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Monoclonal Gammopathy of Renal Significance: Consensus of Hematologists and Nephrologists of Russia on the Establishment of Nosology, Diagnostic Approach and Rationale for Clone Specific Treatment

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Abstract

Monoclonal gammopathy of renal significance (MGRS) is a new nosology group in modern-day nephrology and oncohematology. MGRS is defined as kidney injury due to nephrotoxic monoclonal immunoglobulin produced by the B cell line clone that does not reach the hematological criteria for initiating cancer treatment according to oncological and hematological indications. The action of the monoclonal protein on kidney parenchyma results in the irreversible decline of kidney function to the point of loss of organ function which, in line with the position of International Consensus of hematologists and nephrologists, determinates the necessity for clone specific treatment in patients with MGRS despite the absence of hematological indications for treatment initiation. The main challenge of MGRS in the Russian Federation is the inaccessibility of timely diagnostic and appropriate treatment for the majority of patients due to the following reasons: 1) limited knowledge about MGRS among hematologists and nephrologists; 2) lack of necessary diagnostic resources in most health-care facilities; 3) lack of approved clinical recommendations and medical economic standards for the treatment of this disease. The consensus document comprises the opinion of Russian experts on nosological classification, diagnosis and approaches to the treatment of MGRS and is based on the results of a joint meeting of leading hematologists and nephrologists of the country. The meeting was held on 15–16 of March 2019 in during the "Plasma cell dyscrasias and lymphoproliferative diseases: modern approaches to therapy" conference at I. P. Pavlov First Saint Petersburg State Medical University. The present Consensus is intended to define the principal practical steps to resolve the problem of MGRS in the Russian Federation that are summarized as final clauses.

Key words: *monoclonal gammopathy of renal significance, monoclonal gammopathy of undetermined significance, onconephrology, kidney injury, clone specific treatment, paraprotein, kidney biopsy, plasma cell dyscrasias, light chains*

Conflict of interests

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Introduction

The concept of monoclonal gammopathy renal significance (MGRS), proposed by the International Kidney and Monoclonal Gammopathy Research group [1, 2], implies a **pathological condition due to proliferation of a B cell clone or plasma cell that does not reach criteria necessary to start treatment according to oncohematological indications, but produce nephrotoxic monoclonal immunoglobulin (IG), which leads to specific kidney injury with irreversible decline of kidney function and deterioration of the prognosis for the disease.** The progression of renal dysfunction, right up to loss of organ function, according to the opinion adopted by international experts, is **determinative in deciding whether to prescribe treatment targeted at eliminating the pathological clone, despite the absence of criteria for oncohematological indications.** In recent years, a number of publications on MGRS have been released by nephrologists in Russia [3–6]. At the same time, such clinical cases of an obvious connection between an aberrant clone (sometimes minor) and kidney injury remain poorly recognized by both physicians and public health authorities. Due to the lack of knowledge among hematologists and nephrologists of MGRS, the lack of approved recommendations and medical and economic standards of treatment, a number of organizational problems arise, including the lack of an effective, timely diagnosis and treatment for most patients. The use of effective therapy is limited by outdated approaches and standards of care, **based mainly on hematological criteria for**

beginning treatment. Current recommendations on the treatment of lymphatic tumors associated with the secretion of monoclonal paraprotein suggest specific therapy if clinical indications exist. This practice is currently under review, especially in patients with multiple myeloma (MM). Monoclonal lymphocytosis and monoclonal gammopathy of undetermined significance (MGUS) in modern definitions are not regarded as diseases, but as conditions of predisposition to lymphatic tumors with a different risk of transformation and therefore are not subject to therapy. This approach is not true with respect to MGRS, in which a "small" clone is dangerous and life-threatening [7–11], and timely therapy leads to a significant improvement in prognosis [12–15]. This consensus of the country's leading hematologists and nephrologists is intended to outline ways of practically solving the problems of MGRS diagnosis and treatment in the Russian Federation that are critical for this category of patients.

The Concept of Monoclonal Gammopathy of Renal Significance

Monoclonal gammopathy (MG) is the presence of an aberrant clone of the B cell line of differentiation which produces the IG molecule or its fragments. A modern view of the nosologies due to MG, and the role of MGRS in the classification are presented in Fig. 1. A clone is a cell population derived from a single progenitor cell and inherits all its properties, including the ability to produce a monoclonal paraprotein. The produced monoclonal protein, called paraprotein or M-protein, can have pathological properties that are realized in various ways, including deposition in organs and tissues, leading to their damage. Clonal cells can produce a full-sized IG molecule or its fragment (only light chain (LC) or only heavy chain). Cases with the production of two LC isotypes, two or more full-sized immunoglobulins

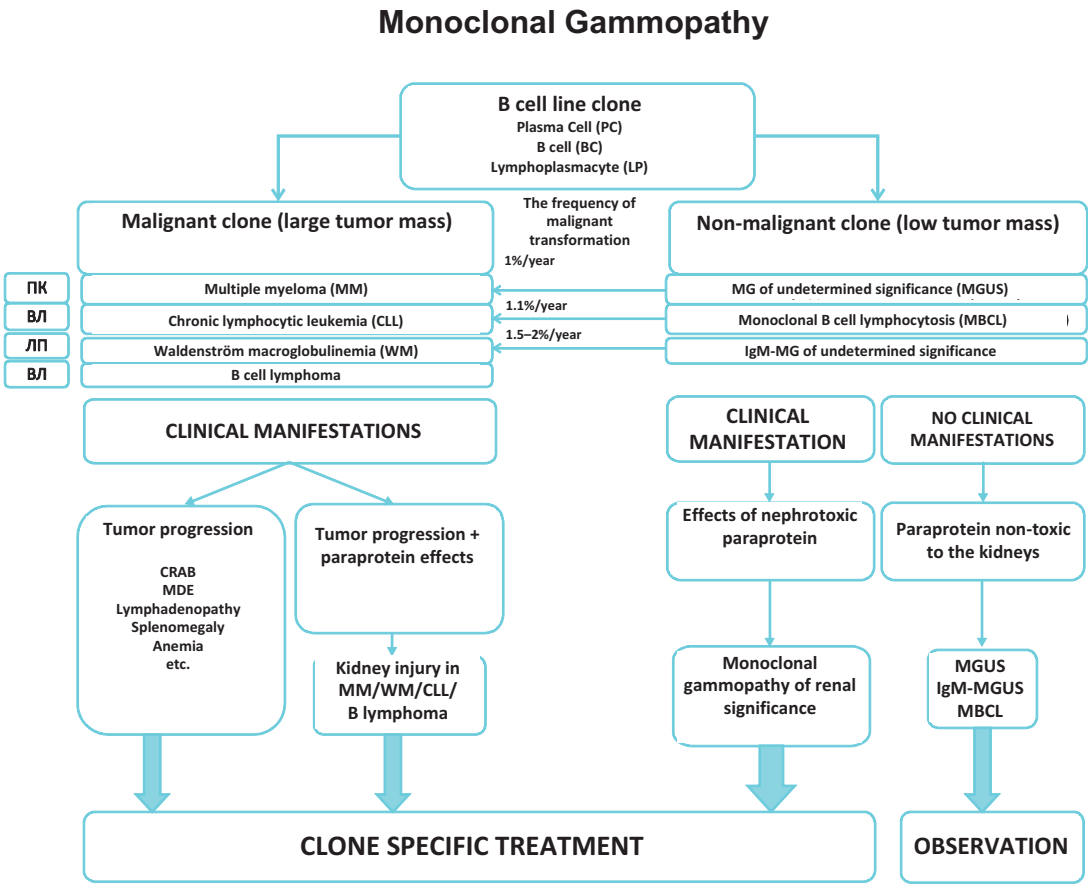

Figure 1. *Clinical variants of monoclonal gammopathies*

CRAB — criteria for organ damage due to plasma cell proliferation in multiple myeloma (hypercalcemia, renal insufficiency, anemia, bone lesions); MDE — myeloma defined events; BC — B cell; LP — lymphoplasmacyte; WM — Waldenström macroglobulinemia; MBCL — monoclonal B cell lymphocytosis; MG — monoclonal gammopathy; MGUS — monoclonal gammopathy of uncertain significance; MM — multiple myeloma, PC — plasma cell, CLL — chronic lymphocytic leukemia

are possible. Depending on the stage of differentiation, B cell clonal proliferation can be divided into: 1) lymphocytic; 2) lymphoplasmacytic; 3) plasma cell. The MG classification based on the type of clonal line, as well as the criteria for each of the states are given in Table 1 [16–20]. Clinical manifestations of MG are associated with: a) an increase in tumor mass; b) the abnormal effects of IG. Most cases of MG occur subclinically, which reflects the early stages of the disease and is included in the concept of MGUS (or monoclonal B cell lymphocytosis in the case of lymphocytic proliferation). In most cases of MGUS, the produced paraprotein does not have nephrotoxicity (i.e., the ability to have any damaging effect on the organ). This condition has a favorable course with a frequency of progression to a malignant form of about 1% per year [21–23]. To assess the low, intermediate, and high risk of MGUS transformation, scales based on an assessment of the ratio of free LCs and the amount of M-protein are used, and treatment is started only when clinical symptoms of the tumor appear (see Table 1).

Table 1. *Classification and Criteria of Monoclonal Gammopathies (According to Leung N. et al. [2] as amended)*

Clone Type	Disease	Clone volume in BM / peripheral blood	M-gradient in peripheral blood	Visceral end organ damage, (criteria for starting treatment)
Plasma cell clone	MGUS	<10 %	<30 g/l	No
	Smoldering (indolent) myeloma	10–60%	≥30 g/l	No
	Multiple myeloma (symptomatic)	≥10% or plasmacytoma	≥30 g/l	Yes *
Clone of lymphoplasmacytic cell line	IgM-MGUS	<10%	<30 g/l	No
	Smoldering Waldenström macroglobulinemia	>10%	≥30 g/l	No
	Waldenström macroglobulinemia (symptomatic)	>10%	≥30 g/l	Yes **
B lymphocyte Clone	Monoclonal B cell lymphocytosis	Monoclonal B cells in peripheral blood $<5 \times 10^9$/l	any	No lymphadenopathy
	Chronic lymphocytic leukemia	Monoclonal B cells in peripheral blood $>5 \times 10^9$ / l	any	Yes ***
	Other forms of B cell LPD	+/–	any	

Note: MGUS — monoclonal gammopathy of uncertain significance; BM — bone marrow; LPD — lymphoproliferative disorder.
* CRAB [15]
C — hypercalcemia R — renal insufficiency; an outdated term in the nephrological literature. In this case, this refers to cylinder nephropathy, which manifests as acute kidney injury (AKI). Previously, the criterion implied serum creatinine >0.177 mmol/l, and creatinine clearance <40 ml/min has now been added [18]. The fact of AKI is not indicated as an essential condition. Before using this criterion as a guide, it is necessary to make sure that the patient does not have kidney injury of any other etiology (diabetic nephropathy, nephroangiosclerosis due to arterial hypertension, etc.). Otherwise, prescribing toxic treatment to such patients may be accompanied by severe adverse reactions.
A — anemia. B — bone lesions
* Myeloma defined events (MDE) [16]
- >60% of plasma cells in the bone marrow
- ratio of involved/uninvolved free LC serum > 100
- >1 focal bone marrow involvement by magnetic resonance imaging with a diameter of more than 5 mm

** Indications for starting treatment of Waldenström macroglobulinemia [17, 27]
- Symptoms associated with tumor growth: lymphadenopathy, splenomegaly, hepatomegaly, organomegaly, anemia, thrombocytopenia, B symptoms
- Symptoms associated with IgM overproduction: cryoglobulinemia, immune hemolytic anemia and/or thrombocytopenia, nephropathy, neuropathy, amyloidosis, hyperviscosity syndrome (increased blood viscosity due to the extremely high plasma protein content due to paraprotein with the development of the following symptoms: mucosal bleeding, neurological deficit, visual impairment), IgM level > 50 g/l

*** Symptomatic lymphadenopathy / cytopenia / splenomegaly / organomegaly / B symptoms

An example is the scale for assessing the risk of progression of MGUS in MM developed at the Mayo Clinic [24]. An increase in tumor mass leads to organ damage in the form of "CRAB" symptoms (C — hypercalcemia; R — renal insufficiency; A — anemia; B — bone lesions) in MM; lymphadenopathy, hepatosplenomegaly, signs of neoplastic suppression of hematogenesis, etc. in chronic lymphocytic leukemia (CLL) and Waldenström macroglobulinemia. The appearance of these symptoms is an indication for treatment. Another part of the clinical spectrum is due to the effects of paraprotein and its damaging effect on tissues and organs, including the kidneys. Symptoms due to paraprotein can occur even with a low tumor mass and a small concentration of paraprotein in circulation. The concept of a "small but dangerous clone" in MG, first proposed by G. Merlini and M.J. Stone in 2006 [25], suggests a clinically dominant organ lesion and poor prognosis due to the pathological effects of paraprotein, but not tumor progression *per se*. To describe such cases, the term MG of clinical significance was recently proposed [26].

MGRS is a term that differentiates the well-known concept of MGUS, removing a number of clinical cases from the confines of "uncertainty". MGRS is also characterized by a clone that is lower than the level corresponding to the criteria for diagnosis of MM or lymphoproliferative disease requiring treatment. According to the Research Institute of Nephrology, the average value of bone marrow plasmatization in case of MGRS was 2.2%, and the level of paraprotein in serum was 1.1 g/l [4]. At the same time, in contrast to cases of MGUS, the produced M-protein in MGRS has nephrotoxicity and leads to clinically significant damage to the kidneys and other organs. Nephrotoxic monoclonal IG can be produced both with low and large tumor mass. If there are grounds for a criteria-based diagnosis of malignant proliferation of a clone of the B cell line of differentiation and kidney injury, this suggests that the produced paraprotein is nephrotoxic. Such cases are not associated with MGRS; a hematological tumor ranks first when articulating the diagnosis, and kidney injury is considered a complication. In the case of nephrotoxicity of monoclonal paraprotein and a "small" clone, the diagnosis should be defined as "MGRS" with a description of the nature of kidney injury, for which the morphological study of renal tissue is crucial. According to the consensus of the International Kidney and Monoclonal Gammopathy Research Group of 2019 [2], the concept of MGRS was expanded compared to the consensus of 2012 [1]. The B cell/plasma cell proliferations, such as "smoldering MM, smoldering Waldenström macroglobulinemia, monoclonal B cell lymphocytosis, as well as CLL and low grade malignant lymphomas (marginal zone lymphoma, mantle cell lymphoma, MALT lymphoma)" were additionally included in the MGRS group as conditions in which the clone produces nephrotoxic IG, but which does not require therapy for hematologic indications.

Epidemiology

Renal damage due to paraprotein is a rare abnormality in the structure of kidney diseases. According to the Research Institute of Nephrology, the prevalence of renal disorders associated with any variant of MG is 7.5% among all patients who underwent diagnostic kidney biopsy. At the same time, MGRS was detected in 4% patients [4]. These figures match the data presented in global literature [11, 28]. According to the Ministry of Health of the Russian Federation, the incidence of "Glomerular, tubulointerstitial kidney diseases, other kidney and ureter diseases" in 2017 amounted to 255 cases per 100,000 adults. Taking into account that a significant part of these cases includes diseases for the diagnosis of which a morphological study of kidney bioptate is not needed (infectious tubulointerstitial nephritis, reflux nephropathy, etc.) and the frequency of MGRS which is 4%, based on morphological verification of the diagnosis, it can be concluded that the incidence of MGRS is generally close to the criteria for orphan disease (10.2 cases per 100,000 adults/year).

Prognosis

MGRS **cannot be considered a benign condition**, because a clone steadily leads to the progression of renal dysfunction due to the effects of paraprotein and, ultimately, to organ death (terminal stage of chronic kidney disease, CKD). The medical and economic importance of CKD is determined by a pronounced increase in the risks of non-fatal and fatal events, disability of patients,

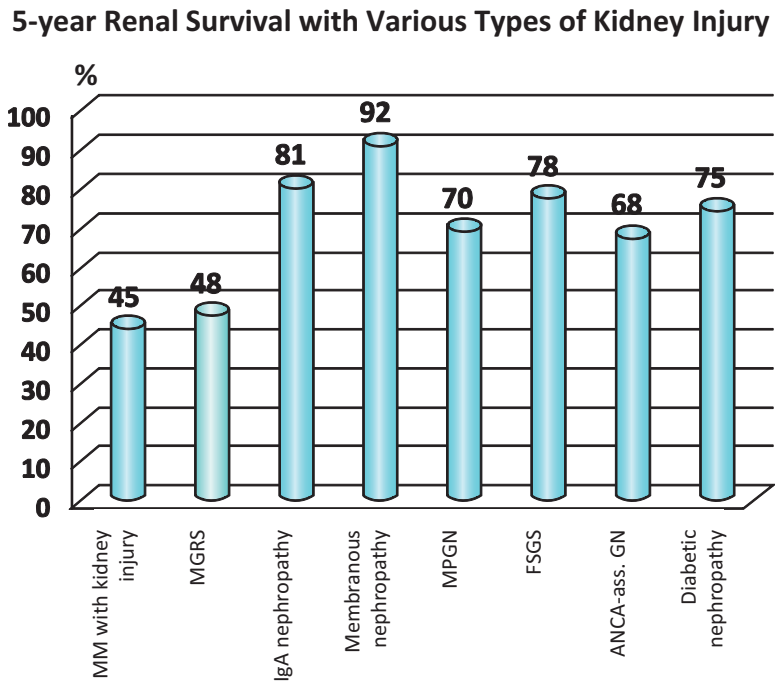

Figure 2. *Renal prognosis for multiple myeloma with kidney injury, monoclonal gammopathy of renal significance, and other nephropathies (according to the Research Institute of Nephrology)*

ANCA-ass. GN – glomerulonephritis associated with anti-neutrophil cytoplasm antibodies; MM – multiple myeloma; MGRS – monoclonal gammopathy of renal significance; MPGN – membrane proliferative glomerulonephritis; FSGS – focal segmental glomerulosclerosis

as well as significant costs of dialysis [29–33]. The renal prognosis for MGRS is comparable to that for MM with kidney injury and significantly worse than for other nephropathies (Fig. 2). In addition, in the presence of MGRS, the risk of malignant clone progression is higher, which means that the prognosis for life expectancy is worse. So, the risk of a clone transforming into a malignant form in MGRS is 3.3 times higher and during the first year is 10% [11], which is comparable with the rate of progression of smoldering MM into symptomatic [34].

The Rationale for Establishment of Nosology of Monoclonal Gammopathy of Renal Significance

The unfavorable prognostic value of MGRS makes obvious the need for treatment of such a "non-life-threatening", from the formal point of view of classical oncohematology, clonal process [2]. A similar "precedent" well known in oncohematology is a systemic AL amyloidosis, a serious disease with a minimal clone of plasmocytes in the bone marrow, which has extremely unfavorable prognosis in the absence of treatment and has long been the subject of irreconcilable differences between hematologists and nephrologists. Effective chemotherapy regimens for AL amyloidosis, designed to eliminate the tumor clone, have been developed and used for a long time, including in Russia [35–38]. The same treatment strategy should be used for non-amyloid forms of kidney injury associated with MG [12, 39–43]. The stereotype of treating only a malignant clone in international practice was overcome in stages with the accumulation of data on the pathophysiology of MG, which is reflected in a number of works in the first decade of the 21st century [7, 25, 44–46]. The most significant milestone was the famous work of N. Leung et al., published in 2012 in the Blood Journal on behalf of the International Kidney and Monoclonal Gammopathy Research Group [1]. The title of this article, "Monoclonal Gammopathy of Renal Significance: When MGUS Is No Longer Undetermined or Insignificant", reveals significant changes in the understanding by the world's leading hematologists and nephrologists of the problem of kidney injury in MG and the awareness of the need for treatment of this condition. Subsequently, numerous articles were published on this subject [47–50], the interest in which, primarily from nephrologists, is due to the possibility of effective etiotropic treatment, minimization/elimination of the effects of nephrotoxic M-protein, and as a result, an improvement in the general and renal prognosis. The recognition by foreign medical communities, including the International Myeloma Working Group [18], of the relationship between clone and kidney injury (monoclonal renal gammopathy) has opened up

the possibility of prescribing highly effective chemotherapy to such patients. The therapeutic effect aimed at suppressing the clone was effective both in terms of renal outcomes and overall survival [7, 9, 12-14].

Mechanisms and Structure of Kidney Injury in MG

The mechanisms of paraprotein action on the renal tissue and body structures are extremely diverse and have not yet been fully elucidated [26, 51]. Due to structural features, physical and chemical properties of the paraprotein molecule itself, as well as the action of local factors, abnormal IG and/or LC can: 1) have a toxic effect on cells; 2) act like antibodies in relation to various molecules; 3) activate the immune system, in particular the complement system; 4) interact with mesangiocytes and other nephron cells and accumulate in the form of deposits of various structures, for example in the form of amyloid fibrils. In MGRS, the pathological effect of monoclonal IG can be realized at the level of any nephron compartment: glomerulus, tubules, interstitium, blood vessels [52]. From here arises the variety of clinical manifestations of MGRS, which may appear as any renal parenchyma lesion syndrome or a combination thereof (Fig. 3). Due to the fact that the PC or B cell clone is "small" and, as a rule, does not cause obvious symptoms associated with the tumor, **patients with MGRS, who have mainly renal manifestations, are primarily nephrologist patients**, complaining of "renal" symptoms (arterial hypertension, edema, hematuria, proteinuria, renal dysfunction, etc.). Fig. 4 shows nephropathy variants associated with MG, according to the Department of Nephrology at the State Budgetary Healthcare Institution "S.P. Botkin City Clinical Hospital" of the Moscow Health Department and the clinic of the Research

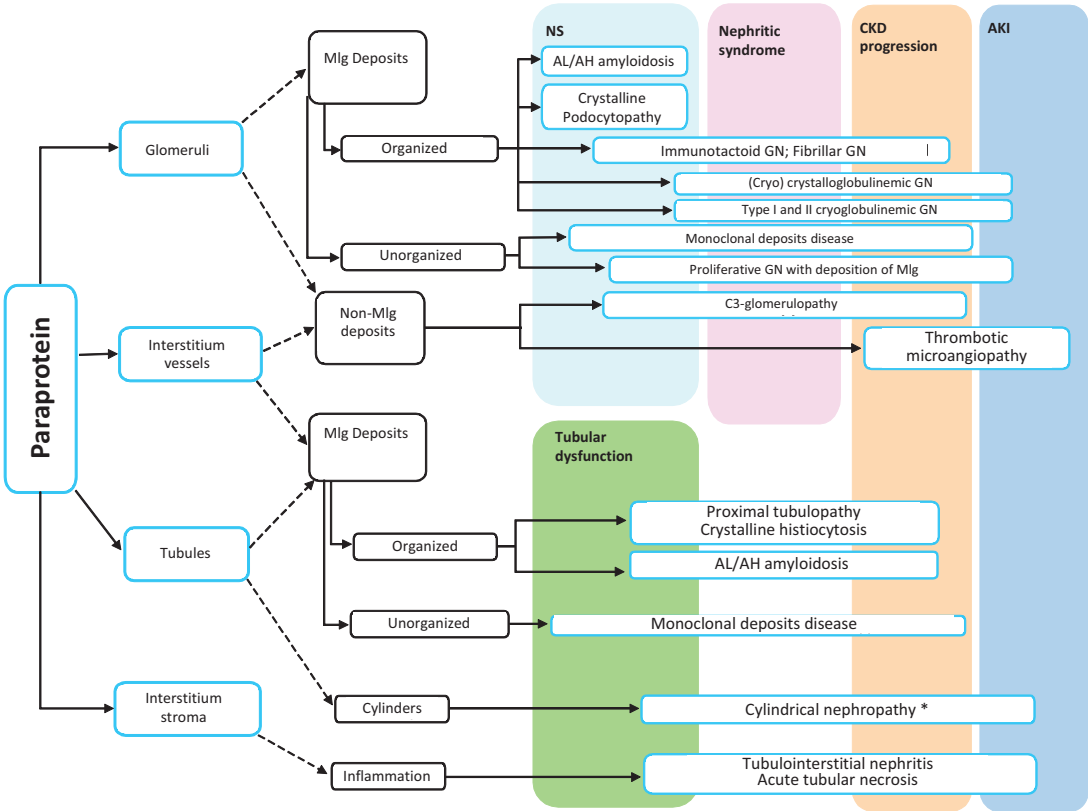

Figure 3. *Pathomorphological variants of kidney injury due to paraprotein and their clinical manifestation*
The variants of kidney injury, the relationship with monoclonal gammopathy of which does not yet have sufficient evidence, include: glomerulonephritis associated with anti-glomerular basement membrane antibodies; membranous nephropathy, including one associated with anti-phospholipase A2 receptor antibodies; IgA nephropathy in Sch nlein—Genoch disease associated with monoclonal IgA [2].
***** Cylindrical nephropathy mainly occurs when there is excessive production of light chains in multiple myeloma and is not associated with MGRS.
MIg — monoclonal immunoglobulin; GN — glomerulonephritis; NS — nephrotic syndrome; AKI — acute kidney injury; CKD — chronic kidney disease.

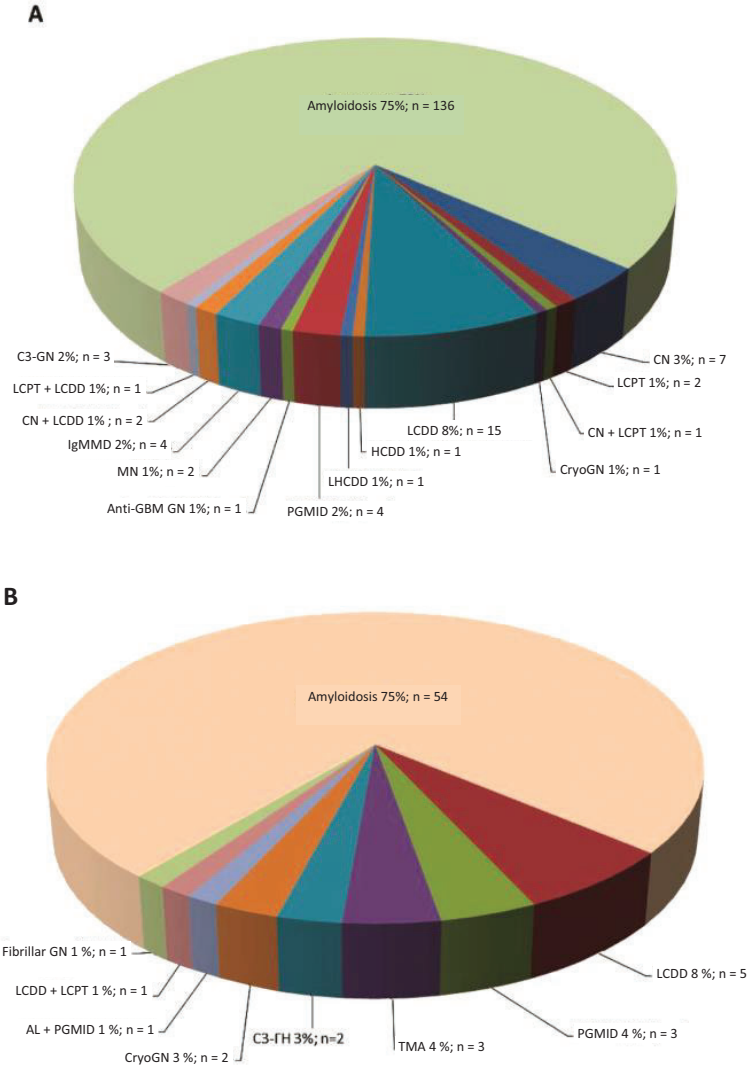

Figure 4. *The spectrum of nephropathies associated with monoclonal immunoglobulins*

A — according to the Department of Nephrology at the State Budgetary Healthcare Institution S. P. Botkin City Clinical Hospital of the Moscow Health Department, 181 patients; B — according to the clinic of the Research Institute of Nephrology at the I. P. Pavlov First Saint Petersburg State Medical University, 72 patients. AL — AL amyloidosis; C3-GN — C3-glomerulonephritis; Anti-GBM GN — glomerulonephritis caused by anti-glomerular basement membrane antibodies; LHCDD — light and heavy chain deposition disease; LCDD — light chain deposition disease; HCDD — heavy chain deposition disease; CryoGN — cryoglobulinemic glomerulonephritis; IgMMD — glomerulonephritis caused by monoclonal IgM deposits; MN — membranous nephropathy; PGMID — proliferative glomerulonephritis with monoclonal immunoglobulins deposition; LCPT — light chain proximal tubulopathy; TMA — thrombotic microangiopathy associated with monoclonal gammopathy; CN — cylinder nephropathy.

Institute of Nephrology at the I. P. Pavlov First Saint Petersburg State Medical University.

Depending on the profile and academic and research orientation of the hospital, the structure of renal lesions associated with monoclonal gammopathy may vary while the tendency towards the dominance of AL amyloidosis remains. According to the multidisciplinary therapeutic hospital at the I. M. Sechenov First Moscow State Medical University, E. M. Tareev Clinic of Nephrology and Internal and Occupational Diseases, 276 patients with monoclonal gammopathy were diagnosed, 51% of whom had AL amyloidosis [3]. Among non-amyloid nephropathies (n = 63, 23%) at an equivalent frequency of morphologically confirmed chronic glomerulonephritis in comparison with a sample from the S. P. Botkin City Clinical Hospital (membrane proliferative — 4%, focal segmental glomerulosclerosis — 1%, membranous — 1%, minimal mesangial changes — 1%), cryglobulinemic glomerulonephritis (6%) is a more significant part, mainly in case of HCV-associated type II cryoglobulinemia, the smaller part is monoclonal immunoglobulin deposition diseases (1%) and cylinder nephropathy (1%).

MGRS and the Structure of the ICD

The recognition by the international community of MGRS as a separate nosology is also reflected in the International Classification of Diseases (ICD). The ICD-11 project, which is available on the official website [53] and scheduled for approval in 2019, includes two of the most common variants for kidney injury in MG: AL amyloidosis and monoclonal immunoglobulin deposition disease (Randall type monoclonal immunoglobulin deposition disease, MIDD). In the new version of the ICD, MIDD is a subsection of the chapter titled "Plasma Cell Neoplastic Diseases" (2A83.0).

Table 2. *The List of Nosologies to Include in the MGRS Group*

AL amyloidosis
AH amyloidosis
Immunoglobulin light chain deposition disease
Immunoglobulin heavy chain deposition disease
Immunoglobulin heavy and light chain deposition disease
Proliferative glomerulonephritis with monoclonal immunoglobulin deposition
Immunotactoid glomerulonephritis
Monoclonal fibrillary glomerulonephritis
Crystalline podocytopathy associated with monoclonal gammopathy
C3-glomerulopathy associated with monoclonal gammopathy
Thrombotic microangiopathy associated with monoclonal gammopathy
Cryoglobulinemic glomerulonephritis as part of type I or II cryoglobulinemia
Light chain proximal tubulopathy
Crystalline histiocytosis
Tubulointerstitial nephritis associated with monoclonal gammopathy
(Cryo)crystal-globulinemic glomerulonephritis
Other forms of glomerulopathy that have been proven to be associated with monoclonal gammopathy, including anti-GBM nephritis associated with monoclonal gammopathy and membranous nephropathy associated with monoclonal gammopathy

Note. MGRS — monoclonal gammopathy of renal significance; anti-GBM nephritis — glomerulonephritis caused by anti-glomerular basement membrane antibodies.

Table 3. *Coding for Kidney Injury Associated with Monoclonal Gammopathy According to ICD-10*

Clone Type	Nomenclature depending on the degree of the clone proliferation and the code of hematological nosology	MGRS type and the code of nephrological nosology
Plasma cell clone	MGUS D47.2 Monoclonal gammopathy of uncertain significance D89.1 Cryoglobulinemia Smoldering (indolent) myeloma C90 Multiple myeloma and plasma cell malignancies AL/AH amyloidosis E85.8 Other forms of amyloidosis	Non-amyloid kidney disease N00-08 Glomerular disorders, including N08.1 Glomerular disorders in neoplastic diseases (MM, WM) N08 * Glomerular disorders in diseases classified elsewhere
Clone of the plasmacyte line	IgM-MGUS D47.2 Monoclonal gammopathy of uncertain significance D89.1 Cryoglobulinemia D89.8 Other specified disorders involving the immune mechanism, not classified elsewhere Smoldering Waldenström macroglobulinemia C88.0 Waldenström macroglobulinemia Monoclonal B cell lymphocytosis D 72.8 Other specified disorders of white blood cells	N10-16 Renal tubulo-interstitial diseases, including N16* Renal tubulo-interstitial disorders in diseases classified elsewhere N16.1 Renal tubulo-interstitial disorders in neoplastic diseases (leukemia, lymphoma, MM) N17-19 Renal failure
B lymphocyte Clone	Chronic lymphocytic leukemia B cell non-Hodgkin lymphoma C91.1 Chronic lymphocytic leukemia C82 Follicular non-Hodgkin lymphoma C83 Diffuse non-Hodgkin lymphoma D89.1 Cryoglobulinemia	Amyloidosis the above codes may apply as well N08.4 Glomerular disorders in amyloidosis

Note: MGUS — monoclonal gammopathy of uncertain significance; MGRS — monoclonal gammopathy of renal significance; WM — Waldenström macroglobulinemia; ICD — International Classification of Diseases; MM — multiple myeloma.

The above is the basis for the recognition of MGRS as a separate group of nosologies in the structure of monoclonal gammopathies, as well as at the level of management by Russian public health authorities. Nosologies that are part of the MGRS group are presented in Table 2.

Hematologists and nephrologists, the authors of this consensus, for the period before the Russian translation of the ICD-11 text in the Russian Federation, came to the conclusion that it was necessary to use the ICD-10 codes to characterize different versions of the MGRS (Table 3). In case of kidney injury associated with MG, the hematological nosology code should be combined with the nephrological nosology code.

A Multidisciplinary Approach to the Diagnosis and Treatment of MGRS

MGRS is a problem at the intersection of two specialties — hematology and nephrology, which **requires a multidisciplinary approach**.

As part of the implementation of the latter, the task of the hematologist is to verify clonality, and at the final stage, decide on the nature of clone specific therapy, i.e., therapy aimed at controlling clone proliferation, including methods of high-dose chemotherapy and hematopoietic stem cell transplantation. The need for the involvement of a nephrologist is due to the fact that in MGRS, a nephrotoxic M-protein is produced, which leads to a wide variety of types of kidney injury and renal dysfunction. The clinical and morphological pattern of MGRS is difficult to differentiate from numerous other abnormalities that are not associated with MG without the use of complex phased research methods and their interpretation.

Diagnosis of MGRS

To establish the diagnosis of MGRS, it is necessary: 1) to determine the presence of a clone of the B cell line of differentiation and 2) establish the specificity of kidney injury due to exposure to a monoclonal protein produced by the clone. In this regard, diagnosis includes hematological and nephrological research methods [2, 52]. Taking into account the significant variety of variants of kidney injury in MGRS, it is obvious that the morphological study of renal tissue is a key step in the diagnosis of this condition [54]. The result of histological examination and clinical and morphological analysis reveal the features of MGRS in each particular case, and also provide information, which is extremely important for the nephrologist with respect to the renal prognosis.

Morphological Diagnosis of MGRS

In order to fully diagnose MGRS, a morphological study of renal tissue should include:

1) **Optical microscopy** with the following staining: hematoxylin/eosin, PAS, Jones staining, Congo red staining, Masson's trichrome stain, stain for elastic fibers;

2) **Immunomorphological examination:** immunofluorescence (IF) or immunohistochemistry (IHC) to detect deposits of monoclonal IG molecules in the renal parenchyma [panel of anti-IgA, IgM, IgG (IgG typing), IgD, kappa, lambda, C3, C1q antibodies]. In some cases, immunomorphological methods should be supplemented with enzymatic demasking of antigen epitopes of monoclonal IG, which allows more efficient diagnosis of MGRS, when routine IHC/IF examinations do not yield results [55–57]. For the differential diagnosis of fibrillary glomerulonephritis, where deposits may be congophilic, an IHC test for DNAJB9, a protein of the chaperone family, is extremely specific for this type of glomerulonephritis [58, 59].

3) **Ultrastructural examination** allows to assess the severity of injury of the kidney structures at the submicroscopic level and the nature of the deposits formed by the monoclonal protein (organized, unorganized). The latter is the key in the differential diagnosis of such forms of MGRS as immunotactoid, fibrillary, cryoglobulinemic glomerulonephritis, etc. Sometimes, in order to detect a monoclonal protein, the examination can be supplemented by ultrastructural IHC with labeled gold nanoparticles [60, 61].

At the final stages of the morphological differential diagnosis of MGRS with the use of omics-technologies and, in particular, proteomics in some centers abroad, laser microdissection is used, followed by separation of the protein components of the renal

tissue by capillary electrophoresis and identification of the molecular composition using MALDI-TOF (matrix-activated laser desorption ionization with time-of-flight analysis and visualizing mass spectrometry) [54, 62, 63].

The above approaches to morphological diagnosis should be carried out exclusively in a highly specialized and well-equipped morphological laboratory, where all the necessary techniques will be applied and evaluated by an experienced nephropathologist.

Hematologic Diagnosis of MGRS

The aim of the hematological examination is to identify paraprotein and a clone of the B cell line of differentiation. The scope of the examination corresponds to that for MM, B lymphoma or Waldenström macroglobulinemia and is described in detail in the relevant recommendations [17–21, 27].

For successful verification of a "small" clone, it is important to use highly sensitive techniques that can detect even a small clone and a small amount of paraprotein: immunophenotyping of bone marrow, genetic studies, immunofixation of blood serum and urine, determination of free LC in serum by the Freelite method or other methods that have been proven to be comparable with Freelite. These methods are the basis not only for primary hematological diagnosis, but also for evaluating the effectiveness of treatment and the progression of the disease.

Treatment of MGRS

The treatment of MGRS should also be based on the **multidisciplinary** approach, it should be clone-specific and include well-known drugs and chemotherapy regimens used for MM, B lymphoma, CLL and Waldenström macroglobulinemia [16–20, 27, 39, 42, 64, 65]. Modern approaches to the etiotropic therapy of MGH are briefly reflected in the Table 4. The aim of treatment is to reduce the production of pathogenic LC/IG, to reduce the deposition of paraprotein in organs and tissues, to prevent further progression of their dysfunction, as well as to prevent the transformation of the clone into a malignant form [11]. In addition to chemotherapy, high-dose polychemotherapy with support for hematopoietic stem cell autotransplantation (autoHSCT) should be considered as an option for the treatment of MGRS.

The tasks of comprehensive nephrological support of therapy include a variety of measures consisting in dose adjustment of drugs taking into account their potential nephrotoxicity, prevention and treatment of AKI, exposure to specific pathogenetic mechanisms of kidney injury (treatment of thrombotic microangiopathy, immunocomplex organ damage, increased clearance of IG deposits), kidney functional evaluation over time and its correction, assessment of the renal response, as well as the use of extracorporeal LC elimination. The latter include renal replacement therapy, such as hemodialysis/hemodiafiltration with high cut-off membranes, as well as SUPRA-HFR (haemodiafiltration with ultrafiltrate regeneration by adsorption on resin). These techniques make it possible to remove free LCs from the body and reduce their toxic effect on tissues and organs, thereby increasing the effectiveness of treatment [66–68]. Also, it is important to prepare potential kidney allograft recipients and include such patients on a waiting list. Given the high frequency of MGRS return to the kidney transplant, the first step is to perform clone specific therapy and consolidate the hematological response using autoHSCT [69].

Consensus is not intended to elucidate MGRS treatment. Issues relating to the treatment of the discussed nosology will be described in detail further in the form of guidelines.

Table 4. *Drugs and Methods Used to Treat Clonal B Cell Line Proliferation [17]*

Cytostatics (cyclophosphamide, bendamustine, chlorambucil, fludarabine, doxorubicin, vincristine, melphalan, etc.)
Corticosteroids (dexamethasone, prednisolone)
Proteasome inhibitors (bortezomib, carfilzomib, etc.)
Monoclonal antibodies (anti-CD20: rituximab, obinutuzumab, ofatumumab; anti-CD 38: daratumumab; etc.)
Bruton tyrosine kinase inhibitors (ibrutinib)
Immunomodulators (lenalidomide, pomalidomide, etc.)
High-dose polychemotherapy followed by autologous transplantation of hematopoietic stem cells

Issues Considering MGRS Treatment in the Russian Federation

At present, in the Russian Federation, MGRS is not considered as a nosology in practical medicine, and such patients are formally assigned to the MGUS group or cases of B cell proliferation without criteria for initiating therapy. As a result of the conventional, but now outdated notions that an exclusively malignant tumor clone should be treated in cases of MG, effective clone specific chemotherapy (bortezomib, lenalidomide, rituximab, etc.) is provided only for patients with malignant forms of MG: MM, lymphomas, CLL. At the same time, MGRS patients, including AL amyloidosis, that do not meet the formal criteria of malignancy, are not included in the programs for providing the necessary medicines (Federal Law No. 299 of August 3, 2018 "On Amending the Federal Law 'On Fundamental Healthcare Principles in the Russian Federation'") and are left without the opportunity to receive therapy that is adequate to the nature and prognosis of the disease. Certainly, this approach to MGRS is unacceptable. The inaccessibility of treatment, primarily due to the fact that the diagnosis "is not listed", as well as due to a lack of understanding of the true nature of the disease and underestimation of its clinical and prognostic value, is detrimental to patients [70]. Patients with this disorder should be provided with the necessary drugs and the possibility of treatment via the high-tech funding channel, including autoHSCT.

Prerequisites for the Establishment of an Onconephrological Center

Renal disorders associated with MG stand at the intersection of two specialties — hematology and nephrology. The understanding of the urgency of this problem in the world has led to the emergence of a new highly specialized field — onconephrology [71, 72]. Obviously, the diagnosis of MGRS, monitoring and treatment of such patients should be conducted in a specialized onconephrological center. The experience of creating and operating such centers was implemented abroad [73]. In the Russian Federation, an onconephrological center can be established at a multidisciplinary hospital, which includes departments of hematology, nephrology, renal replacement therapy, stem cell and kidney transplantation. Another determining factor is the availability of proper diagnostic resources, including an immunomorphological laboratory, which has the necessary techniques for full MGRS diagnosis. It should be noted that the interests of onconephrology are not limited only to renal diseases associated with MG, but include acute kidney injury as a result of treatment of tumor processes, renal lesions associated with solid tumors and hematopoietic stem cell transplantation, secondary tumors in patients with renal allograft, etc. [74].

Conclusion of Consensus of Hematologists and Nephrologists on MGRS

MGRS is not an independent renal disease, a "chronic glomerulonephritis", but a condition in which kidney injury is secondary to clonal B cell proliferation. In other words, MGRS is a precancerous disease in combination with CKD that requires immediate treatment. The latter, however, is not possible for patients in the Russian Federation due to the absence of MGRS diagnosis on the list of nosologies, and therefore, the lack of assistance in case of this disorder.

Within the framework of this consensus, nephrologists and hematologists of national leading clinics came to a collective opinion on MGRS and have submitted a number of proposals for consideration by the professional community and public health authorities of the Russian Federation, the implementation of which will significantly improve the diagnosis and treatment of this category of patients.

The Final Provisions of the Consensus are as Follows:

1. MGRS is a group of diseases in which kidney injury occurs as a result of the pathological action of a monoclonal protein (immunoglobulin or its fragment) produced by a tumor clone of the B cell line of differentiation. At the same time, there are no criteria to start specific therapy for a lymphatic tumor.
2. MGRS is a heterogeneous group of diseases in which the result of the action of a monoclonal

protein on renal tissue can be different, but inevitably leads to progressive renal dysfunction, up to a complete loss of organ function and a decrease in life expectancy.

3. Taking into account the extremely unfavorable prognosis of renal function and life, MGRS should be included in the register of "life-threatening and chronic progressive (orphan) diseases that lead to a reduction in patients' life expectancy or disability", in the form of a generic name that combines a number of separate nosologies, including AL amyloidosis, monoclonal deposit deposition disease, etc. (Table 2).

4. Diagnosis of clonal proliferation in case of MGRS requires immunophenotypic and molecular examination aimed at identifying a "small" clone, including paraprotein in blood and urine using immunofixation and determination of free light chains using Freelite or other methods that have been proven to be comparable with Freelite. These methods should be available, first of all, in specialized oncohematological centers, as well as in other large hospitals in the Russian Federation, as they are the basis not only for primary hematological diagnosis, but also for assessing the effectiveness of treatment and the progression of the disease.

5. Along with the identification of a tumor clone, the diagnosis of MGRS requires a mandatory kidney biopsy with morphological examination to confirm a specific organ lesion. The morphological examination of kidney bioptate should include light-optical, immunomorphological, and ultrastructural methods. The main feature of MGRS is a presence of organized and/or unorganized deposits of monoplastic paraprotein in kidney compartments. The type of monoclonal paraprotein detected in blood serum or in urine should be the same as the type of monoclonal protein, morphologically determined and causing kidney injury.

6. The diagnosis of MGRS should be discussed by a consilium consisting of a hematologist, nephrologist and renal pathologist and should be based on a presence of a pathogenetic relationship between kidney injury and the existing monoclonal proliferation: a clone of a B lymphocyte / plasma cell and/or paraprotein detected in serum/blood.

7. Any variant of MGRS requires the initiation of clone specific treatment, the ultimate goal of which is to preserve renal function and prevent the clone from progressing towards the tumor process. The nature of chemotherapy depends on the type of clonal proliferation. Treatment should be prescribed and performed on a multidisciplinary basis in accordance with the type of clone/paraprotein and the features of kidney injury by a hematologist and nephrologist with similar experience.

8. The group of hematological diseases combined by the term MGRS should be included on the list of disorders which require prescribing expensive chemotherapeutic drugs. Patients should receive treatment via the "high technology" funding channel.

9. Consolidation of the hematological response can be achieved by using high-dose polychemotherapy followed by autoHSCT. Therefore it is advisable to expand the indications for autoHSCT and include other types of MGRS, in addition to AL amyloidosis, in the standards for providing this type of care.

10. For successful diagnosis, timely effective treatment of MGRS and long-term monitoring of patients with this disorder, it is advisable to open specialized departments/centers of oncological nephrology in institutions with proper resources for diagnosis and treatment and qualified medical personnel with relevant experience in oncohematology and nephrology.

11. Based on the consensus provisions, it is advisable to create national guidelines for this clinical issue.

[15] The consensus participants reviewed and expressed solidarity on behalf of the professional communities:

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