA score is a quantitative variable that we will categorize into a polytomous ordinal qualitative variable with the following categories:

-24 to-17	High deterioration
-16 to-9	Moderate deterioration
-8 to-1	Low deterioration
0	Neutral
1 to 8	Low improvement
9 to 16	Moderate Improvement
17 to 24	High improvement

SECONDARY DEPENDENT VARIABLES

SURVIVAL: dichotomous dependent variable, taking the values 'Yes' if the patient survives during his/her ICU stay and 'No' otherwise.

INFLAMMATORY MEDIATORS: continuous quantitative variable, measured in a blood sample. We will measure C-reactive protein (CRP), interleukin-6 (IL-6) and procalcitonin (PCT) levels in each patient at admission and daily thereafter.

LACTATE LEVELS: continuous quantitative variable, measured in a blood sample. While lactate is not considered an inflammatory mediator because don't trigger or perpetuate the inflammatory response, it's accumulation, especially in the context of sepsis or shock, is associated with conditions of metabolic stress and organ dysfunction. It is produced in greater quantities in situation of hypoxia, so the monitoring of the lactate levels can provide important information about the metabolic status, severity of sepsis, early sign of an organ dysfunction and the response to treatment.

REQUIREMENT FOR VASOACTIVE DRUGS: dichotomous nominal qualitative variable, based on medical criteria according to the patient's need, and represented with 'Yes' or 'No'. We will assess this variable at the patient's admission and daily thereafter.

REQUIREMENT FOR MECHANICAL VENTILATION: dichotomous nominal qualitative variable, based on medical criteria according to the patient's need, and represented with 'Yes' or 'No'. We will assess this variable at the patient's admission and daily thereafter.

REQUIREMENT FOR RENAL REPLACEMENT THERAPY: dichotomous nominal qualitative variable, based on medical criteria according to the patient's need, and represented with 'Yes' or 'No'. We will assess this variable at the patient's admission and daily thereafter.

REQUIREMENT FOR RENAL REPLACEMENT THERAPY AT DISCHARGE: dichotomous nominal qualitative variable, based on medical criteria according to the patient's need. The variable will be represented with 'Yes' or 'No'.

TABLE 6. Summary of study variables, measurement method and categories

	VARIABLE		DESCRIPTION	MEASUREMENT	CATEGORIES
INDEPENDENT	**CRRT using oXiris® haemofilters**		Dichotomous nominal qualitative	-	Use of the oXiris® haemofilters during CRRT / Use conventional haemofilters during CRRT
DEPENDENT	**PRINCIPAL**				
	Δ-SOFA score	Δ-SOFA score 0-24	Quantitative	SOFA score 0 hours – SOFA score 24h	Low deterioration:-24 to-17 / Moderate deterioration:-16 to-9 / High deterioration:-8 to-1 / Neutral: 0 / Low improvement: 1 to 8 / Moderate improvement: 9 to 16 / High improvement: 17 to 24
		Δ-SOFA score 0-70		SOFA score 0 hours – SOFA score 72h	
	SECONDARY				
	Survival		Dichotomous nominal qualitative	-	Yes / No
	Inflammatory mediators (CRP, IL-6 and PCT)[a]		Continuous quantitative	Levels in blood sample	Mean value of the punctuation
	Lactate levels		Continuous quantitative	Levels in blood sample	Mean value of the punctuation
	Require for vasoactive drugs		Dichotomous nominal qualitative	Medical criteria	Yes / No
	Require for mechanical ventilation		Dichotomous nominal qualitative	Medical criteria	Yes / No
	Require for renal replacement therapy		Dichotomous nominal qualitative	Medical criteria	Yes / No
	Require for renal replacement therapy at discharge		Dichotomous nominal qualitative	Medical criteria	Yes / No

[a] CPR indicates C-reactive protein; IL-6, Interlukin-6; PCT, procalcitonin

7.5.3 Covariates

There exist additional variables that may influence the dependent and independent variables, although they are not the focus of the study. Since these variables could potentially act as

confounding factors, efforts will be made to control for them in order to increase the internal and external validity of the project.

- **Age**: it is a continuous quantitative variable that we have categorized into a polytomous ordinal qualitative. We will collect the data from the medical history or the anamnesis and categorize it as:
  - 18-39 years
  - 40-59 year
  - 60-79 years
  - 80 or more years
- **Sex**: it is a nominal qualitative variable expressed as male or female. We will collect the data from the medical history or the anamnesis.
- **Comorbidity**: Charlson comorbidity index score (CCI Score) is a method of predicting mortality by classifying 17 different comorbid conditions based on the International Classification of Diseases-10 coding (ICD-10). Every category is associated to weight (from 1 to 6) based on the adjusted mortality risk or resource use, and the sum of all weights results in a comorbidity score. The higher the score, the greater the likelihood that the predicted outcome will lead to death or increased resource use. Absence of comorbidity is considered 0-1 point, low comorbidity 2 points, and high comorbidity >3 points (94,95) (Annex 3). It is a polytomous ordinal qualitative variable, and we will collect the data from the medical history or the anamnesis.
- **Tobacco smoking**: it is well known that tobacco exposure increase the incidence and mortality of various diseases such as cardiovascular and lung disorders. Some research article have suggested that smoking may up-regulate inflammatory factors (96,97) and increase mortality in patients with sepsis (98,99). It is for this reason that tobacco smoking can be a potential confounding factor. We will evaluate this variable with packages/year index:

$$Index\ Packages/year\ = \frac{\frac{Nº\ cigarrets}{day} \times years\ smoking}{20}$$

We will obtain the information for this variable from the medical history or the anamnesis, and the results will be categorized into an ordinal qualitative variable with the following categories:

  - Low: ≤20 package/year
  - Moderate: 21-40 package/year
  - High: ≥40 package/year

- **Alcohol consumption**: consuming large quantities of ethanol compromises the normal functioning of the body, leading to dysfunction of multiple organ systems. The association between sepsis and ethanol is not fully understood, but it is accepted that ethanol consumption plays a role in the development of sepsis, and both contribute to inflammatory dysfunction and promote oxidative stress (100). For this reason, can be a potential confounding factor.

  We will evaluate this variable with the grams of alcohol consumed daily from the medical history or the anamnesis.

  Grams of alcohol consumed daily will be calculated with the following formula (101):

$$Grams\ of\ alcohol = \frac{Volume\ (ml) \times Alcohol\ by\ volume\ (ABV) \times 0{,}8}{100}$$

  The results will be categorized as an ordinal qualitative variable with the following categories:

  - Non consumer: <20g for women and <40g for men
  - Moderate consumer: 20-50g/day for women and 40-60g/day for men
  - High consumer: >40g/day for woman and >60g/day for men
- **Immunodeficiency state**: it is a dichotomous nominal qualitative variable that can be a potential confounding. We will collect the data from the medical history or the anamnesis and represent the variable with Yes or No.
- **Socioeconomic status**: it is a well-known factor that contributes to health outcomes inequalities and can be a potential confounding factor (102). it is an ordinal qualitative variable, and we will use the work of Domingo et al (103). to classify the patients from I to V taking into account their occupational and educational level.
- **Initial dose of vasoactive drugs**: it is a continuous quantitative variable that will be determined according to doctor's criteria to continue with the patient's treatment and improve their survival. SOFA score uses the dose of vasoactive drugs to evaluate the cardiovascular system, and we will categorize the variable with a similar classification:
  - No requirement
  - Epinephrine or Norepinephrine $\leq$ 0,1μg/kg/min
  - Epinephrine or Norepinephrine > 0,1μg/kg/min
  - Norepinephrine and vasopressin
- **Microorganism**: the pathogen type of infection is associated with mortality of sepsis (104), for this reason it can be a potential confounding factor. It is a nominal qualitative variable that we will collect the data from the microbial culture of different secretions or liquids

(blood, endotracheal or bronchial aspirate, urine, etc) or material (urine catheter, wound swab, central venous line tip, etc). We will express the variable with the following categories:

- Gramm negative bacteria (GNB)
- Gramm positive bacteria (GPB)
- Fungi
- Virus

- **Multiresistance**: the global increase in acquired bacterial resistance to antibiotics is compromising the effectiveness of antimicrobial therapy (105). The presence of microorganism with acquired resistance to multiple antibiotics complicates the management and outcome of critically ill patients, and patients in ICUs are especially vulnerable to colonization by multiresistant microorganisms (MRMs) (106). MRMs is defined as resistant to at least one agent in three or more antimicrobial categories (107,108). For this reason, this variable may be a potential confounding factor. We will collect data from the antibiogram, and since it is a dichotomous nominal qualitative variable, we will represent the variable with Yes or No.
- **Days of ICU stay**: it is a continuous quantitative variable based on the medical criteria. It will be expressed as the mean value punctuation.
- **Days of hospital stay**: it is a continuous quantitative variable based on the medical criteria. It will be expressed as the mean value punctuation.
- **Hospital**: dichotomous nominal variable, expressed as Hospital Universitari Josep Trueta (HUJT) or Hospital Santa Caterina (HSC).
- **Hospital admission severity:** we will use the Acute Physiology and Chronic Health disease Classification System II (APACHE II score) to obtain the data. APACHE II (Annex 4) is a severity disease classification system for the first 24 hours after ICU admission (109). We will use an online calculator to determine the values and to set the level of severity for each patient's admission. It is a quantitative discrete variable that we will categorize into a polytomous ordinal qualitative variable, and we will classify with the following states:
  - 0-4
  - 5-9
  - 10-14
  - 15-19
  - 20-24
  - 25-29
  - 30-34
  - 35-100

TABLE 7. **Summary of covariates, measurement method and categories**

VARIABLE	DESCRIPTION	MEASUREMENT	CATEGORIES
Age	Polytomous ordinal qualitative	Computerized medical history or anamnesis	18-39 years / 40-59 years / 60-79 years / 80 or more years
Sex	Dichotomous nominal qualitative		Male / Female
Comorbidity	Polytomous ordinal qualitative	Charlson comorbidity index (CCI) score	Absence / Low / High
Tobacco smoking	Ordinal qualitative	Packages/year index	Low / Moderate / High
Alcohol consumption	Ordinal qualitative	Grams of alcohol consumed daily	Non consumer / Moderate consumer / High consumer
Immunodeficiency state	Dichotomous nominal qualitative	Computerized medical history or anamnesis	Si / No
Socioeconomic status	Ordinal qualitative	Occupational and educational level	Class I to V
Initial dose of vasoactive drugs[a]	Categorical ordinal qualitative	Medical criteria	No requirement / Norepi ≤ 0,1 / Norepi > 0,1 / Norepi and Vaso
Microorganism	Categorical nominal qualitative	Culture	GNB / GPB / Fungi / Virus
Multiresistance	Dichotomous nominal qualitative	Antibiogram	Yes / No
ICU length of stay	Continuous quantitative	Medical criteria	Mean value of the punctuation
Hospital length of stay	Continuous quantitative	Medical criteria	Mean value of the punctuation
Hospital	Dichotomous nominal qualitative	-	HUJT and HSC
Hospital admission severity	Polytomous ordinal qualitative	APACHE II score	0-4 / 5-9 / 10-14 / 15-19 / 20-24 / 25-29 / 30-34 / 35-100

[a] Norepi indicates norepinephrine; Vaso, Vasopressin. Adrenergic agents doses expressed in μg/kg/min

7.6 STUDY INTERVENTION

7.6.1 Enrolment

The study population has been previously defined in the Subjects selection section. The enrolment process will begin with consecutive patients admitted to the ICU of HUJT and HSC presenting with S-AKI and requiring continuous renal replacement therapy. The attending physician will explain the aim of the study to the patients or their families and ask if they are willing to participate.

Patients who are intubated and sedated may not be in a position to make decisions. Therefore, once the patient is extubated and regains consciousness, the clinician will explain the purpose of the study again and ask if they still consent to the use all the data collected in the clinical trial.

If the family agrees to participate in the study after reading the information document (Annex 5), they must sign the informed consent form (IC) (Annex 6).

If the patient is hemodynamically unstable, normal procedures will be performed to provide the best treatment to reverse the haemodynamic instability and secure the airway.

Once admitted to the ICU and within the clinical trial, all patients will be **monitored** as usually, with electrocardiogram (ECG), invasive blood pressure (BP) through a catheter, heart rate (HR), oxygen saturation ($SatO_2$), temperature (Tº), capnograph, central venous pressure through a catheter, respiratory rate (RR), and bedside electroencephalographic monitoring using the Bispectral Index (BIS). BIS monitoring offers an objective and quantitative measure of consciousness levels, helping clinicians to make more accurate drug dosage decisions.

7.6.2 Randomization

Once the patient or the family has understood the study, we will randomise all the participants in the clinical trial in a ratio 1:1 into one of the following two groups using a randomization computer program:

- **Group A**: consecutive patients with S-AKI who require continuous renal replacement therapy and who will be treated using the conventional haemofilters.
- **Group B**: consecutive patients with S-AKI who require continuous renal replacement therapy and who will be treated with oXiris® haemofilters.

Additionally, it is important to make it clear that patient data, including name, phone number, ID number, address and medical history information, will be anonymised to ensure confidentiality. Every patient will be given an identification (ID) code number.

7.6.3 PRE-Intervention

Once we have all the patients enrolled in the clinical trial monitored, we will conduct a **complete blood analysis, as usually performed in the ICU.** This is crucial, especially for completing the diagnosis of a septic or septic shock patient, and to obtain the laboratory parameters necessary for calculating the SOFA score upon admission. Thus, we will measure the inflammatory mediators such as C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin (PCT) levels and lactate levels.

Blood samples will be collected from an arterial line into a heparinized glass vial and a plastic vial coated with ethylene-diamine-tetra-acetic acid (EDTA) immediately at the admission and 24h and 72h after the start of each treatment.

Blood samples must be drawn for culture purposes, and a central venous catheter should be placed using a temporary haemodialysis catheter following the KDIGO guidelines for the preferred order for placement (right internal jugular vein, femoral vein, left internal jugular vein, dominant side of the subclavian vein, and non-dominant side subclavian vein (52). The vascular access will be inserted under echographic guidance.

Furthermore, we will carry out an arterial blood gas (ABG) to assess the patient's partial pressure of gas and acid-base content. Other parameters present in the SOFA score will be collected, such as the mean arterial pressure and Glasgow Coma Scale.

All the obtained data will be recorded on the case report form (CRF) (Annex 7).

7.6.4 Intervention

The treating physician, intensive care nurse and other healthcare professional will be blinded to the type of filter. Each filter will have a code identification provided by an independent database. This way, the professional installing the haemofilter into the CRRT circuit won't be able to see which type of filter it is.

The CRRT will be performed as post-dilution continuous venovenous haemodiafiltration (CVVHDF) and using the Prismaflex; Baxter®. Blood flow rates will be between 150 and

200mL/min, while prescribed haemodiafiltration doses will be in the range of 25-35mL/kg/h based on tolerance. The anticoagulation will be decided based on medical criteria.

All patients will receive a minimum of 24h on the CRRT and underwent additional treatments according to their clinical response. Both filters will be installed into the CRRT machine according to the patient's assigned group (intervention or control) and changed either after clotting or 72h.

At 24 and 72 hours after initiating haemodialysis, samples will be collected again for all variables necessary to obtain the SOFA score. Additionally, levels of inflammatory mediators and lactate levels in the blood will be measured. Arterial blood gas analysis will be repeated to obtain the PaO_2 parameter, and data on Mean Arterial Pressure (MAP) and Glasgow Coma Scale will be obtained.

All patients will receive additional supportive treatment following the recommendations of guidelines, such as controlling the septic source via surgery or antibiotics, providing respiratory support, administering vasopressor drugs, etc.

7.6.5 POST-Intervention

Once patients have responded to therapy, it will be necessary to continue controlling the septic focus and consider de-escalation of fluids and antibiotic, as appropriate. This may occur within hours or days, depending on the patient.

Finally, the last data to be collected for the clinical trial would include the survival, the number of days admitted to the ICU and the hospital, the number of days requiring vasopressor drugs, mechanical ventilation, and CRRT. Additionally, it will be noted whether the patient requires renal replacement therapy at discharge.

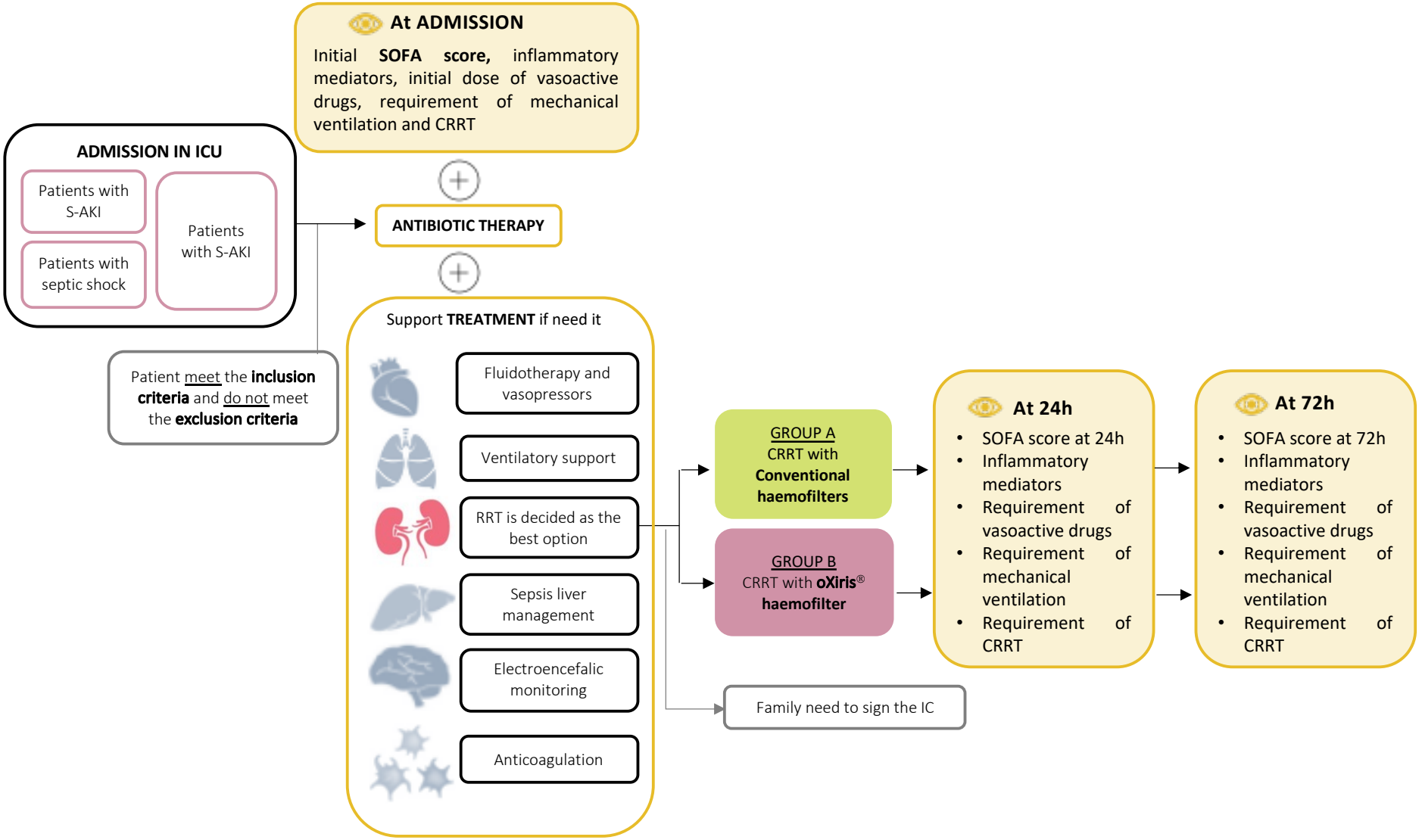


FIGURE 23. **Outline of the study design**

S-AKI, Sepsis-Induced Acute Kidney Injury; SOFA score, Sequential Organ Failure Assessment score; IC, Information Consent; ATB, antibiotic

7.6.6 Safety

The interventions proposed in this clinical trial are invasive, however, it is important to realise that patients admitted to the ICU are critically ill and require intensive care and therapies to survive. Despite a strict protocol, ICU patients who require CRRT have a high incidence of adverse events such as hypotension, hypothermia, arrhythmias, anaemia or thrombocytopenia (110), but it is not known which of these complications are attributable to CRRT. Most adverse effects during CRRT were minor, even that, clinicians need to be cautious and aware of their high prevalence in this patient population. The management of these haemodialysis complications is explained in the Complications of CRRT section. In order to avoid complications, it is essential that the patient is treated by health care professionals experienced in CRRT (both intensive care nurses and intensivists) to handle the haemodialysis machine and any complications that may occur.

Apart from the complications inherent to renal replacement therapy, the use of oXiris® haemofilters does not entail additional complications compared to CRRT with conventional haemofilters.

7.7 DATA COLLECTION

All the information necessary for the clinical trial will be obtained from Centricity™ High Acuity Critical Care platform, which contains a complete record of the medical data of the patients: clinical data from equipment measurements, diagnostic tests and clinical history and exploration. The different sources and timing for the data collection are explained on the Figure 23:

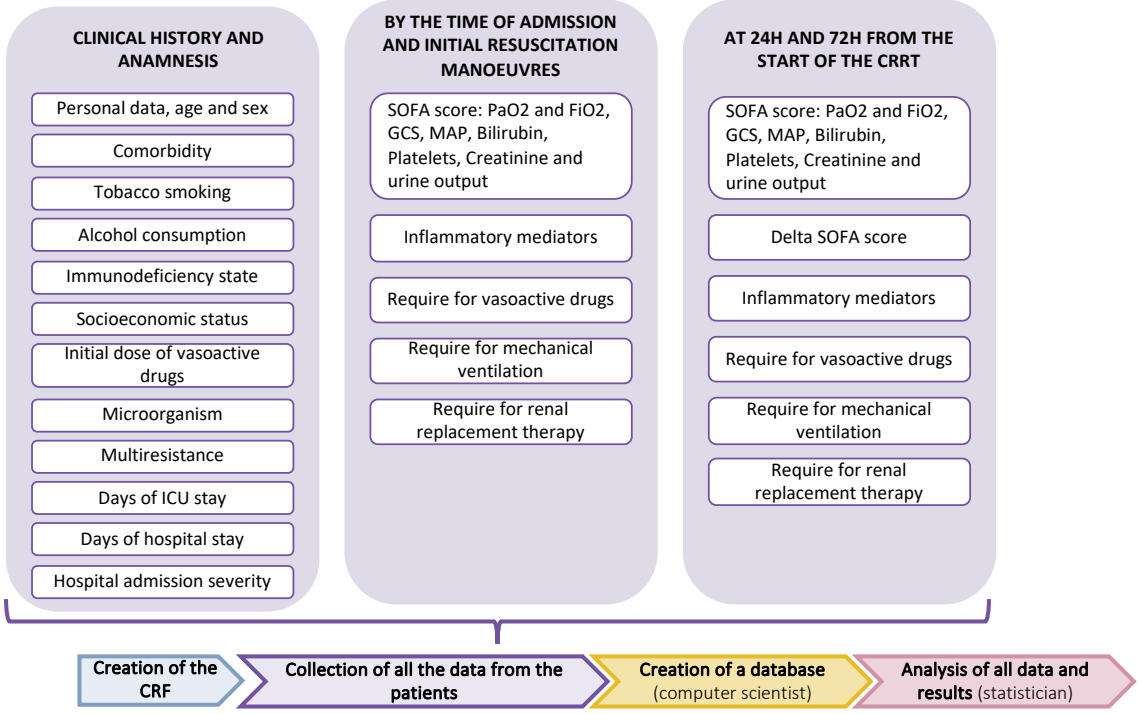
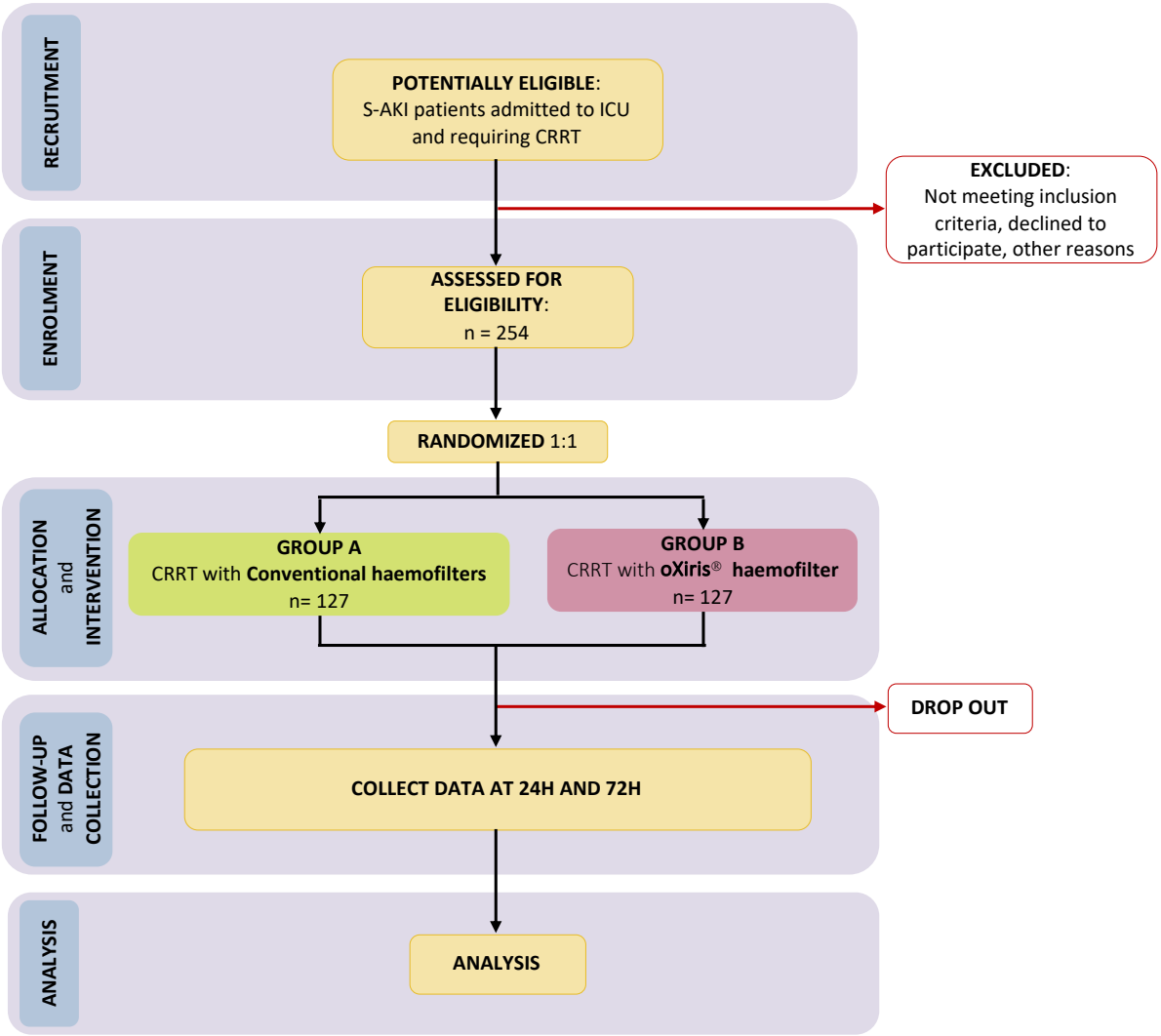


FIGURE 24. **Summary of the data collection source and timing**

The **intensivist** responsible for the patient in the research group will collect all necessary data from the patient and record it in the CRF (Annex 7) with anonymised patient data. The ID will be stored separately to maintain anonymity. All the data collected in the CRF, both from HUDJT and HSC, will be verified by the **general coordinator** to ensure accuracy.

Finally, **computer scientist** will digitise the data to create the database and the **statistician** will conduct the analysis of the data.

7.8 FLOW CHART



8. STATISTICAL ANALYSIS

The research team will perform the statistical analysis using IBM Statistical Package for the Social Sciences (SPSS) software (version 29.0.1). For all analyses, 95% confidence interval will be taken,

and the results will be considered statistically significant when the p-value is ≤0.05. Analysis will be made by intention to treat.

8.1 DESCRIPTIVE ANALYSIS

In both groups - patients that will receive the CRRT with oXiris® haemofilters and patients that will receive CRRT with conventional haemofilters - we will summarise the quantitative variable (inflammatory mediators and lactate levels) by using **means, standard deviation, medians and interquartile range (IQR)**. All the qualitative variables (Δ-SOFA categorised, survival, requirement of vasoactive drugs, mechanical ventilation, renal replacement therapy and renal replacement therapy at discharge) will be described by using **proportions**.

We will stratify these descriptive by the types of treatment that they receive (CRRT with oXiris® haemofilters or CRRT with conventional haemofilters), and additional stratification will be done by the covariates.

8.2 BIVARIATE INFERENCE

Student's t test will be used for those **continuous quantitative variables** such as inflammatory mediators and lactate levels.

We will use **Chi-squared test or Fisher's exact test** (if the expected number of cases will be lower that 5) with the **qualitative variables** (Δ-SOFA categorised, survival, requirement of vasoactive drugs, mechanical ventilation, renal replacement therapy and renal replacement therapy at discharge) for the difference of proportions between the two groups (CRRT with oXiris® haemofilters or CRRT with conventional haemofilters).

We will stratify these analyses by the covariates.

8.3 MULTIVARIATE ANALYSIS

Although theoretically it is not necessary to carry out a multivariate analysis in randomized clinical trials, because with randomization one allows to balance the confounders, we will adjust for them. It is possible that exist interactions and/or unmeasured confounders that we should control for.

The study will employ a **linear regression model** to examine the association between the intervention and quantitative continuous variables (inflammatory mediators and lactate levels), adjusting for the covariates.

Multivariate logistic regressions, controlling for the covariates, will be used to investigate the association between the intervention and qualitative variables (survival, requirement of vasoactive drugs, mechanical ventilation, renal replacement therapy and renal replacement therapy at discharge).

The Δ-SOFA categorised will again be classified in two categories, detriment vs. neutral/improvement. A **logistic regression**, controlling for the covariates**,** will also used in this case.

9. WORK PLAN AND CHRONOGRAM

9.1 RESEARCH TEAM MEMBERS

- **Principal Investigator (PI):** is responsible for leading the trial and overseeing all aspects of the clinical research study. They will develop the study concept, write a detailed description of how the study will be conducted, and submit it for approval. The PI is also responsible for the recruitment and ensuring that participants understand their rights and agree to take part. Additionally, they supervise the collection, analysis, interpretation and presentation of research results.
- **Hospital Coordinator (HC):** is involved in recruitment and ensures participants understand the requirements of the study and agree to participate. They have the responsibility to schedule research visits and complete research interviews. They must collaborate with the PI, research institution and other members of the research team to ensure that the study follows research regulations.
- **Study physicians and research nurses (SP and RN)**: they are the health care professionals responsible for monitoring and caring for patients participating in the study. They treat patients according to the clinical trial design, evaluate and collect data, record patient responses, and document any side effects.
- **Other health care professionals (oHCP):** it includes all the health care professionals who attends the patients of the clinical trial and necessary to carry out the study, such as nurses, TCAI, physiotherapist, medical laboratory professionals, radiologists, surgeons, otorhinolaryngologist, etc.
- **Other staff:** statistician, computer scientist, professional healthcare cleaning, etc.

9.2 STUDY STAGES

The process of creation, implementation, analysis and publication of the results will be carried out in 6 stages, taking into account that the total duration of the study will be **3 years and a half**:

9.2.1 Stage 1. Elaboration of the protocol and study design (3 month: January 2024 – March 2024)

- **First session *(January 2024, completed):*** it is the first meeting between the study hospital coordinator and principal investigator to discuss the aim of the trial and agree to work together to develop the protocol.
- **Bibliographic research and protocol elaboration *(January - February 2024, completed):*** extensive bibliographic research was carried out to incorporate the latest evidence on CRRT, as well as the redaction of the protocol.
- **Hospitals participating contact *(March 2024)*:** the PI will propose to the hospitals selected in the study to participate in it.

9.2.2 Stage 2. Ethical Evaluation (3 month: April 2024 – June 2024)

- **Ethical evaluation and approval:** the PI will present the protocol to *Comitè Ètic d'Investigació Clínica* (CEIC) of HUJT and HSC for its ethical approval. All the suggestions will be considered and consequently modified.

9.2.3 Stage 3. Initial coordination and health professionals training (2 month: July 2024 – August 2024)

- **First meeting of the research team *(July 2024):*** the PI will meet the research team from both hospitals included in the study and decide who will be the HC.
- **Training workshops *(July - August 2024):*** all members of the research team will be trained in the diagnosis of S-AKI. The aim of the workshop is to homogenise the diagnostic of S-AKI and the treatment process of patients requiring CRRT. The workshops will include both theoretical and practical sessions on how to operate the CRRT machine.

9.2.4 Stage 4. Sample recruitment, intervention and data collection (2 years: September 2024 – September 2026)

- **Sample recruitment *(September 2024 - September 2026):*** a non-probabilistic sampling method will be used to recruit patients for this study in HUJT and HSC. Only those patients who meet all the inclusion criteria and none of the exclusion criteria, and whose

family have signed the informed consent will be included in the sample. Each participant will be randomised to one of the intervention groups of the clinical trial. All the patients will be anonymized and give an ID to identify.

- **Pre-Intervention *(September 2024 - September 2026):*** all the diagnostic tests to identify the organ dysfunctionality will be done in this stage. The data at the admission will be collected at the CRF (Annex 7) by the study physicians and research nurses.
- **Intervention *(September 2024 - September 2026):*** during this period, CRRT will be performed, and the data will be collected in the CRF of each patient.
- **Post-Intervention data collection *(September 2024 - September 2026):*** in this phase we will continue to treat the patients until they reach the final outcome (discharge or exitus). The data obtained after the intervention will be collected in the CRF (Annex 7).

9.2.5 Stage 5. Statistical analysis and data interpretation (3 month: October 2026 – December 2026)

- **Creation of the database *(October 2026):*** a computer scientist will create a database with all the anonymous data collected in the CRF (Annex 7) of each patient.
- **Statistical analysis *(November 2026):*** a statistician will analyse all the data collected through a descriptive, bivariate and multivariate analysis. Finally, all the data will be interpretated.
- **Statistical interpretation *(December 2026):*** the statistician will present the results to the research team to discuss and dray the final conclusions. The PI will interpret the analysis and write the final discussion and the conclusion of the study.

9.2.6 Stage 6. Results publication (3 month: January 2027 – March 2027)

- **Paper elaboration *(January 2027):*** the clinical trial will be explained in a scientific paper format with the results after their correct interpretation. It will be written by the PI with the assistance of the HCs.
- **Publication of the results *(February 2027):*** the scientific paper will be sent to different journals related to the topic of the study to be published in a scientific journal.
- **Presentation of the results *(March 2027):*** the paper will be presented in the intensive care conferences and congress.

9.3 CHRONOGRAM

		2024								September 2024 - September 2026	2026			2027		
		J	F	M	A	M	J	J	A		O	N	D	J	F	M
STAGE 1	FIRST SESSION															
	BIBLIOGRAPHIC RESEARCH and PROTOCOL ELABORATION															
	HOSPITALS CONTACT															
STAGE 2	ETHICAL EVALUATION and APPROVAL															
STAGE 3	FIRST MEETING															
	TRAINING															
STAGE 4	RECRUITMENT															
	PRE-INTERVENTION															
	INTERVENTION															
	POST-INTERVENTION and DATA COLLECTION															
STAGE 5	CREATION THE DATABASE															
	STATISTICAL ANALYSIS															
	STATISTICAL INTERPRETATION															
STAGE 6	PAPER ELABORATION															
	PUBLICATION OF THE RESULTS															
	PRESENTATION OF THE RESULTS															

10. ETHICAL AND LEGAL CONSIDERATIONS

10.1 ETHICAL PRINCIPLES AND LAWS

This clinical trial will be realized according to the ethical principles defined in the **Declaration of Helsinki** (1964) of **Ethical Principles for Medical Research Involving Human Subjects** revised in October of 2013 by the World Medical Association. It will also respect the **Principles of Biomedical Ethics from Beauchamp and Childress** from 1970 and reviewed in 2009:

- **Autonomy**: recognising patient's capacity to make certain choices is important for this clinical trial, for this reason all the patients / families will receive an informative document (Annex 5) about the study protocol in order to provide the knowledge and understanding they need to perform an informed decision. Although some patients may be sedated and unable to participate in the decision-making process initially, their family are delegated to sign the IC (Annex 6) on their behalf. After the sedation subsides and the patient regains decision-making capacity, they will receive the information sheet and have the opportunity to make a voluntary and informed decision regarding their continued participation by signing the IC form. This approach respects individual autonomy by facilitating their involvement in the decision-making process, even in cases where families are initially delegated decision-making due to sedation. The clinical trial will be in accordance with the ***Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica.***
- **Non-maleficence**: non malicious intent is directed towards study participants. The study will always prioritise patient safety throughout the study. Rigorous consideration and continuous reassessed is given to balancing the risks and benefits associated with invasive interventions. To minimise harm, the study implements continuous monitoring and safety measures, adhering to hospitals protocols. The informed consent process further contributes to non-maleficence by ensuring that participants, or their families when patients are initially unable to make decision, are fully aware of the interventions and potential consequences. This approach helps to prevent potential harm that could result from delayed or uninformed decisions.
- **Beneficence**: the moral obligation to act for the benefit of the patients will be fulfilled in this clinical trial because all the patients will be attended by intensivists physician and nurses who have expertise in this kind of patients and who are expected to follow evidence-based practices. Moreover, by seeking to understand the comparative effectiveness of different haemofilters, the clinical trial has the potential to identify

interventions that may lead to better patient outcomes, reducing morbidity and mortality.

- **Justice**: the equitable distribution of health resources will be respected in the clinical trial, and any discrimination to any person will be avoided to guarantee the principle of justice. The random assignment process contributes to this principle, making sure that all the participants have an equal chance of being assigned to different groups and distributed fairly. All the patients meeting the inclusion and not the exclusion criteria have an equal opportunity to participate in the study and equal accessibility, following the justice principle.

The clinical trial will be conducted under the following ethic laws:

- ***Real Decreto 192/2023, de 21 de marzo***, por el que se regulan los productos sanitarios
- ***Reglamento (UE) 2017/745 del Parlamento Europeo y del Consejo de 5 de abril de 2017*** sobre los prductos sanitaria, por el que se modifican la ***Directiva 2001/83/CE,*** el ***Reglamento (CE) nº178/2002 y el Reglamento (CE) nº1223/2009*** y por el que se derogan las ***Directivas 90/385/CEE y 93/42/CEE del Consejo.***
- ***Reglamento (CE) 2017/746 del Parlamento Europeo*** y del ***Consejo de 5 abril de 2017*** sobre productos sanitarios para dignóstico in vitro y por el que se derogan la ***Directiva 98/79/CE y la Declaración 2010/227/UE de la Comisión***.

10.2 COMITÈ D'ÈTICA I D'INVESTIGACIÓ CLÍNICA (CEIC)

The present project will be submitted to to the *Comitè Ètic d'Investigació Clínica (CEIC)* of Hospital Universitari Josep Trueta and later to the CEIC of Hospital de Santa Caterina. Any suggestions given will be considered and its approval will be compulsory before starting the clinical trial. The project will be in accordance with the ***Ley 14/2007, de 3 de julio, de Investigación biomédica.***

10.3 PRIVACY AND CONFIDENTIALITY

All the personal and clinical data collected in this study will be anonymous and confidential because all the patients will be identified through a randomised code in the CRF and consequently in the database. Only essential information for the study will be collected, adhering to the principle of minimization. Data access will be restricted to the research team and collaborators, strictly for study-related purposes.

The confidentiality and privacy of the patient will be guaranteed through the ***Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos***

digitales and ***Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.***

10.4 TRANSPARENCY

The pharmaceutical company Baxter will be asked to contribute by providing financial support.

To minimize potential conflicts of interest, it will be explicitly stated that the pharmacist providing financial support will not be involved in the design, execution or interpretation of the study results.

To demonstrate the commitment to transparency, each member of the research team should sign a declaration of independence, affirming that they have disclosed all relevant financial and non-financial interests and that they are committed to conducting the clinical trial objectively and without bias.

The investigators agree to publish all data and results with complete transparency, including unfavourable data or events.

11. BUDGET

11.1 NOT INCLUDED COSTS

- **Staff**: the researchers and other professionals who carry out the clinical trial will not be remunerated extra for their involvement in the project, as this is considered a normal professional activity, and they will be rewarded by the scientific prestige and intellectual gain. An independent professional from the study research team and the ICU will be the responsible to cover the brand mark of the haemofilters to preserve the triple binding. This person will not receive extra paid as we considered part of the professional activity.
- **Available materials**: the hospitals chosen (HUJT and HSC) already dispose of the materials for the care of critically ill patients, so this material not be considered in the study budget.

11.2 INCLUDED COSTS

11.2.1 Personnel expenses

- **Training session**: for all the members of the research team to homogenise the diagnostic of S-AKI and the treatment process of patients requiring CRRT. The sessions will include both theory and practice instructions on operating the CRRT machine. the training sessions will be conducted in two different groups with different schedules to

accommodate the entire research team. Each session will last for 4 hours and will be facilitated by an expert. Considering a base salary of €40 per hour, the estimation cost for two sessions is €320.

- **Independent statistical analyst**: we will subcontract a statistical analysis service, paid 40€/h with an estimated total of 100 hours of work, the estimation cost is 4.000€.
- **Data manager and anonymizer**: we will subcontract a data manager that calculating a base salary of €40/h and expecting a 100h of work, the estimation cost is €4.000.

11.2.2 Execution expenses

- **Haemofilters (oXiris® and AN69ST)**: the estimated cost of the CRRT with oXiris® haemofilter is approximately €1700 per filter. In the intervention group, comprising 127 patients receiving CRRT with the oXiris® membrane, it is anticipated that each patient will require approximately one filter, except in cases where filters become clogged before the standard 72h replacement period. Considering the potential clotting, the overall estimation for the clinical trial is the use of approximately 200 filters. Therefore, the estimation cost is €340.000.

  Taking into account that this clinical study will serve to demonstrate the greater efficacy of the oXiris® filters compared to conventional filters, the pharmaceutical company Baxter will be asked if they would like to participate in the study by providing financial support. The conventional haemofilters will be provided by the hospital as is the standard treatment for patients with S-AKI that requires CRRT. Therefore, there not be extra costs for the haemofilters used in this clinical trial.
- **Printing costs**: each participant and their families must have a copy of the information sheet and the IC. There are 254 patients and therefore 254 families tant may have to sign if the patient is uncapable on that moment, so we will need 508 copies. The information sheet and the IC have together 5 pages, if each side Is printed at €0.05, it will cost €127.

11.2.3 Travel coordination expenses

This study will take place in two hospitals located at the same city, with both the principal investigator (PI) and hospital coordinator (HC) holding positions and working at both institutions. Therefore, there is no anticipation of additional travel and coordination expenses. The PI and HC will coordinate their visits to each hospital based on their respective work schedules.

11.2.4 Publication expenses

After the study will be completed and the results will be analysed, the article will be written and published as a journal paper. We will subcontract a linguistic correction service (€300) and publish the paper in an international Open Access medical journal (€1.500).

11.2.5 Conference expenses

To disseminate at the scientific community the results obtained on this clinical trial, the PI and HC will attend national and international congress such as the *"Congreso annual de la Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronaria"* (SEMICYUC) and the *"Annual Congress of the European Society of Intensive Medicine* (ESICM).

TABLE 8. **Budget details from the study**

TYPE OF COST	UNIT COST	HOURS / UNITS	SUBTOTAL
PERSONNEL EXPENSES			
TRAINING SESSION	€40/h	8h	€320
INDEPENDENT STATISTICAL ANALYST	€40/h	70h	€2.800
DATA MANAGER AND ANONYMIZER	€40/h	100h	€4.000
EXECUTION EXPENSES			
HAEMOFILTERS AND CRRT MACHINE	-	-	-
PRINTING COSTS	€0.05/page	2.540 pages	€127
PUBLICATION EXPENSES			
LINGUISTIC CORRECTION	€300	1	€300
PUBLICATION FEES	€1.500	1	€1.500
CONFERENCE EXPENSES			
NATIONAL CONFERENCE	€1.000/ attendant	1	€1.000
EUROPEAN CONGRESS	€2.500/attendant	1	€2.500
		TOTAL	**€12.547**

12. LIMITATIONS AND STRENGHTS

12.1 STRENGHTS

- **Prospective design**: this clinical trial design allows real-time data to be collected and facilitates the establishment of temporal relationships between the intervention and outcomes, increasing the reliability of the study results.
- **Randomized control**: randomization increases the internal validity of the study by minimising selection bias and ensuring that baseline characteristics are evenly distributed between the two groups.
- **Triple Masking**: the implementation of triple masking in this study helps to minimise different types of bias, including detection bias and performance bias. This rigorous blinding approach increases the objectivity and methodological rigor of the study.
- **Controlled Setting**: the randomisation and masking procedures help to create a controlled experimental environment, which allows a more accurate assessment of the impact of the intervention on the primary outcome.
- **Reliability and reproducibility**: the use of an objective outcome measure such as the SOFA score, is a primary outcome measure that is objective and widely accepted in the context of S-AKI, increasing the reliability and reproducibility of the study results.
- **Clinical relevance**: this clinical trial addresses a significant and clinically relevant question by comparing the reduction of the SOFA score in patients with S-AKI requiring CRRT using different types of haemofilters. The study holds direct implications for patient care and treatment decisions, particularly considering the severity of illness and high mortality rate associated with this patient population. For this reason, the trial directly addresses a vulnerable population with a critical medical condition to improve the understanding of haemofilters effectiveness.

12.2 LIMITATIONS

- **Selective bias**: since the consecutive non-probabilistic sampling method is used, the study population may have a **selection bias**, because people with more fragility are more probable to be critically ill and probably require to be admitted in the ICU. To minimize this problem, we will use a random assignment to ensure that neither researchers nor participants/family know which group each participant is assigned to. In addition, the exclusion criteria have been clearly defined to ensure that the target population match with the sampling frame.

- **Resource-intensive**: generally, clinical trials are resource-intensive and require specialised expertise in addition to the medical or scientific qualifications of academic physicians. To minimize this problem, we will provide a training session for the study team to enhance their expertise in the renal replacement therapy and this type of critically ill patients.
- **Infrastructure and independent person**: this particular clinical trial also requires infrastructure to deal with the triple-blind method, involving the covering of haemofilter brands with non-transparent tape. An independent person is needed to perform this task. To minimize this problem, we will explore the possibility of using existing infrastructures in hospital to avoid additional investment. We will consider asking a critical care nurse to be responsible for covering the brand of the haemofilters with non-transparent tape.
- **Complexity of CRRT**: continuous renal replacement therapy is a complex intervention, and variations in its delivery may occur. For this reason, we will provide training sessions to homogenise the procedure and ensure that the observed effects are due to the type of haemofilter rather than other procedural factors.
- **Interobserver variability**: the study focuses on patients with S-AKI admitted to the ICU of HUJT and HSC, which may introduce some misclassification. The variety introduced could be on the patient population, medical practices, and resources. To address this issue, the study will implement a standardization protocol, clearly define selection criteria, and provide training session. Additionally, the multivariate models will be adjusted for hospital.
- **Ethical concerns**: an ethical consideration or potential limitation is that all participants will receive invasive interventions with known adverse effects and complications. This necessitates careful consideration and mitigation of potential harm. For this reason, it is important to balance risk and benefits for each patient weighing the potential harm of the interventions against the high risk of mortality if the procedures are not performed. To address these ethical concerns, the study will seek approval from the Clinical Ethics and Investigation Committee (CEIC) of HUJT and HSC before the implementation. Moreover, participants in the clinical trial will receive a comprehensive information sheet detailing all pertinent information, and their participation will be contingent upon signing an informed consent. Additionally, continuous monitoring and safety measures will be implemented in accordance with the hospital protocols to minimize the risk of complications.

- **Floor effect**: the Glasgow Coma Scale is a component of the SOFA score that assesses the level of consciousness. However, in sedated patients, the score will be at the lowest level (e.g., 3) due to their sedated state, creating a floor effect. Therefore, this component is unable to capture any decline in neurological function. Although we have considered using other alternative measures, non have been validated at this time. Thus, to address this issue, we will clearly document the level of sedation of patients at the time of GCS assessment, in order to interpret the score in context and understand the potential limitation.

13. IMPACT ON THE HEALTH SYSTEM

Sepsis, identified as the leading cause of AKI in critically ill patients (111), elevates the risk of in-hospital death six to eight times (112). Despite the increasing incidence of sepsis and its associated morbidity such as chronic kidney disease, there seems to be a decline in the mortality rate among septic patients (90). The challenge in preventing S-AKI lies in the fact that patients with sepsis often seek medical attention after AKI has already developed (40). Consequently, this presents a global public health concern due to the significant mortality and morbidity associated with sepsis, along with a substantial economic burden (113).

S-AKI often requires intensive medical interventions such as CRRT (90) and extended hospital stays. The associated costs of these interventions contribute to the financial burden on the health system. The impact of S-AKI highlights the need for continuous research and educational initiatives to improve prevention, early detection and management strategies.

This clinical trial will serve to identify which haemofilter is more effective in patients with S-AKI that requires CRRT, improving the organ dysfunction process and therefore, reducing mortality and need for intensive care. This would reduce the burden on healthcare and optimise the resource allocation within the health system, adopting a more cost-effective or efficient treatment strategies, therefore contributing to the reduction of healthcare costs associated with S-AKI management.

14. FEASIBILITY

The clinical trial is expected to be feasible, and although it is multicentric and somewhat more difficult to coordinate, it will be carried out in two hospitals in the same city that have strong

links between both ICUs, making coordination easy. Furthermore, all these centres have all the relevant resources for the type of patients included in this project, and the research team has extensive research experience. The research team will consist of intensivists and critical care nurses from both units. Therefore, supplementary wages are not expected. The healthcare professionals who carry out the intervention are experienced in managing critically ill patients and the RRT machine. However, they will all receive training to homogenize the intervention process.

By involving both hospitals, it is feasible to achieve the required sample size (254) in 2 years, which is not considered to be a very long period.

In this clinical trial, there is not an extra tests or treatments in addition to those currently performed in routine clinical practice. All the electronic devices for the counting of the data and the elaboration of the statistical analysis will also be provided by the same hospital.

Although deaths will be the main cause of losses during the study, we do not expect significant rejections to participate since the treatment will not differ from the usual clinical practice. We have calculated a high dropout rate of 30% in the sample calculation.

In conclusion, we believe that this study meets all the criteria for execution, including study location, required study population, and expected costs.

15. BIBLIOGRAPHY

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA [Internet]. 2016 Feb 23 [cited 2023 Nov 23];315(8):801–10. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2016.0287
2. on behalf of the Group of Biomedical Research in Critical Care Medicine (BioCritic), Álvaro-Meca A, Jiménez-Sousa MA, Micheloud D, Sánchez-Lopez A, Heredia-Rodríguez M, et al. Epidemiological trends of sepsis in the twenty-first century (2000–2013): an analysis of incidence, mortality, and associated costs in Spain. Popul Health Metr [Internet]. 2018 Dec [cited 2023 Nov 29];16(1):1–11. Available from: https://pophealthmetrics.biomedcentral.com/articles/10.1186/s12963-018-0160-x
3. SOCMIC (Catalonian Critical Care Society) Sepsis Working Group, Yébenes JC, Ruiz-Rodriguez JC, Ferrer R, Clèries M, Bosch A, et al. Epidemiology of sepsis in Catalonia: analysis of incidence and outcomes in a European setting. Ann Intensive Care [Internet]. 2017 Dec [cited 2023 Nov 29];7(1):1–10. Available from: http://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-017-0241-1
4. Yébenes JC, Lorencio C, Esteban E, Espinosa L, Badia JM, Capdevila JA, et al. Interhospital sepsis code in Catalonia (Spain): territorial model for initial care of patients with sepsis. Med Intensiva Engl Ed [Internet]. 2020 Jan [cited 2023 Nov 29];44(1):36–45. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2173572719301705
5. Tsantes AG, Parastatidou S, Tsantes EA, Bonova E, Tsante KA, Mantzios PG, et al. Sepsis-Induced Coagulopathy: An Update on Pathophysiology, Biomarkers, and Current Guidelines. Life [Internet]. 2023 Jan 28 [cited 2023 Dec 3];13(2):1–16. Available from: https://www.mdpi.com/2075-1729/13/2/350
6. Opal SM. Endotoxins and Other Sepsis Triggers. In: Ronco C, Piccinni P, Rosner MH, editors. Contributions to Nephrology [Internet]. S. Karger AG; 2010 [cited 2024 Jan 3]. p. 14–24. Available from: https://www.karger.com/Article/FullText/315915
7. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent JL. Sepsis and septic shock. Nat Rev Dis Primer [Internet]. 2016 Jun 30 [cited 2023 Nov 29];2(1):1–21. Available from: https://www.nature.com/articles/nrdp201645
8. Jarczak D, Kluge S, Nierhaus A. Sepsis—Pathophysiology and Therapeutic Concepts. Front Med [Internet]. 2021 May 14 [cited 2023 Nov 29];8:1–22. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2021.628302/full
9. Boeddha NP, Bycroft T, Nadel S, Hazelzet JA. The Inflammatory and Hemostatic Response in Sepsis and Meningococcemia. Crit Care Clin [Internet]. 2020 Apr [cited 2023 Dec 3];36(2):391–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0749070419301009
10. Tamayo E, Fernández A, Almansa R, Carrasco E, Heredia M, Lajo C, et al. Pro- and anti-inflammatory responses are regulated simultaneously from the first moments of septic shock. Eur Cytokine Netw [Internet]. 2011 Jun [cited 2023 Nov 30];22(2):82–7. Available from: http://www.john-libbey-eurotext.fr/medline.md?doi=10.1684/ecn.2011.0281
11. Toussaint S, Herwig G. Activated Protein C for Sepsis. N Engl J Med [Internet]. 2009 Dec 31 [cited 2024 Jan 19];361(27):2646–52. Available from: https://doi.org/10.1056/NEJMct0808063
12. Sungurlu S, Kuppy J, Balk RA. Role of Antithrombin III and Tissue Factor Pathway in the Pathogenesis of Sepsis. Crit Care Clin [Internet]. 2020 Apr [cited 2023 Dec 3];36(2):255–65. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0749070419300971
13. Levi M, De Jonge E, Van Der Poll T. New treatment strategies for disseminated intravascular coagulation based on current understanding of the pathophysiology. Ann Med [Internet]. 2004 Jan [cited 2023 Dec 11];36(1):41–9. Available from:

http://www.tandfonline.com/doi/full/10.1080/07853890310017251
14. Bergmann S, Hammerschmidt S. Fibrinolysis and host response in bacterial infections. Thromb Haemost [Internet]. 2007 Sep [cited 2023 Dec 3];98(3):512–20. Available from: https://www.thieme-connect.com/products/ejournals/abstract/10.1160/TH07-02-0117
15. Guo RF, Ward PA. ROLE OF C5A IN INFLAMMATORY RESPONSES. Annu Rev Immunol [Internet]. 2005 Apr 1 [cited 2023 Dec 11];23(1):821–52. Available from: https://www.annualreviews.org/doi/10.1146/annurev.immunol.23.021704.115835
16. Ward PA. The Harmful Role of C5a on Innate Immunity in Sepsis. J Innate Immun [Internet]. 2010 [cited 2023 Dec 11];2(5):439–45. Available from: https://www.karger.com/Article/FullText/317194
17. Delano MJ, Scumpia PO, Weinstein JS, Coco D, Nagaraj S, Kelly-Scumpia KM, et al. MyD88-dependent expansion of an immature GR-1+CD11b+ population induces T cell suppression and Th2 polarization in sepsis. J Exp Med [Internet]. 2007 Jun 11 [cited 2023 Dec 11];204(6):1463–74. Available from: https://rupress.org/jem/article/204/6/1463/46956/MyD88-dependent-expansion-of-an-immature-GR-1
18. Park SH, Park BG, Park CJ, Kim S, Kim DH, Jang S, et al. An extended leukocyte differential count (16 types of circulating leukocytes) using the cytodiff flow cytometric system can provide informations for the discrimination of sepsis severity and prediction of outcome in sepsis patients: Extended WBC Differential Counts in Sepsis Patients. Cytometry B Clin Cytom [Internet]. 2014 Jul [cited 2023 Dec 11];86(4):244–56. Available from: http://doi.wiley.com/10.1002/cytob.21123
19. Drewry AM, Samra N, Skrupky LP, Fuller BM, Compton SM, Hotchkiss RS. Persistent Lymphopenia After Diagnosis of Sepsis Predicts Mortality. Shock [Internet]. 2014 Nov [cited 2023 Dec 11];42(5):383–91. Available from: https://journals.lww.com/00024382-201411000-00002
20. Hotchkiss RS, Levy JH, Levi M. Sepsis-Induced Disseminated Intravascular Coagulation, Symmetrical Peripheral Gangrene, and Amputations: Crit Care Med [Internet]. 2013 Oct [cited 2023 Dec 11];41(10):e290–1. Available from: http://journals.lww.com/00003246-201310000-00046
21. Zhang Y, Li J, Lou J, Zhou Y, Bo L, Zhu J, et al. Upregulation of programmed death-1 on T cells and programmed death ligand-1 on monocytes in septic shock patients. Crit Care [Internet]. 2011 [cited 2023 Dec 11];15(1):1–9. Available from: http://ccforum.biomedcentral.com/articles/10.1186/cc10059
22. Krautz C, Maier SL, Brunner M, Langheinrich M, Giamarellos-Bourboulis EJ, Gogos C, et al. Reduced circulating B cells and plasma IgM levels are associated with decreased survival in sepsis - A meta-analysis. J Crit Care [Internet]. 2018 Jun [cited 2024 Jan 5];45:71–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S088394411731688X
23. Bermejo-Martin JF, Andaluz-Ojeda D, Almansa R, Gandía F, Gómez-Herreras JI, Gomez-Sanchez E, et al. Defining immunological dysfunction in sepsis: A requisite tool for precision medicine. J Infect [Internet]. 2016 May [cited 2024 Jan 5];72(5):525–36. Available from: https://linkinghub.elsevier.com/retrieve/pii/S016344531600027X
24. Tomashefski JF. PULMONARY PATHOLOGY OF ACUTE RESPIRATORY DISTRESS SYNDROME. Clin Chest Med [Internet]. 2000 Sep [cited 2023 Dec 13];21(3):435–66. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272523105701581
25. Cardinal-Fernández P, Lorente JA, Ballén-Barragán A, Matute-Bello G. Acute Respiratory Distress Syndrome and Diffuse Alveolar Damage. New Insights on a Complex Relationship. Ann Am Thorac Soc [Internet]. 2017 Jun [cited 2023 Dec 13];14(6):844–50. Available from: https://www.atsjournals.org/doi/10.1513/AnnalsATS.201609-728PS
26. Rios F, Iscar T, Cardinal-Fernández P. What every intensivist should know about acute respiratory distress syndrome and diffuse alveolar damage. Rev Bras Ter Intensiva [Internet]. 2017 [cited 2023 Dec 13];29(3):354–63. Available from:

http://www.gnresearch.org/doi/10.5935/0103-507X.20170044
27. Nuckton TJ, Pittet JF, Alonso JA, Kallet RH. Pulmonary Dead-Space Fraction as a Risk Factor for Death in the Acute Respiratory Distress Syndrome. N Engl J Med [Internet]. 2002 Apr 25 [cited 2023 Dec 13];346(17):1281–6. Available from: https://doi.org/10.1056/NEJMoa012835
28. Geri G, Vignon P, Aubry A, Fedou AL, Charron C, Silva S, et al. Cardiovascular clusters in septic shock combining clinical and echocardiographic parameters: a post hoc analysis. Intensive Care Med [Internet]. 2019 May [cited 2024 Jan 4];45(5):657–67. Available from: http://link.springer.com/10.1007/s00134-019-05596-z
29. A Potz B, Sellke FW, Abid MR. Endothelial ROS and Impaired Myocardial Oxygen Consumption in Sepsis-induced Cardiac Dysfunction. J Intensive Crit Care [Internet]. 2016 [cited 2024 Jan 4];02(01):1–8. Available from: http://criticalcare.imedpub.com/endothelial-ros-and-impaired-myocardial-oxygen-consumption-in-sepsisinduced-cardiac-dysfunction.php?aid=8673
30. Font MD, Thyagarajan B, Khanna AK. Sepsis and Septic Shock – Basics of diagnosis, pathophysiology and clinical decision making. Med Clin North Am [Internet]. 2020 Jul [cited 2024 Jan 4];104(4):573–85. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0025712520300195
31. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care: Crit Care Med [Internet]. 2001 Jul [cited 2024 Jan 4];29(7):1303–10. Available from: http://journals.lww.com/00003246-200107000-00002
32. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med [Internet]. 2021 Nov [cited 2024 Jan 18];47(11):1181–247. Available from: https://link.springer.com/10.1007/s00134-021-06506-y
33. Nesseler N, Launey Y, Aninat C, Morel F, Mallédant Y, Seguin P. Clinical review: The liver in sepsis. Crit Care [Internet]. 2012 [cited 2024 Jan 10];16(5):1–8. Available from: http://ccforum.biomedcentral.com/articles/10.1186/cc11381
34. Brierre S, Deboisblanc BP, Kumari R. The Endocrine System during Sepsis. Am J Med Sci [Internet]. 2004 Oct [cited 2024 Jan 5];328(4):238–47. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002962915339781
35. Sharshar T, Blanchard A, Paillard M, Raphael JC, Gajdos P, Annane D. Circulating vasopressin levels in septic shock: Crit Care Med [Internet]. 2003 Jun [cited 2024 Jan 5];31(6):1752–8. Available from: http://journals.lww.com/00003246-200306000-00024
36. White LE, Hassoun HT, Bihorac A, Moore LJ, Sailors RM, McKinley BA, et al. Acute kidney injury is surprisingly common and a powerful predictor of mortality in surgical sepsis. J Trauma Acute Care Surg [Internet]. 2013 Sep [cited 2023 Dec 21];75(3):432–8. Available from: https://journals.lww.com/01586154-201309000-00013
37. Mehta RL, Pascual MT, Soroko S, Savage BR, Himmelfarb J, Ikizler TA, et al. Spectrum of acute renal failure in the intensive care unit: The PICARD experience. Kidney Int [Internet]. 2004 Oct [cited 2023 Dec 21];66(4):1613–21. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0085253815502329
38. Venkataraman R, Kellum JA. Acute renal failure in the critically ill. Curr Opin Anaesthesiol [Internet]. 2005 Apr [cited 2023 Dec 21];18(2):117–22. Available from: https://journals.lww.com/co-anesthesiology/abstract/2005/04000/acute_renal_failure_in_the_critically_ill.3.aspx
39. Program to Improve Care in Acute Renal Disease (PICARD) Study Group, Mehta RL, Bouchard J, Soroko SB, Ikizler TA, Paganini EP, et al. Sepsis as a cause and consequence of acute kidney injury: Program to Improve Care in Acute Renal Disease. Intensive Care Med [Internet]. 2011 Feb [cited 2023 Dec 21];37(2):241–8. Available from: http://link.springer.com/10.1007/s00134-010-2089-9

40. Peerapornratana S, Manrique-Caballero CL, Gómez H, Kellum JA. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. Kidney Int [Internet]. 2019 Nov [cited 2023 Nov 23];96(5):1083–99. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0085253819306015
41. Kellum JA, Chawla LS, Keener C, Singbartl K, Palevsky PM, Pike FL, et al. The Effects of Alternative Resuscitation Strategies on Acute Kidney Injury in Patients with Septic Shock. Am J Respir Crit Care Med [Internet]. 2016 Feb 1 [cited 2024 Jan 12];193(3):281–7. Available from: https://www.atsjournals.org/doi/10.1164/rccm.201505-0995OC
42. Manrique-Caballero CL, Del Rio-Pertuz G, Gomez H. Sepsis-Associated Acute Kidney Injury. Crit Care Clin [Internet]. 2021 Apr [cited 2024 Jan 12];37(2):279–301. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0749070420301159
43. Prowle JR, Molan MP, Hornsey E, Bellomo R. Measurement of renal blood flow by phase-contrast magnetic resonance imaging during septic acute kidney injury: A pilot investigation. Crit Care Med [Internet]. 2012 Jun [cited 2023 Dec 21];40(6):1768–76. Available from: http://journals.lww.com/00003246-201206000-00011
44. Mendonça A, Cantraine F, Thijs L, Takala J, Sprung C, Antonelli M, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Intensive Care Med [Internet]. 1999 Jul [cited 2024 Jan 8];25(7):686–96. Available from: https://rdcu.be/dwpJL
45. Lambden S, Laterre PF, Levy MM, Francois B. The SOFA score—development, utility and challenges of accurate assessment in clinical trials. Crit Care [Internet]. 2019 Dec [cited 2024 Jan 4];23(1):1–9. Available from: https://ccforum.biomedcentral.com/articles/10.1186/s13054-019-2663-7
46. Vincent JL, Moreno R, Takala J, Willatts S, Mendonça A. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med [Internet]. 1996 Jul [cited 2023 Nov 23];22(7):707–10. Available from: https://link.springer.com/article/10.1007/BF01709751
47. for China Critical Care Clinical Trials Group (CCCCTG), Tian H, Zhou J, Weng L, Hu X, Peng J, et al. Accuracy of qSOFA for the diagnosis of sepsis-3: a secondary analysis of a population-based cohort study. J Thorac Dis [Internet]. 2019 May [cited 2024 Jan 11];11(5):2034–42. Available from: http://jtd.amegroups.com/article/view/28675/21255
48. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA [Internet]. 2016 Feb 23 [cited 2024 Jan 11];315(8):762–74. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2016.0288
49. Marshall JC, Maier RV, Jimenez M, Dellinger EP. Source control in the management of severe sepsis and septic shock: An evidence-based review: Crit Care Med [Internet]. 2004 Nov [cited 2024 Jan 18];32(Supplement):S513–26. Available from: http://journals.lww.com/00003246-200411001-00007
50. Lynn WA, Cohen J. Microbiological Requirements for Studies of Sepsis. In: Vincent JL, Sibbald WJ, editors. Clinical Trials for the Treatment of Sepsis [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 1995 [cited 2024 Jan 18]. p. 71–85. (Vincent JL, editor. Update in Intensive Care and Emergency Medicine; vol. 19). Available from: https://link.springer.com/10.1007/978-3-642-79224-3_5
51. Levy MM, Rhodes A, Phillips GS, Townsend SR, Schorr CA, Beale R, et al. Surviving Sepsis Campaign: Association Between Performance Metrics and Outcomes in a 7.5-Year Study. Crit Care Med [Internet]. 2015 Jan [cited 2024 Jan 8];43(1):3–12. Available from: http://journals.lww.com/00003246-201501000-00002
52. Khwaja A. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. Nephron Clin Pract [Internet]. 2012 Aug 7 [cited 2024 Jan 12];120(4):c179–84. Available from: https://www.karger.com/Article/FullText/339789

53. Fee JA, Phillips WD. The behavior of holo- and apo-forms of bovine superoxide dismutase at low pH. Biochim Biophys Acta. 1975 Nov 18;412(1):26–38.
54. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, et al. Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis. N Engl J Med [Internet]. 2012 Jul 12 [cited 2024 Jan 12];367(2):124–34. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa1204242
55. Ajit Kumar, Fatima Anjum. Ventilator-Induced Lung Injury (VILI). In: Ventilator-Induced Lung Injury (VILI) [Internet]. StatPearls. Treasure Island (FL): StatPearls [Internet]; 2023 [cited 2024 Jan 13]. p. 1–5. Available from: https://www.ncbi.nlm.nih.gov/books/NBK563244/
56. Mega C, Cavalli I, Ranieri VM, Tonetti T. Protective ventilation in patients with acute respiratory distress syndrome related to COVID-19: always, sometimes or never? Curr Opin Crit Care [Internet]. 2022 Feb [cited 2024 Jan 13];28(1):51–6. Available from: https://journals.lww.com/10.1097/MCC.0000000000000904
57. Atul Malhotra. Ut To Date. In: Prone ventilation for adult patients with acute respiratory distress syndrome [Internet]. California, San Diego: Up To Date; 2023 [cited 2024 Jan 17]. p. 1–3. Available from: https://www.uptodate.com/contents/prone-ventilation-for-adult-patients-with-acute-respiratory-distress-syndrome
58. Claure-Del Granado R, Clark WR. Continuous renal replacement therapy principles. Semin Dial [Internet]. 2021 Nov [cited 2024 Jan 13];34(6):398–405. Available from: https://onlinelibrary.wiley.com/doi/10.1111/sdi.12967
59. Alves De Queiroz C, Rodrigues Bacci M. Influence of early hemodialysis on the septic acute kidney injury outcome. Rev Esc Enferm USP [Internet]. 2022 [cited 2024 Jan 13];56:1–6. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0080-62342022000100498&tlng=en
60. Trotman RL, Williamson JC, Shoemaker DM, Salzer WL. Antibiotic Dosing in Critically Ill Adult Patients Receiving Continuous Renal Replacement Therapy. Clin Infect Dis [Internet]. 2005 Oct 15 [cited 2024 Jan 16];41(8):1159–66. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1086/444500
61. Gaudry S, Palevsky PM, Dreyfuss D. Extracorporeal Kidney-Replacement Therapy for Acute Kidney Injury. Ingelfinger JR, editor. N Engl J Med [Internet]. 2022 Mar 10 [cited 2024 Jan 15];386(10):964–75. Available from: http://www.nejm.org/doi/10.1056/NEJMra2104090
62. Bellomo R, Ronco C, Mehta RL. Nomenclature for Continuous Renal Replacement Therapies. Am J Kidney Dis [Internet]. 1996 Nov [cited 2024 Jan 13];28(5):S2–3. Available from: https://www.ajkd.org/article/S0272-6386%2896%2990073-6/fulltext
63. Schetz M. Non-renal indications for continuous renal replacement therapy. Kidney Int Suppl. 1999 Nov;(72):S88-94.
64. Tandukar S, Palevsky PM. Continuous Renal Replacement Therapy. Chest [Internet]. 2019 Mar [cited 2024 Jan 14];155(3):626–38. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0012369218324784
65. Macedo E, Mehta RL. Continuous Dialysis Therapies: Core Curriculum 2016. Am J Kidney Dis [Internet]. 2016 Oct [cited 2024 Jan 14];68(4):645–57. Available from: https://linkinghub.elsevier.com/retrieve/pii/S027263861630097X
66. Alvarez G, Chrusch C, Hulme T, Posadas-Calleja JG. Renal replacement therapy: a practical update. Can J Anesth Can Anesth [Internet]. 2019 May [cited 2024 Jan 14];66(5):593–604. Available from: http://link.springer.com/10.1007/s12630-019-01306-x
67. Karkar A. Continuous renal replacement therapy: Principles, modalities, and prescription. Saudi J Kidney Dis Transplant [Internet]. 2019 [cited 2024 Jan 15];30(6):1201. Available from: https://journals.lww.com/10.4103/1319-2442.275463
68. Kellum JA, Lameire N, editors. KDIGO Clinical Practice Guideline for Acute Kidney Injury.

Kidney Int Suppl [Internet]. 2012 Mar [cited 2024 Jan 15];2(1):1–141. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2157171615310388
69. Donato D, Storr M, Krause B. Design optimization of hollow fiber dialyzers to enhance internal filtration based on a mathematical model. J Membr Sci [Internet]. 2020 Mar [cited 2024 Jan 15];598:117–690. Available from: https://linkinghub.elsevier.com/retrieve/pii/S037673881933220X
70. Li Y, Sun P, Chang K, Yang M, Deng N, Chen S, et al. Effect of Continuous Renal Replacement Therapy with the oXiris Hemofilter on Critically Ill Patients: A Narrative Review. J Clin Med [Internet]. 2022 Nov 13 [cited 2023 Nov 23];11(22):1–17. Available from: https://www.mdpi.com/2077-0383/11/22/6719
71. Thomas M, Moriyama K, Ledebo I. AN69: Evolution of the World's First High Permeability Membrane. In: Saito A, Kawanishi H, Yamashita AC, Mineshima M, editors. Contributions to Nephrology [Internet]. S. Karger AG; 2011 [cited 2024 Jan 15]. p. 119–29. Available from: https://www.karger.com/Article/FullText/328961
72. Verresen L, Fink E, Lemke HD, Vanrenterghem Y. Bradykinin is a mediator of anaphylactoid reactions during hemodialysis with AN69 membranes. Kidney Int [Internet]. 1994 May [cited 2024 Jan 15];45(5):1497–503. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0085253815584767
73. Guan M, Wang H, Tang X, Zhao Y, Wang F, Zhang L, et al. Continuous Renal Replacement Therapy With Adsorbing Filter oXiris in Acute Kidney Injury With Septic Shock: A Retrospective Observational Study. Front Med [Internet]. 2022 Apr 8 [cited 2023 Nov 23];9:1–10. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2022.789623/full
74. Zhang L, Cove M, Nguyen BG, Lumlertgul N, Ganesh K, Chan A, et al. Adsorptive hemofiltration for sepsis management: expert recommendations based on the Asia Pacific experience. Chin Med J (Engl) [Internet]. 2021 Sep 20 [cited 2024 Jan 15];134(18):2258–60. Available from: https://journals.lww.com/10.1097/CM9.0000000000001671
75. Broman ME, Hansson F, Vincent JL, Bodelsson M. Endotoxin and cytokine reducing properties of the oXiris membrane in patients with septic shock: A randomized crossover double-blind study. Dal Pizzol F, editor. PLOS ONE [Internet]. 2019 Aug 1 [cited 2024 Jan 15];14(8):1–14. Available from: https://dx.plos.org/10.1371/journal.pone.0220444
76. Raina R, Mawby I, Datla N, Chakraborty R, Mehra K, Singh S, et al. The Emergency Use of the oXiris Device with Continuous Kidney Replacement Therapy in COVID-19 Patients with Acute Kidney Injury. Arch Clin Biomed Res [Internet]. 2021 [cited 2024 Jan 15];05(04):629–39. Available from: https://www.fortunejournals.com/articles/the-emergency-use-of-the-oxiris-device-with-continuous-kidney-replacement-therapy-in-covid19-patients-with-acute-kidney-injury.html
77. Rimmele T, Assadi A, Cattenoz M, Desebbe O, Lambert C, Boselli E, et al. High-volume haemofiltration with a new haemofiltration membrane having enhanced adsorption properties in septic pigs. Nephrol Dial Transplant [Internet]. 2008 Nov 7 [cited 2024 Jan 15];24(2):421–7. Available from: https://academic.oup.com/ndt/article-lookup/doi/10.1093/ndt/gfn518
78. Malard B, Lambert C, Kellum JA. In vitro comparison of the adsorption of inflammatory mediators by blood purification devices. Intensive Care Med Exp [Internet]. 2018 Dec [cited 2024 Jan 15];6(1):1–13. Available from: https://icm-experimental.springeropen.com/articles/10.1186/s40635-018-0177-2
79. Turani F, Barchetta R, Falco M, Busatti S, Weltert L. Continuous Renal Replacement Therapy with the Adsorbing Filter oXiris in Septic Patients: A Case Series. Blood Purif [Internet]. 2019 [cited 2024 Jan 15];47(Suppl. 3):54–8. Available from: https://www.karger.com/Article/FullText/499589
80. Lumlertgul N, Srisawat N. The haemodynamic effects of oXiris haemofilter in septic shock

patients requiring renal support: A single-centre experience. Int J Artif Organs [Internet]. 2021 Jan [cited 2024 Jan 15];44(1):17–24. Available from: http://journals.sagepub.com/doi/10.1177/0391398820917150
81. Zhai Y, Pan J, Zhang C. The application value of oXiris-endotoxin adsorption in sepsis. Am J Transl Res [Internet]. 2021 Apr 30 [cited 2023 Nov 23];13(4):3839–44. Available from: https://e-century.us/files/ajtr/13/4/ajtr0126267.pdf
82. Zhang L, Yan Tang GK, Liu S, Cai J, Chan WM, Yang Y, et al. Hemofilter with Adsorptive Capacities: Case Report Series. Blood Purif [Internet]. 2019 [cited 2024 Jan 15];47(Suppl. 3):45–50. Available from: https://www.karger.com/Article/FullText/499357
83. Zhou Y, Wu C, Ouyang L, Peng Y, Zhong D, Xiang X, et al. Application of oXiris-continuous hemofiltration adsorption in patients with sepsis and septic shock: A single-centre experience in China. Front Public Health [Internet]. 2022 Sep 29 [cited 2024 Jan 15];10:1–12. Available from: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1012998/full
84. Feng J, Zhang S, Ai T, Wang L, Gao Y, Li W, et al. Effect of CRRT with oXiris filter on hemodynamic instability in surgical septic shock with AKI: A pilot randomized controlled trial. Int J Artif Organs [Internet]. 2022 Oct [cited 2024 Jan 15];45(10):801–8. Available from: http://journals.sagepub.com/doi/10.1177/03913988221107947
85. Corona A, Veronese A, Santini S, Cattaneo D. "CATCH" Study: Correct Antibiotic Therapy in Continuous Hemofiltration in the Critically Ill in Continuous Renal Replacement Therapy: A Prospective Observational Study. Antibiotics [Internet]. 2022 Dec 13 [cited 2024 Jan 15];11(12):1–17. Available from: https://www.mdpi.com/2079-6382/11/12/1811
86. Li L, Li X, Xia Y, Chu Y, Zhong H, Li J, et al. Recommendation of Antimicrobial Dosing Optimization During Continuous Renal Replacement Therapy. Front Pharmacol. 2020;11(29):1–16.
87. Prowle JR, Bellomo R. Continuous renal replacement therapy: recent advances and future research. Nat Rev Nephrol [Internet]. 2010 Sep [cited 2024 Jan 17];6(9):521–9. Available from: https://www.nature.com/articles/nrneph.2010.100
88. Gautam SC, Lim J, Jaar BG. Complications Associated with Continuous RRT. Kidney360 [Internet]. 2022 Nov 24 [cited 2024 Jan 16];3(11):1980–90. Available from: https://journals.lww.com/10.34067/KID.0000792022
89. Kovvuru K, Velez JCQ. Complications associated with continuous renal replacement therapy. Semin Dial [Internet]. 2021 Nov [cited 2024 Jan 16];34(6):489–94. Available from: https://onlinelibrary.wiley.com/doi/10.1111/sdi.12970
90. Poston JT, Koyner JL. Sepsis associated acute kidney injury. Br Med J Publ Group [Internet]. 2019 [cited 2024 Jan 23];364:1–17. Available from: https://www.bmj.com/content/364/bmj.k4891
91. Stegmayr B, Abdel-Rahman EM, Balogun RA. Septic Shock With Multiorgan Failure: From Conventional Apheresis to Adsorption Therapies. Semin Dial [Internet]. 2012 Mar [cited 2024 Jan 23];25(2):171–5. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1525-139X.2011.01029.x
92. Hellman T, Uusalo P, Järvisalo MJ. Renal Replacement Techniques in Septic Shock. Int J Mol Sci [Internet]. 2021 Sep 23 [cited 2024 Jan 23];22(19):10238. Available from: https://www.mdpi.com/1422-0067/22/19/10238
93. Wang G, He Y, Guo Q, Zhao Y, He J, Chen Y, et al. Continuous renal replacement therapy with the adsorptive oXiris filter may be associated with the lower 28-day mortality in sepsis: a systematic review and meta-analysis. Crit Care [Internet]. 2023 Jul 9 [cited 2024 Jan 20];27(1):275. Available from: https://ccforum.biomedcentral.com/articles/10.1186/s13054-023-04555-x
94. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis [Internet].

1987 Jan [cited 2023 Dec 19];40(5):373–83. Available from: https://linkinghub.elsevier.com/retrieve/pii/0021968187901718
95. Halfon P, Eggli Y, Van Melle G, Chevalier J, Wasserfallen JB, Burnand B. Measuring potentially avoidable hospital readmissions. J Clin Epidemiol [Internet]. 2002 Jun [cited 2024 Jan 3];55(6):573–87. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0895435601005212
96. Caliri AW, Tommasi S, Besaratinia A. Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. Mutat Res Mutat Res [Internet]. 2021 Jan [cited 2024 Jan 9];787:1–21. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1383574221000028
97. Purkayastha A, Sen C, Garcia G, Langerman J, Shia DW, Meneses LK, et al. Direct Exposure to SARS-CoV-2 and Cigarette Smoke Increases Infection Severity and Alters the Stem Cell-Derived Airway Repair Response. Cell Stem Cell [Internet]. 2020 Dec [cited 2024 Jan 9];27(6):869-875.e4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1934590920305488
98. Zhang N, Liu Y, Yang C, Zeng P, Gong T, Tao L, et al. Association between smoking and risk of death in patientswith sepsis: A systematic review and meta-analysis. Tob Induc Dis [Internet]. 2022 Jul 15 [cited 2024 Jan 9];20(July):1–9. Available from: http://www.tobaccoinduceddiseases.org/Association-between-smoking-and-risk-of-death-in-patients-nwith-sepsis-A-systematic,150340,0,2.html
99. Alroumi F, Abdul Azim A, Kergo R, Lei Y, Dargin J. The impact of smoking on patient outcomes in severe sepsis and septic shock. J Intensive Care [Internet]. 2018 Dec [cited 2024 Jan 9];6(1):1–11. Available from: https://jintensivecare.biomedcentral.com/articles/10.1186/s40560-018-0312-x
100. Ethanol Consumption and Sepsis: Mechanisms of Organ Damage. J Cell Signal [Internet]. 2021 Dec 31 [cited 2024 Jan 9];2(4):235–41. Available from: https://www.scientificarchives.com/article/ethanol-consumption-and-sepsis-mechanisms-of-organ-damage
101. Campaña 2007: El alcohol te destroza por partida doble. In: Sanidad.gob.es [Internet]. Madrid: Ministerio de Sanidad; 2007 [cited 2024 Jan 9]. Available from: https://www.sanidad.gob.es/campannas/campanas07/alcoholmenores9.htm
102. McHenry RD, Moultrie CEJ, Quasim T, Mackay DF, Pell JP. Association Between Socioeconomic Status and Outcomes in Critical Care: A Systematic Review and Meta-Analysis. Crit Care Med [Internet]. 2023 Mar [cited 2024 Jan 10];51(3):347–56. Available from: https://journals.lww.com/10.1097/CCM.0000000000005765
103. Domingo Salvany A, Alonso JM. Propuesta de un indicador de la 'clase social' basado en la ocupación. Gaceta Sanitaria [Internet]. 1989 Feb [cited 2023 Dec 12];3(10):320–6. Available from: https://www.gacetasanitaria.org/es-pdf-S0213911189709481
104. Guo Q, Qu P, Cui W, Liu M, Zhu H, Chen W, et al. Organism type of infection is associated with prognosis in sepsis: an analysis from the MIMIC-IV database. BMC Infect Dis [Internet]. 2023 Jun 26 [cited 2024 Jan 10];23(1):1–11. Available from: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-023-08387-6
105. Pradipta I, Sodik D, Parwati I, Lestari K, Halimah E, Diantini A, et al. Antibiotic resistance in sepsis patients: Evaluation and recommendation of antibiotic use. North Am J Med Sci [Internet]. 2013 [cited 2024 Jan 10];5(6):344–52. Available from: http://www.najms.org/text.asp?2013/5/6/344/114165
106. López-Pueyo MJ, Barcenilla-Gaite F, Amaya-Villar R, Garnacho-Montero J. Antibiotic multiresistance in critical care units. Med Intensiva Engl Ed [Internet]. 2011 Jan [cited 2024 Jan 10];35(1):41–53. Available from: https://linkinghub.elsevier.com/retrieve/pii/S217357271170008X
107. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international

expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect [Internet]. 2012 Mar [cited 2024 Jan 20];18(3):268–81. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1198743X14616323
108. National Antimicrobial Resistance Monitoring System (NARMS). In: Glossary of Terms Related to Antibiotic Resistance [Internet]. USA: Center for Disease Control and Prevention; 2019 [cited 2024 Jan 20]. p. 1–3. Available from: https://www.cdc.gov/narms/resources/glossary.html
109. Wagner DP, Draper EA, Abizanda Campos R, Nikki P, Roger Le Gall J, Loirat P, et al. Initial International Use of APACHE: An Acute Severity of Disease Measure. Med Decis Making [Internet]. 1984 Aug [cited 2024 Jan 10];4(3):297–313. Available from: http://journals.sagepub.com/doi/10.1177/0272989X8400400305
110. Akhoundi A, Singh B, Vela M, Chaudhary S, Monaghan M, Wilson GA, et al. Incidence of Adverse Events during Continuous Renal Replacement Therapy. Blood Purif [Internet]. 2015 [cited 2024 Jan 16];39(4):333–9. Available from: https://www.karger.com/Article/FullText/380903
111. Hoste EAJ, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med [Internet]. 2015 Aug [cited 2023 Nov 23];41(8):1411–23. Available from: http://link.springer.com/10.1007/s00134-015-3934-7
112. Uchino S. Acute Renal Failure in Critically Ill PatientsA Multinational, Multicenter Study. Am Med Assoc [Internet]. 2005 Aug 17 [cited 2024 Jan 23];294(7):813–8. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.294.7.813
113. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing Sepsis as a Global Health Priority — A WHO Resolution. N Engl J Med [Internet]. 2017 Aug 3 [cited 2024 Jan 23];377(5):414–7. Available from: http://www.nejm.org/doi/10.1056/NEJMp1707170

16. ANNEXES

16.1 ANNEX 1 - GLASGOW COMA SCALE

DOMAIN	RESPONSE	SCORE
EYE-OPENING RESPONSE	Eyes open spontaneously	4
	Eyes opening to sound	3
	Eyes opening to pain	2
	No eye opening	1
VERBAL RESPONSE	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No verbal response	1
MOTOR RESPONSE	Obey commands	6
	Localizing pain	5
	Normal flexion	4
	Abnormal flexion to pain	3
	Abnormal extension to pain	2
	No motor response	1
TOTAL SCORE GCS	**MILD INJURY**	**13-15**
	MODERATE INJURY	**9-12**
	SEVERE INJURY	**3-8**

16.2 ANNEX 2 - KINDEY DISEASE: IMPROVING GLOBAL OUTCOMES (KDIGO)

AKI STAGE	SERUM CREATININE (SCr)	URINE OUTPUT
1	1.5–1.9 times baseline OR ≥0.3 mg/dl (>26.5 µmol/l) increase	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3.0 times baseline OR Increase in SCr to ≥4.0 mg/dl (353.6 µmol/l) OR Initiation of renal replacement therapy (RRT) OR In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m2	<0.3 ml/kg/h for ≥24 h OR Anuria for ≥12 h

Minimum criteria for acute kidney injury include an increase in SCr by ≥ 0.3 mg/dl (>26.5 µmol/l) observed within 48 h; or an increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/h for 6 h

16.3 Annex 3 - CHARLSON COMORBIDITY INDEX

COMORBID CONDITIONS	SCORE
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatic disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes without chronic complication	1
Diabetes with chronic complication	2
Hemiplegia or paraplegia	2
Renal disease	2
Any malignancy without metastasis	2
Leukemia	2
Lymphoma	2
Moderate to severe liver disease	3
Metastatic solid tumour	6
AIDS (excluded asymptomatic infection)	6
Maximum comorbidity score	33

16.4 ANNEX 4 - APACHE II (ACUTE PHYSIOLOGIC AND CHRONIC HEALTH EVALUATION)

(A) ACUTE PHYSIOLOGICAL SCORE

	HIGH ABNORMAL RANGE				NORMAL RANGE	LOW ABNORMAL RANGE			
APS	4	3	2	1	0	1	2	3	4
RECTAL TEMPERATURE (ºc)	≥41	39-40,9	-	38,5-38,9	34-38,4	34-35,9	32-33,9	30-31,9	≤29,0
MEAN ARTERIAL PRESSURE (mmHg)	≥169	130-159	110-129	-	70-109		50-69	-	<50
HEART RATE-VENTRICULAR RESPONSE (lpm)	≥180	140-179	110-129	-	70-109		55-69	40-54	<40
RESPIRATORY RATE (rpm)	≥50	35-49		25-34	12-24	10-11	6-9		<6
OXYGENATION – Fio_2 ≥0,5 (A-a DO_2) – Fio_2 ≤0,5 (PaO_2)	499	350-499	200-349		>200 <70	61-70		56-70	<56
ARTERIAL Ph	>7,9	7,60-7,69		7,50-7,59	7,33-7,49		7,25-7,32	7,15-7,24	<7,15
SERUM Na (mmol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	<111
SERUM K (mmol/L)	>6,9	6,0 – 6,9		5,5-5,9	3,5-5,4	3,0-3,4	2,5-2,9		<2,5
CREATININE (mg/dl)	>3,4	2,0-3,4	1,5-1,9		0,6-1,4		<0,6		
HAEMATOCRIT (%)	≥60		50-59,9	46-49,9	30-45,9		20-29,9		<20
WHITE BLOOD CELL COUNT (x1000/mm^3)	≥40		20-39,9	15-19,9	3-14,9		1-2,9		<1
TOTAL APS									

(B) GLASGW COMA SCALE

15- GCS	

(C) GLASGW COMA SCALE

AGE (in years)	POINTS
≤44	0
45-54	2
55-64	3
65-74	5
≥75	6

(D) PREVIOUS CHRONIC DISEASE

LIVER	2
CARDIOVASCULAR	2
RESPIRATORY: severe COPD, hypercapnia, home O_2, pulmonary hypertension	2
IMMUNOCOMPROMISED	2
RENAL: chronic dialysis	2

A SCORE for APS	B SCORE FOR GCS	C SCORE FOR AGE	D SCORE FOR PREVIOUS CHRONIC DISEASE

TOTAL APACHE II SCORE [A+B+C+D]	

16.5 ANNEX 5 - INFORMATION SHEET

FULL D'INFORMACIÓ ALS PACIENTS I FAMILIARS

NOM DE L'ESTUDI: *Impact on Delta SOFA score in Sepsis-Induced Acute Kidney Injury: A Comparative Study of Hemofilter Efficacy in Continuous Renal Replacement Therapy*
CENTRE ASSISTENCIAL:
INVESTIGADOR/A PRINCIPAL:

INTRODUCCIÓ

Benvolgut/da,

Ens dirigim a vostè per proposar-li participar en un estudi d'investigació dut a terme a les unitats de cures intensives (UCI) dels hospitals Hospital Universitari Doctor Josep Trueta i Hospital Santa Caterina.

L'estudi en qüestió ha estat aprovat pel Comitè d'Ètica i d'Investigació Clínica (CEIC) de tots els hospitals participants, d'acord amb la legislació vigent i respectant els principis enunciats a la Declaració de Hèlsinki.

El nostre objectiu és brindar-li la informació adequada i suficient perquè pugui prendre una decisió raonada i conscient sobre la seva participació en aquest estudi. És per aquest motiu que li preguem llegir detingudament aquest full informatiu i ens pregunti tots els dubtes que li puguin sorgir.

PARTICIPACIÓ VOLUNTÀRIA:

La participació en aquest estudi és completament voluntària, de forma que en qualsevol moment pot abandonar l'estudi i retirar el seu consentiment informat. En cap cas hi haurà cap tipus de repercussió en la relació amb el personal sanitari i la seva atenció sanitària.

OBJECTIU DE L'ESTUDI:

La sèpsia és una resposta inflamatòria generalitzada per l'organisme davant una infecció que provoca una disfunció dels òrgans, posant en perill la vida. És una malaltia amb elevada prevalença i mortalitat, que d'entre altres òrgans als quals afecta, pot acabar afectant els ronyons. Quan els ronyons comencen a fallar, els pacients requereixen de l'ajuda d'una màquina d'hemodiàlisi per tal que els purifiqui la sang, recollint les toxines que el cos no és capaç d'eliminar. Aquesta màquina passa la sang extreta del pacient per uns filtres que a part de netejar-la, retenen partícules inflamatòries que la sèpsia produeix. Actualment, s'estan portant

a terme estudis per determinar quins filtres son els més eficaços en pacients amb insuficiència renal per sèpsia.

L'objectiu d'aquest estudi és avaluar l'eficàcia de dos filtres diferents, els quals varien en qualitats i mecanismes de funcionament, per tal de saber quin dels dos tipus es més eficaç. L'objectiu és millorar la inestabilitat i fallada multiorgànica, millorar la supervivència i reduir els dies de requeriment de teràpies de suport i hospitalització.

DESCRIPCIÓ DE L'ESTUDI:

Aquest estudi es realitzarà als dos hospitals simultàniament i tindrà una durada de 1 any i mig. Durant l'ingrés a la UCI, es realitzaran les proves i el tractament que requereixi el pacient, s'aniran recollint les dades a mesura que el tractament avanci. Totes les proves i tractaments que es realitzin son els estàndards de la clínica habitual, l'únic factor que variarà serà quin tipus de filtre s'utilitza a la màquina.

BENEFICIS I RISCS DE LA PARTICIPACIÓ:

Amb la seva participació en aquest estudi contribuirà a l'ampliació del coneixement científic sobre la matèria d'estudi, facilitant així la possibilitat d'optimitzar els tractaments i de proporcionar recursos terapèutics per al benefici dels pacients en el futur.

Considerem que formar part d'aquest estudi no comporta riscos afegits, ja que la teràpia en estudi és la mateixa que es realitzaria en la clínica habitual.

CONFIDENCIALITAT I PROTECCIÓ DE DADES:

Tota la informació recollida sobre vostè durant l'estudi serà enregistrada en una base de dades amb un codi que assegura l'anonimat per a la seva anàlisi. El seu nom o qualsevol altra informació que pugui identificar-lo no apareixerà en cap document públic, i l'ús comercial d'aquestes dades està estrictament prohibit. En el cas que el participant vulgui abandonar l'estudi, les seves dades seran eliminades i en cap cas s'utilitzaran en l'estudi.

PARTICIPACIÓ I COMPENSACIÓ ECONÒMICA:

Cap membre de l'equip d'investigació d'aquest estudi rebrà benefici econòmic. La participació dels pacients és completament voluntària i, per tant, no rebran cap remuneració, i tampoc hi haurà cap despesa addicional per part seva.

NOTA PER ALS FAMILIARS:

Si vostè és un familiar que té la responsabilitat de prendre la decisió sobre la participació del pacient en l'estudi, tingui en compte que un cop el pacient estigui conscient i tingui la capacitat de decidir sobre el tema, se'l informarà sobre l'estudi clínic. En cas que desitgi continuar amb el projecte i que es faci ús de les seves dades per a l'estudi, haurà de signar un altre consentiment informat amb la seva pròpia decisió. En el cas que el pacient opti per no participar en l'estudi, les seves dades no seran utilitzades en l'anàlisi dels resultats de la investigació.

CONTACTE:

En cas de dubtes abans, durant o després de la realització d'aquest estudi, no dubti en posar-se en contacte amb l'equip investigador a través del següent correu: _____.

Moltes gràcies per l seva col·laboració.

Atentament,

L'equip investigador.

Signatura del pacient / familiar

Signatura de l'investigador

Data i lloc: _____(lloc), a dia _____ (dia / mes / any)

16.6 ANNEX 6 - INFORMED CONSENT

CONSENTIMENT INFORMAT

NOM DE L'ESTUDI: *Impact on Delta SOFA score in Sepsis-Induced Acute Kidney Injury: A Comparative Study of Hemofilter Efficacy in Continuous Renal Replacement Therapy*
CENTRE ASSISTENCIAL:
INVESTIGADOR/A PRINCIPAL:

Jo, _____ (nom i cognoms), amb document d'identificació personal (DNI/NIE) _____, afirmo que:

- He rebut una còpia del full informatiu i n'he llegida, he pogut realitzar preguntes que han sigut correctament i satisfactòriament resoltes
- He rebut informació suficient sobre l'estudi
- He parlat amb _____ (nom i cognoms de l'investigador)

Declaro també que la meva participació en l'estudi és voluntària, i comprenc que puc retirar-me de l'estudi:

- En qualsevol moment
- Sense haver de donar explicacions
- Sense que repercuteixi a la meva atenció sanitària

De conformitat amb el que estableix el Reglament (UE) 2016/679 del Parlament I del Consell, de 27 d'abril 2016, relatiu a la protecció de les persones físiques pel que fa al tractament de dades personals i a la lliure circulació d'aquestes: i les lleis nacionals, declaro haver estat informat/da de:

- L'existència d'una base de dades on s'inclouran les meves dades de caràcter personal
- De la finalitat de la seva recollida i dels destinataris de la informació
- Del procés de codificació i anonimització de les dades personals
- Del dret a la rectificació i cancel·lació de l'ús de les meves dades

Per tant, estic d'acord en que les meves dades resultants de la participació en el projecte siguin utilitzades exclusivament amb finalitats científiques.

En conseqüència, dono lliurement el meu consentiment per tal que _____ (nom i cognoms del pacient), amb DNI/NIE _____, participi en l'estudi.

Rebo una còpia firmada i datada del full d'informació sobre l'estudi i del consentiment informat per guardar-los i poder consultar-los en un futur.

Signatura del pacient / familiar

Signatura de l'investigador

Data i lloc: _____(lloc), a dia _____ (dia / mes / any).

16.7 ANNEX 7 - CASE REPORT FORM (CRF)

FORMULARI DE RECOLLIDA DE DADES DE L'ASSAIG CLÍNIC:

Impact on Delta SOFA score in Sepsis-Induced Acute Kidney Injury: A Comparative Study of Hemofilter Efficacy in Continuous Renal Replacement Therapy

INVESTIGADOR: _____

HOSPITAL: ☐ Hospital Universitari Josep Trueta / ☐ Hospital de Santa Caterina

DADES GENERALS DEL PACIENT

Número d'Identificació (ID): _____

Data de naixement: ___/___/_____

Edat: _____

Sexe: ☐ Dona / ☐ Home

Dia d'admissió al hospital: ___/___/_____

Dia d'admissió a la UCI: ___/___/_____

Box: _____

DADES A L'INGRÉS A UNITAT DE CURES INTENSIVES

ANTECEDENTS I MALALTIES CONCOMITANTS

APACHE II: _____

Estat d'immunodeficiència: ☐ Si / ☐ No

Índex de Comorbiditats de Charlson (ICC): _____

- ☐ Sense comorbiditats (0-1 punt)
- ☐ Comorbiditats lleus (2 punts)
- ☐ Comorbiditats severes (>3 punts)

Tabac:

- ☐ No fumador (Índex paquet/any de 0)
- ☐ Fumador lleu (≤20 paquet/any)
- ☐ Fumador moderat (21-40 paquet/any)
- ☐ Fumador sever (≥40 paquet/any)

Alcohol:

- ☐ No consumidor (<20g en dones i <40g en homes)
- ☐ Consumidor moderat 20-50g/dia en dones i 40-60g/dia en homes)
- ☐ Consumidor sever (>40g en dones i >60g en homes)

Estat socioeconòmic:

- ☐ Classe I: Directius de l'administració i les empreses. Alts funcionaris. Professionals liberals. Tècnics superiors.
- ☐ Classe II: Directius i propietaris-gerents del comerç i dels serveis personals. Altres tècnics (no superiors). Artistes i esportistes.

☐ Classe III: Càrrecs intermitjos. Administratius i funcionaris, en general. Personal dels serveis de protecció i seguretat.

☐ Classe IV: Treballadors manuals qualificats o semiqualificats de la indústria, comerç i serveis, així com del sector primari.

☐ Classe V: Treballadors no qualificats.

☐ Classe VI: Altres casos, mal especificats o desconeixement.

Dosi inicial de drogues vaso-actives:

☐ No n'ha requerit

☐ Epinefrina o Norepinefrina ≤ 0,1μg/kg/min

☐ Epinefrina o Norepinefrina > 0,1μg/kg/min

☐ Norepinefrina i vasopressina

Microorganisme/s presents als cultius:

☐ BGN

☐ BGP

☐ Fong

☐ Virus

És un microorganisme multirresistent?: ☐ Si / ☐ No

Requereix ventilació mecànica: ☐ Si / ☐ No

DADES RELLEVANTS PER L'ESTUDI

Càlcul del SOFA score:

	CRITERI	0	1	2	3	4
SISTEMA RESPIRATORI	PaO_2/FiO_2 (mmHg)	>400	<400	<300	<200	<100
SISTEMA NERVIÓS	Glasgow Coma Scale	15	13-14	10-12	6-9	<6
SISTEMA CARDIOVASCULAR	MAP o requereix administració de drogues vasoactives	>70	<70	Dop ≤5 o Dob qualsevol dosi	Dop >5 o Epi ≤0,1 o Norepi ≤0,1	Dop >15 o Epi >0,1 o Norepi >0,1
HEPÀTIC	Bilirubina (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0

COAGULACIÓ	Plaquetes x10^3/ml	>150	<150	<100	<50	<20
RENAL	Creatinina (mg/dl) o diüresis (mL/dia)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 o diüresis <500 ml/dia	>5.0 o diüresis <200 ml/dia

TOTAL SOFA score: _____

Mediadors Inflamatoris:

PCR: _____ IL-6: _____ Procalcitonina: _____

Nivells de lactat: _____

Requereix drogues vasoactives: ☐ Si / ☐ No

Requereix ventilació mecànica: ☐ Si / ☐ No

Requereix teràpia de reemplaçament renal (RRT): ☐ Si / ☐ No

DADES DE L'INTERVENCIÓ

CRRT

Dia d'inici de la CRRT: ___/___/_____ **Hora d'inici:** ____:_____

Nº de filtre: _____ **Tipus d'anticoagulació:** _____

Modalitat: _____

DADES A LES 24h DE L'INTERVENCIÓ

Càlcul del SOFA score:

	CRITERI	0	1	2	3	4
SISTEMA RESPIRATORI	PaO_2/FiO_2 (mmHg)	>400	<400	<300	<200	<100
SISTEMA NERVIÓS	Glasgow Coma Scale	15	13-14	10-12	6-9	<6
SISTEMA CARDIOVASCULAR	MAP o requereix administració de drogues vasoactives	>70	<70	Dop ≤5 o Dob qualsevol dosi	Dop >5 o Epi ≤0,1 o Norepi ≤0,1	Dop >15 o Epi >0,1 o Norepi >0,1
HEPÀTIC	Bilirubina (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
COAGULACIÓ	Plaquetes $x10^3$/ml	>150	<150	<100	<50	<20
RENAL	Creatinina (mg/dl) o diüresis (mL/dia)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 o diüresis <500 ml/dia	>5.0 o diüresis <200 ml/dia

TOTAL SOFA score: _____

Mediadors Inflamatoris:

PCR: _____ IL-6: _____ Procalcitonina: _____

Nivells de lactat: _____

Requereix drogues vasoactives: ☐ Si / ☐ No

Requereix ventilació mecànica: ☐ Si / ☐ No

CRRT

Modalitat: _____ **Tipus d'anticoagulació:** _____

Nº de filtre: _____

DADES A LES 72h DE L'INTERVENCIÓ

Càlcul del SOFA score:

	CRITERI	0	1	2	3	4
SISTEMA RESPIRATORI	PaO_2/FiO_2 (mmHg)	>400	<400	<300	<200	<100
SISTEMA NERVIÓS	Glasgow Coma Scale	15	13-14	10-12	6-9	<6
SISTEMA CARDIOVASCULAR	MAP o requereix administració de drogues vasoactives	>70	<70	Dop ≤5 o Dob qualsevol dosi	Dop >5 o Epi ≤0,1 o Norepi ≤0,1	Dop >15 o Epi >0,1 o Norepi >0,1
HEPÀTIC	Bilirubina (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
COAGULACIÓ	Plaquetes $x10^3$/ml	>150	<150	<100	<50	<20
RENAL	Creatinina (mg/dl) o diüresis (mL/dia)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 o diüresis <500 ml/dia	>5.0 o diüresis <200 ml/dia

TOTAL SOFA score: _____

Mediadors Inflamatoris:

PCR: _____ IL-6: _____ Procalcitonina: _____

Nivells de lactat: _____

Requereix drogues vasoactives: ☐ Si / ☐ No

Requereix ventilació mecànica: ☐ Si / ☐ No

CRRT

Modalitat: _____ Tipus d'anticoagulació: _____

Nº de filtre: _____

DADES POST-INTERVENCIÓ

Càlcul del DELTA SOFA score:

- Δ-SOFA score 0-24: _____, implica un/a:

  ☐ -24 a-17: deteriorament sever ☐ 0: Neutral ☐ 1 a 8: millora lleu

  ☐ -16-9: deteriorament moderat ☐ 9 a 16: millora moderada

  ☐ -8 a-1: deteriorament lleu ☐ 17 a 24: millora severa

- Δ-SOFA score 0-72: _____

  ☐ -24 a-17: deteriorament sever ☐ 0: Neutral ☐ 1 a 8: millora lleu

  ☐ -16-9: deteriorament moderat ☐ 9 a 16: millora moderada

  ☐ -8 a-1: deteriorament lleu ☐ 17 a 24: millora severa

Dies d'hospitalització a UCI: _____

Dies d'hospitalització: _____

Requereix RRT a l'alta: ☐ Si / ☐ No

16.8 ANNEX 8 - APPLICATION FOR THE WITHDRAWAL OF CONSENT TO STUDY

FORMULARI DE REVOCACIÓ DEL CONSENTIMENT INFORMAT PER PART DEL PACIENT

Jo, _____ (nom i cognoms), amb document d'identificació personal (DNI/NIE) _____, revoco el consentiment informat prèviament firmat per a participar a l'estudi *"Impact on Delta SOFA score in Sepsis-Induced Acute Kidney Injury: A Comparative Study of Hemofilter Efficacy in Continuous Renal Replacement Therapy".*

Signatura del pacient

Signatura de l'investigador

Data i lloc: _____(lloc), a dia _____ (dia / mes / any)

FORMULARI DE REVOCACIÓ DEL CONSENTIMENT INFORMAT DEL FAMILIAR PER PART DEL FAMILIAR

Jo, _____ (nom i cognoms), amb document d'identificació personal (DNI/NIE) _____, revoco el consentiment informat prèviament firmat per a la participació del meu familiar _____ (nom i cognoms), amb document d'identificació personal (DNI/NIE) _____, en l'estudi *"Impact on Delta SOFA score in Sepsis-Induced Acute Kidney Injury: A Comparative Study of Hemofilter Efficacy in Continuous Renal Replacement Therapy"*

Signatura del pacient

Signatura de l'investigador

Data i lloc: _____(lloc), a dia _____ (dia / mes / any)