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The impact of infections on the progression of chronic kidney disease

DOCTORAL THESIS ABSTRACT

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Introduction

Chronic kidney disease (CKD) is defined by the Kidney Disease: Improving Global Outcome international guidelines (KDIGO) as the presence of structural or functional abnormalities that persist for at least three months (Stevens et al., 2024). The most common structural anomalies are: albuminuria – urinary albumin/creatinine ratio over 30mg/g, changes in the urinary sediment – persistent hematuria with dysmorphic red blood cells, leukocyturia, the presence of oval bodies or fatty/granular casts, changes in the macroscopic appearance of the kidneys demonstrated by imaging investigations – multiple cysts, renal asymmetries, congenital or surgical solitary kidney, infiltrative diseases etc., the presence of a renal graft or histopathological changes (Stevens et al., 2024). From a functional point of view, CKD is defined by an estimated glomerular filtration rate below 60ml/min/1.73m2 (Stevens et al., 2024).

The prevalence of CKD is high, affecting approximately 9.1% (8.5%-9.8%) of the population, with major impact on quality of life and on socio-economic status, in 2017 being the 12th cause of death globally (Bikbov et al., 2020; Cockwell and Fisher, 2020). Moreover, mortality caused by CKD, despite diagnostic and therapeutic efforts, unlike other chronic diseases, is not decreasing, on the contrary, it is even estimated that in 2040 it will rise to the 5th place in the list of causes of death (Foreman et al., 2018) (Cockwell and Fisher, 2020).

The main problems caused by CKD are: anemia, caused by a mixed mechanism, both by erythropoietin and iron deficiency – the last one can be relative, caused by the chronic inflammatory status, or absolute, caused by gastrointestinal absorption disorders or bleeding, disorders of mineral metabolism, caused by vitamin D deficiency and secondary hyperparathyroidism, hydro-electrolyte and acid-base disorders, the most common of which being hypervolemia, hyperkalemia and metabolic acidosis, and, last but not least, malnutrition, inflammation and atherosclerosis (MIA syndrome), which is specific to the end stage of CKD (ESKD) (Zyga, Christopoulou and Malliarou, 2011; Bello et al., 2017).

Of these last indicators of severity, perhaps the most often overlooked is malnutrition, despite the fact that its prevalence is very high - up to 31% of adults with CKD, and its presence is correlated with substantially increased mortality (up to four times higher compared to patients within normal limits of nutritional status) (Dai et al., 2017; Rashid et al., 2023). Moreover, by adopting restrictive dietary regimes prior to the

initiation of kidney replacement therapy (KRT), if not changed in time, when the benefits outweigh the risks, malnutrition can be greatly aggravated, especially in the case of association with uncorrected metabolic acidosis, which has an important impact on increasing protein catabolism, with all the risks involved (Iorember, 2018).

The most important risk factors in the occurrence of CKD are: diabetes, hypertension, smoking and obesity (Couser et al., 2011). However, another possible risk factor, often overlooked, can be represented by an infectious episode, the relationship between this and the occurrence of CKD being in both ways, according to several studies. Thus, Ishigami et al. stated, in a study conducted in 2019, that the risk of hospitalization due to an infectious cause increases by 50% in the G3 stage of CKD and two to three times in the G4 and G5 stages compared to the G2 stage (Ishigami and Matsushita, 2019). Moreover, the risk of death following such an episode increases three-fold in the G3b stage compared to the G2 stage, the cause being all the immunological, inflammatory and metabolic changes associated with CKD progression (Thompson et al., 2015; Ishigami et al., 2020). An important aspect is also the link between proteinuria and infectious events, between which a direct proportional relationship has been demonstrated, especially in elderly patients (Iseki et al., 1996; Cravedi and Remuzzi, 2013).

On the other hand, the existence of an infectious episode in the history of a known patient with CKD seems to increase the risk of progression towards the end stage, with the need for KRT, which is why this thesis aims to investigate the impact that infections have on the progression of chronic kidney disease, study conducted on a cohort of 238 patients from the Nephrology section of „Dr. Carol Davila" Clinical Hospital of Nephrology, which is a tertiary reference center in Romania. In addition, another aim was to explore the importance of the hematological parameters as inflammatory markers to help differentiate between acute pyelonephritis and cystitis in patients with chronic kidney disease. For this, another study was conducted, on 70 patients from the database of the same hospital, the motivation being the identification of a cheaper and more widely available substitute for the classic parameters of inflammation, which may be lacking in areas with a low socio-economic level.

Chapter 1. The main infections with renal impact

In the first chapter of the thesis, a literature research was carried out regarding the most common microorganisms that have the potential to cause, directly or indirectly, kidney damage. In the world, it is estimated that there are approximately one trillion species of microorganisms, of which approximately 1400 species are pathogenic for humans, which can be divided into viral, bacterial, fungal and parasitic (217 viruses or prions, 538 bacterial species, 307 fungal species, 66 species of protozoa, and 287 species of helminths) (Rappuoli et al., 2023).

Of these, 22 pathogens that most commonly cause kidney damage were evaluated, comprising ten viral species, ten bacterial species, and two fungal species. The most common types of kidney damage identified in this context were mainly glomerulopathies – IgA nephropathy, minimal change disease, membranous nephropathy, post-infectious or infection-related glomerulonephritis, membrano-proliferative glomerulonephritis and focal and segmental glomerulosclerosis, but they were also described cases of tubulo-interstitial nephropathy and thrombotic microangiopathy. The frequency of acute kidney injury in these situations was variable, explained by the severity of the infection, the immune status of the host, and the rapidity of initiation of antibiotic treatment. Also, the great variability of the types of renal damage induced by the same microorganism requires the detailed investigation of the pathophysiological and immunological mechanisms involved, because the identification of targeted therapies from the beginning could, at least theoretically, minimize the impact of these infectious episodes.

Table I.1. The main microorganisms with renal tropism

Categories	Involved Microorganism	The type of reno-urinary injury	References
Viruses	HIV	HIVAN, HIVICK, FSGS	(Prasad and Patel, 2018b) (Naicker, Rahmanian and Kopp, 2015)
	HAV	Mezangio-proliferative glomerulonephritis, ATN, FSGS, MCD, IgAN, amiloidosis	(Prasad and Patel, 2018b) (An *et al.*, 2023) (Kron and Hedger, 1984) (Han *et al.*, 2010) (Shah and Amarapurkar, 2018)

	HBV	MN, MPGN, mixed cryoglobulinemia, PAN, IgAN, FSGS	(Prasad and Patel, 2018b)
	HCV	MN, MPGN, mixed cryoglobulinemia, PAN, IgAN, TMA, FSGS	(Prasad and Patel, 2018b) (Perico *et al.*, 2009)
	Parvovirus B19	FSGSc, FSGS, MN, MCD, MPGN, TMA, HUS, PAN, granulomatous polyangiitis	(Prasad and Patel, 2018b) (Waldman and Kopp, 2007) (Kauffmann *et al.*, 2020)
	EBV	MN, GN with IC, AIN, CIN, AKI caused by myositis, HUS, hemophagocytic syndrome	(Prasad and Patel, 2018b) (Moretti *et al.*, 2017) (Yang, Lin and Shen, 2023) (Becker *et al.*, 1999)
	Hantavirus	ATIN, Mezangial glomerulonephritis	(Prasad and Patel, 2018b)
	VZV	DPGN, MCD, ATN, primitive MN	(Prasad and Patel, 2018b) (Premužić *et al.*, 2018) (Li *et al.*, 2023)
	CMV	FSGSc, MN, IgAN, GN with IC, MPGN, TMA, risk of graft loss	(Prasad and Patel, 2018b) (López-Oliva *et al.*, 2017)
	Polyoma	PVAN	(Prasad and Patel, 2018b)
Bacterii	Streptococcus pyogenes	PIGN, IAGN, ATN, AIN	(Prasad and Patel, 2018b) (Chang *et al.*, 2011)
	Staphylococcus aures Staphylococcus epidermidis	PIGN, IAGN, ATN, DPGN, AIN, IAGN-IgA, MPGN, persistent UTI	(Prasad and Patel, 2018b) (Xu *et al.*, 2023)
	Salmonella typhi Salmonella paratyphi	ATN, HUS, AIN, rabdomyolysis with AKI, APN	(Prasad and Patel, 2018b) (Ata *et al.*, 2021) (Rus and Kersnik Levart, 2010)
	Escherichia coli	HUS, UTI	(Prasad and Patel, 2018b);

			(Zagaglia *et al.*, 2022)
	Leptospira	ATN, AIN, CTIN, Mezangio proliferative glomerulonephritis	(Prasad and Patel, 2018b) (Silva, Brandão and Esteves, 2016)
	Mycobacterium tuberculosis	CIN, GIN, DPGN, amiloidosis, extensive papillary necrosis and obstructive uropathy	(Prasad and Patel, 2018b); (Merchant, Bharati and Merchant, 2013) (Daher, Barros and da Silva Junior, 2013)
	Legionella	AIN, rabdomyolysis and AKI	(Prasad and Patel, 2018b) (Soni and Peter, 2019)
	Yersinia enterocolitica	AIN, AGN	(Prasad and Patel, 2018b) (Denneberg *et al.*, 1981)
	Brucella	AIN, CTIN, ATN, DPGN, MPGN, APN, IgAN, MCD, MN, vasculitis, mixed cryoglobulinemia	(Prasad and Patel, 2018b) (Ceylan *et al.*, 2009) (Alkan *et al.*, 2022) (Savaj, 2020) (Sabanis *et al.*, 2016)
	Campylobacter jejuni	AIN, DPGN, HUS, IgAN	(Prasad and Patel, 2018b) (Bowen, Hangartner and Macdougall, 2016) (Carter and Cimolai, 1991)
Fungi	Candida	UTI	(Prasad and Patel, 2018b)
	Aspergillus	Renal microabscesses	(Prasad and Patel, 2018b)

AGN – acute glomerulonephritis; AIN – acute interstitial nephritis; AKI – acute kidney injury; APN – acute pyelonephritis; ATN – acute tubular necrosis; CIN – chronic interstitial nephropathy; CMV – cytomegalovirus; CTIN – chronic tubulo-interstitial nephropathy; DPGN – diffuse proliferative glomerulonephritis;EBV – Ebstein-Bar virus; FSGS - focal and segmental glomerulosclerosis; FSGSc – collapsing focal and segmental glomerulosclerosis; GIN – granulomatous interstitial nephropathy; HAV – hepatitis A virus; HBV – hepatitis B virus; HCV – hepatitis C virus;HIV – human immunodeficiency virus; HIVAN – HIV-associated nephropathy; HIVICK – HIV associated immune complex kidney disease; HUS – hemolytic uremic syndrome; IAGN – infection associated glomerulonephritis; IC – immune

complexes; IgAN – IgA nephropathy; MCD – minimal change disease; MN – membranous nephropathy; MPGN – membrano-proliferative glomerulonephritis; PAN – polyarteritis nodosa; PIGN – post-infectious glomerulonephritis; PVAN – polyoma virus nephropathy; UTI – urinary tract infection; TMA – thrombotic microangiopathy; VZV – varicella-zoster virus.

Chapter 2. Septic acute kidney injury – importance, mechanisms involved, long-term prognosis and treatment options

In the second chapter of the thesis was explored the current status of knowledge regarding septic acute kidney injury (sAKI), one of the most severe forms of kidney damage, with a serious prognosis and high in-hospital mortality. Also, there are several aspects that are worth mentioning: firstly, "the incidence of AKI in the general population has remained relatively stable in the last decade"(Kashani et al., 2017), secondly, this incidence can reach 67% in critical patients in intensive care units, with septic AKI being the leading cause of it, with in-hospital mortality ranging from 21% to 70%, (Thakar et al., 2009; Murugan and Kellum, 2011) and, last but not least, a 9-year Mayo Clinic Hospital study claimed that "adjusted risks for AKI and mortality were similar across continents and regions" (Hoste et al., 2015). These arguments demonstrate that almost nothing has improved in the last decade in the management of critically ill patients in terms of preventing or treating AKI in general and sAKI in particular, which is why a closer look at the underlying mechanisms is needed.

The risk of AKI occurrence depends on several factors, the most frequently mentioned being sepsis, coronary artery disease, chronic liver disease, CKD, nephrotoxic medication and the use of vasopressors (Jiang et al., 2021). Another extremely important aspect is that the episode of AKI should not be seen as isolated, but rather as a primum movens to the development of CKD, these two pathologies amplifying each other (Venkatachalam MA, 2010; Murugan and Kellum, 2011). Several mechanisms have been proposed for this, the most frequently mentioned being vascular injury, glomerular hyperfiltration and, finally, interstitial fibrosis, the consequence being an irreversible loss of nephrons that leads, over time, to a decrease in the survival of kidney function, with all the associated complications (Romagnani et al., 2017). As expected, the elderly are most affected due to reduced nephron reserve and comorbidities (Kellum et al., 2021). The pathophysiological mechanisms proposed in the development of sAKI consist of hemodynamic factors that induce microvascular dysfunction, inflammation, and metabolic and cellular responses to injury.

Another aspect that is of great importance and which has not currently entered clinical practice, despite the multiple studies that searched its importance, is represented by the intestinal microbiome, which forms the colo-renal axis (Rabb, Pluznick and Noel,

2018). The role of the intestinal microbiome is complex, having the function of metabolizing nutrients, synthesizing B and K vitamins and certain neurotransmitters, and participating in the regulation of the immune system and in the natural protection against infections (Al Bander et al., 2020; Gomaa, 2020).

On the other hand, the alterations of intestinal microbiome can lead to the occurrence of inflammation, which is linked to many chronic diseases – obesity, atherosclerosis, type 2 diabetes mellitus, inflammatory bowel diseases and even schizophrenia or amyotrophic lateral sclerosis (Al Bander et al., 2020). Moreover, this imbalance is also associated with a particular cytokine pattern, with a pro- or anti-inflammatory role. Regarding sepsis, inflammation caused by the multitude of cytokines involved plays a very important role, and a key element is the inflammation of the digestive tract, because, when combined with altered blood flow, it leads to intestinal injury, damage to the intestinal barrier, consequent bacterial translocation, and, finally, to the amplification of the systemic inflammatory response, with the appearance of multiple organ failure and death (Habes et al., 2018).

The intestinal microbiome is also characterized by the synthesis of short-chain fatty acids (SCFAs) through which it modulates a multitude of functions, both locally and remote, including the kidneys. Locally, it is worth noting that these fatty acids stabilize hypoxia-induced factors, thus interacting with DNA transcription and promoting immune tolerance, which is essential in maintaining homeostasis. Also for this a key role is played by butyrate, one of the types of fatty acids that activates the PPAR-γ receptor and which maintains a hypoxic microenvironment, with the role of suppressing the development of pathogenic species. In the kidneys, these fatty acids have the role of modulating arterial pressure via the olfactory receptor 78, improving kidney function during sAKI - as it was demonstrated in a murine model after administration of SCFA or acetate-producing bacteria and, last but not least, to favor mitochondrial biogenesis, the consequence being the amelioration of the effect of hypoxia in renal epithelial cells (Pluznick, 2016; Prasad and Patel, 2018a; Zhang et al., 2018). Considering these aspects, several therapeutic strategies have been proposed to modulate inflammation by treating dysmicrobism, the most used being the administration of pre- and probiotics, broad-spectrum antibiotics or selective digestive decontaminants, such as non-resorbables antibiotics (usually combinations between tobramycin and colistin) or antiseptics, with promising results,

although not entirely confirmed in all studies (Rabb, Pluznick and Noel, 2018; Zhang et al., 2018; Al Bander et al., 2020; Chávez-Íñiguez et al. al., 2023).

The study also looked for prognostic factors in sAKI, identifying a large number of potential molecules. However, two of these are considered to be the most sensitive and specific predictive markers for the occurrence of AKI in critically ill patients, namely tissue inhibitor of metalloproteinase 2 (TIMP2) and insulin-like growth factor binding protein 7 (IGFBP7), which also have the main advantage that are not influenced by the dysfunction of other organs (Gómez and Kellum, 2016; Wang, Shen and Zhou, 2023). The others are the neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), tumor necrosis factor receptor (TNFR), kidney injury molecule 1 (KIM-1), netrin-1, and osteoprotegerin (Mishra et al., 2005; Zarjou and Agarwal, 2021; Zarjou and Agarwal, 2022; Xie and Mohamed, 2017). Despite intensive research on the identification of the earliest, most sensitive and most specific marker for the occurrence of sAKI, in daily practice the most frequently used and the only one included in the guidelines, remains serum lactate (Singer et al., 2016).

Also, despite the scientific advances related to the mechanisms and molecules involved in the pathogenesis of sAKI, the treatment has not changed significantly, only a few molecules reaching clinical trials and proving their effectiveness. Among these, interleukin 1 receptor antagonist, mesenchymal stem cells, angiotensin II are worth mentioning, although the results are controversial with the last one, given that some large, albeit retrospective, studies reported better survival in those who continued medication with inhibitors of the renin-angiotensin-aldosterone system, the administration of pre- and probiotics, or digestive tract decontaminants, as well as the use of the stress-induced heme-oxygenase 1 (HO-1) enzyme system (Zarjou and Agarwal, 2011; Flannery et al ., 2018; Zhu et al., 2014; Zhang et al., 2014). Other agents have only therapeutic potential, requiring future research to clearly demonstrate their benefit in humans: soluble thrombomodulin, matrix metalloproteinase 9 (MMP9), stem cell factor release, and fenofibrate (Akatsuka et al., 2020; Zarjou and Agarwal, 2011 ; Gómez and Kellum, 2016; Pei et al., 2018). Among the vasopressors, the most commonly used is noradrenaline, to which vasopressin can be added if the response is not optimal (Hamzaoui, Scheeren and Teboul, 2017; Deng et al., 2023; Monnet et al., 2023; Gordon et al.., 2010).

Chapter. 3. The importance of urinary infections in patients with Chronic Kidney Disease

Chronic kidney disease represents a risk factor for infectious events, in general, due to all the immunological, metabolic and inflammatory changes, but also due to the frequent contact of patients with medical services (Scherberich, Fünfstück and Naber, 2021). Moreover, the most frequent cause of hospitalization in these patients is the occurrence of an infectious episode. Given that urinary tract infections (UTIs) affect approximately 50% of women and 5% of men throughout their lifetime, there is a need to explore their importance in patients with BCR, in a first step by researching the medical literature (Hooton and Gupta, 2021).

Susceptibility to urinary tract infections is controlled by innate signaling pathways, which can be modified by different genetic polymorphisms (Godaly, Ambite and Svanborg, 2015). Among them, the genes that affect the expression of Toll-like receptors (TLRs) are of the greatest importance, because these receptors have an essential role in protecting the urothelium and their polymorphisms can enhance or, on the contrary, diminish this function (Ambite et al., 2021). The most important Toll-like receptors are TLR 2, 4 and 5 (Godaly, Ambite and Svanborg, 2015). Other important polymorphisms are those involving vascular endothelial growth factor A (VEGFA) and transforming growth factor beta 1 (TGFβ1), which are associated with renal scarring and CKD progression after UTI, particularly in patients with vesicoureteral reflux (Hussein et al., 2010; Godaly, Ambite and Svanborg, 2015).

Also, CXC chemokines and their receptors have an important role in providing a local inflammatory response against UTI (Olszyna et al., 2001). Thus, polymorphisms in the IL-8 receptor (CXCR1), which is an essential receptor involved in the recruitment of neutrophils, and therefore in ensuring an optimal response of the innate immune system, may be associated with UTI, especially in children (Ragnarsdóttir et al., 2008; Han et al., 2019). On the other hand, further research is needed as the evidence is controversial (Gond, Singh and Agrawal, 2018). Also, a low level of CXCR2 was associated with a higher risk of UTI in premenopausal women (Smithson et al., 2005).

Another important aspect that favors the multiplication of uropathogens is the chronic pro-inflammatory status existing in patients with CKD. Cellular immunity is

deficient and is characterized by a pronounced apoptosis of CD4+ T lymphocytes and high levels of TNF-α and IL-6, which is not, as might be expected, a protective mechanism (Johnson, 1989; Walsh et al., 2012; Hooton and Gupta, 2021; Scherberich, Fünfstück and Naber, 2021). Humoral immunity is not intact either, characterized by a lower level of secretory immunoglobulins (sIgA, sIgM), especially in uremic children, leading to a poorer defense against fimbriated bacteria in the urinary tract (Walsh et al., 2012; Shankar, Narasimhappa and N.S., 2021). Also, perhaps one of the most important aspects is that the patients with CKD almost always have other comorbidities, which have their own impact on the immune system and the host's ability to protect against microbial aggression (Ishigami and Matsushita, 2019).

An aspect that is often overlooked in these situations is represented by the urinary microbiome, which, although in the past it was considered non-existent, currently a multitude of species that form it are known. Thus, a study developed by Modena et al., which compared a healthy control group with renal transplant recipients and those who developed cellular rejection of the graft, associated with fibrosis and tubular atrophy, found that Streptococcus, which is the dominant gene of the microbiome in healthy men, it was reduced in transplant recipients and even more in transplant rejection patients (Modena et al., 2017). Other studies have shown that microbiome diversity is associated with glomerular filtration rate, neurogenic bladder dysfunction, interstitial cystitis and stress urinary incontinence (Whiteside et al., 2015; Wehedy, Shatat and Al Khodor, 2022).

Asymptomatic bacteriuria represents a particular situation in UTI. It is defined as more than 10^5 colony-forming units in urine culture, but without any signs/symptoms of urinary infection (Nicolle et al., 2019). Its prevalence increases with age and predominantly affects women – over the age of 65, more than 15% of women have asymptomatic bacteriuria, and this number rises to almost 50% in those living in social settlements in the general population (Nicolle et al., 2019). In patients with CKD, its prevalence is around 6.6% (Kwon et al., 2020). The occurrence of asymptomatic bacteriuria is favored by genetic alterations of the innate immune system, and among these, the most common polymorphism is the one affecting TLR4 (Iseki et al., 1996; Godaly, Ambite and Svanborg, 2015). The 2019 updated guideline of the Infectious Diseases Society of America states that only pregnant women in the first trimester and patients undergoing urological procedures should be treated with antibiotics (Nicolle et al., 2019).

In patients with CKD, the most common pathogen involved in the occurrence of UTI is E.coli, and the most prone are those with diabetic nephropathy, nephrotic syndrome, polycystic disease, urolithiasis and those receiving immunosuppressive treatment (Scherberich, Fünfstück and Naber, 2021) . The greatest risk of a UTI in such a patient who almost always has multiple co-morbidities and in whom there is a constellation of immunological and metabolic abnormalities is that of urosepsis - especially in those with diabetes, those hospitalized for prolonged time, those who have a permanent urinary catheter and those in whom the causative agent is Klebsiella spp. (Modena et al., 2017). The risk of mortality in these patients with urosepsis was extensively assessed at 1, 2, 6 and 12 months and found to progressively increase from 8.6% in the first month to 17.6% at one year (Tocut et al., 2022). In this category, the predictive factors of mortality at 30 days were the Charlson score - explainable in terms of multiple comorbidities, and infection with a strain of E.coli resistant to the third generation of cephalosporins (Tocut et al., 2022). In addition, it should be taken into account that not only this severe complication of a UTI is to be avoided, but ideally any kind of UTI, as there are studies that show an increased risk of problems in the renal sphere and accelerated progression to end stage kidney disease (ESKD) in patients at G3-G5 stages (Hwang et al., 2013; Ishigami et al., 2020; Kuo et al., 2020).

It should be noted that, in the evaluation of CKD progression after an infectious episode, regardless of its nature or the affected organ, a component that can be essential and that is often overlooked is the nephrotoxicity of antibiotics. Moreover, especially in patients with CKD there is a risk that, in the case of incorrect administration of antibiotics, which can happen in up to 64% of cases regarding the administration of cotrimoxazole or fluoroquinolones, they become nephrotoxic through a multitude of mechanisms: interstitial nephritis, direct tubular toxicity, acute tubular necrosis (the most common cause of AKI), intratubular crystal deposits, immune dysfunction, and decreased renal perfusion, and this may in fact be responsible for the accelerated decline of renal function (Fanos and Cataldi, 2001; Morales-Alvarez, 2020). One solution to minimize the impact of antibiotics on the microbiome, which may help in modulating the general impact, is the co-administration of probiotics, such as Lactobacillus rhamnosus GR-1 or Lactobacillus reuteri, with some studies arguing that they could even be used instead of antibiotics in certain categories of patients who have uncomplicated UTIs (Hiergeist and Gessner, 2017).

Chapter 4. Study I. The impact of infections on the progression of Chronic Kidney Disease

The main hypothesis of the study: an infectious episode occurring in a patient with chronic kidney disease induces a faster progression of it toward ESKD independently of other factors.

A retrospective, observational study was developed on a cohort of 238 dialysis patients, from the Nephrology Clinic of the,,Dr. Carol Davila" Clinical Hospital of Nephrology. Each patient was followed retrospectively from the time of their first consultation in the Clinic for five years or until the initiation of kidney replacement therapy (KRT), if it occurred before the end of the five years. The search was especially focused to identify the appearance of an infectious episode during this period. To test the hypothesis, statistically significant differences between those with and without infections were assessed using Mann-Whitney U and Fischer exact tests, Kaplan-Meier survival curves were created, univariate Cox regression was performed to identify risk factors for KRT in the cohort and finally the variables obtained from the univariate analysis were included in a multivariate Cox model to identify independent predictors of KRT.

The following parameters were recorded for each patient: age, sex, comorbidities - also evaluated by the Charlson score, complete blood count and inflammation markers values at the time of the first visit to the hospital, the presence of an infectious episode, classified as mild, moderate or severe, the microorganism involved, where it could be identified, antibiotic treatment prescribed, episodes of AKI and the need to initiate KRT. Information related to infectious episodes was obtained in several ways: most commonly patients presented directly to the clinic at the time of such an episode, and we used our own clinical and laboratory results; another way used was from information identified in patient discharge notes from other hospitals or clinics, information that was added to the hospital's database at the time the patient presented for follow-up.

In the cohort, 117 patients had at least one infectious episode – these being classified according to severity into mild, moderate and severe. In the evolution of each patient, the occurrence of a maximum number of three infectious episodes was followed, each documented as the type of infection, the microorganism involved, where

identification was possible, and the impact on kidney function estimated on the basis of serum creatinine.

The variables that were significantly different in the group of patients who had at least one infectious episode were: age – higher: p=0.004, hemoglobin and lymphocytes from the first admission – lower: p=0.03 and p=0.02, female gender was frequent – p=0.01, hematuria and leukocyturia from the first admission: p=0.01 and p=<0.001, time to reach the endpoint – lower: p=0.007, initiation of KRT – more frequent: p=0.004 and, as expected, final glomerular filtration rate was lower in the group with infections: p=0.017. An extremely important aspect that must be emphasized is that there were no differences between the two groups - with and without infections, in terms of the initial stage of CKD, the etiology of CKD and the risk group calculated according to creatinine and proteinuria, because a different distribution of these variables could have led to erroneous conclusions, as a patient in a more advanced stage of CKD or at higher risk would be expected to require KRT more rapidly independently of other factors. Also, with the exception of chronic obstructive pulmonary disease, which was more frequent in the group of those who had infections - p=0.008, the other comorbidities evaluated - arterial hypertension, stroke, diabetes, neoplasms, heart failure and chronic venous insufficiency had also equal distribution in the two groups.

Kaplan-Meier analysis reported that there was a significant difference in five-year KRT-free survival between those without infections and those who experienced at least one infectious episode – much lower in the last subgroup – p (Log-Rank)=0.005 . Severity of infectious episodes was also associated with lower kidney function survival - differences emerged between those with no infectious episode versus those with mild infections (p Log-Rank=0.007) and those with severe infections (p Log-Rank=0.043). Notably, there were no significant differences related to moderate infections, most likely due to the small number of these in the cohort. On the other hand, survival of kidney function did not appear to decrease with increasing number of infections, the only significant difference being between those without any infectious episode and those with only one such event – p Log-Rank 0.01, which may argue, however, the need for a careful therapeutic attitude from the first such episode. Last but not least, the presence of a septic AKI was not associated with a faster reaching of the endpoint, an aspect also explained by the small number of these events – p Log-Rank 0.07.

In the univariate Cox model several variables were associated with increased risk of initiation of KRT. Thus, among those recorded at the time of the first visit to the clinic were: advanced age, a lower level of hemoglobin, the presence of chronic obstructive pulmonary disease, the presence of hematuria, as well as increased values of serum creatinine and proteinuria/24h. The presence of an infectious episode was associated with a 1.7-fold increase in the risk of initiating KRT. Among the types of infections in the cohort, only some of those present at the first episode were significant, namely lower urinary tract infections – increased the risk 1.9 times and acute lower respiratory tract infections – increased the risk 3.6 times. Last but not least, elevated serum creatinine values at the time of an infectious episode were associated with increased risk of KRT.

These variables were subsequently included in a multivariate Cox model, which returned advanced age, creatinine and proteinuria/24h at baseline, and the presence of an infectious episode as independent predictors of faster progression to TSFR. The exact values are shown in Table IV.1

Table IV.1. Independent predictors of KRT initiation – comparison between univariate Cox model and multivariate Cox model

Variable	HR	CI	p-value	HR	CI	p-value
Age	1.021	1.005–1.036	0.009	1.034	1.010–1.058	0.004
Serum creatinine (M0)	1.262	1.141-1.396	<0.001	1.421	1.203-1.678	<0.001
Proteinuria (M0)	1.122	1.028-1.224	0.01	1.241	1.126-1.369	<0.001
Presence of an infectious episode	1.748	1.176-2.598	0.006	1.705	1.013-2.868	0.04

CI – confidence interval; HR – hazard ratio; M0 – the time of the first visit in the hospital; KRT – kidney replacement therapy

This study confirmed the hypothesis that an infectious episode occurring in a patient with CKD has an independent capacity to induce a more rapid progression toward the need for KRT initiation. Another important aspect of this study is that there were no

differences between the two subgroups evaluated, the one without infection and the one with infection, in terms of initial stage of CKD, risk group or etiology of CKD, which excluded a very important bias. Also, the importance of the classical predictors of CKD progression – serum creatinine and proteinuria at the time of enrollment – was reconfirmed. On the other hand, the study also has a number of limitations.

Firstly, the cohort is not very large, which did not allow for a better exploration of the impact on kidney function of each type of infection and therefore of the microorganism identified. However, it allowed a good follow-up of the patients, including the treatment followed and the paraclinical parameters. In addition, the study being single-center, performed in a tertiary referral center for kidney disease and having, however, a reasonable number of patients, provide information that is helpful for kidney and infectious pathology in this part of the country.

Secondly, being a retrospective study, it can be assumed that patients had multiple infectious episodes that could not be properly identified, in both groups, even in the one apparently without any such episode, which also may influence the results. Moreover, the antibiotic treatment administered, even if it was recorded for each infectious episode, could not be statistically evaluated because patient compliance could not be verified, many of the antibiotics being prescribed to be followed at home. For this reason, it is possible that, in some situations, the progression of CKD to be causes by the persistent inflammatory status induced by chronic infection.

Last but not least, the nephrotoxicity of antibiotics can also play a very important role, especially since there are studies that state that they are prescribed in up to 64% of cases in much higher doses, and the ways in which they can affect the kidney are well-known: interstitial nephritis, direct tubular toxicity, immune dysfunction or decreased renal perfusion (Fanos and Cataldi, 2001; Morales-Alvarez, 2020).

The mechanisms behind a more rapid progression of CKD in the case of an infectious episode are still not fully understood, but are closely related to the chronicity of the infection, genetic alterations of the complement pathways, tubulo-interstitial changes and pre-existing renal disease (Oda and Yoshizawa, 2021). A number of markers have also been proposed to aid in the easier recognition of patients who need to be monitored more closely due to a higher risk of progression, such as nephritis-associated plasmin receptor and interstitial smooth muscle actin alpha (Oda and Yoshizawa, 2021). The nephritis-

associated plasmin receptor was isolated from group A streptococci and is involved in maintaining glomerular inflammation through local complement activation, and alpha-actin is a marker of tubulo-interstitial fibrosis (Oda and Yoshizawa, 2021; Yoshizawa et al., 2022). In addition, with regard to urinary tract infections, a key element in the pathophysiology, which practically predisposes patients to the development of this type of infection, is represented by the presence of genetic polymorphisms of Toll-like receptors (TLRs) (Godaly, Ambite and Svanborg, 2015; Ambite et al., 2021). Among them, the most important are TLR2, TLR4, and TLR5 ('The role of toll-like receptors (TLRs) in urinary tract infections (UTIs)', 2016). Moreover, genetic changes in vascular growth factor A (VEGFA) and transforming growth factor beta 1 (TGFβ1) are correlated with the appearance of renal scarring and CKD progression after urinary infections, especially those associated with vesicoureteral reflux (Hussein et al. al., 2010).

Correlating the confirmation of the study hypothesis with the results described in the literature that the risk of death from infectious causes increases as kidney function deteriorates, all patients should be educated not to treat infectious episodes lightly and, from the time of their occurrence, be monitored closer. They should also be advised to stop any medications/supplements with nephrotoxic potential to minimize the cumulative negative impact of multiple factors. Last but not least, the doses and duration of antibiotic administration should be carefully adjusted and monitored, so as not to become, in turn, a cause for faster KRT.

Chapter 5. Study II. Usefulness of hematological parameters in differentiating between cystitis and pyelonephritis in patients with BCR

Given the high frequency of infectious diseases, many parameters have been evaluated and analyzed to find those that best describe the biological response to infection, the most well-known of which are the occurrence of leukocytosis/leukopenia and elevated levels of erythrocyte sedimentation rate (ESR), of C-reactive protein (CRP) and of fibrinogen (Litao and Kamat, 2014; Harrison, 2015). However, recently, also the hematological parameters of inflammation, such as erythrocyte distribution width (RDW) and platelet distribution width (PDW), neutrophil/lymphocyte ratio (NLR) or platelet/lymphocyte ratio (PLR), have been correlated with clinical and subclinical systemic inflammation in several pathological situations, including CKD, in which also have a prognostic role (Yonemoto et al., 2018; Yoshitomi et al., 2019; Popa et al., 2021; Han et al., 2022).

Despite the fact that urinary tract infections (UTIs) are very common in the general population (almost 50% of women and 5% of men are expected to have at least one episode in their lifetime), relatively little is known about how they modify the hematological parameters of inflammation (Hooton and Gupta, 2021; Scherberich, Fünfstück and Naber, 2021; Kim et al al., 2023). Because of this, the current study aims to evaluate the potential role of NLR, PLR, RDW and PDW in differentiating in CKD patients between acute pyelonephritis versus cystitis. If their utility is confirmed, this could be particularly useful in patients in resource-limited areas, where more expensive markers such as CRP may often be missing.

The study is retrospective, observational, conducted on a cohort of non-dialyzed 70 patients with G3-G5 CKD and with UTI from the database of the ,,Dr. Carol Davila" Clinical Hospital of Nephrology, Bucharest. They were recruited for a period of one year, between 01.01.2021 and 31.12.2021. Only patients with a glomerular filtration rate below 60 ml/min/1.73m2, who came periodically for control, and who had either pyelonephritis or cystitis were included.

Comparison between cystitis versus pyelonephritis episodes was done with the Mann-Whitney U test for continuous variables and Fisher exact for nominal ones. Correlations between variables were also analyzed using the Spearman rho coefficient. The

multivariate analysis was performed using a binary logistic regression model in which the dependent variable was considered the diagnosis of pyelonephritis, and the independent variables were those with a p-value resulting from the evaluation of the differences between the two subgroups – with cystitis or with pyelonephritis, under 0.1.

NLR was positively correlated in bivariate analysis with PLR, with RDW, with ESR, with CRP, and also with leukocyturia, and negatively correlated with serum albumin. PLR was positively correlated with RDW, and RDW was negatively correlated with baseline glomerular filtration rate. PDW did not correlate with other variables. Also, from the urinary sediment, leukocyturia was positively correlated with hematuria and with NLR, as mentioned above, and negatively with the number of lymphocytes and with glomerular filtration rate from the time of recording, and hematuria was positively correlated with ESR, with fibrinogen and leukocyturia, as noted, and negative with serum albumin, lymphocyte count, and glomerular filtration rate at baseline. Age was negatively correlated with baseline lymphocyte count and glomerular filtration rate, hemoglobin was positively correlated with serum albumin, neutrophil count, and lymphocyte count, and negatively with ESR, and serum albumin was negatively correlated with ESR, with CRP, with fibrinogen, and, as previously mentioned, with NLR.

A binary logistic regression model was built, which included as independent variables those that were significantly different in the pyelonephritis group – NLR, serum albumin, ESR, CRP, fibrinogen, RDW, as well as urinary leukocytes and erythrocytes, considering their correlation with NLR, and as dependent variable the diagnosis of pyelonephritis. The result of this model was that the independent predictors of the diagnosis of pyelonephritis are NLR, CRP and fibrinogen. The accuracy of the model was evaluated using the likelihood ratio – it returned a statistically significant $\chi 2$ of 56.3, $p<0.001$. Also, the Nagelkerke R2 value was 0.876, indicating that approximately 88% of the variability in the diagnosis of acute pyelonephritis can be explained by the model, which is a major improvement over the null model. Last but not least, the model correctly predicted the diagnosis in 92.9% of cases. The exact values are shown in Table V.1.

Table V.1. Independent predictors of pyelonephritis diagnosis

Variable	HR	CI	p-value
NLR	1.718	1.048-2.814	0.03
CRP	1.158	1.035-1.296	0.01
Fibrinogen	1.013	1.001-1.024	0.01

CI – confidence interval; CRP – C-reactive protein; HR – hazard ratio; NLR – neutrophil/lymphocyte ratio. Dependent variable – diagnosis of pyelonephritis; Chi2 – 56.7; p<0.001; Nagelkerke R2=0.799. Variables entered in the first step: NLR, serum albumin, erythrocyte sedimentation rate, CRP, fibrinogen, leukocytes and urinary erythrocytes.

Neutrophils are classically associated with bacterial infections and hospitalization. Moreover, despite the fact that they do not fully activate and reach their potential function due to all the biochemical changes associated with CKD, their response appears to be maintained as would be expected in a UTI, their level being significantly higher in case of pyelonephritis versus cystitis, as confirmed in this study. Moreover, an increase in their number seems to be associated with an increased risk of sepsis in hospitalized patients with pyelonephritis, which may represent a useful parameter, given that it is very easily obtained using only a complete blood count (Kana et al., 2021; Fukui et al., 2022).

The neutrophil/lymphocyte ratio (NLR) is another useful marker, which is associated with 90-day mortality and hospitalization in those with Gram-negative sepsis, and additionally with the occurrence of AKI in those with UTIs (Kana et al., 2021; Roldgaard, Benfield and Tingsgård, 2024). Also, upper urinary tract infections are often complicated with the occurrence of bacteremia, especially when the microorganism involved is Klebsiella spp., and patients have other comorbidities, such as diabetes (Dimitrijevic et al., 2021). It is worth mentioning a recently published study that states that NLR in association with urinary interleukin 8 could differentiate between urinary infections caused by E.coli secreting extended-spectrum beta-lactamases (E.coli ESBL), and those caused by Klebsiella pneumoniae in patients with type 2 diabetes mellitus (Saheb Sharif-Askari et al., 2020). In addition, it seems that NLR can also predict the need for nephrectomy in case of emphysematous pyelonephritis, especially when it is associated with the occurrence of AKI (Punatar et al., 2019).

Since there are studies that state that patients with CKD have an increased risk of infections as kidney function declines, being two to three times higher in the G4 and G5

stages compared to the G2 stage, these aspects become very important because NLR can be used as a marker both for glomerular filtration rate loss and for estimating the severity of an infectious episode, the last aspect being confirmed in this study (Wang et al., 2011; Ishigami and Matsushita, 2019). Last but not least, NLR was found to be an independent predictor of pyelonephritis. The other hematological parameters did not have significant results in the multivariate model, but prospective studies in this area are still needed, as many previous studies give them high prognostic value in terms of survival and kidney functional decline.

This study also has some limitations. Firstly, it is a retrospective study, the data being collected from the hospital's informatic system. However, since a limited group of markers was followed, which are widely accessible and the hospital is a tertiary nephrology center, the probability that the values of certain variables to miss is almost zero. Another limitation is that the number of evaluated patients is relatively small, especially due to the strict inclusion criteria. However, even this number was sufficient to generate significant results and confirm the importance of hematological parameters, especially the neutrophil/lymphocyte ratio in differentiating between cystitis and pyelonephritis in patients with CKD. Probably other hematological parameters such as RDW or PDW would have been representative if the examined group would have been larger, especially since in patients without CKD they seem to have a high prognostic value. Prospective trials are needed for confirmation. Finally, the study was developed in a single center, there were no other collaborations, but being carried out in a tertiary nephrology center, the experience gained with CKD patients is high and also the accuracy of the investigations, and it allowed to obtain some first hypotheses related to the importance of hematological parameters as a useful and inexpensive tool to assess, at first sight, the paraclinical severity of a urinary infection in patients with CKD.

Chapter 6. Final conclusions and personal contributions

Chronic kidney disease remains one of the most common health problems in the world, affecting approximately 10% of the population, with a large negative impact on the quality of life, both at the individual and at the social and economic level. Infectious diseases are also one of the main causes of morbidity and mortality worldwide, which is why it is necessary to carefully evaluate the implications that the association between these two conditions can have.

Thus, following the analysis of a cohort of 238 patients from ,,Dr. Carol Davila" Clinical Hospital of Nephrology, it was found that the presence of an infectious episode in a known patient with chronic kidney disease induces a faster progression towards ESKD, with the need to initiate KRT - p=0.004. Other independent predictors for this negative prognosis are advanced age, serum creatinine and proteinuria at the time of enrollment, the last two being also the best known prognostic factors in this category of patients. The fact that the hypothesis was confirmed is a matter of great importance, because it indicates the need to adopt measures to periodically follow up patients much more closely after the appearance of an infectious episode, even if it seems to have passed without incidents, as well as to identify all measures of prophylaxis to prevent recurrences, aspects which, until now, have been neglected in the guidelines. On the other hand, many studies state that antibiotic therapy is often prescribed in much higher doses and for a much longer period of time than would be necessary in these situations, which raises the suspicion that the faster progression of chronic kidney disease in patients with infections may also be caused by this improper administration of medication. However, in order to confirm this hypothesis, future, prospective studies are needed, given that, in a retrospective design, patient compliance with the received indications cannot be controlled at an appropriate level of confidence.

Also, the second study of the paper aimed to identify some paraclinical markers to help differentiate between lower and upper urinary tract infections. In this context, in addition to the classical parameters of inflammation, whose value was already known in this context, and which were also confirmed in this study, hematological parameters were evaluated. The main motivation for testing them was the fact that the complete blood count is performed on absolutely any patient hospitalized in a health unit, it is cheap and can possibly replace the classic, more expensive parameters in areas with a low socio-

economic level. Thus, using binary logistic regression models and Spearman's correlation, it was found that the neutrophil/lymphocyte ratio is an independent predictor of the diagnosis of pyelonephritis with a p-value of 0.03, along with C-reactive protein and fibrinogen. Although it may seem that the clinical importance of this information is low, given that, in most situations, the diagnosis, and thus the differentiation between a lower and an upper urinary tract infection is predominantly clinical, yet therapy and prognosis are also guided by the inflammation parameters. Moreover, in numerous studies, the values of the hematological parameters – the neutrophil/lymphocyte ratio, the platelet/lymphocyte ratio, the width of the erythrocyte and platelet distribution had a prognostic role both in terms of kidney functional decline and of the general prognosis during severe infectious episodes, which is of particular importance in patients with known chronic kidney disease.

Personal contributions are represented by the research of specialized literature in the field of the relationship between infections and CKD, the elaboration of the thesis plan, the creation and the statistical analysis of the database, necessary for testing the hypotheses. The importance of this work is given by the simultaneous identification of two elements that have the proved ability to be independent predictors, managing to evaluate at the same time the progression of chronic kidney disease, in the long term, thus raising the need to adopt careful preventive measures.

Also, following the research of the medical literature, a very important and often neglected aspect in daily practice is the importance of the intestinal microbiome during severe infections. It undergoes major changes and that can be modulated by the administration of non-resorbable antibiotics, pre - and probiotics, as well as short-chain fatty acids. The benefit is represented by improving kidney function during acute septic injury, by restoring the intestinal barrier and modulating the immune response. The adoption of these measures is all the more necessary since compliance with the other indications included in the guidelines did not lead to a decrease in the incidence of acute septic injury worldwide, which raises the need to identify new therapies to improve the prognosis of these patients.

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List of published papers

1. Chronic kidney disease, urinary tract infections and antibiotic nephrotoxicity: are there any relationships? **Ioana Dicu-Andreescu**, Mircea Penescu, Cristina Căpusă, Constantin Verzan. Medicina, vol 59(1), January 2023 - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9862113/ **ISI indexed, F.I.: 2,6,** Chapter 3 – pag. 69-83

2. Septic acute kidney injury and gut microbiome: should we change our approach? **Ioana Dicu-Andreescu**, Mircea Penescu, Constantin Verzan. Nefrologia vol 44, March-April 2024 - https://www.revistanefrologia.com/es-septic-acute-kidney-injury-gut-articulo-S0211699523000802, **ISI indexed, F.I.: 2,** Chapter 2 – pag. 34-68

3. The impact of infections on the progression of chronic kidney disease. **Ioana Dicu-Andreescu**, Liliana Gârneață, Otilia-Andreea Ciurea, Irinel-Gabriel Dicu-Andreescu, Elena-Alexandra Ungureanu, Denis-Valentin Vlad, Antonia-Constantina Vișan, Victor-Gabriel Ungureanu, Violeta-Valentina Vlad, Patrick-Christian Vasioiu, Elis-Mihaela Ciutacu, Mihaela Neicu, Mircea Penescu, Constantin Verzan, Cristina Căpusă. Medicina, vol 59 (10), October 2023 - https://www.mdpi.com/1648-9144/59/10/1836, **ISI indexed, F.I.: 2,6,** Chapter 4 – pag. 80-95

4. Are the hematological parameters useful in differentiating acute pyelonephritis from cystitis in patients with chronic kidney disease? **Ioana Dicu-Andreescu**, Liliana Gârneață, Otilia-Andreea Ciurea, Irinel-Gabriel Dicu-Andreescu, Elena-Alexandra Ungureanu, Denis-Valentin Vlad, Antonia-Constantina Vișan, Victor-Gabriel Ungureanu, Violeta-Valentina Vlad, Patrick-Christian Vasioiu, Elis-Mihaela Ciutacu, Mihaela Neicu, Mircea Penescu, Constantin Verzan, Cristina Căpusă. Maedica no. 3, September 2024, **PUBMED indexed,** Chapter 5 – pag. 96-106