Antibiotic therapy in septic patients treated with renal replacement and extracorporeal blood purification therapy

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ANTIBIOTIC THERAPY IN SEPTIC PATIENTS TREATED WITH RENAL REPLACEMENT AND EXTRACORPOREAL BLOOD PURIFICATION THERAPY

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List of Abbreviations

SIRS – systemic inflammatory response syndrome

SCCM – The Society of Critical Care Medicine

ESICM – European Society of Intensive Care Medicine

SOFA – Sequential Organ Failure Assessment

MAP – mean arterial pressure

GCS – Glasgow coma scale

qSOFA – quick SOFA

ICU – Intensive care unit

NKs – natural killer cells (NKs)

PAMPS – pathogen-associated molecular patterns

PRR – pattern recognition receptors

HMGB – 1high-mobility group box-1 protein

SSC – Surviving Sepsis Campaign

CRP – C-reactive protein

PCT – Procalcitonin

AKI – Acute kidney injury

GFR – Glomerular filtration rate

CKD – Chronic kidney disease

AKIN – Acute Kidney Injury Network

RIFLE – Risk, Injury, Failure, Loss, ESKD

KDIGO – Kidney Disease Improving Global Outcomes

GI – Gastrointestinal

RRT – Renal replacement therapy

DOAC – Direct acting oral anticoagulant

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Sepsis

1.1.1 Definition

Sepsis is a dysregulated host response to infection that sets in motion a cascade of several pathological processes which culminate in end stage organ dysfunction (1). The term sepsis is derived from the Greek language and translates to “decomposition” or “decay”. Its first documented use was in Homer’s poems around 2700 years ago. Afterwards, the concept of sepsis was described in the works of Hippocrates and Galen during later centuries. Even then, sepsis was already considered a dangerous life-threatening condition (2). Nowadays, sepsis is a medical emergency requiring rapid diagnosis and treatment to prevent progression into septic shock or death. The diversity of the disease process has always made it difficult to recognize and treat sepsis in an appropriate approach. Therefore, definitions of sepsis were put forward during international conferences which were held in 1991, 2001, and ultimately in 2016.

As seen in Table 1, prior to 2016, sepsis diagnosis depended on identifying systemic inflammatory response syndrome (SIRS) in patients affected by an infection.

SIRS is present when two or more criteria of the following are met:

- Body temperature $< 36°C$ or $> 38°C$,
- Heart rate > 90 beats/minute,
- Respiratory rate > 20 breaths/minute or partial pressure of $CO2 < 32$ mmHg,
- Leukocyte count > 12000 or < 4000/microliters or over 10% immature forms or bands (3).

Although the SIRS criteria remain to be a helpful concept, they are considered to be nonspecific as sepsis involves a more complex pathophysiology than infection and an associated inflammatory response alone (4). Thus, in the most recent revision of sepsis, the 2016 SCCM/ESICM task force (The Society of Critical Care Medicine [SCCM] and the European Society of Intensive Care Medicine [ESICM]) aimed to reevaluate previous sepsis definition to enhance recognition and treatment of sepsis. The newest Sepsis-3 definition therefore utilizes the Sequential Organ Failure Assessment (SOFA) (originally the Sepsis-related Organ Failure Assessment) score to better clinically characterize a septic patient.

The SOFA score criteria include different values from multiple organ systems and a higher score is directly related to an increased mortality risk of up to 10% (4). To establish the SOFA score, variables such as mean arterial pressure (MAP), Glasgow coma scale (GCS), serum creatinine and urine output, bilirubin and platelet count must be determined. A SOFA score of 2 or more is descriptive of organ dysfunction (5). Owing to the fact that constituents of SOFA entail laboratory testing to establish the score, quick SOFA (qSOFA) was introduced to ease sepsis recognition which is particularly of importance in clinical settings outside of the ICU. The bedside prompt qSOFA uses three variables which entail an increased respiratory rate (>22/min), altered mental status (GCS < 15) and a low systolic blood pressure value (< 100 mm Hg) (4,6). As with SOFA, a score of 2 or more is indicative of organ dysfunction and should alert physicians of an increased risk of sepsis in patients with suspected infections (7).

Septic shock describes the most severe complication of sepsis in which underlying circulatory and cellular metabolism abnormalities further progress and mortality drastically increases. Septic shock is defined by sepsis with persistent hypotension which requires the use of vasopressor therapy to maintain a MAP ≥ 65 mm Hg or higher plus a serum lactate level > 2 mmol/L (4).

1.1.2 Epidemiology

The epidemiology of sepsis changes with changing definitions (8). Nevertheless, sepsis accounts for one of the most common causes of morbidity and mortality in critically ill patients, with an estimated 48.9 million cases globally. With an incidence of 11 million, sepsis related deaths make up for 19.7% of all global deaths (9). Sakr *et al.* have shown in their 2018 study that up to 30% of ICU patients are affected by sepsis. The mortality rates among patients with sepsis in the ICU was approximately 26%, which shows a twofold increase in comparison to nonseptic patients. According to their cohort study, septic patients were generally older, had multiple comorbidities and commonly received invasive treatment such as mechanical ventilation or renal replacement therapy (10).

Table 1. Definitions of Sepsis

Sepsis 1 (1991)	**Sepsis 2 (2001)**	**Sepsis 3 (2016)**
Sepsis defined as a systemic response to infection which is manifested by two or more SIRS criteria as a result of infection	Documented or suspected infection plus abnormal general, inflammatory, hemodynamic or tissue perfusion parameters	Sepsis is defined as a life-threatening organ dysfunction caused by dysregulated host response to infection
Severe sepsis is defined as Sepsis associated with organ dysfunction, hypoperfusion manifesting as lactic acidosis, oliguria, or an acute alteration in mental status	General: fever, increased heart rate, increased respiratory rate	Clinical criteria: Suspected or documented infection and an acute increase of 2 or more SOFA points
	Inflammatory: leukocytosis, leukopenia, increased CRP, increased PCT	qSOFA criteria to prompt consideration of possible infection
Septic shock is defined as sepsis induced hypotension despite adequate fluid resuscitation manifesting as lactic acidosis, oliguria, or an acute alteration in mental status	Hemodynamic: arterial hypotension, decreased oxygen saturation, oliguria	Septic shock is defined as sepsis with persistent hypotension requiring vasopressor therapy to maintain MAP > 65mmHg plus lactate levels > 2mmol/L despite adequate fluid resuscitation
	Tissue perfusion: hyperlactatemia, decreased capillary refill, skin mottling	

Source: Gyawali B, Ramakrishna K, Dhamoon AS. Sepsis: The evolution in definition, pathophysiology, and management. SAGE Open Med. 2019;7:2050312119835043.

SIRS: Severe inflammatory response syndrome, CRP: C-reactive protein, PCT: Procalcitonin, MAP: Mean arterial pressure

1.1.3 Etiology

As per the most recent sepsis definition, sepsis develops when there is a dysregulated response of the body to infection (11). In 2007, the Extended Prevalence of Infection in Intensive Care (EPIC II) study collected data from 14000 ICU patients from 75 countries. The evidence from this prospective study revealed that the most common sites of primary infection include respiratory infections (64%), abdominal infections (20%) and the blood stream infections (15%) (12).

These results correspond with a 2015 cohort study, where Klouwenberg *et al.* described that the most common source of primary infection was pulmonary (13). Pneumonia, which can be either community or hospital acquired accounted for around 50% of sepsis cases and was associated with the highest mortality (14,15).

Among the 70% of patients with positive microbiology, gram-positive isolates made up 47%, with *Staphylococcus aureus* covering 20% alone. Gram-negative bacteria accounted for 62% of cases, including *Pseudomonas* species (20%) and *Escherichia coli* (16%), while fungal infections were observed in 19% of patients (12,16).

1.1.4 Pathophysiology

The pathophysiology of sepsis consists of a complex interplay of several mechanisms including vascular endothelial injury, inflammation, and activation of coagulation (17). Upon pathogen entry into the body, the immune system gets activated. In sepsis, the normal immunological reaction to a normal uncomplicated infection is disrupted due to imbalance of pro and anti-inflammatory pathways. Generally, in sepsis an early inflammatory cytokine storm is subsequently followed by immune paralysis which then leads to organ dysfunction (18,19).

1.1.4.1 Innate immune response

When a pathogen enters the body, it is recognized as foreign by the innate immune system. The innate immune system consists of leukocytes such as monocytes and macrophages, neutrophils, eosinophils, and natural killer cells (NKs). This innate immunity ensembles cellular and humoral mechanisms which generate an automatic reaction against infecting microorganisms (20).

Pathogenic microbes release molecules such as lipopolysaccharides, peptidoglycans, and bacterial DNA into the host system.

These pathogen derived molecules are referred to as pathogen-associated molecular patterns (PAMPs) and are recognized by either cytoplasmic or cell surface bound pattern recognition receptors (PRRs), setting off the initial immune response (21). Thus far, four families of PRRs have been identified: Toll-like receptors (TLRs), the Nod-like receptors (NLRs), the RIG-like receptors (RLRs), and the C-type lectin receptors (CLRs) (21).

Additionally, host nuclear or cytoplasmic non-microbial molecules, which are referred to as damage-associated molecular pattern (DAMPs), are released from necrotic or injured cells. Examples for DAMPs that have been identified include heat shock proteins, fibrinogen, hyaluronic acids, and high-mobility group box-1 protein (HMGB-1) (16).

DAMPs are also recognized by PRRs and potentiate immune cell activation and systemic inflammation (22). Binding of PRRs to DAMPs and/or PAMPs initiates proinflammatory and antimicrobial responses by stimulating signalling pathways which modulate gene expression and the synthesis of molecules which coordinate the early host response to infection (23).

The aforementioned molecules include cytokines, chemokines, cell adhesion molecules and immunoreceptors (24). Production of pro-inflammatory cytokines, namely tumor necrosis factor (TNF), IL-1β, IL-12 and IL-18, upregulate inflammatory gene expression and a self-propagating cascade is initiated (Figure 1) (21,25).

Under physiologic conditions, pro and anti-inflammatory mediators are usually tightly regulated, whereas in sepsis uncontrolled pro-inflammatory activity causes tissue injury. The primary pathogenic mechanism involved in sepsis is the simultaneous activation of the complement and coagulation systems together with endothelial dysfunction (26).

In addition to direct tissue injury, inflammatory mediators cause venous and arterial dilation resulting in hypotension and subsequent tissue hypoperfusion. Hypotension is further exacerbated by the leakage of intravascular fluid into the interstitial spaces which is being caused by the loss of endothelial barrier function. Consequently, cellular metabolism shift into anaerobic glycolysis which results in the production of lactic acid (1). Therefore, an elevated lactate level is indicative of cellular dysfunction and high levels of lactate are associated with increased mortality rates (27).

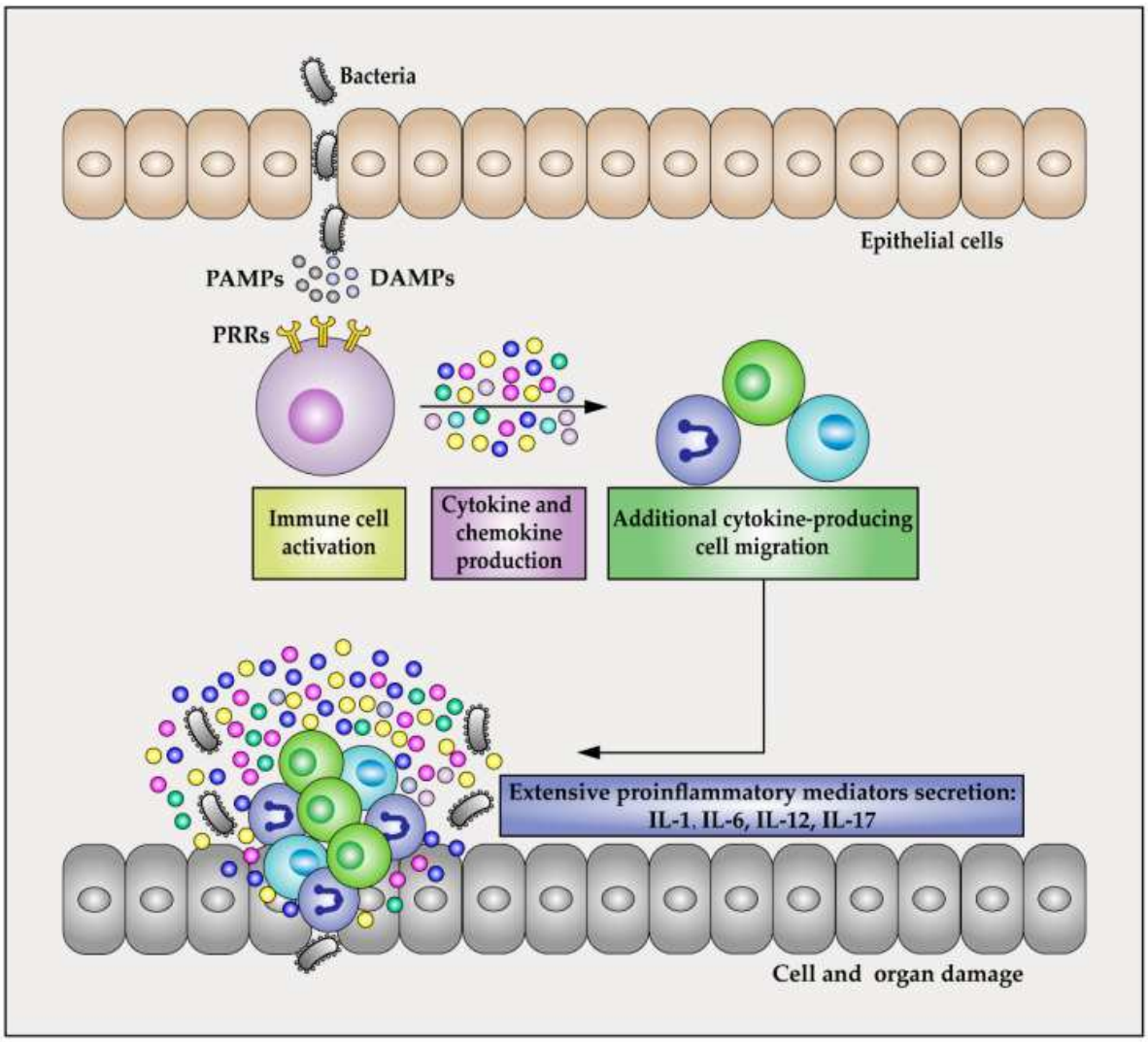

Figure 1. Innate immune response in sepsis

Source: Tang XD, Ji TT, Dong JR, Feng H, Chen FQ, Chen X et al. Pathogenesis and treatment of cytokine storm induced by infectious diseases. Int J Mol Sci. 2021;22:13009.

PAMPs: Pathogen-associated molecular patterns, DAMPs: Damage-associated molecular patterns, PRR: Pattern recognition receptor, IL: Interleukin

1.1.5 Management and Therapy

The timely management and treatment of sepsis is crucial for the patient's outcome. In fact, management should begin with the screening of any critically ill patient for septic signs (Figure 2). To date, there is no specific test to identify sepsis nor is there a gold standard method to determine whether a patient is septic or not. Sepsis can present in various ways and especially in early stages it may manifest with non-specific symptoms. For example, pre-existing comorbidities might impact the manifestations of sepsis (16).

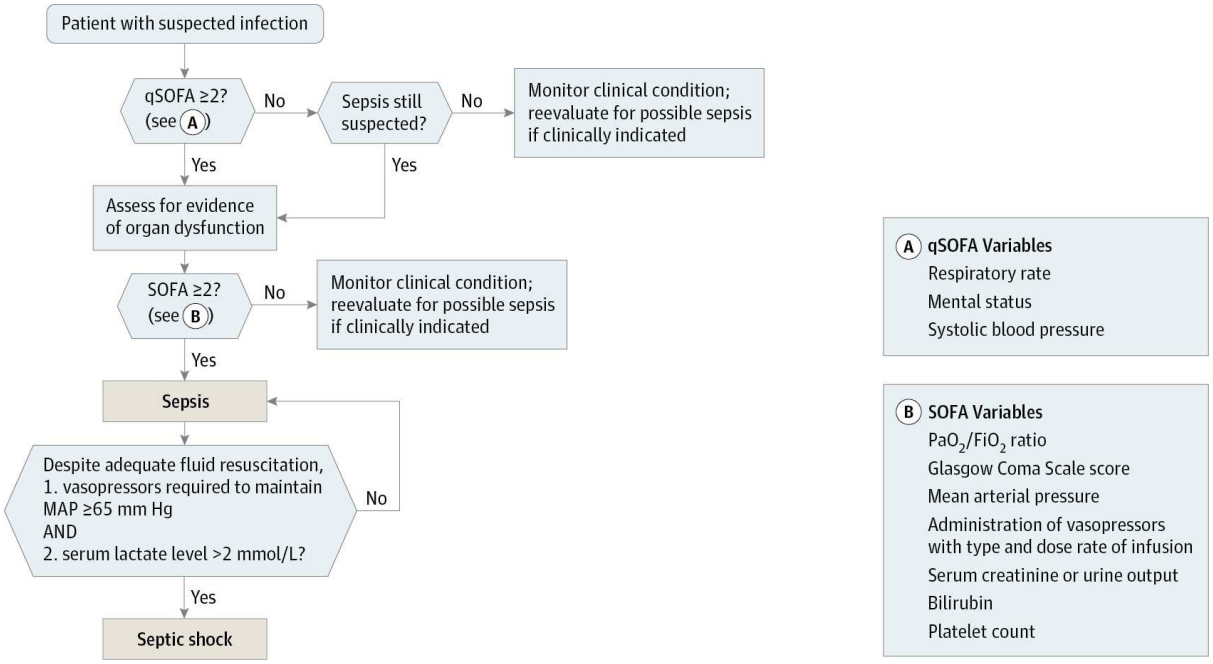

Figure 2: Initial management of patients with suspected sepsis based on qSOFA and SOFA score

Source: 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. 2016;315:801-10. SOFA: Sequential Organ Failure Assesment, MAP: Mean arterial pressure

In October 2021, updated treatment guidelines have been released by the Surviving Sepsis Campaign (SSC). These guidelines are thought to help physicians recognize and treat a septic patient to improve outcome and prevent progression into shock states (28).

Screening patients for sepsis can be done by utilizing easily accessible clinical variables such as the previously mentioned SOFA and qSOFA scores (6) and assessing potential risk factors such as older age, immunocompromised state, recent surgeries, or other potential entry points for infections such as urinary catheters (29).

In the most recent guidelines, the SSC recommends against the use of only screening scores such as qSOFA since studies have shown a relative low sensitivity. Thus, while a positive qSOFA score should prompt the physician's attention, a negative qSOFA score should not be considered as sufficient evidence to exclude sepsis (28). Alternatively, physicians should assess patients by evaluating laboratory results for biomarkers. For clarity, biomarkers are defined by the National Institutes of Health as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (30). Helpful biomarkers in sepsis include pro-inflammatory markers such as C-reactive protein (CRP) and procalcitonin (PCT) and biomarkers of organ dysfunction such as lactate (Table 2) (31).

In addition to early recognition, fluid resuscitation and antimicrobial therapy initiation play an essential role in the early management of sepsis. Relative hypovolemia is one of the main pathogenic mechanisms in sepsis. When circulating fluid volume is decreased, venous return and cardiac preload decrease which ultimately results in insufficient oxygen delivery due to reduced cardiac output (32,33). Hence, the SSC recommends the administration of a minimum of 30 mL/kg of intravenous crystalloid fluid within the initial 3-hour period of resuscitation (28). To further stabilize the patient hemodynamically, vasoactive agent administration should be introduced. In the current guidelines, norepinephrine is recommended as the first-choice vasopressor (28).

Together with fluid resuscitation, initiation of antibiotic therapy plays a key role in treatment of sepsis. Intravenous antimicrobial therapy should be initiated within one hour after sepsis or septic shock recognition. Optimally, blood cultures should be obtained before starting antibiotic therapy.

The first choice of antibiotic treatment are broad spectrum antibiotics which empirically cover pathogens that are frequently encountered in healthcare-associated infections, particularly gram-negative pathogens. Thus, the SSC guidelines recommend an either broad spectrum carbapenem, such as meropenem or an extended range penicillin / β-lactamase inhibitor (e.g., piperacillin / tazobactam, ticarcillin / clavulanate) (28).

For example, Bodmann *et al* suggest treating sepsis with an unknown source of infection, which is frequently caused by bacteria such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella* subspecies or *Pseudomonas* subspecies, with piperacillin / tazobactam plus ciprofloxacin or fosfomycin (34).

In addition, the concept of multidrug therapy should be considered to increase effectiveness of antimicrobial treatment, especially when patients are critically ill and at high risk of infection. Complementary treatment with a gram-negative agent, such as an aminoglycoside or a fluroquinolone in patients where infection with a multidrug resistant pathogen is suspected is recommended as it increases the likelihood of having at least one effective antibiotic (33).

Table 2. Useful biomarkers in sepsis

C-reactive protein	– produced in the acute phase of inflammation, mainly by the liver – rapid rise in CRP levels within a few hours following infection – main mediator stimulating its production is Interleukin-6 – decrease in CRP levels can be indicative of infection resolution and/or or positive treatment response to antibiotics – CRP plasma concentration seems to be concurrent with sepsis severity
Procalcitonin	– inflammatory cytokines and bacterial endotoxins stimulate PCT production – high sensitivity for especially bacterial infections – earlier rise of PCT than CRP
Lactate	– marker for severe hypoperfusion, therefore considered a marker for severe sepsis – provides guidance on the use of vasoactive drugs – lactate levels directly proportional to mortality

Source: Rello J, Valenzuela-Sánchez F, Ruiz-Rodriguez M, Moyano S. Sepsis: A review of advances in management. Adv Ther. 2017;34:2393-411.

CRP: C-reactive protein, PCT: Procalcitonin

1.2 Acute Kidney Injury

1.2.1 Definition

Acute kidney injury (AKI) describes a clinical syndrome commonly seen in hospitalized patients in which kidney function rapidly declines. The decline which usually presents as a decrease in urine output first, is measured via the glomerular filtration rate (GFR) (35). Subsequently, products which are normally excreted in urine such as nitrogenous waste in the form of creatinine and blood urea nitrogen are retained (36). In spite of advances in supportive as well as preventative measures, AKI remains associated with high morbidity and mortality rates (37). Close monitoring of patients in early stages of AKI is vital to prevent disease advancement and to minimize the risk of progression into chronic kidney disease (CKD) (38).

1.2.2 Diagnosis and Classification

Different guidelines have been established to assess the severity and stages of AKI. These guidelines utilize serum creatinine levels, GFR and urine output as prognostic parameters; Acute Kidney Injury Network (AKIN); Risk, Injury, Failure, Loss, End Stage Kidney Disease (RIFLE); and Kidney Disease Improving Global Outcomes (KDIGO) (Table 3). Recently, the latter appeared to be the most used tool (35).

In accordance with the KDIGO guidelines, AKI is present when there is either a ≥ 0.3 mg/dl increase in serum creatinine (sCr) within 48 hours, a sCr increase to ≥ 1.5 times baseline within the previous 7 days, or urine volume ≤ 0.5 ml/kg/h for 6 hours (39). Establishing the diagnosis of AKI based on these markers can present itself difficult and unreliable, especially in the early stages. This is due to the fact that sCr can initially appear unaffected upon renal insult and might only increase after two to three days. Moreover, sCr values are influenced by various factors that impact its production, such as age, gender, muscle mass or external factors such as dilution following fluid administration or excretion after certain medications (40).

Similarly, the use of urine output measurement to ascertain kidney dysfunction appears to be difficult to assess because its accuracy is affected by the patient's fluid balance and overall hemodynamic status. Hence, identification of alternative biomarkers such as cystatin C is thought to improve earlier identification of AKI in the future (41).

Table 3. Comparison of RIFLE, AKIN, and KDIGO Criteria for Diagnosis and Staging of Acute Kidney Injury

	SCR/GFR			URINE OUTPUT
STAGE/CLASS	RIFLE	AKIN	KDIGO	
STAGE 1/ RISK	1.5 x sCr increase within 7 days OR GFR decrease > 25%	sCr increase ≥ 26.5 µmol/L within 48h OR 1.5 – 2x within 7 days	sCr increase ≥ 26.5 µmol/L within 48h or 1.5 – 1,9x within 7 days	< 0.5 mL/kg/h for more than 6 hours
STAGE 2/ INJURY	2 x sCr increase OR GFR decrease > 50%	2 – 3x sCr increase	2 – 2.9x sCr increase	< 0.5 mL/kg/h for more than 12 hours
STAGE 3/ FAILURE	3 x sCr increase OR SCr ≥ 354 µmol/L with acute rise OR GFR decrease > 75%	3x sCr increase OR sCr ≥ 354 µmol/L with acute rise OR need for RRT	3x sCr increase OR sCr ≥ 354 µmol/L or need for RRT	< 0.3 mL/kg/h for more than 24 hours OR anuria for more than 12 hours

Source: Er RE, Ulusal Okyay G, Aygencel B Kmaz G, Türko Lu M, Erten Y. Comparison between RIFLE, AKIN, and KDIGO: acute kidney injury definition criteria for prediction of in-hospital mortality in critically ill patients. Iran J Kidney Dis. 2020;14:365-72.

RIFLE: Risk, Injury, Failure, Loss, End stage kidney disease, AKIN: Acute Kidney Injury Network, KDIGO: Kidney Disease Improving Global Outcome, sCr: Serum creatinine, GFR: Glomerular filtration rate, RRT: Renal replacement therapy

1.2.3 Epidemiology

The incidence of AKI can be categorized as either community-acquired or hospital-acquired. Hospital-acquired AKI describes the occurrence of the clinical syndrome within a healthcare facility and mainly happens in high-income countries. Community-acquired AKI stems from outside a healthcare facility and mostly occurs in lower income regions (43). Depending on which definition is used to define AKI, among hospitalized patients the incidence is significant with prevalence rates reaching up to 7% of hospital admissions and 30% of Intensive care unit (ICU) admissions (35). The incidence is rising with an ageing population and is frequently seen within the context of multiorgan diseases and sepsis (36,43).

1.2.4 Etiology

AKI is a multifactorial condition, and the different etiologies are often interrelated. Generally, AKI is divided into prerenal, intrarenal and postrenal etiologies. Prerenal causes represent the most common form of AKI, with an incidence of up to 60%. Intrarenal etiologies account for 40% whereas postrenal AKI are relatively uncommon with an incidence of < 5% (40).

Prerenal AKI occurs when there is inadequate perfusion of the nephrons, leading to a decrease in GFR. Prerenal AKI can appear subsequent to either (1) total volume depletion or (2) selective renal hypoperfusion.

Total volume depletion with successive hypoperfusion of the kidneys most often occurs secondary to hemorrhage, gastrointestinal (GI) losses such as vomiting, or diarrhea and fluid volume shifts (third spacing) as seen in burn victims. Alternatively, in shock states, decreased vascular resistance creates a relative renal hypoperfusion prompting pre-renal AKI (44).

The same spectrum of causes that can lead to prerenal AKI can progress into intrarenal AKI and lead to direct tubular injury. The most common cause of intrarenal AKI is ischemic induced acute tubular necrosis (45). Aside from ischemic injuries, nephrotoxic agents can also trigger tubular damage to the kidney (46). Examples of such agents include antimicrobials like aminoglycosides or vancomycin, as well as chemotherapeutic medication such as cisplatin. Furthermore, radiocontrast agents for medical imaging are also associated with direct tubular injury and subsequent AKI. To avoid this, it is crucial to adjust the dosage and consider alternative agents (47). Other components of the kidney, such as the glomeruli, renal interstitium, or the renal vascular system, may also be susceptible to injury as is shown in Table 4. Postrenal AKI accounts for the least common form of AKI. The most common cause for renal injury stemming from postrenal issue are anatomic obstructions of the urinary system. Impediment of urine flow away from the kidney can be due to obstructions such as urinary stones, as well as tumor masses or prostate disorders (36).

Table 4. Intrinsic causes of AKI

Tubular Damage	Ischemic induced acute tubular necrosis
	Nephrotoxic agents
Glomerular Damage	Acute Glomerulonephritis
	Vasculitis
Interstitial Damage	Infections
	Nephrotoxic agents
Vascular Damage	Renal artery thrombosis
	Renal vein thrombosis

Source: Turgut F, Awad AS, Abdel-Rahman EM. Acute Kidney Injury: Medical causes and pathogenesis. J Clin Med. 2023;12:375.

1.2.4.1 Risk factors

AKI risk factors can be divided into modifiable and non-modifiable (Table 5) (41). Older age is a non-modifiable risk factor, and the ageing kidney is associated with structural and functional changes, making it more susceptible to injury. With older age (age ≥ 65), renal reserve and autoregulatory mechanisms, which generally allow the kidney to compensate partial dysfunction upon insult, decrease (48). Moreover, older patients frequently have comorbidities necessitating the use of multiple pharmacotherapies. For example, these include angiotensin converting enzyme inhibitors (ACE inhibitors) which are used to treat conditions often seen in elderly patients, such as hypertension and heart failure. Even though ACE inhibitors do not cause direct injury to renal cells, their dehydrating effect can further exacerbate dysfunction, especially when AKI stems from hypovolemia (49).

Apart from age, chronic diseases such as CKD, chronic liver disease or congestive heart failure increase the risk of AKI. The relationship between CKD and AKI is especially interconnected. Pre-existing CKD signifies the most important risk factor, elevating the risk to develop AKI by up to 10 times, in comparison to patients without a history of CKD (50). Similarly, even early stages of AKI are directly linked to the development of new CKD, advancement of pre-existing CKD and increased risk of end-stage renal dysfunction (ESRD) (50–52).

Furthermore, when identifying modifiable risk factors, infection and sepsis should be considered as serious risk factors for developing AKI. Sepsis associated kidney injury (SAKI) can occur with an incidence rate of up to 47.5% (53) and represents the most common cause of AKI in critically ill patients (54).

Table 5. Risk factors of AKI

Modifiable risk factors	**Non-modifiable risk factors**
Infection/Sepsis	Age
Hypercholesteremia	Sex
Hypertension	Race
Surgery	Chronic kidney disease
Nephrotoxic agents	Diabetes mellitus
Hemodynamic instability	Congestive heart failure

Source: Thongprayoon C, Hansrivijit P, Kovvuru K, Kanduri SR, Torres-Ortiz A, Acharya P et al. Diagnostics, risk factors, treatment and outcomes of acute kidney injury in a new paradigm. J Clin Med. 2020;9:1104.

1.2.5 Pathophysiology

Most cases of AKI are multifaceted processes which result from several concomitant insults. Subsequent to an inciting event, multiple pathophysiologic processes can unfold either simultaneously or sequentially. For instance, they can consist of microcirculatory dysfunction, inflammatory processes, or endothelial dysfunction (55).

When renal blood flow decreases, compensatory mechanisms initially act to maintain physiological functioning. However, once oxygen delivery becomes inadequate subsequent cell apoptosis, necrosis and/or kidney dysfunction becomes inevitable (56).

The unique structure of the renal vascular system, which consists of specialized microcirculatory structures; the glomeruli, and the peritubular network, makes certain renal structures particularly susceptible to ischemia. The glomerular blood supply arises form afferent arterioles whereas the peritubular network stems from the efferent glomerular arteriole (57). This microvascular supply pattern marks the proximal renal tubules as specifically vulnerable to hypoperfusion and therefore makes it the most common site of damage during AKI events (58).

Additionally, the proximal tubular cells are responsible for a major part of active reabsorption and transport processes for solutes such as glucose and amino acids and therefore utilize a lot of ATP (adenosine triphosphate). Consequently, if renal cells are deprived of oxygen to maintain cellular processes, ATP depletion prompts cellular injury (59).

Several other mechanisms add to the decline in kidney function during AKI. Morphological manifestations of ischemia include epithelial cell flattening, effacement of the brush-border, and nuclear loss (60).

Following structural damage to tubular cells, an inflammatory cascade is set into motion releasing proinflammatory chemokines and cytokines (61). During reperfusion, inflammatory cells such as neutrophils and macrophages additionally cause direct damage to tubular cells, amplifying cellular injury (37).

Accumulation of metabolic by-products such as reactive oxygen species further exacerbate cell damage (62).

1.2.6 Management and Therapy

Management and therapy of AKI strongly depends on the etiology of the declining kidney function. Therefore, evaluation of pre-existing conditions and history taking, assessment of fluid status and screening for nephrotoxic agents marks an important step in initiating therapy (40). As there is no specific pharmacologic therapy for treatment of AKI yet, management and therapy are limited to supportive care and renal replacement therapy (RRT) (63).

Immediate attention should be given to treatable causes, including nephrotoxic agents. Such nephrotoxic agents are commonly associated with acute tubular necrosis include aminoglycosides and nonsteroidal anti-inflammatory drugs (NSAIDs), which are drug groups regularly used in hospitalized patients. According to the KDIGO guidelines, subsequent discontinuation or dose adjustment should be initiated to prevent further injury and decline of renal function (39,64).

When AKI appears to be originating from a prerenal etiology, fluid resuscitation to correct hypovolemic states and renal hypoperfusion should be established. Nevertheless, fluid administration must be carefully evaluated as though excessive fluid overload tends to worsen renal function.

For this reason, assessment of overall volume status and responsiveness to volume therapy are crucial and fluid is only indicated when intravascular hypovolemia is present (65).

Additionally, management of AKI includes treatment of complications such as hyperkalemia and metabolic acidosis (39).

In critically ill patients, mere supportive management may not be sufficient. Indications for initiating RRT include cases of volume overload unresponsive to diuretic therapy, sudden hyperkalemia, severe metabolic acidosis, and uremic syndrome (63).

1.3 Sepsis-associated acute kidney injury

When Acute Kidney Injury occurs in the setting of sepsis, it is referred to as Sepsis-associated Acute Kidney Injury (SA-AKI). SA-AKI, one of the most common complications of septic patients, is observed in 40 – 50% of critically ill patients and associated with poor clinical outcomes. In fact, SA-AKI is linked to prolonged hospital stays and increased risks of death in hospitalized patients in comparison to AKI stemming from non-septic patients (66). The Acute Disease Quality Initiative (ADQI) recently has come forward with a definition of SA-AKI and it integrates the presence of sepsis, as defined by the Sepsis-3 criteria with the occurrence of AKI, as defined by the (KDIGO) criteria, within 7 days of the sepsis diagnosis (67).

Epidemiologically, it is estimated that SA-AKI affects 10 – 67 % of septic patients, with up to two thirds of septic of septic shock patients developing SA-AKI. Present AKI can indicate that a patient is septic since SA-AKI is an early event in sepsis. Up to 50 % of septic shock patients already manifest with AKI before getting admitted to the hospital (68).

Both Sepsis and AKI result from complex pathophysiological mechanisms and the exact mechanism that leads to SA-AKI is not yet completely understood. As a matter of fact, it is strongly suspected that both disease mechanisms are bidirectional. The underlying mechanism that leads to AKI following sepsis is thought to result from combined inflammatory cascades and macro – and microvascular dysfunction (Figure 3), whereas a setting where a patient is not yet septic but already suffers from AKI, fluid overload and/or immunosuppression can put that patient at risk for becoming septic (69).

Treating SA-AKI appears to be a very challenging task for physicians as there are no standardized treatment guidelines yet. Treatment consists mainly of supportive measures, including maintaining hemodynamic stability, managing fluid balance, ensuring acid-base and electrolyte homeostasis, providing nutritional support such as protein and caloric supplements, and administering renal replacement therapy (RRT) when necessary (70). Pharmacotherapy with vasopressive agents and antibiotics should be adjusted to renal function, however suboptimal dosing can also lead to treatment failure and worse clinical outcomes (71).

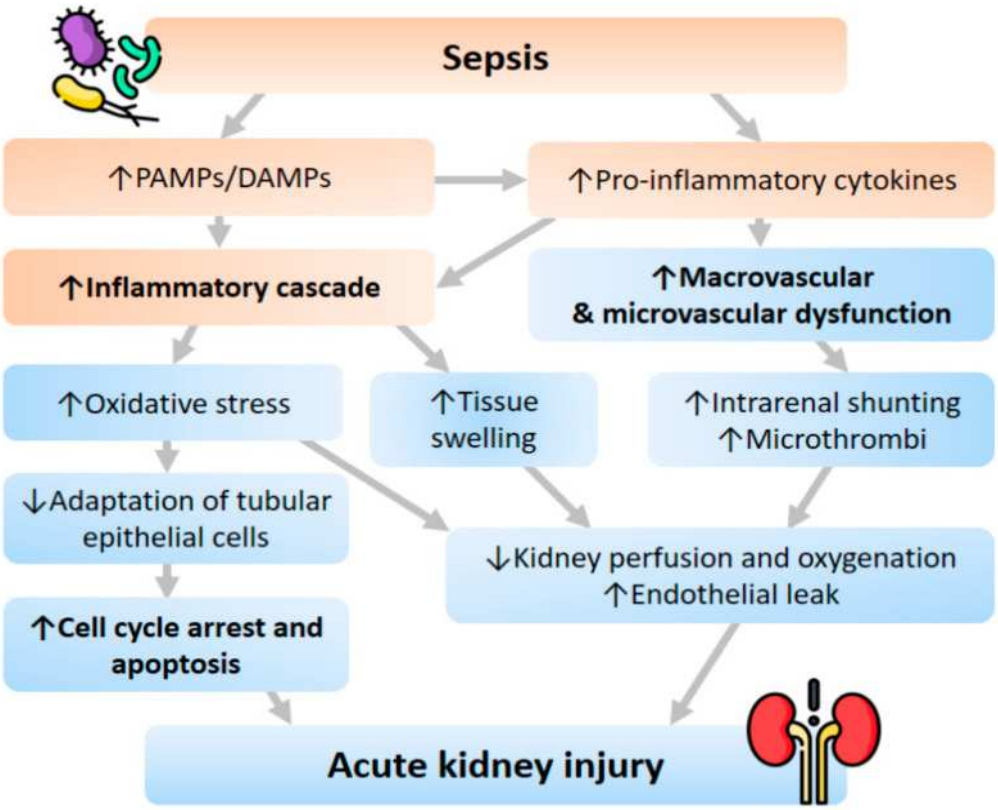

Figure 3. Pathophysiology of AKI following Sepsis

Source: C Chang YM, Chou YT, Kan WC, Shiao CC. Sepsis and Acute Kidney Injury: A review focusing on the bidirectional interplay. Int J Mol Sci. 2022;23:9159.

2. OBJECTIVES

2.1 Aim

The main goal of this research is to determine the frequency and pattern of use of antimicrobial drugs and how is antimicrobial pharmacotherapy related to the treatment outcomes of patients with acute kidney injury who underwent renal replacement therapy and extracorporeal blood purification therapy.

The specific goals of this research are to examine demographic characteristics, comorbidities, causes of sepsis and microbiological isolates, clinical status and laboratory findings at admission, frequency and modalities of renal replacement therapy and extracorporeal blood purification therapy, treatment outcomes, recovery rate and mortality rates on the 7^{th} and 28^{th} day of hospitalization and length of hospitalization of the study population.

Hypotheses:

1. Antimicrobial therapy is associated with improved outcomes in septic patients receiving RRT and BPT.
2. Antibiotic therapy initiation is associated with lower mortality rates and shorter hospitalization rates.

3. SUBJECTS AND METHODS

3.1. Ethical considerations

Data used for this thesis were obtained at the Clinic for Anaesthesiology, Reanimation and Intensive Care and at the Department of Nephrology and Haemodialysis of University Hospital of Split. The data were analysed at the Department of Basic and Clinical Pharmacology of the University of Split School of Medicine. All the procedures in data collection and analysis were approved by the Ethics Committee of University Hospital of Split and Ethics Committee of University of Split School of Medicine.

3.2. Study design

This retrospective cohort study included 67 patients admitted to intensive care at the Clinic for Anesthesiology, Reanimation and Intensive Care in the period from January 1, 2022 to December 31, 2023 with a diagnosis of sepsis (in accordance with the Third International Consensus on the Definition of Sepsis and Septic Shock) who underwent RRT.

Exclusion criteria were death within 48 hours of diagnosis of sepsis, ICU hospitalization for more than 4 weeks (28 days), significant chronic end-stage heart, kidney or liver disease, and insufficient data in the medical records. Out of the total 67 patients, 11 were excluded due to ICU hospitalization for more than 28 days, while 5 were excluded due to unavailability of the extended data. One additional patient was excluded due to end stage renal disease. In the final statistical analysis 49 patients were evaluated and included in our study.

The cohort was defined by the screening of patients with sepsis treated at the Department of Intensive Medicine of the Clinic for Anaesthesiology, Reanimation, and Intensive Medicine.

This was followed by the detection of patients with sepsis who developed acute kidney injury and received renal replacement therapy. Finally, for those patients who met the inclusion criteria detailed search of medical records and the collection of data on pharmacotherapy, clinical status, laboratory findings, microbiological isolates, the outcome of treatment was performed.

3.3 Outcome measures

The study's outcome measures included data on antibiotic and renal replacement or extracorporeal blood purification therapy, clinical status, clinical outcome, and laboratory findings. Pharmacotherapy outcomes included the type and dose of antibiotic administered, the timing of drug initiation relative to admission, the duration of treatment, and the methods and frequency of renal replacement and extracorporeal blood purification therapy.

Clinical status was evaluated by calculation of SOFA and SAPS II scores at admission, data evaluation of comorbidities, the application of mechanical ventilation and daily diuresis.

The length of hospitalization, the number of days spent in the intensive care unit, and survival rate or mortality rates after 7 and 28 days were researched to establish the clinical outcome of our study population.

Several laboratory findings were also investigated, including microbiological isolates, and selected biochemical and inflammatory markers. Microbiological findings focused on bacterial and fungal isolates. Biochemical and inflammatory parameters included urea, creatinine, estimated glomerular filtration rate, C-reactive protein and procalcitonin. We additionally collected data on bicarbonate, lactates, arterial blood gases and haematological and coagulation parameters which included leukocyte count, platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimers which were not statistically analysed as part of this thesis.

3.4 Statistical Analysis

GraphPad Prism for Windows, version 12 (GraphPad Software, Boston, Massachusetts USA, www.graphpad.com) and IBM SPSS Statistics for Windows, version 26.0 St (IBM Corp., Armonk, N.Y., USA) were used for statistical data analysis and graph design. Normality of data distribution was estimated by the Kolmogorov-Smirnov and Shapiro-Wilk tests. Correspondingly, data were expressed as mean ± standard deviation or median and interquartile range.

Age and gender differences were tested by Student’s t-test. Statistical analysis and comparison of data on specific antimicrobial therapy was performed by using a Chi-square test. The correlation between specific antibiotic treatment and recovery rate as the outcome was tested with Pearson Chi-square test.

In order to establish the association of the general type of antimicrobial therapy applied (antibacterials, antivirals and antifungals) with treatment outcomes: recovery, mortality on the 7th day of hospitalization and mortality on the 28th day of hospitalization we used Mann-Whitney U test and performed a logistic regression with the number of antibacterial, antiviral and antifungal drugs as independent variables and recovery, mortality on the 7th day of hospitalization or mortality on the 28th day of hospitalization as dependent variable.

Associations of other variables (length of hospitalization, SAPS II score at admission to ICU and selected laboratory findings (urea, creatinine, estimated glomerular filtration rate, CRP and procalcitonin) with survival rate as outcome were also tested using the Mann-Whitney U test. Differences in creatinine and procalcitonin concentration following RRT and BPT were teste by Wilcoxon matched-pairs signed rank test. Finally, the correlations of the number of antibacterials or antivirals and antifungals with age and length of hospitalization (days spent in the ICU and total days spent in the hospital) were presented by Spearman's correlation coefficients. The level of significance was set at $P < 0.05$.

4. RESULTS

4.1 Demographic characteristics, comorbidities, causes of sepsis and microbiological isolates of the study population

4.1.1 Age and gender distribution

A total of 67 patients with sepsis were treated with RRT at the Clinic for Anesthesiology, Reanimation and Intensive Care in the period from January 1, 2022 to December 31, 2023. Eleven patients were excluded due to incomplete data availability and further 6 patients were excluded due to prolonged hospitalization defined as more than 28 days. One additional patient was excluded due to end stage renal disease. After considering the data collection listed, 49 patients were included in this study.

Among the remaining 49 patients included in the study, the majority were male (N=35, 71%), whereas 14 patients (29%) were female.

The mean age at admission to the hospital was 61.3 ± 13.6 years with the youngest male patient being 31 years old, the youngest female patient being 34 and the oldest patients (both male and female) being 85 years old in our study population (Table 6). Female patients were not significantly older than male ones (66.8 ± 14.1 years vs. 59.1 ± 12.8 years, for female vs male patients, respectively, $P = 0.080$)

Table 6. Gender and age distribution of the study population

Age Group (years)	**Male N (%)**	**Female N (%)**	**Total N (%)**
	35 (71)	14 (29)	49 (100)
30 – 40	5 (14)	1 (2)	6 (12)
41 – 50	2 (4)	1 (2)	3 (6)
51 – 60	9 (18)	1 (2)	10 (20)
61 – 70	11 (22)	4 (8)	15 (30)
71 – 80	8 (16)	5 (10)	13 (26)
81 – 90	0 (0)	2 (4)	2 (4)

4.1.2 Comorbidities, causes of sepsis and microbiological isolates of the study population

Only 14 % of study participants had no comorbidities whereas 25 % of them had more than five comorbidities. The most common comorbidity was arterial hypertension (Table 7).

Table 7. Number and types of comorbidities in the study population

Number of Comorbidities	Patients N (%)
0	7 (9)
1-2	19 (39)
3-4	11 (22)
5+	12 (24)
Comorbidities	**Patients N (%)**
Hypertension	18 (37)
Atrial fibrillation	10 (20)
Diabetes Mellitus Type 2	8 (16)
Atherosclerosis	3 (6)

Our study identified several causes of sepsis with varying incidence rates. In 42.9 % of our study population, the source for sepsis could not be identified.

Where a focus of infection was identified, pneumonia represented the most common cause, responsible for approximately 32.7 % of the cases. Urinary tract infections accounted for 10.2 % of the cases. Abscesses and toxic shock syndrome each contributed to 10.2 % of the sepsis cases. Unspecific gangrene was the cause in 12.2% of cases and meningitis was identified as the cause in 4.1 % of the sepsis cases (Table 8).

Table 8. Distribution of Sepsis causes among the study population

Cause or Foci of Sepsis	Patients N (%)
Unspecified Sepsis	21 (42.9)
Pneumonia	16 (32.7)
Urinary tract infection	5 (10.2)
Abscess (unspecified)	5 (10.2)
Toxic shock syndrome	5 (10.2)
Gangrene (unspecified)	6 (12.2)
Meningitis	2 (4.1)

A variety of pathogens with different incidence rates among the patients were identified among study population. Data are presented in Table 9.

Table 9. Distribution of isolated bacterial and fungal microorganisms in study population

Pathogen	Patients N (%)
Staphylococcus aureus	19 (38.8)
Klebsiella pneumoniae	13 (26.5)
Candida albicans	11 (22.4)
Staphylococcus epidermidis	9 (12.2)
Pseudomonas aeruginosa	9 (12.2)
Streptococcus pyogenes	4 (8.2)

4.2 Data on clinical status, laboratory findings, and duration of hospitalization of study population

Clinical status at admission to ICU was evaluated by calculating SOFA and SAPS II scores and by monitoring need for mechanical ventilation, temperature higher than 39° C and diuresis. The SOFA, and SAPS II together with the values of average daily diuresis and selected laboratory findings, concentration of urea and creatinine, CRP and procalcitonin and value of estimated glomerular filtration rate at admission to ICU are presented in Table 10.

Table 10. Clinical status and laboratory findings of study population at admission to ICU

Parameter	Median	IQR
SOFA score	12.0	10.1 – 13.2
SAPS II score	62.5	49.2 – 74.0
Diuresis (ml/day)	800	400 – 930
Urea (mmol/L)	14.0	8.5 – 25.0
Creatinine (μmol/L)	195.1	122.5 – 335.5
eGFR (mL/min/1.73 m^2)	25.0	14.5 – 52.5
CRP (mg/L)	221.5	77.7 – 304.2
Procalcitonin (ng/mL)	9.0	0.7 – 28.0

N = 49 for all parameters except for CRP (and procalcitonin (N = 42 for both); IQR: interquartile range, eGFR: estimated Glomerular filtration rate, CRP: C-reactive protein

Only five patients (10%) were not mechanically ventilated, whereas most of them (44 patients) did not have temperature higher than 39°C at admission to ICU. Average duration of hospitalization at ICU was 10 (6.5 - 14) days, while patients stayed for further treatment in hospital outside the ICU for additional 9 days with average total hospitalization days of 19 (8.5 - 25).

4.3 Clinical outcomes, recovery, and mortality on 7th and 28th days of hospitalization

After the treatment, 43 % of the patients recovered, while the remaining patients died. On the 7th and 28th day of hospitalization, mortality rates were 20 % and 37 %, respectively (Figure 4).

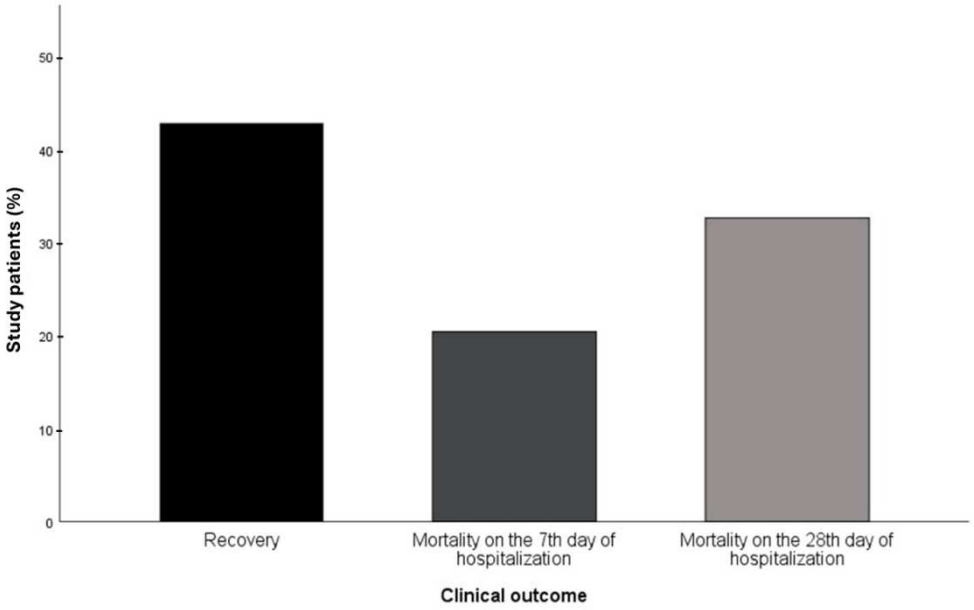

Figure 4. Clinical outcomes following the treatment

Patients with lower SAPS II score values and a longer stay both in the ICU and in the hospital, had a higher probability of complete recovery ($P = 0.045$, $P = 0.013$ and $P = 0.001$ for SAPS II, hospitalization days in ICU, and total hospitalization days, respectively).

4.4 Renal replacement and blood purification therapy of study population

All patients included in the study were treated either with only renal replacement therapy (RRT, 26 patients) or with additional blood purification therapy (BPT, 23 patients). The frequency of RRT varied among study participants with e.g. 2 patients receiving therapy only once, 6 patients receiving therapy twice, 6 patients receiving therapy 3 times. On the other end, one patient received RRT 22 times, and another patient received RRT 27 times during the ICU hospitalization (Figure 5).

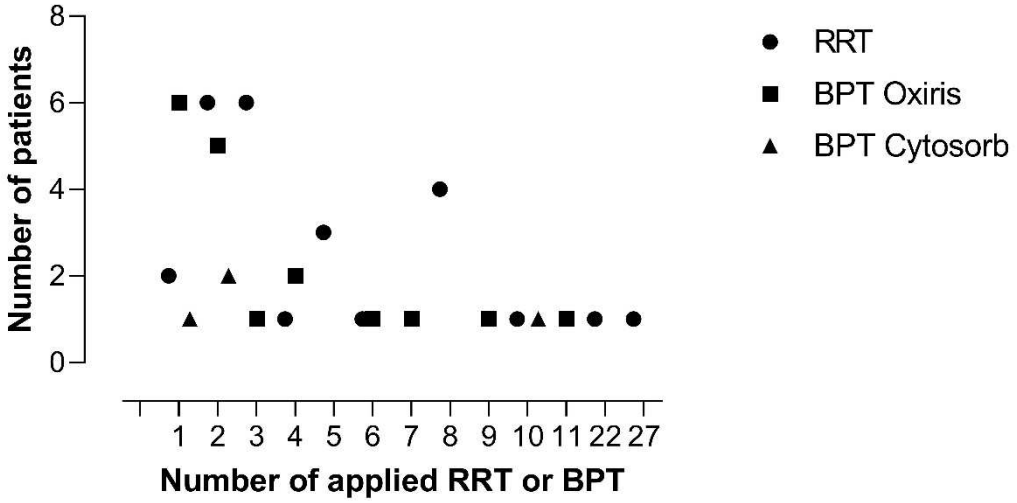

Figure 5. Distribution of RRT and BPT sessions among the study participants. RRT: Renal replacement therapy, BPT: Blood purification therapy

In BPT oXiris® (19 patients) and CytoSorb® (4 patients) were used. Similarly to RRT, the frequency of BPT varied among study participants with most of the patients undergoing therapy only once or twice (6 and 1 patients or 5 and 2 patients for oXiris® and CytoSorb®, respectively). On the other end, multiple BPT was performed in two patients, where oXiris® was applied 11 times, and CytoSorb®10 times (Figure 5). When applied. BPT induced significant decrease in creatinine and procalcitonin concentrations (Table 11).

Table 11. Effects of applied BPT on concentration of creatinine and procalcitonin

Parameter	Before BPT	Following BPT	*P*
Creatinine (µmol/L)	166.0 (91.7 – 295.7)	95.0 (60.8 – 201.7)	0.050
Procalcitonin (ng/mL)	28.3 (9.5 – 90.6)	9.7 (1.4 – 37.4)	0.033

N = 18 for creatinine; N = 17 for procalcitonin. The values refer to both types of applied BPT. *P* value was calculated by Wilcoxon matched-pairs signed rank. BPT: Blood purification therapy

4.5 Antibiotic therapy of study population

A total of 30 different antibacterial drugs were used in the treatment of subjects. Each subject was treated with an average of 4 different antibacterial drugs with minimum of one and maximum of 10 antibiotics. Study patients were most commonly treated with meropenem (36 patients), vancomycin (29 patients), metronidazole (24 patients), linezolid (15 patients) and clindamycin (11 patients). Meropenem was most often administered in a dose of 3x1g/day, vancomycin 2x1g/day, metronidazole 3x500mg/day, linezolid 2x600mg/day and clindamycin 3x900mg/day. The mentioned antibiotics were administered intravenously. The percentage of patients treated with each individual antibacterial drug is shown in Figure 6.

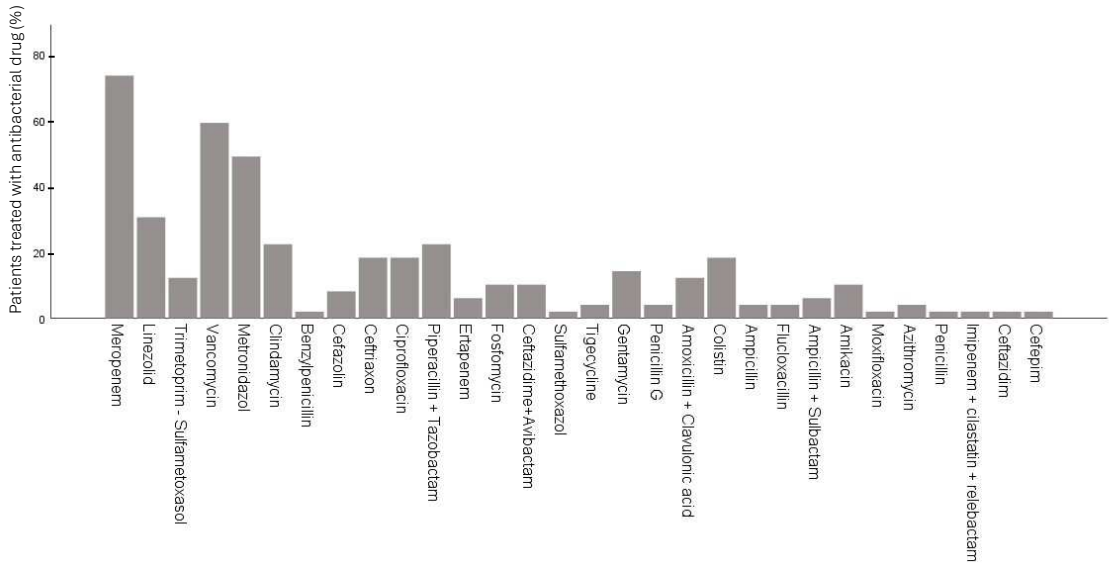

Figure 6. Percentage of patients treated with each individual antibacterial drug

Exclusively patients treated with piperacillin with tazobactam had a higher probability of recovery compared to patients treated with other antibiotics (Figure 7).

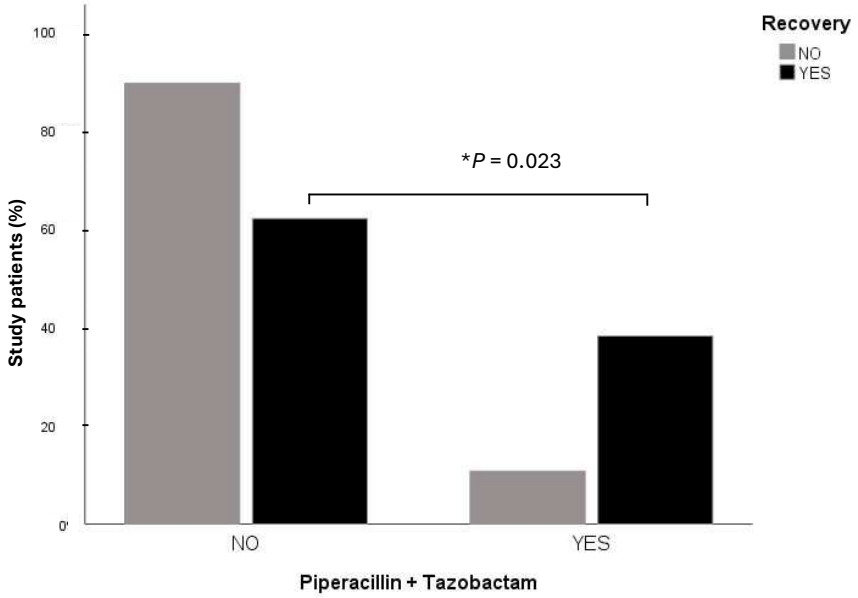

Figure 7. The frequency of the use of piperacillin+tazobactam considering the patients' recovery

*P = 0.023 by Pearson Chi-Square test

Antifungal drugs were also prescribed for 18 patients, namely: voriconazole (N = 1), fluconazole (N = 11), itraconazole (N = 1), caspofungin (N = 2), and micafungin (N = 3). Furthermore, antiviral drugs were ordinated for 2 patients, one patient with concomitant infection of influenza and SARS-CoV 2 viruses was treated with oseltamivir whereas another patient was HIV positive and was treated with bictegravir + emtricitabine + tenofovir alafenamide.

Taking into consideration all three groups of antimicrobial therapy, antibacterials, antifungals and antivirals, only use of antibacterials correlated with the 7th day mortality rate. Namely, patients treated with more antibacterial drugs had a lower probability of mortality 7 days after hospitalization (P = 0.009. The number of antibacterials was a independent predictor of the 7th day mortality rate in contrast to number of antivirals and antifungals. It was shown that higher number of antibacterial drugs used significantly lowers the mortality rate 7 days after the hospitalization with odds ratio of 0.457 (95% CI of 0.216 – 0.963).

This association was not observed in the case of 28th day mortality ($P = 0.649$), nor of the recovery rate ($P = 0.888$).

Moreover, it was shown that patients treated with more antibacterial drugs have longer length of hospitalization in general ($r = 0.494$, and $r = 0.503$ for hospitalization days in ICU and total hospitalization days, respectively; $P < 0.001$). Also, younger patients were treated with higher number of antibacterial drugs ($r = -0.442$, $P = 0.001$).

5. DISCUSSION

Sepsis is the leading cause of death in intensive care units worldwide. Despite development of novel therapies, diagnostics as well as tests, the mortality rates of patients with sepsis, particularly those with renal impairment has increased in recent years (72).

Rational antibiotic therapy is crucial for improving outcomes in critically ill septic patients who undergo RRT and BPT. Our research demonstrated that patients treated at the ICU at the University Hospital of Split were treated with intensive antibiotic therapy, which included as many as 30 different antibacterial agents, five antifungal and two antiviral drugs. Additionally, antibiotic polytherapy was carried out with an average of four antibiotics included in the treatment of each patient. In one patient, only one antibiotic was used, whilst another patient was treated with as many as ten different antibiotics.

Upon further analysis of the prescribing patterns in our study, we identified that antibiotic therapy was initiated immediately upon admission to the ICU, usually on the first day after hospitalization. Two exceptions were noted, which included two subjects diagnosed with viral illness, who commenced antibiotic therapy on the second day of their ICU admission instead.

Although the time from sepsis diagnosis to the initiation of therapy cannot be definitively deduced from our study, it is well-documented that timely initiation of antimicrobial therapy reduces sepsis-related mortality (73). Furthermore, according to current guidelines, when sepsis is suspected or confirmed, antimicrobials should be administered immediately, ideally within one hour of recognition (74). The 2021 Surviving Sepsis Campaign recommends that antimicrobial therapy should be initiated with a loading dose and optimized thereafter according to specific pharmacokinetic/pharmacodynamic principles drug characteristics (28). Septic patients are often in a hyperdynamic states which may heighten antibiotic clearance and lead to alterations in volume of distribution following resuscitation (28).

Moreover, AKI accompanied by RRT may significantly interfere with both pharmacokinetic and pharmacodynamic changes of drugs (75). Consequently, the necessity of antibiotic dose adjustment in these patients highlights a pertinent issue. In our research, dosing of certain antibiotics varied considerably. For the majority of patients, no dose adjustment according to kidney function occurred, however in some cases antibiotic doses were adjusted accordingly. For instance, vancomycin was used in a range of doses from 1x1 g or 2x500 mg/day, over 2x1 g or 4x250 mg/day to 3x1 g/day. As ninety percent of vancomycin is excreted by glomerular filtration, significant drug accumulation can occur in the presence of renal insufficiency.

Additionally, a significant amount of vancomycin is removed during a standard hemodialysis run (76). Adjustment of the dose can be performed according to the creatinine clearance or estimated glomerular filtration rate, and the adjusted dose is usually expressed as percentage of normal dose.

In the case of vancomycin, therapeutic drug-monitoring should be employed especially when vancomycin is used in combination with other potentially nephrotoxic drugs, e.g., aminoglycosides (76). In contrast, it has been shown that combination of vancomycin with piperacillin and tazobactam or cefepime did not induce progression of renal impairment in sepsis induced AKI patients (77). However, most studies have shown that in the population of critically ill septic patients with renal insufficiency, early adjustment of the antibiotic dose with regard to renal function increases mortality (78,79). These findings underscore the importance of carefully customizing therapeutic strategies for septic patients and suggests a possible advantage of delaying adjustments to antibiotic doses, particularly in the first seventy-two hours following diagnosis.

Moreover, it has been shown that piperacillin and tazobactam, cefepime and ceftazidime should ideally be used in higher doses and/or extended infusions, while the recommended dose of meropenem is adequate in the treatment of *Pseudomonas aeruginosa* positive septic patients receiving RRT (80). In 57% of our study patients where the source of sepsis was identified pneumonia represented the most common cause. These findings are consistent with other sources of literature (79). Empirical broad-spectrum antibiotic treatment is usually initiated, and after obtaining specific microbiological findings, targeted therapy is then commenced.

Our study analyzed the microbial etiologies responsible for sepsis, identifying a variety of pathogens with different incidence rates among the patients. The most prevalent pathogen was *Staphylococcus* species, which accounted for 33 cases, representing 67% of the total. Within this group, *Staphylococcus aureu*s was particularly significant, isolated in 19 patients during their hospitalization in the ICU. In our study one of the antistaphylococcal semisynthetic antibiotic, piperacillin+tazobactam was used in 11 patients in the intermittent dosing regimen of 3 or 4x4.5g intravenously and induced recovery in 8 patients, therefore representing the most efficacious antibiotic which was associated with overall recovery rate in our study. Recovery was defined as the complete resolution of clinical signs and symptoms of infection, with no new signs or symptoms associated with the original infection (81). In the study of Aldardeer *et al.* piperacillin+tazobactam was prescribed as initial empiric therapy in 55% patients (79).

Recently, it was suggested that continuous administration of piperacillin+tazobactam can improve clinical outcome when compared with traditional intermittent administration (82). Beyond its apparent benefits, broad-spectrum antibiotics, like piperacillin+tazobactam can cause adverse effects and life-threatening complications due to antimicrobial resistance (83). The number of infections due to multidrug-resistant microorganisms has dramatically increased worldwide and it is suggested that antimicrobial resistance will be responsible for around ten million deaths annually by 2050 (84).

Thus, it is our goal to augment antimicrobial efficacy and prevent the emergence of resistant strains during treatment. In this context, antimicrobial stewardship represents a good strategy for sepsis management. Antimicrobial stewardship has been defined as 'the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact in subsequent resistance (85). Beyond conventional antibiotic therapy and fluid resuscitation therapy, renal replacement therapy has also been widely used in ICU to provide renal support and to modulate the dysregulated immune response for patients with AKIs and immune dysfunctions (86). Traditional RRT mainly removes solutes and water to maintain hemostasis through diffusion and convection mechanisms using semipermeable hemofilters (87). However, contemporary RRT is also proposed as a promising therapy to remove proinflammatory cytokines, pathogen-associated molecular patterns, and damage associated molecular patterns through the adsorption mechanism (88).

In 47% of our study population oXiris® and CytoSorb® were used as modalities for BPT and induced decreases in both creatine and procalcitonin concentration. oXiris® is a hemofilter which functions through its unique three-layer membrane structure to remove endotoxins, eliminate cytokines, and provide renal replacement for critically ill patients with AKIs and immune dysfunctions. CytoSorb® hemadsorption device, can be used as a stand-alone therapy or in combination with extracorporeal circuits, both in pre-dialyzer and post-dialyzer mode (98). It can reduce the level of hydrophobic molecules with a molecular mass up to 55 kDa, like cytokines, bile acids, and myoglobin. CytoSorb® is in clinical use in patients with an excessive immune response such as in sepsis, ARDS, SARS-CoV-2 infections, hyperinflammatory syndromes, and during and after cardiac surgery using cardiopulmonary bypass. In addition, CytoSorb® may be useful in liver failure, elimination of direct acting oral anticoagulants (DOACs) or certain acute intoxications. However, a recent systematic review and meta-analysis reported that there is no evidence of decreased mortality in treatment with CytoSorb® in any of the examined conditions (90).

Based on the KDIGO criteria, all the included patients presented with AKI stage 3. According to a recent meta-analysis and systematic review (66) the most common risk factors for sepsis-associated AKI were septic shock, hypertension, diabetes mellitus, abdominal infection, a history of smoking, positive blood cultures, use of vasopressors, and mechanical ventilation. Based on our results we cannot definitively conclude if sepsis induced renal impairment which required the initiation of RRT.

According to the laboratory findings, our population had higher creatinine and urea concentration, similar daily diuresis and lower estimated glomerular filtration when compared with previous studies conducted in patients with sepsis - associated AKI (77,91). Additionally, duration of hospitalization was twice as long compared to their subjects (77). However, most of our patients had majority of listed risk factors. For example, 39% had one or two comorbidities with arterial hypertension being the most common (37%), and 92 % were treated with mechanical ventilation. Although it was beyond the scope of our study to search for the background and characteristics of AKI in our patients, it is important to emphasize that septic AKI is in general associated with greater alterations in laboratory parameters, greater severity of illness and higher need for mechanical ventilation (66). Results from our retrospective study, with rather small study population of critically ill patients, are in line with larger prospective studies (92). For example, SOFA score was 12.0 in our study and reported to be 11.5 in the study of Bagshaw *et al.* In contrast, our SAPS II score was higher (62.5 vs. 54.1) and duration of hospitalization shorter (19 vs. 37), suggesting our patients, although more seriously ill, had shorter duration of hospital stay. Furthermore, it was observed that 50% of patients with sepsis and AKI had renal recovery within 48 h (79,93). Similarly, our cohort showed a rather high recovery rate (43 %) and low seven-day mortality rate (20 % in our study vs. 53 % in study of Bagshaw *et al.* (92). However, another possible reason for this discrepancy may be the difference in exclusion criteria in our study in comparison to the other ones. Namely, we excluded the patients who stayed in the ICU for longer than 28 days. This exclusion criterion was unavoidable due to practical reasons that prevented us from analyzing the therapeutic lists of patients who had admitted to the ICU for longer than a month. This is also one of the limitations of the present study.

Additionally, as our study was a single center, retrospective, observational and included a relatively small sample size, there may be inherent biases that affected our results. Our study has several strengths. First, we used patient's paper medical histories and daily therapeutic lists instead of discharge letters for the collection of numerous data on clinical status, laboratory findings and therapy. Second, we calculated SOFA and SAPS II scores.

Finally, together with the information on days of hospitalization, these data allowed us to compare patients (with respect to the values of other variables) and draw conclusions about the effects of the applied pharmacotherapy.

6. CONCLUSION

1. Septic patients who underwent RRT and BPT were treated with intensive antimicrobial therapy which included 30 antibacterials, 5 antifungals and 2 antivirals. Although the most used antibiotics were meropenem, vancomycin and metronidazole, the use of piperacillin and tazobactam was the only one associated with patients' recovery rate.
2. The use of antibiotic therapy had no effect on the 28th day of hospitalization mortality rate but was associated with lower 7th day of hospitalization mortality and longer length of hospitalization both in and out of the ICU.

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8. SUMMARY

Introduction: Sepsis accounts for one of the leading causes of death in critically ill patients in the ICU. One of the most common and severe complications of sepsis is acute kidney injury. Due to its high mortality, early recognition and treatment initiation is crucial to prevent severe outcomes. Rational and rapid prescription of antibiotic therapy is essential in the treatment of these patients.

Objectives: The main goal of this research was to determine the frequency and pattern of use of antimicrobial drugs and how the use of antimicrobial pharmacotherapy was associated with the recovery rate and mortality rates on the 7th and 28th day of hospitalization and length of hospitalization of patients with acute kidney injury who underwent renal replacement and blood purification therapy.

Subjects and Methods: This is a retrospective cohort study using data from patients treated in the intensive care unit at the Clinic for Anesthesiology, Reanimation, and Intensive Care in the period from January 1, 2022, to December 31, 2023. Inclusion criteria were the diagnosis of sepsis and a set indication for renal replacement therapy and exclusion criteria included death within 48 hours of diagnosis of sepsis, ICU hospitalization more than 4 weeks (28 days), significant chronic end-stage heart, kidney or liver disease, and insufficient data in the medical records. The study included 49 patients out of 67 patients after applying of these criteria. Patient data and characteristics were extracted from their medical records and data on pharmacotherapy, renal replacement and blood purification therapy, clinical and laboratory findings, microbiological isolates were collected, and the treatment outcomes were performed.

Results: Each subject was treated with an average of four different antibacterial drugs. A total of 30 antibacterials, 5 antifungals and 2 antivirals were prescribed, with meropenem (73 %), vancomycin (59 %) and metronidazole (49 %) being most commonly used ones. Younger patients were treated with higher number of antibacterials (r = -0,442, *P* = 0,001) and those treated with combination of piperacillin and tazobactam had higher probability of complete recovery (*P* = 0,023). Intensive antibiotic therapy was associated with less 7th day mortality rate (*P* = 0,009) and longer in-hospital stay (r = 0,494, and r = 0,503, for ICU and total hospitalization days, respectively, *P* <0,001).

Conclusion: Although septic patients with acute kidney injury who underwent renal replacement and blood purification therapy were treated with intensive antibiotic therapy that included different antibiotics, only the use of a combination of piperacillin and tazobactam increased the recovery rate. The use of antibiotic therapy generally had no effect on the long-term mortality rate but was associated with lower short-term mortality and longer hospitalization of these patients**.**

9. CROATIAN SUMMARY

Naslov: Antibiotsko liječenje u septičnih bolesnika kojima je primjenjena bubrežna nadomjesna terapija i terapija izvantjelesne purifikacije krvi

Ciljevi: Utvrditi učestalost i obrazac antimikrobne terapije te kako je ona povezana s ishodima liječenja, oporavkom i stopom smrtnosti nakon sedam i 28 dana hospitalizacije te trajanjem liječenja.

Ispitanici i metode: U povijesno kohortno istraživanje uključeni su bolesnici liječeni u Jedinici intenzivnog liječenja Klinike za anesteziologiju, reanimaciju i intenzivno liječenje u razdoblju od 1. siječnja 2022. do 31. prosinca 2023. Uključni kriteriji bili su dijagnoza sepse i indicirana bubrežna nadomjesna terapija, a isključni kriteriji uključivali su smrt unutar 48 sati od dijagnoze sepse, hospitalizaciju u JILu liječenja duze od 4 tjedna (28 dana), značajnu kroničnu bolest srca, bubrega ili jetre u završnom stadiju i nedostatne podatke u medicinskoj dokumentaciji. Nakon primjene ovih kriterija, u istraživanje je uključeno 49 od 67 pacijenata. Provedeno je prikupljanje podataka o farmakoterapiji, bubrežnoj nadomjesnoj terapiji, kliničkom statusu te laboratorijskim nalazima, mikrobiološkim izolatima i ishodima liječenja iz medicinske dokumentacije.

Rezultati: Svaki je ispitanik liječen u prosjeku s četiri različita antibakterijska lijeka. Propisano je ukupno 30 antibakterijskih lijekova, pet antimikotika i dva antivirusna lijeka, a meropenem (73 %), vankomicin (59 %) i metronidazol (49 %) bili su najčešće korišteni. Mlađi bolesnici liječeni su većim brojem antibakterijskih lijekova (r = -0,442, P = 0,001), a oni liječeni kombinacijom piperacilina i tazobaktama imali su veću vjerojatnost oporavka (P = 0,023). Intenzivna antibiotska terapija bila je povezana s nižom stopom smrtnosti sedmog dana liječenja (P = 0,009) i dužim boravkom u bolnici (r = 0,494, odnosno r = 0,503, za trajanje intenzivnog liječenja i ukupni broj dana bolničkog liječenja, P <0,001).

Zaključak: Iako su septični bolesnici s akutnom bubrežnom ozljedom podvrgnuti nadomjesnoj bubrežnoj funkciji i terapiji izvantjelesne purifikacije krvi liječeni intenzivnom antibiotskom terapijom koja je uključivala različite antibiotike, samo je primjena kombinacije piperacilina i tazobaktama povećala stopu oporavka. Primjena antibiotske terapije općenito nije imala utjecaja na dugoročnu smrtnosti, ali je bila povezana s nižom kratkoročnom smrtnošću i duljom hospitalizacijom ovih bolesnika.