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ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state

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1 | SUMMARY OF WHAT IS NEW/DIFFERENT

Recommendations concerning fluid management have been modified to reflect recent findings from a randomized controlled clinical trial showing no difference in cerebral injury in patients rehydrated at different rates with either 0.45% or 0.9% saline.

2 | EXECUTIVE SUMMARY

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

- Hyperglycemia (blood glucose >11 mmol/L [≈200 mg/dL])
- Venous pH <7.3 or serum bicarbonate <15 mmol/L
- Ketonemia (blood ß-hydroxybuyrate ≥3 mmol/L) or moderate or large ketonuria.

The **clinical signs of DKA** include: Dehydration, tachycardia, tachypnea, deep sighing respiration, breath smells of acetone, nausea and/or vomiting, abdominal pain, blurry vision, confusion, drowsiness, progressive decrease in level of consciousness and, eventually, loss of consciousness (coma).

Risk factors for DKA in newly diagnosed patients include younger age, delayed diagnosis, lower socioeconomic status, and residence in a country with a low prevalence of type 1 diabetes mellitus (T1DM).

Risk factors for DKA in patients with known diabetes include omission of insulin for various reasons, limited access to medical services, and unrecognized interruption of insulin delivery in patients using an insulin pump.

The following recommendations are based on currently available evidence and are intended to be a general guide to DKA management. Because there is considerable individual variability in presentation of DKA (ranging from mild with only minimal dehydration to severe with profound dehydration), some patients may require specific treatment that, in the judgment of the treating physician, may be within or, occasionally, outside the range of options presented here. Clinical judgment should always be used to determine optimal treatment for the individual patient, and timely adjustments to treatment (electrolyte composition and rate of infusion of rehydration fluids, insulin dose) should be based on ongoing, careful clinical and biochemical monitoring of the patient's response.

Emergency assessment should follow the general guidelines for Pediatric Advanced Life Support (PALS) and includes: Immediate measurement of blood glucose, blood or urine ketones, serum electrolytes, blood gases and complete blood count; assessment of severity of dehydration, and level of

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consciousness **(E)**. A second peripheral intravenous (IV) catheter should be inserted **(E).**

Management should be conducted in a center experienced in the treatment of DKA in children and adolescents and where vital signs, neurological status and laboratory results can be monitored frequently **(E).** Where geographic constraints require that management be initiated in a center with less experience and with fewer resources, there should be arrangements in place for telephone or videoconference support from a physician with expertise in DKA **(E).**

Meticulous monitoring of the clinical and biochemical response to treatment is necessary so that timely adjustments in treatment can be made when indicated by the patient's clinical or laboratory data **(E)**.

Goals of therapy are to correct dehydration, correct acidosis and reverse ketosis, gradually restore hyperosmolality and blood glucose concentration to near normal, monitor for complications of DKA and its treatment, and identify and treat any precipitating event.

Fluid replacement should begin before starting insulin therapy. Expand volume using crystalloids, as required, to restore peripheral circulation **(E)**. Calculate the subsequent rate of fluid administration, including the provision of maintenance fluid requirements, aiming to replace the estimated fluid deficit over 24 to 48 hours **(A)**.

Insulin therapy: begin with 0.05 to 0.1 U/kg/h at least 1 hour AFTER starting fluid replacement therapy **(B)**.

Potassium: If the patient is hyperkalemic, *defer* potassium replacement therapy until urine output is documented. Otherwise, begin with 40 mmol potassium/L (or 20 mmol potassium/L if the patient is receiving fluid at a rate ≥10 mL/kg/h) **(E)**.

Bicarbonate administration is not recommended except for treatment of life-threatening hyperkalemia or unusually severe acidosis (vpH <6.9) with evidence of compromised cardiac contractility **(C).**

Warning signs and symptoms of cerebral edema include: Onset of headache after beginning treatment or progressively worsening or severe headache, slowing of heart rate not related to sleep or improved intravascular volume, change in neurological status (restlessness, irritability, increased drowsiness, confusion, incontinence), specific neurological signs (eg, cranial nerve palsies), rising blood pressure, and decreased oxygen saturation **(C)**.

In patients with multiple risk factors for cerebral edema (elevated serum urea nitrogen concentration, severe acidosis, severe hypocapnia), have mannitol or hypertonic saline at the bedside and the dose calculated **(E)**. If neurologic status deteriorates acutely, hyperosmolar fluid therapy should be given immediately **(C)**.

Prevention: Management of an episode of DKA is not complete until an attempt has been made to identify and treat the cause.

DKA without a preceding febrile illness or gastroenteritis in a patient with known diabetes is almost always the result of psychosocial problems and failure to appropriately administer insulin.

In new onset diabetes, DKA is frequently the consequence of a delay in diagnosis **(E)**.

The criteria for **hyperglycemic hyperosmolar state (HHS) include:**

- Plasma glucose concentration >33.3 mmol/L (600 mg/dL)
- Venous pH >7.25; arterial pH >7.30
- Serum bicarbonate >15 mmol/L
- Small ketonuria, absent to mild ketonemia
- Effective serum osmolality >320 mOsm/kg
- Altered consciousness (eg, obtundation, combativeness) or seizures (in approximately 50%)

In HHS, the goals of initial fluid therapy are to expand the intra- and extravascular volume, restore normal renal perfusion and promote a gradual decline in corrected serum sodium concentration and serum osmolality.

In HHS, begin **insulin administration** at a dose of 0.025 to 0.05 U/kg/h once plasma glucose is decreasing less than 3 mmol/L (50 mg/dL) per hour with fluid alone **(C)**.

DKA results from deficiency of circulating insulin and increased levels of the counterregulatory hormones: catecholamines, glucagon, cortisol, and growth hormone.[1,2] Severe insulin deficiency occurs in previously undiagnosed T1DM and when treated patients deliberately or inadvertently do not take insulin, especially the long-acting component of a basal-bolus regimen, or markedly reduce the doses of insulin, for example, in association with an intercurrent illness such as gastroenteritis. 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 markedly increase in response to stress in conditions such as sepsis, trauma, or febrile illness, which overwhelm homeostatic mechanisms and lead to metabolic decompensation despite the patient taking the usual recommended dose of insulin.

The combination of absolute or relative insulin deficiency and high counterregulatory hormone concentrations causes an accelerated catabolic state with increased glucose production by the liver and kidney (via glycogenolysis and gluconeogenesis) and impaired peripheral glucose utilization, which result in hyperglycemia and hyperosmolality. Insulin deficiency and high counterregulatory hormone concentrations also increase lipolysis and ketogenesis and cause ketonemia and metabolic acidosis. Hyperglycemia exceeding the usual renal threshold of approximately 10 mmol/L (180 mg/dL) together with hyperketonemia cause osmotic diuresis, dehydration, and obligatory loss of electrolytes, often aggravated by vomiting associated with severe ketosis. These changes stimulate further stress hormone production, which induces more severe insulin resistance and worsening hyperglycemia and hyperketonemia. Lactic acidosis from hypoperfusion or sepsis may contribute to the acidosis (Figure 1).[4]

If this cycle is not interrupted by exogenous insulin together with fluid and electrolyte therapy, fatal dehydration and metabolic acidosis will ensue.

DKA is characterized by severe depletion of water and electrolytes from both the intra- and extracellular fluid (ECF) compartments[5]; the typical range of losses is shown in Table 1. Despite their dehydration, patients generally continue to maintain normal blood pressure or even have high blood pressure,[6] possibly due to elevated plasma catecholamine concentrations, increased release of

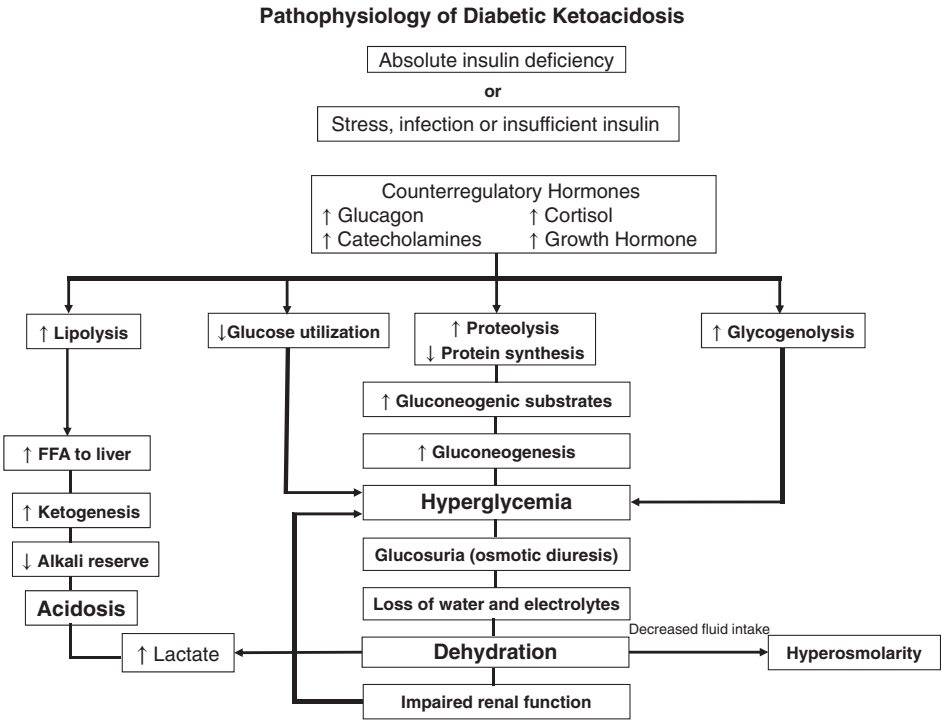

FIGURE 1 Pathophysiology of diabetic ketoacidosis. Copyright© 2006 American Diabetes Association. From diabetes care, Vol. 29, 2006:1150-1159. Reprinted with permission of *The American Diabetes Association*

antidiuretic hormone (ADH) in response to hyperosmolality (which increases blood pressure via V2 receptors), increased osmotic pressure from marked hyperglycemia, or other factors.[6] Considerable urine output persists because of glucosuria until extreme volume depletion leads to a critical decrease in renal blood flow and glomerular filtration. At presentation, the specific deficits in an individual patient vary 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) may exacerbate the hyperglycemia.[7] Conversely, though uncommonly, modest hyperglycemia in the setting of severe acidosis may be an indication that the patient has maintained increased water intake and may be only modestly hypovolemic. Rapid emptying of stomach contents containing an abundant quantity of sugar, which occurs as gastroparesis is relieved with therapy, accounts for the rise in plasma glucose concentration observed in some patients after onset of therapy despite ongoing large loss of glucose in the urine.[8]

Clinical manifestations of diabetic ketoacidosis

- Dehydration
- Tachypnea; deep, sighing (Kussmaul) respiration
- Nausea, vomiting, and abdominal pain that may mimic an acute abdominal condition
- Confusion, drowsiness, progressive obtundation, and loss of consciousness

TABLE 1 Losses of fluid 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 h
		11-20 kg	1000 mL + 50 mL/kg/24 h for each kg from 11 to 20
		>20 kg	1500 mL + 20 mL/kg/24 h for each kg >20
Sodium	6 mmol (5-13)	2-4 mmol†	
Potassium	5 mmol (3-6)	2-3 mmol	
Chloride	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.[9–13] In any individual patient, actual losses may be less or more than the ranges shown in Table 1.

Three methods for determining maintenance water requirements in children are commonly used: *the Holliday-Segar formula[14] (shown in Table 1), a simplified Holliday-Segar formula (see below), and a formula based on body surface area for children who weigh more than 10 kg (1500 mL/m^2/24 h).[15]

† (shown in Table 1) Maintenance electrolyte requirements in children are per 100 mL of maintenance IV fluid.[15,16]

Simplified method based on Holliday-Segar: <10 kg 4 mL/kg/h; 11-20 kg 40 + 2 mL/kg/h for each kg between 11 and 20; >20 kg 60 + 1 mL/kg/h for each kg >20.

To avoid excessive fluid administration in obese patients, fluid calculations should be based on an approximation of ideal body weight for height.

TABLE 2 Fluid maintenance and replacement volumes based on body weight and an assumption of 10% dehydration

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 volume of fluid has been calculated to be given over 48 hours. The table shows volumes for maintenance and rehydration per 24 hours and per hour. Fluid given orally (when patient has improved) should be subtracted from the volume in the table. Fluid volumes are calculated based on data from Darrow.[17] For body weights >32 kg, the volumes have been adjusted so as not to exceed twice the maintenance rate of fluid administration.

3 | DEFINITION OF DIABETIC KETOACIDOSIS

The **biochemical criteria** for the diagnosis of DKA are[18]:

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

*Although not universally available, blood beta-hydroxybutyrate (BOHB) concentration should be measured whenever possible; a level ≥3 mmol/L is indicative of DKA.[19]

Urine ketones are typically ≥2+ "moderate or large" positive. Partially treated children and children who have consumed little or no carbohydrate may, rarely, have only modestly elevated blood glucose concentrations, referred to as "euglycemic ketoacidosis".[20,21] This can be caused by starvation (anorexia or religious fasting),[22] a low carbohydrate high fat diet, or the off-label use of SGLT2-inhibitors.[23–25] Serum bicarbonate concentration alone can substitute for vpH to diagnose DKA and classify severity in children with new onset diabetes mellitus and is suggested as an alternative to reliance on vpH in settings where access to vpH measurement is limited.[26]

The frequency of type 2 diabetes mellitus (T2DM) in the pediatric age range is increasing.[27,28] The worldwide incidence and prevalence of type 2 diabetes in children and adolescents vary substantially among countries, age categories, and ethnic groups, which can be explained by variations in population characteristics and methodological dissimilarities between studies.[29] DKA at diagnosis is more common in younger children, minority race, and male gender.[30] At some centers in the United States, type 2 diabetes now accounts for approximately one-half of newly diagnosed diabetes in children aged 10 to 21 years.[31] The SEARCH for Diabetes in Youth Study in the United States found that DKA has decreased over time; the most recent data show that it occurred in nearly 6% of youth with type 2 diabetes.[30,32] Overall, 5% to 25% of patients with type 2 diabetes have DKA at the time of diagnosis.[33,34]

The **severity of DKA** is categorized by the degree of acidosis[35]:

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

HHS, formerly referred to as hyperosmolar non-ketotic coma, may occur in young patients with T2DM,[34,36–38] in type 1 diabetes patients,[39] and in infants, especially those with 6q24-related transient neonatal diabetes mellitus.[40] **The criteria for HHS** include[2,41]:

- plasma glucose concentration >33.3 mmol/L (600 mg/dL)
- arterial pH >7.30; venous pH >7.25
- serum bicarbonate >15 mmol/L
- small ketonuria, absent to small ketonemia*
- effective serum osmolality >320 mOsm/kg
- obtundation, combativeness, or seizures (in approximately 50%)

Overlap between the characteristic features of HHS and DKA may occur, and some patients with HHS, especially when there is severe dehydration, have mild or moderate acidosis that is mainly due to hypoperfusion and lactic acidosis. Conversely, some children with type 1 diabetes may have features of HHS (severe hyperglycemia) especially if high-carbohydrate containing beverages have been used to quench thirst and replace urinary losses before diagnosis.[7] Therapy

must be appropriately modified to address the pathophysiology and particular biochemical disturbances of the individual patient (see below). See below regarding specific therapy of HHS.

4 | FREQUENCY OF DKA

4.1 | 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 type 1 diabetes. Frequencies range from approximately 15% to 70% in Europe and North America.[30,42–49] DKA at diagnosis is more common in younger children (especially <2 years of age), including infants with both transient and permanent neonatal diabetes (overall frequency 66%), often the consequence of diagnostic error or delayed treatment.[50–53] It is also more common in ethnic minority groups, and in children whose families do not have ready access to medical care for social or economic reasons.[21,32,46,51,54,55]

4.2 | In children with established diabetes

The risk of DKA in established type 1 diabetes is 1% to 10% per patient per year[3,56–61]:

Risk is increased in[59]:

- Children who omit insulin[58]
- Children with poor metabolic control or previous episodes of DKA
- Gastroenteritis with persistent vomiting and inability to maintain hydration
- Children with psychiatric disorders, including those with eating disorders
- Children with difficult or unstable family circumstances (eg, parental abuse)
- Peripubertal and adolescent girls
- Binge alcohol consumption[62]
- Children with limited access to medical services

In the early days of insulin pump therapy, DKA was more common than in patients using injection therapy (only rapid- or short-acting insulin is used in pumps; therefore, interruption of insulin delivery for any reason rapidly leads to insulin deficiency).[3,63] However, a recent matched comparison of patients using insulin pump therapy with multiple daily injections showed that DKA occurred less frequently (3.64 vs 4.26 per 100 patient-years) in patients using pump therapy.[64]

In recurrent DKA, insulin omission or failure to follow sick day or pump failure management guidelines accounts for almost all episodes.

5 | MANAGEMENT OF DKA

Figure 2 shows an algorithm for the management of DKA.

5.1 | Emergency assessment

Acute management should follow the general guidelines for PALS,[65,66] with particular attention to the following:

- Immediately measure blood glucose and blood BOHB concentrations with bedside meters or with urine test strips that measure only acetoacetic acid if bedside blood ketone measurements are not available. Perform a clinical evaluation to identify a possible infection.
  - Measurement of blood BOHB concentration with a point-of-care meter, if available, is useful to confirm ketoacidosis (≥3 mmol/L in children)[19] and to monitor the response to treatment.[67–73]
- **Weigh** the patient. If body surface area is used for fluid therapy calculations, measure height or length to determine surface area. The current weight should be used for calculations and not the weight from a previous office visit or hospital record.
- **Assess severity of dehydration**.
  - Estimation of the degree of dehydration is imprecise and generally shows only fair to moderate agreement among examiners,[74–76] and should be based on a combination of physical signs. The most useful signs for predicting 5% dehydration in young children aged 1 month to 5 years are:
    - prolonged capillary refill time (normal capillary refill is ≤1.5-2 seconds)
    - abnormal skin turgor ("tenting" or inelastic skin)
  - Other useful signs in assessing the 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.[77]
  - ≥10% dehydration is suggested by the presence of weak or impalpable peripheral pulses, hypotension, oliguria.
- **Assess level of consciousness** (Glasgow coma scale [GCS]—see Table 3).[78]
- In the unconscious or severely obtunded patient without normal airway protective reflexes, **secure the airway** and empty the stomach by continuous nasogastric suction to prevent pulmonary aspiration.
  - Intubation should be avoided if possible; an increase of pCO_2 during or following intubation above the level that the patient had been maintaining may cause cerebrospinal fluid (CSF) pH to decrease and contribute to worsening of cerebral edema.[79]
- If there is a history of recent large consumption of glucose-containing fluids, consider emptying the stomach even in the patient who is not obtunded.
  - When large quantities of fruit juice or sweetened soft drinks have been ingested, the stomach may contain a large volume of water with little sodium. Spontaneous gastric emptying early in the course of therapy leads to absorption of glucose and electrolyte-free water from the intestinal tract.[8,80]
- Give **oxygen** to patients with circulatory impairment or shock.
- A **cardiac monitor** should be used for continuous electrocardiographic monitoring to assess T-waves for evidence of hyper- or hypokalemia.[81,82]
- A second **peripheral IV catheter** should be placed for convenient and painless repetitive blood sampling. An **arterial catheter** may, rarely, be necessary in some critically ill patients managed in an intensive care unit.
  - Unless absolutely necessary, **avoid placing a central venous catheter** because of the high risk of thrombosis, especially in the very young child. If a central catheter has been inserted, the catheter should be removed as soon as the patient's clinical

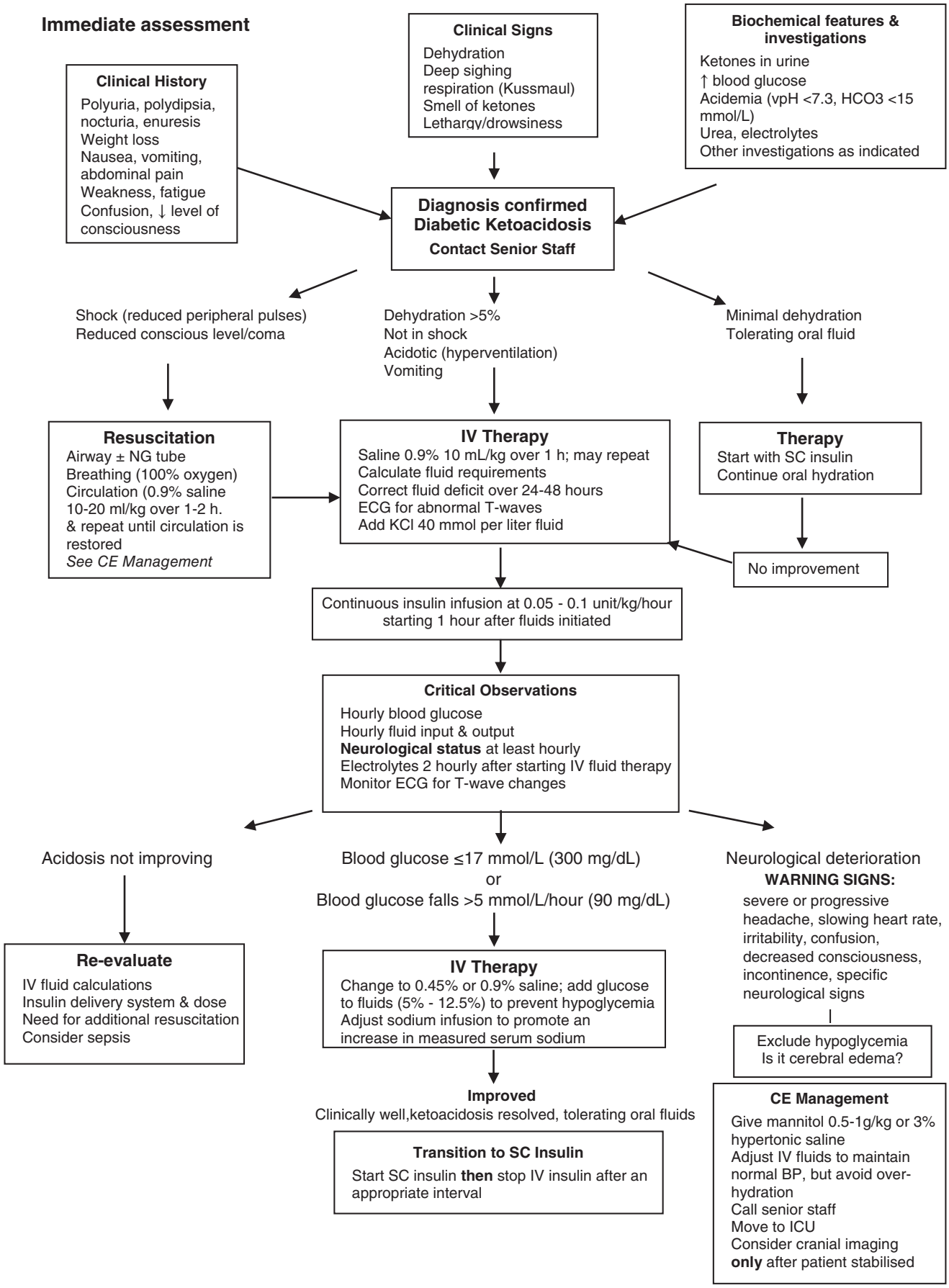

FIGURE 2 Algorithm for the management of diabetic ketoacidosis. Adapted from Pinhas-Hamiel and Sperling.[271] NG, nasogastric; SC, subcutaneous

TABLE 3 Glasgow coma scale or score (GCS)

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

The GCS consists of three parameters and is scored between 3 and 15; 3 being the worst and 15 the best.[78] 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.

[a] Inappropriate words, random or exclamatory articulated speech, but no sustained conversational exchange.

[b] Attention can be held; patient responds to questions coherently, but there is some disorientation and confusion.

status permits.[83–85] Mechanical and pharmacologic prophylaxis (low molecular weight heparin) should be considered especially in children >12 years.

- Insulin should preferably not be given through a central line unless it is the only available option because its infusion may be interrupted when other fluids are given through the same line.

- **Give antibiotics** to **febrile patients** after obtaining appropriate cultures of body fluids.
- Bladder catheterization usually is not necessary, but if the child is unconscious or unable to void on demand (eg, infants and very ill young children) the bladder should be catheterized.
- Obtain a **blood sample for laboratory measurement** of:
  - serum or plasma glucose
  - electrolytes (including serum bicarbonate)
  - blood urea nitrogen, creatinine
  - serum osmolality
  - venous pH, pCO2[†]
  - hemoglobin, hematocrit and complete blood count. Note that an increased white blood cell count in response to stress is characteristic of DKA and is not indicative of infection.[86]
  - albumin, calcium, phosphate, magnesium concentrations (if possible)
- Perform a **urinalysis** for ketones if blood or serum ketones have not been measured.
- Obtain appropriate **specimens for culture** (blood, urine, throat), only if there is evidence of infection (eg, fever).
- If laboratory measurement of serum potassium is delayed, perform an **electrocardiogram** (ECG) for baseline evaluation of potassium status.[81,82]
- Although not essential for management of DKA per se, HbA1c may be useful in the evaluation and management of specific patients as it provides information about the duration of hyperglycemia.

6 | WHERE SHOULD THE CHILD WITH DKA BE MANAGED?

After initial life support, the child should receive care in a unit that has:

- Experienced nursing staff trained in monitoring and management of DKA in children and adolescents
- Written guidelines or, if unavailable, access to online guidelines for DKA management in children
- Access to a laboratory that can provide frequent and timely measurements of biochemical variables

Whenever possible, a specialist/consultant pediatrician with training and expertise in the management of DKA should direct inpatient management. Where geographic constraints require that management be initiated in a center with less experience and with fewer resources, there should be arrangements in place for telephone or videoconference support from a physician with expertise in DKA.

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 (eg, <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.[18,87] Transport teams should be knowledgeable about DKA management (or have access to a medical control physician who is knowledgeable) and should have rescue medications available during the transport, including high concentration dextrose IV solutions and mannitol or 3% hypertonic saline.

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 (eg, emergency ward), provided an experienced diabetes team supervises the care.[35,88,89]

7 | CLINICAL AND BIOCHEMICAL MONITORING

Successful management of DKA and HHS requires **meticulous monitoring** and recording 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.

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; Table 3) for warning signs and symptoms of cerebral edema (see below)
  - onset of headache after starting DKA treatment or worsening of headache already present before commencing treatment
  - inappropriate slowing of heart rate
  - recurrence of vomiting
  - change in neurological status (restlessness, irritability, increased drowsiness, confusion, incontinence) or specific neurologic signs (eg, cranial nerve palsies, abnormal pupillary responses)
  - rising blood pressure
  - decreased oxygen saturation
  - rapidly increasing serum sodium concentration suggesting loss of urinary free water as a manifestation of diabetes insipidus (from interruption of blood flow to the pituitary gland due to cerebral herniation)
- Amount of administered insulin
- Hourly (or more frequently as indicated) accurate **fluid input** (including all oral fluid) **and output**.
- **Capillary blood glucose** concentration 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, and is limited in measuring extremely high levels).
- **Laboratory tests**: serum electrolytes, glucose, blood urea nitrogen, calcium, magnesium, phosphate, hematocrit, and blood gases should be repeated 2 to 4 hourly, or more frequently, as clinically indicated, in more severe cases.
- Blood BOHB concentrations, if available, every 2 to 4 hours.[68–72]
  - Near-patient (also referred to as point-of-care) BOHB measurements correlate well with a reference method up to 3 mmol/L, but are not accurate above 5 mmol/L.[70,90]
- Lipids and triglycerides can be grossly elevated causing the blood sample to show a visible rim of lipids, which can interfere with accuracy of laboratory tests.[91]
- If the laboratory cannot provide timely results, a portable biochemical analyzer that measures serum electrolytes and blood gases on fingerstick blood samples at the bedside is a useful adjunct to laboratory-based determinations. Blood glucose and blood or urine ketone concentrations can be measured with a bedside meter while awaiting results from the laboratory.
- Measure body weight each morning.
- **Calculations**:

  - Anion gap = Na − (Cl + HCO_3): normal is 12 ± 2 mmol/L
    - In DKA the anion gap is typically 20 to 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 or measured Na + 2([plasma glucose − 100]/100) mg/dL[‡]
  - Effective osmolality (mOsm/kg) = 2 × (plasma Na) + plasma glucose mmol/L[93]; normal range is 275 to 295 mOsm/kg

Goals of therapy

- Correct acidosis and reverse ketosis
- Correct dehydration
- Restore blood glucose to near normal
- Monitor for complications of DKA and its treatment
- Identify and treat any precipitating event

7.1 | Fluids and salt

Patients with DKA have a deficit in ECF volume that usually is in the range 5% to 10% of body weight.[9,10] Shock with hemodynamic compromise is rare in pediatric DKA. Clinical estimates of the volume deficit are subjective and inaccurate[74–76]; therefore, in moderate DKA assume 5% to 7% and in severe DKA 7% to 10% dehydration. The effective osmolality (formula above) is frequently in the range of 300 to 350 mmol/kg. Increased serum urea nitrogen and hematocrit or hemoglobin concentration or, alternatively, plasma albumin or total protein concentration if anemia is suspected[94] are useful markers of the degree of ECF contraction,[89,95,96] and should be determined frequently during fluid resuscitation and deficit replacement.[97] 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,[98,99] 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 concentration. It is useful to calculate the corrected sodium concentration (using the above formula), to help assess the magnitude of the deficit of sodium and water.[5] The "corrected" sodium represents the expected serum sodium concentration in the absence of hyperglycemia. Changes in the corrected sodium should be monitored throughout the course of therapy. As the plasma glucose concentration decreases after administering fluid and insulin, the measured serum sodium concentration should increase and the glucose-corrected sodium concentration (formula above) should slowly decrease or remain in the normal range. It is important to appreciate that the increase in measured serum sodium concentration 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.[100–102] A rapid and ongoing rise in serum sodium concentration may also indicate possible cerebral edema as a result of loss of free water in the urine from diabetes insipidus.

The objectives of fluid and electrolyte replacement therapy are to:

- Restore circulating volume
- Replace sodium and the extracellular and intracellular water deficits

- Improve glomerular filtration and enhance clearance of glucose and ketones from the blood

7.2 | Principles of water and salt replacement

Despite much effort to identify the cause of cerebral edema, its pathogenesis is incompletely understood and controversy continues concerning the association between the rate of fluid or sodium administration used in the treatment of DKA and the development of cerebral edema.[103–105] No treatment strategy can be definitively recommended as being superior to another based on current evidence.[104] A recently completed prospective randomized clinical trial (the PECARN FLUID Study) compared acute and long-term neurological outcomes in 1389 episodes of DKA in 1255 children treated with slower vs more rapid fluid administration using either 0.45% or 0.9% saline.[106] The PECARN FLUID Study showed no significant differences in the frequency of either altered mental status or clinical diagnoses of cerebral edema in any of the treatment arms, and long-term neurocognitive outcomes were similar in all groups. Point estimates suggested lower frequencies of altered mental status in children rehydrated more rapidly with 0.45% saline, but these differences did not reach statistical significance.[106] The results of this study suggest that an assumed fluid deficit between 5% and 10% of body weight should be replaced over 24 to 48 hours along with maintenance fluids, using fluids with a sodium content between 0.45% and 0.9% saline. The risk of cerebral injury does not appear to be associated with differences in fluid protocols within these ranges. Therefore, clinicians should not unnecessarily restrict fluid administration if clinical signs suggest the need for circulatory volume expansion.

The principles described below are based on the consensus statement from a panel of expert physicians representing the Lawson Wilkins Pediatric Endocrine Society (LWPES), the European Society for Pediatric Endocrinology (ESPE), and the International Society for Pediatric and Adolescent Diabetes (ISPAD)[18,107] and incorporate the recommendations from the PECARN FLUID Study.[106]

- Water and salt deficits must be replaced.
- IV or oral fluids that may have been given in another facility before assessment should be factored into calculations of deficit and replacement volumes.

7.2.1 | Resuscitation fluids

For patients who are volume depleted but not in shock, volume expansion (resuscitation) should begin immediately with 0.9% saline to restore the peripheral circulation. The volume administered typically is 10 mL/kg infused over 30 to 60 minutes; however, if tissue perfusion is poor the initial fluid bolus is given more rapidly (eg, over 15-30 minutes) and a second fluid bolus may be needed to ensure adequate tissue perfusion.

- In the rare patient with DKA in shock, rapidly restore circulatory volume with isotonic saline in 20 mL/kg boluses infused as quickly as possible through a large bore cannula with reassessment of circulatory status after each bolus.
- Use crystalloid not colloid. There are no data to support the use of colloid in preference to crystalloid in the treatment of DKA.

7.2.2 | Deficit replacement fluids

Subsequent fluid management (deficit replacement) can be accomplished with 0.45% to 0.9% saline or a balanced salt solution (Ringer's lactate, Hartmann's solution or Plasmalyte).[95,100,108–114]

- Fluid therapy should begin with deficit replacement plus maintenance fluid requirements.
  - All children will experience a decrease in vascular volume when plasma glucose concentrations fall during treatment; therefore, it is essential to ensure that they receive sufficient fluid and salt to maintain adequate tissue perfusion.
- Deficit replacement should be with a solution that has a tonicity in the range 0.45% to 0.9% saline, with added potassium chloride, potassium phosphate or potassium acetate (see below under potassium replacement).[95,100,108,112,113,115–117] Decisions regarding use of isotonic vs hypotonic solution for deficit replacement should depend on clinician judgment based on the patient's hydration status, serum sodium concentration and osmolality.
- In addition to providing the usual daily maintenance fluid requirement, replace the estimated fluid deficit at an even rate over 24 to 48 hours.[18,95,118] Except for severely ill individuals, oral intake typically begins within 24 hours.[118] Although rehydration is generally planned to occur over longer periods, in a study of 635 episodes of DKA the mean time to correction of DKA and complete restoration of the circulation was 11.6 ± 6.2 hours. At this point, any remaining deficits were replenished by oral intake once DKA had resolved and patients were transitioned to subcutaneous insulin.[118]
- Satisfactory outcomes have also been reported using an alternative simplified method: After the initial fluid administration of 20 mL/kg of normal saline, 0.675% saline (3/4 normal saline, 115.5 mmol sodium) is infused at 2 to 2.5 times the usual maintenance rate of fluid administration regardless of the degree of dehydration, and decreased to 1 to 1.5 times the maintenance rate after 24 hours, or earlier if acidosis resolved.[112]
- Clinical assessment of hydration status and calculated effective osmolality are valuable guides to fluid and electrolyte therapy. The aim is gradually to reduce serum effective osmolality to normal.[97,118,119] There should be a concomitant increase in serum sodium concentration as the serum glucose concentration decreases (sodium should rise by 0.5 mmol/L for each 1 mmol/L decrease in glucose concentration).
- Urinary losses should not routinely be added to the calculation of replacement fluid, but this may be necessary in rare circumstances.
- The sodium content of the fluid should be increased if measured serum sodium concentration is low and does not rise appropriately as the plasma glucose concentration falls.[100,111,119,120]

- The use of large amounts of chloride-rich fluids (combined with preferential renal excretion of ketones over chloride) may be associated with the rapid development of hyperchloremia[121–123] (defined as a ratio of chloride:sodium [Cl^-:Na^+] > 0.79[124]) and hyperchloremic metabolic acidosis.[117,122,125–127]
  - The acidifying effect of chloride can mask recognition of resolution of ketoacidosis when total base deficit is used to monitor biochemical improvement.[123]
  - When hyperchloremia develops, a persisting base deficit or low bicarbonate concentration can be erroneously interpreted as being due to ongoing ketosis.[128]
  - To avoid this misinterpretation, measurement of bedside BOHB levels will prevent any confusion and can demonstrate that ketoacidosis has resolved. Hyperchloremic acidosis resolves spontaneously.
  - Although the anion gap is useful to track resolution of ketosis, it has two limitations in this setting: it is unable to differentiate a mixed metabolic acidosis (hyperchloremic and ketotic), and the degree of hyperchloremic acidosis is not quantifiable.
    - Normally the difference between the serum sodium and chloride concentrations is 30 to 35 mmol/L. To partition the chloride component of the base deficit, the following formula has been proposed to enable clinicians to track resolution of ketoacidosis at the bedside: Chloride-induced base deficit = (plasma sodium − plasma chloride − 32).[123]
    - The chloride load can be reduced by not giving potassium as potassium chloride (use potassium acetate instead) and by using fluids such Ringer's lactate or Plasmalyte in which a portion of the chloride is replaced by lactate or acetate, respectively.[129]

7.3 | Insulin therapy

DKA is caused by a decrease in the effective circulating insulin level associated with increases in counter-regulatory hormone concentrations. Although rehydration alone frequently causes a marked decrease in blood glucose concentration,[130,131] insulin therapy is essential to restore normal cellular metabolism, to suppress lipolysis and ketogenesis, and to normalize blood glucose concentrations.[132]

So-called **low dose** IV insulin administration is safe and effective.[118,133]

- Start insulin infusion at least 1 hour after starting fluid replacement therapy; that is, after the patient has received initial volume expansion[105]
- Correction of insulin deficiency
  - Dose: 0.05 to 0.1 unit/kg/h (eg, one method is to dilute 50 units regular [soluble] insulin in 50 mL normal saline, 1 unit = 1 mL)[134–141]
  - Route of administration IV
  - An IV bolus should *not* be used at the start of therapy; it is unnecessary,[140,142] may increase the risk of cerebral edema,[105,119,143] can precipitate shock by rapidly decreasing osmotic pressure, and can exacerbate hypokalemia
- The dose of insulin should usually remain at 0.05 to 0.1 unit/kg/h at least until resolution of DKA (pH >7.30, serum bicarbonate >15 mmol/L, BOHB <1 mmol/L, or closure of the anion gap), which invariably takes longer than normalization of blood glucose concentrations.[144] Monitor venous pH and serum BOHB concentration every 2 hours to ensure steady improvement of biochemical parameters. If the insulin effect is adequate serum BOHB should decrease by approximately 0.5 mmol/L/h.[72] Increase the insulin dose if the expected rate of biochemical improvement does not occur.
- If the patient shows marked sensitivity to insulin (eg, some young children with DKA, patients with HHS, and some older children with established diabetes), the insulin dose may be decreased provided that metabolic acidosis continues to resolve. For example, if a young child is receiving 0.05 unit/kg/h, it may be necessary to reduce the insulin dose to 0.03 unit/kg/h to prevent hypoglycemia despite the addition of IV glucose.
- For less severe DKA (pH >7.1-7.2), 0.05 U/kg/h (0.03 U/kg/h for age <5 years with mild DKA) is usually sufficient to resolve the acidosis.
- Uncontrolled retrospective and observational studies have reported comparable efficacy and safety using 0.05 unit/kg/h,[145,146] and some pediatric centers routinely use this dose for treatment of DKA. A recent small RCT in children ≤12 years old showed that low dose (0.05 unit/kg/h) was comparable to standard dose (0.1 U/kg/h) with respect to rate of blood glucose decrease and resolution of acidosis; however, there was also no evidence that the higher dose (0.1 U/kg/h) is harmful.[113]
- Insulin has an aldosterone-like effect leading to increased urinary potassium excretion.[147–151] High doses administered intravenously for a prolonged period of time may contribute to a decrease in serum potassium concentration due to increased urinary potassium excretion despite potassium administration.
  - Time on IV insulin infusion and dose of insulin should be minimized to avoid severe hypokalemia.[152]
- During initial volume expansion the plasma glucose concentration falls steeply.[130] Thereafter, and after commencing insulin therapy, the plasma glucose concentration typically decreases at a rate of 2 to 5 mmol/L/h, depending on the timing and amount of glucose administration[134–137,139,140,153]
- To prevent an unduly rapid decrease in plasma glucose concentration and hypoglycemia, 5% glucose, initially, should be added to the IV fluid when the plasma glucose falls to approximately 14 to 17 mmol/L (250-300 mg/dL), or sooner if the rate of fall is precipitous.
  - 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. These glucose concentrations are often necessary to prevent hypoglycemia when insulin is infused at a rate of 0.1 unit/kg/h.
- 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 (300 mg/dL).
- If biochemical parameters of DKA (venous pH, anion gap, BOHB concentration) do not improve, reassess the patient, review

insulin therapy, and consider other possible causes of impaired response to insulin; for example, infection, errors in insulin preparation or route of administration.

- In circumstances where continuous IV administration is not possible and in patients with uncomplicated DKA, hourly or 2-hourly SC rapid-acting insulin analog (insulin lispro or insulin aspart) is safe and may be as effective as IV regular insulin infusion,[153–158] but, ideally, should not be used in patients whose peripheral circulation is impaired. 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 to 0.20 units/kg every 2 to 3 hours.[158]
- If blood glucose falls to <14 mmol/L (250 mg/dL) before DKA has resolved, reduce SC insulin lispro or aspart to 0.05 unit/kg/h to keep BG ≈11 mmol/L (200 mg/dL) until resolution of DKA.
- Subcutaneous administration of short-acting insulin (regular) every 4 hours is also a safe and effective alternative to IV insulin infusion in children with pH ≥7.0.[159]
- A suggested starting dose is 0.8 to 1 unit per kg per 24-hours; the calculated 24-hour dose is divided by 6 to provide an insulin dose injected every 4 hours. Doses are increased or decreased by 10% to 20% based on the blood glucose level before the next insulin injection. For example, if a child weighs 45 kg: 45 × 0.8 = 36 units; starting dose is 6 units.[159]

7.4 | Potassium replacement

Children with DKA suffer total body potassium deficits on the order of 3 to 6 mmol/kg.[9–13] The major loss of potassium is from the intracellular pool. Intracellular potassium is depleted because of transcellular shifts caused by hypertonicity (increased plasma osmolality causes solvent drag in which water and potassium are drawn out of cells), acidosis, and glycogenolysis and proteolysis secondary to insulin deficiency also cause potassium efflux from cells.[5] 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. Total body depletion of potassium occurs; however, at presentation serum potassium levels may be normal, increased, or decreased.[160] Renal dysfunction, by enhancing hyperglycemia and reducing potassium excretion, contributes to hyperkalemia.[160] Administration of insulin and the correction of acidosis drive potassium back into the cells, decreasing serum potassium levels.[161] The serum potassium concentration may decrease abruptly, predisposing the patient to cardiac arrhythmias.

Replacement therapy is required regardless of the serum potassium concentration, except if renal failure is present.[10,162]

- 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.
- If immediate serum potassium measurements are unavailable, an ECG may help to determine whether the child has hyper- or hypokalemia.[81,82] Prolongation of the PR interval, T-wave flattening and inversion, ST depression, prominent U waves, apparent long QT interval (due to fusion of the T and U waves) indicates 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.
  - 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; for example, 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)**. Administration of potassium entirely as potassium chloride contributes to the risk of hyperchloremic metabolic acidosis, whereas administration entirely as potassium phosphate can result in hypocalcemia.
- Potassium replacement should continue throughout IV fluid therapy.
- The maximum recommended rate of IV potassium replacement is usually 0.5 mmol/kg/h.
- If hypokalemia persists despite a maximum rate of potassium replacement, then the rate of insulin infusion can be reduced.
- Profound hypokalemia (<2.5 mmol/L) in untreated DKA is rare and necessitates vigorous potassium replacement while delaying the start of insulin therapy until serum potassium levels are >2.5 mmol/L to reduce the risk of cardiopulmonary and neuromuscular compromise.[163]

7.5 | Phosphate

Depletion of intracellular phosphate occurs in DKA and phosphate is lost as a result of osmotic diuresis.[5,9–11] Plasma phosphate levels fall after starting treatment and this is exacerbated by insulin, which promotes entry of phosphate into cells.[164–166] Total body phosphate depletion has been associated with a variety of metabolic disturbances.[167–169] Clinically significant hypophosphatemia may occur if IV therapy without food consumption is prolonged beyond 24 hours.[9–11]

- Prospective studies involving relatively small numbers of subjects and with limited statistical power have not shown clinical benefit from phosphate replacement.[170–175]
- Severe hypophosphatemia combined with phosphate depletion (ie, when not solely due to intracellular phosphate translocation) is uncommon, but can have severe consequences. Manifestations depend on the severity and chronicity of the phosphate depletion; patients usually do not have symptoms until plasma phosphate is <1 mg/dL (0.32 mmol/L).
- Severe hypophosphatemia can occur during treatment of DKA; however, symptoms are uncommon because the hypophosphatemia usually is acute and there typically is no antecedent chronic phosphate deficiency.
- Clinical manifestations of hypophosphatemia are largely due to intracellular phosphate depletion. Decreased intracellular ATP levels impair cellular functions that depend on energy-rich

phosphate compounds, and a decrease in 2,3-diphosphoglycerate (DPG) level increases the affinity of hemoglobin for oxygen and reduces oxygen release in tissues.[175] Many organ systems can be affected.[168,176] Manifestations include:

- Metabolic encephalopathy (irritability, paresthesias, confusion, seizures, coma); impaired myocardial contractility and respiratory failure due to weakness of the diaphragm; muscle dysfunction with proximal myopathy, dysphagia and ileus; rare hematologic effects include hemolysis, decreased phagocytosis and granulocyte chemotaxis, defective clot retraction, and thrombocytopenia. Acute hypophosphatemia in a patient with preexisting severe phosphate depletion can lead to rhabdomyolysis.[168,177,178]
- Severe hypophosphatemia associated with any of the above symptoms should be treated.[179,180]
- Administration of phosphate may induce hypocalcemia.[181,182]
- 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)**.[181,182]

7.6 | Acidosis

Severe acidosis is reversible by fluid and insulin replacement; insulin stops further ketoacid production and allows ketoacids to be metabolized, which generates bicarbonate. 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.[183–186] Bicarbonate therapy may cause paradoxical CNS acidosis[187,188] and rapid correction of acidosis with bicarbonate causes hypokalemia.[187,189,190] Bicarbonate administration may be beneficial in the rare patient with life-threatening hyperkalemia or unusually severe acidosis (vpH <6.9) that has compromised cardiac contractility.[191]

- If bicarbonate is considered necessary, cautiously give 1 to 2 mmol/kg over 60 minutes.

Complications of therapy

- Cerebral edema
- Hypokalemia
- Hyperchloremic acidosis
- Hypoglycemia
- Inadequate rehydration

8 | 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).
  - Persistent ketonuria (measurement of urine ketones with test strips is based on the nitroprusside reaction, which measures acetoacetate and acetone) characteristically occurs for several hours after serum BOHB levels have returned to normal.[68,72]
  - Absence of ketonuria should *not* be used as an end-point for determining resolution of DKA.
- When ketoacidosis has resolved, oral intake is tolerated, and the change to SC insulin is planned, a dose of basal (long- or intermediate-acting) insulin should be administered in addition to rapid- or short-acting insulin.[158] The most convenient time to change to SC insulin is just before a mealtime. There may, also, be benefits to earlier administration of a dose of basal insulin while the patient is still receiving IV insulin infusion. For example, in one uncontrolled study, 0.3 units/kg of SC insulin glargine was given in the first 6 hours of management and led to faster resolution of DKA.[192] Another retrospective uncontrolled study showed that co-administration of insulin glargine (approximately 0.4 units/kg) early in the course of DKA treatment was well tolerated, did not increase the risk of hypoglycemia, but was associated with more frequent hypokalemia.[193]
- To prevent rebound hyperglycemia the first SC injection should be given 15 to 30 minutes (with rapid-acting insulin) or 1 to 2 hours (with regular insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed. With intermediate- or long-acting insulin, the overlap should be longer and the rate of IV insulin administration gradually decreased. For example, for patients on a basal-bolus insulin regimen, the first dose of basal insulin may be administered in the evening and the IV insulin infusion is stopped the next morning.
- The regimen, 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.

8.1 | Morbidity and mortality

In population studies, the mortality rate from DKA in children is 0.15% to 0.30%[194–196] and may be decreasing.[196,197] The Centers for Disease Control and Prevention (CDC) from US National Vital Statistics System data 1968 to 2009 found that mortality has decreased from an annual rate of 2.69 per million for the period 1968 to 1969 to a rate of 1.05 per million in 2008 to 2009.[197] A number of possible reasons have been proposed for the reduction in diabetes-related deaths in children, including improved diabetes care and treatment, increased awareness of diabetes symptoms, possibly resulting in earlier recognition and treatment, and advances in education regarding diabetes and management of DKA. However, recent data show that DKA is still the leading cause of death in subjects with T1D diagnosed less than 15 years of age[198] and mortality risk is substantially increased in patients with chronically poor glycemic control and recurrent DKA.[199,200]

Cerebral injury is the major cause of mortality and morbidity[195,201] and cerebral edema accounts for 60% to 90% of all DKA deaths.[102,202] From 10% to 25% of survivors of cerebral edema have significant residual morbidity.[102,202,203] Children without overt neurological symptoms during DKA treatment may have subtle evidence of brain injury, particularly memory

deficits, after recovery from DKA.[204] Recent studies have shown that acutely impaired cognition ("mental state") is common at presentation with newly diagnosed type 1 diabetes and more likely to occur in children who present with DKA. Impaired cognition at presentation also is associated with poorer attention and memory in the week following diagnosis and lower intelligence quotient at 6 months compared to children with unimpaired cognition at diagnosis.[205] Magnetic resonance imaging (MRI), spectroscopy, and cognitive assessments at diagnosis and up to 6 months postdiagnosis show morphologic and functional brain changes that are associated with adverse neurocognitive outcomes in the medium term.[206] Furthermore, DKA at onset of type 1 diabetes predicts worse long-term glycemic control independent of demographic and socioeconomic factors.[207,208]

Other rare causes of morbidity and mortality include:

- Hypokalemia*
- Hypocalcemia, hypomagnesemia
- Severe hypophosphatemia*
- Hypochloremic alkalosis[209]
- Hypoglycemia
- Other central nervous system complications include dural sinus thrombosis, basilar artery thrombosis, intracranial hemorrhage, cerebral infarction[210–212]
- Venous thrombosis[83,84]*
- Pulmonary embolism*
- Sepsis
- Rhinocerebral or pulmonary mucormycosis[213]
- Aspiration pneumonia*
- Pulmonary edema*
- Adult respiratory distress syndrome (ARDS)
- Pneumothorax, pneumomediastinum and subcutaneous emphysema[214]
- Rhabdomyolysis*
- Ischemic bowel necrosis
- Acute kidney injury including renal failure[215]*
- Acute pancreatitis[216]*

*These complications, often with fatality, have been more frequent in HHS (see Reference 41). The pathophysiology and management of HHS are discussed below.

8.2 | Cerebral edema

The incidence of clinically overt cerebral edema in national population studies is 0.5% to 0.9% and the mortality rate is 21% to 24%.[102,202,203] Mental status abnormalities (GCS scores <14), however, occur in approximately 4% to 15% of children treated for DKA and are associated with evidence of cerebral edema on neuroimaging.[217,218] Cerebral edema is rarely seen after adolescence. Neuroimaging studies have led to the appreciation that cerebral edema is not a rare phenomenon in children with DKA, but occurs frequently and with varying severity.[217,219,220] Clinically overt cerebral edema represents the most severe manifestation of a common phenomenon.[221]

The cause of cerebral edema is controversial. Some have explained the pathogenesis as the result of rapid fluid administration with abrupt changes in serum osmolality.[120,222–226] More recent investigations, however, have found that dehydration and cerebral hypoperfusion may be associated with DKA-related cerebral injury,[102,227–230] which have led to the formulation of an alternative hypothesis; namely, that factors intrinsic to DKA may be the cause of brain injury, which could be worsened during treatment.[231,232] It is noteworthy that the degree of cerebral edema that develops during DKA correlates with the degree of dehydration and hyperventilation at presentation, but not with initial osmolality or osmotic changes during treatment.[218] Disruption of the blood-brain-barrier has been found in cases of fatal cerebral edema associated with DKA,[233,234] which further supports the view that cerebral edema is not simply caused by a reduction in serum osmolality.

Demographic factors associated with an increased risk of cerebral edema include:

- Younger age[235]
- New onset diabetes[195,235]
- Longer duration of symptoms[236]

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[102,218,237]
- Increased serum urea nitrogen at presentation[102,218]
- More severe acidosis at presentation[105,238,239]
- Bicarbonate treatment for correction of acidosis[102,240]
- A marked early decrease in serum effective osmolality[119,239]
- An attenuated rise in serum sodium concentration or an early fall in glucose-corrected sodium during therapy[100–102,239]
- Greater volumes of fluid given in the first 4 hours[105,237,239]
- Administration of insulin in the first hour of fluid treatment[105]

Signs and symptoms of cerebral edema include:

- Onset of headache after beginning treatment or progressively worsening headache.
- Change in neurological status (irritability, confusion, inability to arouse, incontinence).
- Specific neurological signs (eg, cranial nerve palsies, papilledema).
- Cushing's triad (rising blood pressure, bradycardia, and respiratory depression) is a late but important sign of increased intracranial pressure.
- Decreased O_2 saturation.

Clinically significant cerebral edema usually develops within the first 12 hours after treatment has started but can occur before treatment has begun[102,203,241–244] or, rarely, may develop as late as 24 to 48 hours after the start of treatment.[102,235,245] Symptoms and signs are variable. Although mild to moderate headache at

presentation may not be unusual, development of a severe headache after commencing treatment is always concerning. A method of clinical diagnosis based on bedside evaluation of neurological state is shown below.[246] 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%. Signs that occur before treatment should not be considered in the diagnosis of cerebral edema. Neuroimaging is not required for diagnosis of cerebral edema.

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 (eg, grunting, tachypnea, Cheyne-Stokes respiration, apneusis)

Major criteria

- Altered mentation, confusion, 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

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.

The appearance of diabetes insipidus, manifested by increased urine output with a concomitant marked increase in the serum sodium concentration, reflecting loss of free water in the urine, is a sign of cerebral herniation causing interruption of blood flow to the pituitary gland.

8.3 | Treatment of cerebral edema

- Initiate treatment as soon as the condition is suspected.
- Adjust fluid administration rate as needed to maintain normal blood pressure while avoiding excessive fluid administration that might increase cerebral edema formation. Assiduously avoid hypotension that might compromise cerebral perfusion pressure.
- Hyperosmolar agents should be readily available at the bedside.
- Give mannitol, 0.5 to 1 g/kg IV over 10 to 15 minutes.[247–249] The effect of mannitol should be apparent after ~15 minutes, and is expected to last about 120 minutes. If necessary, the dose can be repeated after 30 minutes.
- Hypertonic saline (3%), suggested dose 2.5 to 5 mL/kg over 10 to 15 minutes, may be used as an alternative to mannitol, or in addition to mannitol if there has been no response to mannitol within 15 to 30 minutes.[250,251]
  - Hypertonic saline (3%) 2.5 mL/kg is equimolar to mannitol 0.5 g/kg.
  - A recent 11-year retrospective cohort study showed that hypertonic saline has replaced mannitol as the most commonly used hyperosmolar agent in many US institutions. Although controversial and further investigation is needed, the data suggest that hypertonic saline may not have benefits over mannitol and may be associated with a higher mortality rate.[196,252]
- Elevate the head of the bed to 30° and keep the head in the midline position.
- Intubation may be necessary for the patient with impending respiratory failure due to severe neurologic compromise.
- *After* treatment for cerebral edema has been started, cranial imaging may be considered as with any critically ill patient with encephalopathy or acute focal neurologic deficit. However, treatment of the clinically symptomatic patient should not be delayed in order to obtain imaging.[253] The primary concern that would warrant neuroimaging is whether the patient has a lesion requiring emergency neurosurgery (eg, intracranial hemorrhage) or a lesion that may necessitate anticoagulation (eg, cerebrovascular thrombosis), as suggested by clinical findings of focal or severe, progressive headache, or focal neurologic deficit.[211,254–256]

8.4 | Hyperglycemic hyperosmolar state

This syndrome is characterized by extremely elevated serum glucose concentrations and hyperosmolality without significant ketosis.[41] The incidence of HHS is increasing[37,38,257] and a recent study found HHS in 2% of youth with type 2 diabetes at presentation[34]; nonetheless, it is considerably less frequent in children and adolescents than DKA.

Unlike the usual symptoms of DKA (hyperventilation, vomiting, and abdominal pain), which typically bring children to medical attention, the gradually increasing polyuria and polydipsia of HHS may go unrecognized resulting in profound dehydration and electrolyte losses at the time of presentation. In adults, fluid losses in HHS have been estimated to be twice those of DKA; furthermore, obesity and hyperosmolality can make the clinical assessment of dehydration challenging. Despite severe volume depletion and electrolyte losses, hypertonicity preserves intravascular volume and signs of dehydration may be less evident.

During therapy, decreasing serum osmolality (from enhanced glucosuria and insulin-mediated glucose uptake) results in movement of water out of the intravascular space resulting in decreased intravascular volume, and pronounced osmotic diuresis may continue for many hours in patients with extremely increased plasma glucose concentrations. Early in the course of treatment, urinary fluid losses may be considerable and because intravascular volume may decrease rapidly during treatment in patients with HHS, more aggressive replacement of intravascular volume (as compared to treatment of children with DKA) is required to avoid vascular collapse.

8.5 | Treatment of HHS

There are no prospective data to guide treatment of children and adolescents with HHS. The following recommendations are based on extensive experience in adults and an appreciation of the pathophysiological differences between HHS and DKA[41]; see Figure 3. Patients

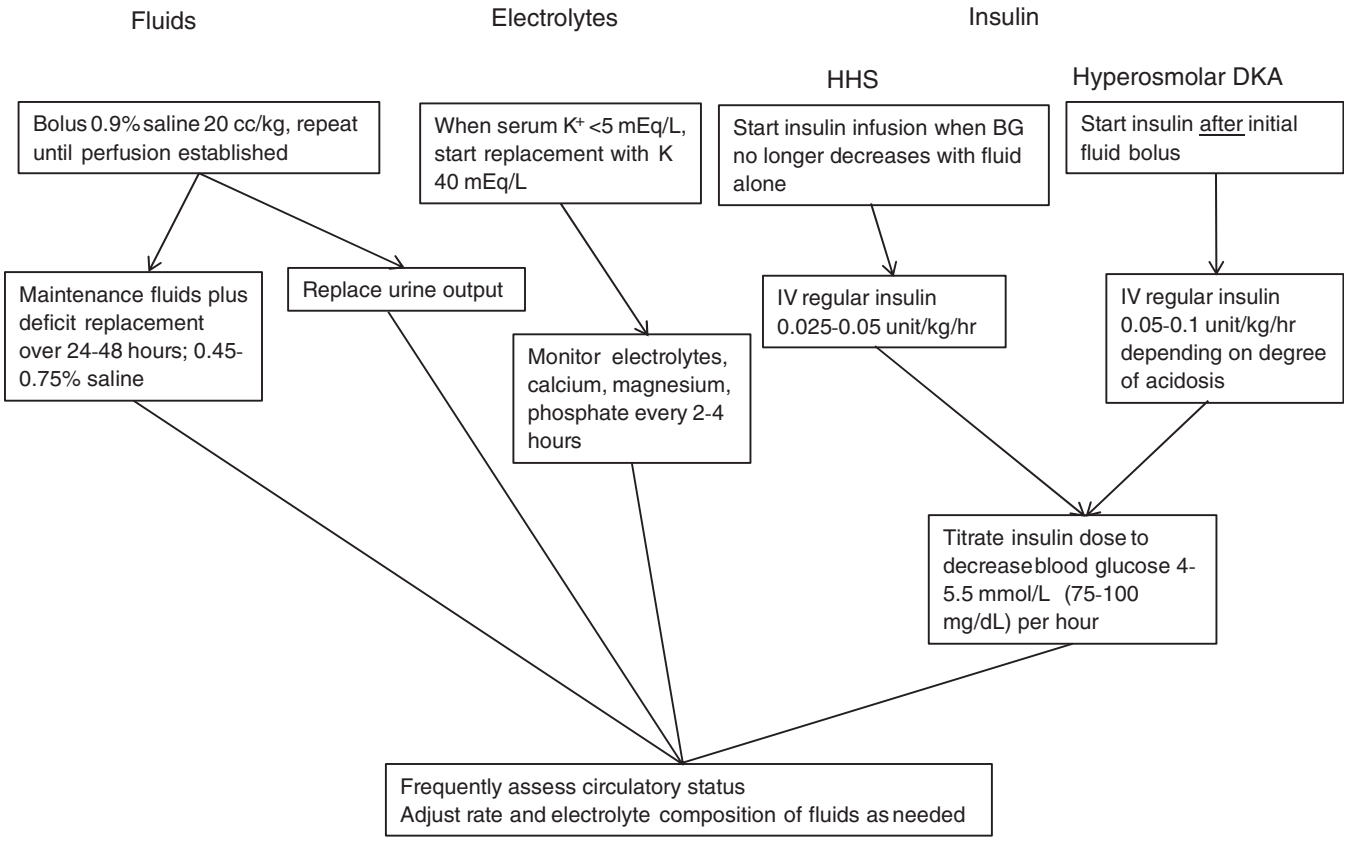

FIGURE 3 Treatment of hyperglycemic hyperosmolar syndrome (HHS) (from Reference 41)

should be admitted to an intensive care unit or comparable setting where expert medical, nursing and laboratory services are available.

8.6 | Fluid therapy

The goal of initial fluid therapy is to expand the intra- and extravascular volume and restore normal renal perfusion. The rate of fluid replacement should be more rapid than is recommended for DKA.

- The initial bolus should be ≥20 mL/kg of isotonic saline (0.9% NaCl) and a fluid deficit of approximately 12% to 15% of body weight should be assumed. Additional fluid boluses should be given rapidly, if necessary, to restore peripheral perfusion.
- Thereafter, 0.45% to 0.75% NaCl should be administered to replace the deficit over 24 to 48 hours.
- The goal is to promote a gradual decline in corrected serum sodium concentration and serum osmolality.
- Because isotonic fluids are more effective in maintaining circulatory volume, isotonic saline should be restarted if perfusion and hemodynamic status appear inadequate as serum osmolality declines.
- Serum sodium concentrations should be measured frequently and the sodium concentration in fluids adjusted to promote a gradual decline in corrected serum sodium concentration. Mortality has been associated with failure of the corrected serum sodium concentration to decline with treatment, which may be an indication for hemodialysis. Hemodialysis has resulted in 80% survival in contrast to 20% with peritoneal dialysis.[38]

- Although there are no data to indicate an optimal rate of decline in serum sodium concentration, 0.5 mmol/L/h has been recommended for hypernatremic dehydration.[258] With adequate rehydration alone (ie, before commencing insulin therapy), serum glucose concentrations should decrease by 4.1 to 5.5 mmol/L (75-100 mg/dL) per hour.[259,260]
- A more rapid rate of decline in serum glucose concentration is typical during the first several hours of treatment when an expanded vascular volume leads to improved renal perfusion. If there is a continued rapid fall in serum glucose (>5 mmol/L, 90 mg/dL/h) after the first few hours, consider adding 2.5% or 5% glucose to the rehydration fluid. Failure of the expected decrease of plasma glucose concentration should prompt reassessment and evaluation of renal function.
- Unlike treatment of DKA, replacement of urinary losses is recommended.[141] The typical urine sodium concentration during an osmotic diuresis approximates 0.45% saline; however, when there is concern about the adequacy of circulatory volume, urinary losses may be replaced with a fluid containing a higher sodium concentration.

8.7 | Insulin therapy

Whereas tissue hypoperfusion in HHS commonly causes lactic acidosis, ketosis usually is minimal. Early insulin administration is unnecessary in HHS. Fluid administration alone causes a marked decline in serum glucose concentration as a result of dilution, improved renal perfusion leading to increased glucosuria, and increased tissue glucose uptake with improved circulation. The osmotic pressure exerted by glucose within the vascular space contributes to the maintenance of blood volume. A rapid fall in serum glucose concentration and osmolality after insulin administration may lead to circulatory compromise and venous thrombosis unless fluid replacement is adequate. Patients with HHS also have extreme potassium deficits; a rapid insulin-induced shift of potassium to the intracellular space can trigger an arrhythmia.

- Insulin administration should be initiated when serum glucose concentration is no longer declining at a rate of at least 3 mmol/L (~50 mg/dL) per hour with fluid administration alone.
- In patients with more severe ketosis and acidosis, however, insulin administration should be initiated earlier.
- Continuous administration of insulin at a rate of 0.025 to 0.05 units/kg/h can be used initially, with the dosage titrated to achieve a decrease in serum glucose concentration of 3 to 4 mmol/L (~50-75 mg/dL) per hour.
  - Insulin boluses are not recommended.

8.8 | Electrolytes

In general, deficits of potassium, phosphate, and magnesium are greater in HHS than DKA.

- Potassium replacement (40 mmol/L of replacement fluid) should begin as soon as serum potassium concentration is within the normal range and adequate renal function has been established.
  - Higher rates of potassium administration may be necessary after starting an insulin infusion
  - Serum potassium concentrations should be monitored every 2 to 3 hours along with ECG monitoring
  - Hourly potassium measurements may be necessary if the patient has hypokalemia
- Bicarbonate therapy is contraindicated; it increases the risk of hypokalemia and may adversely affect tissue oxygen delivery.
- Severe hypophosphatemia may lead to rhabdomyolysis, hemolytic uremia, muscle weakness and paralysis. Although administration of phosphate is associated with a risk of hypocalcemia, an IV solution that contains a 50:50 mixture of potassium phosphate and another suitable potassium salt (potassium chloride or potassium acetate), generally permits adequate phosphate replacement while avoiding clinically significant hypocalcemia.
  - Serum phosphate concentrations should be measured every 3 to 4 hours.
- Patients with HHS frequently have large magnesium deficits, but there are no data to determine whether replacement of magnesium is beneficial.
- Replacement of magnesium should be considered in the occasional patient who experiences severe hypomagnesemia and hypocalcemia during therapy. The recommended dose is 25 to 50 mg/kg per dose for 3 to 4 doses given every 4 to 6 hours with a maximum infusion rate of 150 mg/min and 2 g/h.

8.9 | Complications

- Venous thrombosis associated with use of central venous catheters is a common hazard in HHS.[83] Prophylactic use of low-dose heparin has been suggested in adults but there are no data to indicate benefit from this practice. Heparin treatment should be reserved for children who require central venous catheters for physiologic monitoring or venous access and are immobile for more than 24 to 48 hours.[41] The central venous catheter should not be used for insulin administration because the large dead space may cause erratic insulin delivery.
- Rhabdomyolysis may occur in children with HHS resulting in acute kidney failure, severe hyperkalemia, hypocalcemia, and muscle swelling causing compartment syndrome.[261] The classic symptom triad of rhabdomyolysis includes myalgia, weakness, and dark urine; monitoring creatine kinase concentrations every 2 to 3 hours is recommended for early detection.
- For unknown reasons, several children with HHS have had clinical manifestations consistent with malignant hyperthermia, which is associated with a high mortality rate.[36,262–264] Patients who have a fever associated with a rise in creatine kinase concentrations may be treated with dantrolene, which reduces release of calcium from the sarcoplasmic reticulum and stabilizes calcium metabolism within muscle cells. Nonetheless, of the three reported patients with HHS treated with dantrolene only one survived.[262,264]
- Altered mental status is common in adults whose serum osmolality exceeds 330 mOsm/kg; however, cerebral edema is rare.[38] Among 96 cases of HHS reported in the literature to 2010, including 32 deaths, there was only one instance of cerebral edema.[38] A decline in mental status after hyperosmolality has improved with treatment is unusual and should be promptly investigated.

8.10 | Mixed HHS and DKA

Treatment must take into account potential complications of both DKA and HHS. Mental status must be closely monitored and frequent reassessment of circulatory status and fluid balance is necessary to guide therapy. To maintain an adequate circulatory volume, the rate of fluid and electrolyte administration usually exceeds that required for the typical case of DKA. Insulin is necessary to resolve ketosis and arrest hepatic gluconeogenesis; however, insulin infusion should be deferred until after the patient has received an initial fluid bolus and the circulation has been stabilized. Serum potassium and phosphate concentrations should be carefully monitored as described above for HHS.

8.11 | 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.
- 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.
- 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.[265] 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 at a time when a urine ketone test is negative or shows only trace or small ketonuria.[266]
- 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,
  - depression or other reason for inability of the patient to manage the diabetes unassisted.
- A psychiatric social worker or clinical psychologist should be consulted to identify the psychosocial reason(s) contributing to development of DKA.
- An infection is rarely the cause of DKA 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.[267–269]
- Insulin omission can be prevented by comprehensive programs that provide education, psychosocial evaluation and treatment combined with adult supervision of the entire process of insulin administration.[270]
  - Parents and patients should learn how to recognize and treat ketosis and impending DKA with additional rapid- or short-acting insulin and oral fluids
  - Families should have access to a 24-hour telephone helpline for emergency advice and treatment[267]
  - When a responsible adult administers insulin there may be as much as a 10-fold reduction in frequency of recurrent DKA.[270]

ENDNOTES

*Nitroprusside reaction method.

†Serum bicarbonate concentration alone can substitute for vpH to diagnose DKA and classify severity in children with new onset diabetes mellitus. It is suggested as an alternative to reliance on vpH, especially in settings in which access to vpH measurement is limited.[26]

‡Some experts use 1.6 rather than 2 as the coefficient in the equation.[92]

CONFLICT OF INTEREST

J.W. receives royalties as a section editor for UpToDate. M.F. is member of Lilly Diabetes, Eli Lilly Ges.m.b. (advisory board); Medtronic (speaker fee); Ferring pharmaeuticals Ges m.b.h. (prize for best scientific presentation). R.H. receives lecture honoraria from Novo Nordisk, Medtronic; Advisory Board Novo Nordisk, Medtronic, Insulet; Data Monitoring Committee Astra Zeneca. M.A.S. was a member of a Scientific Advisory Board for NovoNordisk during 2017 and 2018. A.R., N.G., M.A. and E.C. have no conflicts of interest to declare.

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