Understanding the Disease: ***Management of Diabetic Ketoacidosis***

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Diabetic ketoacidosis (DKA) commonly requires critical care admission. Guidelines however provide differing recommendations [1, 2]. We propose a pathophysiology-based approach to management. DKA diagnosis and resolution criteria are described in the Supplemental File.

Pathophysiology

The primary reason underlying development of DKA is insulin deficiency, either absolute or relative in the context of an insult that generates higher levels of counter-regulatory hormones.

In the liver, the high glucagon-to-insulin ratio increases gluconeogenesis and glycogenolysis through enzymatic stimulation, further increasing glycemic levels. In adipose tissue, the increased glucagon-to-insulin ratio increases lipolysis through hormone-sensitive lipase and thus availability of circulating free fatty acids (FFA). FFA undergo beta-oxidation in hepatic mitochondria with conversion to acetoacetate and β-hydroxybutyrate with resulting ketonemia and acidosis. Ketonemia is responsible for some features of DKA such as nausea and vomiting, abdominal pain, and ketone halitosis. Biochemically, a high anion gap acidosis is a hallmark of DKA [3].

In most circumstances, blood glucose levels >180-200 mg/dL(10-11 mmol/L) surpass maximum glucose reabsorption capacity within the renal proximal tubule. This results in increased intratubular osmolarity and osmotic diuresis which contributes to free water wasting and loss of electrolytes such as sodium and potassium. β-hydroxybutyrate is excreted in the urine, contributing to hyperchloremic metabolic acidosis when excreted with sodium instead of ammonium.

If this pathophysiological process is allowed to continue, hypovolemia will impact on glomerular filtration, resulting in decreased glycosuria and urinary excretion of ketoacids, further worsening metabolic acidosis and hyperglycemia [3].

The combination of hyperglycemia, ketonemia and acidosis represents the complete picture of DKA. Exceptions exist, especially with the increasingly common euglycemic DKA presentation related to SGLT-2 inhibitors [4]. Tubular inhibition of

SGLT-2 enhances excretion and decreases the threshold for filtered glucose reabsorption. With an intercurrent event, counterregulatory hormone levels increase and DKA ensues with normal-to-slightly-raised glycemia. Not all features of DKA may be evident, except for high anion-gap acidosis and ketosis.

Management

Three main issues should be addressed:

- ***Insulin*** to resolve the condition at its root cause (glucagon-to-insulin ratio).
- ***Fluid repletion*** to correct hypovolemia (if present) and total body water.
- ***Electrolyte replacement***, with particular attention to potentially life-threatening shifts in serum potassium.

A first-do-no-harm approach is essential. At the very outset, assess whether the patient has overt signs of hypovolemia and urgently measure the serum potassium level.

If the patient has signs of hypovolemia, such as hypotension and tachycardia, then administer 250-500mL fluid boluses until its correction (usually within 1 hour of presentation). After this, guidelines recommend 250-500 mL/h infusion rate of crystalloids with added potassium until hyperglycemia is corrected, and then 150-250 mL/h until DKA is corrected. These rates are largely expert guidance-based but are often excessive and potentially harmful. With n-saline such rates lead to a worsening hyperchloremic acidosis [5, 6]. The clinician may not recognize this and respond unwittingly by increasing the n-saline infusion rate, further aggravating the acidosis. We would advise using such fluid replacement guidelines as a guide only and *not* an absolute. We recommend titrating volume replacement to patient need with regular re-assessment of volume status. Patients vary in the degree of volume replacement needed and may be compromised by excess fluid. Buffered crystalloids should perhaps be favored over saline [7, 8], though potassium replacement may need to be given separately. We suggest that once hypovolemia is corrected with fluid boluses, give some fluid intravenously to allow potassium replenishment but, as soon as nausea is no longer a concern, give oral liquids to correct the total body water deficit.

Before insulin is given, check serum potassium levels. The patient is usually hyperkalemic because of the concomitant acidosis but may occasionally be hypokalemic. In such situations insulin infusion is best delayed as this will further worsen the hypokalemia. Ideally, administer ≤20 mEq of potassium per hour but, occasionally, more will be necessary if serum levels become dangerously low. Continuous or intermittent; concurrent to fluid replacement or separately, potassium can be administered per clinician's discretion. Levels must be checked regularly due to transcellular shifts during management and maintained within a range of 3.5-5.5 mmol/L. Even though total potassium deficit in DKA is often 600-800 mEq, this is mainly intracellular and does not need aggressive replacement.

After initial correction of hypovolemia and serum potassium exceeds 3.5 mmol/L, start an insulin infusion. The goal here is not only to correct hyperglycemia but to correct acidosis, the hallmark of DKA, by correcting the glucagon-to-insulin ratio and reversing abnormal metabolic enzymatic pathways and biochemical abnormalities. Be careful to avoid hypoglycemia, both for safety reasons and as undue interruptions in insulin infusion will delay DKA correction. Commence an initial infusion rate of 0.1 U/Kg/h of rapid-acting insulin and titrate as needed, aiming for a smooth reduction in glycemia of 50-70 mg/dL/h (2.7-3.9 mmol/L/h). Continue until the high end of normoglycemia is reached (e.g. 200-250 mg/dL, 11-14 mmol/L). At this point, the patient has often received sufficient initial sodium replacement so 10% glucose can be substituted enough to avoid hypoglycemia (guidelines suggest 125 mL/h but lower rates may suffice) or the patient may be well enough to take oral fluid and calories. If necessary, continue n-saline but be careful about fluid overload. The aim is to avoid hypoglycemia while reducing insulin infusion to 0.05 U/Kg/h until DKA correction is achieved. Alternative regimens to intravenous insulin infusion exist (Table 1).

Bicarbonate infusion is generally discouraged due solely to arbitrary pH levels [9] but could be considered in circumstances such as a low strong ion difference manifest by concurrent hyponatremia and significant hyperchloremia. In such rare circumstances, administer a slow isotonic infusion with careful monitoring of serum potassium levels and the Na^+-Cl^- gap. Serum phosphate levels should not usually either be ordered nor replenished.

The bottom line

Knowledge of DKA pathophysiology allied to current evidence may better guide DKA management. In Table 1, we present seven myths of DKA pathophysiology that the clinician should be aware of. Although a rigid prescriptive approach may prove adequate in many situations, pathophysiological reasoning is necessary for the increasingly more common atypical situations and for managing patients with underlying comorbidities.

Table 1: Seven myths about diabetic ketoacidosis pathophysiology and management
Myth 1: DKA is a state of extreme hypovolemia with need for large volume resuscitation (e.g. 100 mL/Kg)
• Although substantial renal losses can occur due to hyperglycemia, especially over a longer duration, true hypovolemia usually ensues when patients are unable to drink due to nausea and vomiting. The body usually compensates for osmotic diuresis through increased oral intake through activation of physiologically effective circulating volume operators such as increased thirst and other neuro-hormone pathways. • Some patients may not be hypovolemic, e.g. patients undergoing chronic dialysis or those with euglycemic DKA, where fluid losses are smaller.
Myth 2: NaCl 0.9% should be standard of care for volume repletion in DKA
• NaCl 0.9% causes iatrogenic hyperchloremic acidosis and does not prevent cerebral oedema [5]. • Buffered crystalloids such as Plasmalyte-148® or Hartmann's solution will hasten pH correction but with no difference in anion-gap closure [6, 7]. **Potassium replacement may however need to be given separately.**
Myth 3: Weight-fixed fluid infusion rates are necessary for the treatment of DKA
• A lower rate of fluid infusion leads to less hyperchloremic acidosis, reduces risk of fluid overload, and does not affect overall DKA correction rates [5]. Treatment should be personalized to patient needs.
Myth 4: Glucose-corrected serum sodium follows a linear relationship
• A non-linear relationship for glucose-corrected serum sodium is most likely [10]. • The clinical significance of glucose-corrected serum sodium is usually low, since fluid tonicity does not influence the rate of clinically significant cerebral oedema [5].
Myth 5: Hyperchloremic acidosis in DKA is the sole consequence of iatrogenesis
• Hyperchloremic acidosis is not only a function of large volumes of salt-containing solutions, but also of the severity and duration of DKA before treatment is started. • In DKA, renal reabsorption of chloride is increased to allow renal excretion of ketoacids, especially β-hydroxybutyrate [3].
Myth 6: DKA should be treated only with intravenous insulin
• In patients who are not very sick, an ultra-rapid subcutaneous insulin regimen (hourly dose of 0.1 U/Kg) may shorten time to DKA treatment and avoid the need for intravenous insulin [11]. • With current very long-acting insulins, it is advisable to use only small doses (usually 0.2 U/Kg) in patients with severe DKA at the onset of treatment. This allows a smoother transition from an IV to a SC insulin regimen.
Myth 7: DKA correction criteria include glucose levels and ketonemia
• pH > 7.30 and bicarbonate > 15 mEq/L are the usual minimum criteria for DKA correction. • Full correction of hyperglycemia does not ensure DKA reversal, neither is it necessary. • Although point-of-care ketonemia may hasten the diagnosis of DKA [12], its use as a routine treatment target has not been compared to standard approaches [13]. Optimal monitoring and rate of reduction have not been identified. • Anion-gap closure is the best lab surrogate for DKA reversal as it is devoid of confounding by hyperchloremic acidosis and can be easily assessed through the Na-Cl gap [14, 15] in most circumstances.

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