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INTENSIVE CARE OF COMPLICATIONS OF DIABETES MELLITUS IN CHILDREN

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Abstract. *Introduction.* Complications of diabetes mellitus are one of the most common life-threatening conditions in pediatric practice. The *aim of the study* was to analyze modern principles of intensive therapy of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic coma (HHC) in children. *Results.* The peculiarities of volemic load and insulin therapy were demonstrated, special attention was paid to prevention and correction of intracranial hypertension, treatment of cerebral edema. The necessity of prevention of sharp fluctuations of blood plasma osmolarity, timely and step-by-step correction of water-electrolyte disorders was noted. *Conclusion.* The basis of successful treatment of diabetes mellitus complications in children is early diagnosis and correction of systemic hypoperfusion, prevention of cerebral ischemia and intracranial hypertension.

Key words: *type 1 diabetes mellitus; complications; children; diabetic ketoacidosis; intensive therapy.*

ИНТЕНСИВНАЯ ТЕРАПИЯ ОСЛОЖНЕНИЙ САХАРНОГО ДИАБЕТА У ДЕТЕЙ

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Резюме. *Введение.* Осложнения сахарного диабета являются одними из наиболее распространенных жизнеугрожающих состояний в педиатрической практике. *Цель исследования* — анализ современных прин-

ципов интенсивной терапии диабетического кетоацидоза (ДКА) и гиперосмолярной гипергликемической комы (ГГК) у детей. *Результаты.* Продемонстрированы особенности волемической нагрузки и инсулинотерапии, особое внимание уделено профилактике и коррекции внутричерепной гипертензии, лечению отека головного мозга. Отмечена необходимость предотвращения резких колебаний осмолярности плазмы крови, своевременной и поэтапной коррекции водно-электролитных нарушений. *Заключение.* Основой успешного лечения осложнений сахарного диабета у детей является ранняя диагностика и коррекция системной гипоперфузии, предотвращение церебральной ишемии и внутричерепной гипертензии.

Ключевые слова: *сахарный диабет 1-го типа; осложнения; дети; диабетический кетоацидоз; интенсивная терапия.*

INTRODUCTION

Diabetes mellitus (DM) is one of the most severe systemic diseases of childhood with extremely high risk of developing life-threatening conditions. The diabetic ketoacidosis, hyperosmolar hyperglycemic nonketotic coma, and hypoglycemia are the most dangerous of these disorders, because all of them can lead to severe neurological deficits [1, 2].

The incidence of diabetic ketoacidosis (DKA) is 1–10% per year in children with type 1 diabetes mellitus in developed countries with adequate health care resources, and it is the first manifestation of diabetes mellitus in approximately 30% of patients [3]. The risk of DKA is the highest in children of first two years of life and in adolescent girls, especially from socially disadvantaged families [4]. The high probability of diabetic ketoacidosis in early-age patients is possible due to an insufficient caution and late diagnosis of diabetes. At the same time, the main cause of diabetes decompensation in adolescents is a low adherence to treatment [4, 5].

The diabetic ketoacidosis (DKA) is the most common cause of death in children with DM, its incidence is 2–5%. An irreversible damage of central nervous system (CNS) in children with DKA is a consequence of cerebral edema. The risk of the condition is about 1–1.2%, and mortality rates with refractory intracranial hypertension are 20–25% [6]. A severe neurologic deficit is observed in more than 35% of surviving patients.

The most common reason for the onset of cerebral edema is severe metabolic disorder, which has a damage effect to the main metabolic pathways. At the same time, in some cases the progression of intracranial hypertension has a clear relationship with the peculiarities of the therapy, which can be quite aggressive and after a while become the cause of patient deterioration [1, 2, 4–6].

The rarest complications of DKA include acute respiratory distress syndrome, rhabdomyolysis, and acute renal failure.

K. Lah Tomulić et al (2022) had evaluated the epidemiology of DKA in patients of intensive care unit (ICU) over the last 10 years and demonstrated that ketoacidosis as the first manifestation of type 1 DM was in 24.7% of children. A moderate and severe dehydration was noted in 76% on admission, 5.2% of patients developed cerebral edema, one child died [7].

All these facts show the relevance and clinical significance of the problem, because timely diagnosis and adequate intensive therapy of complications of DM in children will significantly improve results of treatment and outcome of the disease.

The diabetic ketoacidosis is an acute diabetic decompensation of metabolism, manifested by a sharp increase in the concentration of glucose and ketone bodies in the blood, their appearance in the urine and development of a metabolic acidosis. It can be leaded with varying states of impaired consciousness or without them, which requires emergency hospitalization of the patient [4].

Due to international and domestic clinical guidelines, the criteria for the diagnosis of DKA in children are blood glucose concentration > 11 mmol/L, blood pH below 7.30, bicarbonate (HCO_3) concentration less than 15 mmol/L, increased anion gap, and ketosis (blood β-hydroxybutyrate concentration > 3 mmol/L) or ketonuria (moderate or severe). The symptoms of clinical manifestation of DKA are a weakness, nausea, vomiting, abdominal pain, polydipsia, polyuria, polyphagia, depression of consciousness, Kussmaul's breathing, and acetone odor from the mouth. Three stages are distinguished, depending on the severity of the clinical picture of DKA (Table 1).

Table 1. Degrees of severity of diabetic ketoacidosis

Таблица 1. Степени тяжести диабетического кетоацидоза

Клинические рекомендации Российской Федерации / Clinical Recommendations of the Russian Federation		
Степень тяжести / Degree of severity	pH	HCO_3, ммоль/л / HCO_3, mmol/l
Легкая / Mild	<7,3	<15
Средняя / Moderate	<7,2	<10
Тяжелая / Severe	<7,1	<5

Педиатрия по Нельсону / Nelson Textbook of Pediatrics			
Степень тяжести / Degree of severity	pH	pCO_2, мэкв/л / pCO_2, mEq/l	Клинические признаки / Clinical signs
Легкая / Mild	7,25–7,35	16–20	Пациент ориентирован, может быть возбужденным или вялым / Orient, alert but fatigued
Средняя / Moderate	7,15–7,25	10–15	Дыхание Куссмауля, пациент сонлив, но приходит в ясное сознание при стимуляции / Kussmaul respiration, oriented but sleepy, arousable
Тяжелая / Severe	<7,15	<10	Дыхание Куссмауля или брадипноэ, угнетение сознания вплоть до комы / Kussmaul or depression respirations, sleepy to depressed sensorium to coma

Table 2. Differential diagnosis of diabetic ketoacidosis and hyperosmolar hyperglycemic coma

Таблица 2. Дифференциальная диагностика диабетического кетоацидоза и гиперосмолярной гипергликемической комы

Лабораторные критерии / Laboratory criteria	Диабетический кетоацидоз / Diabetic ketoacidosis	Гиперосмолярная кома / Hyperosmolar hyperglycemic coma
Концентрация глюкозы в крови, ммоль/л / Glucose, mmol/l	>13,9	33,3
pH артериальной крови / pH arterial blood	<7,3	>7,3
Бикарбонат, ммоль/л / Bicarbonate, mmol/l	<15	>15
Осмолярность, мОсм/кг / Osmolarity, mOsm/kg	<320	>330
Кетонурия / Ketonuria	+++	±
Анионный градиент / Anion gap	>12	<12

A differential diagnosis of DKA should be done with hyperosmolar hyperglycemic nonketotic coma occurring in type 2 diabetes, although it is extremely rare in children (Table 2).

PECULIARITIES OF INTENSIVE THERAPY OF DIABETIC KETOACIDOSIS

The intensive therapy of diabetic ketoacidosis includes mandatory components: elimination of the phenomena of shock if it is presented, step-by-step correction of dehydration and electrolyte disorders, management of ketoacidosis and hyperglycemia, prevention and treatment of cerebral edema. For this purpose, an infusion and insulin therapy is used. The algorithm of intensive therapy of DKA, taking into account the available recommendations, is presented in figure 1. If a heart rate and blood pressure are stable, the infusion therapy should be started, including fluid supplementation (maintenance requirements and compensation of the deficit taking into account current pathologic losses). The degree of dehydration is based on the clinical and laboratory examination. Main characteristics are presented in Table 3.

The approximate fluid administration and electrolyte requirements are demonstrated in Table 4.

The first-line infusion is NaCl solution or any balanced polyionic solution in the absence of clinically significant hyperkalemia. The choice of the concentration of the NaCl solution (0.9%

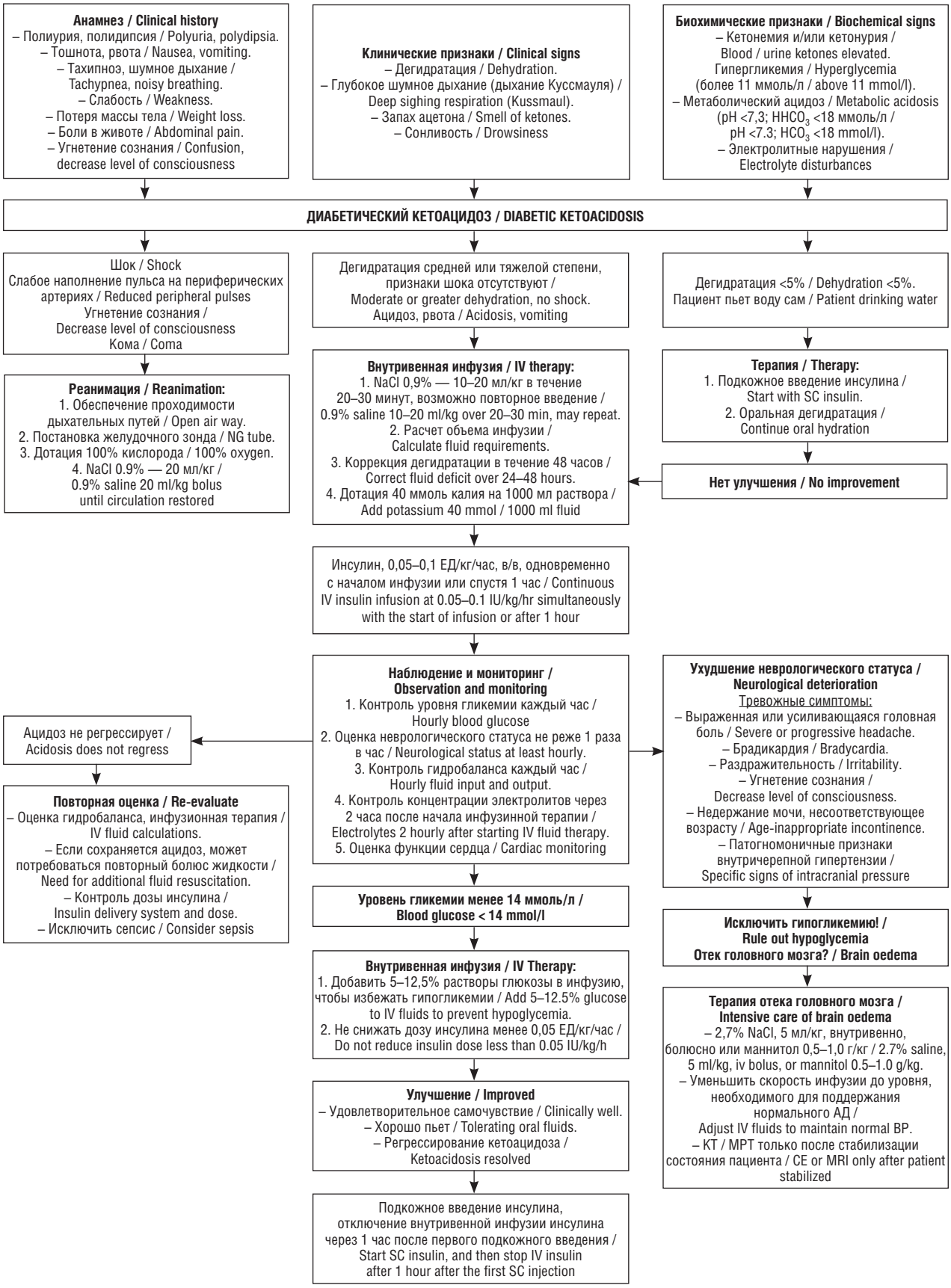

Fig. 1. Algorithm of intensive care of diabetic ketoacidosis in children

Рис. 1. Алгоритм интенсивной терапии диабетического кетоацидоза у детей

or 0.45%) depends on the concentration of sodium in the plasma. In case of the normonatremia, 0.9% solution is used, and in hypernatremia (Na+ > 150 mmol/L) — 0.45% solution. Although, the use of its appointment is not recognized by all authors. In case of the hyponatremia, the plasma sodium concentration should be calculated due to the level of glycemia:

$$[Na^+] = [Na^+] + \frac{[\text{blood glucose}] - 5{,}6}{5{,}6} \cdot 1{,}6.$$

The use of hypertonic solutions for hyponatremia in patients with DKA is categorically contraindicated! The drug of choice in this situation is 0.9% NaCl solution.

When glucose concentration decreases by 1 mmol/L, the plasma sodium concentration should be increased by 1.6 mmol. **The decrease sodium concentration in dynamics against hyperglycemia is a sign of progression of cerebral edema!**

A fluid deficiency should be compensated for at least 24–36 hours, and if there is a high risk of cerebral edema — 48 hours. The faster elimination of dehydration can cause a sharp decrease in plasma osmolarity and progression of an intracranial hypertension. The rate of decrease in plasma osmolarity should not exceed 1.5–2.0 mOsm/hour.

A necessary component of the infusion program is the donation of potassium in order to eliminate its deficiency and prevent the development of cardiac arrhythmias (Table 4).

The potassium treatment is prescribed only after elimination of pronounced manifestations of a hypovolemia, in the presence of adequate diuresis and serum K+ concentration less than 5.0 mmol/L [9]. It should be noted that in DKA the need for potassium is at least 150% of the age requirement: 1.5–3.0 mEq/kg per day.

In case of normokalemia (4-6 mmol/L) the potassium is administered at the rate of 40 mEq in 1L of infusion solution, and in hypokalemia — 60 mEq/L.

In case of severe hypokalemia (blood potassium concentration less than 3.0 mmol/L), potassium solutions are administered in dose of 0.5 mmol/kg per hour for one hour with subsequent assessment of potassium levels in blood.

When the blood glucose concentration drops to 14-17 mmol/L, a 5 or 10% glucose solutions should be added to the infusion on the background of insulin therapy, and it is better to use the concept of "two packets". So, each of these bags contains the same amount of electrolytes, but only one of them is added glucose. The technique allows faster, more economical and accurate correction of the dose of administered glucose, which is titrated due to its concentration in the blood. This approach can pre-

Table 3. Assessing the severity of dehydration in children with diabetic ketoacidosis

Таблица 3. Оценка степени тяжести дегидратации у детей с диабетическим кетоацидозом

Степень тяжести / Degree of severity	Степень дегидратации / Degree of dehydration
Легкая, средняя степень / Mild, moderate	5% от массы тела / 5% of body weight
Тяжелая / Severe	10% от массы тела / 10% of body weight

Table 4. Fluid and electrolyte requirements in diabetic ketoacidosis [5]

Таблица 4. Потребность в жидкости и электролитах при диабетическом кетоацидозе [5]

Компонент / Component	Потери при ДКА, ЕД/кг / Average (range) losses per kg	Возрастная суточная потребность / 24-hour maintenance requirements	
Вода / Water	70 (30–100) мл/ml	<10 кг / kg	100 мл/кг / 100 ml/kg
		11–20 кг / kg	1000 мл + 50 мл/кг на каждый кг после 10 кг веса / 1000 ml + 50 ml/kg/24 h for each kg from 11 to 20
		>20 кг / kg	1500 мл + 20 мл/кг на каждый кг после 20 кг веса / 1500 ml + 20 ml/kg/24 h for each kg >20
Натрий / Sodium	6 (5–13) ммоль / mmol	2–4 ммоль / mmol	
Калий / Potassium	5 (3–6) ммоль / mmol	2–3 ммоль / mmol	
Хлор / Chloride	4 (3 – 9) ммоль / mmol	2–3 ммоль / mmol	
Фосфор / Phosphate	0,5–2,5 ммоль / mmol	1–2 ммоль / mmol	

vent the hypoglycemia despite the constant need for insulin [10].

Both insufficient and excessive fluid administration can cause a significant increase or decrease in blood plasma osmolarity and progression of intracranial hypertension [4, 5, 11].

Against the background of circulating blood volume recovery and stabilization of hemodynamic parameters, insulin therapy at a starting dose of 0.05-0.1 U/kg per hour until regression of ketoacidosis is mandatory [5, 12, 13]. The insulin is prescribed immediately after administration of a fluid bolus or at the same time with the start of infusion therapy. In patients with DKA, only short-acting insulin preparations (Novorapid, Actrapid NM, etc.) should be used. The pharmacokinetics of short-acting insulins is presented in Table 5.

Until a ketoacidosis regression, an insulin dose of less than 0.05 units/kg per hour should not be used. The optimal blood glucose level should be maintained by infusion of 5 or 10% glucose solutions.

The main objective in the treatment of patients with DKA is not to eliminate hyperglycemia, but to eliminate the signs of ketoacidosis [11].

An intravenous and subcutaneous bolus injection of insulin is absolutely contraindicated in DKA. The dose of insulin and the rate of infusion of solutions for infusion therapy are selected so that the rate of decline of blood glucose does not exceed 5.0 mmol/L per hour, although the optimal rate of decline is 2 mmol/L per hour. If there is no effect of insulin therapy within two hours, the insulin dose can be increased to 0.15 IU/kg per hour, but this is a last resort way that can only be used as an exception to the rule.

After a complete elimination of ketoacidosis signs, a child should be examined by an endocrinologist to decide a possibility to change IV infusion of insulin to subcutaneous injections.

During infusion and insulin therapy, sharp spikes in blood glucose levels and a hypoglycemia should be avoided, because both a significant decrease and increase in blood plasma osmolarity can cause progression of intracranial hypertension [4, 5, 11].

Against the background of fluid and insulin administration, a significant decrease in blood plasma osmolarity can be observed with its simultaneous increase within the cellular structures of the CNS. This is the one of the factors that can lead to or aggravate an already existing cerebral edema [11].

Table 5. Pharmacokinetics of short-acting insulins

Таблица 5. Фармакокинетика инсулинов короткого действия

Характеристика / Characterization	Описание / Description
Начало действия / Start of action	Через 20–30 минут от начала инфузии / After 20–30 minutes from the beginning of infusion
Максимум действия / Maximum action	Через 2,5–3,5 часа / After 2.5–3.5 hours
Продолжительность действия / Duration of action	6–8 часов / 6–8 hours

A rapid decrease in plasma glucose concentration may also contribute to the development of cerebral edema in patients with DKA. In particular, it may cause a decrease in plasma osmolarity and fluid movement into the CNS structures; therefore, glucose levels of plasma should be kept in the range of 8–12 mmol/L [4, 5, 11].

The most controversial issue of intensive therapy of diabetic ketoacidosis is the use of sodium bicarbonate solution to correct metabolic acidosis [4–6].

According to many authors, the use of a sodium bicarbonate is the main risk factor for the cerebral edema in DKA. They think, that against the background of infusion of sodium bicarbonate solution, secondary hypoxemia of CNS neurons develops due to the shift of oxyhemoglobin dissociation curve [6].

Both in acidosis and alkalosis there is a shift of the oxyhemoglobin dissociation graph. There is a shift to the left in alkalosis characterized by an increase in the affinity of hemoglobin to oxygen. The hemoglobin is quickly saturated with oxygen in the lungs and very slow gives it to tissues. It is always an unfavorable sign and indication a marked disturbance of oxygenation. Even an increase in blood oxygen content does not improve tissue oxygenation, which should be noticed when there are a cerebral edema and performing artificial respiration. Several studies demonstrate that the use of sodium bicarbonate is accompanied by paradoxical acidosis of cerebrospinal fluid, which was the basis for the negative attitude of different researchers to the use of sodium bicarbonate in patients with DKA [6]. The sodium bicarbonate is extremely harmful in patients with diabetic ketoacidosis and can be used

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only if there is a high probability of myocardial depression on the background of metabolic acidosis [2, 6, 11, 14, 15].

The ketoacidosis gradually regresses with adequate infusion and insulin therapy in the majority of clinical cases. But sometimes the decompensated metabolic acidosis may persist and sodium bicarbonate (0.5–1.0 mEq/kg for 30–60 minutes) can be appropriate. Both we and other authors believe that the use of sodium bicarbonate can be justified only in the presence of decompensated metabolic acidosis (pH < 7.1) and a high risk of acute myocardial depression [11, 14, 15]. There is a small experience of correction of metabolic acidosis and hyperglycemia in children with DKA using infusion solutions containing succinate [16].

In some cases, even while an adequate infusion and insulin therapy, progression of intracranial hypertension and clinical symptoms of cerebral edema are noted. Its diagnostic criteria are presented in Table 6. The necessary components of therapy are restriction of the volume of fluid, using of osmotic diuretics, tracheal intubation and transfer the patient to invasive mechanical ventilation in case of progression of cerebral edema in patients with DKA [4, 5, 11]. If the patient has depressed consciousness without obvious clinical signs of progression of intracranial hypertension and consciousness of the level of coma, use of osmotic diuretics is categorically contraindicated.

An artificial ventilation should be used only if it is a last way and there is a decompensated respiratory failure and high risk of aspiration syndrome. It is important to note that severe hypocapnia is a risk factor for the progression of cerebral edema, because low levels of carbon dioxide tension in the blood lead to a cerebral vasospasm, impaired autoregulation of cerebral blood flow and ischemia in CNS [17].

In patients with DKA it is advisable to maintain the level of pCO_2 as it was before tracheal intubation, avoiding excessive decrease and increase of pCO_2, because the hypocapnia is a compensatory mechanism aimed at eliminating ketoacidosis [11].

Drugs of choice for correction of intracranial hypertension are mannitol and/or hypertonic sodium chloride. The intravenous drip mannitol is administered at a dose of 0.5–1.0 g/kg for 20 minutes. If there is no effect, it can be done again. While using mannitol, improvement of cerebral blood flow and cerebral oxygenation is noted.

A hypertonic sodium chloride (3%) is used drip intravenously at a dose of 5-10 ml/kg for 30 minutes. The main advantage of hypertonic sodium chloride compared with mannitol is the prevention of hyponatremia and hypovolemia while there is an osmotic diuresis [3]. It can be used as a "second-line" drug in the absence of effect from mannitol.

Table 6. Criteria for the diagnosis of cerebral edema in patients with diabetic ketoacidosis [11]

Таблица 6. Критерии диагностики отека мозга у пациентов с диабетическим кетоацидозом [11]

Диагностические критерии / Diagnostic criteria	«Большие» критерии / "Major" criteria	«Малые» критерии / "Minor" criteria
1. Неадекватная двигательная или вербальная реакция в ответ на болевой раздражитель / Abnormal motor or verbal response to pain. 2. Декортикационная или децеребрационная ригидность / Decorticate or decerebrate posture. 3. Паралич черепно-мозговых нервов (особенно III, IV и VI) / Cranial nerve palsy (especially III, IV, VI). 4. Наличие патологических типов дыхания (дыхание по типу «гасп», тахипноэ, дыхание Чейна–Стокса, апноэ) / Abnormal neurogenic respiratory pattern (eg, grunting, tachypnea, Cheyne–Stokes, apneustic)	1. Угнетение или ундулирующее сознание / Altered mentation or fluctuating level of consciousness. 2. Уменьшение частоты сердечных сокращений (более чем на 20 в минуту), не связанное со сном или стабилизацией показателей гемодинамики / Sustained heart rate deceleration (decline more than 20 per minute) not attributable to improved intravascular volume or sleep state. 3. Несоответствующее возрасту возбуждение / Age-inappropriate incontinence	1. Рвота / Vomiting. 2. Головная боль / Headache. 3. Диастолическое артериальное давление более 90 мм рт.ст. / Diastolic blood pressure greater than 90 mm Hg. 4. Возраст менее 5 лет / Age <5 years

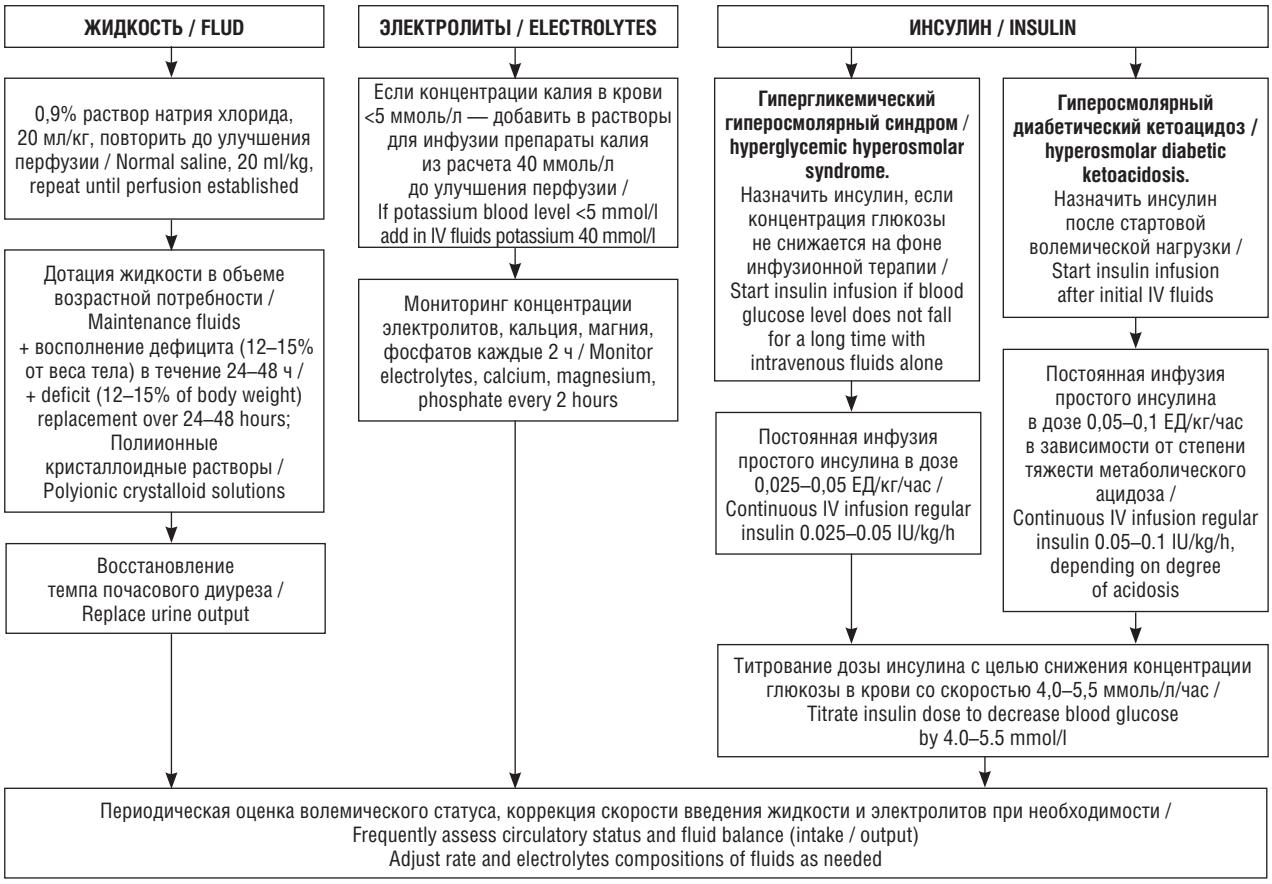

Fig. 2. Algorithm of intensive care of hyperosmolar hyperglycemic coma

Fig. 2. Algorithm of intensive care of hyperosmolar hyperglycemic coma

PECULIARITIES OF INTENSIVE CARE OF HYPEROSMOLAR HYPERGLYCEMIC NONKETOTIC COMA

The main distinguishing feature of treatment of hyperosmolar hyperglycemic nonketonic coma is the correction of water and electrolyte disorders. The use of insulin preparations is justified if the blood glucose level does not decrease while the patient is giving an infusion therapy. The starting dose of insulin should not exceed 0.05 U/kg per hour (Fig. 2).

CONCLUSION

At the end of the review of modern principles of intensive care of complications in children with diabetes mellitus, it should be noted that any rash and routine intervention can bring both benefit and harm. Thus, cautious and timely assessment of the patient's condition and subsequent correction of therapy are necessary.

ADDITIONAL INFORMATION

Author contribution. Concept and design of the study: Aleksandrovich Yu.S., Pshenisnov K.V.; collection and processing of primary material: Pshenisnov K.V., Muratov P.A., Ditkovskaya L.V.; writing the text of the article: Pshenisnov K.V., Prometnoy D.V., Kopylov V.V., Muratov P.A.; editing: Ivanov D.O., Aleksandrovich Yu.S. All authors read and approved the final version before publication.

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Вклад авторов. Концепция и дизайн исследования: Александрович Ю.С., Пшениснов К.В.; сбор и обработка первичного материала: Пшениснов К.В., Муратов П.А., Дитковская Л.В.; написание текста статьи: Пшениснов К.В., Прометной Д.В., Копылов В.В., Муратов П.А.; редактирование: Иванов Д.О., Александрович Ю.С. Все авторы прочли и одобрили финальную версию перед публикацией.

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