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[Review] Drug-induced causes of renal damage and dysfunction in patients with complicated COVID-19

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Abstract

The literature review provides up-to-date data on the main causes of acute renal injury in patients with COVID-19 with complications of hypoxia, respiratory failure and sepsis against the background of various types of drug treatment. The relationship of renal insufficiency with the effect of the use of diuretics and nonsteroidal anti-inflammatory drugs is analyzed. The assessment of the combined use of angiotensin converting enzyme inhibitors and angiotensin-II receptor blockers and their possible role in the pathogenesis of acute renal injury is given.The nephroprotective effect of antiviral drugs, steroid hormones and azithromycin is evaluated.

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As of mid-August 2020, the 2019 coronavirus disease (COVID-19) has been reported in >21 million people worldwide and is responsible for more than 750,000 deaths [1]. Acute kidney injury (AKI) is a common and important complication of coronavirus disease (COVID-19), there is a noticeable variability in its reported incidence and outcomes. The frequency of acute renal failure (acute renal failure) according to large observational studies and meta-analyses ranges from 28-34% in the population of inpatient patients and 46-77% in intensive care units (ICU). The incidence of the most severe forms of acute renal failure requiring renal replacement therapy (RRT) in the ICU seems to decrease over time. According to

nephrologists from the William Harvey Research Institute (Queen Mary University of London. Intensive Care Unit for Adults, Royal London Hospital, Barts Health, NHS Trust, London, UK), who studied this aspect of AKI progression, the use of RRT decreased in the country from 26% at the beginning of the pandemic, to 14% in 2022. Most of the survivors appear to have recovered kidney function by the time they are discharged from the hospital, however, these patients seem to still be at increased risk of developing CRF (chronic renal failure), decreased glomerular filtration rate (GFR) and chronic kidney disease (CKD) in the future, [2].

The main causes and factors of AKI development in COVID-19 patients were evaluated based on the results of prospective studies conducted in various countries of the world. The analysis of the state of renal function, frequency and causes of AKI in COVID-19 patients (198 hospitalized patients) was carried out by the staff of the intensive care unit of Al-Adan Hospital (Kuwait). The authors analyzed age, gender, nationality, history of hypertension, diabetes mellitus, coronary heart disease, congestive heart failure, bronchial asthma, chronic obstructive pulmonary disease. In patients, the indicators of the need for artificial lung ventilation (MV), extracorporeal membrane oxygenation, in drugs with inotropic activity and other types of medications were evaluated. The causes of acute renal failure, indications for dialysis, the modality of dialysis, the results of dialysis and mortality were analyzed. The study showed that 61 out of 198 (30.8%) ICU patients with a positive test result for COVID-19 developed AKI (in accordance with the definition of AKI according to the criteria of the international recommendations "To improve global kidney disease outcomes" (KDIGO 2012). Forty-eight of 61 (79%) patients required continuous renal replacement therapy using continuous venous hemodiafiltration. Thirty-seven (61%) of 61 patients showed signs of severe sepsis. The most common causes of kidney damage in the inpatient contingent of the most severe patients with COVID-19 were named: the use of nephrotoxic drugs, sepsis, cytokine storm, hypovolemia, heart failure [3].

The importance of drug-induced causes of causes in the development of AKI in COVID-19 patients has been evaluated only in a few original studies. Including in a retrospective cohort study of employees of the Department of Nephrology, Beijing Medical College Hospital, Chinese Academy of Sciences (China), on a small sample, a total of 82 patients with COVID-19 AKI were diagnosed in 41 (50.6%). The main factors in its development, including the frequency of drug effects, were evaluated. The proportion of stage 1, 2 and 3 AKI according to the criteria for improving global kidney disease outcomes (KDIGO) in the sample was 26.8%, 31.7% and 41.5%, respectively. The main causes of acute renal failure were: septic shock (25 out of 41, 61.0%), volume insufficiency (8 out of 41, 19.5%) and adverse drug effects in 12.2% (5 out of 41), [4].

The incidence of AKI and its clinical symptoms in patients with COVID-19 infection has been evaluated in a number of analytical reviews. In one of them, performed by Belarusian nephrologists from Vitebsk University, statistics are given that kidney damage is observed in severe COVID-19 in 25-50% of cases, manifested by proteinuria, hematuria and tubular dysfunction, and acute kidney injury (AKI) develops in about 15% of cases. Patients with AKI and with a history of chronic kidney disease (CKD) are a group of high mortality with the development of COVID-19 infection. In case of kidney damage caused by SARS-CoV-2, general principles of treatment are used - symptomatic and renal replacement therapy, and the administration of nephrotoxic drugs is monitored. For patients who have had this infection, with the development of AKI, in the post-stationary period, it is necessary to determine the tactics of subsequent dispensary follow-up, including

the choice of adequate drug therapy and assessment of the need for supportive renal replacement therapy), [5].

Possible causes and mechanisms of AKI development in patients with complicated forms of COVID-19 were named in the literature review of the staff of the French Hospital St. Louis (Paris, France), including hemodynamic disorders, right ventricular heart failure, high PEEP levels in patients requiring artificial ventilation, hypovolemia, nosocomial sepsis and the introduction of nephrotoxic drugs [6].

The complexity of the problem of prevention and early diagnosis of AKI in COVID-19 infection is that the ongoing drug pathogenetic therapy, including antiviral drugs, antibiotics, NSAIDs, diuretics and other drugs itself can be a source of kidney damage. According to Italian clinicians from the Department of San Bortolo Hospital in Padua (Department of Medicine, Università di Padova, Padua, Italy; Department of Nephrology, Dialysis and Kidney Transplantation, San Bortolo Hospital, Vicenza, Italy; International Renal Research Institute of Vicenza, Vicenza, Italy) and German Nephrologists (Division of Nephrology, Pulmonology and Critical Care Medicine, Member of the German Centre for Lung Research, University Hospital Giessen and Marburg, Giessen, Germany), described in an analytical review published in the Lancet Respir journal.Med. (2020), there are no specific and safe treatment options for AKI secondary to COVID-19. Intensive therapy of these patients largely supports modern approaches to the prevention and treatment of acute kidney injury. At the same time, modern nephrology is largely aware of groups of medications with nephrotoxic properties, including those used in complex therapy for complications of COVID-19 hyperthermia, pneumonia, as well as in violation of the water-releasing function of the kidneys [7].

According to a number of clinical studies conducted, pre-existing renal insufficiency, hypovolemia and the use of diuretics occupy the most prominent place in the list of causes and factors of AKI development in patients with COVID-19 and pneumonia.When assessing the main pathogenesis factors and the effect of drug therapy on the risk of developing AKI in COVID-19 patients by the staff of the Nephrology department of the Royal Hospital of London (King's College Hospital NHS Foundation Trust, Denmark Hill, London, SE5 9RS, UK), it was noted that 487 (39%) of the 1248 inpatient patients included in the study developed AKI (51% have stage 1, 13% have stage 2 and 36% have stage 3). The weekly incidence rate of AKI gradually increased to a peak at week 5 (3.12 cases / 100 patient days) before decreasing to its nadir (0.83 cases / 100 patient days) at the end of the study period (week 10). Pre-existing renal insufficiency [odds ratio (OR) 3.05] and the use of diuretics in hospital (OR 1.79) were independently associated with a higher risk of developing AKI, [8].

In a study of the same orientation, performed by the staff of the Department of Nephrology, Albert Einstein Israel Hospital (Sao Paulo, Brazil), the main causes of AKI in COVID-19 were analyzed. In this multicenter, retrospective, cohort study of adult patients diagnosed with COVID-19 admitted to the intensive care unit (ICU) in the period from March 2020 to May 2020, it was found that 101 (50.2%) patients developed AKI (72% on the first day of invasive mechanical ventilation (Ventilator), and 34 of them (17%) required a PTA. The main risk factors for the development of acute renal failure included a higher baseline serum creatinine level (HR 2.50) and the use of diuretics in the hospital (HR 4.14), [9].

Another group of nephrotoxic agents may be nonsteroidal anti-inflammatory drugs (NSAIDs), which are often used in the treatment of infectious diseases accompanied by high hyperthermia and are considered by a number of authors as

frequent causes of both acute and chronic nephropathies that endanger the lives of patients.Medicinal kidney lesions, including with the development of drug-induced nephropathies and AKI, according to a study by Belarusian nephrologists of the staff of the Medical Academy (Belarusian Medical Academy of Post-Graduate Education, Minsk), mainly develop in the treatment of older age groups, the proportion of which reached 66%. They often have concomitant pathology in the form of diabetes mellitus and diseases of the cardiovascular system. They are the ones who use many different medications at the same time and undergo diagnostic and therapeutic procedures that are potentially dangerous for kidney damage and impairment of their function [10]. In order to study this problem, the authors analyzed the case histories of 672 patients diagnosed with toxic nephropathy (ICD - 10 code N14), acute tubulointerstitial nephritis (N10), who were on inpatient treatment in the nephrological departments of the 1st City Clinical Hospital in Minsk (Republic of Belarus) and the 4th Clinical Hospital N.E. Savchenko Hospital" G. In 2010-2012 and 6 months of 2015, 72 of them (10.7%) found that these kidney injuries were associated with taking medications taken mainly for the treatment of infectious diseases accompanied by high hyperthermia. The most frequent component of such therapy was nonsteroidal anti-inflammatory drugs, the proportion of which was 88% [11].

The risk assessment of AKI development in the use of NSAID drugs by the UK population in the pre-covid period (2005) was performed by Spanish clinical pharmacologists from the Center for Pharmacological Research (Centro Español de Investigación Farmacoepidemiológica, Spanish Centre for Pharmaco-epidemiological Research, Madrid, Spain). They conducted a meta-analysis of studies conducted in the UK (nested case-control study using the United Kingdom General Practice Research Database) to assess the nature of therapy in 386,916 patients aged 50-84 years. The researchers found that the risk factors for the development of renal failure when taking NSAIDs were - the duration of administration, the presence of a history of hypertension, heart failure, diabetes mellitus. There was no connection between the development of renal insufficiency and the type of NSAIDs, but there was a clear relationship with the doses of drugs: in patients taking medium / small doses. The overall relative risk of developing kidney damage was 2.51, and against the background of high doses – 3.38. Current NSAID users had a relative risk (HR) for the development of AKI (HR 3.2) and its decrease after discontinuation of treatment. The increased risk was present with both short-term and long-term therapy and was slightly higher among high-dose users. A history of heart failure (HF), hypertension, diabetes, as well as hospitalization and specialist consultations in the previous year were associated with a high risk of AKI. The researchers suggested a modification of the nephropathogenic effect of NSAIDs in patients with arterial hypertension and HF. According to the analysis, the use of certain cardiovascular drugs was associated with a 5-fold increase in the risk of developing AKI. Taking diuretics presented the greatest risk, it increased with the simultaneous use of NSAIDs and diuretics (HR 11.6) and NSAIDs and calcium channel blockers (HR 7.8). The researchers concluded that patients who used NSAIDs had a 3-fold higher risk of developing the first clinical AKI in their history, compared with people without NSAIDs in the general population. In their opinion, NSAID class drugs should be used with extreme caution in patients with arterial hypertension and/or heart failure [12].

The kidney-damaging effect of many drugs is due to the fact that the cells of the renal epithelium, especially the proximal tubule, are very sensitive to the direct toxic effect of certain drugs that enter the lumen of the tubules by glomerular filtration and concentrate here due to fluid reabsorption [13]. Damage to the tubular apparatus can be caused by

aminoglycosides, amphotericin B, antiviral drugs (adefovir, cidofovir, tenofovir), cisplatin, X-ray contrast agents, etc. [13][14][15]. Some medications can cause inflammatory changes simultaneously in the glomeruli, tubules and interstitium, leading to fibrosis and wrinkling of the kidneys. Such drugs as gold preparations, hydralazine, interferon-alpha, NSAIDs, propylthiouracil, pamidronate (high doses or a long course of treatment) can be the causes of glomerulonephritis – inflammation primarily caused by immune mechanisms and often occurring with nephrotic proteinuria [13][14][16]. Drug-induced acute glomerulonephritis, as an allergic reaction to medications, develops in the form of idiosyncrasy and is a dose-independent condition. Drugs circulating in the blood can bind to antibodies and form immune complexes deposited in the capillaries of the glomerulus, causing an immune response [17]. Nephrologists have described a number of drugs that can cause such damage: allopurinol, antibiotics (especially beta-lactams), rifampicin, sulfonamides, vancomycin, antiviral drugs (acyclovir, indinavir), diuretics (loop, thiazide), NSAIDs, phenytoin, proton pump inhibitors (omeprazole, pantoprazole, lansoprazole), ranitidine [14][17][18][19][20]. Medicinal acute interstitial nephritis is diagnosed in 2-3% of patients undergoing renal biopsy [21]. According to large, controlled studies, medications are the most common cause of acute interstitial nephritis (OIN) – 71.8%, and among the other causes are autoimmune diseases, infections [22][23]. According to the available international statistics, antibiotics play a leading role among the drugs causing the development of OIN – from 30 to 49%, proton pump inhibitors – up to 14% and NSAIDs – up to 11% [22][23]. The clinical picture of drug-induced OIN is quite diverse and often proceeds without the presence of the classical triad (fever, rash, eosinophilia) against the background of changes in urine (proteinuria) and blood (increased creatinine, hyperkalemia, metabolic acidosis), [11]. The diagnosis of OIN is verified based on the results of a kidney biopsy[21][23]. Signs of interstitial inflammation and tubulitis are more often detected in the biopsy. Interstitial infiltrate consists mostly of lymphocytes, monocytes, less often of eosinophils, plasma cells and neutrophils. According to histochemical studies, in patients with OIN after taking antibiotics and NSAIDs, about 72% of the cellular infiltrate consists of mononuclear cells (CD4+ and CD8+), 15% – monocytes and 7% – B-limophytes [21].

The main types of kidney damage and disorders of their function associated with the use of NSAIDs were mainly determined in evidence-based studies. Their detailed description is given in a number of literature reviews. Thus, in the publication of the staff of the Department of Nephrology from New Haven (Section of Nephrology, Yale University School of Medicine, New Haven, CT, USA), the main types of kidney damage and disorders of their function associated with the use of NSAIDs are called prerenal azotemia, acute tubular necrosis, acute papillary necrosis, acute interstitial nephritis, chronic tubulointerstitial nephritis (analgesic nephropathy), glomerulonephritis of the type of minimal change disease, membranous nephropathy, hyperkalemia, metabolic acidosis, hyponatremia and arterial hypertension [24].

In the available literature of the COVID-19 outbreak period in Asia, the USA and Europe, cases of nephropathy with AKI in patients treated with NSAIDs have been described, including verified by methods of lifetime kidney biopsy and immunological diagnostics. A study by employees of the New York Department of Pathology (Department of Pathology, Division of Renal Pathology, Columbia University Irving Medical Center, New York, New York, USA) described a case of COVID-19 complicated by analgesic nephropathy when using ibuprofen in a 46-year-old West African man admitted to the emergency department 15 March 2020 with severe acute kidney injury. The patient reported that 2-3 weeks before his hospital admission he had fever, myalgia, sore throat and cough, which he treated with several doses of ibuprofen. These

symptoms were resolved 1 week before this hospitalization, but subsequently he developed a deterioration in his condition - abdominal pain, nausea and anorexia, which persisted for the next week, which led to his hospitalization in the hospital. At the hospital, there was a decrease in diuresis, but he denied hematuria, foamy urine or pain in the kidney area. In addition to the recent use of ibuprofen, the patient denied any other medications, vitamin supplements or herbal remedies. The patient underwent a percutaneous kidney biopsy to verify the nature of kidney damage. 20 glomeruli were obtained in the preparation, none of which was totally sclerosed. In 14 glomeruli, there was a pattern of segmental-global collapse of glomerular capillaries, combined with hypertrophy and hyperplasia of overlying glomerular epithelial cells, some of which contained protein droplets that gave a positive color with Schiff reagent. Among the modified ones, 6 intact glomeruli turned out to be normal in size and cellular composition. No inflammatory half-moons, Bowman capsule ruptures or fibrinoid necrosis were detected. There were diffuse and severe tubular degenerative and regenerative changes in the renal cortex, characterized by flattening of the epithelium, loss of the boundaries of the cell layer, an increase in nuclei with protruding nucleoli and focal mitotic figures. Some proximal tubular cells contained abundant intracytoplasmic protein droplets positive for stained with Schiff reagent. There were non-compactly arranged tubular microcysts. The interstitium was swollen with moderate interstitial inflammation, consisting mainly of mononuclear leukocytes and single plasma cells, without signs of tubulitis. Minimal focal tubular atrophy and interstitial fibrosis with approximately 10% of the cortical parenchyma were observed. There were signs of atherosclerosis and moderate arteriosclerosis in the vessels. According to the authors, the patient had COVID-19 viral disease and analgesic nephropathy with the development of AKI while taking the NSAID ibuprofen [25].

In patients with COVID-19, viral and drug-induced nephropathogenic factors can apparently be summed up and it is important to identify the types of kidney damage characteristic of each of them for the choice of methods for their prevention and pathogenetic therapy. The main variant of kidney damage in patients with COVID-19, according to large statistics of lifetime and pathomorphological studies of kidney biopsies with the development of COVID-19 infection, is considered to be collapsing nephropathy. Other morphological variants of kidney damage are less frequently detected, they are given in the literature review of nephrologists of the Volgograd State Medical University (Department of Internal Diseases). In addition to collapsing nephropathy, researchers also identified minimal change disease, membranous glomerulopathy, anti-GBM nephritis, acute tubular necrosis, exacerbation of autoimmune glomerulonephritis, allograft rejection [26]. In connection with such types of damage to renal structures, in the studies of microbiologists performed during the COVID-19 pandemic, it was found that coronaviruses have high contagiousness and high tropicity to renal tissue. A new coronavirus infection can cause a wide range of kidney damage, due to the content of RNA and angiotensin-converting enzyme type 2, transmembrane serine protease 2 and cathepsin L in organs, which are considered targets for SARS-CoV-2 [10][27].

Verified using methods of in vivo and postmortem kidney biopsy, the main types of acute renal injury in patients with COVID-19 with AKI were characterized in a review article by Dutch authors from the Intensive Care Unit of Groningen (Department of Critical Care, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands). According to them, in the group of lifetime diagnostic biopsy, the average age of patients was 56 years, and the frequency of AKI exceeded 96%. In the postmortem biopsy group, the average age of the deceased was 69 years,

and the frequency of AKI reached 80%. In this group, the prevalence of acute glomerular pathology was 74%. The most frequent of them were collapsing focal segmental glomerulosclerosis (c-FSGS) in 54% and thrombotic microangiopathy (TMA) in 9% of patients. Kidney damage of the TMA type was also found in 10% of patients in the postmortem biopsy group. The most common acute variant of tubular lesion in COVID-19 was acute tubular necrosis (OCN), which was noted in 87% of patients in the diagnostic and 77% of patients in the postmortem biopsy group. In addition, the authors note the high prevalence of previously developed chronic lesions in both groups, such as atherosclerosis and glomerulosclerosis. Histopathological changes in kidney biopsies of patients with COVID-19 showed a heterogeneous picture with acute glomerular lesions, mainly of c-FSGS and TMA types, with acute lesions of the cannula, mainly in AKI. In many patients, these lesions were present against the background of previous chronic kidney damage [28].

Related to COVID-19 – associated collapsing glomerulopathy (KG), according to American morphologists from the Mayo Clinic (Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA.Kidney Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA), is an aggressive and distinct histological variant of focal segmental glomerulosclerosis (cFSGS), characterized by segmental or global collapse of glomerular capillaries with hypertrophy and hyperplasia of overlying podocytes. It is assumed that the pathogenesis of cFSGS in COVID-19 is associated with direct viral damage to podocytes, as described in HIV-associated glomerulopathy. Tubulopathy with acute damage and dilation of the tubules, with the formation of microcysts and interstitial inflammation is also characteristic of this viral nephropathy [29].

The pathophysiology of acute kidney injury (AKI) in patients with the 2019 coronavirus (COVID-19) has not yet been clearly determined. It is assumed that direct kidney damage occurs as a result of virus penetration through angiotensin-converting enzyme-2 (ACE2) receptors, which are highly expressed by podocytes and proximal convoluted tubules, while "virus-like" particles are detected on electron microscopy [29]. However, the relationship between the presence of viral particles in kidney tissue and kidney damage has not been fully explained. In addition, it is also assumed that collapsing focal segmental glomerulosclerosis (FSGS), myoglobin toxicity, sepsis-related fibrin aggregates and blood clots are part of the AKI mechanism. The reported cases are associated with the development of cFSGS and the presence of the apolipoprotein 1 (APOL1) allele, which causes a high risk of kidney damage in patients of African descent. As a rule, such patients develop AKI and nephrotic proteinuria when infected with the virus. Nevertheless, there is growing evidence that not direct viral damage, but a systemic inflammatory cascade activated in acute viral infections, such as COVID-19, is the most significant factor in the violation of the basic cellular functions of podocytes.

The incidence of acute renal failure in severe patients hospitalized in hospitals and ICU is high and is associated with a higher mortality rate in the elderly and patients with concomitant diseases. Even higher mortality rates are observed in patients with chronic kidney disease and kidney transplant recipients, due to the dysfunction of the immune system present in most of them [30].

In addition to infectious causes, immune disorders, factors of hypoxia and acute glomerular ischemia, medicinal factors are also considered to be kidney-damaging factors that cause the development of KG in COVID-19 patients. The development of collapsing glomerulopathy was previously described in patients treated with osteoporosis with

biphosphonates (pamidronate), viral infections with interferon preparations and malignant tumors with chemotherapeutic drugs from the anthracycline class [29]. However, in the currently available scientific studies and thematic literature, there is practically no information on the assessment of the nephropathogenic effect of these classes of drugs in patients with COVID-19 with complication of the disease by the development of AKI. Basically, researchers evaluate the nature of the nephropathogenic effect of such groups of drugs as diuretics, NSAIDs and drugs blocking the effects of renin-angiotensin system of the kidneys.

During the 2019-2022 pandemic, controlled, comparative, prospective studies were conducted worldwide to assess possible nephropathogenic effects in the treatment of patients with COVID-19 and such classes of drugs as angiotensin-converting enzyme inhibitors and angiotensin type II receptor blockers. The interest of clinicians and pathologists in this class of drugs is justified by the fact that direct kidney damage verified at the cell-receptor level in COVID-19 can occur as a result of virus penetration through angiotensin-converting enzyme-2 (ACE2) receptors, which are highly expressed both in podocytes and in the epithelium of the proximal convoluted tubules, as This is assumed when "virus-like" particles are detected there during electron microscopy [21][10].

Clinical studies to assess possible nephropathogenic effects, including with the development of AKI, in patients with COVID-19 determined by the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, including when co-prescribed with NSAIDs, were conducted in 2020-2022, including in several medical centers in the USA. So, in a single-center retrospective cohort study of nephrologists from the Department of Nephrology, University Hospital and Brookdale Medical Center (Brooklyn, New York, USA. The Department of Hematology/Oncology, University Hospital and Brookdale Medical Center, Brooklyn, New York, USA) analyzed the data of 469 patients with COVID-19 admitted to this hospital. The average age of patients was 66 years (interquartile range [IQR] 25-75; range 19-101 years), and 268 (57.1%) patients were men. The estimated glomerular filtration rate (gFR) was low (<60 ml/min / 1.73 m2) in 207 (44.1%) patients. During hospitalization, 128 (27.3%) patients developed acute renal failure, which was detected much more often in patients with initially low GFR (81 patients, 39.1%). Risk factors for the development of nosocomial AKI were both the use of angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs, as well as factors of hemodynamic instability, artificial lung ventilation, acute respiratory distress syndrome, male gender and hypertension [31].

Evaluation of the possible effect of ACE inhibitors on the incidence of AKI in infection with COVID-19 virus was the subject of a Canadian retro-spective cohort study in the registry of patients with COVID-19 (Department of Internal Medicine of McMaster University, Hamilton, Ontario, Canada and 10 other Canadian institutions), in which a total of 815 patients were examined who were admitted to the hospital with COVID-19 in the period from March 4, 2020 to April 23, 2021. In this cohort of patients, an analysis was conducted of the possible impact of outpatient multicomponent therapy performed before hospitalization on the risk of AKI. The researchers found that 439 (53.9%) developed AKI, including 253 (57.6%) before hospitalization and 186 (42.4%) had kidney damage in the hospital. The likelihood of hospitalization in the intensive care unit, artificial ventilation and death increased as the stage of AKI worsened. The frequency of use of angiotensin-converting enzyme inhibitors before hospitalization was 20.5% in the group without AKI (367 patients), and 26.4% in the group with AKI (261 patients), 14.4 and 17.6% of A–II receptor blockers, 5.3 and 9.2% of NSAIDs, respectively. The differences between the groups were not statistically significant, which allowed the authors to conclude that there was no

significant effect on the incidence of AKI of drugs of these groups on the development of COVID-19 at the prehospital stage [32].

In the same time period, to evaluate the concept of the possible nephropathogenic effect of therapy with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (RASi) in patients with hypertension and heart failure with COVID-19, researchers from the Australian George Institute, the Italian University of Bolonia and the Canadian University of Ottawa (The George Institute for Global Health University of New South Wales Sydney NSW Australia. Department of Medical and Surgical Sciences University of Bologna Italy.Department of Cellular and Molecular Medicine, Kidney Research Centre, Ottawa Hospital Research Institute University of Ottawa Canada), conducted a meta-analysis using information bases and registers. including MEDLINE, EMBASE, ClinicalTrials.gov and the Cochrane Register of Controlled Trials. They analyzed data from thematic randomized controlled trials. The authors randomly assigned patients with COVID-19 to groups with continuation/with the onset of RASi and with the absence of RASi therapy. The main outcome was mortality from all causes at <30 days. A total of 14 randomized controlled trials met the inclusion criteria. The total number of 1838 participants (aged 59 years, 58% men, the average duration of follow-up is 26 days). According to the analysis, the authors found no signs of the effect of RASi drug therapy, compared with the control, on mortality from all causes (7.2% vs. 7.5%; relative risk [HR, 0.95], both in general and in subgroups combined by severity of COVID-19 or by type of study. A network meta-analysis revealed no differences between the risk of complications, both with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (RASi). In patients taking RASi drugs, there was a slight decrease in the incidence of acute myocardial infarction (2.1% vs. 3.6%; HR 0.59), but there was an increased risk of acute kidney injury (7.0% vs. 3.6%; HR 1.82) in those groups of patients in whom treatment with RASi drugs was initiated and continued before hospitalization. The researchers found that during such therapy, there was no increase in the need for dialysis or differences in the frequency of detection of signs of congestive heart failure, cerebrovascular events and in the frequency of venous thromboembolism, as well as the need for hospitalization in the hospital and in intensive care units, as well as in the frequency of use of inotropes or artificial ventilation. This meta-analysis of clinical trials evaluating the safety of treatment with angiotensin converting enzyme inhibitors / angiotensin II receptor blockers, when compared with the control, did not find any differences in all-cause mortality rates in patients with COVID-19, but found an increased risk of acute kidney injury in the treatment of RASi and a tendency to decrease the incidence of myocardial infarction. The researchers concluded that the obtained results provide convincing evidence that RASi drugs can be used relatively safely in patients with COVID-19 [33].

A study to assess the safety of the use of renin-angiotensin-aldosterone system (RAAS) blockers in infection with COVID-19 virus was also conducted by Bulgarian nephrologists from the Department of Nephrology, Sofia Internal Medicine Clinic (St. Anna University Hospital, Faculty of Medicine, Sofia Medical University, Bulgaria) in collaboration with French nephrologists. This was a comparative, prospective, observational study to assess the effect of maintenance therapy with RAAS blockers on the course of SARS-CoV-2 infection, on its complications and outcomes. The study included 120 inpatient patients with COVID-19, of whom 70 had previously suffered from CKD, and 50 had normal kidney function. A total of 30% of patients (a total of 36 patients, 21 women) received RAAS therapy upon admission and continued it throughout hospitalization. Total mortality was 19.2% (23 patients) and there was no significant difference in the 2 groups,

with the exception of patients with hypertension treated with RAAS blockers, who had significantly lower mortality compared to patients with hypertension who did not receive RAAS blockers. The deterioration of the condition with subsequent transfer to the intensive care unit in the RAAS group was 50% less (4 patients out of 36, i.e. 11%) compared with 19 out of 84 (26.6%) from the group who did not receive RAAS, the difference was significant. Overall, 37 patients developed acute kidney injury (any stage of KDIGO); 14 of them (37.8%) received RAAS blockers. Acute kidney injury was not significantly associated with the use of RAAS blockers. Similarly, both in patients without CKD and in patients with CKD, the use of RAAS blockers had no effect on the restoration of kidney function after SARS-CoV-2 infection. The authors concluded that the use of RAAS blockers had a prognostically favorable value in patients with hypertension, positively affecting the mortality rate. In addition, continued therapy with RAAS blockers during SARS-CoV-2 infection in patients with and without CKD did not significantly affect the main outcomes [34].

Somewhat earlier than such studies, experts from different research groups expressed concerns about the possible risk of developing severe forms of COVID-19 in patients taking inhibitors of the renin-angiotensin-aldosterone system (RAAS). To test this hypothesis, the staff of the Spanish Department of Clinical Pharmacology and the University Hospital of Principe de Asturias, Department of Biomedical Sciences (Department of Pharmacology of the University of Alcala, Madrid, Spain) conducted a population study in Madrid after the outbreak of COVID-19. The authors sequentially selected patients aged 18 years and older with a PCR-confirmed diagnosis of COVID-19 requiring hospitalization in seven hospitals of the city who were hospitalized between March 1 and March 24, 2020. As a reference group, ten patients were randomly selected by age, gender, region and date of hospitalization (month and day; index date) from the BIFAP register (Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria), the Spanish primary health care database, in its last available year (2018). The researchers collected information about concomitant diseases and prescriptions one month before the index date (i.e. current use) from electronic clinical records of both cases of the disease and in control group individuals. The main analysis included an assessment of the relationship between COVID-19 cases requiring hospitalization and the use of RAAS inhibitors, compared with the use of other antihypertensive drugs. Data on 1,139 cases of the disease were analyzed in comparison with 11,390 control individuals in the study population. Among the patients, 444 (39.0%) were women, and the average age was 69.1 years. Compared with patients receiving other antihypertensive drugs, patients taking RAAS inhibitors had an adjusted odds ratio (OR) for COVID-19, the need for hospitalization equal to 0.94. The researchers found that there was no increased risk of developing the disease either when treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Gender, age, and background cardiovascular risk did not affect the adjusted odds ratio between the use of RAAS inhibitors and COVID-19 requiring hospitalization, and a decrease in the risk of COVID-19 requiring hospitalization was found in diabetic patients treated with RAAS inhibitors. The results of the study were published by the Lancet journal in May 2020 [35].

The safety of treatment with RAAS inhibitors was also studied in a single-center, retrospective study by Portuguese nephrologists from the Central Hospital of Lisbon (Centro Hospitalar Lisboa Norte, Departamento de Nephrologia e Transplante Renal, Lisboa, Portugal.Universidade de Lisboa, Faculdade Medicina, Lisboa, Portugal). Of the 544 patients with COVID-19, 330 (60.7%) developed AKI: 166 of them had stable AKI, 164 had transient AKI. Patients with uOPP were older, had a higher incidence of previous kidney diseases, a higher need for treatment with RAAS inhibitors, higher serum

creatine (SCr) levels (1.60 mg/dl versus 0.87 mg/dl) at hospitalization, a higher ratio of NL (neutrophils/leukocytes) in peripheral blood, more pronounced acidosis at hospitalization. They more often required hospitalization in the intensive care unit, artificial lung ventilation and the use of vasopressors. Patients with transient acute renal failure had higher serum creatinine SCr (1.71 mg/dl versus 1.25 mg/dl) at hospitalization. Nosocomial mortality was 14.0% in the group, and it was higher in patients with acute renal failure (18.5% vs. 7.0%). At the same time, the presence of CKD and the concentration of serum ferritin were independent predictors of the development of AKI. The rate of uOPN development was an independent predictor of mortality, as well as the age of patients and the level of lactate in the blood, but not an indicator of the need for treatment with RAAS inhibitors [36].

The opposite – the nephroprotective effect of medications and the ability to prevent the development of acute renal damage in COVID-19 has been noted in modern studies in antiviral drugs from the group of JAK inhibitors of cytokinin receptors - yakinins, which are a type of immunomodulatory drugs that suppress the activity of one or more enzymes of the Janus kinase family (JAK1, JAK2, JAK3, TYK2), thereby disrupting the JAK-STAT signaling pathway in lymphocytes. Employees of the Department of Pathology, Brigham Hospital and Harvard Medical School (Boston, Massachusetts, USA). In an open comparative study, it was shown that recombinant cytokines induced by SARS-CoV-2 acted synergistically, stimulating the expression of APOL1 via the JAK/STAT pathway in primary human podocytes, GECs and kidney microorganoids obtained from the carrier of 2 APOL1 risk alleles, but expression was blocked by the inhibitor JAK1/2 - baricitinib. Based on 9 kidney biopsy-proven cases of COVID-19 with AKI (COVAN patients), the researchers demonstrated for the first time that the APOL1 protein was expressed in podocytes and glomerular endothelial cells (GEC) of COVAN kidneys, but not in the control group. Moreover, most COVAN patients carried 2 APOL1 risk alleles. Cytokine-induced JAK/STAT/APOL1 signaling reduced the viability of organoid kidney podocytes, but was blocked by the administration of baricitinib. The results of the study confirm the conclusion that cytokines induced by COVID-19 are sufficient to cause COVAN-associated podocytopathy through the transmission of JAK/STAT/APOL1 signals and that JAK inhibitors can block this pathogenic process. The researchers concluded that JAK inhibitors may have therapeutic benefits for the treatment of cytokine-induced, APOL1-mediated podocytopathy [37].

The ability to reduce the risk of developing AKI in COVID-19 patients with the use of another antiviral drug - remdesivir - was investigated in a joint Bulgarian-French study by employees of the nephrology department of the Sofia Clinic of Internal Diseases (Internal Disease Clinic, University Hospital "Saint Anna", 1750 Sofia) and the Grenoble University Hospital (Grenoble University Hospital, 38700 Grenoble, France.Grenoble Alpes University, 38400 Grenoble, France). The drug remdesivir is an inhibitor of RNA-dependent RNA polymerase SARS-CoV-2 (RdRp), which is necessary for virus replication. A single-center, prospective, cohort study in Bulgarian patients included the evaluation of data from 120 inpatient patients with COVID-19, of whom 70 had CKD and 50 had normal kidney function. Such accompanying pathology as diabetes mellitus, hypertension, obesity and cardiovascular diseases were more often diagnosed in the CKD group, compared with patients without CKD. Upon admission to the hospital, the levels of D-dimer, creatinine and urea were significantly higher in the CKD group, while the estimated glomerular filtration rate was significantly lower compared to patients without CKD. During hospitalization, 23 patients (19.1%) died, of which 19 were in the CKD group.38 patients developed AKI (31.6%), of which 31 cases were in the CKD group. Using the binary logistic regression method, the

authors found that male gender, the development of AKI and the absence of remdesivir in therapy were independent risk factors for mortality caused by COVID-19. The presence of COVID-19-related symptoms for more than 6 days prior to hospitalization, the presence of a history of CKD and the absence of remdesivir therapy were independent prognostic factors for the development of acute renal failure after hospitalization [38].

Portuguese nephrologists from the Central Hospital of Lisbon (Centro Hospitalar Universitário Lisboa Norte, Departamento de Medicina, Divisão de Nephrologia e Transplante Renal, Lisboa, Portugal.Centro Hospital) did not reveal a significant nephroprotective effect in antiviral drugs in COVID-19 in a study of 130 COVID-19 patients with CKD (average age 73.9 years, men 60.0%). Hypertension (81.5%), cardiovascular diseases (36.2%) and diabetes (54.6%) were frequent conditions. Almost 60% of patients had anemia, 50% hypoalbuminemia, 13.8% hyperlactacidemia and 17% acidemia. The average serum ferritin level was 1531 mcg/l, the average CRP was 8.3 mg/dl and the average LDH enzyme activity was 336.9 U/l. Most patients were treated with a combination of antiviral drugs lopinavir/ritonavir, hydroxychloroquine or corticosteroids and only 2 – remdesivir. Eighty percent of them had symptoms of acute kidney injury, and 16.2% needed hospitalization in the intensive care unit. The 34 patients who died were older and had heart failure with a higher frequency, they had a higher ratio of neutrophils/lymphocytes in the blood, higher concentrations of ferritin, lactate and LDH levels. Multivariate analysis revealed an association between old age (odds ratio - OR 1.1), higher ferritin levels (OR 1.0), higher LDH levels (OR 1.0) and mortality [39].

In a study by Lebanese doctors from the Beirut Medical Institute, treatment with antiviral agents such as ezetimab and remdesivir, antithrombotic agents – clopidogrel and beta-blockers in COVID-19 patients was not associated with a reduction in the risk of inpatient death and the development of AKI, but when using enoxaparin, a significant decrease in the probability of death during inpatient treatment was noted. By authors from the Beirut Medical Institute (School of Medicine and Medical Sciences, Holy Spirit University of Kaslik, Jounieh, Lebanon.School of Medicine, Lebanese American University, Byblos, Lebanon.Institut National de Santé Publique, Epidemiologie Clinique et Toxicologie (INSPECT-LB), Beirut, Lebanon) a retrospective cohort study was conducted in 416 adults with PCR-confirmed COVID-19 who were sequentially hospitalized in three institutions with COVID-19 infection.nineteen, from the opening of the COVID profiled branches until their closure (the period from March 2020 to June 2021). Patients with incomplete information, patients under the age of 18, as well as patients with negative PCR test results for COVID-19 or unconfirmed COVID-19 test results were excluded. Using variables related to the baseline characteristics introduced as independent variables, the researchers found that acute kidney injury (aOR = 4.057) and old age (aOR = 1.053) were associated with a higher probability of inpatient death. After adjusting for baseline characteristics and intake-related factors introduced as independent variables, enoxaparin intake (aOR = 0.435) was significantly associated with a lower probability of death, whereas old age (aOR = 1.049) and ventilation (aOR = 1.2) were significantly associated with higher chances of death. Treatment with antiviral agents such as ezetimab and remdesivir, antithrombotic drug clopidogrel and beta-blockers was not associated with a reduction in the risk of inpatient death and AKI [40].

The nephroprotective effect of glucocorticoids, known to nephrologists, has been shown in severe COVID-19 patients with simultaneous development of AKI and respiratory failure, if necessary, hardware support. The staff of the Department of Nephrology and Kidney Transplantation of Barcelona (Clinical Hospital, IDIBAPS, University of Barcelona, Spain)

described the study data of 52 out of 237 ICU patients who developed stage 2 AKI or higher. The use of corticosteroids in 69.2% of patients was associated with a decrease in the need for renal replacement therapy, a relative risk index of 0.13 [41].

Polish nephrologists from the Department of Nephrology, Hypertension and Kidney Transplantation, Medical University of Lodz (Lodz, Poland) evaluated the effectiveness of high-dose glucocorticoid therapy in the treatment of non-collapsing FSGS associated with COVID-19 in a young white man with a low-risk APOL1 genotype who had COVID-19 pneumonia. His past history included hypertension, anabolic steroids, and a high-protein diet. He fully recovered from type 1 respiratory failure and AKI after plasma transfusion from a donor recovered from COVID-19 and intravenous dexamethasone treatment administered for 16 days at a dose reduced from 16 to 2 mg/day. Due to progressive severe nephrotic proteinuria (22.6 g/24 h), the patient was injected intravenously with methylprednisolone (1500 mg divided into 3 pulses for 3 days). Repeated kidney biopsy, at that time, showed a decrease in the number of glomeruli with podocytopathy, but progression of interstitial lesions. After 23 weeks of therapy, partial remission of FSGS was achieved and proteinuria decreased to 3.6 g/24 h. After 43 weeks, proteinuria decreased to 0.4 g/ 24 h, and serum creatinine concentration remained stable. The researchers concluded that corticosteroid therapy may have a positive effect on immunological changes in the kidneys, causing their acute damage and the subsequent development of acute renal failure in patients with COVID-19 [42].

A comparable nephroprotective effect of steroid hormones on the risk of developing AKI in COVID-19 patients was revealed in the drug azithromycin in a study of Porugal clinicians from the Central Hospital of Leiria (Department of Internal Medicine, Centro Hospitalar de Leiria, Leiria, PRT.Physical Medicine and Rehabilitation, Centro Hospitalar de Leiria, Leiria, PRT). Broad-spectrum antibacterial drug azithromycin from the group of macrolides-azalides, acts bacteriostatically. By binding to the 50S subunit of ribosomes, it inhibits peptidtranslase at the translation stage, suppresses protein synthesis, slows down the growth and reproduction of bacteria, and has a bactericidal effect in high concentrations. The drug acts on both extracellularly and intracellularly located pathogens. During the third wave of the COVID-19 pandemic, the authors evaluated the nature of therapy in elderly and very elderly patients at a tertiary care hospital in Portugal. The observational study in the Department of Internal Medicine of the tertiary hospital was conducted from November 1, 2020 to January 31, 2021. The data of all patients with COVID-19 aged over 65 years were analyzed. Of the 824 patients with SARS-CoV-2 infection, 586 (71%) were over the age of 65. Of these, 61.7% were very elderly and 32.9% were elderly. The hospital registered 53 (27.5%) deaths in the elderly group and 182 (46.3%) in the group over 80 years old. In the elderly population, only 32% of patients had critical conditions, compared with 79% in the very elderly group. In addition to respiratory disorders, the severity of their condition was determined by acute renal failure and liver dysfunction. In both groups, mortality was higher when acute kidney injury (AKI) developed. The authors found no statistically significant difference in the effect on the incidence of AKI and liver failure between the groups of patients treated with dexamethasone and azithromycin [43].

Thus, the cited studies have shown the possible involvement in the development of acute renal injury in the treatment of COVID-19 patients of such groups of medications as diuretics and anti-inflammatory drugs from the NSAID group.

According to their data, in the development of renal damage during treatment with NSAIDs, it is not so much the type of drug that matters, as its dose and duration of use. Currently, there is no evidence-based personal statistics evaluating the nephrotoxic properties of individual representatives of the NSAID class, possibly with the exception of ibuprofen. At the same time, a lower risk of developing AKI can probably be expected with the use of paracetamol, which was included in the National Russian Recommendations for the treatment of hyperthermia in COVID-19 in 2022 [44]. It has been convincingly proven that the risk of renal damage increases significantly when using drugs in combinations, including diuretics and NSAIDs, NSAIDs and drugs from the group of antagonists of slow L-calcium channels. In the damaged kidney of patients with drug-induced nephropathies and signs of AKI, signs of interstitial inflammation and tubulitis are more often detected. The study of the possible nephropathogenic effect of drugs of the class of angiotensin-converting enzyme inhibitors and angiotensin-converting enzyme inhibitors in COVID-19 patients has so far yielded contradictory results. In some studies, it was found that risk factors for the development of nosocomial AKI were both the use of angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs. In others, there was an increased risk of acute kidney injury during treatment with RASi drugs and a tendency to decrease the incidence of myocardial infarction. At the same time, the use of RAAS blockers had a prognostically favorable value in patients with hypertension, positively affecting the mortality rate, and in the treatment of COVID-19 patients with diabetes mellitus. There was no increased risk of COVID-19 disease development either during treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, from which it was concluded that RASi drugs can be used relatively safely in patients with COVID-19. Nephroprotective properties of medications used in the complex therapy of this disease, including the possibility of reducing the risk of AKI in COVID-19, were noted only in one type of antiviral drugs – in inhibitors of JAK cytokinin receptors - yakini-ba (in baricitinib), which is a type of immunomodulatory drug that suppresses the activity of one or more enzymes of the Janus family-kinase (JAK1, JAK2, JAK3, TYK2). High efficacy in preventing the development of AKI in COVID-19 patients was shown with the use of corticosteroids, which reduced the need for renal replacement therapy in at least 60% of patients with this viral pathology. The given literature data indicate the need for additional studies to assess the characteristics of the action of both nephrotoxic components of the recommended COVID-19 complex therapy and drugs with nephroprotective properties, in order to develop measures to optimize antiviral and symptomatic therapy of the disease and measures to prevent the development of acute renal injury.

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Conflict of interest

Not stated. “The authors declare that there is no conflict of interest.”

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