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Neurological Status Deterioration in Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

Zuazaga Marcela, MD[*]
Fustiñana Ana, MD
Pellegrini Solana, MD
Arpi Lucrecia, MD
Prieto Mariana, MD
Martinez Mateu Carolina, MD
Krochik Gabriela, MD

Address
[*]Interdisciplinary Working Group on Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State Standards, Hospital de Pediatria J. P. Garrahan, Buenos Aires, Argentina
Email: marcelazuazaga@gmail.com

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Abstract

Purpose of review To emphasize the pathophysiological and therapeutic approach differences between diabetic ketoacidosis (DK) and hyperosmolar hyperglycemic state (HHS).
Recent findings This manuscript depicts the different therapeutic protocols and potential complications in DK and HHS based on the best current evidence, in order to improve their management. Novel studies show quite different fluid management between DK and HHS, encouraging bicarbonate avoidance whenever possible.
Summary Diabetic ketoacidosis is one of the most severe and life-threatening complications in diabetes. Cerebral edema may sometimes appear (less than 1%) as a consequence of DK, and it carries out high morbidity (serious neurocognitive sequelae) and mortality itself. The younger the patient, the higher the risk for developing CE, especially in recently diagnosed patients. This life-threatening complication must be clinically suspected in

front of a patient undergoing a DK episode, and treatment should be started as soon as possible.

Other diabetic patients may decompensate with an HHS, which is pathophysiologically different from DK. Indeed patients with DK complication must have a cautious fluid management. On the contrary, HHS should be treated with an aggressive fluid reposition. Pediatric patients undergoing severe DK or HSS should to be admitted to a PICU for monitoring and especial care.

Cerebral edema (CE) in diabetic ketoacidosis (DK)

Diabetic ketoacidosis (DK), which is caused by a relative or absolute insulin deficiency, is the most severe and life-threatening complication of diabetes. This clinical presentation has a frequency that ranges between 15 and 60% of patients [1••]. In the known diabetic patients, DK is usually the result of insufficient insulin due to missing doses or otherwise triggered by an acute illness. Severe complications may occur in pediatric patients who suffer a DK episode, being cerebral edema (CE) the worst one, carrying a high morbidity and mortality. Though its incidence is less than 1%, CE may cause serious neurocognitive sequelae.

Multiple pathophysiological mechanisms, including vasogenic and/or cytotoxic mechanisms, have been proposed for CE development [2, 3]. Several studies evaluated the association between CE and rapid fluid administration, sudden changes in osmolarity, and aggressive fluid administration. Other groups propose that CE is caused by cytotoxic edema secondary to hypoperfusion and cerebral reperfusion. Rapid hydration could limit the area of ischemia, latter worsening vasogenic edema during reperfusion, due to a secondary increase in blood-brain barrier permeability. Initial high urea levels and acidosis in CE patients support this hypothesis [4].

Every patient with DK is at risk for developing CE [1••].

Patient risk factors:

- Younger age
- Recent diagnosis of diabetes
- Longer duration of symptoms before diagnosis
  Laboratory risk factors:

- Hypocapnia
- Increased urea
- Severe acidosis
  Related to treatment:

- Sodium bicarbonate administration
- Rapid decrease in osmolality
- Lack of changes in increased or decreased sodium during glucose levels correction

Clinically, cerebral edema develops within 12 h after starting DK treatment, and it can even occur before treatment has started. It rarely occurs after 24–48 h from the initial treatment.

Clinical case:

1-year-old boy with 24-h respiratory distress, vomiting, and drowsiness.

In regular condition, pale, looks dehydrated sleepy, weak peripheral pulses, and 2-s capillary refill. RR 60/min, HR 160/min, BP: 107/69 mmHg, and temp 36.7 °C. Abnormal motor response to pain.

Background: Tachypnea, polyuria, and polydipsia lasting 48 h.

Due to suspected DK, blood samples showed:

Glycemia: 650 mg/dl; pH 6.9/pCO$_2$ 15/bic 2.7/BE – 25; Na + 123 mEq/l, K + 3.5 mEq/l Cl- 108 mEq/L, Ca ++ 1.08 mmol/L Lactic: 1.8 mmol/L HMG: BWC 30,000 mm3 (60/30), Hb 14 g/dl, platelets 300,000/ mm3 Urea: 100 mg/dl, Cr: 0.52 mg/dl, P: 4.8 mEq/L

In front of a patient with a severe DK: (Fig. 1)

- Perform primary survey (ABC) to assess clinical condition and start initial support and stabilization.
- Rule out other potentially serious diagnoses, such as poisonings, respiratory infections, asthmatic status, acute surgical abdomen, organic acidemias, central nervous system
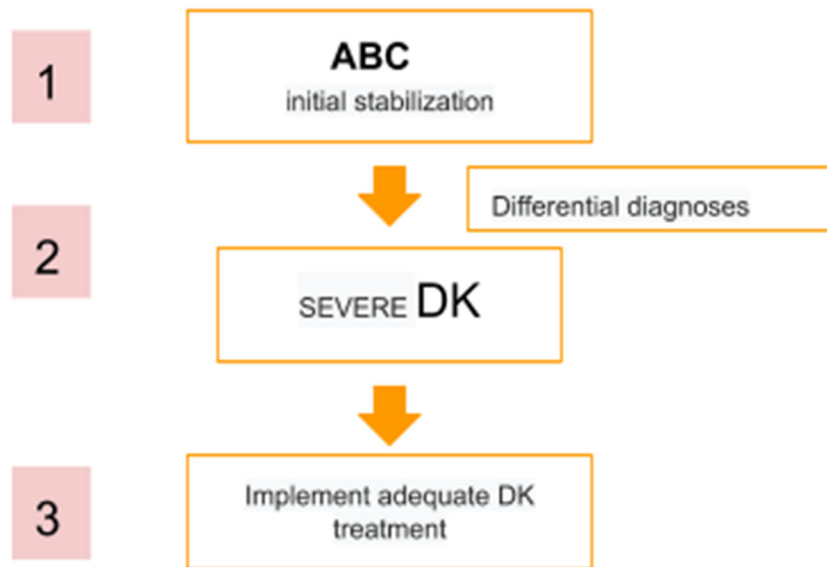
Fig. 1. Expected clinical pathway

infections, sepsis, alcohol consumption and/or drugs abuse.

• Initiate adequate DK treatment.

Most differential diagnoses can be quickly ruled out through complementary studies, especially due to glycemia, acid-base status, and ketonemia or ketonuria.

If the condition meets the diagnostic criteria for DK (blood glucose > 200, acidosis and ketosis) but the patient does not have polyuria, sepsis should be considered an alternative diagnosis. Sepsis may mimic DK, but the absence of polyuria almost rules it out. Remember that severely acidotic, dehydrated, or septic patients may present with encephalopathy or a conscious disturbances. On the other hand, some patients with DK may associate renal failure and oliguria or rarely even anuria.

A meticulous questioning looking for recent weight loss, polyuria, nocturia, and polydipsia may have important implications towards a DK diagnosis.

In the aforementioned severe clinical case, we must consider the possibility of cerebral edema. The incidence of severe CE in ketoacidosis ranges 0.5 to 0.9%, carrying 21 to 24% mortality rate [1••]. So in order to make an earliest as possible CE diagnosis, we must check the following: (Fig. 2)

• Child's risk factors for CE
• Diagnostic criteria for CE in children with DK

Our patient had intrinsic risk factors for CE (age, recent DK diagnosis). Indeed, a DK episode, with severe

hypocapnia, acidosis, and increased urea levels due to dehydration, implies a serious clinical picture.

Brain edema signs and symptoms usually appear during the first 12 h after starting treatment, but they even may be present before. Neurological status alterations (Glasgow Score < 14) are more frequently described during ketoacidosis treatment (4 to 15%) and may be associated with CE.

Cerebral edema diagnosis is based on some clinical criteria that allows to determine which patients are going to require specific treatment. The presence of any main diagnostic criteria or 2 major criteria or 1 major criteria and 2 minor criteria have a 92% sensitivity and 96% specificity for a CE diagnosis [1••] (Table 1).

Some studies show CE images even in asymptomatic patients with DK. On the other hand, other symptomatic patients show early normal neuroimages. That is why neuroimaging is not initially necessary in order to confirm a diagnosis of cerebral edema. So diagnosis lays on clinical and neurological evaluation. Neuroimaging is only indicated to rule out other pathologies, and CE treatment should not be delayed [3].

Other risk factors that contribute to the development of CE are those related to the treatment itself. Therefore it is crucial to:

• Check how much fluid to deliver during the first 4 h of treatment.
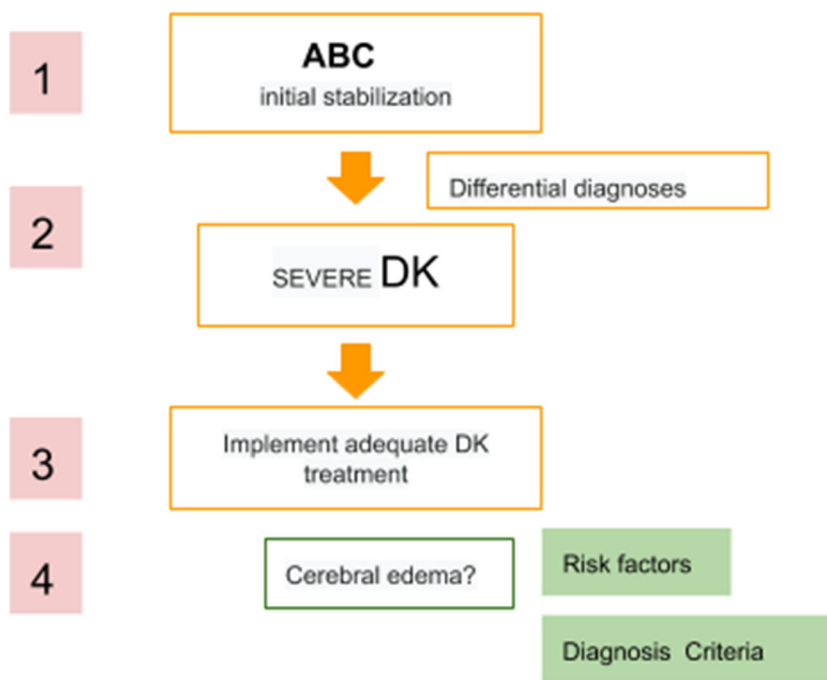• Check how much fluid is scheduled for the first 24 h.

Fig. 2. Expected stock flow chart

Regarding the initial fluid delivery, international guidelines recommend restoring the circulatory capacity as the main treatment goal. The International Society for Pediatric and Adolescents Diabetes (ISPAD) recommends in moderate and severe DK (without shock) to immediately start the initial fluid replacement with 0.9% saline at 10 to 20 mL/kg, during the first hour [1••, 4]. Following so and depending on the picture severity, fluid replacement may vary between 2000 to 3500 mL/m^2 of body surface area in the first 24 h, excluding previous fluid deficits and basal needs [4]. The clinical estimation of dehydration severity is seldom reliable, being frequently overestimated [5]. Most treatment guidelines suggest avoiding fluids over 4000 mL/m^2. Diuresis replacement fluids are not recommended [1••]. A risk factor study for the development of CE found a relationship between the administrations of more than 50 mL/kg in the first 4 h of treatment [6].

Hospital Garrahan's (*Buenos Aires*, *Argentina*) DK guidelines propose that the amount of fluid should be administered according to the patient's status. In mild/moderate DK, fluids should be started at 10 mL/kg in the first hour followed by 3000 mL/m^2/day. In severe DK, fluids should be infused at 20 mL/kg in the first hour, followed by 3500 mL/m^2/day [7].

Table 1. Diagnostic criteria for CE [1••]

Main diagnostic criteria	Major criteria	Minor criteria
Abnormal motor or verbal response to pain	Altered mental state, confusion, consciousness fluctuation	Persistent or increasing vomiting after starting treatment
Decorticate or decerebrate posture	Low heart rate	Headache
Cranial nerve palsy	Inappropriate urinary incontinence	Drowsiness or lethargy
Neurogenic abnormal breathing pattern		Arterial diastolic tension >90 mmHg
		≤ 5 years

To avoid excessive fluid administration in obese patients, fluid calculations should be based on the ideal body weight according to their height. In obese adolescents, maximum replacement volume should not exceed 6000 mL/day.

- Check if the patient started insulin immediately *after* the first fluid infusion is completed.

We suggest to start insulin after the infusion of the first hour fluids. A study by Edge et al. showed an increase in CE (OR 4.7 CI 95% 1.5–13.9, $p < 0.007$) when insulin treatment was started before the initial fluid administration. It is postulated that this increased CE risk could depend on sudden changes in electrolyte levels secondary to the activation of the sodium/potassium pump of the cell membrane [8].

- Verify if the patient received bicarbonate administration during his initial treatment.

In several controlled studies, no benefit has been found in the administration of bicarbonate. On the contrary, bicarbonate administration has been associated with central nervous system paradoxical acidosis and hypokalemia [9–11]. In 2011, a systematic review looking for bicarbonate administration in DK showed no benefit regarding mortality, hospital length of stay, acidosis and ketosis resolution time, insulin sensitivity, glycemic control, potassium balance, tissue oxygenation, hemodynamic stability, neurological evaluation, and CE [12]. It was concluded that there is lack of evidence to support bicarbonate administration in DK treatment [11]. This seems to be especially true in the pediatric population. Nor is there sufficient evidence to justify giving bicarbonate when the pH is < 6.90 [11]. Currently, international treatment guidelines refer to its use only in severe hemodynamic compromise needing specific treatment or in the exceptional case of severe hyperkalemia [1••].

In the new Hospital Garrahan DK guidelines, we propose *that bicarbonate administration should be limited for patients in severe metabolic acidosis* (pH LESS THAN 6.8) and severe hemodynamic impairment with low cardiac contractility. It should be remembered that in DK patients, fluids and insulin supply are nearly always enough severe acidosis improvement. [7]

- Be sure that to prevent an abrupt fall in sodium during glucose correction and even an early decrease in osmolarity.

During the DK treatment, sodium level must be strictly controlled. Corrected sodium level should be calculated and evaluated to ensure that it does not drop abruptly (for every 100 mg/dL of glucose decrease, sodium level should increase 1.6 mEq/L) in order to prevent brain swelling. Several publications show no difference in patient evolution according to sodium concentrations in fluids replacement, when a safety margin between 75 and 150 mEq/L is maintained [4, 13, 14].

In the new Hospital Garrahan DK guidelines, we recommend that the sodium concentration in maintenance fluids should be administered as follows: [7].

- Calculated/corrected sodium ≥ 130 mEq/L, use a 100 mEq/L sodium fluid concentration.
- Calculated/corrected sodium < 130 mEq/L, use a 140 mEq/L sodium fluid concentration.

If serum sodium does not increase by at least 1 mEq/L for every 100 mg/ dL in blood glucose decrease, then sodium concentration in intravenous fluid therapy should be increased to 140 mEq/L.

CE treatment in DK

The main guidelines for the treatment of cerebral edema are only supportive and lay upon a proper DK management:

- Start quickly when CE is suspected.
- Monitoring in PICU.
- Adjust fluid administration to maintain normal blood pressure.
- Hyperosmolar fluid administration: mannitol 0.5 to 1 g/kg i.v. in a 10 to 15 min i.v. infusion. This may be repeated after 30 min and/or hypertonic saline (3%) 2.5 to 5 ml/kg in a 10 to 15 min i.v. infusion.
- Position the head at 30°.

Clinical case resolution

The patient is admitted to the PICU with continuous monitoring, for severe DK management. A CE clinical diagnosis is made (patient is younger than 5 years of age, abnormal motor pain response, conscious alteration), so mannitol 5 g i.v. is infused and DK treatment is started. His condition improves within 15 h.

Neurological status deterioration in hyperosmolar hyperglycemic state HHS

Hyperosmolar hyperglycemic state (HHS) is characterized by extreme hyperglycemia (glucose > 600 mg/dL) and hyperosmolarity, in the absence of significant ketosis (pH > 7.3 and HCO3 > 15 mEq/L). These cases are uncommon, and their treatment is different from DK itself, becoming a challenge for pediatricians, the emergency department, and intensivists.

Typically the patient has polyuria, polydipsia, weakness, weight loss, tachycardia, dry mucosa, reduced capillary refill, hypotension, and, in severe cases, shock. Unlike DK where vomiting and hyperventilation are almost the rule, HHS highlights intense polyuria and polydipsia, with dehydration and important electrolyte loss [15]. Frequently overweight makes more difficult to assess the degree of dehydration. It should be remembered that intravascular volume is preserved because of hyperosmolarity, masking a real shock state [15].

An altered level of consciousness (lethargy, disorientation, stupor) occurs frequently and is related to effective serum osmolality. Coma is infrequent and, if observed, generally associated with a serum osmolality > 340 mOsm/kg.

Cerebral edema is uncommon and has a different pathophysiology than in DK. Longstanding hypertonicity determines idiogenic osmoles production. Hypertonic conditions, disruption of endothelial cells, increasing thromboplastin, and vasopressin release contribute to a hypercoagulability state, and though thrombosis is a frequent complication in HHS.

Hyperglycemic hyperosmolar state clinical picture

Obese 10-year-old girl. Her obese sister died 12 years old, probably because of DK. She has an aunt with diabetes mellitus (DM) and a grandmother with high blood pressure. She had fever, polyuria, and polydipsia 5 days prior to admission. In the last 24 h, vomiting, diarrhea, and respiratory distress appeared. On physical examination, she was found drowsy, eutrophic, pale, with dry oral mucosa, isochoric hypo reactive pupils, hyperemic pharynx, bilateral basal thin rales, moderate respiratory distress, and 13/15 Glasgow Coma Scale.

First approach to this patient should be:

- Adequate clinical support and stabilization (ABC).
- Make a quick and accurate diagnosis in order to start the appropriate treatment. Distinguish between DK or HHS.
  Diagnostic criteria for HHS:

- Blood glucose > 600 mg/dL
- Serum osmolarity > 330 mOsm/kg
- Serum bicarbonate > 15 mEq/L
- Urine ketones (acetoacetate) < 1.5 mmol/L, negative or trace in test strips
- Impaired consciousness

Our patient meets all the diagnostic criteria for HHS. A frequent practice mistake is a DK inaccurate diagnosis and missing HHS. In thirsty patients, carbohydrate-rich beverages consumption may have worsen hyperglycemia and confuse the clinical picture with an HHS. If acidemia and positive ketones are present, DK is the most probable diagnosis, and specific treatment should not be delayed.

Then some questions might come up:

- Should I fear that the same potential complications regarding DK might happen?
- Should I give the same treatment as I did for DK? Could CE appear as a treatment complication?

Despite severe electrolyte loss and volume depletion in HHS, marked hypertonicity leads to preservation of intravascular volume, making dehydration signs less evident. However, compared with DK patients, HHS show more dehydration, ranging between 12 to 15%.

The reduction in effective circulating insulin and tissue-increased resistance, or both, contributes to an increase in counterregulatory hormones. Unlike in DK, the amount of insulin is enough to decrease lipolysis and inhibit ketogenesis, making metabolic acidosis less frequent. On the contrary, insulin is less than needed to inhibit glycogenolysis and gluconeogenesis and stimulate cellular glucose uptake. This ends in a marked hyperglycemia typical in this hyperosmotic state, inducing osmotic diuresis with significant volume depletion.

Based on pathophysiology differences between HHS and DK, medical approach will be different too. In HHS, treatment will focus in restoring volume more than on insulin administration. If insulin is administered early before volume is restored, glycemia will be lowered; hence, osmolarity will fall. Consequently, the intravascular fluid moves to the intracellular space enhancing hypovolemia which might end in shock. For this reason, children with HHS require an aggressive fluid treatment which is the opposite as in DK treatment. These differences are quite important. On the other hand, given the lack of ketone bodies and acidosis in HHS, hypocapnia will not appear and neither cerebral vasoconstriction as happens in DK. This makes CE less frequent in this clinical picture [16••]

- Should I fear other complications in HHS?

Unlike in DK in which the most feared complication is CE, HHS might develop rhabdomyolysis and malignant hyperthermia as one of the most serious complications. A high incidence of venous thrombosis may also be observed, especially associated with the use of central venous accesses. Whenever possible, these should be avoided.

Rhabdomyolysis is a potentially fatal complication. It should be suspected in front of myalgia, muscle weakness, and dark urine. A rise in the blood, CPK value should alert on this diagnosis. For this reason, we recommended checking CPK every 2 to 3 h. Morbidity and mortality is associated with acute renal failure, severe hyperkalemia, and hypocalcemia [15, 16••, 17]. For unknown reasons, malignant hyperthermia may occur too, usually associated with fever

and increased CPK. Treatment for both complications is beyond the scope of this chapter. We strongly recommend treating HHS patients in a PICU setting.

In obese patients, volume must be calculated according to the corresponding weight for height. Only then, use body surface formula for fluid management (maximum 70 kg).

With fluid administration, blood glucose is supposed to decrease from 75 to 100 mg/dL/h. A further decrease in blood glucose by insulin administration may cause a dangerous and sudden drop in intravascular osmotic pressure with circulatory collapse, venous thrombosis, and severe acute hypokalemia. Insulin administration should not be started if blood glucose falls above a rate of 50 mg/dL/h with an adequate fluid replacement input.

Treatment by steps suggested in the new Hospital Garrahan HHS treatment guidelines [7]:

1. *Unlike in DK*, start rapid fluid resuscitation (bolus) with 20 ml/kg of saline.
2. Continue fluid administration as follows:
a) Maintenance fluids: previous deficit and basal needs will be calculated at 6000 ml/m^2 to be infused in 24 h (total volume/ day do not exceed 10,500 ml). In addition, concurrent losses, including urine output, should be replaced. If the glycemia should decrease at a rate greater than 90 mg/dl/h or the absolute value is less than 250 mg/dL, dextrose 2.5% should be added in the infusion.

b) Initial sodium concentration in maintenance fluids should be 125 mEq/L. This electrolyte concentration must be measured frequently (we recommend an hourly basis) and adjusted to achieve a smooth decrease (we suggest a gradual decline rate of 0,5 mEq/L/h).

c) Potassium in concentration in maintenance fluids should be 40 mEq/L, regarding renal function in not affected. As with sodium, potassium values must be checked on an hourly basis and continually adjusted as needed. Remember that plasma concentration may decrease when starting insulin administration.

Insulin use in HHS

Insulinization is unnecessary at the beginning of the treatment.

Insulin administration should be started only when blood glucose drops more than 50 mg/dl/h with fluid administration. Start with regular insulin at 0.05 U/kg/h in continuous intravenous infusion. If this is not feasible, administer 0.05 U/kg subcutaneously hourly. The insulin dose is calculated with the real weight and not with the ideal weight and must be adjusted to achieve a decrease in blood glucose between 50 and 75 mg/dL/h.

Clinical case resolution 2

> A correct HHS diagnosis was made. Insulin administration was avoided. Therapeutic approach was focused on aggressive fluid treatment. The girl slowly recovered, and 24 h latter, she was discharged from the PICU to the ward.

Conclusions

Diabetic ketoacidosis and HHS are clinical pictures that may complicate diabetic patients. Both therapeutic approaches are somehow different, regarding fluid management and timing in insulin administration. Cerebral edema is a severe and life-threatening complication in DK which must be strongly suspected and treated in front of neurological signs. This is not common in HHS, where dehydration, rhabdomyolysis, renal failure, and thrombosis may be serious complications. These should be prevented with an aggressive fluid approach and a correct insulin time administration.

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Compliance with ethics guidelines

Conflict of interest
The authors declare that they have no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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