# Diabetic Ketoacidosis: A Consensus Statement of the Associazione Medici Diabetologi (AMD), Società Italiana di Diabetologia (SID), Società Italiana di Endocrinologia e Diabetologia Pediatrica (SIEDP).

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KEYWORDS: diabetic ketoacidosis, euglycemic ketoacidosis, ketoacidosis management, ketoacidosis complications

Summary - Diabetic ketoacidosis (DKA) is a serious medical emergency once considered typical of type 1 diabetes (T1DM), but now reported in type 2 and GDM patients too. Though, DKA can cause severe complications and even prove fatal. These recommendations, based on international and national guidelines, are designed to help healthcare professionals reduce the frequency and burden of DKA.

## DEFINITION

According to the ISPAD [1], diabetic ketoacidosis (DKA) - characterized by hyperglycemia, metabolic acidosis, ketonuria and excessive serum ketone bodies - represents the most serious acute metabolic complication of diabetes mellitus.

## IMPACT AND HOSPITALIZATION RATE

The annual incidence of DKA has been estimated at 13.6 and 14.9 episodes/1000 patients with T1DM in the UK and Sweden, respectively [2,3], and at 4 to 8 episodes/1000 patients in the United States, depending on the patients' age (but data on populations under 30 indicate up to 13.4 episodes/1000 patients) [4–6]. According to the most robust pediatric data, about 65,000 children under the age of 15 worldwide develop T1DM each year. The changing prevalence of T1DM has clearly emerged from the World Health Organization's Diamond project [7]. The prevalence of DKA in children varies from 15% to 70% of cases of diabetes at onset [8] in developed countries, and in Italy is between 32% and 41.1%, based on four reports (the most recent in 2016) [9–12].
Hospitalization for DKA has increased by 30% in the last decade in the US [6], accounting for over 500,000 days in hospital in 2009, and direct and indirect costs of 2.4 billion dollars a year. In developing countries the numbers are even higher: in Africa 80 in every 1000 patients with T1DM are hospitalized each year for DKA, with a mortality rate over 30%. DKA should no longer be seen as a complication of type 1 alone, however, since about one in three hospitalizations for DKA in the US and Sweden involve patients with type 2 diabetes [2,3].

## PATHOPHYSIOLOGY

Diabetic patients' relative or absolute insulin deficiency results in a low glucose uptake in insulin-dependent tissues (muscle, liver, fat), triggering a counter-regulatory insulin response that may be accentuated by the production of proinflammatory cytokines [13,14]. At the onset of T1DM, an absolute insulin deficiency prompts proteolysis, lipolysis and an increased hepatic and renal glucose output. The production and accumulation of ketones deriving from the oxidation of hepatic fatty acids is due to the failure of the citric acid cycle [15]. (Figure 1).

## CAUSES

Infections are the most common precipitating condition in DKA, but other precipitating (Table 1) and risk factors (Table 2, 3) in adult and children are known. [15,16]
Risk Factors for Recurrent Diabetic Ketoacidosis in Adults and children are shown in table 4 and 5.

Protective factors for DKA in children are shown in Table 6.

New-onset diabetes is not the most frequent association with DKA: only 20% of patients hospitalized for DKA have no history of diabetes. This is extremely important because it might point to action to contain the frequency of DKA at the onset of diabetes, which is associated with lower remission rates and a lower residual functional reserve of pancreatic beta cells [75].

## DKA IN CHILDHOOD AND ADOLESCENCE

The pathophysiology of DKA is similar in children and adults, but several pathophysiological and clinical features may make it difficult to diagnose and to cure in children (Table 7 )[1].
In a condition of organic acidosis (es lactic acidosis, DKA, ingestion of substances that are metabolised in organic acids), the production of organic acids is proportionally higher in pediatric age.
Children have a high basal metabolism and a high body surface compared with their weight: special attention must be given to the estimation of dehydration and to the fluid therapy, considering also that, in infants, dehydration and hyperosmolarity are often severe because of their inability of liquids intake. The severity of dehydration and hyperosmolarity is inversely related to the adequacy of their fluid intake.
Besides, also the clinical features in children could be more difficult to interpretate: for example, if the diabetes is not suspected, Kussmaul sign could be confused with dyspnea due to asthmatic bronchitis or bronchiolitis (in younger patients) and this could induce to start corticosteroidal therapy. The children crying may not be interpreted as a sign of thirst, or it may be misinterpreted as a sign of hunger, prompting the administration of milk, which aggravates their hyperglycemia and hyperosmolarity.

## DKA IN PREGNANCY

Pregnancy is associated with insulin resistance, accelerated fasting, facilitated anabolism, and respiratory alkalosis, especially in the second and third trimesters [76–78]. These physiological mechanisms facilitates glucose supply to the fetus, and coincides with a gradually increasing insulin secretion to maintain normal glucose tolerance [76,77]. In pregnancy complicated by T1DM, the lack of exogenous insulin disrupts the balance between the facilitated anabolism and accelerated fasting so explaining the difficulty of keeping blood sugar levels within normal range. If hyperglycemia is not treated promptly, the pregnancy-induced increase in lipolysis makes patients more susceptible to DKA.
In pregnant women with type 2 diabetes, a low insulin sensitivity overlaps a pre-existing insulin resistance, necessitating insulin therapy from the start of the pregnancy to avoid DKA. The levels of maternal ketone bodies are 35% higher in the third trimester of pregnancy than postpartum [79]. The greater alveolar ventilation in pregnant women also determines a state of respiratory alkalosis, compensated by an increased renal excretion of bicarbonates, which reduces the kidney’s buffer capacity. Fetal and placental glucose needs (about 150 g/day), an increased renal

excretion of glucose, and the mother's higher glucose consumption and physiological hemodilution explain why DKA can occur more quickly and with lower blood glucose levels in diabetic women during pregnancy [79,80]. (Table 8).

DKA WITH LOWER-THAN-EXPECTED GLUCOSE LEVELS (euglycemic ketoacidosis)

Euglycemic ketoacidosis is a severe form of DKA, with serum bicarbonate levels of 10 mEq/L or slightly lower in the absence of hyperglycemia (blood glucose <14 mmol/l), reported in young individuals with T1DM, and in pregnant women with pregestational diabetes types 1 or 2, or gestational diabetes. [81,82] The use of SGLT2 inhibitors has been associated with this type of DKA, dampening enthusiasm for this new class of drugs, but a recent review found this association still rare (in <0.1% of treated patients with type 2 diabetes), and mostly related to off-label use in patients with LADA, or triggered by controllable precipitating factors such as insulin omission or dose reduction, severe acute illness, dehydration, extensive exercise, low carbohydrate diets, or excessive alcohol intake [83,84].

DEFINITION and DIAGNOSIS

The **biochemical criteria** for the **diagnosis** of DKA are [85,86]:

- Hyperglycemia (blood glucose >11mmol/L [200mg/dL])
- Venous pH <7.3 or serum bicarbonate <15mmol/L
- Ketonemia or ketonuria

Blood beta-hydroxybutyrate (BOHB) concentration ≥3mmol/L is indicative of DKA.
Urine ketones are typically moderate or large positive (≥2+).

The **severity** of DKA is categorized by the degree of acidosis [85]:

- Mild: venous pH<7.3 or serum bicarbonate <15mmol/L
- Moderate: pH<7.2, serum bicarbonate <10mmol/L
- Severe: pH 7.1, serum bicarbonate <5mmol/L

DKA is a medical emergency requiring rapid diagnosis and prompt treatment (Table 9) [87–89].

PECULIARITIES of DKA in CHILDREN

The DKA is an important mortality and morbidity cause in pediatric age. [90] The metabolic alterations, as the electrolyte disorders or cerebral edema, are responsible for an high long-term morbidity rate. [90–92]
Patients should be treated at pediatric sub-intensive or intensive care units, especially for children aged <5 years with longstanding symptoms and a risk of cerebral edema [1,93]. The team should be led by a pediatrician diabetologist with expertise in DKA therapy. The Pediatric Glasgow Coma

Scale [94] should be used for children under 36 months old, because of their limited language development.

At the moment of the first medical examination, 23% of children with onset of DMT1 are not diagnosed. [74] A diagnostic fault can increase the risk of DKA at the onset of DMT1 up to 4-fold. [56,64,95–97] The elapsed time since the last health check is longer in children with DKA (median 172 vs 263 days, P=0.01). Patients without DKA at the onset of DMT1 are submitted to ambulatory glycemic control more often and they report less symptoms at the first medical examination (compared with DKA patients). Besides, "non-DKA children" parents know diabetes symptoms and so they can suspect it. The awareness campaigns objectives should include: a bigger ambulatory use of glycemic and ketonemic test strips, increased DMT1 knowledge in the general population, a good understanding of socio-economic factors that can delay the DMT1 diagnosis[74] Among the socio-familiar causes we can find: the lack of medical insurance, the lack of time to accompany the children to the medical examination, the difficulty in setting up an appointment, problems at work (and the fear to loosing it). [74, 98]

The cerebral edema prevalence is higher in pediatric age and its pathogenesis isn't completely understood: there are some disputes about the type and the rate of infusion in the treatment of DKA because an excessive liquid intake can represent a risk factor for cerebral edema (Table 10) [99–101]

A prospective study (the PECARN FLUID study) [101] has made a comparison between acute and cronic DKA effects in 1255 children treated with two different protocols: one with rapid and the other with slow infusion; one with NaCl 0.45% and the other with NaCl 0.9% infusion. The study has disclosed no differences about cerebral edema incidence or long-term neuro-cognitive outcomes between the two protocols.[102] In the case of a liquid deficit of 5-10% replaced in 24-48 hours with the maintenance infusion (NaCl 0.45-0.9%), the risk of cerebral edema is similar in both the situations. For these therapeutic ranges, the liquid intake can be modified in order to replace the volume deficit. [85,102] The study shows that it's possible to administer all the necessary fluids, in the case of severe dehydration, but rapid overhydration should be avoided. Besides, it's possible that a slow fluid resuscitation might prolong the cytotoxic effects of dehydration and acidosis. [103]

Monitoring of acute phase of DKA should be done according the general guidelines PALS [104, 105] *(Pediatric Advanced Life Support)* and it includes glycemic and BOHB detection, the assessment of weight and height and of the dehydration severity; the state of consciousness should be evaluated through the Pediatric Glasgow Coma Scale (it is specific for children under the age of 36 months). [94]

PECULIARITIES of DKA in PREGNANT WOMEN

The symptoms of DKA are the same in pregnancy, but its onset is faster. Abdominal pain can be intense and accompanied by uterine contractions. When infection is the precipitating factor, patients may have fever or, in some cases, hypothermia [106]. The same blood tests should be

performed as in other cases of DKA, but bearing in mind that blood glucose levels may be lower in pregnant women with diabetes (normoglycemic ketoacidosis).
Intensive monitoring of maternal and fetal conditions is essential because DKA can cause fetal hypoxia and acidosis. Fetal heart rate variability should be monitored from 24 weeks of gestation onwards. The fetal biophysical profile may be abnormal, and blood flow redistributed. The timing of delivery will depend on the condition of mother and child, and their response to medical treatment. [106,107]

METHODS FOR ASSESSING DKA

Blood glucose should initially be measured hourly until it stabilizes, and electrolytes, BUN and serum creatinine every 2-4 hours, depending on the case's severity and clinical response. There is no need to obtain arterial pH. Venous pH (which is 0.02-0.15 units below arterial pH) suffices to assess response to therapy, and venous bicarbonate levels (which are 1.88 mmol/L higher than arterial levels). [108]
Beta-hydroxybutyrate (BHB) assay in blood is used to is the preferred method for assessing ketone levels. Table 11. Noyes indicates an optimal BHB descent rate of 0.5 mmol / L / h during DKA therapy. [109]

The serum anion gap is measured to provide an estimate of the plasma anions, as shown in Table 12.

Anion gap monitoring is useful as its normalization reflects the correction of DKA, though ketonuria and ketonemia may persist for more than 36 hours due to the slower removal of (chemically neutral) acetone, which occurs partly through the lungs. (Level of evidence 1+). Hyponatremia is often seen at onset, and at least partly associated with hypertriglyceridemia, which causes a reduction in the aqueous phase of the serum in which Na+ is present. Corrected sodium is calculated by formula shown in (Table 12).

The ketone body mainly increased in DKA is beta-hydroxybutyrate (BHB). Systematic BHB point-of-care tests (POCTs) are useful for monitoring DKA treatment in the presence of significant ketosis (>1.5 mmol/L) [109,110], as they are now accurate for values <3.0-4.0 mmol/l [111,112]

THERAPY

The goals of therapy in DKA are to correct acidosis, to reverse ketosis, to correct the dehydration and to normalize blood glucose level.
Treating DKA includes rehydration, administering insulin, stabilizing blood glucose, restoring normal serum potassium levels, correcting global potassium deficiencies and acidosis, and treating associated processes e.g. infections or myocardial infarction. [112,113]

**Rehydration**

This is the first mandatory step to normalize blood volume and renal perfusion and increase urinary clearance of glucose and ketone bodies. Net body water loss due to osmotic diuresis may reach 3-6 liters in DKA patients and, since the sodium lost in urine is around 70 mmol/L, the net water loss is more severe than the loss of sodium. Rehydration must be gradual, however, to avoid cerebral edema. [114,115]

Normal saline (NaCl 0.9%) infusions promptly reduces osmolarity and glucose levels by dilution and increase urinary glucose loss by improving renal perfusion. Dehydration should be corrected within 24 hours, frequently checking hemodynamics, urine output and laboratory data. Fluid overload must be avoided in patients with heart or kidney problems. [117,118]

**Insulin therapy**

Insulin lowers blood glucose levels by reducing liver glucose synthesis (rather than increasing peripheral glucose disposal), and ketone body synthesis (by lowering lipolysis and glucagon secretion), and increasing ketone body usage. Lipolysis is affected at much lower insulin concentrations than those needed to influence blood glucose [119].
Adequate insulin should reduce serum ketone bodies by 0.5 mmol/L/hour or increase circulating bicarbonates by 3 mmol/L/hour and reduce capillary blood glucose by 3 mmol/L/hour [113].
Insulin is usually administered intravenously, but intramuscular or subcutaneous routes are feasible in patients with normal hemodynamics.
*Subcutaneous insulin* should only be given to patients with mild DKA, checking glucose hourly [120]. (Level of evidence 1+) An appropriate schedule for administering subcutaneous insulin would be: 0.3 U/kg BW, then 0.1 U/kg hourly until blood glucose falls below 200 mg/dl; then 0.1 U/kg every two hours or 0.05 U/kg hourly until resolution.
*Intravenous insulin* - Several studies have shown that small doses of intravenously-administered insulin suffice for DKA.

**Glucose administration**

As soon as blood glucose levels drop to 200-250 mg/dl, normal saline is replaced with 5-10% glucose solutions. The insulin infusion rate is maintained or reduced to 0.02-0.05 U/kg/hour [1,14]. (Level of evidence 1+). Insulin and fluids are adjusted to maintain blood glucose between 150 and 200 mg/dl until the DKA episode is over [1,14]. Reducing blood glucose too quickly carries a risk of cerebral edema.

**Potassium supplementation, resolution of acidosis, and correction of other electrolyte derangements**

*Potassium supplementation*

Patients with DKA have whole-body potassium deficiency (usually 2-5 mmol/kg) due to urinary or gastrointestinal losses, so they tend to have high serum potassium levels as their intracellular potassium shifts to the extracellular space due to lack of insulin and high plasma osmolarity [121,122]. After starting treatment for DKA, their serum potassium drops (sometimes to very low values) as potassium is shifted back into the cells and lost in the urine.

Potassium is osmotically active, so when solutions containing 40 mEq/L are used in patients with high serum osmolarity, 40 mEq of potassium should be added to a liter of a hemitonic solution. The final solution will have 117 mEq of cations/L (77 mEq/L sodium plus 40 mEq/L potassium) and 75% of the osmolarity of normal saline.

**Bicarbonate administration**

Bicarbonate is not routinely recommended because most patients reach metabolic equilibrium with rehydration and insulin, especially if their arterial pH is >7.0 [1,14]. (Level of evidence 1++) However some patients benefit from alkali administration if they have a pH <7.0, a poorly perfused periphery due to impaired heart function and vasodilation, or dangerous levels of serum potassium (a bicarbonate infusion of 100 mEq in a volume of 400 ml over 2 hours is recommended if serum potassium is >6.9).

Bicarbonate administration doesn't give any advantage [85,123]; it can promote paradox acidosis in CNS and hypokalemia. [124] So, bicarbonate administration should be reserved to patients with hearth failure and pH <6.9. [125]

**Phosphate deficiency**

Global phosphate deficiency is common in DKA, but serum levels are usually normal, or even high, due to intracellular phosphate shifting to the extracellular space.

Some recommend administering phosphate if phosphatemia is <1 mg/dl (0.32 mmol/L), or patients have low Hb or PaO2 levels, or muscle weakness. In such cases 20-30 mEq of phosphate may be added to each liter of solution infused, monitoring calcium levels to avoid tetany [1,14]. (Level of evidence 2++)

**Sodium balance**

High blood glucose levels due to an increased extracellular osmolarity, make intracellular water move to the extracellular space, diluting extracellular sodium. This effect is counteracted by osmotic diuresis, so the loss of water is greater than the loss of sodium and potassium. Insulin administration reduces blood glucose and plasma osmolarity, favoring the shift of sodium inside the cells and restoring its extracellular concentration. Patients with initially normal sodium levels may consequently become hypernatremic when treated with insulin and normal saline. This can be avoided by calculating the serum sodium concentration (Table 12) to expect under the effect of administering insulin alone (corrected sodium concentration).

## Specific aspects of DKA therapy in children

About the liquid intake, initially 10ml/kg of saline solution are administered in 30-60 minutes only if poor peripheral pulses, poor capillary filling with tachycardia, and/or hypotension are present. Higher volumes are used only if low perfusion or shock signs persist after initial bolus.

The liquid infusion should be started before insulin administration; crystalloid solutions (saline) are used. All fluid loss (and the liquid requirement) should be replaced in 24-48 hours. [85,102]

Maintenance water requirement is calculated in children with specific formulas (Table 13) [85,126–128].

**Calculation of dehydration**

The calculation of dehydration degree is often inaccurate and overestimated. [129] In a study, dehydration was detected in 67% of the patients and authors recommended to consider it moderate and to adjust fluids on the basis of clinical response. [130]
Liquid intake generally isn't 1.5-2 higher than the estimated volume required (Table 14). In this liquid calculation, urinary losses are not to be considered. [131] Instead, the estimation of liquid intake must be based on ideal weight. [85]
The signs that are most frequently considered are: prolonged capillary refill (generally >2 seconds), reduced skin turgidity and abnormal breathing pattern. Besides, combinations of signs and symptoms are used to predict dehydration [132] level as absence of tears, dry mucous and compromised general condition; the presence of two or more of these signs showed a fluid deficit of at least 5%. [133] In a study there was a moderate dehydration in the greater part of patients (4-8%). [130] The clinical evaluation was a bad predictor of dehydration severity and it overestimated the dehydration level in 67% of patients. In another prospective study, dehydration was about 5,7% (median) and the rate fluid administration was 48,8 ml/Kg/h (38,5-60,3 ml/Kg/h: 25°C-75°C). [134] If there are hypotension, weak peripheral pulses and oliguria, dehydration of 10% should be suspected. [85] In the study of Ugale et al., the dehydration median was of 5,2% (interquartile range: 3,1-7,8%) and the 95% of patients presented a mild-moderate dehydration. [135] Fluid administraion seems appropriate in the majority of patients when a 6% dehydration is estimated. [135] The British Society for Paediatric Endocrinology and Diabetes (BSPED) considers a initial deydration assumption of 5% as adequate, in patients with a mild-moderate DKA (pH≥7.1). Besides, it suggest to assume a dydration level of 10% only in patients with a severe DKA (pH<7.1). [136].

A gradual correction of hyperosmolarity and a simultaneous increase of the "corrected" sodium are important objectives of rehydration. [137] In fact the "corrected" sodium represents the expected serum concentration in absence of hyperglycemia. It's very important to control corrected sodium concentrations during the therapy (Table 12), since that its increase or its decline could be a sign of impending cerebral edema (Table 10). [85]

Insulin administration is started at least an hour after the beginning of saline solution infusion (0.05-0.1 U/Kg/day). In the cases of less severe DKA, slower infusion rate have been used (0.03 U/Kg/h) in children of pre-school age. [85]

About the BOHB, the ideal rate of decrease should be 0.5mmol/L/h and about the glycemia, it should be 50-100 mg/dl/h. [85,109] For glycemic values under 250-300 mg/dl, glucose solution should be administered, in order to slow down the rate of glycemia decrease; glucose solution at 10% can be used to prevent hypoglycaemia and to provide a minimum energy intake in order to inhibit ketosis.

Even if potassium can be normal at the onset of DKA, total deficit can be up to 6 mmol/Kg. [85] Potassium administration should be delayed only in case of hyperkalaemia, after verifying adequate urine output. In case of hypokalaemia, potassium is administered already during the re-expansion phase (20mmol/L) and the start of insulin infusion can be appropriately delayed. [85] In the other cases (normal kalaemia) infusion administration is started with the maintenance and rehydration phases. The potassium is in the form of KCl + acetate (50%-50%) or KCl + phosphate (50%-50%) at a dose of 40 mmol/L. Later, the concentrations are adjusted depending on electrolytes detected values. The maximum potassium rate infusion is 0.5mmol/Kg/h. Phosphate administration is appropriate only in the case of severe hypophosphatemia, with its clinical signs (metabolic encephalopathy, cardiac and breathing failure). [85]

About the bicarbonate administration (1-2 mmol/Kg over 60 minutes), it is necessary only for extreme acidosis (pH<6.9) or in case of life-threatening hypokalaemia. [85,138]

Mannitol and hypertonic saline solution (for cerebral edema treatment) should be always available in pediatric centres specialised in DKA management. Mannitol dose is 0.5-1 g/Kg in 10-15 minutes; instead hypertonic salin (3%) dosages are 2.5-5 ml/Kg in 10-15 minutes, in alternative or in addition to mannitol or if there is no response to it in 15-30 minutes. Even if a recent meta-analysis reports a prevalent use of hypertonic salin, it's important to emphasise that it seems to be associated to higher mortality rate. [139]

In any case, cerebral edema therapy should be started when clinical criteria for its diagnosis are fulfilled, without waiting until the neuroradiological confirmation. [140]

**Resolution of DKA**

A DKA episode can be considered over when the anion gap is <12 mEq/L and patients resume eating. Serum and urine ketone levels may remain high for another 36 hours due to the slow elimination of acetone through the lungs.
Subcutaneous insulin can be administered when blood glucose is <200 mg/dl, the anion gap <12 mEq (or < the local upper limit), plasma bicarbonate ≥18 mEq/L, and venous pH >7.3.
It is important to continue venous insulin administration for 1-2 hours after starting subcutaneous insulin to avoid serum glucose or ketone body rebound.

Previously insulin-treated patients should resume their usual insulin dose, while insulin-naive patients should start with multiple daily injections for a daily insulin dose (basal + boluses) of 0.5-0.8 U/kg.

**Complications**

**Thrombosis** DKA is proinflammatory and stimulates blood coagulation, raising the risk of thrombosis [14,141,142], so prophylactic heparin may be beneficial. (Level of evidence 4).

**Cerebral edema** may complicate DKA in children, accounting for 70-80% of DKA mortality. Symptoms (altered state of consciousness) usually appear within 12-24 hours. The pathogenic mechanism remains unknown. Infusions of mannitol (0.25-1.0 g/kg ) or 3% saline (5-10 mL/kg in 30 min) are recommended [100,143–145].

**Pulmonary edema** is a rare complication of DKA, usually occurring early in patients with heart problems, and after an excessively rapid infusion of crystalloids.

**Hypoglycemia** caused by overcorrecting high blood glucose levels may stimulate counter-regulatory hormone secretion, with acidosis, cardiac arrhythmias and acute brain damage. It can be avoided by starting with 5-10% glucose infusions when blood glucose falls below 200 mg/ml.

## DKA Prevention

Strategies for the early diagnosis of T1DM help to prevent DKA, and include: health education to improve people's awareness [146]; identifying high-risk individuals based on family history, genetic and immunological screening.

Other preventive strategies are: patients' active involvement in diabetes treatment, and careful use of medication prescribed by doctors. In particular patients needs to know the importance of blood glucose monitoring (at least 4 times a day, and more frequently in case of illness, use of medication that raises blood sugar, or stress) to identify any significant variations outside normal range. Then they must be able to make insulin dose adjustment based on diabetologists' recommendations according to blood glucose levels, physical exercise, and other factors influencing glycemic control. They need to know to check on hematic or urinary ketone levels in the event of high blood glucose levels (above 250 mg/dl, or 200 mg/dl in pregnancy) in two separate, successive tests. And that if the ketone test is positive, a doctor, diabetologist or emergency service should be contacted immediately. In this context the early detection of BHB in the capillary blood is essential for patients on CSII [147,148].

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Figure 1. Flowchart of the onset of DKA

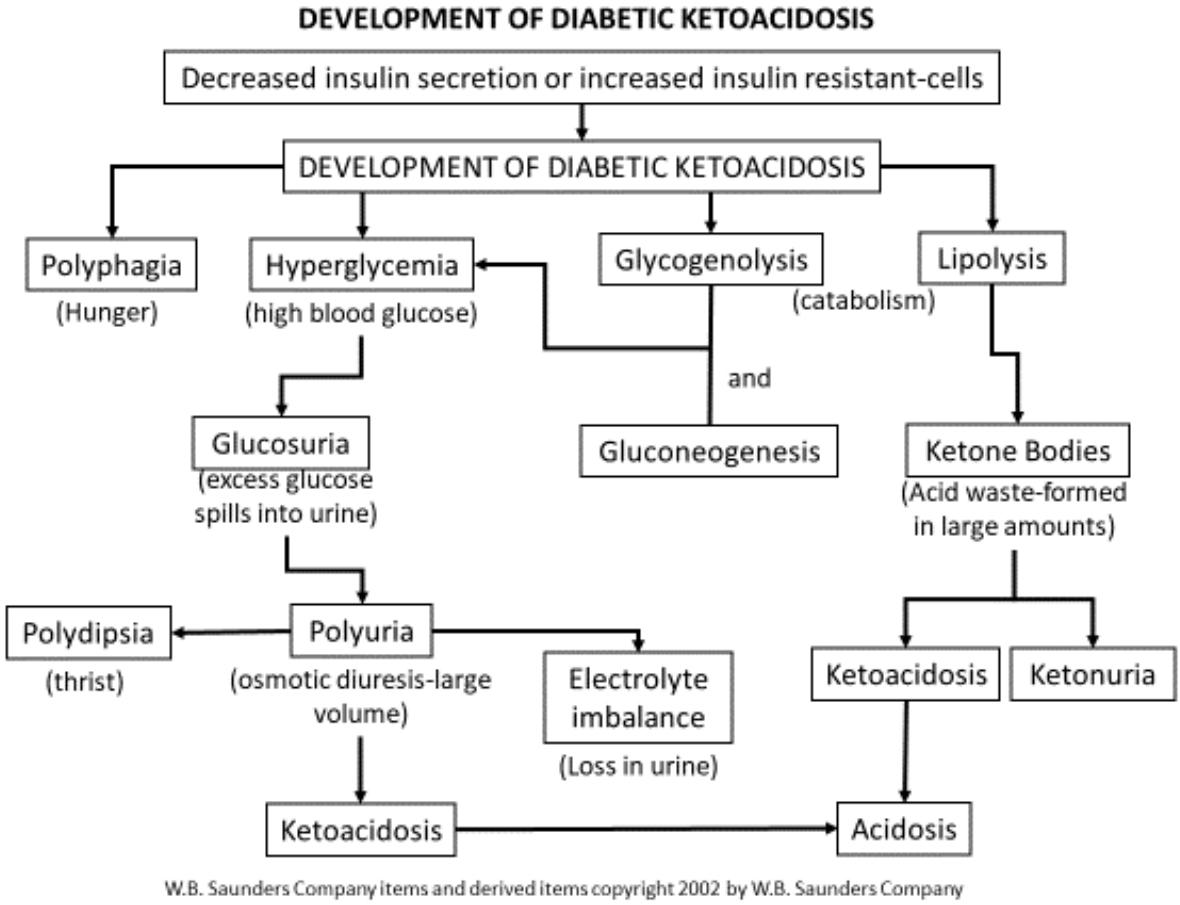
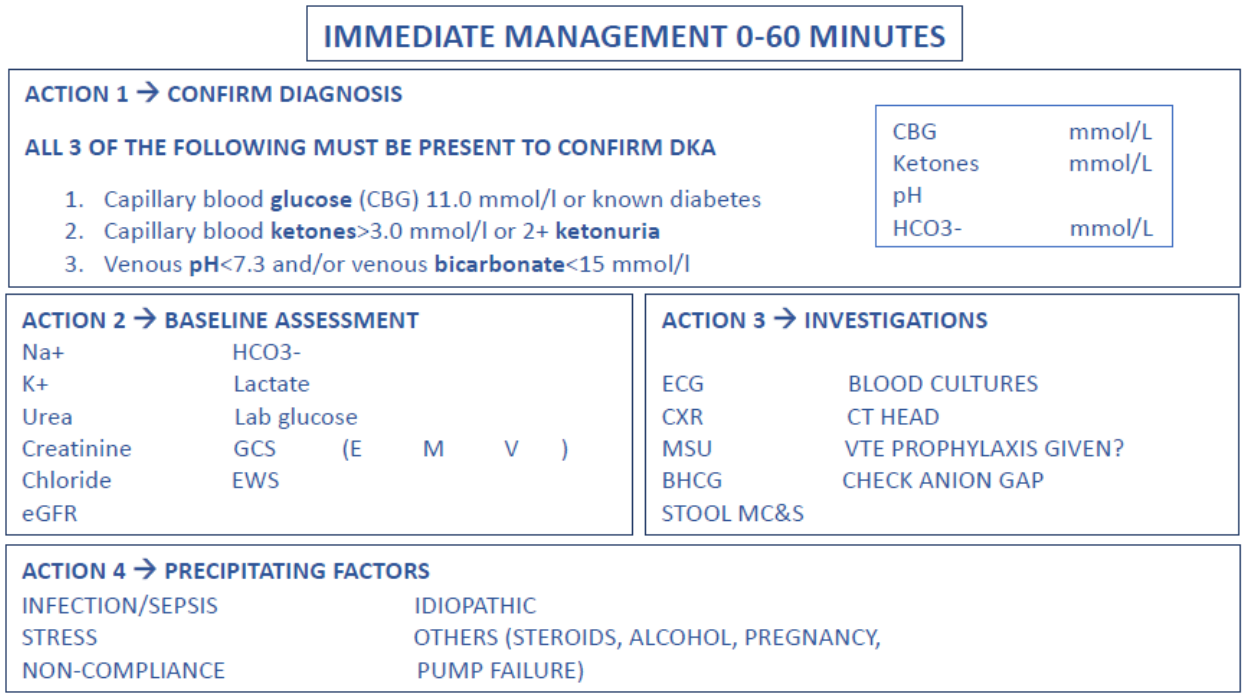


Figure 2. Adult DKA management and monitoring.



**ACTION 5 → IS THE PATIENT SHOCKED?**

**YES →** Give 500ml 0.9% NaCl over 15 mins and give another 500ml bolus over 15 mins if SBP still<100mHg (Hypotension is likely to be due to low circulating volume but consider other causes such as sepsis/heart failur etc.)

**NO →** Give 1L 0.9% NaCl over an hour

**Patient shocked (SBP<90mmHg) or severe DKA***

**SpR/Consultant informed?**
**Time:**

***Severe DKA**
Ketones>6, pH<7.1, HCO3- <5,
K+<3.5, GCS<12, SpO2<92%,
SBP<90, Pulse>100/60
Call ITU

**ACTION 6 → INSULIN** **Done?** **Initial** **Time**

- Prescribe 50 units of Actrapid in 49.5ml 0.9%NaCl (1unit/ml)
- Commence a fixed rate insulin infusion at 0.1unit/Kg/hour ☐
- Maximum 15ml/hour (starting dose)

**Weight:** Kg **Initial insulin rate:** ml(units)/hour

**If patient takes long acting insulin (e.g. Insuman Basal, Humulin I, Glargine, Levemir, Degludec, Youjeo) continue as normal** ☐ **Dose:** units

**ACTION 7 → POTASSIUM REPLACEMENT**

| **Venous K level** | **KCL replacement** |
|---|---|
| >5,5mmol/L | None |
| 3,5-5,5mmol/L | 40mmol/L |
| <3,5mmol/L | SENIOR ADVICE, additional K+ requires |

Life threatening hypokalemia can occur with insulin infusion.

☐ If k+ infusion is greater than 20mmol/hour cardiac monitoring is nedeed

DO NOT GIVE KCL IF ANURIC

**ACTION 8 → REASSESS PATIENT**

Poor urine output (<0,5ml/Kg/hour)→catheterise

Persistent vomiting or reduced CGS→ consider NGT

SpO2<94% on air → ABG/CXR

Persistent acidosis? → consider other causes

GCS<13 → consider CT head

Senior review? Name Time

## 60 MINUTES to 6 HOURS – ADMIT TO Monitored

**ACTION 1 → MONITORING**

CBG/BLOOD KETONES → HOURLY
VBG → 2,4,6,12,18 hrs
U&ES → 6,12,24 hrs
FLUID BALANCE → HOURLY
EWS → HOURLY

**PLEASE CHART THESE VALUES ON THE MONITORING CHART**

**ACTION 2 → IV FLUIDS**

1L 0.9% NaCl +/- KCl over 2 hrs (500ml/hour)
1L 0.9% NaCl +/- KCl over 2 hrs (500ml/hour)
1L 0.9% NaCl +/- KCl over 4 hrs (250ml/hour)

NOTE – Caution in elderly, CCF, ESRF, adolescence, pregnancy (risk of cerebral and pulmonary oedema)

**When CBG<14.0mmol/L add 125ml/hour of 10% glucose to run alongside 0.9% NaCl** (consider reducing rate of 0.9% NaCl to reduce risk of fluid overload)

**ACTION 3 → IV FLUID ADJUSTMENTS**

- Continue 0.9% NaCl (+KCl) as required to restore circulating volume
- Reassess patients volume status frequently (HR, BP, Urine Output, JVP, chest auscultation) and adjust fluid appropriately
- When CBG<14.0mmol/L start 10% glucose IV at 125ml/hour alongside 0.9% NaCl + KCl

**ACTION 4 → TREATMENT TARGETS** **Ensure treatment targets are being met**

1. Fall in CBG of>3mmol/L (until CBG<14.0mmol/L)
2. Fall in capillary blood ketones of>0.5mmol/L/hour
3. Rise in venous bicarbonate of>3.0mmol/L

**If the patient is not improving as expected, check the patency of the lines and infusion pumps before increasing insulin by 1-2 unit(ml)/hour**

## 6 – 12 HOURS

**ACTIONS**

- 1L 0.9% NaCl +/- KCl over 4 hours (250ml/hour)
- 1L 0.9% NaCl +/- KCl over 6 hours (125ml/hour)
- If CBG<14.0mmol/L add 10% glucose 125ml/hour, using a separate port
- Reassess CV status
- Check CBG, blood ketones, VBG, chloride, U&Es as above and signs of DKA resolution
- Ensure early referral to ThinkGlucose (TG) team

## BEYOND 12 HOURS

**RESOLUTION OF DKA**

**Resolution of DKA is defined as pH>7.3 and blood ketones<0.3mmol/L**

1. If DKA has resolved and the patient is eating and drinking – switch to SC insulin (refer to TG team)
2. If DKA has resolved but the patient cannot eat or has another indicationfor IV insulin (severe sepsis/MI)-use a VRI infusion
3. Inform DSN/TG team

**By 24 hours ketonaemia and acidosis should have been resolved. Seek senior review or Diabetes Team support if not improving**

# MONITORING CHART

| | |
|---|---|
| Surname | Reg no |
| Forename | Sex |
| Address | Date of birth |
| Cons | Ward/debt |
| | Hosp |

## TREATMENT AIMS

1. Blood ketones to fall by at least 0,5mmol/L/hour
2. Venous bicarbonate to rise by at least 3mmol/L
3. Bloog glucose to fall by at least 3mmol/L/hour

**IF THIS IS NOT BEING ACHIEVED, CHECK LINES, THEN INCREASE RATE OF INSULIN 1-2unit/hour**

## MONITORING

HOURLY CBG, CAPILLARY KETONES, Urinary Ourput
pH – 2,4,6,12,18,24 hours (or until resolved)
U+Es – 4,6,12,24 hours
EWS – hourly
RESOLUTION OF SKA: Blood ketones<0.3/L AND pH>7.3

| Hours from start of treatment (h) | | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Actual Time | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Capillary Blood Glucose (mmol/L) | >20 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 20 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 19 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 18 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 17 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 16 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Start 10% Glucose at 100ml/hour when CBG<14 | 15 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 14 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 13 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 12 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 11 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 10 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 9 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 8 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 7 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 6 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 5 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 4 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 3 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 2 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 1 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood ketones (mmol/L) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Insulin rate (ml/h) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 0.9% NaCl (ml/h) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 10% Glucose rate (ml/h) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urine Output (ml/h) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Venous pH | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Venous K+ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Venous HCO3- | | | | | | | | | | | | | | | | | | | | | | | | | | |

## Table 1. Precipitating Factors in adult and pediatric DKA

| **Causes** | |
|---|---|
| **Adults** | **ref** |
| Poor compliance with insulin therapy and skipped anti-diabetic treatment | [17–27] |
| The rates of acute cardiovascular event, stroke, venous thromboembolism | [20,21,26–28] |
| Infection (Urinary tract infection, respiratory tract infection, cellulitis, gastroenteritis) | [5,17–23,26,27,29–35] |
| Newly detected diabetes | [26][19] |
| Alcohol abuse | [17,36,37] |
| Cocaine abuse | [17,36,37] |
| Underlying medical illness (glucose-6-phosphate dehydrogenase deficiency, Acromegaly, pancreatic adenocarcinoma) | [38–43] |
| Medications (SGLT-2, Nivolumab, Pembrolizumab, Isoproterenol) | [38,44–48] |
| Diabetic ketoacidosis complicating pregnancy (67% with type 1 diabetes) | [49] |
| **Children and adolescent** | |
| insulin omission | [16,50,51] |
| Insulin error or manipulation | [51,52] |
| Viral Infection or bacterial infection | [34,51] |
| Insufficient education and inadeguate technical handling of the pump | [16,53] |
| Alcohol and drugs | [16] |

## Table 2. Risk Factors in pediatric DKA

| | |
|---|---|
| Low prevalence of T1DM in general population | [54] |
| Age (teens vs youngers) | [55–58] |
| Higher HbA1c | [55,59] |
| Duration (longer) | [55] |
| Sex (Females) | [55–57] |
| Younger children (<2-4 years of age) | [8,56,60] |
| Migration background or Etnic minority group | [8,55–57] |
| Family history of diabetes | [61] |
| Lack of private insurance | [8,56,59,62] |
| Lower body mass index | [8,56,58,60,63] |
| Developing countries | [51] |
| Limited medical care | [19] |
| Psychiatric disorders | [57,59] |
| Medical error | [64] |
| Low family income | [65] |

## Table 3. Predictors of DKA in adults with type 1 diabetes

| | |
|---|---|
| Glucose control | [66] |
| CSII | [66] |
| Smoking and alcohol consumption | [66,67] |
| Raised HDL cholesterol and triglycerides | [66] |
| Diabetic nephropathy | [66] |
| Area deprivation | [68] |
| Low socioeconomic status | [68] |
| highest in patients aged 18–30 (emerging adult) | [69] |
| Migration background | [69] |
| Diabetes duration <2 years or > 20 years | [69] |
| HbA1c > 9,0% | [69] |
| Treatment in a small center | [69] |

**Table 4. Risk Factors for Recurrent Diabetic Ketoacidosis in Adults With Type 1 Diabetes**

| | |
|---|---|
| Alcohol or illicit drug abuse | [70,71] |
| Higher glycated hemoglobin levels | [70,71] |
| Non-adherence to insulin therapy | [70,71] |
| Psychiatric illness | [70] |
| SGLT2 inhibitors consumption | [45] |
| Clinic non-attendance | [71] |

**Table 5. Risk Factors for Recurrent Diabetic Ketoacidosis in children and adolescents With Type 1 Diabetes**

| | |
|---|---|
| Higher HbA1c | [57,59] |
| Higher age | [57,72] |
| Higher Insulin dose | [57,59] |
| Sex (female) | [57][72] |
| Migration background | [57] |
| Etnic minority group | [72] |
| Publicly insured or underinsured | [59,72] |
| Psychiatric disorders | [59] |

## Table 6. Protective Factors for DKA in children

| | |
|---|---|
| High back-ground incidence of type 1 diabetes (protective) | [56] |
| Parental education (protective) | [56,73] |
| Higher parental education (protective) | [56] |
| First degree relative with Type 1 diabetes (protective) | [56] |
| increasing provider glucose and ketone testing (protective) | [74] |
| Mention of diabetes at first visit? (protective) | [74] |
| Blood glucose at first visit? (protective) | [74] |

## Table 7. Characteristics of DKA in children.

- Polyuria and nocturnal enuresis are difficult to detect in early years
- Greater propensity to produce acids
- Difficulty in estimating dehydration and in calculating fluids to be infused
- Age-related lower demand for fluids and electrolytes per kg
- Kussmaul breathing can be mistaken for dyspnea associated with asthmatic bronchitis or bronchiolitis, prompting the administration of corticosteroids
- General immaturity of homeostatic systems predisposes to cerebral edema

## Table 8. DKA triggers in pregnancy

- Fasting
- Protracted vomiting
- Infections
- Malfunctioning insulin pump
- Undiagnosed diabetes
- Poorly controlled diabetes or poor compliance
- Use of beta-sympathomimetic drugs for tocolysis
- Use of steroids for fetal lung maturation
- Diabetic gastroparesis

## Table 9. Patient assessment

**Initial patient assessment includes:**

- Heart rate and breathing, pulse and blood pressure, temperature
- State of consciousness (plasma osmolarity >330 mosm/L is associated with stupor, >350 with coma; in cases of coma at lower osmolarity, an organic cause is likely)
- Glasgow Coma Scale (GCS)
- Ventilation (acidosis is accompanied by hyperventilation and hypocapnia)
- Cardiovascular compensation
- Fluid balance
- Precipitating events (i.e. infections, myocardial infarction, malfunctioning insulin pump)

**Blood chemistry and instrumental variables to check if DKA is suspected**:

- Glucose
- Electrolytes (calculating the anion gap)
- BUN and creatinine
- Complete blood cell count
- Urinalysis with ketonuria
- Serum osmolarity (Table 12)
- Ketonemia/ketonuria
- Arterial pH and bicarbonate
- ECG
- Chest X-ray

## Table 10. Risk factors for cerebral edema

| |
|---|
| Younger age |
| New onset diabetes |
| Longer duration of symptoms |
| Greater hypocapnia at presentation |
| Increased serum urea nitrogen at presentation |
| More severe acidosis at presentation |
| A marked early decrease in serum effective osmolality |
| An attenuate rise in serum sodium concentration or an early fall in glucose-corrected sodium during therapy (see Table 12) |
| Administration of insulin in the first hour of fluid treatment |

## Table 11. Reference capillary blood BHB concentrations

| Capillary blood concentration of BHB | Interpretation and intervention |
|---|---|
| < 0.6 mmol/L | Normal |
| 0.6-1.0 mmol/L | Ketosis, adjust insulin therapy |
| 1.0-3 mmol/L | Risk of DKA; warrants medical intervention |
| > 3 mmol/L | DKA medical emergency; contact emergency department |

## Table 12. Formulas for DKA assessment and treatment

- anion gap (AG) = [Na +] - [Cl- + HCO3-]
- effective plasma osmolarity = actual measured plasma osmolarity - (BUN/28)
- effective plasma osmolarity = 2 x ([Na +] + [K +] + glucose in mg/dL/18)
- corrected serum sodium [Na +] = ([Na +] + 2 x [glucose mg/dl] - 100/100

## Table 13. Twenty-four-hour maintenance water requirement in children

| **Holliday-Segar** | |
|---|---|
| ≤10 kg | 100 mL/kg/24 hr |
| 11–20 kg | 1000 mL + 50 mL/kg/24 hr for each kg from 11–20 |
| >20 kg | 1500 mL + 20 mL/kg/24 hr for each kg >20 |
| **Simplified method (based on Holliday-Segar)** | |
| <10 kg | 4 mL/kg/hr |
| 11–20 kg | 40 + 2 mL/kg/hr for each kg between 11–20 |
| 60 + 1 mL/kg/hr for each kg >20 | |
| **Body surface area method** | |
| 1500 mL/$m^2$/24 hr | |
| | |
| Adult estimate | |
| 2–3 L/24 hrs | |

**Table 14. Suggested Daily Maintenance Fluid Replacement Rates for 5% dehydration**

| Weight (Kg) | Maintenance (ml/24 h) | 5% Dehydration (ml/24 h) | Initial Infusion rate (ml/h) |
|---|---|---|---|
| 5 | 405 | 125 | 22 |
| 10 | 1000 | 250 | 43 |
| 11 | 1050 | 275 | 46 |
| 15 | 1250 | 375 | 60 |
| 20 | 1500 | 500 | 72 |
| 40 | 1900 | 1000 | 119 |
| 60 | 2300 | 1500 | 158 |
| 80 | 2700 | 2000 | 196 |