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## Diabetic Ketoacidosis: Challenging Cases

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Diabetic ketoacidosis (DKA) is a hyperglycemic emergency that occurs in Type 1 diabetes mellitus (T1DM) and only very rarely in Type 2 DM. The incidence of DKA is reported to be 4.6-12.5 per 1000 diabetic persons per year.<sup>1,2</sup> With current therapy, there are still some patients who die. Patients hospitalized for acute hyperglycemia in Ontario have an in-hospital mortality ranging from <1% in those aged 20-49 years to 16% in those aged >75 years (1990),<sup>3</sup> with mortality rates from DKA alone ranging from 0.65% to 3.3%.<sup>4,7</sup> This issue of *Endocrinology Rounds* reviews several potential pitfalls that may occur when diagnosing and treating DKA.

DKA occurs when the absence of insulin action results in:

- hyperglycemia with urinary osmotic losses of water and electrolytes (sodium [Na<sup>+</sup>], potassium [K<sup>+</sup>], chloride [Cl<sup>-</sup>]) leading to extracellular fluid volume (ECFV) depletion
- a shift of K<sup>+</sup> out of cells
- ketoacidosis.

The management of DKA requires first, recognition and second, appropriate treatment. The diagnosis of DKA is usually straightforward; patients with T1DM are acutely ill when they present, revealing ECFV contraction and possibly a decreased level of consciousness. Often, patients have either withheld insulin and/or developed a concurrent illness. Laboratory investigations reveal hyperglycemia, dilutional hyponatremia, plasma concentrations of K<sup>+</sup> usually in the high-normal range, an anion-gap metabolic acidosis, and low plasma bicarbonate, low arterial pH, and elevated serum ketones.

Standard treatment consists of ECFV replacement with normal saline, intravenous (IV) administration of regular insulin (0.1 unit/kg bolus followed by 0.1 unit/kg/hr infusion), IV potassium replenishment, and IV glucose, once the plasma glucose concentration reaches 14 mmol/L.<sup>8,9</sup> IV sodium bicarbonate (NaHCO<sub>3</sub>) is used only in rare circumstances. The patient's clinical status and laboratory tests are closely monitored, often in an intensive care unit (ICU) setting. It is important to search for evidence of a precipitating illness. Table 1 summarizes the important issues for management and Table 2 summarizes the therapy of DKA, including the parameters that should be monitored to assess the success of each intervention, as well as potential complications of therapy.

It is important for the clinician to be aware of exceptions to the presentation described above. In such cases, the initial presentation of the patient may obscure the diagnosis of DKA or complications may arise that can be avoided if anticipated. A series of cases, based on real patients, will be used to illustrate these points.

**Case 1:** Ms. PA, a 24-year-old overweight woman, presents to her family doctor with polyuria and polydipsia. Her capillary glucose in the doctor's office is 15 mmol/L. He makes the diagnosis of T2DM, counsels her about diet, and starts her on metformin 500 mg bid. She presents to the emergency room (ER) twice during the next 2 weeks with worsening symptoms and hyperglycemia (glucose levels of 23 mmol/L and 26 mmol/L). On each occasion, she is given a bolus of rapid acting insulin and sent home. One week later, she is brought to the ER by friends because of a decreased level of consciousness; she is in profound DKA, with an arterial pH of 6.95.

**Discussion of Case 1:** In our current obesogenic environment, the incidence of T2DM is rapidly increasing, even among children.<sup>10</sup> When a young adult presents with polyuria, polydipsia, and hyperglycemia, they may be misdiagnosed as having T2DM. As a result, they may not be immediately treated with insulin. Therefore, when assessing a newly diagnosed patient with DM who is ill or has significant hyperglycemia (glucose level >15 mmol/L), it is impor-



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Table 1: Priorities in the management of patients presenting with hyperglycemic emergencies <sup>8</sup>		
Metabolic	Precipitating cause of DKA/HHS	Complications of DKA/HHS
1. ECFV contraction	New diagnosis Insulin omission Infection Myocardial infarction Drugs (eg, glucocorticoid) Other	Hyper/hypokalemia ECFV over-expansion Aspiration Cerebral edema Hypoglycemia Pulmonary emboli
2. K <sup>+</sup> deficit and concentration		
3. Metabolic acidosis		
4. Hyperosmolality (water deficit leading to increased Na <sup>+</sup> concentration plus hyperglycemia)		

ECFV = extracellular fluid volume; Na<sup>+</sup> = sodium ion; K<sup>+</sup> = potassium ion  
DKA = diabetic ketoacidosis; HHS = hyperglycemic hyperosmolar state

tant to check for an increased plasma anion gap. If the decision is made to treat them with diet and/or oral hypoglycemic agents on the basis of a diagnosis of T2DM, the patient should be followed very closely.

In addition, there are well-described cases of patients who present with DKA and are subsequently found to have T2DM.<sup>11</sup> In the correct hormonal milieu, patients with T2DM can develop DKA. This usually happens when very high levels of circulating catecholamines suppress endogenous insulin production to a sufficient degree that ketoacid production occurs. Once the ketoacidosis

resolves, the patient can frequently be treated with oral agents.

**Message:** Always consider the diagnosis of DKA in a patient with newly-diagnosed DM, especially if they are young. Consider the possibility of DKA, even in the context of T2DM.

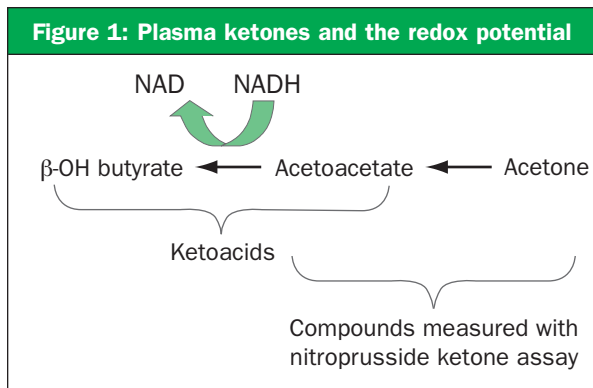
**Action:** Check for an elevation in the plasma anion gap in sick patients with hyperglycemia, especially with newly-diagnosed DM, where the patient may have unrecognized T1DM.

*Case 2: Mr. JL has longstanding T1DM. He presents to the ER with a 4-day history of nausea and vomiting. He stopped his insulin 2 days ago because he was unable to eat or drink. He appears ill and has significant postural hypotension. His arterial pH is 7.39, partial pressure of carbon dioxide (pCO<sub>2</sub>) is 40 mm Hg, HCO<sub>3</sub><sup>-</sup> is 25 mmol/L, plasma sodium (Na<sup>+</sup>) is 139, and plasma chloride (Cl<sup>-</sup>) is 90 mmol/L. His serum is negative for ketones. Could he still have DKA?*

**Discussion of Case 2:** When patients have a combination of DKA and metabolic alkalosis, if hydrogen (H<sup>+</sup>) ion production due to the DKA roughly equals the HCO<sub>3</sub><sup>-</sup> production from the alkalosis, the arterial pH, pCO<sub>2</sub> and HCO<sub>3</sub><sup>-</sup> levels may all be normal. The clue for an acid-base disorder will be an elevation in the plasma anion gap that occurs due to ketoanion accumulation. In Mr. JI's case, his

Table 2: Overview of the treatment of DKA					
Issue	Typical deficit	Diagnosis	Therapy	Monitoring	Complication of therapy
1. ↓ ECFV	Na <sup>+</sup> (mEq/kg) 7-10	Clinical examination Urine output	Normal saline 500-1000 mL/hr for 4 hours then 250 mL/hr for 4 hours, with the higher initial rate used to treat hypotension	ECFV Urine output	CHF ?cerebral edema
	H <sub>2</sub> O (mL/kg) 100				
2. K <sup>+</sup> depletion	K <sup>+</sup> (mEq/kg) 3-5	History of osmotic diuresis: plasma K <sup>+</sup> determines urgency of treatment	IV KCl 10-40 mmol/L	Plasma K <sup>+</sup>	Hypo- or hyperkalemia
3. Metabolic acidosis		↓ arterial pH ↓ HCO <sub>3</sub> <sup>-</sup> ↑ Anion gap presence of plasma and urine ketones. Positive assay for β-OH butyrate	Insulin 0.1 units/kg/hr IV (+/- bolus) (delay until K <sup>+</sup> >3.3)	Anion gap β-OH butyrate	Hypokalemia Hypoglycemia (add glucose to infusion when plasma glucose <10-14 mmol/L)
			NaHCO <sub>3</sub> consider if in shock or arterial pH <7.0	Arterial blood gases Vital signs	Hypokalemia Salt load ↑ pCO <sub>2</sub> Metabolic alkalosis once ketoacid anions metabolized
4. Osmolality	Often water deficit > Na deficit (osmotic diuresis is diluted relative to plasma)	Plasma effective osmolality = 2X plasma Na <sup>+</sup> + plasma glucose	- usually ½ NS @ 200 to 500 mL/hr after initial NS - continue NS if plasma osmolality falls too quickly - IV KCl adds to the osmolality - add glucose to IV once plasma glucose < 10-14 mmol/L	Δ Plasma osmolality <3 mOsm/kg H <sub>2</sub> O/hr	Cerebral edema
5. Underlying disorder		History, physical, CBC Blood and urine cultures CXR, ECG, drug screen			
6. Phosphate deficiency			No evidence therapy is beneficial		

ECFV = extracellular fluid volume; CHF = congestive heart failure; Δ = change; NS = normal saline; CXR = chest x-ray; ECG = electrocardiogram; CBC = complete blood count; IV = intravenous



NADH = nicotinamide adenine dinucleotide plus hydrogen

plasma anion gap was 24 mEq/L, which is significantly elevated above normal (12 mEq/L). In his case, vomiting led to metabolic alkalosis that masked the ketoacidosis.

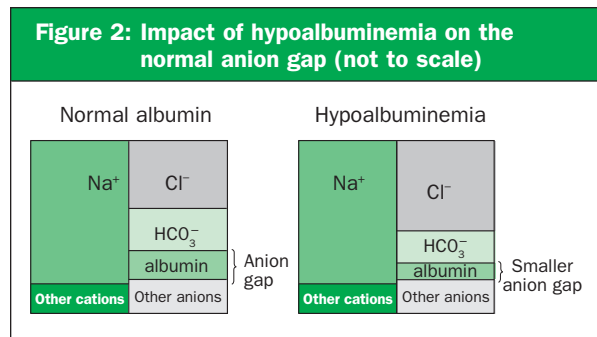
The second confusing aspect of Mr. JL's case is the negative test for serum ketones. Patients with DKA can have negative serum ketones if there is a shift to a high NADH:NAD ratio, which typically occurs in profound ECFV contraction. This ratio favours the shift of acetone and acetoacetate to β-hydroxybutyrate (β-OH butyrate). The test generally used to detect ketones in the serum is the nitroprusside ketone assay, but it only detects acetoacetate and acetone. As a result, the accumulation of β-OH butyrate – which could be very significant – may be missed (Figure 1).

Although plasma β-OH butyrate levels can be directly measured in this situation, they are not usually measured because studies on the clinical utility of β-OH butyrate measurement have indicated that they provide mixed results. Some clinicians suggest that β-OH butyrate measurement is useful to identify the resolution of ketoacidosis,<sup>12</sup> while others suggest it cannot be used as the sole test for DKA diagnosis and management. β-OH butyrate does not offer additional information over standard tests (eg, pH, [HCO<sub>3</sub><sup>-</sup>], anion gap, serum ketones [nitroprusside])<sup>13</sup> unless there is a reason that these tests may be wrong (as in the “challenges” above).

The diagnosis of DKA may be missed in patients with hypoalbuminemia because low albumin levels result in a lowering of the normal anion gap. For every 10 g/L reduction in the albumin level, the corrected anion gap falls by 2.3 mmol/L.<sup>14</sup> This is because albumin is negatively charged; therefore, when its level is lower than normal, the charge on Na<sup>+</sup> is balanced by extra Cl<sup>-</sup> and the anion gap is lower than usual due to the higher measured anion levels (Figure 2). For instance, in a patient with a serum albumin level of say 10 g/L, the normal plasma anion gap would be around 5 mEq/L. Patients with T1DM and hyperglycemia with this degree of hypoalbuminemia who apparently have a normal plasma anion gap of 12 meq/L, may well have DKA, with an increase in their plasma anion gap of 7 mEq/L.

**Message:** Do not miss ketoacidosis in patients with mixed acid-base disorders.

**Action:** Always check for an increased anion gap, even when the other acid-base parameters (pCO<sub>2</sub>, pH, H<sub>2</sub>CO<sub>3</sub>) are normal. When serum ketone levels are



normal, also consider whether there is a reason for a false result. If so, check the β-OH butyrate levels (if available in your lab). Hydrogen peroxide can also be added to a sample of plasma to convert β-OH butyrate to the other ketones, then the usual ketone assay can be used. If the patient is treated on the basis of having DKA, as the patient improves, it is important to recall that the measured serum ketone levels will in fact rise before falling, as β-OH butyrate is converted back to acetoacetate before being metabolized to CO<sub>2</sub> and water. Do not forget to correct the anion gap for hypoalbuminemia.

**Case 3:** Mr. DD, a 32-year-old man with no significant past medical history, presents to the emergency room with gastroenteritis and somnolence. His plasma glucose level is 42 mmol/L and he has an anion-gap metabolic acidosis with a plasma bicarbonate of 5 mmol/L. He is given a bolus of 10 units of regular insulin and then an IV infusion of 10 units/hr. One hour later, he develops an arrhythmia on his cardiac monitor. It is then noticed that his plasma potassium on presentation was 3.0 mmol/L. He is treated with 40 mmol of potassium over 1 hour, and his repeat plasma potassium level is 2.5 mmol/L.

**Discussion of Case 3:** Patients in DKA typically present with a potassium deficit of 3-5 mmol/kg<sup>15</sup> due to prior urinary losses of potassium during the osmotic diuresis induced by hyperglycemia. They usually have a high-normal plasma K<sup>+</sup> concentration at presentation, resulting from the shift of K<sup>+</sup> out of cells due to the lack of insulin. Ketoacidosis itself does not cause the K<sup>+</sup> to shift<sup>16</sup> since the ketoacid anion can pass into the cell with H<sup>+</sup> (unlike non-anion-gap acidosis, when H<sup>+</sup> enters the cell in exchange for K<sup>+</sup>, leaving Cl<sup>-</sup> behind in the ECF). When insulin is administered to treat acidosis, K<sup>+</sup> will shift into cells. Bicarbonate administration also exacerbates this shift, with a resultant further fall in plasma K<sup>+</sup> levels. Hypokalemia is one of the major causes of mortality in DKA.

**Message:** Take the risk of hypokalemia during therapy of DKA seriously.

**Action:** When patients are hypokalemic at presentation with DKA, it implies a very significant total body potassium deficit. Potassium replacement should begin immediately. Insulin should be withheld until the potassium level is >3.3 mmol/L. Bicarbonate administration also worsens hypokalemia and should be avoided in hypokalemic patients.

**Case 4:** Ms. AC is being treated for DKA with IV regular insulin, 8 units/hr. She was also vigorously ECFV resuscitated and now has polyuria. Her plasma glucose concentration level fell from 28 mmol/L to 12 mmol/L within 2 hours. At this point, her dose of insulin was reduced to 1 unit/hr. Four hours later, she still had an anion gap of 22 mEq/L and a plasma  $\text{HCO}_3^-$  concentration of 8 mmol/L. Her insulin dose was increased to 5 units/hr and IV glucose was administered. Her next anion gap had dropped to 16 mEq/L.

**Discussion of Case 4:** The Canadian Diabetes Association Clinical Practice Guidelines<sup>8</sup> recommend that, in the treatment of DKA, the insulin infusion rate should not be reduced until the plasma anion gap has normalized, since this is the most direct indication that the DKA has responded to insulin.

The fall in plasma glucose levels or the rise in plasma  $\text{HCO}_3^-$  levels could be considered to monitor the effectiveness of insulin; however, both of these approaches have their pitfalls. Resolution of hyperglycemia is multifactorial; insulin enhances the uptake of glucose into cells and reduces the ongoing production of glucose via glycogenolysis and gluconeogenesis. The administration of IV fluids alone, however, lowers glucose levels both by diluting the plasma glucose as the ECFV is re-expanded<sup>17</sup> and improving the glomerular filtration rate (GFR) with resultant osmotic loss of glucose.<sup>18</sup> In fact, studies in hyperosmolar hyperglycemic syndrome have indicated that administering IV fluids without insulin can normalize elevated plasma glucose levels.<sup>17</sup> Patients with DKA require insulin for the resolution of hyperglycemia and acidosis.<sup>19</sup> Thus, because the fall in glucose levels is multifactorial, plasma glucose concentration is not the best indication that insulin has been effective and DKA has resolved.

A small randomized controlled trial<sup>20</sup> studied whether glucose or  $\beta$ -OH butyrate levels are the best indicator of insulin action. It found that ketoacidosis resolved faster when insulin dosage was titrated to resolving ketoacidosis and not glucose,<sup>20</sup> which suggests it is better to monitor ketoacidosis resolution.

Plasma  $\text{HCO}_3^-$  concentration is also not the best test to follow insulin action because, as the osmotic diuresis resumes following ECFV replenishment, ketoacid anions are often lost in the urine, along with  $\text{Na}^+$  or  $\text{K}^+$  cations. The  $\text{H}^+$  ions left behind result in a non-anion gap type of metabolic acidosis.<sup>21</sup> Typically, plasma  $\text{HCO}_3^-$  levels are 18-20 mmol/L after the resolution of DKA, since the lost ketoacid anions are unavailable for metabolization to regenerate bicarbonate.

Serum ketones also cannot be used to monitor the effectiveness of insulin therapy because, as noted above, as DKA resolves,  $\beta$ -OH butyrate converts to acetoacetate. As the serum ketone test measures the

latter compound, the test is expected to rise early in effective therapy.

**Message:** Elevated glucose levels fall during treatment of DKA for multiple reasons, only one of which is due to insulin action. DKA may be ongoing, even when glucose levels have fallen to nearly normal levels.

**Action:** Reduce the insulin dose only when the anion gap has fallen. There is a faster resolution of ketoacidosis when the insulin dose is titrated using the normalization of anion gap rather than the normalizing of glucose.

**Case 5:** Ms. AB presents with T1DM and DKA. She has a normal level of consciousness, her blood pressure (BP) is 100/70 mm Hg, and she has evidence of ECFV contraction. She has Kussmaul breathing, her glucose level is 31 mmol/L, her arterial pH is 7.0, her  $\text{HCO}_3^-$  is 6 mmol/L, and her  $p\text{CO}_2$  is 24 mm Hg. Should IV  $\text{NaHCO}_3$  be administered?

**Discussion of Case 5:** The use of  $\text{NaHCO}_3$  in DKA has been studied in small randomized trials<sup>22-25</sup> in patients with severe ketoacidosis (pH levels between 6.85-7.2) who were not in circulatory shock. These studies found that when doses of  $\text{NaHCO}_3$  between 45-150 mEq were given, along with moderate doses of insulin, there was no effect on the rate of recovery from ketoacidosis, insulin dose, or administered fluids. Potential risks associated with  $\text{NaHCO}_3$  use include hypokalemia, increased  $\text{CO}_2$  production, and a delayed or “rebound” metabolic alkalosis. There is also a theoretical risk of cerebral edema associated with the use of  $\text{NaHCO}_3$  (which was not found in the 3 studies cited above; however, only 1 of the studies was done in a pediatric population).<sup>25</sup>

The use of  $\text{NaHCO}_3$  has not been well-studied in patients with arterial pH < 6.95 or in the presence of circulatory shock. Patients with either of these presentations can be considered for therapy with  $\text{NaHCO}_3$  as an isotonic solution (3 ampoules [45 mEq]) added to 1000 mL of water, given at a dose of 300 mL/hr for 1-3 hours until the pH is > 7.0.<sup>8</sup>

**Message:**  $\text{NaHCO}_3$  administration should be used judiciously, as there are potential complications associated with its use.

**Action:** Use IV  $\text{NaHCO}_3$  for patients in circulatory shock with low arterial pH and consider for all patients with arterial pH < 7.0.

**Case 6:** Ms. SW is a 17-year-old girl who presents to the emergency room with new-onset polyuria, polydipsia, and a weight loss of 8 kg during the past month. On examination, she is significantly ECFV-contracted. Her plasma glucose level is 54 mmol/L, plasma  $\text{Na}^+$  140 mmol/L,  $\text{K}^+$  4.5 mmol/L, and anion gap 25 mEq/L. Serum ketones are positive. The diagnosis of DKA is correctly made. She is resuscitated with a total of

5 liters of normal saline given over 2 hours. Regular insulin (8 units IV) is given as a bolus, followed by 8 units IV per hour. Potassium is added early to the IV fluids. Her plasma anion gap responds well and within 6 hours her glucose level and plasma anion gap are normal. However, during the resuscitation, her level of consciousness deteriorates and she becomes unrousable. What complication of DKA has occurred and how might it have been avoided?

**Discussion of Case 6:** Cerebral edema (CE) typically occurs in approximately 1% of pediatric patients admitted for DKA and, while rare in adults, it is important to be aware that it has been reported in individuals even in their late 20s.<sup>26,27</sup> In computed tomography (CT) brain scans in adults with DKA, increased brain density consistent with CE can be seen fairly frequently, although it is very rarely symptomatic.<sup>28</sup>

In children with DKA, 0.7% to 3.0% of cases are complicated by CE<sup>29-32</sup> and it is associated with significant morbidity (21% to 35%) and mortality (21% to 24%).<sup>33</sup> Although the precise cause of CE is still unknown, several factors are associated with increased risk, including age <5 years, new-onset T1DM, high initial serum urea, low initial pCO<sub>2</sub>, rapid administration of hypotonic fluids, failure of serum sodium to rise during treatment, and possibly the use of NaHCO<sub>3</sub>.<sup>29-31, 33-36</sup> Besides the above known associated risk factors, it can be logically predicted that several treatments for DKA may contribute to CE, based on physiological processes after administration;<sup>37</sup> for example rapid saline administration, allowing plasma osmolality to fall too quickly, and insulin administration itself. Increasing the ECFV with saline administration expands intravascular volume, including cerebral veins and capillaries and, therefore, intracranial pressure rises. Furthermore, it reduces plasma oncotic pressure, allowing fluid to be transferred into the cerebral interstitium. Using hypotonic fluids reduces plasma osmolality, resulting in a shift of water from extracellular fluid to intracellular.

There is also a theoretical reason why insulin itself may contribute to cerebral edema:<sup>37</sup> insulin shifts Na<sup>+</sup> into cells in exchange for intracellular H<sup>+</sup> via the Na<sup>+</sup>/H<sup>+</sup> exchanger (NHE). Since the H<sup>+</sup> was previously buffered by (ie, bound to) intracellular proteins, a new intracellular osmole (the Na<sup>+</sup> ion now in the cell replacing the H<sup>+</sup>) is created, so the ICF has more effective osmoles, resulting in a further shift of water into the cell.<sup>37</sup> To minimize the chances of CE, the following factors should be considered in the therapeutic approach to the child and young adult with DKA:

- **Initial saline rate of administration:** Avoid overcorrection or too rapid correction of ECFV deficiencies in the hemodynamically-stable patient. One study,<sup>38</sup> although under-powered, revealed equivalent rates of recovery from DKA using a rate of normal saline infusion of 500 cc/hr for the first 4 hours, fol-

lowed by 250 cc/hour, versus a rate of 1000 cc/hour for the first 4 hours. Since there are theoretical reasons why the lower rate may benefit the small subpopulation at risk of CE, it seems prudent to use the lower rate when the patient is not in shock.

- **Insulin bolus:** Insulin can be given as a bolus (0.1 unit/kg) prior to infusion;<sup>8</sup> however, this did not offer any faster resolution of DKA in children in 2 studies.<sup>39,40</sup> The bolus dose is not recommended in children. The necessity of the bolus in adults has only been assessed in 1 small study and, while it made no difference to the rate of resolution of DKA, a higher rate of insulin infusion was used in this study (0.15 units/kg/hr).<sup>41</sup>

- **Rate of reduction of plasma osmolality:** Plasma osmolality is typically high when patients present with DKA, but it is usually <320 mOsm/kg. It is elevated due to hyperglycemia and there is often relative hypernatremia due to urinary water losses in excess of sodium. Because of the risk of CE, Canadian and American guidelines recommend lowering plasma osmolality no faster than 3 mosm/kg/hr.<sup>8,9</sup> Plasma effective osmolality can be calculated using the formula:  $2 \times ([Na^+] + [plasma\ glucose\ in\ mmol/L])$ . Plasma effective osmolality should be monitored every 2-4 hours and glucose should be infused when required to maintain plasma glucose at approximately 14 mmol/L. The concentration of infused saline will depend upon how quickly the effective osmolality is falling. Potassium increases the osmolality of infused solutions; therefore, if it is added to normal saline, the resulting solution will be somewhat hypertonic. Because urinary losses in most patients with DKA are typically hypo-osmolar (similar approximately to half-normal saline), half normal saline may be required during therapy, typically after volume re-expansion. However, when the plasma osmolality falls too rapidly, despite giving glucose as required, consider continuing the infusion with normal saline, not half-normal saline. **Message:** Remember that CE can occur during the treatment of DKA in young adults, as well as in children.

**Action:** In a person at risk, consider the following modifications to usual care: use slower fluid resuscitation, 500 cc/hr for the first 4 hours if not in shock, followed by 250 cc/hr; avoid the initial insulin bolus (important in children, since minimal data indicate whether a bolus is beneficial or detrimental in young adults); correct hyperosmolality slowly (not >3 mOsm/kg/hr).

## Conclusion

DKA is a common diabetic hyperglycemic emergency. Mortality is rare, but it does occur, most commonly due to hypokalemia, cerebral edema, or the illness that precipitated the DKA. This issue of *Endocrinology Rounds* discussed several cases to draw attention to the situations when the diagnosis of DKA can be missed and to the subtle, but important, management issues.

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