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Diabetic ketoacidosis in children and adolescents with diabetes

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2009 Compendium*. The complete set of guidelines can be found at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 2 (the Introduction in *Pediatric Diabetes* 2009; 10 (Suppl. 12): 1–2).

Diabetic ketoacidosis (DKA) results from absolute or relative deficiency of circulating insulin and the combined effects of increased levels of the counterregulatory hormones: catecholamines, glucagon, cortisol and growth hormone (1, 2). Absolute insulin deficiency occurs in previously undiagnosed type 1 diabetes mellitus (T1DM) and when patients on treatment deliberately or inadvertently do not take insulin, especially the long-acting component of a basal-bolus regimen. Patients who use an insulin pump can rapidly develop DKA when insulin delivery fails for any reason (3). Relative insulin deficiency occurs when the concentrations of counterregulatory hormones increase in response to stress in conditions such as sepsis, trauma, or gastrointestinal illness with diarrhea and vomiting.

The combination of low serum insulin and high counterregulatory hormone concentrations results in an accelerated catabolic state with increased glucose production by the liver and kidney (via glycogenolysis and gluconeogenesis), impaired peripheral glucose utilization resulting in hyperglycemia and hyperosmolality, and increased lipolysis and ketogenesis, causing ketonemia and metabolic acidosis. Hyperglycemia that exceeds the renal threshold (approximately 10 mmol/L [180 mg/dL]) although the range in normal and diabetic individuals is very wide) and hyperketonemia cause osmotic diuresis, dehydration, and obligatory loss of electrolytes, which often is aggravated by vomiting. These changes stimulate further stress hormone production, which induces more severe insulin resistance and worsening hyperglycemia and hyperketonemia. If this cycle is not interrupted with exogenous insulin, fluid and electrolyte therapy, fatal dehydration and metabolic acidosis will ensue. Ketoacidosis may be

Table 1. Losses of fluids and electrolytes in diabetic ketoacidosis and maintenance requirements in normal children

	Average (range) losses per kg	24-hour maintenance requirements	
Water	70 mL (30–100)	*≤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
Sodium	6 mmol (5–13)		2–4 mmol†
Potassium	5 mmol (3–6)		2–3 mmol
vChloride	4 mmol (3–9)		2–3 mmol
Phosphate	(0.5–2.5) mmol		1–2 mmol

Data are from measurements in only a few children and adolescents (45–49). In any individual patient, actual losses may be less or greater than the ranges shown in Table 1 (E). Three methods for determining maintenance water requirements in children are commonly used: *the Holliday-Segar formula (50) (shown in Table 1), a simplified Holliday-Segar formula (see below and Appendix), and a formula based on body surface area for children more than 10 kg (1,500 mL/m^2/24 hr) (51).
† Maintenance electrolyte requirements in children are per 100 mL of maintenance IV fluid (51, 52).
† 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 and 20; >20 kg 60 + 1 mL/kg/h for each kg >20.

aggravated by lactic acidosis from poor tissue perfusion or sepsis.

DKA is characterized by severe depletion of water and electrolytes from both the intra- and extracellular fluid compartments; the range of losses is shown in Table 1. Despite their dehydration, patients continue to maintain normal blood pressure and have considerable urine output until extreme volume depletion and shock occurs leading to a critical decrease in renal blood flow and glomerular filtration. At presentation, the magnitude of specific deficits in an individual patient varies depending upon the duration and severity of illness, the extent to which the patient was able to maintain intake of fluid and electrolytes, and the content of food and fluids consumed before coming to medical attention. Consumption of fluids with a high-carbohydrate content (juices or sugar containing soft drinks) exacerbate the hyperglycemia (4).

Clinical manifestations of diabetic ketoacidosis

- Dehydration
- Rapid, deep, sighing (Kussmaul respiration)
- Nausea, vomiting, and abdominal pain mimicking an acute abdomen
- Progressive obtundation and loss of consciousness
- Increased leukocyte count with left shift
- Non-specific elevation of serum amylase
- Fever only when infection is present

Definition of diabetic ketoacidosis (DKA)

The **biochemical criteria** for the diagnosis of DKA are (5):

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

Partially treated children and children who have consumed little or no carbohydrate may have, on rare occasion, only modestly increased blood glucose concentrations (“euglycemic ketoacidosis”) (6, 7).

Type 2 diabetes mellitus (T2DM), associated with increased rates and severity of obesity, in some centers now accounts for as much as one half of newly diagnosed diabetes in children aged 10 to 21 years, depending on the socioeconomic and ethnic composition of the population (8). Acute decompensation with DKA has been recognized to occur at the time of diagnosis in as many as 25% of children with T2DM (8). This is more likely in those of African-American descent, less so in Hispanic, and least in Canadian First Nation teenagers (9–14). The majority of new cases of diabetes in Japanese children and adolescents are detected in asymptomatic individuals by routine urine screening (15, 16); however, overall, approximately 5% of patients with type 2 diabetes have DKA at the time of diagnosis (17).

The **severity of DKA** is categorized by the degree of acidosis (18):

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

Hyperglycemic hyperosmolar state (HHS), also referred to as hyperosmolar nonketotic coma, may occur in young patients with T2DM (19–21), but rarely in T1DM subjects. **The criteria for HHS** include (22):

- plasma glucose concentration >33.3 mmol/L (600 mg/dL)

- arterial pH >7.30
- serum bicarbonate >15 mmol/L
- small ketonuria, absent to mild ketonemia
- effective serum osmolality >320 mOsm/kg
- stupor or coma

It is important to recognize that overlap between the characteristic features of HHS and DKA may occur. Some patients with HHS, especially when there is very severe dehydration, have mild or moderate acidosis. Conversely, some children with T1DM may have features of HHS (severe hyperglycemia) if high carbohydrate containing beverages have been used to quench thirst and replace urinary losses prior to diagnosis (4). Therapy must be appropriately modified to address the pathophysiology and unique biochemical disturbances of each individual patient.

Frequency of DKA

At disease onset

There is wide geographic variation in the frequency of DKA at onset of diabetes; rates inversely correlate with the regional incidence of T1DM. Frequencies range from approximately 15% to 70% in Europe and North America (A) (23–27). DKA at diagnosis is more common in younger children (<5 years of age), and in children whose families do not have ready access to medical care for social or economic reasons (A) (7) (27–30).

In children with established diabetes (recurrent DKA)

The risk of DKA in established T1DM is 1–10% per patient per year (A, C) (3, 31–34):

Risk is increased in (34):

- children with poor metabolic control or previous episodes of DKA
- peripubertal and adolescent girls
- children with psychiatric disorders, including those with eating disorders
- children with difficult or unstable family circumstances
- children who omit insulin (33) (C)
- children with limited access to medical services
- insulin pump therapy (as only rapid- or short-acting insulin is used in pumps, interruption of insulin delivery for any reason rapidly leads to insulin deficiency) (3) (C)

Management of DKA

Emergency Assessment

- Perform a clinical evaluation to **confirm the diagnosis** and determine its cause Carefully look for evidence of infection. In recurrent DKA, insulin omission or failure to follow sick day or pump failure management guidelines accounts for almost all episodes, except for those caused by acute severe febrile or gastrointestinal illness.

  Weigh the patient. This weight should be used for calculations and not the weight from a previous office visit or hospital record.
- **Assess clinical severity of dehydration**.
- Clinical assessment of dehydration is imprecise, inaccurate and generally shows only fair to moderate agreement among examiners. It should be based on a combination of physical signs. The three most useful individual signs for assessing dehydration in young children and predicting at least 5% dehydration and acidosis are:
  - o prolonged capillary refill time (normal capillary refill is $\leqslant$ 1.5-2 seconds)
  - o abnormal skin turgor ('tenting' or inelastic skin)
  - o hyperpnea (35).
- Other useful signs in assessing degree of dehydration include: dry mucus membranes, sunken eyes, absent tears, weak pulses, cool extremities. More signs of dehydration tend to be associated with more severe dehydration (35).
  - o $\geq$10% dehydration is suggested by the presence of weak or impalpable peripheral pulses, hypotension, and oliguria.
- **Assess level of consciousness** (Glasgow coma scale [GCS] - see Table 2) (36).

Biochemical assessment

- Obtain a **blood sample for laboratory measurement** of serum or plasma glucose, electrolytes (including bicarbonate or total carbon dioxide), blood urea nitrogen, creatinine, osmolality, venous (or arterial in critically ill patient) pH, pCO_2, calcium, phosphorus, and magnesium concentrations (if possible), HbA1c, hemoglobin and hematocrit or complete blood count. Note, however, that an elevated white blood cell count in response to stress is characteristic of DKA and is not necessarily indicative of infection (30).
- Perform a **urinalysis** for ketones.
- Measurement of blood ß-hydroxybutyrate concentration, if available, is useful to confirm ketoacidosis and may be used to monitor the response to treatment (37–39).
- Obtain appropriate **specimens for culture** (blood, urine, throat), if there is evidence of infection.
- If laboratory measurement of serum potassium is delayed, perform an **electrocardiogram** (ECG) for baseline evaluation of potassium status (40, 41).

Table 2. Glasgow coma scale or score (GCS). The GCS consists of three parameters and is scored between 3 and 15; 3 being the worst and 15 the best (36). One of the components of the GCS is the best verbal response, which cannot be assessed in non-verbal young children. A modification of the GCS was created for children too young to talk.

Best eye response	Best verbal response	Best verbal response (nonverbal children)	Best motor response
1. No eye opening	1. No verbal response	1. No response	1. No motor response
2. Eyes open to pain	2. No words, only incomprehensible sounds; moaning	2. Inconsolable, irritable, restless, cries	2. Extension to pain (decerebrate posture)
3. Eyes open to verbal command	3. Words, but incoherent*	3. Inconsistently consolable and moans; makes vocal sounds	3. Flexion to pain (decorticate posture)
4. Eyes open spontaneously	4. Confused, disoriented conversation†	4. Consolable when crying and interacts inappropriately	4. Withdrawal from pain
	5. Orientated, normal conversation	5. Smiles, oriented to sound, follows objects and interacts	5. Localizes pain 6. Obeys commands

*Inappropriate words, random or exclamatory articulated speech, but no sustained conversational exchange.
†Attention can be held; patient responds to questions coherently, but there is some disorientation and confusion.

Supportive measures

- **Secure the airway** and if there is deterioration in conscious level, empty the stomach by continuous nasogastric suction to prevent pulmonary aspiration.
- A **peripheral intravenous (IV) catheter** should be placed for convenient and painless repetitive blood sampling. An **arterial catheter** may be necessary in some critically ill patients managed in an intensive care unit.
- A **cardiac monitor** should be used for continuous electrocardiographic monitoring to assess T-waves for evidence of hyper- or hypokalemia (40, 41).
- Give **oxygen** to patients with severe circulatory impairment or shock.
- **Give antibiotics** to **febrile patients** after obtaining appropriate cultures of body fluids.
- Catheterization of the bladder usually is not necessary, but if the child is unconscious or unable to void on demand (e.g., infants and very ill young children) the bladder should be catheterized.

Where should the child be managed?

The child should receive care in a unit that has:

- Experienced nursing staff trained in monitoring and management
- Written guidelines for DKA management in children
- Access to laboratories that can provide frequent and timely measurements of biochemical variables
- Effective osmolality (mOsm/kg) = 2x

A specialist/consultant pediatrician with training and expertise in the management of DKA should direct inpatient management.

Children with severe DKA (long duration of symptoms, compromised circulation, or depressed level of consciousness) or those who are at increased risk for cerebral edema (e.g., <5 years of age, severe acidosis, low pCO_2, high blood urea nitrogen) should be considered for immediate treatment in an intensive care unit (pediatric, if available) or in a unit that has equivalent resources and supervision, such as a children's ward specializing in diabetes care (C,E) (5, 42).

In a child with **established diabetes**, whose parents have been trained in sick day management, hyperglycemia and ketosis without vomiting or severe dehydration can be managed at home or in an outpatient health care facility (e.g., emergency ward), provided an experienced diabetes team supervises the care (C,E) (18, 43, 44).

Further clinical and biochemical monitoring

Successful management of DKA and HHS requires **meticulous monitoring** of the patient's clinical and biochemical response to treatment so that timely adjustments in treatment can be made when indicated by the patient's clinical or laboratory data (E).

There should be documentation on a **flow chart** of hour-by-hour clinical observations, IV and oral medications, fluids, and laboratory results. Monitoring should include the following:

- Hourly (or more frequently as indicated) **vital signs** (heart rate, respiratory rate, blood pressure)
- Hourly (or more frequently as indicated) **neurological observations** (Glasgow coma score) for warning signs and symptoms of cerebral edema (see below)
  - headache
  - inappropriate slowing of heart rate
  - recurrence of vomiting
  - change in neurological status (restlessness, irritability, increased drowsiness, incontinence) or

specific neurologic signs (e.g., cranial nerve palsies, abnormal pupillary responses)
  - o rising blood pressure
  - o decreased oxygen saturation

- Amount of administered insulin
- Hourly (or more frequently as indicated) accurate **fluid input** (including all oral fluid) **and output**.
- **Capillary blood glucose** should be measured hourly (but must be cross-checked against laboratory venous glucose, as capillary methods may be inaccurate in the presence of poor peripheral circulation and acidosis).
- **Laboratory tests**: serum electrolytes, glucose, blood urea nitrogen, calcium, magnesium, phosphorus, hematocrit, and blood gases should be repeated 2-hourly for the first 12 hours, or more frequently, as clinically indicated, in more severe cases.
- Urine ketones until cleared or blood ß-hydroxybutyrate (BOHB) concentrations, if available, every 2 hours (38, 39).
- If the laboratory cannot provide timely results, a portable biochemical analyzer that measures plasma glucose, serum electrolytes and blood ketones on fingerstick blood samples at the bedside is a useful adjunct to laboratory-based determinations.
- **Additional calculations that may be informative:**
  - Anion gap = Na − (Cl + HCO3): normal is 12 ± 2 (mmol/L)
  - In DKA the anion gap is typically 20–30 mmol/L; an anion gap >35 mmol/L suggests concomitant lactic acidosis (E)
  - Corrected sodium = measured Na + 2([plasma glucose −5.6]/5.6) (mmol/L)
  - Effective osmolality = (mOsm/kg) 2x(Na + K) + glucose (mmol/L)

Goals of therapy

- Correct dehydration
- Correct acidosis and reverse ketosis
- Restore blood glucose to near normal
- Avoid complications of therapy
- Identify and treat any precipitating event

Fluids and salt

Patients with DKA have a deficit in extracellular fluid (ECF) volume that usually is in the range 5–10% **(C)** (45, 46). Shock with hemodynamic compromise is rare in pediatric DKA. Clinical estimates of the volume deficit are subjective and inaccurate (53, 54); therefore, in moderate DKA use 5–7% and in severe DKA 7–10% dehydration.

The effective osmolality (formula above) is frequently in the range of 300–350 mmol/Kg. Increased serum urea nitrogen and hematocrit may be useful markers of the severity of ECF contraction (44, 55). The serum sodium concentration is an unreliable measure of the degree of ECF contraction for two reasons: (1) glucose, largely restricted to the extracellular space, causes osmotic movement of water into the extracellular space thereby causing dilutional hyponatremia (56, 57) and, (2) the low sodium content of the elevated lipid fraction of the serum in DKA. The latter is not a concern with most modern methods for measuring sodium. Therefore, it is important to calculate the corrected sodium (using the above formula) and monitor its changes throughout the course of therapy. As the plasma glucose concentration decreases after administering fluid and insulin, the measured serum sodium concentration should increase, but it is important to appreciate that this does not indicate a worsening of the hypertonic state. A failure of measured serum sodium levels to rise or a further decline in serum sodium levels with therapy is thought to be a potentially ominous sign of impending cerebral edema (58–60).

The objectives of fluid and electrolyte replacement therapy are:

- Restoration of circulating volume
- Replacement of sodium and the ECF and intracellular fluid deficit of water
- Improved glomerular filtration with enhanced clearance of glucose and ketones from the blood
- Reduction of risk of cerebral edema

Principles of Water and Salt Replacement

Despite much effort to identify the cause of cerebral edema its pathogenesis is incompletely understood. There is no convincing evidence of an association between the rate of fluid or sodium administration used in the treatment of DKA and the development of cerebral edema (61). No treatment strategy can be definitively recommended as being superior to another based on evidence. The principles described below were developed after a comprehensive review of the literature and were accepted and endorsed by a panel of expert physicians representing the Lawson Wilkins Pediatric Endocrine Society (LWPES), the European Society for Paediatric Endocrinology (ESPE), and the International Society for Pediatric and Adolescent Diabetes (ISPAD) (5, 62).

- Water and salt deficits must be replaced (A).
- IV or oral fluids that may have been given in another facility before assessment should be factored into calculation of deficit and repair (E).
- For patients who are severely volume depleted but not in shock, volume expansion (resuscitation)

should begin immediately with 0.9% saline to restore the peripheral circulation (E).

- In the rare patient with DKA who presents in shock, rapidly restore circulatory volume with isotonic saline (or Ringer's lactate) in 20 mL/kg boluses infused as quickly as possible through a large bore cannula with reassessment after each bolus.
  - o The volume and rate of administration depends on circulatory status and, where it is clinically indicated, the volume administered typically is 10 mL/kg/h over 1–2 hours, and may be repeated if necessary (E).
  - o Use crystalloid not colloid (E). There are no data to support the use of colloid in preference to crystalloid in the treatment of DKA.
- *Subsequent* fluid management (deficit replacement) should be with 0.9% saline or Ringer's acetate for at least 4–6 hours (C,E) (55, 58, 63–65).
  - o Thereafter, deficit replacement should be with a solution that has a tonicity equal to or greater than 0.45% saline with added potassium chloride, potassium phosphate or potassium acetate (see below under potassium replacement) (C,E) (55, 58, 63, 66, 67).
  - o The rate of fluid (IV and oral) should be calculated to rehydrate evenly over 48 hours (C, E) (5, 55).
  - o As the severity of dehydration may be difficult to determine and frequently is under- or overestimated (C) (54), infuse fluid each day at a rate rarely in excess of 1.5–2 times the usual daily maintenance requirement based on age, weight, or body surface area (E) (5). See Tables 1 and 3 for examples of calculations.
- In addition to clinical assessment of dehydration, calculation of effective osmolality may be valuable to guide fluid and electrolyte therapy (E).
- Urinary losses should not routinely be added to the calculation of replacement fluid, but may be necessary in rare circumstances (E).
- The sodium content of the fluid may need to be increased if measured serum sodium is low and does not rise appropriately as the plasma glucose concentration falls (C) (58, 68).
- The use of large amounts of 0.9% saline has been associated with the development of hyperchloremic metabolic acidosis (69, 70).

Insulin therapy

DKA is caused by a decrease in effective circulating insulin associated with increases in counter-regulatory hormones (glucagon, catecholamines, GH, cortisol). Although rehydration alone causes some decrease in blood glucose concentration (71, 72), insulin therapy is essential to normalize blood glucose and suppress lipolysis and ketogenesis (A) (73).

Extensive evidence indicates that **'low dose'** IV insulin administration should be the standard of care (A) (74).

- Start insulin infusion 1–2 hours after starting fluid replacement therapy; i.e. after the patient has received initial volume expansion (E,C) (75).

Table 3. This table shows an alternative example of fluid volumes for the subsequent phase of rehydration

Body weight kg	Maintenance mL/24 h	DKA: Give maintenance + 5% of body weight/24-h	
		mL/24 h	mL/h
4	325	530	22
5	405	650	27
6	485	790	33
7	570	920	38
8	640	1040	43
9	710	1160	48
10	780	1280	53
11	840	1390	58
12	890	1490	62
13	940	1590	66
14	990	1690	70
15	1030	1780	74
16	1070	1870	78
17	1120	1970	82
18	1150	2050	85
19	1190	2140	89
20	1230	2230	93
22	1300	2400	100
24	1360	2560	107
26	1430	2730	114
28	1490	2890	120
30	1560	3060	128
32	1620	3220	134
34	1680	3360	140
36	1730	3460	144
38	1790	3580	149
40	1850	3700	154
45	1980	3960	165
50	2100	4200	175
55	2210	4420	184
60	2320	4640	193
65	2410	4820	201
70	2500	5000	208
75	2590	5180	216
80	2690	5380	224

*After initial resuscitation, and assuming 10% dehydration, the total amount of fluid should be given over 48 hours. Table 3 gives volumes for maintenance and rehydration per 24 hours and per hour. If fluid has been given for resuscitation, the volume should **not** be subtracted from the amount shown in the table. Fluids given orally (when patient has improved) **should** be subtracted from the amount in the table. Table 3 is based on maintenance volumes according to Darrrow (152). For body weights >32 kg, the volumes have been adjusted so as not to exceed twice the maintenance rate of fluid administration.

- Correction of insulin deficiency
  - o Dose: 0.1 unit/kg/hour (for example, one method is to dilute 50 units regular [soluble] insulin in 50 mL normal saline, 1 unit = 1 mL) (74, 76)
  - o Route of administration IV (A)
  - o An IV bolus is unnecessary (77), may increase the risk of cerebral edema (75), and should *not* be used at the start of therapy (C)
- The dose of insulin should usually remain at 0.1 unit/kg/hour at least until resolution of DKA (pH >7.30, bicarbonate >15 mmol/L and/or closure of the anion gap), which invariably takes longer than normalization of blood glucose concentrations (B) (78).
- If the patient demonstrates marked sensitivity to insulin (e.g., some young children with DKA, patients with HHS, and some older children with established diabetes), the dose may be decreased to 0.05 unit/kg/hour, or less, provided that metabolic acidosis continues to resolve.
- During initial volume expansion the plasma glucose concentration falls steeply (71) (C). Thereafter, and after commencing insulin therapy, the plasma glucose concentration typically decreases at a rate of 2–5 mmol/L/hour, depending on the timing and amount of glucose administration (C) (79–85).
- To prevent an unduly rapid decrease in plasma glucose concentration and hypoglycemia, 5% glucose should be added to the IV fluid (e.g., 5% glucose in 0.45% saline) when the plasma glucose falls to approximately 14–17 mmol/L (250–300 mg/dL), or sooner if the rate of fall is precipitous (B).
  - o It may be necessary to use 10% or even 12.5% dextrose to prevent hypoglycemia while continuing to infuse insulin to correct the metabolic acidosis.
- If BG falls very rapidly (>5 mmol/L/h) after initial fluid expansion, consider adding glucose even before plasma glucose has decreased to 17 mmol/L (E).
- If biochemical parameters of DKA (pH, anion gap) do not improve, reassess the patient, review insulin therapy, and consider other possible causes of impaired response to insulin; e.g., infection, errors in insulin preparation (E).
- In circumstances where continuous IV administration is not possible, hourly or 2-hourly SC or IM administration of a short- or rapid-acting insulin analog (insulin lispro or insulin aspart) is safe and may be as effective as IV regular insulin infusion (C) (80, 86–89), but should not be used in subjects whose peripheral circulation is impaired (E).
  - o Initial dose SC: 0.3 unit/kg, followed 1 hour later by SC insulin lispro or aspart at 0.1 unit/kg every hour, or 0.15–0.20 units/kg every two hours.
  - o If blood glucose falls to <14 mmol/L (250 mg/dL) before DKA has resolved, (pH still <7.30), add 5% glucose and continue with insulin as above.
  - o Aim to keep blood glucose at about 11 mmol/L (200 mg/dL) until resolution of DKA.

Potassium replacement

Children with DKA suffer total body potassium deficits of the order of 3 to 6 mmol/kg (45–49). The major loss of potassium is from the intracellular pool. Intracellular potassium is depleted because of transcellular shifts of this ion caused by hypertonicity (increased plasma osmolality causes solvent drag in which water and potassium are drawn out of cells) and glycogenolysis and proteolysis secondary to insulin deficiency cause potassium efflux from cells. Potassium is lost from the body from vomiting and as a consequence of osmotic diuresis. Volume depletion causes secondary hyperaldosteronism, which promotes urinary potassium excretion. Thus, total body depletion of potassium occurs, but at presentation serum potassium levels may be normal, increased or decreased (90). Renal dysfunction, by enhancing hyperglycemia and reducing potassium excretion, contributes to hyperkalemia (90). Administration of insulin and the correction of acidosis will drive potassium back into the cells, decreasing serum levels (91). The serum potassium concentration may decrease abruptly, predisposing the patient to cardiac arrhythmias.

- Replacement therapy is required regardless of the serum potassium concentration (A) (92, 93).
- If the patient is hypokalemic, start potassium replacement *at the time of* initial volume expansion and before starting insulin therapy. Otherwise, start replacing potassium *after* initial volume expansion and concurrent with starting insulin therapy. If the patient is hyperkalemic, *defer* potassium replacement therapy until urine output is documented (E).
- If immediate serum potassium measurements are unavailable, an ECG may help to determine whether the child has hyper- or hypokalemia (C) (40, 41). Flattening of the T wave, widening of the QT interval, and the appearance of U waves indicate hypokalemia. Tall, peaked, symmetrical, T waves and shortening of the QT interval are signs of hyperkalemia.
- The starting potassium concentration in the infusate should be 40 mmol/L. Subsequent potassium replacement therapy should be based on serum potassium measurements (E).
  - o If potassium is given with the initial rapid volume expansion, a concentration of 20 mmol/L should be used.

- Potassium phosphate may be used together with potassium chloride or acetate; e.g., 20 mmol/L potassium chloride and 20 mmol/L potassium phosphate or 20 mmol/L potassium phosphate and 20 mmol/L potassium acetate (C,E).
- Potassium replacement should continue throughout IV fluid therapy (E).
- The maximum recommended rate of intravenous potassium replacement is usually 0.5 mmol/kg/hr (E).
- If hypokalemia persists despite a maximum rate of potassium replacement, then the rate of insulin infusion can be reduced.

Phosphate

Depletion of intracellular phosphate occurs in DKA and phosphate is lost as a result of osmotic diuresis (45–47). Plasma phosphate levels fall after starting treatment and this is exacerbated by insulin, which promotes entry of phosphate into cells (94–96). Total body phosphate depletion has been associated with a variety of metabolic disturbances (97–99). Clinically significant hypophosphatemia may occur if intravenous therapy without food intake is prolonged beyond 24 hours (45–47).

- Prospective studies have not shown clinical benefit from phosphate replacement (A) (100–105).
- Severe hypophosphatemia in conjunction with unexplained weakness should be treated (E) (106).
- Administration of phosphate may induce hypocalcemia (C) (107, 108).
- Potassium phosphate salts may be safely used as an alternative to or combined with potassium chloride or acetate, provided that careful monitoring of serum calcium is performed to avoid hypocalcemia (C) (107, 108).

Acidosis

Severe acidosis is reversible by fluid and insulin replacement; insulin stops further ketoacid production and allows ketoacids to be metabolized, which generates bicarbonate (A). Treatment of hypovolemia improves tissue perfusion and renal function, thereby increasing the excretion of organic acids.

Controlled trials have shown no clinical benefit from bicarbonate administration (B,C) (109–112). Bicarbonate therapy may cause paradoxical CNS acidosis (113, 114); rapid correction of acidosis with bicarbonate causes hypokalemia (113, 115, 116), and failure to account for the sodium being administered and appropriately reducing the NaCl concentration of the fluids can result in increasing osmolality (113). Nevertheless, there may be selected patients who may benefit from *cautious* alkali therapy. These include: patients with severe acidemia (arterial pH <6.9) in whom decreased cardiac contractility and peripheral vasodilatation can further impair tissue perfusion, and patients with life-threatening hyperkalemia (E) (117).

- Bicarbonate administration is not recommended unless the acidosis is profound and likely to affect adversely the action of adrenaline/epinephrine during resuscitation (A).
- If bicarbonate is considered necessary, cautiously give 1–2 mmol/kg over 60 minutes (E).

Complications of therapy
- Inadequate rehydration
- Hypoglycemia
- Hypokalemia
- Hyperchloremic acidosis
- Cerebral edema

Introduction of oral fluids and transition to SC insulin injections

- Oral fluids should be introduced only when substantial clinical improvement has occurred (mild acidosis/ketosis may still be present) (E).
- When oral fluid is tolerated, IV fluid should be reduced (E).
- When ketoacidosis has resolved, oral intake is tolerated, and the change to SC insulin is planned, the most convenient time to change to SC insulin is just before a mealtime (E).
- To prevent rebound hyperglycemia the first SC injection should be given 15–30 minutes (with rapid-acting insulin) or 1–2 hours (with regular insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed (E). With intermediate- or long-acting insulin, the overlap should be longer and the IV insulin gradually lowered. For example, for patients on a basal-bolus insulin regimen, the first dose of basal insulin may be administered in the evening and the insulin infusion is stopped the next morning (E).
- The dose and type of SC insulin should be according to local preferences and circumstances.
- After transitioning to SC insulin, frequent blood glucose monitoring is required to avoid marked hyperglycemia and hypoglycemia (E).

Morbidity and mortality

In national population studies, the mortality rate from DKA in children is 0.15% to 0.30% (C,B) (118, 119). Cerebral edema accounts for 60% to 90% of all DKA deaths (C,B) (60, 120). From 10% to 25% of survivors

of cerebral edema have significant residual morbidity (C,B) (60, 120, 121).
Other rare causes of morbidity and mortality include:

- Hypokalemia
- Hyperkalemia
- Severe hypophosphatemia
- Hypoglycemia
- Other central nervous system complications (disseminated intravascular coagulation, dural sinus thrombosis, basilar artery thrombosis)
- Peripheral venous thrombosis
- Sepsis
- Rhinocerebral or pulmonary mucormycosis
- Aspiration pneumonia
- Pulmonary edema
- Adult respiratory distress syndrome (ARDS)
- Pneumothorax, pneumomediastinum and subcutaneous emphysema
- Rhabdomyolysis
- Acute renal failure
- Acute pancreatitis (122)

Cerebral edema

The incidence of cerebral edema in national population studies is 0.5–0.9% and the mortality rate is 21–24% (60, 120, 121). The pathogenesis of both its initiation and progression is unclear and incompletely understood. Demographic factors that have been associated with an increased risk of cerebral edema include:

- Younger age (C) (123)
- New onset diabetes (B) (119) (C) (123)
- Longer duration of symptoms (C) (124)

These risk associations may reflect the greater likelihood of severe DKA.

Epidemiological studies have identified several potential risk factors at diagnosis or during treatment of DKA. These include:

- Greater hypocapnia at presentation after adjusting for degree of acidosis (C) (60, 125, 126)
- Increased serum urea nitrogen at presentation (C) (60, 126)
- More severe acidosis at presentation (C) (75, 127)
- Bicarbonate treatment for correction of acidosis (C) (60, 128)
- An attenuated rise in measured serum sodium concentrations during therapy (C) (58–60)
- Greater volumes of fluid given in the first 4 hours (75)
- Administration of insulin in the first hour of fluid treatment (75)

Evidence for disruption of the blood–brain barrier has been found in cases of fatal cerebral edema associated with DKA (129). In recent studies, the degree of edema formation during DKA in children correlates with the degree of dehydration and hyperventilation at presentation, but not with factors related to initial osmolality or osmotic changes during treatment. These data have been interpreted as supporting the hypothesis that cerebral edema is related to cerebral hypoperfusion during DKA, and that osmotic fluctuations during DKA treatment do not play a primary causal role (126).

Warning signs and symptoms of cerebral edema include:

- Headache & slowing of heart rate
- Change in neurological status (restlessness, irritability, increased drowsiness, incontinence)
- Specific neurological signs (e.g., cranial nerve palsies)
- Rising blood pressure
- Decreased O_2 saturation

Clinically significant cerebral edema usually develops 4–12 hours after treatment has started, but can occur before treatment has begun (60, 121, 130–133) or, rarely, may develop as late as 24–48 hours after the start of treatment (C,B) (60, 123, 134). Symptoms and signs are variable. A method of clinical diagnosis based on bedside evaluation of neurological state is shown below (C) (135):

Diagnostic criteria

- Abnormal motor or verbal response to pain
- Decorticate or decerebrate posture
- Cranial nerve palsy (especially III, IV, and VI)
- Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne-Stokes respiration, apneusis)

Major criteria

- Altered mentation/fluctuating level of consciousness
- Sustained heart rate deceleration (decrease more than 20 beats per minute) not attributable to improved intravascular volume or sleep state
- Age-inappropriate incontinence

Minor criteria

- Vomiting
- Headache
- Lethargy or not easily arousable

- Diastolic blood pressure >90 mm Hg
- Age <5 years

One diagnostic criterion, two major criteria, or one major and two minor criteria have a sensitivity of 92% and a false positive rate of only 4%.

A chart with the reference ranges for blood pressure and heart rate, which vary depending on height, weight, and gender, should be readily available, either in the patient's chart or at the bedside.

Treatment of cerebral edema

- Initiate treatment as soon as the condition is suspected.
- Reduce the rate of fluid administration by one-third.
- Give mannitol 0.5–1 g/kg IV over 20 minutes and repeat if there is no initial response in 30 minutes to 2 hours (C,E) (136–138).
- Hypertonic saline (3%), 5–10 mL/kg over 30 minutes, may be an alternative to mannitol or a second line of therapy if there is no initial response to mannitol (C) (139, 140).
  - Mannitol or hypertonic saline should be available at the bedside
- Elevate the head of the bed
- Intubation may be necessary for the patient with impending respiratory failure, but aggressive hyperventilation (to a pCO_2 <2.9 kPa [22 mm Hg]) has been associated with poor outcome and is not recommended (C) (141).
- *After* treatment for cerebral edema has been started, a cranial CT scan should be obtained to rule out other possible intracerebral causes of neurologic deterioration (≈10% of cases), especially thrombosis (142–145) or hemorrhage, which may benefit from specific therapy.

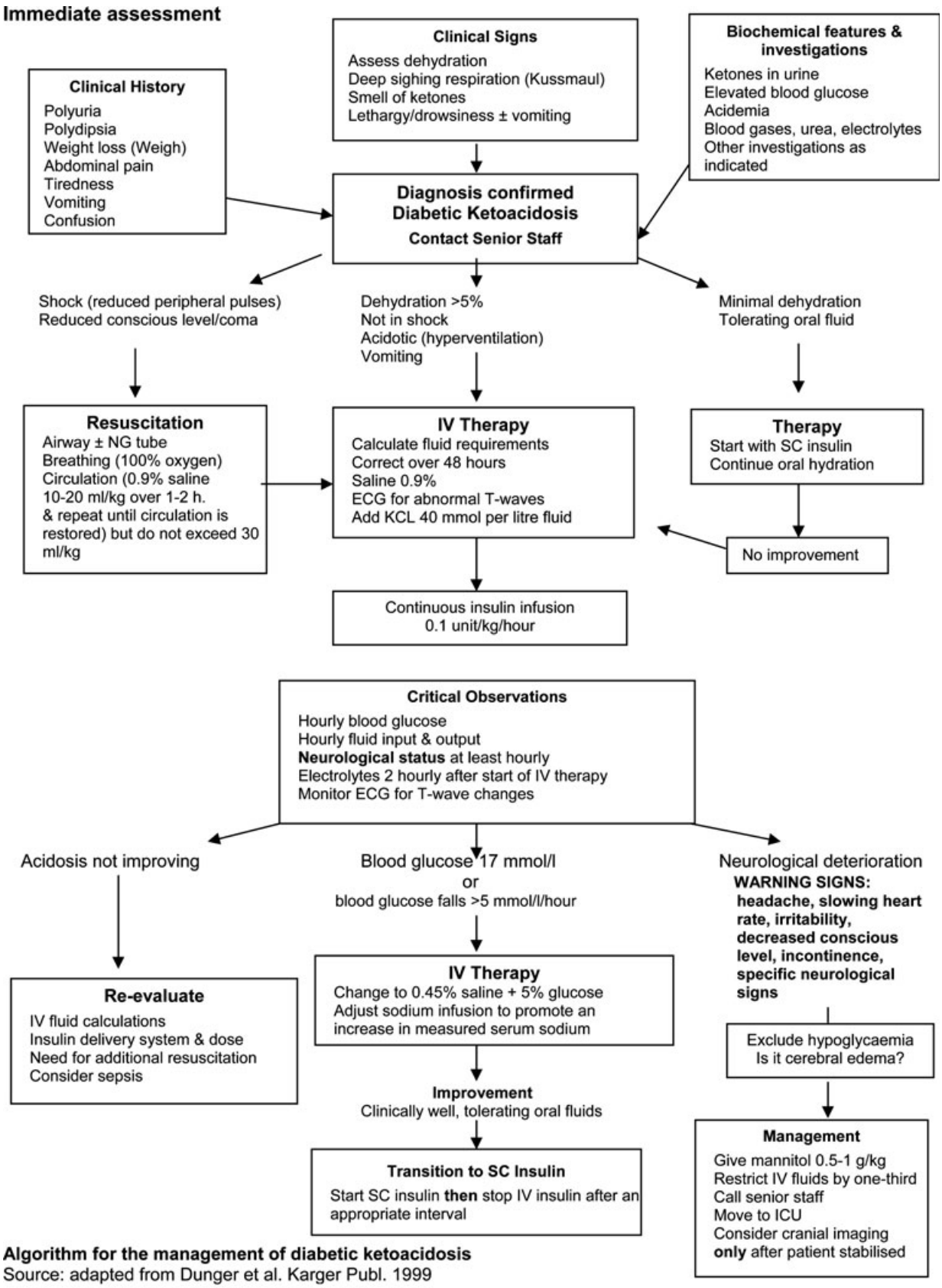
Prevention of recurrent DKA

Management of an episode of DKA is not complete until its cause has been identified and an attempt made to treat it.

- Insulin omission, either inadvertently or deliberately, is the cause in most cases (C,A) (33,34).
- The most common cause of DKA in insulin pump users is failure to take extra insulin with a pen or syringe when hyperglycemia and hyperketonemia or ketonuria occur (E).
- Home measurement of blood BOHB concentrations, when compared to urine ketone testing, decreases diabetes-related hospital visits (both emergency department visits and hospitalizations) by the early identification and treatment of ketosis (146). Blood BOHB measurements may be especially valuable to prevent DKA in patients who use a pump because interrupted insulin delivery rapidly leads to ketosis.
  - There may be dissociation between urine ketone (sodium nitroprusside only measures acetoacetate and acetone) and serum BOHB concentrations, which may be increased to levels consistent with DKA when a urine ketone test is negative or shows only trace or small ketonuria (147).
- There usually is an important psychosocial reason for insulin omission.
  - an attempt to lose weight in an adolescent girl with an eating disorder,
  - a means of escaping an intolerable or abusive home situation,
  - clinical depression or other reason for inability of the patient to manage the diabetes unassisted.
- An infection that is not associated with vomiting and diarrhea is seldom the cause when the patient/family is properly educated in diabetes management and is receiving appropriate follow-up care by a diabetes team with a 24-hour telephone helpline (B) (148–150).
- A psychiatric social worker or clinical psychologist should be consulted to identify the psychosocial reason(s) contributing to development of DKA (E).
- Insulin omission can be prevented by schemes that provide education, psychosocial evaluation and treatment combined with adult supervision of insulin administration (B) (151).
  - Parents and patients should learn how to recognize and treat impending DKA with additional rapid- or short-acting insulin and oral fluids (E)
  - Patients should have access to a 24-hour telephone helpline for emergency advice and treatment (B) (148)
  - When a reliable adult administers insulin there may be as much as a tenfold reduction in frequency of recurrent DKA (B) (151).

Recommendations/key points

- DKA is caused by either relative or absolute insulin deficiency.
- Children and adolescents with DKA should be managed in centers experienced in its treatment and where vital signs, neurological status and laboratory results can be monitored frequently
- Begin with fluid replacement before starting insulin therapy.
- Volume expansion (resuscitation) is required only if needed to restore peripheral circulation.
- Subsequent fluid administration (including oral fluids) should rehydrate evenly over 48 hours at a rate rarely in excess of 1.5–2 times the usual daily maintenance requirement.
- Begin with 0.1 U/kg/h. 1–2 hours AFTER starting fluid replacement therapy.



Algorithm for the management of diabetic ketoacidosis
Source: adapted from Dunger et al. Karger Publ. 1999

NG, nasogastric; SC, subcutaneous.

- If the blood glucose concentration decreases too quickly or too low before DKA has resolved, increase the amount of glucose administered. Do NOT decrease the insulin infusion
- Even with normal or high levels of serum potassium at presentation, there is always a total body deficit of potassium.
- Begin with 40 mmol potassium/L in the infusate or 20 mmol potassium/L in the patient receiving fluid at a rate >10 mL/kg/h.
- There is no evidence that bicarbonate is either necessary or safe in DKA.
- Have mannitol or hypertonic saline at the bedside and the dose to be given calculated beforehand.
- In case of profound neurological symptoms, mannitol should be given immediately.
- All cases of recurrent DKA are preventable

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