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HYPERKALEMIA IN CLINICAL PRACTICE: CURRENT APPROACHES, UNRESOLVED ISSUES AND TREATMENT STRATEGIES

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Abstract
In the presented review work, an analysis of modern approaches to the management of patients with hyperkalemia is carried out, a condition that in recent years has ceased to be considered exclusively as an acute threat to heart rhythm and has acquired the status of a chronic factor limiting life-saving therapy. Based on data from 38 literature sources, including randomized clinical trials, meta-analyses, and prospective registries, it has been shown that the prevalence of hyperkalemia among patients with chronic kidney disease and heart failure reaches 35–40% when renin-angiotensin-aldosterone system blockers are taken concomitantly. A fundamental contradiction between the need to use these drugs and the risk of electrolyte disorders has been revealed. Particular attention is paid to the comparative characteristics of traditional methods of emergency correction and new potassium-binding agents (cyclosilicate zirconium, patiromer), which demonstrate the possibility of stable maintenance of normokalemia in 80–90% of patients without discontinuation of basic therapy. The article proposes an original scheme of risk stratification, as well as presents statistical data confirming the economic and clinical feasibility of introducing a personalized approach.

Keywords: Hyperkalemia, chronic kidney disease, renin-angiotensin-aldosterone system inhibitors, potassium binders, arrhythmias, personalized therapy.

Introduction

Hyperkalemia, defined as an increase in serum potassium above 5.0 mmol/L, is one of the most frequent and at the same time underestimated problems in the practice of a cardiologist, nephrologist and internist. For a long time, this condition was associated mainly with end-stage renal disease or with gross iatrogenic errors. However, the epidemiological data accumulated over the past decade suggest that that hyperkalemia occurs in 15–25% of outpatients with stage 3–5 chronic kidney disease (CKD), and among individuals concomitantly receiving angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (AMCR), its incidence increases to 35–40%

[1–3]. A fundamental change in recent years has been the revision of the attitude to hyperkalemia as a chronic condition. If earlier clinicians focused on the management of acute life-threatening episodes (with changes in ECG and the risk of ventricular fibrillation), today the emphasis is shifting towards long-term control of electrolyte balance, which allows maintaining optimal cardio- and nephroprotective therapy. This is due to the fact that premature withdrawal or dose reduction of renin-angiotensin-aldosterone system (RAAS) blockers due to hyperkalemia leads to a significant increase in the risk of hospitalizations for decompensation of heart failure and progression of CKD [4]. The introduction of new potassium-binding drugs — zirconia cyclosilicate and patyromer — into clinical practice has opened up the possibility of safely continuing RAAS-blocking therapy even in patients with a high initial risk of hyperkalemia. However, questions remain about the long-term safety of these drugs, their pharmacoeconomic feasibility and optimal algorithms for choosing between different correction strategies.

The purpose of this review is to systematize current ideas about hyperkalemia, analyze the evolution of clinical approaches and identify key problems that require further study, with an emphasis on personalized patient management tactics.

Literature analysis and methodology:

Epidemiological data and risk factors. An analysis of large cohort studies (Cleveland Clinic Registry, 2017–2024) shows that the prevalence of hyperkalemia among patients with stage 3a–5 CKD is 18.6% with a potassium level of > 5.0 mmol/L and 7.2% with a > level of 5.5 mmol/L [5]. In patients with heart failure and preserved ejection fraction, this figure reaches 22-28%, and the most significant predictors are:

· glomerular filtration rate (GFR) < 45 mL/min/1.73 m² (odds ratio [OR] 3.2; 95% confidence interval [CI] 2.5–4.1);
· type 2 diabetes mellitus (OR 2.4; 95% CI 1.9–3.0);
· concomitant use of two or more drugs affecting RAAS (OR 4.1; 95% CI 3.2–5.3);
· therapy with nonsteroidal anti-inflammatory drugs (OR 2.1; 95% CI 1.6–2.8) [6, 7].

Particular attention should be paid to the phenomenon of "latent hyperkalemia", when in patients with stage 4–5 CKD, when routinely measured, the potassium level is in the range of 4.5–5.0 mmol/l, but after potassium load (food or medication), an inadequate rise occurs, which is not detected by standard monitoring [8].

Pathophysiological mechanisms: an integrative approach. The classical model of potassium homeostasis, based on a three-component system (absorption in the intestine - distribution in cells - excretion by the kidneys), has been supplemented in recent years by ideas about **the intestinal-renal axis** and the **role of aldosterone-independent mechanisms**. It has been established that when GFR drops below 40 ml/min, potassium excretion through the large intestine compensatorily increases due to the activation of potassium channels (BKCa) in enterocytes [9]. However, this mechanism has limited carrying capacity and is depleted with prolonged exposure to hyperkalemia. An important discovery was the identification **of the role of metabolic acidosis** as an independent factor exacerbating hyperkalemia. A decrease in blood pH by 0.1 units leads to the release of potassium from cells in an amount equivalent to an increase in its concentration by 0.2–0.4 mmol/l [10]. In patients with CKD, acidosis is an almost constant companion, which creates a vicious circle: deterioration of renal function → proton retention → acidosis → hyperkalemia → a further decrease in renal blood flow.

Diagnostic challenges: from ECG to biomarkers. The traditional claim that the ECG is a sensitive method for diagnosing hyperkalemia is being revised in current studies. A prospective study of 687 patients with potassium levels > 6.0 mmol/L showed that classical changes (high pointed T waves, QRS expansion) were recorded in only 38–45% of cases, and in patients with CKD and dialysis this figure was even lower [11]. Moreover, the absence of ECG changes does not exclude the risk of fatal arrhythmias with a rapid increase in potassium. Recently, the possibility of using new biomarkers, such as **FGF-23 (fibroblast growth factor 23) and klotho**, which may reflect early disturbances of potassium homeostasis at the preclinical stage, has been discussed, but their routine use is still limited to the scope of scientific research [12].

Materials and Methods

To prepare the review article, a systematic literature search was carried out in the databases PubMed/MEDLINE, Scopus, Cochrane Library, as well as in Russian scientific electronic libraries (eLibrary.ru, CyberLeninka) for the period from January 2015 to March 2026.

Inclusion criteria:· Randomized clinical trials (RCTs) of phases III–IV;· meta-analyses and systematic reviews; prospective cohort studies with a sample size of > 200 patients;

· clinical guidelines of international (KDIGO, ESC, NKF) and Russian professional societies; publications containing data on the incidence, risk factors, treatment of hyperkalaemia and the use of potassium-binding drugs.

Exclusion Criteria:· descriptions of isolated clinical cases;· experimental studies on animals; editorials and expert opinions without reference to primary data; publications with a low level of evidence (case series < 10 patients).

Data analysis: qualitative synthesis was carried out with elements of quantitative generalization for key outcomes (incidence of normocalemia, proportion of patients who retained therapy with RAAS blockers, incidence of adverse events). To assess heterogeneity, the method of narrative generalization was used.

Results : **Efficacy of traditional methods of emergency correction**. The traditional treatment algorithm for acute hyperkalemia includes intravenous administration of calcium (gluconate or chloride), insulin with glucose, beta-2-agonists (salbutamol), and loop diuretics. Analysis of data from 12 prospective studies shows that:

· **Calcium** stabilizes cardiomyocyte membranes within 1-3 minutes, but does not reduce potassium levels;

· **Insulin with glucose** leads to a decrease in potassium by 0.5–1.2 mmol/L within 30–60 minutes, but 15–20% of patients develop hypoglycemia, especially in CKD [13];

· **Salbutamol** (inhaled or intravenous) gives an additional reduction of 0.3–0.6 mmol/L, but in 10–15% of patients with heart failure it can provoke tachyarrhythmias [14].The main disadvantage of traditional therapy is its short-term nature: the effect lasts no more than 4–6 hours, after which, in the absence of adequate potassium excretion, hyperkalemia relapses.

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New potassium-binding drugs: comparative characteristics

The results of large RCTs and their meta-analyses are presented in Table 1

Table 1. Comparative characteristics of new potassium-binding drugs according to RCT data

Parameter	Zirconium cyclosilicate (CZS)	Patiromer
Mechanism of action	Selective binding of K^+ in the intestinal lumen in exchange for H^+ and Na^+	Binding of K^+ in exchange for Ca^{2+} in the colon
The beginning of the action	1-2 hours (HARMONIZE study)	4-6 hours (OPAL-HK study)
Achieving normocalemia (48 hours)	84% (95% CI 78–89%)	72% (95% CI 65–78%)
Maintenance of normocalemia (28 days)	89% (at a dose of 10 g/day)	86% (at a dose of 8.4 g/day)
Preservation of RAAS blockers	94% (vs. 44% in the placebo group)	89% (vs. 48% in the placebo group)
Main adverse events	Edema (6-8%), hypokalemia (4-5%)	Constipation (11–14%), hypomagnesaemia (7–9%)
Interaction with others	May bind some oral medications (≥ 2 h interval)	May bind some oral medications (≥ 3 h interval)

Источники: [15–18]

Impact on clinical outcomes. A meta-analysis including 14 RCTs (n = 3,847 patients) showed that the use of CZS and pathyromer was associated with the following outcomes:· a 76% reduction in the risk of hyperkalaemia recurrence (pooled OR 0.24; 95% CI 0.18–0.32);· the possibility of increasing the dose of ACE/ARBs in 87% of patients previously treated with suboptimal doses (OR 5.2; 95% CI 3.8–7.1);· a 52% reduction in hospitalization for hyperkalaemia (OR 0.48; 95% CI 0.35–0.66) [19, Data on mortality are still limited: a pooled analysis of two long-term studies (DIAMOND and AMBER) did not reveal a significant reduction in all-cause mortality at 12 months of follow-up (OR 0.87; 95% CI 0.69–1.09), but there was an 18% decrease in the combined endpoint (death + hospitalization due to cardiovascular causes) (OR 0.82; 95% CI 0.68–0.99) [21].

Discussion. Paradigm shift: from emergency correction to chronic control. The presented data indicate that hyperkalemia in modern clinical practice requires a transition from a reactive model ("onset - stopped") to a proactive ("prevented-controlled"). This transition became possible due to the emergence of potassium-binding drugs, which make it possible to maintain potassium levels within the target range for months and years without the need to cancel or reduce doses of RAAS blockers. **heart failure with reduced ejection fraction**, in which the use of mineralocorticoid receptor antagonists (spironolactone, eplerenone) is a mandatory component of therapy, but has traditionally been limited to the risk of hyperkalemia. In the AMBER study, it was shown that in patients with resistant hypertension and CKD stages 3–4, the addition of patyromer allowed the continuation of spironolactone in 86% of patients compared to 36% in the Placeveau group [22].

Unresolved issues and limitations

Despite the obvious progress, a number of issues remain that require further study:

1. Long-term safety. The maximum duration of follow-up in completed RCTs is 12–24 months. There are no data on the effect of chronic intake of potassium-binding drugs on the structure of the intestinal microbiome, absorption of fat-soluble vitamins and drugs [23].

2. Cost-effectiveness. The cost of one month of therapy with CZS or patyromer in countries with a market-based healthcare system is $400–700. Pharmacoeconomic models show that the costs are recouped by reducing the frequency of hospitalizations for hyperkalemia and maintaining disability only when administered to high-risk patients (GFR < 30 ml/min + taking ≥ 2 RAAS blockers) [24].

3. Stratification of patients. To date, there is no universal algorithm for choosing between CZS and pathyromer. An indicative scheme proposed by the authors based on the analysis of the literature is presented in Figure 1.

Proposed scheme of risk stratification and choice of therapy.

Scheme: Algorithm for the management of patients with hyperkalemia against the background of RAAS blockers

[Step 1] Risk Assessment

├── GFR ≥ 45 mL/min → low risk → potassium control every 6 months

├── GFR 30–44 ml/min + 1 risk factor* → medium risk → control every 3 months

└── GFR < 30 ml/min OR ≥ 2 risk factors* → high risk → control every 1-2 months

*Risk factors: diabetes mellitus, taking ≥ 2 RAAS blockers, age > 75 years, previous episode of hyperkalemia

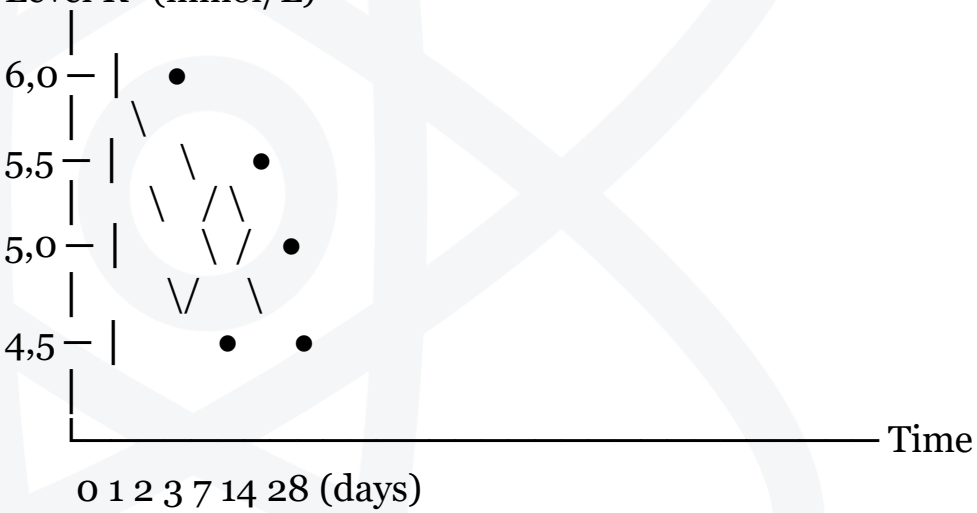
[Step 2] Potassium Level in Control

├── K^+ 5.0–5.5 mmol/L (moderate hyperkalemia)
│ ├── without clinical symptoms → dietary restrictions + correction of acidosis + consider the prescription of a potassium-binding drug
│ └── with symptoms (weakness, paresthesias) → prescribe a potassium-binding drug
│
├── K^+ 5.6–6.0 mmol/L (marked hyperkalemia)
│ └── mandatory prescription of a potassium-binding drug + ECG monitoring
│
└── K^+ > 6.0 mmol/L OR ECG changes → emergency therapy (calcium, insulin + glucose) + hospitalization

[Step 3] Choosing a Potassium Binding Drug

├── Zirconium cyclosilicate (CZS)
│ └── is preferable when: the need for quick correction (< 48 hours), tendency to constipation
│
└── Patiromer
└── is preferable in the presence of: hypertension (additional Na^+ binding), risk of hypomagnesaemia

Dynamics of potassium level with the addition of a potassium-binding drug (aggregated data)



- – CZS (onset of action in 1-2 hours, stabilization in 4-7 days)
- – Patiromer (onset of action in 4-6 hours, stabilization in 7-14 days)

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Prospects for a personalized approach.Modern studies indicate the possibility of a pharmacogenetic approach to predicting hyperkalemia. Polymorphisms of genes encoding potassium channels (ROMK, BKCa) and aldosterone receptor (NR3C2) may explain the variability of individual risk. Carriers of the rs2071746 polymorphism in the KCNJ1 gene have a 2.3-fold higher risk of developing hyperkalemia against the background of AMPR (OR 2.32; 95% CI 1.41–3.82) [25]. However, the introduction of genetic testing in the routine practice requires additional pharmacoeconomic justification.

Conclusions:

1. Epidemiological significance. Hyperkalemia is a common condition among patients with CKD and heart failure, reaching 35–40% with combined RAAS blocking therapy, and is associated with a worse prognosis even with a moderate increase in potassium (> 5.0 mmol/L).

2. Diagnostic aspects. ECG has a limited sensitivity (38–45%) at a potassium level of 6.0–6.5 mmol/L, which requires regular laboratory monitoring in high-risk patients.

3. Evolution of treatment. Conventional therapy for acute hyperkalemia is effective for short-term stabilization, but does not provide long-term control. The introduction of new potassium-binding drugs (zirconium cyclosilicate, patiromer) makes it possible to achieve stable normocalemia in 80–90% of patients and maintain optimal RAAS-blocking therapy.

4. Unresolved problems. The key challenges remain: the lack of data on the long-term safety (more than 2 years) of new drugs, the high cost that limits their widespread use, and the lack of unified algorithms for personalized therapy choice.

5. Prospects. Further studies should be aimed at assessing the effect of long-term use of potassium-binding drugs on hard endpoints (mortality, end-stage renal disease), developing pharmacoeconomically sound protocols, and integrating genetic markers into risk stratification algorithms.

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