Updates in the management of Diabetic ketoacidosis

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Diabetic ketoacidosis (DKA) is a common hyperglycemic emergency and acute life-threatening complication of diabetes mellitus. (1) DKA incidence increased at an annual rate of 6.3% most notably in persons aged <45 years with a significant increase in hospitalization rate between 2008 and 2018. (2)

Though life-threatening, it is largely a preventable complication of type-1 diabetes with thirty percent of the cases that could be attributed to type-2 diabetes. (2) DKA occurs most often in patients with type 1 diabetes; however, patients with type 2 diabetes are also susceptible to DKA under stressful conditions. The severity of presentation and DKA duration are similar in both type 1 and type 2 diabetes, suggesting that the same clinical management protocol is equally effective, however, patients with type 2 diabetes have longer hospital stays. (3)

One of the most important guidance for the management of Diabetic ketoacidosis (DKA) and Hyperosmolar non-ketotic state (HNS) is the JBDS -IP (Joint British Diabetes Societies for Inpatient Care) guidelines that were first published in 2010 and were recently updated in 2023 owing to updated evidence and highlighting management in special groups. (4)
The JBDS-IP was the first to introduce a change from glucose-based management of the metabolic disorder to ketone which was shown to result in faster resolution of ketoacidosis and shorter length of stay in repeated audits. (4)
This review is aimed at exploring the new guidance, the important changes and updates brought, and highlighting the differences in management in special groups

Key updates and changes:

1. Diagnosis of DKA

All of these must be present to make the diagnosis
The 'D' – a blood glucose concentration of >198 mg/dl or **known to have diabetes mellitus**
The 'K' – **The 'K'** – a capillary or blood ketone concentration of >3.0 mmol/L or significant ketonuria (2+ **or** more on standard urine sticks)
The 'A' – a bicarbonate concentration of <15.0 mmol/L **and/or** venous pH <7.3

The lowered cutoff blood glucose level accounts for the more frequent diagnosis of Euglycemic diabetic ketoacidosis since the introduction of SGLT2 inhibitors to the armamentarium of oral hypoglycemic agents (4)

2. Euglycemic DKA

This is the development of raised anion gap metabolic acidosis, ketonemia (>3.0 mmol/L), or significant ketonuria (2+ or more on standard urine sticks) in people known to have diabetes but where the glucose is normal, or not particularly raised. Improved education for those with diabetes with increased home capillary glucose and ketone monitoring has led to partial treatment of DKA prior to admission with consequent lower blood glucose levels at presentation. (4)

Additionally, in adults with type 2 diabetes, SGLT2 inhibitors were found to increase the risk of DKA (and euglycemic DKA), in observational studies and randomized clinical trials [56]. In addition, patients with DKA and SGLT2 inhibitors treatment had longer time to resolution than type 1 diabetes patients. (3)

Patients with a longstanding history of type 2 diabetes mellitus and poor glucose control appear to have a higher susceptibility to the development of DKA, other risk factors include pancreatic insufficiency, alcohol dependence, and ketogenic diets. It is therefore advisable to avoid these medications until risk factors are appropriately addressed. (5)
To further minimize the risk of euglycemic DKA with SGLT2 inhibitors, it is advised to discontinue these drugs for at least three to five days before planned surgical procedures, during periods of acute illness, or prolonged fasting. (4)
The mechanisms by which SGLT2 inhibitors are associated with ketoacidosis are not fully understood. It may be related to the insulin-independent reduction of blood glucose through increased urine glucose excretion, which allows for glycemic control with concomitant reduction in insulin requirement. Moreover, the potential increase in glucagon secretion leads to a decrease in the insulin-to-glucagon ratio and promotes ketogenesis. (3)

This condition is treated in exactly the same way as hyperglycemic DKA.
1) Initiate glucose 10% straight away at 125 ml/hr because the glucose is <14 mmol/L
2) Begin with 0.1units/kg/hr insulin rate
3) If glucose falls by 10% glucose reduces to 0.05 units/kg/hr to avoid hypoglycemia. (4)

3. Ketosis-prone type 2 diabetes

This most often occurs in people of Afro-Caribbean or Hispanic descent. The treatment for this condition is the same as for others with DKA, but they often come off insulin quickly after
the resolution of the DKA and underlying precipitating condition. (4)

4. Point of care testing (‘bedside monitoring’)

Blood glucose is routinely checked using point-of-care testing, but portable ketone meters now also allow point-of-care testing of 3-beta-hydroxybutyrate, the main blood ketone. Blood ketone measurement represents best practice in monitoring the response to treatment. There have been some concerns raised about their accuracy, but to date, no harm has been reported from their use, and the data from these meters is just one of the measurements that helps to guide therapy and diagnose resolution. (6)

Currently, in Egypt, there is a need to introduce serum ketone measurement (beta-hydroxybutyrate mainly) within the lab panel for DKA diagnosis and follow-up. As the shift from a glucose-centric approach to ketone-centric is being progressively adopted by many societies in diagnosis and prognosis.

5. Controversial areas:

There were a number of issues that were considered 'controversial' in the previous versions of this guideline, which have now become standard practice. These are as follows:

a) Measure venous rather than arterial bicarbonate and pH
b) Blood ketone meters should be used for point-of-care testing

c) 0.9% sodium chloride solution is the recommended fluid of choice in the general medical ward
d) Subcutaneous long-acting analog/human insulin should be continued

e) Insulin should be administered as an FRIII (fixed rate insulin infusion) calculated on body weight
f) Do not use a priming (bolus) dose of insulin. (4)

Current controversial areas in these updated guidelines include:

A. Rate of insulin infusion:

Consider reducing the rate of insulin infusion to 0.05 units/kg/h when glucose drops to <250 mg/dl. Evidence showed that rates of hypoglycemia and hypokalemia are higher while using 0.1 U/kg/h especially when the type of fluid is not changed when blood sugar drops < 250 mg/dl and when potassium IV infusion is interrupted or delayed. (4)

B. Colloid versus crystalloid:

Crystalloid rather than colloid solutions are recommended for fluid resuscitation. A 2007 Cochrane review also did not support the use of colloid in preference to crystalloid fluid. A further 2013 consensus document suggested that colloids should be avoided where possible, due to a potential risk of increased mortality and morbidity associated with their use. (7)

C. 0.9% sodium chloride solution or balanced crystalloid solution for resuscitation:

Studies comparing 0.9 % NaCl with other IV solutions showed no superiority and, in some studies, better and faster resolution of ketonemia with 0.9% NaCl. Furthermore, diabetes specialists and physicians have vast experience in the safe use of this fluid. An ongoing systematic review could provide more conclusive evidence. (4)

D. Rate of fluid replacement:

Cautious fluid replacement in young adults.

For many years, there has been concern that rapid fluid replacement may lead to cerebral edema in children and young adults. Until 2018, no randomized controlled trials existed to guide decision-making in this area. However, a large, randomized controlled trial of 1389 episodes of ketoacidosis randomized children between 0 and 18 years of age to either 0.45% or 0.9% sodium chloride solution given fast or slow. (8) Reassuringly, these authors found no differences in neurological outcomes in children with ketoacidosis treated with rapid versus slower volume correction or with the use of 0.9% versus 0.45% sodium chloride. It is felt that the development of cerebral edema is multifactorial but often idiosyncratic. (9)

E. Intravenous bicarbonate:

Bicarbonate administration is not recommended routinely.

Adequate fluid and insulin therapy will resolve the acidosis in DKA, and the use of bicarbonate is not indicated. The acidosis may be an adaptive response as it improves oxygen delivery to the tissues by causing a right shift of the oxygen dissociation curve. Excessive bicarbonate may cause a rise in the CO2 partial pressure in the cerebrospinal fluid (CSF) and may lead to a paradoxical increase in CSF acidosis. Intensive care teams may occasionally use intravenous bicarbonate if the pH remains low and inotropes are required. (10)

F. Use of intravenous phosphate:

Phosphate should not be supplemented routinely. Severe phosphate deficiency can worsen respiratory failure, precipitate cardiac arrhythmias and cause rhabdomyolysis. If

any of these are present phosphate measurement and replacement should be considered as per local guidance. (4)

G. What should the rate of glucose lowering be:

The rate of glucose-lowering should be at least 54 mg/dl/hr. (4)

6. DKA in special groups:

The following groups need specialist input as soon as possible and special attention needs to be paid to their fluid balance:

- Pregnant

DKA in pregnancy can occur at near normal levels of blood glucose (euglycemic DKA) and often progresses more rapidly as compared with nonpregnancy. DKA in pregnancy is a poorly understood condition due to limited published evidence of risk factors and outcomes. DKA in pregnancy is an obstetric and medical emergency for both the pregnant woman and the fetus and therefore requires prompt and aggressive treatment [3].

The major risk factors are intractable vomiting and starvation (53%), inadequate insulin management (18%), and infection (27%) including pyelonephritis, respiratory, chorioamnionitis, ear infection, cellulitis, or tooth abscess. Additional common causes include steroid administration for fetal lung maturation) and diabetic gastroparesis. (3)

Cautious slower fluid therapy infusion and continuous monitoring due to higher risk of developing cerebral and pulmonary edema. (4)

- kidney failure

Rarely do patients with ESRD develop DKA

Possible pathogenesis:

Driven mainly by accumulated uremic toxins, ESRD can increase hepatic gluconeogenesis reduce utilization of insulin peripherally, and drive insulin resistance The lack of renal insulin clearance means that DKA is much less likely to occur. It may also be difficult to determine because of the chronic metabolic acidosis associated with advanced chronic kidney disease (stages 4 and 5). Recent data suggest that those presenting with DKA with end-stage renal disease have lower ß-hydroxybutyrate concentrations and higher glucose and anion gaps than those with preserved renal function (11).

Fluid replacement

The inability to develop osmotic diuresis means that dialysis-associated hyperglycemia and ketosis can occur without much dehydration. A mixed picture of DKA and HHS may also occur because of the high serum tonicity. there may be no need for fluid replacement in those with end-stage renal failure or those on dialysis. However, for those who are deemed hypovolemic, aliquots of 250 ml (0.9% sodium chloride or 10% dextrose) may be given with frequent clinical assessments (12).

Insulin treatment

For people with end-stage renal failure or those on dialysis, insulin replacement is the mainstay of treatment. This should be given as an FRIII at an initial rate of 0.1 units/kg/hr., but may need to increase if the required rate of glucose fall is not achieved with careful monitoring for hypoglycemia due to increased bioavailable active insulin. (4)

Potassium

Potassium supplementation is not usually required because the lack of osmotic diuresis means that there is significantly less potassium loss than for those with preserved renal function. However, acidosis may lead

to significant hyperkalemia, and this is more common in those with renal failure (54). In this circumstance, continuous cardiac monitoring is essential and critical care or the specialist renal team should be involved to consider urgent hemodialysis/hemofiltration.(13)

- Elderly, Young people 18–25 years of age: careful fluid infusion monitoring and need for a slower rate of infusion due to increased risk of cerebral and pulmonary edema. (4)
- Heart failure: careful fluid infusion monitoring and need for a slower rate of infusion due to increased risk of cerebral and pulmonary edema. (4)

7. Recurrent DKA:

- Those with recurrent admission with DKA have multiple social and economic risk factors Recurrent episodes of DKA are associated with increased risk of long-term cognitive decline and premature mortality (27; 28). Strategies to help individuals may include frequent telephone contacts, formal referral to psychology, and supervised insulin administration – e.g., using ultra-long-acting insulin analogs. (14)

Conclusion

DKA is the most common acute diabetic emergency, though commonly occurs in people with type 1 diabetes about one-third of patients are people with type 2 diabetes. JBDS-IP updated guidelines provided evidence-based insights that proved to improve outcomes and shorten hospital stays, and also highlighted new changes related to the increased use of SGLT2 inhibitors.

A special section on special groups widened the scope of care and issues encountered in these groups. Still, we have a gap of knowledge and a need for solid evidence for a number of controversial issues that need well-designed studies to explore.

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