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ISPAD GUIDELINES

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ISPAD Clinical Practice Consensus Guidelines 2022: Diabetic ketoacidosis and hyperglycemic hyperosmolar state

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1 | SUMMARY OF WHAT IS NEW OR DIFFERENT

Changes to previous recommendations include:

- Biochemical criteria to diagnose diabetic ketoacidosis (DKA) include serum bicarbonate <18 mmol/L
- Infusion of initial fluid bolus(es) over 20–30 min
- Promoting a rise in serum sodium concentrations during DKA treatment is no longer considered necessary
- Increased emphasis on differences in treatment recommendation for HHS and mixed presentation of DKA and HHS (hyperosmolar DKA) compared to standard DKA treatment

2 | EXECUTIVE SUMMARY

The **biochemical criteria** for the diagnosis of DKA are:

- Hyperglycemia (blood glucose >11 mmol/L [≈200 mg/dl])
- Venous pH <7.3 or serum bicarbonate <18 mmol/L(C)
- Ketonemia (blood ß-hydroxybuyrate ≥3 mmol/L) (C) or moderate or large ketonuria.

Not all children or caregivers volunteer classic symptoms of diabetes (polyuria, polydipsia) at the time of diagnosis of DKA, and other symptoms of DKA are non-specific. Therefore, fingerstick blood glucose measurements should be considered for all children presenting with rapid breathing or with vomiting and abdominal pain without diarrhea.

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 to severe and life threatening), some children may require specific treatment that, in the judgment of the treating physician, may occasionally be outside the range of options presented here. Clinical judgment should be used to determine optimal treatment for the individual child, and timely adjustments to treatment should be based on ongoing clinical and biochemical monitoring of the response to treatment.

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 and blood gases; and assessment of level of consciousness. (E) Two peripheral intravenous (IV) catheters should be inserted (E).

Management should be conducted in a center experienced in the treatment of DKA in children 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, there should be telephone or videoconference support from a physician with expertise in DKA (E).

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Meticulous monitoring of the clinical and biochemical response to treatment is necessary so that timely adjustments in treatment can be made when indicated by 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 acute complications, and identify and treat any precipitating event.

Fluid replacement should begin before starting insulin therapy. Expand volume using one or more boluses of 0.9% saline infused over 20–30 min to restore peripheral circulation (E). Calculate the subsequent rate of fluid administration (0.45% to 0.9% saline), including the provision of maintenance fluid requirements, aiming to replace the estimated fluid deficit over 24 to 48 h (A).

Insulin therapy: begin with 0.05–0.1 U/kg/h (0.05 U/kg/h can be considered with pH > 7.15) at least 1 h AFTER starting fluid replacement therapy (B).

Potassium: If the child has hyperkalemia (potassium >5.5 mmol/L), *defer* potassium replacement therapy until urine output is documented. Begin intravenous fluid treatment with non-potassium containing fluids and measure potassium hourly. Begin potassium infusion when potassium <5.5 mmol/L. In the rare child with hypokalemia (potassium <3.0 mmol/L), *defer* insulin treatment and give a bolus of potassium (not to exceed 0.5 mEq/Kg/h), along with cardiac monitoring. Otherwise, begin with 40 mmol potassium/L (E).

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

Warning signs and symptoms of cerebral injury include: Onset of headache or vomiting 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 (irritability, lethargy, confusion, incontinence), specific neurological signs (e.g., cranial nerve palsies), decreased oxygen saturation. (C) Hypertension occurs commonly in children with DKA and should not be considered a warning sign for cerebral injury, in the absence of other findings.

In children with multiple risk factors for cerebral injury (elevated serum urea nitrogen concentration (>20 mg/dl), severe acidosis (pH < 7.1), severe hypocapnia (pCO_2 < 21 mmHg), age < 5 years), have mannitol or hypertonic saline at the bedside and the dose calculated. (E) If neurologic status deteriorates acutely, hyperosmolar therapy with mannitol or hypertonic saline should be given immediately (C).

Prevention: Management of DKA is not complete until an attempt has been made to identify and treat the cause. DKA without a preceding illness in a child with known diabetes is almost always the result of failure to appropriately administer insulin injections or interruption of insulin delivery, most often as a result of insulin pump infusion set dysfunction. In new onset diabetes, DKA is frequently the consequence of a delay in diagnosis (E).

The criteria for **Hyperglycemic Hyperosmolar State (HHS)** include all the following:

- 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

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. Differences in treatment strategy between HHS and DKA include the volume of fluid administered, the timing of insulin administration, and monitoring of the decline in corrected serum sodium concentration.

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). Rates of fluid administration, both as initial fluid boluses to restore circulation and as ongoing deficit replacement, are substantially higher than for DKA.

3 | PATHOPHYSIOLOGY

Diabetic ketoacidosis (DKA) results from deficiency of circulating insulin and increased levels of the counterregulatory hormones: glucagon, catecholamines, cortisol and growth hormone.[1–3] In most cases, DKA is caused by new onset of diabetes, omission of insulin injections, interruption of insulin delivery in children using an insulin pump, or inadequate management of an infection. Severe insulin deficiency occurs in previously undiagnosed T1D and when patients deliberately or inadvertently do not inject insulin, especially the long-acting component of a basal-bolus regimen, or markedly reduce the doses of insulin, for example, during an intercurrent illness such as gastroenteritis. Children who use an insulin pump can rapidly develop DKA when insulin delivery fails for any reason.[4] Relative insulin deficiency occurs when the concentrations of counterregulatory hormones markedly increase in conditions such as sepsis, trauma, or febrile illness, which overwhelm homeostatic mechanisms and lead to metabolic decompensation despite the patient injecting 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 and obligatory loss of electrolytes (sodium, potassium, phosphate, magnesium) leading to dehydration, 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

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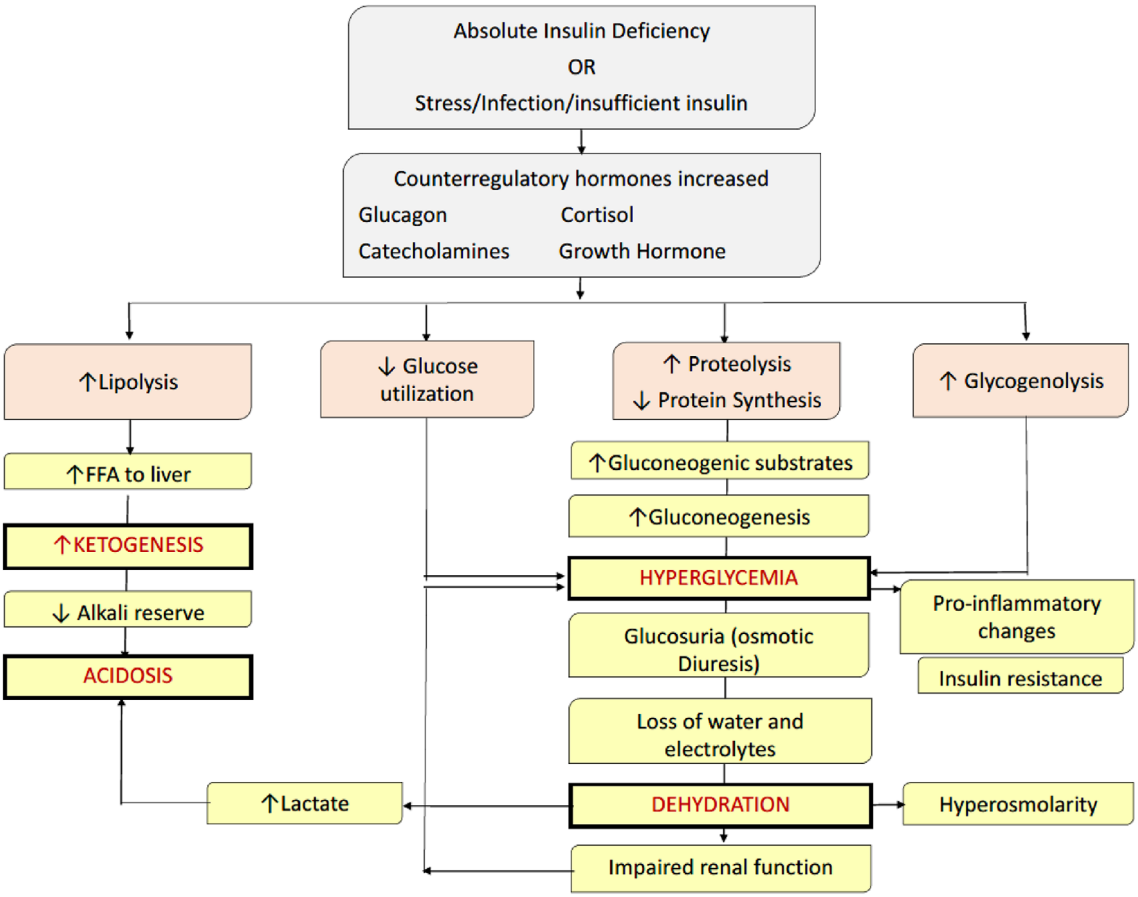


FIGURE 1 Pathophysiology of diabetic ketoacidosis. Copyright © 2006 American Diabetes Association. Adapted from diabetes care, Vol. 29, 2006:1150–1159. Reprinted with permission of *The American Diabetes Association*

hyperketonemia. Lactic acidosis from hypoperfusion may contribute to the acidosis.[5,6] Hyperglycemia also causes a hyperinflammatory state that increases insulin resistance and is involved in the pathophysiology of several DKA complications. If this cycle is not interrupted by exogenous insulin together with fluid and electrolyte therapy, fatal dehydration and metabolic acidosis will ensue (Figure 1).

Diabetic ketoacidosis (DKA) is characterized by severe depletion of water and electrolytes from both the intra- and extracellular fluid compartments[5]; the typical range of losses is shown in Table 1. Despite substantial dehydration, children generally continue to maintain normal blood pressure or even have high blood pressure,[7,8] possibly due to elevated plasma catecholamine concentrations, increased release of antidiuretic hormone (ADH) in response to hyperosmolality (which increases blood pressure via vasporessin 2 receptors), increased osmotic pressure from marked hyperglycemia, or other factors.[7,8] 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 child vary depending upon the duration and severity of illness, the extent to which the child 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 (fruit juices or sugar-containing soft drinks) may exacerbate hyperglycemia.[9]

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

4 | DEFINITION OF DIABETIC KETOACIDOSIS

The diagnosis of DKA is based on the triad of hyperglycemia, ketosis and metabolic acidosis; however, specific biochemical criteria used to

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TABLE 1 Losses of fluid and electrolytes in diabetic ketoacidosis and maintenance requirements in normal children

	Average (range) losses per kg	24-h 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 11–20 >20 kg 1500 ml + 20 ml/kg/24 h for each kg >20
Sodium	6 mmol (5–13)	2–4 mmol[a]
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

Note: Data are from measurements in only a few children and adolescents.[124–128] In any individual patient, actual losses may be less or more than the ranges shown.
Note: Three methods for determining maintenance water requirements in children are commonly used: *the Holliday–Segar formula[273] (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).[274]
Note: 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.
[a]Maintenance electrolyte requirements in children are per 100 ml of maintenance IV fluid.[274,275]

define DKA vary in different parts of the world and among different research studies.[3] All three biochemical criteria are required to diagnose DKA[10]:

- Hyperglycemia (blood glucose >11 mmol/L [200 mg/dl])
- Venous pH < 7.3 or serum bicarbonate <18 mmol/L
- Ketonemia* or ketonuria

*Although not universally available, blood beta-hydroxybutyrate (BOHB) concentration should be measured whenever possible. BOHB ≥3 mmol/L is a sensitive indicator of DKA[11] but is not as specific as a value of ≥5.3 mmol/L, which has optimal accuracy (~91%) for predicting DKA in children with hyperglycemia presenting to an Emergency Department.[12] Urine ketones are typically ≥2+ ("moderate or large"). Urine ketone testing detects acetoacetate and acetone but not BOHB, the main ketone in DKA.[13] Therefore, reliance on urine testing alone may underestimate the severity of ketonemia. Several sulfhydryl-containing drugs (captopril, N-acetylcysteine, mesna, penicillamine) and valproic acid, which is partly eliminated as a ketone-containing metabolite,[14] give false positive urine tests.[15,16] Expired or improperly stored urine test strips can give false negative results.[17]

Partially treated children and those who have consumed little or no carbohydrate may have only modestly elevated blood glucose concentrations, referred to as euglycemic ketoacidosis.[18,19] This can be caused by starvation/fasting, a low carbohydrate-high fat diet, or the off-label use of SGLT2-inhibitors.[20–23] Management of euglycemic ketoacidosis should follow standard DKA guidelines except that dextrose-containing fluids should be started earlier, immediately after initial volume expansion. Serum bicarbonate concentration alone can substitute for venous pH to diagnose DKA and classify severity in children with new onset diabetes mellitus and is an alternative to venous pH in circumstances where pH measurement is not available.[24]

The frequency of type 2 diabetes in the pediatric age range is increasing worldwide.[25–28] Overall, 5% to 25% of children with type 2 diabetes have DKA at the time of diagnosis.[29,30] In the SEARCH for Diabetes in Youth Study in the USA, DKA occurred in nearly 6% of youth with type 2 diabetes.[31,32]

The **severity of DKA** is categorized by the degree of acidosis[10,33]

- Mild: venous pH < 7.3 or serum bicarbonate <18 mmol/L[24]
- Moderate: pH < 7.2 or serum bicarbonate <10 mmol/L
- Severe: pH < 7.1 or serum bicarbonate <5 mmol/L

Diabetic ketoacidosis (DKA) should be distinguished from HHS, which is characterized by severe hyperglycemia and markedly increased serum osmolality without substantial ketosis and acidosis. HHS may occur in children with type 2 diabetes,[30,34–36] type 1 diabetes,[37] cystic fibrosis,[35] and in infants, especially those with neonatal diabetes.[38,39] Medications such as corticosteroids[40] and atypical antipsychotics[41] can precipitate HHS. Although definitions vary slightly,[3] a committee of the Pediatric Endocrine Society proposed the following **criteria for HHS** in the pediatric age range[42]:

- 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%)

The characteristic features of HHS and DKA may overlap and some children with HHS, especially those with severe dehydration, may have mild or moderate acidosis that is mainly due to hypoperfusion and lactic acidosis. Conversely, some children with DKA may have features of HHS (severe hyperglycemia).[9] Therapy must be appropriately modified to address the pathophysiology and particular biochemical disturbances of the individual child (see below).

5 | FREQUENCY AND CAUSES OF DKA

Children with new onset of type 1 diabetes (T1D) frequently present with DKA. Frequencies range from approximately 15% to 70% in Europe and North America.[32,43–51] Several countries have reported recent increases in the frequency of DKA at diagnosis of T1D.[51–53] Very young children and those of underserved ethnic groups are at increased risk of presenting with DKA.[54,55] Delayed diagnosis of diabetes is an important factor increasing the risk of DKA and this association has been particularly evident during the SARS-CoV2 pandemic.[56–59] Prevention campaigns targeting awareness of diabetes

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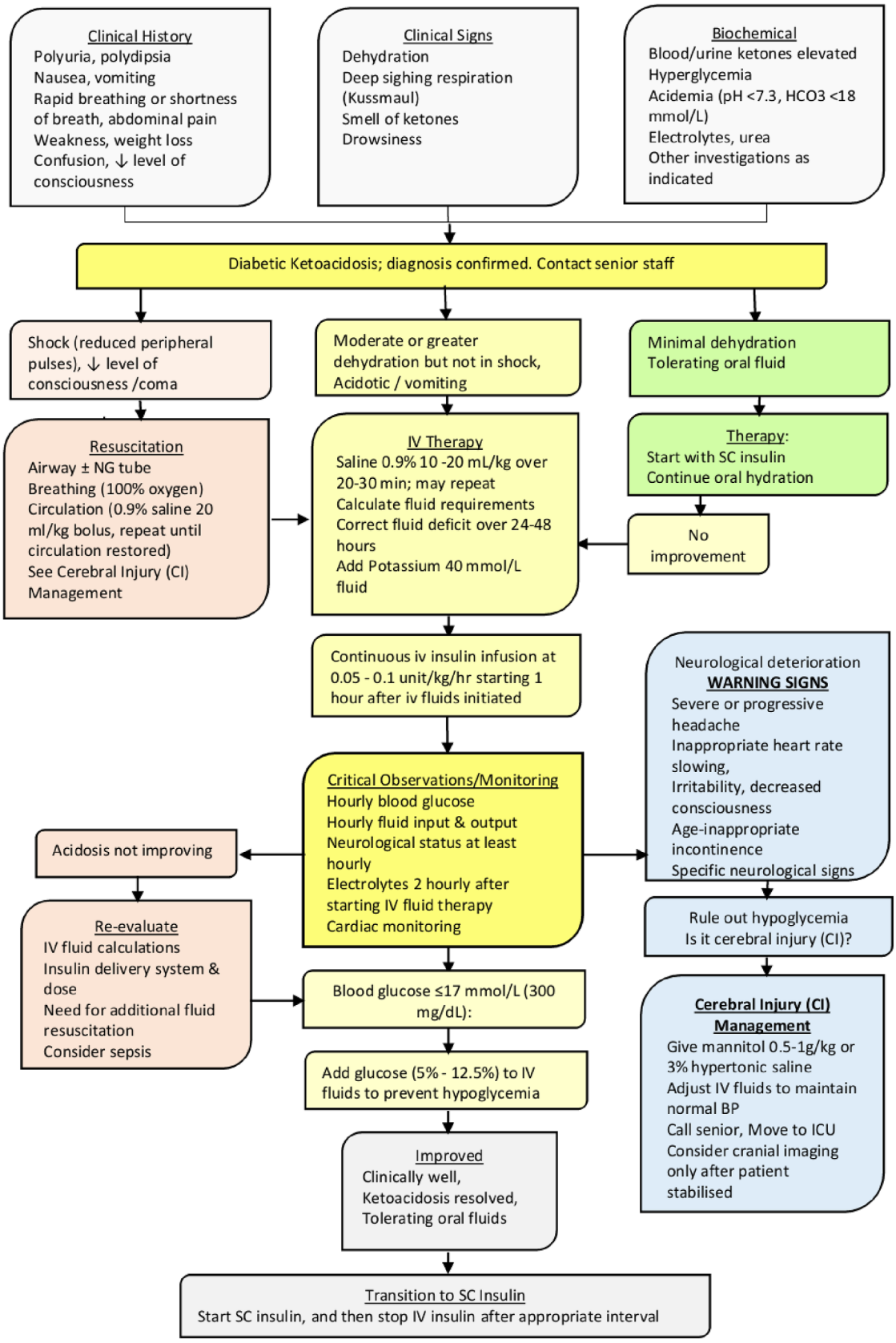


FIGURE 2 Algorithm for the management of DKA. Adapted from Pinhas-Hamiel and Sperling.[272] NG, nasogastric; SC, subcutaneous.

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TABLE 2 Glasgow coma scale (GCS)

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[a]	3. Inconsistently consolable and moans; makes vocal sounds	3. Flexion to pain (decorticate posture)
4. Eyes open spontaneously	4. Confused, disoriented conversation[b]	4. Consolable when crying and interacts inappropriately	4. Withdrawal from pain
	5. Oriented, normal conversation	5. Smiles, oriented to sound, follows objects and interacts	5. Localizes pain
			6. Obeys commands

Note: The GCS consists of three parameters and is scored between 3 and 15; 3 being the worst and 15 the best.[81] 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.

symptoms have been successful in reducing DKA frequency.[60] In children with established diabetes, the risk of recurrent DKA is 1%–10% per patient-year.[4,61–66] Most cases of DKA in children with established diabetes are due to insulin omission or interruption of insulin delivery in children using insulin pumps.[63,64] A minority of DKA cases in children are caused by infections (mainly gastroenteritis).

6 | MANAGEMENT OF DKA

6.1 | Emergency assessment

Acute management (Figure 2) should follow the general guidelines for PALS,[67,68] with particular attention to the following:

- Obtain vital signs and measure weight–The current weight should be used for calculations and not a weight from a previous visit. If body surface area is used for fluid therapy calculations, measure height or length to determine surface area. Note that despite severe dehydration, hypertension occurs in 12% of children with DKA at presentation and develops during treatment in an additional 16%.[7]
- Insert peripheral intravenous line, obtain blood for laboratory evaluation, and start intravenous fluid therapy following guidelines (see Section 6.3).
- Immediately measure blood glucose and blood BOHB levels with bedside meters or urine acetoacetic acid concentrations with urine test strips if bedside blood ketone measurements are not available. Measurement of blood BOHB concentration with a point-of-care meter, if available, is very useful to confirm ketoacidosis (≥3 mmol/L in children)[11] and to monitor the response to treatment.[12,69–75]
- Measure venous pH, pCO_2, glucose, electrolytes (including serum bicarbonate), serum urea nitrogen, and creatinine.
- Perform a detailed history and physical exam with particular attention to mental status and any possible source of infection.
- **Severity of dehydration**
  - Estimation of the degree of dehydration is imprecise in DKA and shows only fair to moderate agreement among examiners.[76–78] The most useful clinical signs for predicting dehydration are:
    - prolonged capillary refill time (normal capillary refill is ≤2 s), abnormal skin turgor ('tenting' or inelastic skin), dry mucus membranes, sunken eyes, absent tears, weak pulses, cool extremities.[79]
  - Laboratory measures have been found to be better predictors of dehydration severity than clinical signs.[80] These include:
    - Higher serum urea nitrogen (>20 mg/dl)
    - Lower pH (<7.1)
  - ≥10% dehydration is suggested by the presence of weak or impalpable peripheral pulses, hypotension or oliguria.
- **Assess level of consciousness** (Glasgow coma scale [GCS]–see Table 2)[81,82]
- In the unconscious or severely obtunded child **without normal airway protective reflexes**, **secure the airway** by rapid sequence intubation.
  - Insert a nasogastric tube with continuous 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 injury.[83,84]
- Give **oxygen** to patients with circulatory impairment or shock.
- A continuous **cardiac monitor** should be used to assess degree of tachycardia, monitor for arrhythmias, and assess T-waves for evidence of hyper- or hypokalemia.[85,86]
- A second **peripheral intravenous (IV) catheter** should be placed for convenient and painless repetitive blood sampling. An **arterial catheter** may, rarely, be necessary in some critically ill children managed in an intensive care unit.
  - Unless absolutely necessary, **avoid placing a central venous catheter** because of the high risk of thrombosis. If a central catheter has been inserted, the catheter should be removed as soon as the child's clinical status permits.[87,88] Mechanical and pharmacologic prophylaxis (low molecular weight heparin) should be considered for those with central venous catheters, especially in children >12 years.

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- Insulin should 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.
- **Antibiotics** may be required for **children with evidence of infection** after obtaining appropriate cultures such as blood, urine, spinal fluid, throat, or tracheal aspirate as indicated.
- Bladder catheterization usually is not necessary but should be considered if the child is unconscious or severely ill.
- **Additional laboratory measurements** include:
  - Hemoglobin/ hematocrit
  - Albumin, calcium, phosphate and magnesium concentrations
  - Hemoglobin A1c may be useful to confirm the diagnosis of diabetes (e.g., in a child with hyperglycemia suspected to be due to a stress response and metabolic acidosis caused by dehydration) or as an indicator of duration of hyperglycemia
  - Complete blood counts (CBC) frequently show increased WBC and left shift in children with DKA, even without infection. Infection evaluation should be based on the clinical scenario and not on the white cell count.
- If laboratory measurement of serum potassium is delayed, perform an **electrocardiogram** (ECG) for baseline evaluation of potassium status.[85,86]

6.2 | Where should the child with DKA be managed?

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

- Experienced nursing and medical staff trained in pediatric DKA management who are available to perform meticulous monitoring until DKA has resolved.
- Care policies and procedures based on clinical practice guidelines. Staff should have access to clinical practice guidelines in written or electronic format.
- 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. If this is not possible due to geographic or resource constraints, arrangements should be made to access telephone or videoconference support from a physician with expertise in DKA 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 injury (e.g., <5 years of age, pH < 7.1, pCO_2 < 21 mmHg, blood urea nitrogen > 20 mg/dl) 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. Transport teams should be knowledgeable about DKA management or have access to a medical control physician with appropriate expertise and have rescue medications available during transport, including high concentration IV dextrose 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 with subcutaneous insulin, or in an outpatient health care facility (e.g., emergency ward) with supervision from an experienced diabetes team.[33,89,90]

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

6.3 | Fluid and electrolyte replacement

6.3.1 | Principles of fluid and electrolyte therapy

Children with DKA have a deficit in extracellular fluid (ECF) volume that is typically about 7% of body weight.[76,78,80] Shock with hemodynamic compromise is rare in pediatric DKA. Clinical estimates of the volume deficit based on physical exam and vital signs are inaccurate[76,78,80]; therefore, in mild DKA assume 5%, moderate DKA 7% and severe DKA 10% dehydration. Increased serum urea nitrogen and anion gap at presentation are the measures most strongly correlated with volume deficit.[80] The serum sodium concentration is an unreliable measure of the degree of ECF contraction because glucose largely restricted to the extracellular space, causes osmotic movement of water into the extracellular space thereby causing dilutional hyponatremia.[91] It is useful to calculate the corrected sodium concentration to help assess relative deficits of sodium and water (the formula for corrected sodium can be found in the Monitoring section).[5,92] The "corrected" sodium represents the expected serum sodium concentration in the absence of hyperglycemia. As the plasma glucose concentration decreases after administering fluid and insulin, the measured serum sodium concentration should increase and the glucose-corrected sodium concentration should slowly decrease or remain in the normal range.

The objectives of fluid and electrolyte replacement therapy are to:

- Restore circulating volume

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- Replace sodium and water deficits
- Improve glomerular filtration and enhance clearance of glucose and ketones from the blood

Controversies surrounding optimal fluid treatment regimens for children with DKA have largely focused on the role of intravenous fluids in causing or contributing to risk of cerebral edema and cerebral injury.[93–95] Although the pathogenesis of DKA-related cerebral injury remains incompletely understood, recent evidence suggests that abnormalities in cerebral perfusion and the hyperinflammatory state caused by DKA play important roles, and that variations in fluid treatment likely have minimal effects.[95–99] A large prospective randomized clinical trial (the PECARN FLUID Trial) compared acute and long-term neurological outcomes in 1389 children with DKA treated with slower versus more rapid fluid administration using either 0.45% saline or 0.9% saline.[96] The PECARN FLUID Trial showed no significant differences in the frequency of either altered mental status or clinical diagnoses of cerebral injury 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.[96] The results of this study suggest that a range of fluid protocols can be safely used to treat DKA in children, and that clinicians should not unnecessarily restrict fluid administration if clinical signs suggest the need for circulatory volume expansion. As protocols outside of the range used in the PECARN FLUID Trial have not been thoroughly investigated, we recommend that fluid treatment remain within the variations used in the trial. These include assumed fluid deficits between 5% and 10% of body weight, replacement of deficits over 24 to 48 h,† provision of maintenance fluids, and use of fluids with a sodium content between 0.45% and 0.9% NaCl. Although previous retrospective studies have found associations between declines in serum sodium concentrations during DKA treatment and DKA-related cerebral injury,[100,101] a recent large prospective study found no such association.[102] In that study, declines in glucose-corrected sodium concentrations were not associated with altered mental status or clinically apparent cerebral injury. Serum sodium trends during DKA treatment largely reflected the balance of sodium and water losses at presentation, with those presenting with higher initial sodium concentrations (greater free water losses) normalizing sodium concentrations during treatment. The study also found that the sodium content of intravenous fluids significantly influenced changes in sodium concentrations during treatment, but the rate of infusion of intravenous fluids had minimal effects. These findings suggest that promoting a rise in the serum sodium concentration need not be a routine focus of DKA treatment. In the event that changes in serum sodium concentration are required, the sodium content of intravenous fluids should be adjusted, but not the rate of infusion.

The principles described below are based on consensus statements from panels of expert physicians representing the Pediatric Endocrine Society (PES), the European Society for Pediatric Endocrinology (ESPE), and the International Society for Pediatric and Adolescent Diabetes (ISPAD)[10,103–105] and incorporate the recommendations from the PECARN FLUID Trial[96] and other recent data. Note that IV fluids given in another facility before assessment should be factored into calculations of deficit and replacement volumes.

6.3.2 | Resuscitation fluids

For children who are volume depleted but not in shock, volume expansion (resuscitation) should begin immediately with 0.9% saline, 10 to 20 ml/kg infused over 20–30 min to restore the peripheral circulation. If tissue perfusion is poor the initial fluid bolus volume should be 20 ml/kg.

- In the rare child with DKA in shock, rapidly restore circulatory volume with 0.9% 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.

6.3.3 | Deficit replacement fluids

Subsequent fluid management (deficit replacement) can be accomplished with 0.45%–0.9% saline or a balanced salt solution (Ringer's lactate, Hartmann's solution or Plasmalyte).[96,100,102,106–114]

- 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 intravenous fluid to maintain adequate tissue perfusion.
- Deficit replacement should be with a solution that has a tonicity in the range of 0.45%–0.9% saline, with added potassium chloride, potassium phosphate or potassium acetate (see below under potassium replacement).[96,100,102,106–108,110,113,115,116] Decisions regarding use of isotonic versus hypotonic solution for deficit replacement should depend on clinician judgment based on the child's hydration status, serum sodium concentration, and osmolality.
- In addition to providing the usual daily maintenance fluid requirement, replace the estimated fluid deficit (minus initial fluid bolus amount) over 24–48 h.[96] Although rehydration is generally planned to occur over 24 h or longer, DKA typically resolves before 24 h and remaining fluid deficits are replaced by oral intake after transition to subcutaneous insulin.
- Clinical assessment of circulatory status, fluid balance, and trends in serum sodium levels are valuable guides to fluid and electrolyte therapy. The serum sodium concentration typically increases as the serum glucose concentration decreases.
- Avoiding declines in intravascular volume is of particular importance for children with severe dehydration or circulatory

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compromise. In these situations, the sodium content of the fluid should be increased if the measured serum sodium concentration is low and does not rise appropriately as the plasma glucose concentration falls.[102,112]

- Urinary losses should not routinely be added to the calculation of replacement fluid, but this may be necessary in some circumstances, particularly in children with a mixed presentation of DKA and HHS (see below). Careful monitoring of fluid intake and output is essential to ensure positive fluid balance.
- Calculation of fluid infusion rates for obese children should be similar to those of other children. Using ideal body weight for fluid calculations for these children is not necessary. If fluid calculations for obese children exceed those typically used in adult protocols, then adult DKA fluid protocols can be used (e.g., 1 L maximum per bolus and 500 ml/h fluid infusion).
- The use of large amounts of chloride-rich fluids (combined with preferential renal excretion of ketones over chloride) is often associated with development of hyperchloremic metabolic acidosis.[116–121]
  - When hyperchloremia develops, a persisting base deficit or low bicarbonate concentration can be erroneously interpreted as being due to ongoing ketosis.[122]
  - To avoid this misinterpretation, measurement of bedside BOHB levels (or calculation of anion gap if bedside BOHB is not available) should be used to determine resolution of ketoacidosis.
  - Hyperchloremic acidosis is generally asymptomatic and resolves spontaneously.
  - The chloride load can be reduced by using potassium salts other than potassium chloride, or by using fluids such Ringer's lactate or Plasmalyte in which a portion of the chloride is replaced by lactate or acetate, respectively.[123]

6.3.4 | Potassium replacement

Children with DKA have total body potassium deficits on the order of 3 to 6 mmol/kg.[124–128] 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) and acidosis, as well as glycogenolysis and proteolysis secondary to insulin deficiency.[5] Potassium is lost from the body via vomiting and osmotic diuresis. In addition, volume depletion causes secondary hyperaldosteronism, which promotes urinary potassium excretion. The incidence and severity of hypokalemia (potassium < 3.5 mmol/L) may be higher in malnourished children.[129] In spite of total body depletion, serum potassium levels may be normal, increased, or decreased at presentation.[130] Renal dysfunction caused by DKA enhances hyperglycemia and reduces potassium excretion, thereby raising serum potassium concentrations at presentation.[130] Administration of insulin and the correction of acidosis drives potassium back into the cells, decreasing serum potassium levels during DKA treatment.[131] Insulin also has an aldosterone-like effect leading to increased urinary potassium excretion. High doses administered intravenously for a prolonged period may contribute to hypokalemia despite potassium administration. The duration and dosage of intravenous insulin should be minimized to decrease the risk of hypokalemia. The serum potassium concentration may decrease rapidly during treatment, predisposing to cardiac arrhythmias. Severe hypokalemia (<2.5 mmol/L) is an independent marker of poor treatment outcome and mortality.[132,133]

Potassium replacement is required regardless of the serum potassium concentration, except if renal failure is present.[125,134]

- If the child is hypokalemic, start potassium replacement *at the time of* initial volume expansion and before starting insulin therapy. For rare children with initial potassium levels <3.5 mmol/L, *defer* insulin treatment and give a bolus of potassium (not to exceed 0.5 mmol/Kg/h), along with cardiac monitoring.[135] Otherwise, start-replacing potassium *after* initial volume expansion and concurrent with starting insulin therapy. If the child is hyperkalemic, *defer* potassium replacement therapy until urine output is documented. Begin infusion with non-potassium fluids, remeasure potassium hourly, and begin potassium infusion when serum potassium is below 5.5 mmol/L.
- If immediate serum potassium measurements are unavailable, an ECG may help to determine whether the child has hyper- or hypokalemia.[85,86] 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.[136] Subsequent potassium replacement therapy should be based on serum potassium measurements.
- If there is hypokalemia, potassium replacement should begin concurrent with initial volume expansion, using a separate IV infusion.
- 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. 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 intravenous 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.

6.3.5 | Phosphate

Phosphate depletion occurs in DKA due to osmotic diuresis and a shift of intracellular phosphate to the extracellular compartment as a result of metabolic acidosis.[5,124–126,137,138] Plasma phosphate levels

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decrease during treatment due to dilution by fluid replacement and insulin-mediated entry of phosphate into cells.[137,139–141] During treatment, 50%–60% of children develop hypophosphatemia.[96] The degree of metabolic acidosis is a main determinant.[138] Although severe hypophosphatemia can occur at any time during DKA treatment, continuation of intravenous therapy without food consumption beyond 24 h is a risk factor for clinically significant hypophosphatemia.[124–126] To date, studies of phosphate replacement in children with DKA have involved small numbers of children with limited statistical power, therefore data for evidence-based guidelines is lacking.

- Severe hypophosphatemia is uncommon but can have serious consequences. Clinical manifestations are largely due to intracellular phosphate depletion. Decreased intracellular adenosine triphosphate (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.[142] Many organ systems can be affected. Manifestations of severe hypophosphatemia include metabolic encephalopathy, seizures,[143] impaired myocardial contractility, ventricular arrhythmia,[144] respiratory failure,[137] hemolytic anemia,[145] muscle dysfunction with proximal myopathy, dysphagia, ileus, and rhabdomyolysis.[146–149]
- Severe hypophosphatemia (<1 mg/dl [0.32 mmol/L]) with or without associated symptoms should be treated promptly.[143,150] Insulin infusion may need to be reduced or temporarily halted until phosphorus levels increase.
- Routine phosphate replacement to prevent hypophosphatemia is advisable in locations where this treatment is readily available, particularly for children with severe DKA.
- Potassium phosphate can be combined with potassium chloride or potassium acetate to provide phosphate replacement without substantial risk of hypocalcemia.
- Carefully monitor serum calcium and magnesium concentrations during phosphate infusion to avoid hypocalcemia.[151,152]

6.4 | Insulin therapy

Diabetic ketoacidosis (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,[153,154] insulin therapy is essential to restore normal cellular metabolism, to suppress lipolysis and ketogenesis, and to normalize blood glucose concentrations.[155]

- Start insulin infusion 1 h after initiation of IV fluid treatment.[156]
- Correction of insulin deficiency
  - Dose: 0.05–0.1 U/kg/h of regular (soluble) insulin (e.g., one method is to dilute 50 units regular [soluble] insulin in 50 ml 0.9% saline, 1 unit = 1 ml).[157–164] The lower dosage (0.05 U/kg/h) can be considered for children with pH > 7.15.
  - Route of administration: Intravenous (IV)
  - An IV insulin bolus should *not* be used at the start of therapy; it is unnecessary,[163,165] can precipitate shock by rapidly decreasing osmotic pressure, and can exacerbate hypokalemia.
- Infusion tubing should be flushed with the insulin solution before administration.
  - If IV cannulation is not possible due to severe dehydration, insulin can be administered IM.
  - Central venous catheters should not be used for insulin administration because the large dead space may cause erratic insulin delivery.
- The dose of insulin should usually remain at 0.05–0.1 unit/kg/h at least until resolution of DKA (pH > 7.30, serum bicarbonate >18 mmol/L, BOHB <1 mmol/L, or closure of the anion gap), which invariably takes longer than normalization of blood glucose concentrations.[166] Monitor venous pH (and serum BOHB concentration where possible) every 2 h to ensure steady improvement. If the insulin effect is adequate, serum BOHB should decrease by approximately 0.5 mmol/L per hour.[70] Increase the insulin dose if the expected rate of biochemical improvement does not occur.
- If the child shows marked sensitivity to insulin (e.g., some young children with DKA, children with HHS, and some older children with established diabetes), the insulin dose may be decreased, provided that metabolic acidosis continues to resolve.
- For less severe DKA (pH > 7.15), 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 studies and small RCTs have reported comparable efficacy and safety using 0.05 unit/kg/h compared to 0.1 unit/kg/h,[113,167–169] and some pediatric centers routinely use this dose for treatment of DKA.
- During initial volume expansion, the plasma glucose concentration falls steeply.[153] Thereafter, and after commencing insulin therapy, the plasma glucose concentration typically decreases at a rate of 2–5 mmol/L per hour.[157–160,163,170]
- To prevent an unduly rapid decrease in plasma glucose concentration and hypoglycemia, 5% dextrose should be added to the IV fluid when the plasma glucose falls to approximately 14–17 mmol/L (250–300 mg/dl), or sooner if the rate of fall is precipitous (>5 mmol/L/h after initial fluid expansion).
  - 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 biochemical parameters of DKA (venous pH, anion gap, BOHB concentration) do not improve, reassess the child, 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 children with uncomplicated mild to moderate DKA, hourly or 2-hourly subcutaneous (SC) rapid-acting insulin analog (insulin lispro or insulin aspart) is safe and may be as effective as IV regular insulin infusion.[170–174] This method should not be used in children whose peripheral circulation is impaired. Dose SC:

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0.15 units/kg every 2 h (initiated 1 h after the start of fluid replacement). The dose can be reduced to 0.1 unit/kg every 2 h if BG continues to decrease by >5 mmol/L (90 mg/dl) even after adding dextrose.[175–177]

- Subcutaneous administration of short-acting (regular) insulin every 4 h is another alternative in mild DKA when IV infusion or rapid-acting insulin analogs are not available.[178] A suggested starting dose is 0.13–0.17 units/kg/dose of regular insulin every 4 h (0.8–1 unit/kg/day in divided doses). Doses are increased or decreased by 10%–20% based on the blood glucose level before the next insulin injection.[178] Dosing frequency may be increased to every 2 or 3 h if acidosis is not improving.

6.5 | Acidosis

Fluid and insulin replacement reverses acidosis. 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. A recent large study of children with DKA showed that faster compared to slower fluid administration caused earlier normalization of the anion gap; however, pH did not normalize more rapidly with more rapid fluid infusion, likely due to increased frequency of hyperchloremic acidosis.[117]

Lack of resolution of acidosis is most frequently due to development of hyperchloremic acidosis. This is generally a benign condition and should not delay transition to subcutaneous insulin. Rare causes of persistent acidosis include insufficient fluid administration, infection/sepsis and incorrect preparation of the intravenous insulin infusion.

Controlled trials have shown no clinical benefit from bicarbonate administration.[179–182] Bicarbonate therapy may cause paradoxical CNS acidosis[183,184] and rapid correction of acidosis with bicarbonate causes hypokalemia.[183,185,186] Bicarbonate administration may be beneficial in rare children with life-threatening hyperkalemia or unusually severe acidosis (venous pH < 6.9) that have compromised cardiac contractility.[187]

6.6 | 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).
  - Measurement of urine ketones with test strips is based on the nitroprusside reaction, which measures acetoacetate and acetone. Persistent ketonuria characteristically occurs for several hours after serum BOHB levels have returned to normal.[70,71]
  - Absence of ketonuria should *not* be used as an endpoint 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-acting) insulin should be administered in addition to rapid- or short-acting insulin. The most convenient time to change to SC insulin is just before a mealtime. Alternatively, basal insulin may be given while the child is still receiving intravenous insulin infusion. This method is safe and may help to facilitate transition to a subcutaneous regimen.[188,189]
- To prevent rebound hyperglycemia, the first SC injection should be given 15–30 min (with rapid-acting insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed. With long-acting insulin, the overlap should be longer, and the rate of IV insulin administration gradually decreased. For example, for children 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.

7 | CLINICAL AND BIOCHEMICAL MONITORING

Successful management of DKA and HHS requires **meticulous monitoring** and recording of the clinical and biochemical response to treatment so that timely adjustments in treatment can be made when indicated by clinical or laboratory data. There should be documentation on a **flow chart** of hour-by-hour clinical observations, medications, fluids, and laboratory test results.

Monitoring during the initial treatment of DKA should include the following:

- **Hourly (or more frequently as indicated)**
  - **Vital signs** (heart rate, respiratory rate, blood pressure)
  - **Neurological assessment** (Glasgow coma scale score or similar assessments; Table 2) for warning signs and symptoms of cerebral injury (see Section 8.2)
  - Amount of administered insulin
  - Accurate **fluid input** (including all oral fluid) **and output**.
  - **Capillary blood glucose** concentration should be measured hourly (but must be crosschecked against laboratory venous glucose because capillary methods may be inaccurate when there is poor peripheral circulation and when plasma glucose levels are extremely high). The utility of continuous monitoring of interstitial glucose during DKA management is currently being evaluated.[190]
- **At admission and every 2–4 h,** or more frequently, as clinically indicated
  - Serum electrolytes, glucose, blood urea nitrogen, calcium, magnesium, phosphate, and blood gases
  - Blood BOHB concentrations, if available, are useful for tracking DKA resolution.[11,12,69–71,73,75] Point-of-care BOHB measurements correlate well with a reference method up to 3 mmol/L, but are not accurate above 5 mmol/L.[73,191]

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- Laboratory observations
  - Serum may be lipemic, which in extreme cases can interfere with accuracy of electrolyte measurements in some laboratories.[192]
  - If the laboratory cannot provide timely results, a portable biochemical analyzer that measures serum electrolytes and blood gases on finger stick blood samples at the bedside is a useful adjunct to laboratory-based determinations. Blood glucose and blood or urine ketone concentrations can also be measured at the bedside 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 20–30 mmol/L; an anion gap >35 mmol/L suggests concomitant lactic acidosis[193,194]
  - Corrected sodium = measured Na + 1.6([plasma glucose − 5.6]/5.6) mmol/L or measured Na + 1.6([plasma glucose − 100]/100) mg/dL[91,92,195]
  - Effective osmolality (mOsm/kg) = 2 × (plasma Na) + plasma glucose mmol/L; normal range is 275–295 mOsm/kg

8 | COMPLICATIONS

8.1 | Morbidity and mortality

Diabetic ketoacidosis (DKA) is associated with a wide range of complications. These include:

- **Mortality** mainly due to cerebral injury. In developed countries, the death rate from DKA is <1%, while in developing countries it is much higher reaching 3%–13%.[196–199] The mortality rate in HHS is reported to be higher; however, reliable data are lacking in pediatric populations.
- **Permanent severe neurological sequelae** resulting from DKA-related brain injuries are infrequent. However, alterations in memory, attention, verbal intelligence quotient, and brain microstructure may result from apparently uncomplicated DKA episodes. Even a single DKA episode is associated with subtle memory declines soon after a T1D diagnosis.[200,201]
- **Renal tubular damage (RTD) and acute kidney injury (AKI)**[202–204] occurs in a high proportion (43% to 64%) of children hospitalized for DKA and is more common among children with more severe acidosis and volume depletion.[203,204] AKI is defined by the Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine criteria (AKI Stage 1, 2, or 3 defined by serum creatinine 1.5, 2, or 3 times estimated baseline creatinine).[205] RTD and AKI are managed with the restoration of fluid, electrolyte and glycemic balance.

Other complications include:

- Hypokalemia*
- Hypoglycemia
- Hypocalcemia, hypomagnesemia[151]
- Severe hypophosphatemia[138,143,145,149] *
- Hyperchloremic acidosis[117]
- Hypochloremic alkalosis[206]
- Other central nervous system complications including cerebral venous sinus thrombosis, basilar artery thrombosis, intracranial hemorrhage, cerebral infarction[207–209]
- Deep venous thrombosis[87,88,210] *
- Pulmonary embolism[211] *
- Rhinocerebral or pulmonary mucormycosis[212,213]
- Aspiration pneumonia*
- Pulmonary edema[214,215] *
- Adult respiratory distress syndrome (ARDS)[216]
- Prolonged QTc[217,218]
- Pneumothorax, pneumomediastinum and subcutaneous emphysema[219,220]
- Rhabdomyolysis[221] *
- Ischemic bowel necrosis[222]
- Renal failure*
- Acute pancreatitis[223] *

*These complications, often with fatality, have been more frequent in HHS.[224] The pathophysiology and management of HHS are discussed in the other sections of this guideline.

8.2 | Cerebral injury

The incidence of clinically overt DKA-related cerebral injury is 0.5%–0.9% and the mortality rate is 21%–24%.[101,225,226] Mental status abnormalities (GCS scores <14) occur in approximately 4%–15% of children treated for DKA and are often associated with mild cerebral edema on neuroimaging.[227,228] 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.[227,229,230] Clinically overt cerebral injury represents the most severe manifestation of a common phenomenon.[231]

The cause of DKA-related cerebral injury is a topic of ongoing investigation. Rapid fluid administration resulting in changes in serum osmolality was initially thought to be the cause, however, more recent evidence suggests that cerebral hypoperfusion and the hyperinflammatory state caused by DKA play central roles.[98,232–236] 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.[228] Evidence of neuroinflammation has been demonstrated in animal models of DKA, including elevated cytokine and chemokine concentrations in brain tissue, activation of brain microglia and reactive astrogliosis.[98,99,237–240] Disruption of the blood–brain-barrier has also been found in DKA, particularly in cases of fatal cerebral injury.[236,241,242]

Cerebral injury occurs more frequently in younger children,[243] those with new onset of diabetes,[198,243] and those with longer

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duration of symptoms.[244] These risk associations may reflect the greater likelihood of severe DKA in these children. Epidemiological studies have identified several biochemical risk factors at diagnosis including:

- Greater hypocapnia at presentation after adjusting for degree of acidosis[101,228,245]
- Increased serum urea nitrogen at presentation[101,228]
- More severe acidosis at presentation[156,246,247]

Bicarbonate treatment for correction of acidosis has also been associated with increased risk of cerebral injury. This association was found to persist after adjusting for DKA severity.[101,248]

Clinically significant cerebral injury usually develops within the first 12 h after treatment has started but can occur before treatment has begun[101,225,249–251] or, rarely, may develop as late as 24–48 h after the start of treatment.[101,243,252] Symptoms and signs are variable. Mild to moderate headache at presentation is not unusual in children with DKA, however, development of headache or substantial worsening of headache after commencing treatment is concerning. A method of clinical diagnosis based on bedside evaluation of neurological state is shown below.[253] 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. Neuroimaging is not required for diagnosis of cerebral injury.

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, 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 mmHg
- Age <5 years

8.2.1 | Treatment of cerebral injury

- 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, 0.5–1 g/kg IV over 10–15 min.[254–256] The effect of mannitol should be apparent after ~15 min and is expected to last about 120 min. If necessary, the dose can be repeated after 30 min.
- Hypertonic saline (3%), suggested dose 2.5–5 ml/kg over 10–15 min, may be used as an alternative to mannitol, or in addition to mannitol if there has been no response to mannitol within 15–30 min.[257,258]
  - 3% Hypertonic saline 2.5 ml/kg is equimolar to mannitol 0.5 g/kg. Intubation may be necessary for the patient with impending respiratory failure due to severe neurologic compromise. For intubated patients, the PCO_2 level should approximate that predicted for the level of metabolic acidosis. Hypocapnia beyond this level should be avoided except when necessary to treat clinically overt elevated intracranial pressure.[259]
- *After* hyperosmolar treatment has been started, cranial imaging may be considered. However, treatment of the clinically symptomatic patient should not be delayed in order to obtain imaging.[260] The primary concern that would warrant neuroimaging is whether the patient has a lesion requiring emergency neurosurgery (e.g., intracranial hemorrhage) or a lesion that may necessitate anticoagulation (e.g., cerebrovascular thrombosis), as suggested by clinical findings, particularly focal neurologic deficits.[207,261,262]

9 | PREVENTION OF RECURRENT DKA

Most episodes of DKA in children with previously diagnosed diabetes are the result of insulin omission, either inadvertent or deliberate. Families of children with recurrent episodes of DKA should work with a diabetes professional to ensure proper understanding of procedures for managing sick days and insulin pump failures. A social worker or clinical psychologist should be consulted to identify the psychosocial reason(s) contributing to DKA episodes when deliberate insulin omission is suspected.

10 | HYPERGLYCEMIC HYPEROSMOLAR STATE

This syndrome is characterized by extremely elevated serum glucose concentrations and hyperosmolality without significant ketosis. Rates of treatment complications and mortality are substantially higher than those of DKA.[42] The incidence of HHS in children and adolescents is increasing[35] with up to 2% of children presenting with HHS at onset of type 2 diabetes.[30] HHS manifests with gradually increasing polyuria and polydipsia that may go unrecognized resulting in profound dehydration and electrolyte losses at the time of presentation. Frequently it is accompanied by lethargy, weakness, confusion, dizziness, and behavioral change.[35,263] Obesity and hyperosmolality can make the

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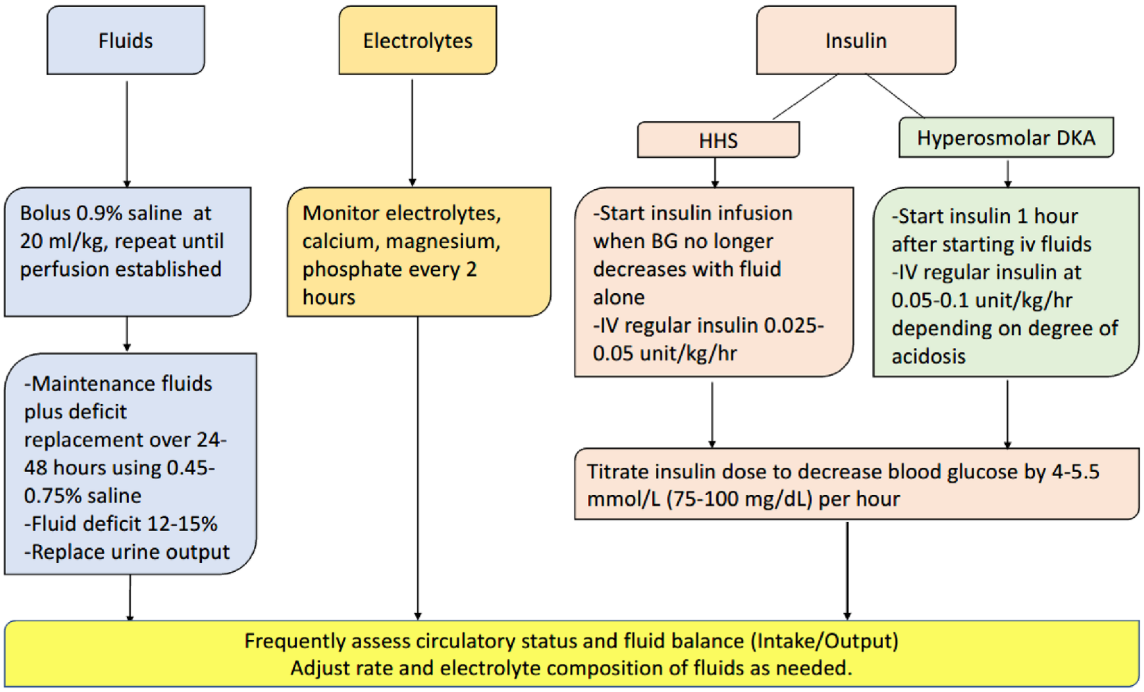


FIGURE 3 Treatment of hyperglycemic hyperosmolar syndrome (HHS)[224]

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 results in movement of water out of the intravascular space resulting in decreased intravascular volume. In addition, pronounced osmotic diuresis may continue for many hours in children with extremely increased plasma glucose concentrations. Early during treatment, urinary fluid losses may be considerable. Because intravascular volume may decrease rapidly during treatment in children with HHS, more aggressive replacement of intravascular volume (as compared to treatment of children with DKA) is required to avoid vascular collapse.

10.1 | 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[2] and an appreciation of the pathophysiological differences between HHS and DKA[224] (Figure 3). Children should be admitted to an intensive care unit or comparable setting where expert medical, nursing and laboratory services are available.

10.1.1 | Fluid therapy in HHS

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 h.
- 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 and osmolality.
  - Although there are no data to indicate an optimal rate of decline in serum sodium concentration, 0.5 mmol/L per hour has been recommended for hypernatremic dehydration.[264] With adequate rehydration alone (i.e., before commencing insulin therapy), serum glucose concentrations should decrease by 4.1 to 5.5 mmol/L (75 to 100 mg/dl) per hour.[265,266]
  - Mortality has been associated with failure of the corrected serum sodium concentration to decline with treatment.[35]
  - A more rapid rate of decline in serum glucose concentration is typical during the first several hours of treatment due to expansion of the intravascular volume leading to improved renal perfusion. If there is a continued rapid fall in serum glucose (>5.5 mmol/L, 100 mg/dl per hour) after the first few hours, consider adding 2.5% or 5% glucose to the rehydration fluid. Failure of the expected decrease in plasma glucose concentration should prompt reassessment and evaluation of renal function.

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- Unlike treatment of DKA, replacement of urinary losses is recommended.[164] 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.

10.1.2 | Insulin therapy in HHS

Early insulin administration is unnecessary in HHS as ketosis usually is minimal and fluid administration alone causes a marked decline in serum glucose concentration. 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. Children 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 children with more severe ketosis and acidosis (mixed presentation of DKA and HHS – see later), however, insulin administration should be initiated earlier.
- Continuous administration of insulin at a rate of 0.025 to 0.05 units per kg per hour can be used initially, with the dosage titrated to achieve a decrease in serum glucose concentration of 3–4 mmol/L (~50–75 mg/dl) per hour.
  - Insulin boluses are not recommended.

10.1.3 | Electrolytes in HHS

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 the serum potassium concentration is within the normal range and adequate renal function has been established.
  - Higher rates of potassium administration may be necessary, particularly after starting an insulin infusion
  - Serum potassium concentrations should be monitored every 2–3 h along with cardiac monitoring.
  - Hourly potassium measurements may be necessary if the child has hypokalemia.
- Bicarbonate therapy is contraindicated; it increases the risk of hypokalemia and may adversely affect tissue oxygen delivery.
- In children with hypophosphatemia, an intravenous solution that contains a 50:50 mixture of potassium phosphate and either potassium chloride or potassium acetate generally permits adequate phosphate replacement while avoiding clinically significant hypocalcemia.
  - Serum phosphorus concentrations should be measured every 3 to 4 h.
- 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 h with a maximum infusion rate of 150 mg/min and 2 g/h.

10.2 | Complications of HHS

- To prevent venous thrombosis, mechanical and pharmacologic prophylaxis (low molecular weight heparin) should be considered, especially in children >12 years.[224]
- Rhabdomyolysis may occur in children with HHS resulting in acute kidney failure, severe hyperkalemia, hypocalcemia, and muscle swelling causing compartment syndrome.[221,263,267,268] The classic symptom triad of rhabdomyolysis includes myalgia, weakness, and dark urine. Monitoring creatine kinase concentrations every 2 to 3 h 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.[269,270] Children who have a fever associated with a rise in creatine kinase concentrations may be treated with dantrolene, which reduces calcium release from the sarcoplasmic reticulum and stabilizes calcium metabolism within muscle cells; however, mortality rates are high, even with treatment.[269,270]
- Altered mental status is common in adults whose serum osmolality exceeds 330 mOsm/kg; however, cerebral edema is rare.[35] Among 96 cases of HHS reported in the literature up to 2010, including 32 deaths, there was only one instance of cerebral edema,[35] and there have been no further reports of cerebral edema in children with HHS to date. A decline in mental status after hyperosmolality has improved with treatment is unusual and should be promptly investigated.

10.3 | Mixed HHS and DKA

Mixed presentation of HHS and DKA is frequently unrecognized and managed inappropriately which may increase the risk of complications.[271] Children with mixed presentation meet criteria for diagnosis of DKA and have hyperosmolality (blood glucose concentration > 33.3 mmol/L (600 mg/dl) and effective osmolality >320 mOsm/Kg). Treatment must account for 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 adequate circulatory volume, the rate of fluid and electrolyte administration usually exceeds that required for the typical case of DKA. Insulin is

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necessary to resolve ketosis and arrest hepatic gluconeogenesis; however, insulin infusion should be deferred until the child has received initial fluid boluses and the circulation has been stabilized. Severe hypokalemia and hypophosphatemia may occur, and potassium and phosphate concentrations should be carefully monitored as described above for HHS.

CONFLICT OF INTEREST

None of the authors has any conflicts of interest relevant to the subject matter of the article.

AUTHOR CONTRIBUTIONS

All authors reviewed and summarized literature about Pediatric DKA and drafted one or more sections of the manuscript. All authors reviewed and edited the manuscript drafts. NG coordinated revisions of the manuscript based on input from ISPAD membership, the co-authors and ISPAD leadership.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

This article is an invited review/consensus statement. Data sharing is not applicable.

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ENDNOTES

* Nitroprusside reaction method

† In the PECARN FLUID Trial, the rapid fluid infusion arm rates were calculated to replace ½ of the estimated fluid deficit over 12 h and the remaining deficit over the subsequent 24 h. As DKA typically resolves within 12 h for most children, these rates are equivalent to those calculated to replace the full deficit over 24 h in the majority. Therefore, for simplicity, we have recommended a range of 24 to 48 h for deficit replacement.

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