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ACUTE KIDNEY INJURY: CONCEPTUAL PROBLEMS

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ABSTRACT

The term acute kidney injury (AKI) has replaced the former acute renal failure (ARF) term. This replacement is dictated by a number of motives, including an attempt to unify the diagnostic criteria and severity stratification of acute injury / renal dysfunction. In the article, the advantages and shortcomings of contemporary AKI classification schemes are considered. However, these necessarily reflect not only injury to, but also failure of the organ. Among the promising approaches for optimising the classification scheme, the distinction of the stage (or addition to the AKI first stage) by the transient detection of AKI biomarkers is discussed, as well as the use of absolute rather than relative alterations of serum creatinine concentration (SCr) for the severity stratification of this state and the rejection of criteria based on variation in urinary volume. The issues concerning the AKI classification are relevant due to its wide expansion; this state remains an important reason for the formation and / or progression of chronic kidney disease and is considered an important determinant of cardiovascular risk.

Keywords: acute kidney injury, concept, definitions, classifications, epidemiology, outcomes.

INTRODUCTION

The term "acute renal injury" (AKI) has entered the medical lexicon rather recently, having ubiquitously replaced the formerly well-known term "acute renal failure" (ARF). This replacement is due to several circumstances, including the need to unify the diagnostic criteria and severity stratification of acute renal injury / dysfunction. At the present time, a number of schemes for diagnosing, classifying and stratifying AKI severity have been developed. However, from our point of view, while remaining ostensibly consistent with the AKI classifications, these schemes do not fully correspond to the AKI concept. Among the promising directions that allow such approaches to be improved are included the expediency of isolating the stage (or addition to the AKI first stage) by transient detection of acute kidney injury biomarkers, the use of absolute rather than relative alterations of serum creatinine (SCr) concentration for the severity stratification of this state and the elimination of criteria based on variations in urinary volume. All of these circumstances will be discussed in detail below.

The constantly increasing incidence of AKI in the general population has now surpassed 0.25%, making it comparable with the incidence of acute myocardial infarction. AKI remains an important factor in the development both of terminal renal failure and less severe stages of chronic kidney disease. In addition, AKI (whether in the short- or long-term) can be considered an important determinant of cardiovascular risk. However, despite the continuous improvement of therapeutic technologies – in particular, the methods of renal replacement therapy – there have been no significant improvements in the results of AKI treatment. Thus, with the mortality rate exceeding 70%, the outcomes of severe AKI variants remain unsatisfactory. In this case, even a short-term, transitory increase of SCr is associated with an increase in the length of hospitalisation, as well as with an increase in mortality as time passes. AKI therapy requires huge material costs, placing a heavy burden on healthcare financing systems. All this makes us consider AKI as among the most critical medical and social problems.

A brief history of the AKI issue

Historical sources indicate that in ancient times humanity was already aware of kidney diseases, clinically manifested by changes in diuresis [1]. A mention of "empty bladder" (*ischuria*) is even found in the works of Galen, the great doctor of antiquity (Fig. 1). In 1796 Giovanni Battista Morgagni, the eminent 18th-century anatomist and pathologist, revised the concept of *ischuria*, subdividing it into *ischuria urethralis, ischuria vesicalis, ischuria ureterica* and *ischuria renalis.* The late 19th century works of Richard Bright, the British founder of modern clinical nephrology, would later form the conceptual basis for acute Bright's disease. Bright's ideas were developed not only on the basis of the results of clinical observations but also morphological studies. A significant stimulus for the development of acute renal dysfunction theory was the medical experience gained as a result of military conflicts. During the First World War, use of the term *trench nephritis*, which had ol-

iguria or even anuria acting as its leading symptoms, was widespread (see Fig. 1). In 1941, E. Bywaters and D. Beall reported on four cases of so-called crush syndrome [2]. They not only presented the features of the clinical course of this state, but also described the pathological changes in the kidneys, drawing attention to the presence of pronounced tubular damage and pigmentary cylinders in the lumen of the renal tubules. These studies served as the basis for the development of the concept of acute renal failure (ARF) that was to be engrained in medicine for as many as five decades (see Fig. 1).

However, by the end of the last century, for a number of reasons discussed in detail below, the concept connoted by the term ARF started to outlive its usefulness to the nephrological community. Consequently, the fundamentally new concept of AKI proposed in 2004 has by now been adopted practically universally (see Fig. 1).

Conceptual AKI model

Basic outline of the AKI concept

As noted above, AKI is a relatively new concept, largely replacing the previously familiar ARF acronym. While, to date, some specialists still apparently view this replacement as purely terminological, the reasons for developing the AKI concept are more fundamental since determined by the developmental logic of contemporary medicine. The main reason for creating this concept was the accumulation of information that even an insignificant transient increase in serum creatinine concentration (*SCr*) is associated with a sharp increase in mortality. Such an increase in mortality is observed both in the early and the distant period. At the same time, the lethal outcome is far from always determined by the "renal" causes [1, 3-5].

All this allows us to assume that in certain situations a rather complex system of pathogenetic connections is activated, leading not only to injuries of the kidney tissue itself but also to damage of other organs and systems (Fig. 2).

Such representations formed the basis of the AKI conceptual model, which, in the presence of an etiological cause and – possibly – predisposing circumstances (risk factors), provides for a transition from "norms" to a possibly lethal outcome (Fig. 3). This transition is carried out through a number of stages, many of which are still potentially reversible (see Fig. 3).

In other words, the model reflects the stage-by-stage formation of this state in close connection with the development of various extrarenal complications or AKI manifestations. In this sense, the AKI concept closely approximates the concept of chronic kidney disease (CKD) in terms of ideology [6, 7].

In principle, the AKI conceptual model allows us to regard it as a broader concept than ARF [9]. In particular, within its parameters should be included acute kidney dysfunctions, arising, for example, with glomerular lesions ("acute nephritic syndrome") [9]. However, the actual "saturation" of this model with the corresponding clinical algorithms does not lead to a solution of this problem. Despite protestations, for example, it fails to provide a solution for acute parenchymal kidney damage ("Renal AKI"). Thus, such a model, despite its complete rectitude, is unlikely to satisfy nephrologists in principle since existing representations appear more "resuscitative" than "nephrological". Nevertheless, the AKI concept as currently formulated leaves open many ways for its development and improvement. Some of our thoughts and suggestions on this issue will be discussed later.

Terminological issues in the AKI problem.

In nephrology, as in other fields of medicine, there are many conditional terms that do not fully reflect the essence of the pathological processes they char-

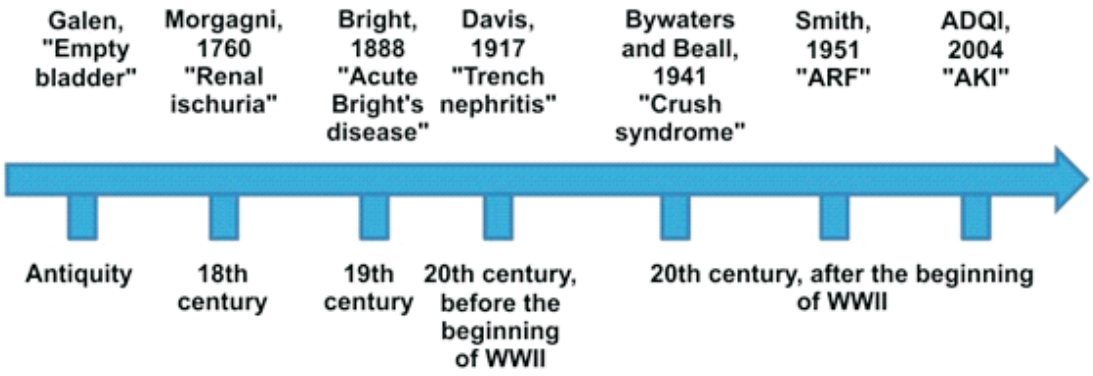

Fig. 1. Historical stages of the development of AKI ideas. According to N. Srisawat et al. [1].

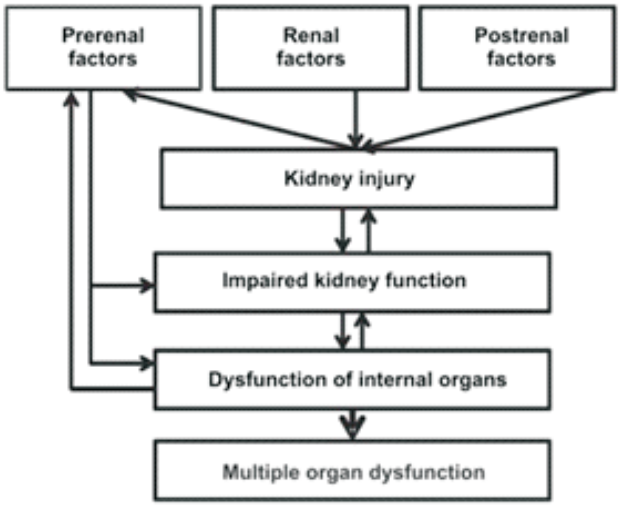

Fig. 2. Pathogenetic relationships arising during the AKI development.

acterise. In the overwhelming majority of cases, these terms have historical roots for which reason it is not possible to abandon them. However, when it comes to the introduction of new terms, especially those borrowed from foreign literature, it is necessary not only to know the grammar of a foreign language for their translation into Russian but also to consider the term's semantic burden, since a literal translation is impossible in most cases.

We already addressed this issue when discussing the translation of the English term "chronic kidney disease" into Russian [10]. At that time such translations as "khronicheskoe zabolevanie pochek" ["chronic disease of the kidney"], " khronicheskie zabolevaniia pochek" ["chronic renal disease"] and "khronicheskoe pochechnoe zabolevanie" ["chronic kidney disease"] were used. Today, no one doubts that the "khronicheskaia bolezn' pochek" ["chronic kidney disease"] version of the translation, which was proposed by us for the first time in Russia [11], is the only correct one that reflects the essence of the "chronic kidney disease" concept proposed by the US National Kidney Foundation in 2002.

In 2008, a leading article was published in the Journal of Nephrology, in which the "acute kidney injury" concept of the international community of nephrologists was outlined and a translation of this term into Russian proposed as "ostroe povrezhdenie pochek" ["acute kidney injury"] (AKI) [12].

In the same article, criticisms were expressed with respect to such AKI classifications as RIFLE and AKIN, and our own variants proposed (Classification of the Research Institute of Nephrology of Pavlov First Saint Petersburg State Medical University, 2008). Three years later R. Murugan and J. A. Kellum [8] made similar proposals (see below). Recently, the "acute kidney injury" term has been used by many Russian-speaking nephrologists in translation into Russian as "ostroe pochechnoe povrezhdenie" ["acute kidney injury"]. We consider it necessary to express our views on such a translation and clarify our own position on this matter, since the problem is not in the play of words or in their rearrangement, as it may seem at first glance, and not even in priorities, but touches upon the very essence of the "acute kidney injury" concept.

First, from the point of view of the grammar of the Russian language, "renal" is a consistent definition in relation to the word "injury". In other words, the term "acute renal injury" indicates the acute na-

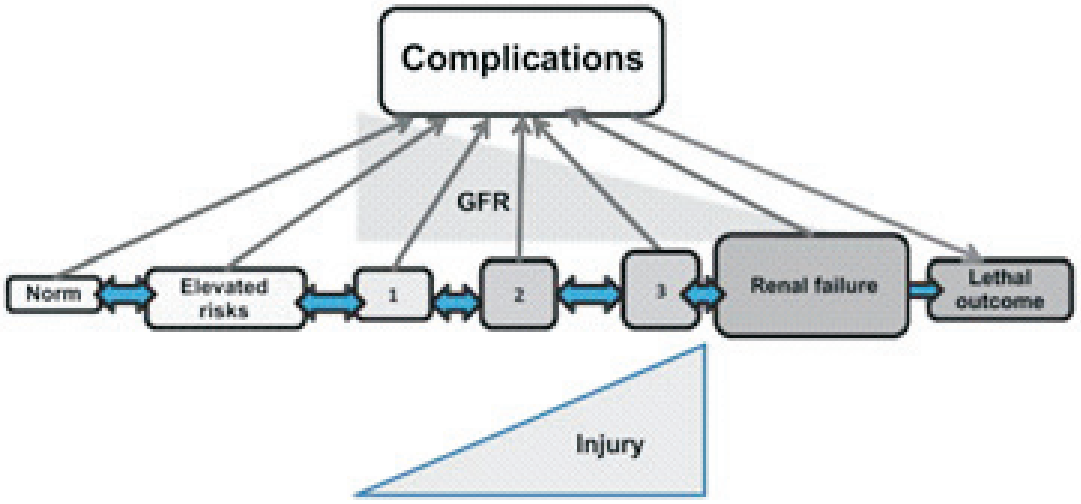

Fig. 3. AKI conceptual model. According to R. Murugan, J.A. Kellum [8] with amendments. 1, 2, 3 - stages of damage.

ture of the already existing kidney injury. However, the concept of "acute kidney injury" suggests that the injury can also be extrarenal: prerenal and postrenal. Some authors distinguish even the stage of pre-prerenal injury. If we return to the Russian language and carefully comprehend the two similar at first glance phrases: "good road surface" and "good surface of the road ", it will be difficult to recognise their identity of meaning. ***The concept of "acute kidney injury" states that there is a pathogenic factor called "acute injury" that can be extrarenal (not only renal), for example, prerenal or postrenal, and that only then does it damage the kidney.***

Secondly, in judicial practice, when dealing with contentious issues, one often turns to precedents. The precedent in medical science of terms is the translation of such phrases from English into Russian in other areas. For example, "acute myocardial infarction" is the acute infarction of myocardium (and not "acute myocardial infarction"); "polycystic kidney disease" is polycystic disease of the kidneys (and not "polycystic renal disease"), etc. Thus, the only correct translation, in terms of the provisions of the scientific concept itself, is the translation of the English "acute kidney injury" term into Russian as "ostroe povrezhdenie pochek".

Grounds for introducing the AKI concept. RIFLE classification.

Despite the fact that the ARF concept had been existing in medicine for about 50 years, many issues relating to its screening, diagnosis, prevention and treatment remained unresolved [6,13-19]. A separate and very serious problem was the lack of generally accepted approaches to the definition and criteria for assessing the severity of ARF. For example, in the English-language literature up until the present time there have been more than 35 definitions of acute renal failure [6,13-19]. In such a situation, it is impossible to give even a minimal objective assessment of the results of epidemiological studies or a study of the outcomes of this state. In particular, the incidence of ARF, according to a number of developments, ranged from 1% to 31%, while the mortality rate varied between 19% and 83% [6,13-19].

ARF was most often defined as a "sudden and persistent decline in kidney function" [14,15]. The main issues that ensued from this definition remained the following:

- What does "sudden" mean?
- What does "persistent" mean?
- What is the specific kidney "function"?

Regarding the last question, it should be borne in mind that the kidney performs a large number of functions in the body. A significant number of them ensures the maintenance of relative constancy of the internal environment of the organism, i.e. homeostasis. The implementation of homeostatic functions is provided by intrarenal processes: glomerular ultrafiltration, tubular reabsorption and secretion, synthesis of biologically active substances and some others.

At present, many methods have been developed for evaluating the kidney's ability to perform a particular function in humans. However, due to the complexity and instability of the results obtained, high costs and organisational problems, the vast majority of these methods are not applicable in wide clinical practice, especially in patients with AKI, who are often in a critical condition [6]. In such patients, in order to assess the severity of kidney injury, it is necessary to resort to the simplest and easiest methods for the patient and staff, such as measuring the volume of urine (diuresis), serum creatinine concentration (SCr) and, in some situations, creatinine clearance rate (CCR).

In any case, the intolerance of the current situation with regard to the definition and stratification of the ARF severity required some solution that would correspond to contemporary ideas about the physiology and pathophysiology of the kidneys and, most importantly, the possibilities of real clinical practice. An attempt to find such a solution was made by the groups of experts of Acute Dialysis Quality Initiative (ADQI), and later by Acute Kidney Injury Network (AKIN). As noted above, the results of the work of these expert groups turned out to be largely similar to the results of the activities of the participants of K/DOQI and KDIGO committees who developed the concept of chronic kidney disease and proposed principles underpinning the severity stratification of this state [16, 17]. Thanks to the efforts of a number of experts, this concept has earned recognition in our country [11, 20-22].

As noted above, ADQI experts rightly believed that the diagnosis of acute renal failure (currently AKI) should be based on simple indicators, accessible to any medical institution. It should be borne in mind that the amount of urinary volume (diuresis) is an integral but rather unspecific characteristic of the functional state of the kidneys, since it depends on a number of extrarenal and renal factors. In this case, the mechanisms of final urinary volume formation are completely different [23]. However, while diuresis is reduced below the necessary minimum in adult people, **oliguria** (the secretion of less than 5 ml of urine per kg of the body mass during the twenty-four hours) is developed in a patient [15]. The appearance

of oliguria is the unequivocal sign of severe kidney damage [14,15]. In addition, during AKI, changes in urinary volume may appear long before the other conventional markers of renal dysfunction (such as SCr [6]) will respond.

We assume that the role of urinary volume as a criterion for the AKI diagnosis and severity will be returned to when discussing the current classifications of this state.

Serum creatinine concentration and creatinine clearance are the most common clinical tests of the functional kidney state in clinical practice. In general, these factors reflect the value of the glomerular filtration rate (GFR). Despite their serious shortcomings and significant limitations, there are no alternatives to these parameters for the assessment of renal function under clinical acute situations (especially SCr) [15]. At that, it must be considered that the possibility of using more reliable methods of GFR determination associated with the introduction of exogenous glomerulotropic markers (inulin, polyfructosan, EDTA, DTPA, X-ray contrasts) is close to zero in patients with AKI, especially those in critical condition, due to the complexity, labour-intensity, duration and high costs [15].

Nevertheless, when assessing the GFR level using the level of serum creatinine in patients with AKI, it is necessary to consider the effect of a number of factors on the value of this indicator. Among such factors, the accumulation of fluid in AKI patients can be one of the most significant. In this regard, attempts are being made to develop adjustments to the SCr values that take the latter circumstance into account. As was to be expected, the results of such studies suggest that the use of uncorrected SCr values may significantly underestimate the severity of kidney damage in AKI patients [23]. Nevertheless, at the level of current recommendations, these approaches have yet to receive any significant support.

At the same time, attempts to find better, but simple and inexpensive ways of assessing GFR in AKI patients are continuing [25]. Thus, in acute clinical situations, the use of the modified CCR evaluation method was suggested by R. Jelliffe [26, 27], which does not require the collection of urine. The results of the undertaken analysis showed that this method of GFR estimating during AKI significantly better corresponds to the results of the CCR determination than the methods of D.W. Cockcroft, M.H. Gault or MDRD (Modification of Diet in Renal Disease).

It is possible that cystatin C may be a more realistic alternative to SCr or creatinine clearance in the future. There is also evidence that, during AKI, the serum level of cystatin C may surpass SCr as the early detector of GFR reduction [13, 18]. However, from the clinical standpoint, the place of cystatin C as a severity index of renal dysfunction, both with acute [13] and chronic [19, 28] renal damage, is not definitively determined at present.

However, in the practice of managing patients with AKI, the need to accurately determine the GFR value is rather rare. It is much more important to be able to predict whether kidney function will tend to remain stable, improve or worsen. In such a situation, SCr measurements are a perfectly acceptable clinical test [15].

Currently, the literature discusses the possibility of using some other substances (biomarkers) at least for forecasting the development and outcomes of AKI. Their role in the contemporary diagnosis of AKI requires a separate discussion and will not be considered here.

ADQI experts suggested the following definition of AKI as **"sudden and persistent decline in glomerular filtration or urinary volume or both together"** [15]. In this case, the renal dysfunction, which exists even for more than 1 month, can be treated as "acute". Usually the AKI development occurs within 1-7 days. The criterion of dysfunction's "persistence" is its registration during 24 hours or more [15].

Considering the problem of definition and severity stratification of AKI, ADQI experts proceeded from a number of principles:

• Changes in kidney function should be counted from a certain basal level;

• The possibility of an acute impairment of kidney function in patients with already existing chronic renal dysfunction should be considered ("AKI on CKD");

• Criteria for diagnosis and severity assessment AKI should be easily applicable in various clinical centres;

• Sensitivity and specificity of these criteria should be determined.

The system according to such criteria is referred to using the RIFLE abbreviation: **R**isk, **I**njury, **F**ailure, **L**oss (of kidney function), **E**SKD (end stage kidney disease, i.e. terminal renal failure) (Table 1).

This classification system includes separate criteria for creatinine and urinary volume (UV). Consideration should be given to the values of the criteria that lead to the selection of the most severe class of kidney damage. It should be borne in mind that with an initially elevated serum creatinine concentration,

the RIFLE-F class is also diagnosed in cases where the increase in SCr does not reach a threefold excess above the basal level. In such a situation, increase in SCr should be more than 44 μmol/l per day, up to the values of this parameter over 354 μmol/L. The RIFLE-FC designation should be used in the case of "AKI on CKD". Similarly, if F class is diagnosed on the basis of UV-criteria, the RIFLE-FO designation should be applied in the presence of oliguria [6,14,15].

Among the above-mentioned principles of AKI severity stratification, attention should be paid to the "basal level" of kidney function. This mainly relates to the problem of GFR estimation. In the vast majority of cases in patients with suspected AKI, the baseline levels of neither SCr nor GFR are known. In this connection, a simple and original solution is proposed. As noted above, in practice, in order to estimate GFR during AKI, it is really possible to use the SCr value, which, in turn, depends on a number of extrarenal factors. Knowing the values of these factors, one can calculate the creatinine concentration serum values. The basis for such calculations was the results of the well-known study "Modification of Diet in Renal Disease (MDRD)". Recall that in this development, a number of empirical formulae have been derived to allow the GFR level to be calculated with some degree of reliability, based, for example, on the values of serum creatinine concentration, as well as the age, sex and ethnicity of the patient ("short" MDRD formula) [16]. Obviously, however, if GFR value is known (or preset), the inverse problem of the calculation of SCr value corresponding to a certain GFR level can be solved. Such a preset GFR level was assumed to be 75 ml/min [15]. The motives for choosing such a value are determined, at least, by the fact that the probability of cardiovascular risks increases significantly with a GFR decrease lower than this value [29, 30].

In practice, especially when managing AKI patients who are typically in severe or critical conditions, doctors generally do not have enough time to make such recalculations. Therefore, a table has been compiled to allowing quick orientation to the proper initial SCr values (Table 2).

Another important problem is the acute deterioration of kidney function in patients with pre-existing renal pathology ("ARF on CRF", "AKI on CKD"). It is not always easy to get an unambiguous answer to the question as to whether there is a given state. This is especially true when (as is often the case in practice) the initial level of SCr is unknown. The calculated basal value of serum creatinine (Table 3) will not help much here either, since it can be very different from the actual value. Moreover, it is impossible to be guided by the relative increase in SCr alone. Therefore, in such situations, one must rely on a combination of relative and absolute criteria. Nevertheless, the increase in SCr at least 44 μmol/l per day to a level above 354 μmol/l may serve as a basis for identifying patients with AKI who did not initially have normal serum creatinine levels [15].

As the results of a number of studies have shown, the RIFLE criteria system has proven itself in practice, at least in terms of predicting outcomes in patients with AKI [13,14,18].

AKIN / KDIGO classifications of AKI.

When using the RIFLE system, nephrologists are faced with a number of problems. As already indicated above, it has been shown that even minimal changes in SCr (less than 44 μmol/l) are associated with an increase in mortality among hospitalised patients. In addition, there were certain difficulties in assessing the severity of kidney damage at a particular time in a particular patient. For example, with increasing serum creatinine concentration, it was possible to detect the AKI stages from R to F in the patient [18].

Table 1

RIFLE classification

Class	GFR criteria	Diuresis criteria	Specificity/ sensitivity
R (risk)	Increase of *SCr* × 1.5 or GFR decrease more than 25%	<0.5 ml/kg/h × 6 h	High sensitivity
I (injury)	Increase of *SCr* × 2 or GFR decrease more than 50%	<0.5 ml/kg/h × 12 h	
F (failure)	Increase of *SCr* × 3 or GFR decrease more than 75%, or *SCr* > 4 mg/dl (> 354 μmol/l) with a rapid increase> 0.5 mg/dl (> 44 μmol/l)	<0.3 ml/kg/h × 24 h or anuria ×12 h	High specificity
L (loss of kidney function)	Persistent ARF = complete loss of kidney function> 4 weeks		
E (end stage kidney disease)	Terminal renal failure > 3 months		

Table 2

Estimation of the "basal" values of *SCr,* μmol/l, corresponding to the GFR values of 75 ml/min/m²

Age, years	Men	Women
20-24	115	88
25-29	106	88
30-39	106	80
40-54	97	80
55-65	97	71
>65	88	71

Finally, we emphasise a very important feature from our point of view. As noted by the developers, **"criteria for ARF [RIFLE criteria, auth.] can be applied to all forms of acute renal failure in patients in critical conditions, with the exception of primary kidney diseases such as glomerulonephritis"** [15]. It is clear that this approach, although justified by the positions of the ADQI experts, cannot satisfy the nephrological community, since it excludes from consideration a large amount of acute renal damage that occurs against the background of primary parenchymal pathology (renal AKI).

During the discussion of the existing problems by the participants of the ADQI group, the representatives of three nephrological associations (ASN, ISN and NKF) and the European Society of Intensive Care Medicine proposed the concept of "**acute kidney injury"** (AKI) at the meeting in Vicenza (Italy) in 2004. At the same time, AKI was considered to be a broader concept than the actual ARF [31]. In the same place, a group of experts from various specialties of the Acute Kidney Injury Network (AKIN) was established in order to conduct further development of the AKI problem.

The first results of the activity of this group were published in 2007 and touched upon the issues of specification of diagnostic criteria and severity stratification of AKI [9]. At the same time, a definition and a new classification of AKI were proposed, which were later modified by KDIGO [7] (see Table 3).

AKI was defined as having one of the following criteria:

• accretion of SCr for ≥ 0.3 mg/dl (≥26.5 μmol/l) during 48 hours

or

• accretion of SCr for ≥1.5 times from the initial, when it is known or assumed that occurred within 7 days

or

• Urinary volume <0.5 ml/kg/h during 6 hours.

At the same time, at least a two-time determination of SCr is required within 48 hours.

This system, based on changes in SCr and/or urinary volume, is largely similar to the RIFLE system, but still differs from it with respect to a number of features. L and E classes in the RIFLE system are derived from this classification and are considered as outcomes of acute renal damage. At the same time, the R category in the RIFLE system coincides with the criteria for the diagnosis of the 1st stage of the AKI in the AKIN or KDIGO system, and I and F RIFLE classes correspond to the 2nd and 3rd stages according to AKIN or KDIGO.

It should be noted that, when it first appeared, the KDIGO system was the subject of a number of interesting, sometimes critical comments from various nationally-based nephrological communities. Thus, the experts from the US Kidney Disease Outcomes Quality Initiative (KDOQI) noted two very interesting points [68]. Firstly, they pointed to low informative criteria based on the diuresis level for diagnosing and severity-stratifying the AKI, at least for adults. If the appropriate calculations are made, then, for the 1st stage of AKI (minimum 0.5 ml/kg/h for 6 hours) per day in a person with a body weight of 70 kg, the volume of urine should be 840 ml. Such diurnal diuresis, generally speaking, is quite sufficient for deducing the necessary quantity of osmotic active substances and therefore it can hardly be regarded as oliguria. In addition, a diuresis of about 800 ml/day is quite a frequent value for women consuming little liquid and, accordingly, releasing a small quantity of highly concentrated urine. Secondly, KDOQI experts dispute the prognostic and diagnostic significance of minor changes in SCr on the basis of a lack of sufficient reliability of the studies confirming this [32].

Table 3

AKI stages [KDIGO, 2012]

Stage	SCr	The volume of excreted urine
1	1.5-1.9 times higher than the initial or increasing for ≥0.3 mg/dl (≥26,5 μmol/l)	<0.5 ml/kg/h for 6-12 hours
2	2.0-2.9 times higher than the initial	<0.5 ml/kg/h for ≥ 12 hours
3	3.0 times higher than the initial or increasing for ≥4.0 mg/dl (≥353.6 μmol/l), or the beginning of the renal replacement therapy, or in patients <18 years, a decreasing in rGFR to <35 mL/min at 1.73 m²	<0.3 ml/kg/h for ≥24 h or anuria for ≥12 h

The general conclusion of KDOQI experts concerning KDIGO system looks rigid enough. In general, they did not find this classification system suitable for clinical practice. Moreover, they stressed that the diagnosis of AKI cannot be based only on the KDIGO system and that the choice of managing tactics should be based, first of all, on clinical manifestations [32].

It is necessary to agree with these provisions in many respects. In addition, from our point of view, the KDIGO system (as well as in the RIFLE and AKIN classifications) contains a number of other shortcomings, some of which we have already paid attention to, and others that we will try to consider. Nevertheless, one must keep in mind the following. Although the KDIGO system is far from ideal, it gives the doctor some general guidelines in the diagnosis, severity stratification and tactics of managing patients with AKI. Moreover, it requires the doctor to pay attention to the kidney function of the patient and, especially, maintain alertness to possible changes in their condition after any effects, including medical ones. Unfortunately, as many nephrologists know, some of our colleagues do not pay enough attention even to the magnitude of a minute diuresis, and we sometimes receive patients in an extremely severe condition, when, however, the timely adoption of fairly simple measures could prevent such cases. Thus, the KDIGO classification has an important preventive value. Therefore, the AKI concept and its severity stratification occupy a place in medicine that is close to the CKD concept although it remains to be regretted that many of the provisions of the KDIGO Recommendations on AKI in actuality appear to be unnecessarily formalised.

Acute kidney disease.

AKI and CKD were identified by independent development teams, according to different criteria. There are situations that do not meet the criteria of either CKD or AKI, but they require attention.

For these reasons, a group of developers [KDIGO] found it necessary to propose the **definition of acute kidney diseases and disorders (AKD)**. At the same time, the following definition and the criteria for AKD were proposed [7].

Definition of AKD:

1. **Functional criteria**

AKI presence

or

GFR reduction <60 ml/min/1,73 m 2 during <3 months

or

GFR reduction ≥35%

or

Increase of SCr >50% during <3 months.

2. **Structural criteria**

Signs of the kidney damage during <3 months.

It remains obscure in what sense the isolation of this concept is expedient and consequently what role it will be able to take up in contemporary medicine. However, one cannot fail to recognise the logic in this approach.

Modified AKI classification systems.

Again, the KDIGO classification system (as well as the RIFLE and AKIN systems) is still focused on patients with acute secondary kidney damage. In fact, it is a system of severity stratification of the acute renal dysfunction (possibly even only acute tubular necrosis), but does not cover cases of acute renal damage on the background of their primary parenchymal diseases. This, in our opinion, is at odds with the very concept of AKI. This view seems to be shared by the authors of the chapter on acute kidney injury in the manual edited by B.M. Brenner [33], as well as by some other researchers of this problem. For example, S.S. Waikar et al. [13] noted in their very thorough work that "**decrease in GFR** is not always observed even in cases of **severe parenchymal renal damage [**highlighted by us, auth.]". At the same time, "the reduction of GFR can occur in situations without apparent [renal – auth.] pathology, in particular, in certain variants of "prerenal azotemia". It follows that the replacement of the usual ARF term for the AKI may not have a significant meaning, because the diagnostic criteria of AKIN or KDIGO are built on purely functional parameters".

It's hard to disagree with this. As already noted in the section on the AKI conceptual model, the "saturation" of the model with specific clinical content (whether using the RIFLE, AKIN or KDIGO systems) does not fully encompass the concept itself since the actual data continue to conform to ARF and not AKI classifications and as such do not adequately meet the objectives of nephrology. For example, with the whole series of parenchymal diseases of the kidneys, the organ can be overtaken by acute processes, leading to the appearance of signs of damage (e.g., microalbuminuria or even proteinuria, especially when evaluated by rather rough criteria such as diuresis or SCr), but not significantly impacting the renal function. In the future, this process has the potential to be more or less successfully resolved. **In our opinion, it is unlikely that anyone will assert that no AKI is present in this situation.** At the same

time, it will not be diagnosed from the positions of RIFLE, AKIN or KDIGO systems.

At one time, we proposed minor changes to the AKIN classification system, which, in our opinion, could resolve the above contradictions. [12]. Firstly, we proceeded from the fact that a clearly-worded specification of the AKI definition is yet to be proposed by the developers of this concept [9]. We proposed to understand AKI as an **acute (hours, weeks), potentially reversible injury of the renal parenchyma of various aetiology and pathogenesis with or without decrease of excretory renal function.** Secondly, we considered it appropriate to separately consider the AKI risk factors. Thirdly, in our opinion, it made sense to single out as the first stage of AKI the conditions characterised by a transient presence of kidney damage markers, and to supplement the interpretation of the stages by GFR changes. Fourthly, we considered that it is worthwhile to consider the AKI outcomes separately.

It is worth noting that following the publication of our proposals, similar initiatives were made by R. Murugan (2008) and J.A. Kellum (2011) [8]. However, in our opinion, the proposed AKI classification model represents, in a certain sense, "one step forward, two steps back". For example, by entering into the system the criteria of "damage", based on the assessment of the biomarker levels, they proceeded from the RIFLE system, preserving the notorious "risk" category, which, in their opinion, should be regarded as insignificant increase in serum creatinine levels or decreased diuresis.

As noted by the very authors who proposed the AKIN system (we recall that the KDIGO system is a minor modification of the AKIN classification), it is not ideal and possibilities for its clinical use should be tested in further studies. Although the results of some of them have already been published, it seems to be too early to give them a final assessment [34, 35].

However, the results of subsequent developments allow us to look a little differently at the problem of determination, severity stratification, diagnostics and AKI differential diagnostics. S.S. Waikar and J.V. Bonventre [36] conducted a mathematical analysis of the SCr dynamics, depending on the initial state of renal function (CKD stage), using two-compartment and one-compartment clearance models. As a result of their development, they concluded that AKI severity stratification should be guided not by relative, **but by absolute SCr changes over time.**

The results obtained by S.S. Waikar and J.V. Bonventre [36] lay behind our decision to conduct our own analysis of this problem. In this case, unlike our American colleagues, who used the generally accepted speculative and average data on the volumes of fluid spaces of the body, the rate of creatinine production, etc., we were able to refer to information detailing the amount of extracellular fluid volume (defined by the space distribution of99mTc- DTPA) and daily creatinine excretion in 55 patients with different stages of CKD [37].

As expected, the results of our calculations fully confirmed the ideas (which have already become almost classical) that under the accepted conditions (stability of production, volume of extracellular fluid and GFR after its sharp decrease) and after a certain time, SCr reaches a "plateau". At the same time, the level of excretion of this metabolite is gradually restored to the initial level (due to the growth of SCr, despite the persistent decline in GFR). In other words, in this case, the balance between creatinine production and excretion is restored at higher concentration values of this metabolite in blood serum.

Next, we calculated the average absolute and relative changes of SCr per day, starting from the initial state of kidney function (CKD stage). With this method of analysis, it turned out that the **increase in average expected absolute values of SCr do not depend on the initial state of the kidney function (CKD stage), whereas the daily average values of ΔScr% in patients with III-IV CKD stages are significantly lower than in patients with slightly disturbed initial kidney function.** In any case, both our data and the results of our American colleagues regarding the absolute and relative increases in serum creatinine concentration, as well as the rates of its growth after a sharp instant GFR decrease in patients with chronic pre-existing renal dysfunction, required verification in direct clinical observations.

To date, at least one other such study has been carried out by Brazilian specialists, whose results turned out to be quite interesting, although in some ways predictable. In this investigation, a cohort of 584 patients with myocardial infarction, of which 34.1% initially had signs of CKD, was carried out during the first 7 days of observation in the hospital. The diagnosis of possible AKI was established both using the KDIGO criteria and by the system of S.S. Waikar and J.V. Bonventre. It was found that, in general, AKI, when diagnosed according to KDIGO criteria, is detected significantly more often than when according to the parameters proposed by the researchers from the United States (25.7 vs 18.0%, P <0.001). At the same time, the KDIGO system reliably detected AKI in patients who did not have CKD. On the other hand, the criteria based on creatinine kinetics were better

than KDIGO for the AKI diagnosis in patients with pre-existing CKD [38]. The latter was to be expected, since such systems were developed precisely for the purpose of revealing "AKI on CKD". Nevertheless, the results of this study, as well as a number of others, including those cited in this chapter, indicate that the optimal system for diagnosing and severity stratifying the AKI has not yet been created. Moreover, even the latest proposals by KDIGO in this direction do not solve all problems.

Epidemiology of AKI

As a consequence of differences in definitions, classifications and populations of patients studied, the prevalence of AKI is difficult to assess. Data on the incidence of AKI may differ significantly if detected in the general population, among hospitalised patients, or in patients in intensive care units (ICUs) [39].

AKI in the general population.

Estimating prevalence and incidence of AKI is the most difficult task. Population studies give very contradictory results. The total incidence of AKI varies from 140 to 2880 cases per million of population per year. At the same time there is an increase in the incidence rate by 400% from 1988 to 2002 [40].

More uniform results are obtained by only considering cases of AKI requiring dialysis (Table 4) [41-45].

Non-hospitalised (or "extramural") AKI may also occur in the context of mass disasters such as wars, earthquakes and other causes of crush syndrome [46]. In developing countries, "herbs" (traditional medicines) and infections remain the most common etiological factors of AKI [47,48]. In any case, the integrated research results of recent years unequivocally confirm that AKI is a large-scale, worldwide medical and social problem. The incidence of AKI in the general population reaches 0.25% [49, 50], which is comparable with the incidence of acute myocardial infarction [51]. In this case, the number of AKI cases is continuously growing. For example, in the United States, the AKI detection rate has increased from 61 cases per 100 000 population in 1988 to 288 per 100 000 population in 2002. When only the AKI cases that required RRT were considered, a growth from 0.03% in 1988 to 0.20% in 2002 was recorded. In the conversion to actual population, this incidence corresponds to a rate of increase from 4 cases per 100,000 population in 1988 to 27 cases per 100,000 population in 2002. [52]

In-hospital AKI

The incidence of in-hospital AKI is approximately 5-10 times higher than that of extramural, despite studies of in-hospital AKI underestimating their true frequency. This underestimation is due to the fact that in some cases (for example, patients in the terminal state), there is no AKI screening and no treatment measures are undertaken [39]. Currently, there is a large number of studies, sometimes carried out on a huge number of observations, in which the incidence and prevalence of in-hospital AKI was assessed [52-58]. Sometimes the data of such studies are difficult to compare because of the arbitrariness of the AKI criteria chosen by these or that authors. In this connection, we attempted to compile a brief table reflecting the incidence and mortality rates of in-hospital AKI, where only modern RIFLE or AKIN classification and diagnostic systems were used to detect it. At the same time, only the minimum and maximum values for morbidity and mortality given by individual researchers are considered (Table 5). Analysis of this table leads to a number of speculations. It turns out that with the same aetiology, morbidity and mortality can differ by several times. Clearly, it is necessary to consider differences in the severity of the patients' conditions, which cannot be discussed in detail here. **However, it seems to us that these data largely reflect the imperfection of both classification systems. In our opinion, they do not succeed in fully providing an opportunity for the diagnosis of AKI or an assessment of its severity. It is unlikely that this problem can be solved using the KDIGO classification, which only represents a minor modification of the AKIN system. Therefore, this issue needs further development.**

Table 4

Prevalence of AKI requiring renal replacement therapy (RRT) in the general population

Authors:	Country, region	Prevalence, patients per million population per year
C.Y. Hsu et al. [41]	Northern California, USA	295
T. Ali et al. [42]	Grampian, Scotland	183
W. Metcalfe et al. [43]	Grampian, Highland, Tayside, Scotland	203
G.J. Prescott et al. [44]	Scotland	286
F. Liano, J. Pascual [45]	Spain	209

AKI in patients in critical conditions

Severe AKIs requiring admission to an intensive care unit (ICU) are observed in 11 patients per 100,000 population per year. These "critical" patients account for up to 30% of all ICU hospitalisations, with the majority of them being admitted with multiple organ dysfunction syndrome [59-62]. If we use more "liberal" criteria for RIFLE, then we can assume that approximately two thirds of patients in the ICU suffer an episode of acute renal dysfunction [14]. AKI was detected in a shocking 67% of patients, with 12% of them categorised as the highest R (risk), 27% I (injury) and 28% F (failure) classes. Of the 1510 patients who were first categorised as R class, 56% progressed further to I or F class. The most common factors contributing to the AKI development were prerenal causes and sepsis. Approximately 30% of patients had pre-existing renal dysfunction [59-62]. The results of some studies suggest that an estimate of the AKI incidence detection of 36% in patients admitted to ICU is quite realistic [35]. However, these data are more like the "average temperature for hospital". Firstly, as noted above, the severity level of AKI can vary. Secondly, AKI is a dynamic state and its functional class or stage may change during the period observation. Thirdly, the results of AKI diagnosed in patients in critical conditions summarised in a recent paper by J. Case et al. [40] were dependant on the RIFLE or AKIN aetiological criteria used (see Table 5). As already indicated earlier, both morbidity and mortality in AKI may vary quite extensively depending on the different aetiologies. Both the prevalence of more aggressive therapeutic and surgical technologies and population aging, leading to an increase in the comorbidity of the pathology, have been offered as an explanation for the increasing incidence of AKI in both developed and developing countries [63].

AKI outcomes and prognosis

AKI initial outcomes and short-term prognosis.

The initial results of the international observational study of patients in critical condition with AKI made for depressing reading. Mortality in the ICU was 52%, with another 8% of patients dying in transfer from the ICU, combining to form a general in-hospital mortality rate of 60.3%. Meanwhile, 13.8% of the survivors would require dialysis [60]. The increase in the RIFLE class correlated with the increase in mortality of patients [14, 61, 76, 77]. At the same time, according to the results of multifactor analysis, each class was independently associated with hospital mortality [35].

In this regard, the results of a recent study carried out in Taiwan, which examined the mortality of patients with AKI after surgical interventions depending on the timing of RRT initiation, are of great interest. The study included 648 patients who were divided into three groups: those with early initiation of RRT (EIRRT, a day or less from the time of admission to the ICU), standard initiation (SIRRT, 2-3 days) and late initiation (LIRRT, more than 4 days). The observation period was limited to 180 days. Deaths occurring during this period were considered as in-hospital – 379 patients (58.5%) died during hospitalisation. The probabilities of occurrence of death and in-hospital mortality in the three studied groups were described by a U-shaped curve [78].

Table 5

Morbidity and mortality from AKI, classified by RIFLE or AKIN systems (adapted according to J. Case et al. [40])

Population of patients	frequency (%) AKI definition	Sources		Mortality, (%), AKI definition	Sources	
Mixed	10.8-67.2 (RIFLE-RIFLE)	D.N. Cruz et al. [62]*	E.A.J. Hoste et al. [14]	7.1-72.6 (AKIN-AKIN)	T. Mandelbaum et al. [64]	H.R. Samimagham et al. [65]*
Sepsis	36.1-65.8 (RIFLE-RIFLE)	S.M. Bagshaw et al. [35]	N. Lerolle et al. [66]	24.2–62.8 (RIFLE-RIFLE)	S.M. Bagshaw et al. [35]	N. Lerolle et al. [66]
Burns	26.6-53.3 (RIFLE-RIFLE)	S.G. Coca et al. [67]	T. Palmieri et al. [68]	7.6–34.4 (RIFLE-RIFLE)	S.G. Coca et al. [67]	T. Palmieri et al. [68]
Injury	18.1-50 (RIFLE-RIFLE)	S.M. Bagshaw et al. [35]	E. Gomes et al. [69]*	8.2 - 16.7 (RIFLE-RIFLE)	E. Gomes et al. [69]*	S.M. Bagshaw et al. [35]
CIN (contrast-induced nephropathy)	11.5–14 (RIFLE-AKIN)	A.H. Rashid et al. [70]*	K. Lakhal et al. [71]*	18–31 (AKIN–RIFLE)	K. Lakhal et al. [71]*	A.H. Rashid et al. [70]*
Cardiac surgery	16.7–54 (RIFLE-RIFLE)	G. Mariscalco et al. [72]	G.U. Roh et al. [73]	1.3–12.6 (RIFLE-RIFLE)	L. Englberger et al. [74]	M.D.N. Machado et al. [75]

To date, despite the increasing effectiveness of technologies for supporting such patients, the question as to whether the AKI outcomes have actually been improving over the past decades remains outstanding. According to one analysis, it can be assumed that the outcomes in patients with AKI, which required RRT, have actually been improving for more than a decade [57,79]. On the other hand, the results of other researchers suggest that the mortality rate among patients with AKI who needed RRT has remained more or less constant throughout 1970-2004 [80]. It should be noted that it is not only changes in the quality of technologies for managing patients with AKI that are difficult to compare the when analysing the results of studies carried out at different times. It is also necessary to bear in mind that the initial characteristics of hospitalised patients have changed over time. AKI patients who received RRT recently became more "severe", older and suffering from a combined pathology. One way or another, the KDIGO experts concluded that the mortality in AKI is, in fact, somewhat lower [39]. However, in any case, the presence of AKI is associated with an increase in the patient's length of stay (LOS) in the hospital by 2 bed-days and the need for subsequent short- or long-term care.

AKI long-term outcomes.

The long-term outcomes of AKI have been less thoroughly studied than the short-term ones. Recently, the relationship between the presence of AKI and mortality after a long period following various cardiac surgical interventions from 1992-2002 was retrospectively analysed. When evaluated on the basis of the RIFLE classification, survival rates were worse in patients with AKI in proportion to its severity [81]. According to a major analytical review on the risk of developing adverse AKI outcomes during at least 6 months following discharge from hospital, it was found that the mortality rate was 8.9 deaths per 100 person-years in AKI survivors and 4.3 deaths per 100 person-years in patients without AKI. In patients with AKI, the cardiovascular risk was significantly higher. For example, myocardial infarction developed in 15.4% of patients with AKI and in 7.0% of patients without AKI [82].

In our opinion, the probability of CKD developing following a previous AKI is a serious problem. And, while it cannot be claimed that this issue has not been given attention, it turns out that many epidemiological studies estimate the recovery of kidney function solely according to the criterion of "needs or does not need dialysis" [83]. Therefore, although attempts have been made to summarise the results of small-scale, prospective studies on this issue, strictly speaking, the exact role of AKI as a potential cause of CKD remains unknown. The results of these observations are consistent with the fact that a month after the initial damage in patients there was a decrease in GFR, even with the complete restoration of renal blood flow. Reduced GFR was seldom less than 50 ml/min from the initial values (about 100 ml/min) and was often ignored, the effect of such changes on mortality in the long-term perspective was often underestimated [84].

In addition, it was shown that even in the optimal situation in which a patient survives severe AKI and acute dialysis is stopped within a month, there is an almost 10% chance that chronic dialysis will be required at some point in the next few years [39, 85].

The results of a relatively recent study, which have already resonated through the nephrological community, resemble these results closely in many respects. In this study, an attempt is made to determine whether the complete restoration of kidney function following an AKI episode is associated with the development of de novo C3 CKD and mortality in patients with normal initial kidney function. Recovery was considered complete if SCr had exceeded basal by less than 1.10 times by the end of the observation. In terms of outcomes, the formation of a C3 CKD incident case persisting for three months and death from all causes were considered. Over a period of 2.5 years, the incidence of C3 CKD was 15% and 3% in the samples of patients with and without AKI respectively. Mortality was 35 and 24% in patients with and without AKI, respectively. Nevertheless, although the complete restoration of kidney function after an AKI episode in patients with an initially undisturbed functional state of the organ was associated with an increased risk of occurrence of incident C3 CKD cases, it did not affect the total mortality rate [86].

The need for constant replacement therapy in AKI patients is difficult to estimate. First, such studies are likely to be multicentre, since it is difficult to find a representative group of corresponding patients in one, even a very large, hospital. Secondly, the observation of such patients should be long enough. And no one can say exactly how long. It is well known that dialysis in AKI patient may last for several months and even longer (everybody believes that the patient is already on a permanent dialysis), and then the kidney function is gradually restored. Therefore, such studies are difficult to organise, and their results should be treated with great care.

As follows from Table 6, the data obtained by different authors are very significantly different. From

the data available it is difficult to understand with what such differences are connected, but most likely the main factor determining the AKI patient's transition to a constant RRT is etiologic. Let's note that RRT in a patient with AKI, continuing for 60 or even 90 days, can hardly be considered as a constant (see Table 6).

AKI and cardiovascular risks

A close relationship between the state of kidney function and the lesions of the cardiovascular system is now considered to be axiomatic. At the same time, the decline in GFR is one of the most important determinants of cardiovascular risk. In turn, the pathology of the cardiovascular system contributes to the development of renal damage (cardiorenal continuum, acute and chronic cardiorenal and renocardial syndromes) [21, 29, 30, 94].

It is well known that various acute cardiovascular problems can become the causes of AKI [3, 13, 40, 72-75, 95, 96 and many others] (acute cardiorenal syndrome, cardiorenal syndrome type 1) [94]. On the other hand, the current classification presupposes the isolation of acute renocardial syndrome (cardiorenal syndrome type 3). In this case, the AKI episode leads to the development of acute injury/dysfunction of the cardiovascular system [94, 97]. However, as a recent study in Taiwan showed, AKI requiring dialysis with complete restoration of renal function is associated with a greater probability of coronary pathology and the extent of cardiovascular mortality in comparison with non-AKI patients [98]. These data give grounds for allocating such patients to the group of increased cardiovascular risk.

AKI associated costs.

Due to the very fact of AKI determining not only a bad prognosis, but also being associated with significant additional costs [89, 99-102], the cost per survivor with AKI within the 6-month period had reached $ 80,000 as early as in 2000 [89].

Epidemiology, prognosis and outcomes of AKI in the Russian Federation. In attempting to analyse epidemiological problems of AKI in Russia, we encountered a number of unsolvable issues. It turned out that it is impossible to obtain any information about the incidence and prevalence of AKI from available literature sources. While information about CKD can be obtained from the National CKD Registry [103], there is nothing of the kind regarding AKI. It is paradoxical that the AKI epidemiological situation is quite conceivably better known in poor, developing countries in Africa, Asia and Latin America than in a nuclear superpower, space-exploration pioneer and resource-rich country like Russia. At the same time, there is no good reason to suppose that Russia is better off than anywhere else in the world regarding AKI problems.

A little more information can be obtained regarding the structure of AKI and results of its treatment. However, this information is typically limited to materials derived from one-off and very small-scale studies, which are rarely multicentre and almost all focused on studying RRT results in patients with severe AKI. In almost every case, in-hospital mortality appears as an end point. In addition, most of these studies are characterised by a very poor, if not primitive, design. Finally, many of them use outdated or incorrect terminology. The results of RRT use were very variable and depended on the AKI aetiology. Mortality varied from 8.3 ("urosepsis") to 70.6% (patients with multiple organ dysfunction syndrome) [104-107].

CONCLUSION

The analysis of the available data shows that AKI remains a very urgent and widespread medical problem. At 0.25%, the incidence of AKI in the general

Table 6

Need for continuous replacement therapy in AKI patients (according to R. Murugan, J.A. Kellum [8] with amendments)

Author	Study period	Number of surveyed patients	Percentage of patients requiring constant RRT
G.M. Chertow et al. [87]	1991-1993	132	33%
J.T. McCarthy [88]	1977-1979; 1991-1992	142	21%
M. Korkeila [89]	1989-1990	3447	8%
S. Morgera et al. [90]	1993-1998	979	10%
F. Liano et al. [45]	1977-1992	748	2%
P.M. Palevsky et al. [91]	2003–2007	1124	24.6% within 60 days
R. Bellomo et al. [92]	2005–2008	1508	5.4% within 90 days
A.M. Van Berendoncks et al. [93]	2001–2004	595	10.3% within 2 years

population is comparable with that of acute myocardial infarction [49, 50]. At the same time, there has been a progressive increase in the incidence of AKI, by about 400% from the end of the last to the beginning of the present century. The latter is connected with a number of circumstances, but, in our opinion, the tendency towards population aging, which is to a greater or lesser extent observed worldwide, has the greatest significance. Despite the development of medical technologies, mortality from AKI remains high and, apparently, has not significantly decreased. In some situations, it can reach 60-70%. The treatment of AKI patients is very costly and puts a heavy burden on society. It is significant that AKI can cause CKD; moreover, cardiovascular risks also increase sharply in AKI patients. As already mentioned above, according to some data, the incidence of myocardial infarction in such people increases more than twofold.

There is also the impression that the available methods of AKI treatment – especially RRT when applied in the case of AKI – are approaching their limit and breakthroughs in this direction are not anticipated. Therefore, at present, the early detection of AKI is becoming the main line of enquiry along with its primary and secondary prevention. However, this is possible only on the basis of unified approaches to the definitions and severity stratification of this state. While contemporary AKI classification schemes contribute to some extent to a solution to the problem, they are far from ideal. Therefore, this problem should remain at the centre of attention of the world's *nephrological community.*

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