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Diagnosis and Intensive Care in Children's Diabetic Acidosis: an Interdisciplinary Viewpoint

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Summary

Diabetic ketoacidosis (DKA) is the main cause of death and disability in children with type I diabetes mellitus (T1DM). Children's mortality from T1DM reaches 1% in developed countries and 13% in developing countries. The main cause of death in DKA is cerebral edema, clinical manifestations of which develop in 0.5–0.9% of children with DKA, while mortality riches 24%.

Objective. Developing recommendations to prevent life-threatening complications of children with DKA using analysis of literature data and consolidated opinion of experts on the issues of intensive care in children with T1DM.

Materials and methods. We analyzed and discussed studies in diagnosis and treatment of DKA in children with type 1 diabetes and 1200 literature sources since January 1970, published in Russian peer-reviewed scientific journals and international publications presented in the online repository Medline (Pubmed). The search for publications was carried out using the keywords: «children», «DKA», «DM1», «dehydration», «cerebral edema».

Results. We considered issues of epidemiology, pathogenesis, clinical manifestations, diagnosis, intensive care for DKA, as well as clinical and diagnosis, treatment, prevention of cerebral edema issues in children. Limitations of the study were the small number of modern studies with a high level of evidence (randomized controlled trials, meta-analyses) over the past 5 years on DKA in children.

Conclusion. Taking into account the national and international experience, joint recommendations on a consensus format were developed and formulated for the diagnosis of DKA, its leading complications and treatment recommendations for children with T1DM and DKA. Timely and accurate diagnosis of DKA, intensive therapy options based on proven therapeutic efficacy, laboratory and clinical monitoring are warranted to interrupt the DKA pathogenesis, prevent the development of life-threatening conditions, and improve treatment outcomes for children with DKA.

Key words: type 1 diabetes mellitus; diabetic ketoacidosis; children; dehydration; cerebral edema; intensive therapy

Conflict of interest. The authors declare no conflict of interest.

Introduction

Diabetic ketoacidosis (DKA) is a life-threatening complication of type 1 diabetes mellitus (T1DM), which develops due to absolute insulin insufficiency, manifested by dehydration, hyperglycemia, metabolic acidosis, ketonemia and ketonuria, and can lead to cerebral edema and death if not diagnosed and treated in time [1, 2].

Federal Law 323 «Fundamentals of Health Protection of Citizens of the Russian Federation» defines

clinical guidelines as «documents containing structured information based on scientific evidence on prevention, diagnosis, treatment and rehabilitation, including protocols of patient management (treatment protocols), options for medical intervention and algorithm of actions of a health care provider based on the course of the disease, complications and comorbidities» [3]. In the Russian Federation, clinical guidelines «Type 1 diabetes mellitus in children» have been in effect since 2019, providing brief information on the diagnosis and treatment of DKA, without addressing intensive care. Treatment of children with DKA remains the domain of anesthesiologists and intensive care specialists.

In view of the above, there is an urgent need to summarize the accumulated experience and literature data on DKA in children with a focus on intensive therapy, diagnosis and management of complications.

The goal of the Russian Consensus is to formulate guidelines through a collaborative review of existing literature and expert opinion in the intensive care of pediatric diabetic ketoacidosis (DKA) to prevent serious complications. The goals of this collaboration between endocrinologists and intensive care specialists include:

1) Reviewing and summarizing both international and Russian literature, including clinical guidelines, standards of care, algorithms, and protocols that currently present different and sometimes conflicting methods of management of pediatric DKA, with the goal of finding a unified stance among endocrinologists and intensivists.

2) Summarizing the basic principles of insulin therapy for diabetes, with the goal of mimicking the natural insulin release patterns seen in individuals without diabetes.

3) Establishing a consensus on the importance of glucose as the primary fuel for insulin-dependent tissues and the role of insulin in reducing and halting the production of ketones, which are critical in the management of the metabolic acidosis seen in DKA.

4) Reevaluating current methods of managing dehydration in DKA by gaining a better understanding of the underlying mechanisms of hypovolemia, including the often overlooked aspect of chronic dehydration. This goal includes challenging conventional emergency protocols for managing hypovolemic shock resulting from rapid fluid loss.

5) Creating and implementing a straightforward intensive care protocol for DKA that is both understandable and feasible for healthcare providers at all levels of care, specifically designed for the unique healthcare environment of the Russian Federation.

The adoption of local protocols specifically tailored to the management of pediatric diabetic ketoacidosis (DKA), based on clinically validated diagnostic and treatment strategies, has been shown to significantly minimize instances of noncompliance with national standards and reduce the likelihood of adverse outcomes. The approach to treating children with DKA has recently evolved from broad, aggressive interventions to more tailored treatments. This includes a shift toward prioritizing subcutaneous over intravenous insulin administration at the earliest opportunity, favoring oral rehydration over intravenous fluids, using isotonic (0.9%) saline for fluid replacement, and employing the Holiday-Segar formula for calculating daily fluid needs.

Epidemiology

DKA is a leading cause of death and long-term disability in children diagnosed with type 1 diabetes mellitus (T1DM). The prevalence of DKA in pediatric patients with T1DM varies widely across demographic groups and has been reported to range from 13% to 80% [9–13]. In developed countries with advanced healthcare systems, DKA mortality rates are reported to be as low as 1.0%, while in countries with lower socioeconomic status, this figure rises to between 3% and 13% [14, 15]. Cerebral edema is the most common cause of death in DKA cases, occurring in 0.5–0.9% of pediatric DKA patients and resulting in a mortality rate of 21–24% [16–19].

The frequency of DKA episodes in children with T1DM is lower in more economically developed regions than in less developed regions. The incidence of DKA is also higher in rural areas than in urban areas and their suburbs [20,21]. Factors such as low body mass index, ethnic minority, age between 6 and 15 years, HbA1c $\geqslant$ 8.87%, non-use of short-acting insulin and continuous glucose monitoring systems, presence of nephrotic syndrome, severe hypoglycemia or hypoglycemic coma, autoimmune thyroiditis and COVID-19 have been associated with an increased risk of DKA in children [22, 23]. In addition, children with a history of DKA have been found to have lower IQ scores than their peers with T1DM who have not experienced DKA [24].

Etiology and Pathogenesis

Pathogenesis of diabetic ketoacidosis. DKA occurs predominantly with the onset of T1DM due to insulin deficiency. This condition involves the autoimmune destruction of islet cells in the pancreas, coupled with a surge of insulin-antagonistic hormones (such as glucagon, catecholamines, cortisol, and growth hormone) in the bloodstream. This results in stimulated glycogenolysis and gluconeogenesis in the liver and kidneys, decreased tissue glucose uptake, and progressive elevation of blood glucose levels and hyperosmolarity. Inadequate availability of glucose, which is essential for energy production in cellular mitochondria through oxidative phosphorylation, results in increased lipolysis

and ketogenesis (production of acetone, beta-oxybutyric acid, acetoacetic acid). This sequence of events results in metabolic acidosis and elevated blood ketone levels. When blood glucose levels rise significantly (more than 10 mmol/L above normal), in addition to elevated ketone levels, osmotic diuresis is induced which is associated with loss of electrolytes such as sodium, potassium, phosphorus, and magnesium, as well as water. These losses are exacerbated by vomiting, which is common in severe ketosis. Dehydration from these losses can lead to tissue hypoperfusion, which promotes lactate accumulation and lactate acidosis [25–32,13,19].

Etiology and pathogenesis of cerebral edema in DKA. A serious complication of DKA is cerebral edema, a potentially fatal condition that can occur about 12 hours after the start of intensive DKA treatment, although it sometimes develops before treatment begins. While therapeutic errors in the treatment of DKA can lead to brain edema, it's important to recognize that this condition is not necessarily iatrogenic.

The underlying causes of cerebral edema in DKA are not completely understood. However, several key factors are known to be involved, including increased permeability of the blood-brain barrier, swelling of cerebral astrocytes, and dysfunction of cell membranes. Recent theories have proposed a «two-hit» mechanism involving initial ischemia followed by reperfusion. The «first hit» is ischemia: high blood glucose leads to dehydration and osmotic diuresis, which increases blood osmolarity and results in metabolic acidosis. This condition is compensated by respiratory alkalosis and reduced carbon dioxide levels, resulting in prolonged vasospasm in the brain, which induces cerebral ischemia and impairs the self-regulation of cerebral blood flow. With the administration of fluids and insulin during treatment, these factors are reversed, with a decrease in blood osmolarity and normalization of CO_2 levels after prolonged low levels, which can lead to cerebral hyperemia.

The second «hit» is osmotic and vasogenic cerebral edema. Changes in blood osmolarity and increased cerebral blood flow, along with increased capillary permeability, lead to the development of leak syndrome, which underlies vasogenic edema. Osmotic edema occurs with a rapid decrease in blood osmolality (reduction in glycemia), while the concentration of osmotically active substances in cells (primarily glucose) normalizes more slowly [33].

Brain dysfunction in DKA is also associated with impaired glutamatergic and dopaminergic systems, as evidenced by a significant increase in the concentration of autoantibodies to the glutamatergic NMDAR1 type 1 receptor and the dopaminergic DAR 2 type 2 receptor, especially in children with severely impaired consciousness [35, 36]. Children with cognitive impairment after DKA are characterized by low levels of antioxidant protective enzymes, such as superoxide dismutase and glutathione peroxidase, confirming the role of oxidative stress in brain dysfunction [37].

Factors that increase the risk of cerebral edema in children with DKA include

1. Younger age (less than 5 years).
2. Newly diagnosed diabetes (almost 3 times higher risk).
3. Longer duration of DKA prior to treatment.
4. Prolonged hyperglycemia, high blood urea concentration, severe hypocapnia, metabolic acidosis with low pH, increased blood urea nitrogen [38, 39].

Computed tomography changes (lateral ventricular narrowing) are found in 50–100% of patients on admission to hospital, but only 4–15% of them have mental status disorders [40, 41].

Therapeutic errors that contribute to the development of cerebral edema include

1. Excessive rate and volume of fluid therapy [1].
2. Inappropriate composition of fluid solutions.
3. Inappropriate use of sodium bicarbonate.
4. Rapid lowering of glycemia (>5 mmol/L/hour) [19].

Diagnosis

Signs and symptoms.

Dehydration. Varying degrees of dehydration have been reported in DKA [19]. Severe dehydration is associated with a significant decrease in pH, base depletion, anion gap, increased urea, and diastolic hypertension [42]. The severity of dehydration is assessed using the dehydration assessment scale (Table 1). Assessment of the severity of dehydration, fluid and body weight deficits is approximate.

Recommendation. The severity of dehydration should always be assessed during hospitalization and treatment.

Changes in respiration. In severe cases, tachypnea, deep sighing breathing, respiratory rhythm disturbances, and even Kussmaul breathing may be observed [43, 44].

Gastrointestinal syndrome. It is caused by irritation of the peritoneum by released ketones. Its manifestations include nausea, vomiting, and abdominal pain, which may lead to misdiagnosis of surgical or infectious gastrointestinal conditions, inappropriate patient referral, and delayed medical care [45].

In diabetic patients, vomiting may be associated with esophagitis with fungal mucosal lesions [45].

Recommendation. If pain syndrome persists, diagnostic esophagogastroduodenoscopy should be performed.

Drowsiness and impaired consciousness. The level of consciousness (alertness, activity) is assessed according to the Glasgow Coma Scale (Table 2).

Table 1. Dehydration assessment scale.

Signs	Severity (frequency)		
	Mild (≤5%)	**Moderate (6–9%)**	**Severe (≥10%)**
General appearance	Thirsty, restless, alert	Thirsty, drowsy, postural hypotension	Drowsy, limp, cold, sweaty, cyanotic extremities
Radial pulse	Normal rate and strength	Rapid and weak	Rapid, thready, sometimes impalpable
Respirations	Normal	Deep, may be rapid	Deep and rapid
Anterior fontanelle	Normal	Sunken	Very sunken
Systolic blood pressure	Normal	Normal or low	Low
Skin elasticity	Pinch retracts immediately	Pinch retracts slowly	Pinch retracts very slowly
Eyes	Normal	Sunken	Grossly sunken
Tears	Present	Absent	Absent
Mucous membranes	Moist	Dry	Very dry

Note. After [34, 81].

Recommendation. Level of consciousness should always be assessed in patients with DKA.

Acute kidney injury. The incidence of acute kidney injury (AKI) in children with DKA is 41.5–47%. Moderate to severe and severe AKI are reported in 15.5%, and the incidence decreases with age. AKI is more common in children with DKA with a level of consciousness less than 14 points on the Glasgow Coma Scale and a high blood chloride level [46]. The incidence of severe AKI is as high as 28% [47]. The underlying causes of AKI in DKA are fluid depletion and hyperglycemia leading to renal tubular injury and inflammation. Low pH, serum bicarbonate and corrected sodium, high glycemia and urea nitrogen, and male sex are also risk factors for renal injury [46–50]. In DKA, AKI is associated with hyperchloremia in 90% of patients compared to 56% in children without AKI. Chloride is directly and significantly correlated with length of hospital stay, blood creatinine level, and albumin/creatinine ratio [51]. The median time to development of AKI from the onset of DKA is 13.21±6.78 hours [48]. Dialysis is required in 4% of patients with DKA. AKI in DKA is characterized by favorable outcomes, but the long-term effects of AKI are not fully understood [47]. AKI in pediatric DKA is associated with the development of cerebral edema [52].

DKA is characterized by aminoaciduria. Urinary amino acid levels are highest at the onset of DKA and then decrease. During the first 8 hours of DKA, urinary levels of histidine, threonine, tryptophan, and leucine are highest [53].

Recommendation. In patients with DKA, creatinine and urea, markers of AKI, should be measured.

Laboratory signs. The predominant ketone body in DKA is β-oxybutyric acid (β-oxybutyrate). The proportion of acetoacetate is 15–40%. The laboratory reaction with nitroprusside, which is widely used to detect ketone bodies, detects only acetoacetate, which may underestimate the true levels. Importantly, patients receiving anticonvulsant treatment with valproic acid may have a false-positive nitroprusside test. Ketones appear earlier in the blood than in the urine, making their determination in the blood more meaningful [13].

Recommendation. The laboratory criterion for the development of DKA in a child is hyperglycemia >11 mmol/L with a pH<7.3.

Recommendation. The severity of DKA should be assessed.

Severity of diabetic ketoacidosis is defined according to Table 3. The principles of intensive care do not depend on the severity of DKA.

Laboratory criteria for control of diabetic ketoacidosis

a) pH > 7.3;

b) serum bicarbonate (SB) > 15 mmol/L [45].

Table 2. Assessment of activity in children.

Sign	Response in children		Points
	<1 year old	**≥1 year old**	
Best eye response	To sound	To sound	3
	To pain only	To pain only	2
	No response	No response	1
Best verbal response	«Cooing» or babbling	Spontaneous, conscious	5
	Excited scream	With a delay	4
	Scream in response to pain	Individual words	3
	Moaning in response to pain	Individual sounds	2
	No response	No response	1
Best motor response	Spontaneous or purposeful movements	Obeys commands	6
	Withdrawal on touch	Localizing response	5
	Withdrawal on pain	Withdrawal on pain	4
	Abnormal flexion to pain	Flexion to pain	3
	Abnormal extension to pain	Extension to pain	2
	No response	No response	1

Note. Summarized from [82].

Treatment

Antibacterial and antifungal therapy. Routine antibacterial and antifungal therapy is not used; it is prescribed only when an infection is detected [45].

Principles of intensive therapy. The main components of intensive care in DKA are

1) insulin therapy
2) fluid therapy
3) control of electrolyte disturbances.

Fluid and insulin therapy in DKA has been shown to prevent complications (multiple organ dysfunction with acute kidney injury, rhabdomyolysis, pancreatitis, arrhythmias) and poor outcomes [54].

Insulin therapy. *Recommendation.* Only short-acting insulin or an ultra-short acting human insulin analog should be administered intravenously [43, 44].

Bolus insulin administration is not recommended because of the increased risk of cerebral edema. The mechanism of cerebral edema in this case is a rapid decrease in blood plasma osmotic pressure and worsening of hypokalemia. For ease of use, the calculated dose of insulin (1 unit of insulin per 1 kg of body weight) is diluted with solvent until the final volume of the solution is 20 mL. At this dilution, an infusion rate of 1 mL/h is equivalent to an insulin infusion rate of 0.05 U/kg/h.

Recommendation. The recommended initial insulin infusion rate is 0.05–0.1 U/kg/h.

A lower dose of insulin (0.05 U/kg/h) than the standard dose (0.1 U/kg/h) has also been shown to be effective [55, 56].

When choosing the dose of insulin, it is important to remember that the goal of ketoacidosis treatment is to achieve a consistent reduction in acidosis rather than a decrease in blood glucose. The criterion for adequate insulin therapy (along with appropriate fluid therapy), according to expert consensus, is an increase in BE of at least 5 mmol/L over 6 hours. In the absence of such progress, treatment strategies should be reconsidered.

Recommendation. Insulin should be started at the same time as fluid therapy or at least one hour after fluid therapy is initiated.

Adjustment of the insulin rate (dose) and glucose infusion is based on changes in glycemia during the interval between measurements [43, 44].

The strategy depends on the changes in glycemia and the current fluid therapy and includes the following principles.

1. In patients receiving saline only (first stage of treatment, before glucose infusion):

a) if glycemia does not decrease or increases by more than 5 mmol/L, the rate of insulin administration should be increased by 0.025 U/kg/hour;

b) if glycemia decreases by less than 5 mmol/L, do not change the delivery rate;

c) if glycemia decreases by more than 5 mmol/L, start glucose without changing the insulin delivery rate. Reducing the insulin dose at this stage may halt the resolution of ketoacidosis or even cause its progression.

2. In patients already receiving glucose-containing solutions:

a) if glycemia decreases by less than 5 mmol/L/hour, do not change the insulin delivery rate;

b) if glycemia decreases by more than 5 mmol/L/hour, decrease the insulin delivery rate by 25% or increase the glucose infusion rate. The choice depends on the severity of the ketoacidosis: if it decreases, the insulin dose should be reduced (but not below 0.05 U/kg/h); if it persists, the rate of glucose infusion should be increased;

c) if there is no change in glycemia, increase the insulin infusion rate by 0.025 U/kg/h or decrease the glucose infusion rate. The strategy depends on the severity of the ketoacidosis: if it decreases, the dose of glucose should be decreased; if it persists, the rate of insulin infusion should be increased.

3. Complete withdrawal of intravenous insulin is not recommended until the metabolic acidosis is reversed (minimum dose, 0.025 units/kg/hour).

4. Upon normalization of pH and/or disappearance of urinary ketones, the patient is switched to subcutaneous insulin injections (according to standard regimens), and intravenous insulin is discontinued 30–40 minutes after the first subcutaneous injection.

The rate of glycemic lowering of 5 mmol/L per hour is critical and can lead to fatal cerebral edema. At the same time, no significant differences in neurologic outcomes of DKA and residual neurologic impairment were found when the rate of glycemic reduction was increased to 5.5 mmol/L/h [57]. However, we do not recommend allowing a glycemic lowering rate greater than 5 mmol/L/h.

Recommendation. The optimal rate of glycemic lowering is 1–2 mmol/L per hour, and the acceptable rate is up to 3–5 mmol/L per hour.

Recommendation. During the management of DKA, a safe level of glycemia should be 10–15 mmol/L.

Transcutaneous continuous glucose monitoring in children with DKA is a promising method of glycemic control. However, glycemic values measured

Table 3. Severity of diabetic ketoacidosis.

Degree	Values	
	pH	SB, mmol/L
Mild	<7.3	<15
Moderate	<7.2	<10
Severe	<7.1	<5

Note. After [83].

by this method differ by 11.33–13.40% (average 13.20%) from capillary glucometry values. This may be due to acidosis and decreased blood bicarbonate, which affect the accuracy of monitoring [58].

Fluid therapy. *Recommendation.* Fluid therapy should be continued until pH normalizes (7.35–7.45).

The rate of resolution of ketoacidosis depends on its severity [59]. Rapid fluid administration has been shown to result in more rapid normalization of anion gap, blood sodium, and pCO_2 than slow fluid administration in DKA, which reduces the risk of cerebral edema but is associated with the frequent development of hyperchloremic acidosis. The use of 0.9% sodium chloride compared with 0.45% solution reduces potassium levels more slowly due to a greater increase in chloride levels [60].

Recommendation. The approach to fluid therapy depends on the severity of dehydration and glycemia.

Volume of fluid therapy

Fluid therapy for DKA consists of 2 steps:

1. Primary «fluid resuscitation» (Table 4).
2. Rehydration therapy to replace the remaining deficit.

Table 4. Volume of fluid for primary fluid resuscitation.

Dehydration	
Mild	Not administered
Moderate	10–20 mL/kg in 30–60 minutes, then MFR
Severe	1020 mL/kg in 20 minutes (if there is no effect, repeat up to 2 times), then MFR

Note. Consensus opinion of the authors based on guidelines [45]. MFR — maintenance fluid requirement.

Primary «resuscitation» by fluid infusion:

Performed with isotonic (0.9%) sodium chloride solution only [42, 43, 61].

The use of high (>15 mL/kg) or low (<5 mL/kg) bolus doses not affect the rate of resolution of AKI in children with DKA [62].

For mild dehydration, oral fluids are given if the patient can tolerate the water load. Oral rehydration solutions are preferred [43, 44].

Maintenance fluid requirements can be calculated using Table 5. In overweight children, the calculation is based on ideal body weight for actual height [43, 44].

Table 5. Calculation of the daily maintenance fluid requirement.

Body weight	Required volume	
	Hourly	Daily
≤10 kg	4 mL/kg/h	100 mL/kg/24 hrs
11–20 kg	40 mL + 2 mL/kg/h for each kg from 11 to 20	1000 mL + 5 mL/kg/24 h for each kg from 11 to 20
>20 kg	60 mL + 1 mL/kg/h for each kg >20	1500 mL + 20 mL/kg/24 h for each kg >20

Note. Data summarized after [84].

Excessive fluid volume leads to delayed recovery of renal function in AKI and to the development of hyperchloremia [52].

Fluid therapy. *Recommendation.* For fluid composition, fluid adjustment, and insulin therapy based on changes in glycemia are shown in Figure.The issue of adjusting the composition of fluid therapy should be addressed every 2 hours of therapy after glycemia has been controlled. The use of balanced electrolyte solutions compared with isotonic solutions has been shown in small randomized trials to result in faster reversal of acidosis [63, 64]. There are no statistically significant differences in the length of hospital stay, the incidence of cerebral edema, and the rate of recovery of consciousness when a liberal infusion strategy is used compared with a restrictive strategy [65].

Recommendation. Potassium chloride solution should be added to infusion therapy [43, 44].

Treatment of electrolyte disturbances.

Sodium. The majority of patients with DKA have normal or decreased serum sodium levels.

Hyponatremia (<130 mmol/L) may result from

- hemodilution due to displacement of free fluid from interstitial tissues
- secondary hypoaldosteronism (decreased adrenal cortical function), in cases of extremely late referral to a healthcare provider
- pseudohyponatremia due to elevated blood lipid levels.

In most cases, hyponatremia can be treated without the use of high sodium solutions. As plasma volume is replenished and osmotic diuresis is abolished, aldosterone levels normalize, transmembrane Na^+-K^+ exchange stabilizes, and additional sodium administration is rarely required [45].

Hypernatremia may be caused by compensatory hyperaldosteronism leading to increased sodium reabsorption in response to hypovolemia. Significant hypernatremia is associated with severe cerebral edema and is a poor prognostic indicator [33,39,45].

Fluid therapy has been shown to reduce high sodium and chloride levels. A high infusion rate significantly reduces the initially elevated sodium concentration only 12 hours after the start of therapy, even when 0.45% sodium chloride solution is used. The Glasgow Coma Scale level of consciousness was similar in patients with spontaneous sodium reduction and patients with sodium reduction after fluid therapy. The sodium concentration in the infusion fluid and the ratio of water to sodium losses at the onset of DKA both affect sodium levels. There was no correlation between sodium reduction during fluid therapy for DKA and the severity of mental status disorders [18, 45].

Recommendation. Correct hypernatremia only with 5% glucose solution (an isotonic solution without sodium or hydrochloric acid) until plasma sodium levels return to normal.

Potassium. In ketoacidosis, the following processes occur:

• transmineralization, in which intracellular potassium is replaced by protons
• loss of urinary potassium with polyuria.

As a result, the measurement of plasma potassium does not accurately represent the total depletion of the body's potassium reserves, which generally fall to levels 2–3 times lower than the daily potassium requirement [45].

Potassium chloride solution is added at the rate of 40 mmol K^+ per 1 liter of fluid at the earliest 2 hours after the start of infusion therapy if the documented blood potassium concentration is <5.3 mmol/L. For accurate dosing, 1 mL of KCl 7.5% solution contains 1 mmol K^+, while 1 mL of KCl 4% solution contains approximately 0.5 mmol K^+.

Recommendation. Do not use potassium chloride solution if potassium concentration ≥6.5 mmol/L and anuria (hourly urine output ≤0.5 mL/kg/h).

Recommendation. If initial hypokalemia is less than 3 mmol/L, administer 0.5 mmol/kg potassium chloride solution before starting insulin therapy.

Monitor blood potassium at least every 6 hours. If necessary, administer additional intravenous potassium chloride at a rate not to exceed

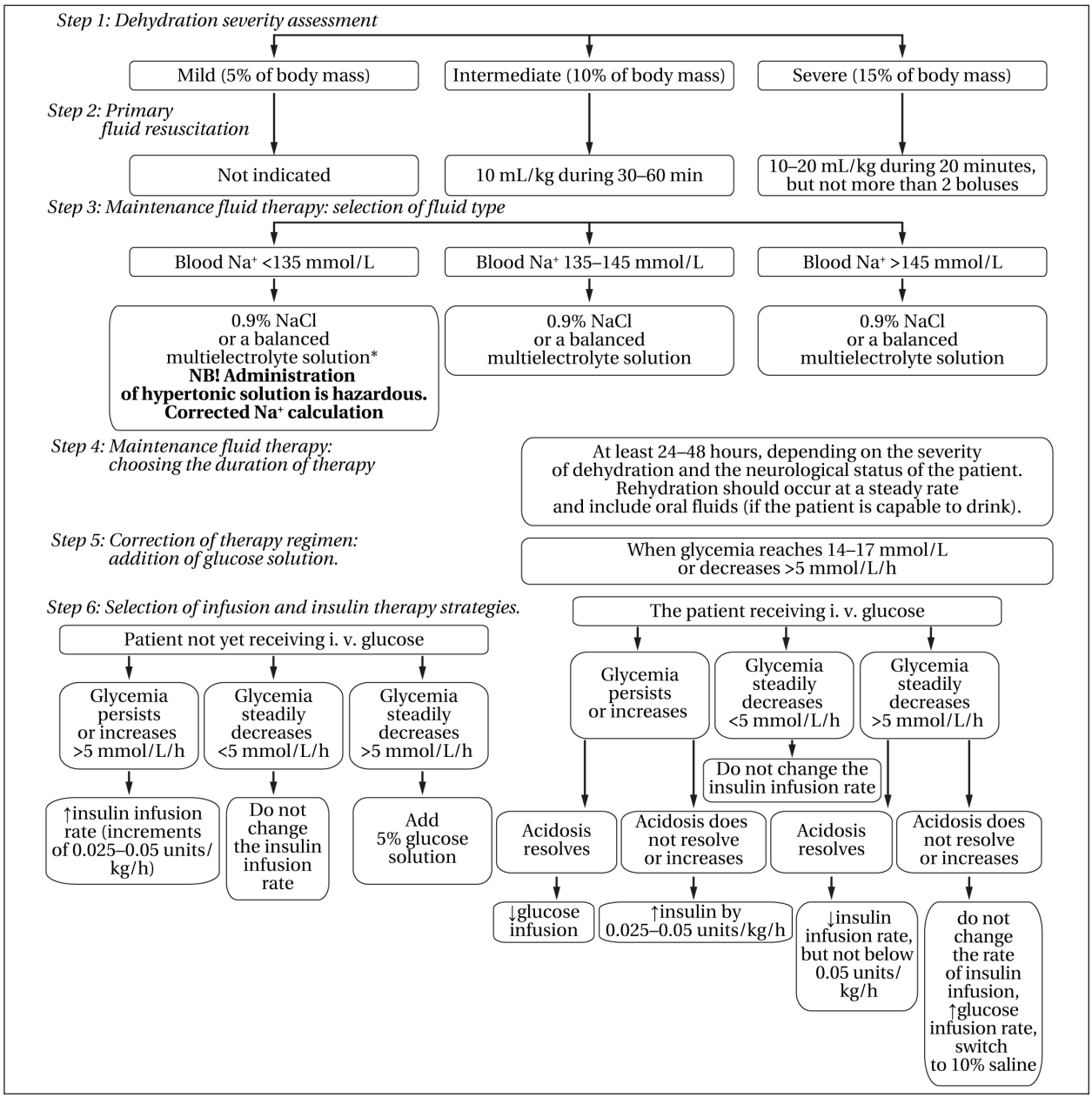

Fig. Fluid therapy algorithm for diabetic ketoacidosis (original illustration).
Note. A 0.45% NaCl solution can be used. For glycemia above 17 mmol/L, starting with 5% dextrose solution has been shown to be effective [28]. Insulin therapy is started concurrently with fluid therapy according to the «4 NOTs» rule: 1) do not give a bolus; 2) do not reduce the rate below 0.05 U/kg/h until the acidosis is stabilized; 3) do not stop the insulin infusion until the ketoacidosis is completely reversed (the minimum insulin infusion rate is 0.025 U/kg/h); 4) do not switch the patient to total subcutaneous insulin until 30 minutes after the first subcutaneous injection.

0.5 mmol/kg per hour, including potassium administered in glucose solution [45].

The use of potassium magnesium aspartate (Panangin®, Asparkam®, KMA®) does not increase blood potassium concentration and cannot correct hypokalemia.

Recommendation. The administration of sodium bicarbonate solutions in DKA is not recommended!

These studies suggest that bicarbonate has no clinical benefit in DKA [66–69]. The use of bicarbonate may result in paradoxical central nervous system acidosis [70–72].

Recommendation. At a minimum, no negative clinical or laboratory changes such as worsening mental status, increasing glycemia, hypocapnia, or decreasing pH should be observed in DKA from the first hour.

If no improvement or negative clinical and laboratory changes are observed, the following causes should be considered:

1) technical, such as proper dilution of insulin solutions, placement of venous catheters, adherence to the prescribed rate of fluid administration by infusion pumps, etc;

2) clinical, such as comorbidities and nutritional or insulin therapy errors that can cause both the onset and slow progression of DKA. The most common of these are

- otolaryngologic conditions (e. g., otitis media, sinusitis), which may present with less obvious manifestations;
- intestinal infection;
- acute surgical abdominal conditions (abdominal pain should not always be interpreted solely as a manifestation of ketoacidosis);
- urinary tract infection requiring urinalysis and examination of the patient's external genitalia for signs of balanoposthitis, vulvovaginitis, bartholinitis;
- soft tissue infections such as perineal inflammation, which may progress to phlegmon or abscess.

Patient routing. *Recommendation*. Children with DKA should be treated in a tertiary T1DM center or under its guidance.

Hospitalized children with DKA and pH=7.07±0.07 without mental status impairment can be safely managed in non-intensive care units [73].

Recommendation. Children with DKA and pH<7.3 with impaired consciousness below 14 on the Glasgow Coma Scale should be treated in an intensive care unit.

Patients should be consulted by intensivists of a regional intensive care consultation center or a remote federal pediatric intensive care consultation center with endocrinologist involvement. These centers determine the sequence and timing of transfer of patients with DKA.

Transportation of children with DKA is not allowed:

1) until recovery of consciousness level of 10 or more points. Transportation may begin at a lower level of consciousness if deemed necessary by an intensive care specialist from a regional intensive care consultation center who has arrived at the scene;

2) if there is no possibility of intensive therapy (precise dosing of insulin, fluid therapy, device monitoring of vital body parameters) and blood glucose control during transportation of the child.

If admission to a pediatric intensive care unit is not possible, DKA should be managed in an adult intensive care unit [74].

Complications of Diabetic Ketoacidosis

Arrhythmias, infections, and kidney injury are all possible complications of DKA, but cerebral edema is the most serious and common. Cerebral edema is responsible for the vast majority of DKA deaths. It is diagnosed using clinical criteria (Table 6).

Symptomatic cerebral edema is associated with increased systolic blood pressure and heart rate. Patients with cerebral edema are characterized by prolonged hospital stay and correction of acidosis [59].

Table 6. Diagnostic criteria for cerebral edema in diabetic ketoacidosis.

Criteria	
Diagnostic	— abnormal motor or verbal response to pain — decorticatie or decerebrate posturing — cranial nerve paresis (especially III, IV, VI) — abnormal neurogenic respiratory patterns («grunting», tachypnea, Cheyne-Stokes breathing, apnea).
Major	— impaired thinking, lethargy, changes in the level of consciousness — constant slowing of the heart rate (decrease by more than 20 in 1 min.), not associated with an increase in fluid volume or sleep — urinary incontinence
Minor	— vomiting — headache — drowsiness or difficulty waking up — diastolic blood pressure >90 mmHg — age <5 years

Note. Summarized from [78]. One diagnostic + two minor criteria or one major + two minor criteria have a sensitivity of 92%.

Neuroimaging is performed only at the start of treatment. Brain computed tomography is preferable [45].

For early diagnosis of cerebral edema in DKA, point-of-care ultrasonography with measurement of optic nerve sheath diameter over time is recommended. This parameter is measured 3 mm posterior to the eyeball in the anterior axial transbulbar position. The transverse and vertical diameters of the eyeball are also measured and the ratios of optic nerve sheath diameter to transverse diameter and optic nerve sheath diameter to vertical diameter are calculated. These parameters should decrease with treatment, indicating reduction of optic nerve edema. The values of the optic nerve sheath diameter more than 4.5 mm, the ratio of the optic nerve sheath diameter to the transverse diameter more than 0.22 and to the vertical diameter more than 0.29 are considered abnormal [75].

Another method of assessing the severity of cerebral edema in DKA is the ratio of neutrophils to lymphocytes. This ratio is 2.82 (2.28–4.23) in children with DKA without cerebral edema, 5.66 (3.95–7.88) in those with subclinical edema, and 8.60 (4.73–12.17) in those with clinical manifestations of cerebral edema (P<0.001) [59].

The following methods are used to treat cerebral edema.

1. Hyperosmolar solutions:

a) mannitol 0.5–1 g/kg intravenous (i. v.) drip for 10–15 min [76]. The effect develops in 15 min, its duration is 120 min. The repeated dose is administered in 30 min. Contraindicated in hypernatremia (>165 mmol/L) [45].

b) hypertonic saline 3% 2.5–5 ml/kg i. v. over 10–15 min. May be an alternative to mannitol [77] but is associated with higher mortality [78]. At the same time, the use of cerebral oximetry along with administration of 3% hypertonic saline may improve outcomes in DKA and cerebral edema [79].

2. Patient positioning:

a) head end elevation at 30°;

b) centering the head on the midline;

c) «sniffing» position of the head;

d) lowering the feet end of the bed.

3. Tracheal intubation and lung ventilation. It is used when the level of consciousness is <9 points on the Glasgow Coma Scale.

When selecting the initial parameters of the ventilator, it is necessary that the PCO_2 after the patient is placed on the ventilator should be the same as before the tracheal intubation, in order to avoid the increase of acidosis and cerebral edema.

Normalization of pCO_2 should proceed in parallel with normalization of BE and pH.

Monitoring

Recommendation. Blood glucose should be measured every hour for the first 6 hours, then every 2 hours if blood glucose is falling steadily [45].

Recommendation. ABB should be checked at least once every 6 hours. In initially severe DKA, the first check should be performed within 3 hours of starting therapy [45].

In children with DKA on admission and every 2 hours of treatment in the ICU, the minimum necessary monitoring includes calculation and assessment of fluid balance, measurement of blood glucose, sodium, and potassium. Every hour the level of consciousness (alertness) is assessed, respiratory rate, heart rate, blood pressure (systolic, diastolic, mean), arterial saturation (SpO_2), ECG for changes in the T wave (hypokalemia below 3 mmol/L may cause its flattening or inversion) should be constantly monitored [45].

The high prognostic value of the blood urea nitrogen/albumin ratio in predicting the likelihood of death in DKA has been demonstrated [80].

Rehabilitation

Rehabilitation follows the basic principles of rehabilitating pediatric patients who have experienced critical illness and children with T1DM. If neurological deficits develop as a result of cerebral edema, a comprehensive rehabilitation program that involves a team of specialists is necessary.

Conclusion

DKA is a significant issue because it is associated with a comparatively high mortality rate in children, primarily due to the development of cerebral edema. Based on the integration of Russian and international best practices, we have developed guidelines for the diagnosis of DKA, its major complications, and the management of children with T1DM and DKA. Adherence to the diagnostic criteria for DKA, the use of short-acting insulin agents in combination with regular monitoring of blood glucose levels, the correction of dehydration with the appropriate use of glucose solutions based on the glycemic level, the prevention and early detection of signs of cerebral edema and its timely treatment can prevent poor outcomes in DKA.

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