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ACUTE KIDNEY INJURY: PRESENT AND FUTURE NARRATIVE REVIEW

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ABSTRACT:
ACUTE RENAL INJURY (AKI) IS A CLINICAL SYNDROME THAT HAS MULTIPLE ETIOLOGIES AND IS CHARACTERIZED BY A DECREASE IN KIDNEY FUNCTION. AKI IS A FAIRLY COMMON DIAGNOSIS IN HOSPITALIZED PATIENTS, WITH AN INCREASING INCIDENCE IN RECENT DECADES, BEING ASSOCIATED WITH LOW OUTCOMES AND HIGH HOSPITALIZATION COSTS. GIVEN THE STEADY PROGRESS OF THE LAST DECADE IN THIS REVIEW, WE BRIEFLY DISCUSS THE EVOLUTION OVER TIME OF THE AKI DEFINITION, CLASSIFICATION, NEW METHODS OF DIAGNOSIS AND TREATMENT.

KEYWORDS: ACUTE KIDNEY INJURY, BIOMARKERS, PENTOXIFILINE, NEPHROTOXICS, SARS COV-2.

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INTRODUCTION

Acute kidney failure is the clinical syndrome with multiple etiology and variable severity that is defined by a rapid reduction in glomerular filtration rate (eGFR)[14], (rapid decrease in hours or in weeks), phenomenon leading to nitrogen retention, which can affect free kidneys or those with coexisting chronic kidney disease (CKD)[15].

Many patients have a mixed etiology in which the presence of ischemia, sepsis and nephrotoxicity often co-exist and complicate treatment and early diagnosis. However, this syndrome is quite common among patients without comorbidities and is essential that doctors, especially those without specialization in kidney disease[16], make an early diagnosis[17].

The incidence of AKI has increased in recent decades, as the recognition of the diagnosis is increased, another reason is the increase in life expectancy, the presence of comorbidities such as CKD, and prolonged exposure to nephrotoxics. Although there has been a global decline in global mortality in recent years, it is well recognized that mortality increases with more severe AKI and can reach up to 60% in those with severe conditions[18].

In recently published meta-analyzes, the incidence of AKI in hospital patients using the definition of KDIGO was approximately 22.3% in North America, 31.0% in South America, Australia, and approximately 16.9% in New Zealand 19,3% and 25.2% in Europe. Incidence rate increases globally over 10 years[19].

MATERIAL AND METHODS

This study was conducted in accordance with published guidelines for systematic review, analysis, and reporting of meta-analyses of observational studies.

DIAGNOSIS AND NEW BIOMARKERS FOR AKI

The definition of AKI has undergone significant changes in recent years[20], because it does not adequately define the complexity of the phenomena that occur in a kidney impairment, and has been replaced in the literature with Acute Kidney Injury (AKI). This term, more correctly, includes all changes that occur when there is a kidney injury[21], because

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[14] J. Gameiro, F. J. Agapito, S. Jorge and J. Lopes, "Acute Kidney Injury Definition and Diagnosis: A Narrative Review," *J Clin Med.*, vol. 7, no. 10, p. 307, 2018; A. Covic, M. Apetrii, Ș. Ardeleanu and et al, "Nefrologie," in *Principii teoretice și practice*, Iași, Demiurg, 2011, p. 531.

[15] A. Covic, M. Apetrii, Ș. Ardeleanu and et al, "Nefrologie," in *Principii teoretice și practice*, Iași, Demiurg, 2011, p. 531.

[16] R. Wiersema, S. Jukarainem, R. Eck and et al, "Different aplications of the KDIGO criteria for AKI lead to different incidences in critically ill patients: a post hoc analysis from the prospective observational SICS-II study," *Crit Care*, vol. 24, no. 1, p. 164, 2020.

[17] Z. Li, L. Cai, X. Liang, Z. Du, Y. Chen, S. An, N. Tan, L. Xu, R. Li, L. Li and W. Shi, "Identification and predicting short-term prognosis of early cardiorenal syndrome type 1: KDIGO is superior to RIFLE or AKIN," *PLoSONE*, vol. 9, no. 12, p. e114369, 2014.

[18] J. Gameiro, J. Fonseca, F. Marques and J. Lopes, "Management of Acute Kidney Injury Following Major Abdominal Surgery: A Contemporary Review," *J Clin Med*, vol. 9, no. 8, p. 2679, 2020.

[19] S. Goldstein, B. Jaber, S. Faubel and L. Chawla, "Acute Kidney Injury Advisory Group of American Society of Nephrology. AKI transition of care: a potential opportunity to detect and prevent CKD," *Clin J Am Soc Nephrol.*, vol. 8, no. 3, pp. 476-83, 2013.

[20] S. L. Makris K, "Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes," *Clin Biochem Rev*, vol. 37, no. 2, pp. 85-98, 2016.

[21] A. Covic, M. Apetrii, Ș. Ardeleanu and et al, "Nefrologie," in *Principii teoretice și practice*, Iași, Demiurg, 2011, p. 531.

the earliest and most standardized diagnosis of AKI is important for epidemiological, scientific and clinical purposes[22].

In 2004, at the initiative of the ADQI group (Acute Dialysis Quality Improvement Initiative) proposed an AKI classification system ("Risk, injury, failure, loss, end stage kidney disease" -RIFLE)[23]. RIFLE criteria are commonly based on: acute changes in serum creatinine and the presence of oligo-anuria[24], which have been slightly updated in a new AKIN (Acute Kidney Injury Network) classification to increase the sensitivity of the diagnosis[25]. The definition of KDIGO (Kidney Disease Improving Global Outcomes) is based[26] on three diagnostic criteria: increased serum creatinine, oligo-anuria, initiation of renal function replacement therapy[27].

The AKIN classification emerged from the joint work of nephrologists and intensive care physicians to make the AKI criteria more sensitive and reliable compared to the RIFLE criteria. These definitions did not show a better prognostic acuity in terms of mortality, although it allowed the identification of a larger number of patients with AKI[28]. KDIGO group instead has implemented changes in AKI staging, this new classification has been important for medical practice, especially in terms of time, KDIGO covering both AKIN and RIFLE criteria, taking into account creatinine changes in serum within 48 hours or a decrease in eRFG within 7 days. Furthermore, patients under 18 years of age with eRFG < 35 mL/min and patients with serum creatinine > 4.0 mg/dL were added in AKIN stage 3[29].

[22] W. Huber, J. Schneider, T. Lahmer and et al, "Validation of RIFLE, AKIN, and a modified AKIN definition ("backward classification") of acute kidney injury in a general ICU: Analysis of a 1-year period," *Medicine (Baltimore)*, vol. 97, no. 38, p. e12465, 2018.

[23] C. Ronco, J. Kellum, R. Bellomo and R. Mehta, "Acute Dialysis Quality Initiative (ADQI)," *Contrib Nephrol.*, vol. 182, pp. 1-4, 2013.

[24] A. Libório, K. Branco and C. Torres de Melo Bezerra, "Acute kidney injury in neonates: from urine output to new biomarkers," *Biomed Res Int.*, vol. 2014:601568., 2014.

[25] J. Lopes and S. Jorge, "The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review," *Clin Kidney J.*, vol. 6, no. 1, pp. 8-14, 2013; R. Chu, C. Li, S. Wang, W. Zou, G. Liu and L. Yang, "Assessment of KDIGO definitions in patients with histopathologic evidence of acute renal disease," *Clin J Am Soc Nephrol.*, vol. 9, no. 7, pp. 1175-1182, 2014.

[26] J. Jonny, M. Hasyim, V. Angelia and et al. , "Incidence of acute kidney injury and use of renal replacement therapy in intensive care unit patients in Indonesia," *BMC Nephrol*, vol. 21, no. 191, 2020.

[27] R. Wiersema, S. Jukarainem, R. Eck and et al, "Different aplications of the KDIGO criteria for AKI lead to different incidences in critically ill patients: a post hoc analysis from the prospective observational SICS-II study," *Crit Care*, vol. 24, no. 1, p. 164, 2020.

[28] J. Lopes and S. Jorge, "The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review," *Clinical Kinney Journal*, vol. 6, no. 1, p. 8–14, 2013.

[29] T. Levi, S. de Souza, J. de Magalhães, M. de Carvalho, A. Cunha, J. Dantas, M. Cruz, Y. Guimarães, M. Cruz, Y. Guimarães and C. Cruz, "Comparison of the RIFLE, AKIN and KDIGO criteria to predict mortality in critically ill patients," *Rev Bras Ter Intensiva.*, vol. 25, no. 4, pp. 290-296, 2013.

Table 1 Classifications for AKI: RIFLE, AKIN and KDIGO (adapted from Shin SR et al.)[30].

Criterion (name for RIFLE)		RIFLE	KDIGO	AKIN	The value of diuresis
Stage 1 (Risk)		**≥1,5 the baseline creatinine or ↓ eRFG > 25%**	**≥ 0,3mg/dl increase in creatinine or ↑ ≥ 1,5 times baseline creatinine**	**≥ 0,3mg/dl increase in creatinine in 48h or ↑ ≥ 1,5 − 1,9 times baseline creatinine within 7 days**	**< 0,5 ml/kg/h in > 6 hours**
Stage 2 (Injury)		**≥ 2,2 baseline creatinine or ↓ *eRFG* > 50%**	**≥ 2 x baseline creatinine**	**2,0-2,9 times baseline within 7 days**	**< 0,5 ml/kg/h within 12 hours**
Stage 1 (End stage)		**≥ 3 *x* baseline creatinine or creatinine ≥ 4 mg/dl or ↓ eRFG ≥ 75%**	**≥ 3 x baseline creatinine**	**≥3 times baseline within 7 days or increase to ≥ 4 mg/dl with an acute increase of initation of initation dialisys**	**< 0,3 ml/kg/h in 24 hours or anuria for > 12hours**
Loss of kidney function		**Complete loss of kidney function for > 4 weeks**	-	-	-
Kidney disease in the end stage		**Complete loss of kidney function > 3 months**	-	-	-

The use of non-invasive biomarkers in the diagnosis and management of various pathologies is increasingly reported in the literature, also, their use is particularly important for certain age groups[31].

Serum creatinine is an imperfect biological marker of eGFR that does not allow the identification of mild forms of AKI or CKD in the early stages, thus does not allow the differentiation of prerenal AKI from intrinsic AKI (acute tubular necrosis (ATN), acute glomerulonephritis) or in lupus nephropathy where intrinsic AKI is present but serum creatinine may be normal or elevated[32].

The increase in serum creatinine above the upper limit occurs at a reduction of more than 50% eGFR, and therefore it is necessary to calculate eGFR, by creatinine clearance. The

[30] S. Shin, W. Kim, D. Kim, I. Shin and J. Sohn, "Prediction and Prevention of Acute Kidney Injury after Cardiac Surgery," *Biomed Res. Int.*, vol. 2016, 2016.
[31] R. Ali, F. Al-Obaidi and H. Arif, "The Role of Urinary N-acetyl Beta-D-glucosaminidase in Children with Urological Problems," *Oman Med J*, vol. 29, no. 4, pp. 285-288, 2014.
[32] R. Musa, L. Brent and A. Qurie, "Lupus Nephritis," *StatPearls [Internet]. Treasure Island (FL)*, 2021.

value of serum creatinine also varies depending on age, sex, muscle mass of the patient and eGFR (creatinine excretion)[33].

Currently, eGFR is the standard marker for AKI or CKD. However, eGFR is almost never measured directly in the clinical setting, and surrogate markers of renal function are frequently used. The current eGFR equations (MDRD Study, Cockcroft-Gault and CKD-EPI) cannot be used when the creatinine concentration is not at steady state, as is the case with those who develop AKI because the patient may become oligo-anuric where it should be considered. that eGFR is <10 ml/min[34].

eGFR values are associated with age, sex and body surface area and normal values are between 120 and 130 mL/min at 1.73 m2 in young men and women, respectively (eGFR decreases with age)[35], or co-occurring disease states (heart disease, diabetes, sepsis, etc.)[36].

Recently, the new biomarkers identified for AKI are either low molecular weight proteins that are present in the systemic circulation. They are glomerular filtered (ie markers of glomerular function), either inflammatory mediators released by renal cells or infiltrating inflammatory cells (ie markers of the degree of damage and indicators of the location of the lesion). Small proteins could be enzymes that are released by tubular cells in the urine after tubular cell damage (ie markers of tubular damage)[37].

Modern genomics and proteomics techniques have identified several renal biological markers, such as: cystatin C, kidney injury molecule-1, N-acetyl- β-D-glucosaminidase (NAG), α1/β2-microglobulin neutrophil gelatinase-associated lipocalin, interleukin-18, liver-type fatty acid-binding protein, γ-glutamyl transpeptidase, pi-glutathione S-transferase (pi-GST), retinol binding protein (RBP), etc[38].

The urinary NAG index value is expressed as the ratio of NAG to urinary creatinine, as this relationship shows less variability than urinary enzyme excretion as a function of volume or time[39], which has the ability to change its values early compared to other markers traditionally used (urea, creatinine)[40].

Another study demonstrates the variation of the urinary NAG index before the increase in serum urea and serum creatinine[41].

Among patients, the evaluation of urinary NAG activity is used to monitor the nephrotoxic effects of aminoglycosides, heavy metals or to diagnose diabetic nephropathy.

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[33] E. Mota and et al, "Compendiu de Nefrologie," in *Compendiu de Nefrologie*, Craiova, Editura Medicală Universitară, 2010, p. 55.

[34] K. M. Peter, K. H. Raymond and D. L. Kathleen, "Management of Acute Kidney Injury: Core Curriculum 2018," *Americal Journal Kidney Diseases*, vol. 72, no. 1, pp. 136-148, 2018.

[35] S. Lopez-Giacoman and M. Madero, "Biomarkers in chronic kidney disease, from kidney function to kidney damage," *World J Nephrol*, vol. 4, no. 1, pp. 57-73, 2015.

[36] V. Vaidya, M. Ferguson and J. Bonventre, "Biomarkers of acute kidney injury," *Annu Rev Pharmacol Toxicol.*, vol. 48, pp. 463-493, 2008;48:463-493.

[37] M. Ostermann, B. Philips and L. Forni, "Clinical review: Biomarkers of acute kidney injury: where are we now?," *Crit Care*, vol. 16, no. 5, p. 233, 2012.

[38] S. Firu, C. Streba, D. Firu, D. Tache and I. Rogoveanu, "Neutrophil Gelatinase Associated Lipocalin (NGAL) - a biomarker of renal dysfunction in patients with liver cirrhosis: Do we have enough proof?," *J Med Life.*, vol. 8, pp. 15-20, 2015.

[39] R. Ali, F. Al-Obaidi and H. Arif, "The Role of Urinary N-acetyl Beta-D-glucosaminidase in Children with Urological Problems," *Oman Med J*, vol. 29, no. 4, pp. 285-288, 2014.

[40] W. Han, S. Waikar, A. Johnson, R. Betensky, C. Dent, P. Devarajan and J. Bonventre, "Urinary biomarkers in the early diagnosis of acute kidney injury," *Kidney Int*, vol. 73, no. 7, pp. 863-869, 2008.

[41] R. Sato, S. Soeta, M. Miyazaki, B. Syuto, J. Sato, Y. Miyake, J. Yasuda, K. Okada and Y. Naito, "Clinical availability of urinary N-acetyl-beta-D-glucosaminidase index in dogs with urinary diseases," *J Vet Med Sci*, vol. 64, no. 4, pp. 361-5, 2002.

Elevated values of urinary NAG have been found in patients with nephrotic syndrome or in patients with kidney malformations[42]. Although it may be a good biomarker for AKI, false positive values have been reported in patients with diabetes, rheumatoid arthritis or hyperthyroidism[43].

Serum cystatin C (Cys C) has emerged as a possible alternative to creatinine, but its accuracy may be adversely affected by thyroid dysfunction or systemic inflammatory syndrome. Cys C concentration increases in serum earlier in AKI than serum creatinine, therefore Cys C is often considered a “better creatinine"[44].

New biomarkers can complete the measurement of creatinine clearance or most likely improve the accuracy of AKI diagnosis when used in combination. However, new biomarkers need to demonstrate their clinical applicability, accuracy and cost-effectiveness before implementation in clinical practice[45]. Another reason for new biomarkers applicability in clinical practice is that they have not yet been evaluated with sufficient data in very specific populations for example (infants and the elderly)[46].

CLASIFICATION AND PHISIOPATHOLOGY AKI

An essential function of the kidneys is the excretion and filtration of nitrogen toxins from the body. To achieve this, the kidneys usually receive a quarter of the cardiac output, and when AKI occurs there is a rapid decrease in eGFR which leads to significant nitrogen retention[47]. From a pathophysiological point of view, AKI can be grouped into three broad categories from an etiological point of view[48].

Prerenal AKI causes:

AKI etiology of prerenal cause includes: hypovolemia (hemorrhage, vomiting, excessive sweating, diarrhea, low fluid intake, burns, kidney loss, congestive heart failure), drug-induced vasodilation, autonomic neuropathy, anaphylactic shock, or renal vasoconstriction, decreased cardiac output. The latter can be caused by a heart attack, pulmonary hypertension and excessive peripheral vasodilation associated with sepsis. Usually, a rapid volume recovery therapy will improve renal function, so maintaining an eGFR within normal limits largely depends on optimal renal infusion[49].

[42] S. Kovarikova, "Urinary biomarkers of renal function in dogs: a revew," *Veterinarni Medicina*, vol. 60, no. 11, p. 589–602, 2015.
[43] F. Lombia, A. Muryan, R. Canzonieri and H. Trimarchi, "Biomarkers in acute kidney injury: Evidence or paradigm?," *Nefrologia*, vol. 36, no. 4, pp. 333-464, 2016.
[44] B. Griffin, K. Gist and S. Faubel, "Current Status of Novel Biomarkers for the Diagnosis of Acute Kidney Injury: A Historical Perspective," *J Intensive Care Med.*, vol. 35, no. 5, pp. 415-424, 2020.
[45] M. Schmid, D. Dalela, R. Tahbaz, J. Langetepe, M. Randazzo, R. Dahlem, M. Fisch, Q. Trinh and F. Chun, "Novel biomarkers of acute kidney injury: Evaluation and evidence in urologic surgery," *World J Nephrol.*, vol. 4, no. 2, pp. 160-168, 2015.
[46] S. Pozzoli, M. Simonini and P. Manunta, "Predicting acute kidney injury: current status and future challenges," *J Nephrol.*, vol. 31, no. 2, pp. 209-223, 2018.
[47] H. Manzoor and H. Bhatt, "Prerenal Kidney Failure," *In: StatPearls [Internet]. Treasure Island (FL)*, 2020.
[48] S. Bindroo, B. Quintanilla Rodriguez and H. Challa, "Renal Failure," *StatPearls [Internet]. Treasure Island (FL)*, 2021.
[49] A. M. S. T. Basile DP, "Pathophysiology of acute kidney injury," *Compr Physiol*, vol. 2, no. 2, pp. 1303-1353, 2012.

Intrinsic AKI causes

AKI is results from damage to the renal tubules, vascular structures, glomerulus interstitial, or from obstruction of the renal tubules. intrinsic causes are 10% -50% of all cases of AKI[50]. Ischemic ATN and prerenal nitrogen retention have the same pathophysiological spectrum, so any precipitating factor leading to prerenal nitrogen retention can produce ischemic ATN and may have the same etiology the prerenal causes previously mentioned[51].

Drug-induced intrinsic AKI

Drugs exert therapeutic effects as well as side effects by interacting with certain molecules. These molecular targets are often receptors or enzymes, which propagate a signal from the drug through the effector pathways that ultimately determine the effects of the drug on an organ or the function of the whole body. Drug side effects are additional side effects, usually undesirable, which may occur through the same mechanism of action as the therapeutic effect or through a mechanism distinct from it[52].

The presence of certain pharmaceutical agents can produce ATN leading to damage to the cells of the proximal tubes by the formation of free radicals, alteration of mitochondrial cells and damage to transport systems. The main nephrotoxic substances that are frequently associated with ATN[53] are most commonly caused by antibiotics, contrast agents, cocaine, cisplatin and antiretroviral agents (adefovir, cidofovir, tenofovir, foscarnet)[54], organic solvents, bacterial toxins, administration of intravenous immunoglobulins, natural poisons (mushroom poisoning, snake venom) and synthetics, pigments, myoglobin, crystalloids (uric acid, oxalates, calcium deposited at the tubular level), methemoglobin or tumor necrosis products[55].

Medications are the most common cause of acute interstitial nephropathy (AIN) in all age groups. Non-steroidal antibiotics and anti-inflammatory drugs are commonly associated with AINs, rifampicin, allopurinol and acyclovir are other drugs that can cause AINs. In theory, any drug can precipitate AINs, and the list of contraventional drugs has grown over time[56].

Crystal nephropathy is caused by antivirals (acyclovir), and antibiotics (such as ampicillin)[57]. Chemotherapy used in leukemia can also induce tumor lysis syndrome, a condition characterized by the release of uric acid from dead blood cells and the monosodium urate crystal that precipitates in tubular lumen[58].

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[50] B. McDaniel and M. Bentley, "The role of medications and their management in acute kidney injury," *Integr Pharm Res Pract.*, vol. 4, pp. 21-29, 2015.
[51] M. Hanif, A. Bali and K. Ramphul, "Acute Renal Tubular Necrosis," *StatPearls [Internet]. Treasure Island (FL)*, 2020.
[52] S. Berger and R. Iyengar, "Role of systems pharmacology in understanding drug adverse events," *Wiley Interdiscip Rev Syst Biol Med*, vol. 3, no. 2, pp. 129-135, 2011.
[53] A. Covic, M. Apetrii, Ș. Ardeleanu and et al, "Nefrologie," in *Principii teoretice și practice în nefrologie*, Iași, Demiurg, 2011, p. 536.
[54] B. McDaniel and M. Bentley, "The role of medications and their management in acute kidney injury," *Integr Pharm Res Pract.*, vol. 4, pp. 21-29, 2015.
[55] A. Covic, M. Apetrii, Ș. Ardeleanu and et al, "Nefrologie," in *Principii teoretice și practice în nefrologie*, Iași, Demiurg, 2011, pp. 536-537.
[56] R. Naik and P. Annamaraju, "Interstitial Nephritis," *In: StatPearls [Internet]. Treasure Island (FL)*, 2021.
[57] J. Patel and A. Sapra, "Nephrotoxic Medications," *StatPearls [Internet]. Treasure Island (FL)*, 2020.
[58] S. R. Mulay, C. Shi, X. Ma and H. Anders, "Novel Insights into Crystal-Induced Kidney Injury," *Kidney Dis*, vol. 4, no. 2, pp. 49-57, 2018.

Table 2 Examples of nephrotoxic drugs (adapted from Janak Patel[59]).

Drug	Class	Affected Aria
Acetaminophen	Analgesic	**ATN,**
Acetazolamide	Carbonic anhydrase inhibitor	**Acidosis TP**
Allopurinol	Hypouricemic	**AIN**
Furosemide	Diuretic loop	**AIN**
Rifampicin	Antibiotic	**AIN**
Tacrolimus	Immunosuppressive	**ATN**
Tertracycline	Antibiotic	**ATN**
VAN	Antibiotic	**AIN**

SARS COV-2 ASSOCIATED AKI

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an infection that causes coronavirus disease 2019[60], this disease affects people around the world, with an increased mortality rate between 0, 9% and 7.2%, depending on demographic data, implementation of preventive measures, testing strategies and availability of health care resources[61].

The most common and important clinical manifestations of COVID-19 are febrile conditions (98%), dry cough (76%), fatigue and myalgia (18% each), with the presence of leukopenia (25%) and lymphopenia (63%). Symptoms of upper respiratory tract infection with productive cough and rhinorrhea are uncommon in adults, but more common in adolescents and children. The clinical course of SARS-CoV-2 infection is unpredictable and shows great variability, ranging from asymptomatic infection to multi-organ systemic failure or death (16% -20% being classified as severe or critical)[62].

In addition, the mortality rate is high when the patient has associated pathologies, such as lung or kidney pathologies. A close association between AKI and coronavirus infection has been reported in SARS-CoV and MERS-CoV epidemics. Data from the literature reported that AKI developed in approximately 5% to 15% of cases and the mortality rate was high (70% to 90%) in MERS-CoV and SARS infections[63].

AKI during COVID-19 infection is due to different triggers. Such as: ATN, renal hypoperfusion, irregular inflammatory response, microcirculatory dysfunction, cytokine storm syndrome present in sepsis, direct viral damage and metabolic changes. The presence of angiotensin 2 conversion enzyme receptors in renal tissues could also facilitate viral invasion, resulting in direct damage[64].

Histopathological examinations in COVID-19 infected patients with AKI are limited, but the available evidence suggests that there are many causes of AKI in COVID-19. A study of 26 patients with COVID-19 and AKI showed acute tubular lesions and the presence of

[59] J. Patel and A. Sapra, "Nephrotoxic Medications," *StatPearls [Internet]. Treasure Island (FL)*, 2020.

[60] A. Ahmed, C. Ebad, S. Stoneman, M. Satti and P. Conlon, "Kidney injury in COVID-19," *World J Nephrol*, vol. 9, no. 2, pp. 18-32, 2020; N. Saraladevi, Y. Chih-Wei, H. Shang-Jyh, L. Bi-Cheng, C. Jiang-Hua and J. Vivekanand, "The Novel Coronavirus 2019 epidemic and kidneys," *Kidney International*, vol. 97, no. 5, pp. 824-828, 2020.

[61] A. Ahmed, C. Ebad, S. Stoneman, M. Satti and P. Conlon, "Kidney injury in COVID-19," *World J Nephrol*, vol. 9, no. 2, pp. 18-32, 2020.

[62] N. Saraladevi, Y. Chih-Wei, H. Shang-Jyh, L. Bi-Cheng, C. Jiang-Hua and J. Vivekanand, "The Novel Coronavirus 2019 epidemic and kidneys," *Kidney International*, vol. 97, no. 5, pp. 824-828, 2020.

[63] F. Fabrizi, C. Alfieri, R. Cerutti, G. Lunghi and P. Messa, "COVID-19 and Acute Kidney Injury: A Systematic Review and Meta-Analysis," *Pathogens*, vol. 9, no. 12, p. 1052, 2020.

[64] T. Mallhi, Y. Khan and A. Adnan, "Stratification of Acute Kidney Injury in COVID-19," *Am J Trop Med Hyg*, vol. 103, no. 6, pp. 2164-2167, 2020.

viral particles in both the tubular epithelium and the podocyte at microscopic examination on histopathological examination, which demonstrates a direct kidney infection[65].

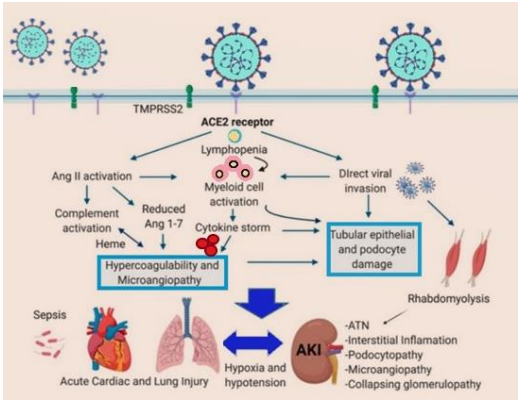

Figure 1: AKI physiopathology in Covid-19 Adapted from Batlle D. et al.[66]

CONTRAST SUBSTANCES-INDUCED AKI

Contrast substances-induced AKI formerly known as contrast-induced nephropathy is a syndrome in which acute kidney dysfunction is diagnosed after intravascular administration of contrast agents. Contrasting agents are widely used for therapeutic and diagnostic purposes. Their nephrotoxicity was first reported 50 years ago and today is one of the most common causes of AKI in hospitalized patients. The pathophysiology is not very well defined. Animal models of AKI suggest several potential mechanisms of nephrotoxicity, including renal ischemia, vasoconstriction, reactive oxygen species formation, and direct tubular toxicity, leading to decreased renal perfusion[67].

Postrenal cause AKI

The most common causes of postrenal AKI are obstruction created by kidney stones, ureteral stones, tumors and thrombi, from those the most encountered etiology of post-renal AKI is obstruction of the ureter. Another noteworthy fact is that a unilateral obstruction of the ureter cannot always produce AKI, the other kidney can compensate for the malfunction of the contralateral kidney and also because the obstruction is gradually formed (as in the case of the tumors)[68].

[65] M. Nadim, L. Forni, R. Mehta and e. al., "COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup," *Nat Rev Nephrol*, vol. 16, p. 747–764, 2020.
[66] D. Batlle, M. Soler, M. Sparks, S. Hiremath, A. South, P. Welling and S. Swaminathan, "Acute Kidney Injury in COVID-19: Emerging Evidence of a Distinct Pathophysiology," *JASN*, vol. 31, no. 7, pp. 1380-1383, 2020.
[67] S. L. Makris K, "Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes," *Clin Biochem Rev*, vol. 37, no. 2, pp. 85-98, 2016.
[68] A. Goyal, P. Daneshpajouhnejad, M. Hashmi and e. al., "Acute Kidney Injury (Acute Renal Failure)," *StatPearls [Internet]. Treasure Island (FL)*, 2020.

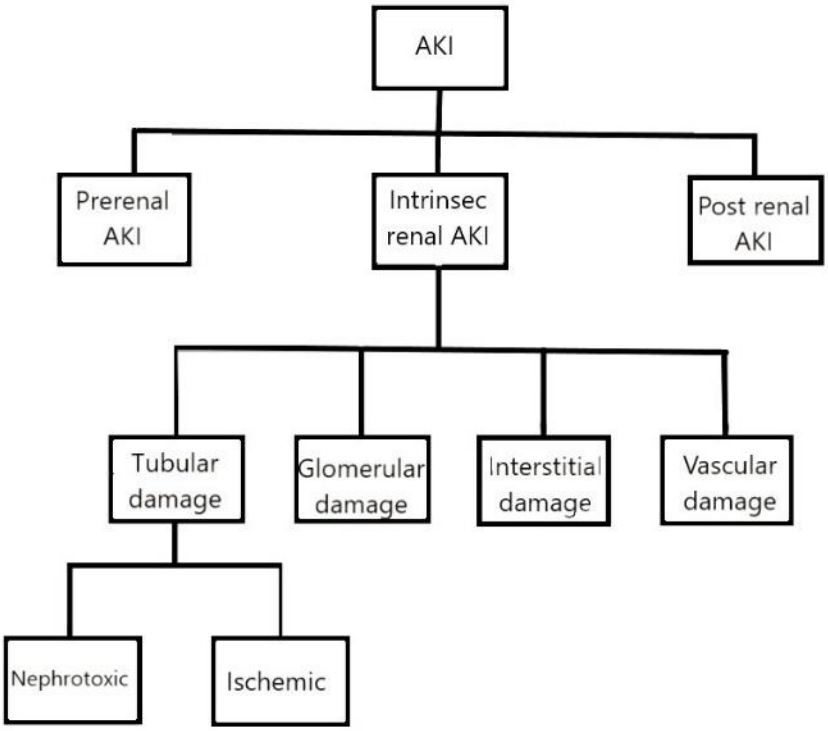

Figure 2: Classification physiopathology for AKI (Adapted from Makris K and colab[69].

TREATMENT AND NEPHROPROTECTION IN AKI

Treatment goals in patients with AKI include: optimization or preservation of renal function done through hydro-electrolytic and acid-base balancing. Also, mineral deficiency compensation is necessary in order to minimize the damage to secondary organs from AKI and good management of the effects of decreased renal function[70].

THERAPY WITH FLUIDS

The main indication for fluid administration in AKI is to optimize intravascular circulating volume, increase cardiac output and increase infusion with the main purpose of improving renal blood flow and glomerular function. Although hypotension is a strong risk factor for AKI, preserving blood pressure alone is not enough to ensure adequate renal perfusion[71].

Hypovolemia can precipitate drug-induced AKI, however, current evidence supporting preventive hydration is merely observational studies, with no consensus on the timing, type of solution used saj volulum required. Extension of prophylactic volume has been shown to prevent damage caused by antivirals, amphotericin B foscarnet, adefovir or

[69] S. L. Makris K, "Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes," *Clin Biochem Rev*, vol. 37, no. 2, pp. 85-98, 2016.
[70] V. Kher, N. Srisawat, E. Noiri and e. al., "Prevention and Therapy of Acute Kidney Injury in the Developing World," *Kidney Int Rep.*, vol. 2, no. 4, pp. 544-558, 2017.
[71] M. Ostermann, K. Liu and K. Kashani, "Fluid Management in Acute Kidney Injury," *Contemporary Reviews In Critical Care Medicine*, vol. 3, pp. 594-603, 2019.

cidofovir, as well as drugs that cause crystalline nephropathy, such as acyclovir, indinavir and sulfadiazine[72].

Crystalloids are fluids used for the treatment of AKI, which contain ionic solutions, which are able to circulate through the semipermeable membranes. Crystalloids are the most commonly used in-hospital fluids worldwide and are financially less expensive than colloids. Crystalloids contain NaCl and other anions that cause increased extracellular fluid tonicity, with the exception of glucose. These physicochemical properties are important factors that determine the effectiveness of the crystalloids for the expansion of vascular volume[73]. In the same time, those physicochemical properties rise the potential of crystalloids for renal toxicity.

Hydration can also have adverse effects especially in patients with reduced cardiac and renal function. It creates an increased risk of pulmonary edema, the main recommendation being to reduce the volume of hydration to prevent fluid overload (which may increase the risk of suboptimal renal treatment)[74].

The SAFE study compares the effect of saline administration on albumin on mortality in a heterogeneous population of UTI patients. In principle, the study did not indicate statistically significant differences in the risk of death among patients receiving saline compared with those receiving albumin[75].

VASSOPRESOR DRUGS

Vasoactive drugs produce systemic vasoconstriction, thus increasing renal infusion[76] vasopressin is one of the drugs that is gaining popularity in the treatment of refractory shock of norepinephrine. Noradrenaline improves diuresis compared to vasopressin, but it has not yet been shown to increase survival or reduce the need for dialysis. It has not yet been established exactly which vasopressor agent is most effective in preventing or treating patients with AKI septic shock. Most studies have focused on dopamine, norepinephrine or vasopressin[77].

THERPAY WITH DIURETICS

Patients with AKI may develop fluid retention and oligo-anuria, which are associated with additional complications, such as respiratory failure or anasarca. In many studies, oliguric AKI has been associated with poorer results than non-oliguric AKI and the use of diuretics in oliguric AKI is common[78].

Furosemide is a loop diuretic that is intensively used in emergency medicine and intensive care because it provides the opportunity to eliminate large amounts of water and

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[72] M. Joannidis, W. Druml, L. Forni and et al, "Prevention of acute kidney injury and protection of renal function in the intensive care unit: update 2017," *Intensive Care Med*, vol. 43, p. 730–749, 2017.
[73] S. Finfer, J. Myburgh and R. Bellomo, "Intravenous fluid therapy in critically ill adults," *Nat Rev Nephrol*, vol. 14, p. 541–557, 2018.
[74] W. Vandenberghe and E. Hoste, "Contrast-associated acute kidney injury: does it really exist, and if so, what to do about it?," *F1000 Research*, vol. 8, no. F1000, p. 753, 2019.
[75] J. Myburgh, D. Cooper, S. Finfer, R. Bellomo, R. Norton, N. Bishop, L. S. Kai and V. Shirley, "Saline or albumin for fluid resuscitation in patients with traumatic brain injury," *N Engl J Med.*, vol. 357, no. 9, pp. 874-84, 2007.
[76] D. Hertzberg, L. Rydén, J. Pickering, U. Sartipy and M. Holzmann, "Acute kidney injury-an overview of diagnostic methods and clinical management," *Clin Kidney J.*, vol. 10, no. 3, pp. 323-331, 2017.
[77] "Section 3: Prevention and Treatment of AKI," *Kidney Int Suppl (2011)*, vol. 2, no. 1, pp. 37-68, 2012.
[78] N.-F. Annie-Claire and J. Bouchard, "Fluid Management and Use of Diuretics in Acute Kidney Injury," *Advances in Chronic Kidney disease*, vol. 20, no. 1, pp. 45-55, 2013.

electrolytes, as long as the kidneys are functional, so hyperhydration can be controlled. However, only low renal function cannot indicate the etiology of AKI. Although loop diuretics are commonly used if fluid retention results from impaired renal function, it is still debatable whether the renal prognosis itself can be improved[79].

Furosemide reduces oxygen consumption in the thick portions of the ascending branch of the Henle loop by interfering with its function and thus will protect it from ischemia. Another benefit is the inhibition of prostaglandin dehydrogenase production, as a result of which decomposes prostaglandin E which is a renal vasodilator. This decomposition of prostaglandin E is also maintaining urinary flow and could prevent renal obstruction[80].

DIALISYS AND AKI

AKI has a high frequency in the UTI, being one of the most serious complications of patients with comorbidities in the UTI. Approximately 4% of patients in the UTI with AKI require dialysis, because specific drug therapy is not effective in patients with AKI[81].

Common indications for dialysis can be 'renal' or 'non-renal', usually for the acute management of life-threatening AKI complications, such as severe uremia, oligo-anuria, severe hyperkalemia, pulmonary edema, hemorrhagic diathesis, pericarditis, uremic or uremic encephalopathy[82]. Another indication of dialysis is metabolic acidosis refractory to treatment, because the kidneys lose their excretory function, thus developing the progression of acidosis[83]. In the meta-analysis performed by Lin WT suggested that dialisys initiated in early stages does not improve survival compared to dialisys initiated late[84].

Figure 3. Kidney function replacement device in operation

[79] D. Patschan, S. Patschan, I. Buschmann and O. Ritter, "Loop Diuretics in Acute Kidney Injury Prevention, Therapy, and Risk Stratification," *Kidney Blood Press Res*, vol. 44, pp. 457-464, 2019.

[80] A. Hegde, "Diuretics in Acute Kidney Injury." Indian journal of critical care medicine : peer-reviewed," *Indian Society of Critical Care Medicine*, vol. 24, no. 3, pp. S98-S99, 2020.

[81] S. Negi, D. Koreeda, S. Kobayashi and e. al, "Renal replacement therapy for acute kidney injury," *Ren Replace Ther 2*, vol. 31, 2016.

[82] C. Nickson, "Renal replacement therapy Indications," 2020.

[83] M. Diaconu, R. Popa, L. Stanescu, N. Guta, C. Georgescu and M. Tancu, "Pharmacological and interdisciplinary therapeutic approach of a patient with cardiac disease, sepsis and chronic kidney disease," *Research & Science Today*, vol. 2, no. 20, pp. 205-212, 2020.

[84] W. Lin, C. Lai, . S. Chang and et al, "Effects of early dialysis on the outcomes of critically ill patients with acute kidney injury: a systematic review and meta-analysis of randomized controlled trials," *Sci Rep*, vol. 9, p. 18283, 2019.

OTHERS THERAPEUTIC STRATEGIES

Glucosteroids are drugs widely used in acute or chronic inflammatory pathology[85], and their efficacy in the treatment of drug-induced AIN has not yet been evaluated by prospective, controlled studies. Glucosteroids are frequently used in the treatment of drug-induced NSAIDs and studies have shown a good recovery of renal function[86]. A multicenter, placebo-controlled, randomized, double-blind study by Laviolle B et al. indicated that low-dose hydrocortisone appears to improve renal function[87].

Pentoxifylline (PTX) administered in AKI for 14 days reduced the values of nitrogen retention and the continuation of treatment for another 14 days after stopping the administration of nephrotoxic, reduced the values of renal function within normal limits[88].

Another experimental study demonstrated the usefulness of PTX have been shown that this drug has improved microcirculation, reduced blood viscosity[89], exerts hemorrhoidal effects, erythrocyte stiffness and platelet aggregation. Its potential to reduce intraglomerular pressure has led to various studies in which PTX has been used as a nephroprotective agent. In fact, data from clinical trials and animal models support the use of PTX as an antiproteinuric agent, this property having a strong anti-inflammatory effect[90].

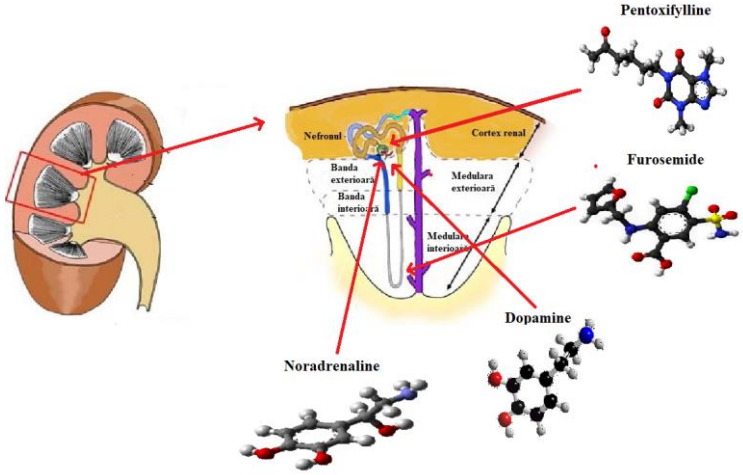

Figure 4.: Actions zone at kidney for different theraputical drogs in AKI

[85] R. Popa, L. Lautaru, R. Lucretiu, D. Ruiu, D. Caragea, M. Olteanu, A. Mihailovici, C. Ene, V. Padureanu, R. Padureanu and V. Cirlig, "Therapy Side Effects in Systemic Lupus Erythematosus," *Current health sciences journal*, vol. 44, no. 3, p. 31, 2018.

[86] G. Fernandez-Juarez, J. Perez, F. Caravaca-Fontán, L. Quintana, A. Shabaka, E. Rodriguez, L. Gadola, A. de Lorenzo, M. Cobo, A. Oliet, M. Sierrax and C. Cobelo, "“Duration of Treatment with Corticosteroids and Recovery of Kidney Function in Acute Interstitial Nephritis.” Clinical journal of the American Society of Nephrology," *CJASN*, vol. 13(12), no. doi:10.2215/CJN.013901, pp. 1851-1858, 2018.

[87] B. Laviolle, D. Annane, C. Fougerou and E. Bellissant, "Gluco- and mineralocorticoid biological effects of a 7-day treatment with low doses of hydrocortisone and fludrocortisone in septic shock," *Intensive Care Medicine*, vol. 38, no. 8, pp. 1306-1314, 2012.

[88] M. Mohammad Waheed El-Anwar, M. Said Abdelmonem, M. Ebtessam Nada, M. Dalia Galhoom and M. Ahmed A. Abdelsameea, "Protective effect of pentoxifylline on amikacin-induced ototoxicity," *ENT-Ear, Nose & Throat Journal*, 2018.

[89] N.-T. Zahra, D.-K. Simin, K. Hossein and L.-P. Mahboob, "A review of the potential protective effects of pentoxifylline against drug-induced nephrotoxicity," *European journal of clinical pharmacology*, vol. 69, 2012.

[90] D.-C. Javier, G. T. Víctor, F. Carla, M.-N. Ernesto, H.-C. Carolina, U.-T. Pablo, R.-O. Marta and O. Alberto, "Pentoxifylline for Renal Protection in Diabetic Kidney Disease. A Model of Old Drugs for New Horizons," *J. Clin. Med*, vol. 8, no. 3, p. 287, 2019.

CONCLUSION

AKI is an increased complexity syndrome with a significant impact on patient outcomes; thus, prevention, early detection and prompt treatment are important to minimize mortality and morbidity. Research in the field of nephrology, especially experimental studies, has led to an improvement in the understanding of the pathophysiology of AKI, an increase in awareness of the incidence and prognostic impact. The perfect biomarker for AKI is still under study and in the future, we need to focus on early diagnostic measures, predictors and new therapeutic protocols.

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All authors report no pottential conflict of interest.

REFERENCES

1. **J. Gameiro, F. J. Agapito, S. Jorge and J. Lopes**, "Acute Kidney Injury Definition and Diagnosis: A Narrative Review," *J Clin Med.,* vol. 7, no. 10, p. 307, 2018.
2. **A. Covic, M. Apetrii, Ș. Ardeleanu and et al,** "Nefrologie," in *Principii teoretice și practice*, Iași, Demiurg, 2011, p. 531.
3. **R. Wiersema, S. Jukarainem, R. Eck and et al,** "Different aplications of the KDIGO criteria for AKI lead to different incidences in critically ill patients: a post hoc analysis from the prospective observational SICS-II study," *Crit Care,* vol. 24, no. 1, p. 164, 2020.
4. **Z. Li, L. Cai, X. Liang, Z. Du, Y. Chen, S. An, N. Tan, L. Xu, R. Li, L. Li and W. Shi,** "Identification and predicting short-term prognosis of early cardiorenal syndrome type 1: KDIGO is superior to RIFLE or AKIN," *PLoSONE,* vol. 9, no. 12, p. e114369, 2014.
5. **J. Gameiro, J. Fonseca, F. Marques and J. Lopes,** "Management of Acute Kidney Injury Following Major Abdominal Surgery: A Contemporary Review," *J Clin Med,* vol. 9, no. 8, p. 2679, 2020.
6. **S. Goldstein, B. Jaber, S. Faubel and L. Chawla**, "Acute Kidney Injury Advisory Group of American Society of Nephrology. AKI transition of care: a potential opportunity to detect and prevent CKD," *Clin J Am Soc Nephrol.,* vol. 8, no. 3, pp. 476-83, 2013.
7. **S. L. Makris K,** "Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes," *Clin Biochem Rev,* vol. 37, no. 2, pp. 85-98, 2016.
8. **W. Huber, J. Schneider, T. Lahmer and et al,** "Validation of RIFLE, AKIN, and a modified AKIN definition ("backward classification") of acute kidney injury in a general ICU: Analysis of a 1-year period," *Medicine (Baltimore),* vol. 97, no. 38, p. e12465, 2018.
9. **C. Ronco, J. Kellum, R. Bellomo and R. Mehta**, "Acute Dialysis Quality Initiative (ADQI)," *Contrib Nephrol.,* vol. 182, pp. 1-4, 2013.
10. **A. Libório, K. Branco and C. Torres de Melo Bezerra**, "Acute kidney injury in neonates: from urine output to new biomarkers," *Biomed Res Int.,* vol. 2014:601568., 2014.
11. **J. Lopes and S. Jorge**, "The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review," *Clin Kidney J.,* vol. 6, no. 1, pp. 8-14, 2013.
12. **R. Chu, C. Li, S. Wang, W. Zou, G. Liu and L. Yang**, "Assessment of KDIGO definitions in patients with histopathologic evidence of acute renal disease," *Clin J Am Soc Nephrol.,* vol. 9, no. 7, pp. 1175-1182, 2014.
13. **J. Jonny, M. Hasyim, V. Angelia and et al**. , "Incidence of acute kidney injury and use of renal replacement therapy in intensive care unit patients in Indonesia," *BMC Nephrol,* vol. 21, no. 191, 2020.
14. **J. Lopes and S. Jorge**, "The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review," *Clinical Kinney Journal,* vol. 6, no. 1, p. 8–14, 2013.
15. **T. Levi, S. de Souza, J. de Magalhães, M. de Carvalho, A. Cunha, J. Dantas, M. Cruz, Y. Guimarães, M. Cruz, Y. Guimarães and C. Cruz**, "Comparison of the RIFLE, AKIN and KDIGO criteria to predict mortality in critically ill patients," *Rev Bras Ter Intensiva.,* vol. 25, no. 4, pp. 290-296, 2013.
16. S**. Shin, W. Kim, D. Kim, I. Shin and J. Sohn**, "Prediction and Prevention of Acute Kidney Injury after Cardiac Surgery," *Biomed Res. Int.,* vol. 2016, 2016.
17. **R. Ali, F. Al-Obaidi and H. Arif,** "The Role of Urinary N-acetyl Beta-D-glucosaminidase in Children with Urological Problems," *Oman Med J,* vol. 29, no. 4, pp. 285-288, 2014.
18. **R. Musa, L. Brent and A. Qurie**, "Lupus Nephritis," *StatPearls [Internet]. Treasure Island (FL),* 2021.
19. **E. Mota and et al,** "Compendiu de Nefrologie," in *Compendiu de Nefrologie*, Craiova, Editura Medicală Universitară, 2010, p. 55.
20. **K. M. Peter, K. H. Raymond and D. L. Kathleen,** "Management of Acute Kidney Injury: Core Curriculum 2018," *Americal Journal Kidney Diseases,* vol. 72, no. 1, pp. 136-148, 2018.
21. **S. Lopez-Giacoman and M. Madero**, "Biomarkers in chronic kidney disease, from kidney function to kidney damage," *World J Nephrol,* vol. 4, no. 1, pp. 57-73, 2015.

22. **V. Vaidya, M. Ferguson and J. Bonventre**, "Biomarkers of acute kidney injury," *Annu Rev Pharmacol Toxicol.*, vol. 48, pp. 463-493, 2008;48:463-493.
23. **M. Ostermann, B. Philips and L. Forni**, "Clinical review: Biomarkers of acute kidney injury: where are we now?," *Crit Care*, vol. 16, no. 5, p. 233, 2012.
24. **S. Firu, C. Streba, D. Firu, D. Tache and I. Rogoveanu**, "Neutrophil Gelatinase Associated Lipocalin (NGAL) - a biomarker of renal dysfunction in patients with liver cirrhosis: Do we have enough proof?," *J Med Life.*, vol. 8, pp. 15-20, 2015.
25. **W. Han, S. Waikar, A. Johnson, R. Betensky, C. Dent, P. Devarajan and J. Bonventre**, "Urinary biomarkers in the early diagnosis of acute kidney injury," *Kidney Int*, vol. 73, no. 7, pp. 863-869, 2008.
26. **R. Sato, S. Soeta, M. Miyazaki, B. Syuto, J. Sato, Y. Miyake, J. Yasuda, K. Okada and Y. Naito**, "Clinical availability of urinary N-acetyl-beta-D-glucosaminidase index in dogs with urinary diseases," *J Vet Med Sci*, vol. 64, no. 4, pp. 361-5, 2002.
27. **S. Kovarikova**, "Urinary biomarkers of renal function in dogs: a revew," *Veterinarni Medicina*, vol. 60, no. 11, p. 589–602, 2015.
28. **F. Lombia, A. Muryan, R. Canzonieri and H. Trimarchi**, "Biomarkers in acute kidney injury: Evidence or paradigm?," *Nefrologia*, vol. 36, no. 4, pp. 333-464, 2016.
29. **B. Griffin, K. Gist and S. Faubel**, "Current Status of Novel Biomarkers for the Diagnosis of Acute Kidney Injury: A Historical Perspective," *J Intensive Care Med.*, vol. 35, no. 5, pp. 415-424, 2020.
30. **M. Schmid, D. Dalela, R. Tahbaz, J. Langetepe, M. Randazzo, R. Dahlem, M. Fisch, Q. Trinh and F. Chun**, "Novel biomarkers of acute kidney injury: Evaluation and evidence in urologic surgery," *World J Nephrol.*, vol. 4, no. 2, pp. 160-168, 2015.
31. **S. Pozzoli, M. Simonini and P. Manunta**, "Predicting acute kidney injury: current status and future challenges," *J Nephrol.*, vol. 31, no. 2, pp. 209-223, 2018.
32. **H. Manzoor and H. Bhatt**, "Prerenal Kidney Failure," *In: StatPearls [Internet]. Treasure Island (FL)*, 2020.
33. **S. Bindroo, B. Quintanilla Rodriguez and H. Challa**, "Renal Failure," *StatPearls [Internet]. Treasure Island (FL)*, 2021.
34. **A. M. S. T. Basile DP**, "Pathophysiology of acute kidney injury," *Compr Physiol*, vol. 2, no. 2, pp. 1303-1353, 2012.
35. **B. McDaniel and M. Bentley**, "The role of medications and their management in acute kidney injury," *Integr Pharm Res Pract.*, vol. 4, pp. 21-29, 2015.
36. **M. Hanif, A. Bali and K. Ramphul**, "Acute Renal Tubular Necrosis," *StatPearls [Internet]. Treasure Island (FL)*, 2020.
37. **S. Berger and R. Iyengar**, "Role of systems pharmacology in understanding drug adverse events," *Wiley Interdiscip Rev Syst Biol Med*, vol. 3, no. 2, pp. 129-135, 2011.
38. **A. Covic, M. Apetrii, Ș. Ardeleanu and et al**, "Nefrologie," in *Principii teoretice și practice în nefrologie*, Iași, Demiurg, 2011, p. 536.
39. **A. Covic, M. Apetrii, Ș. Ardeleanu and et al**, "Nefrologie," in *Principii teoretice și practice în nefrologie*, Iași, Demiurg, 2011, pp. 536-537.
40. **R. Naik and P. Annamaraju**, "Interstitial Nephritis," *In: StatPearls [Internet]. Treasure Island (FL)*, 2021.
41. **J. Patel and A. Sapra**, "Nephrotoxic Medications," *StatPearls [Internet]. Treasure Island (FL)*, 2020.
42. **S. R. Mulay, C. Shi, X. Ma and H. Anders**, "Novel Insights into Crystal-Induced Kidney Injury," *Kidney Dis*, vol. 4, no. 2, pp. 49-57, 2018.
43. **A. Ahmed, C. Ebad, S. Stoneman, M. Satti and P. Conlon**, "Kidney injury in COVID-19," *World J Nephrol*, vol. 9, no. 2, pp. 18-32, 2020.
44. **N. Saraladevi, Y. Chih-Wei, H. Shang-Jyh, L. Bi-Cheng, C. Jiang-Hua and J. Vivekanand**, "The Novel Coronavirus 2019 epidemic and kidneys," *Kidney International*, vol. 97, no. 5, pp. 824-828, 2020.
45. **F. Fabrizi, C. Alfieri, R. Cerutti, G. Lunghi and P. Messa**, "COVID-19 and Acute Kidney Injury: A Systematic Review and Meta-Analysis," *Pathogens*, vol. 9, no. 12, p. 1052, 2020.

46. **T. Mallhi, Y. Khan and A. Adnan**, "Stratification of Acute Kidney Injury in COVID-19," *Am J Trop Med Hyg*, vol. 103, no. 6, pp. 2164-2167, 2020.
47. **M. Nadim, L. Forni, R. Mehta and e. al.,** "COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup," *Nat Rev Nephrol*, vol. 16, p. 747–764, 2020.
48. **D. Batlle, M. Soler, M. Sparks, S. Hiremath, A. South, P. Welling and S. Swaminathan**, "Acute Kidney Injury in COVID-19: Emerging Evidence of a Distinct Pathophysiology," *JASN*, vol. 31, no. 7, pp. 1380-1383, 2020.
49. A**. Goyal, P. Daneshpajouhnejad, M. Hashmi and e. al**., "Acute Kidney Injury (Acute Renal Failure)," *StatPearls [Internet]. Treasure Island (FL)*, 2020.
50. **V. Kher, N. Srisawat, E. Noiri and et. al**., "Prevention and Therapy of Acute Kidney Injury in the Developing World," *Kidney Int Rep.*, vol. 2, no. 4, pp. 544-558, 2017.
51. **M. Ostermann, K. Liu and K. Kashani**, "Fluid Management in Acute Kidney Injury," *Contemporary Reviews In Critical Care Medicine*, vol. 3, pp. 594-603, 2019.
52. **M. Joannidis, W. Druml, L. Forni and et al**, "Prevention of acute kidney injury and protection of renal function in the intensive care unit: update 2017," *Intensive Care Med*, vol. 43, p. 730–749, 2017.
53. **S. Finfer, J. Myburgh and R. Bellomo**, "Intravenous fluid therapy in critically ill adults," *Nat Rev Nephrol*, vol. 14, p. 541–557, 2018.
54. **W. Vandenberghe and E. Hoste**, "Contrast-associated acute kidney injury: does it really exist, and if so, what to do about it?," *F1000 Research*, vol. 8, no. F1000, p. 753, 2019.
55. **J. Myburgh, D. Cooper, S. Finfer, R. Bellomo, R. Norton, N. Bishop, L. S. Kai and V. Shirley**, "Saline or albumin for fluid resuscitation in patients with traumatic brain injury," *N Engl J Med.*, vol. 357, no. 9, pp. 874-84, 2007.
56. **D. Hertzberg, L. Rydén, J. Pickering, U. Sartipy and M. Holzmann**, "Acute kidney injury-an overview of diagnostic methods and clinical management," *Clin Kidney J.*, vol. 10, no. 3, pp. 323-331, 2017.
57. "Section 3: Prevention and Treatment of AKI," *Kidney Int Suppl (2011)*, vol. 2, no. 1, pp. 37-68, 2012.
58. **N.-F. Annie-Claire and J. Bouchard**, "Fluid Management and Use of Diuretics in Acute Kidney Injury," *Advances in Chronic Kidney disease*, vol. 20, no. 1, pp. 45-55, 2013.
59. **D. Patschan, S. Patschan, I. Buschmann and O. Ritter,** "Loop Diuretics in Acute Kidney Injury Prevention, Therapy, and Risk Stratification," *Kidney Blood Press Res*, vol. 44, pp. 457-464, 2019.
60. **A. Hegde**, "Diuretics in Acute Kidney Injury." Indian journal of critical care medicine : peer-reviewed," *Indian Society of Critical Care Medicine*, vol. 24, no. 3, pp. S98-S99, 2020.
61. **S. Negi, D. Koreeda, S. Kobayashi and et. al**, "Renal replacement therapy for acute kidney injury," *Ren Replace Ther 2*, vol. 31, 2016.
62. **C. Nickson**, "Renal replacement therapy Indications," 2020.
63. **M. Diaconu, R. Popa, L. Stanescu, N. Guta, C. Georgescu and M. Tancu**, "Pharmacological and interdisciplinary therapeutic approach of a patient with cardiac disease, sepsis and chronic kidney disease," *Research & Science Today*, vol. 2, no. 20, pp. 205-212, 2020.
64. **W. Lin, C. Lai, . S. Chang and et al**, "Effects of early dialysis on the outcomes of critically ill patients with acute kidney injury: a systematic review and meta-analysis of randomized controlled trials," *Sci Rep*, vol. 9, p. 18283, 2019.
65. **R. Popa, L. Lautaru, R. Lucretiu, D. Ruiu, D. Caragea, M. Olteanu, A. Mihailovici, C. Ene, V. Padureanu, R. Padureanu and V. Cirlig**, "Therapy Side Effects in Systemic Lupus Erythematosus," *Current health sciences journal*, vol. 44, no. 3, p. 31, 2018.
66. **G. Fernandez-Juarez, J. Perez, F. Caravaca-Fontán, L. Quintana, A. Shabaka, E. Rodriguez, L. Gadola, A. de Lorenzo, M. Cobo, A. Oliet, M. Sierrax and C. Cobelo,** "“Duration of Treatment with Corticosteroids and Recovery of Kidney Function in Acute Interstitial Nephritis.” Clinical journal of the American Society of Nephrology," *CJASN*, vol. 13(12), no. doi:10.2215/CJN.013901, pp. 1851-1858, 2018.
67. **B. Laviolle, D. Annane, C. Fougerou and E. Bellissant**, "Gluco- and mineralocorticoid biological effects of a 7-day treatment with low doses of hydrocortisone and fludrocortisone in septic shock,"

Intensive Care Medicine, vol. 38, no. 8, pp. 1306-1314, 2012.

68. **M. Mohammad Waheed El-Anwar, M. Said Abdelmonem, M. Ebtessam Nada, M. Dalia Galhoom and M. Ahmed A. Abdelsameea**, "Protective effect of pentoxifylline on amikacin-induced ototoxicity," *ENT-Ear, Nose & Throat Journal,* 2018.
69. **N.-T. Zahra, D.-K. Simin, K. Hossein and L.-P. Mahboob**, "A review of the potential protective effects of pentoxifylline against drug-induced nephrotoxicity," *European journal of clinical pharmacology,* vol. 69, 2012.
70. **D.-C. Javier, G. T. Víctor, F. Carla, M.-N. Ernesto, H.-C. Carolina, U.-T. Pablo, R.-O. Marta and O. Alberto**, "Pentoxifylline for Renal Protection in Diabetic Kidney Disease. A Model of Old Drugs for New Horizons," *J. Clin. Med,* vol. 8, no. 3, p. 287, 2019.
71. **R. P. et. all,** "Vancomicina efecte adverse," *o revista anume,* vol. 13, 2021.
72. **M. Bokhari and S. Bokhari** , "Renal Artery Stenosis.," *[Updated 2020 May 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing;*, no. https://www.ncbi.nlm.nih.gov/books/NBK430718/, 2020 .
73. **J. Bouchard and R. Mehta** , "Acute Kidney Injury in Western Countries.," *Kidney Dis (Basel),* vol. 2, no. 3, pp. 103-110, 2016.
74. **C. S. Dhar and A. Oommen**, "Epidemiology of COVID-19," *Journal of Digestive Endoscopy,* vol. 11, no. 1, pp. 3-7, 2020.