Hyperglycemic Crises in Patients With Diabetes Mellitus

AMERICAN DIABETES ASSOCIATION

Ketoacidosis and hyperosmolar hyperglycemia are the two most serious acute metabolic complications of diabetes, even if managed properly. These disorders can occur in both type 1 and type 2 diabetes. The mortality rate in patients with diabetic ketoacidosis (DKA) is <5% in experienced centers, whereas the mortality rate of patients with hyperosmolar hyperglycemic state (HHS) still remains high at ~15%. The prognosis of both conditions is substantially worsened at the extremes of age and in the presence of coma and hypotension (1–10).

This position statement will outline precipitating factors and recommendations for the diagnosis, treatment, and prevention of DKA and HHS. It is based on a previous technical review (11), which should be consulted for further information.

PATHOGENESIS — Although the pathogenesis of DKA is better understood than that of HHS, the basic underlying mechanism for both disorders is a reduction in the net effective action of circulating insulin coupled with a concomitant elevation of counterregulatory hormones, such as glucagon, catecholamines, cortisol, and growth hormone. These hormonal alterations in DKA and HHS lead to increased hepatic and renal glucose production and impaired glucose utilization in peripheral tissues, which result in hyperglycemia and parallel changes in osmolality of the extracellular space (12,13). The combination of insulin deficiency and increased counterregulatory hormones in DKA also leads to the release of free fatty acids into the circulation from adipose tissue (lipolysis) and to unrestrained hepatic fatty acid oxidation to ketone bodies (β-hydroxybutyrate [β-OHB] and acetoacetate), with resulting ketonemia and metabolic acidosis. On the other hand, HHS may be caused by plasma insulin concentrations that are inadequate to facilitate glucose utilization by insulin-sensitive tissues but adequate (as determined by residual C-peptide) to prevent lipolysis and subsequent ketogenesis, although the evidence for this is weak (14). Both DKA and HHS are associated with glycosuria, leading to osmotic diuresis, with loss of water, sodium, potassium, and other electrolytes (3,15–20). The laboratory and clinical characteristics of DKA and HHS are summarized in Tables 1 and 2. As can be seen, DKA and HHS differ in magnitude of dehydration and degree of ketosis (and acidosis).

PRECIPITATING FACTORS — The most common precipitating factor in the development of DKA or HHS is infection. Other precipitating factors include cerebrovascular accident, alcohol abuse, pancreatitis, myocardial infarction, trauma, and drugs. In addition, new-onset type 1 diabetes or discontinuation of or inadequate insulin in established type 1 diabetes commonly leads to the development of DKA. Elderly individuals with new-onset diabetes (particularly residents of chronic care facilities) or individuals with known diabetes who become hyperglycemic and are unaware of it or are unable to take fluids when necessary are at risk for HHS (6).

Drugs that affect carbohydrate metabolism, such as corticosteroids, thiazides, and sympathomimetic agents (e.g., dobutamine and terbutaline), may precipitate the development of HHS or DKA. In young patients with type 1 diabetes, psychological problems complicated by eating disorders may be a contributing factor in 20% of recurrent ketoacidosis. Factors that may lead to insulin omission in younger patients include fear of weight gain with improved metabolic control, fear of hypoglycemia, rebellion from authority, and stress of chronic disease (13).

DIAGNOSIS

History and physical examination

The process of HHS usually evolves over several days to weeks, whereas the evolution of the acute DKA episode in type 1 diabetes or even in type 2 diabetes tends to be much shorter. Although the symptoms of poorly controlled diabetes may be present for several days, the metabolic alterations typical of ketoacidosis usually evolve within a short time frame (typically <24 h). Occasionally, the entire symptomatic presentation may evolve or develop more acutely, and the patient may present in DKA with no prior clues or symptoms. For both DKA and HHS, the classical clinical picture includes a history of polyuria, polydipsia, polyphagia, weight loss, vomiting, abdominal pain (only in DKA), dehydration, weakness, clouding of sensoria, and finally coma. Physical findings may include poor skin turgor, Kussmaul respirations (in DKA), tachycardia, hypotension, alteration in mental status, shock, and ultimately coma (more frequent in HHS). Up to 25% of DKA patients have emesis, which may be coffee-ground in appearance and guaiac positive. Endoscopy has related this finding to the presence of hemorrhagic gastritis. Mental status can vary from full alertness to profound lethargy or coma, with the latter more frequent in HHS. Although infection is a common precipitating factor for both DKA and HHS, patients can be normothermic or even hypothermic primarily because of peripheral vasodilation. Hypothermia, if present, is a poor prognostic sign (21). Caution needs to be taken with patients

The recommendations in this paper are based on the evidence reviewed in the following publication: Management of hyperglycemic crises in patients with diabetes (Technical Review). *Diabetes Care* 24:131–153, 2001.

The initial draft of this position statement was prepared by Abbas E. Kitabchi, PhD, MD; Guillermo E. Umpierrez, MD; Mary Beth Murphy, RN, MS, CDE, MBA; Eugene J. Barrett, MD, PhD; Robert A. Kreisberg, MD; John I. Malone, MD; and Barry M. Wall, MD. The paper was peer-reviewed, modified, and approved by the Professional Practice Committee and the Executive Committee, October 2000. Revised 2001.

Abbreviations: β-OHB, β-hydroxybutyric acid; AKA, alcoholic ketoacidosis; DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state.

Table 1—*Diagnostic criteria for DKA and HHS*

	DKA			
	Mild	Moderate	Severe	HHS
Plasma glucose (mg/dl)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Serum bicarbonate (mEq/l)	15–18	10 to <15	<10	>15
Urine ketones*	Positive	Positive	Positive	Small
Serum ketones*	Positive	Positive	Positive	Small
Effective serum osmolality (mOsm/kg)†	Variable	Variable	Variable	>320
Anion gap‡	>10	>12	>12	<12
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

*Nitroprusside reaction method; †calculation: 2[measured Na (mEq/l)] + glucose (mg/dl)/18; ‡calculation: $(Na^+) - (Cl^- + HCO_3^-)$ (mEq/l). See text for details.

who complain of abdominal pain on presentation, because the symptoms could be either a result or an indication of a precipitating cause (particularly in younger patients) of DKA. Further evaluation is necessary if this complaint does not resolve with resolution of dehydration and metabolic acidosis.

Laboratory findings

The initial laboratory evaluation of patients with suspected DKA or HHS should include determination of plasma glucose, blood urea nitrogen/creatinine, serum ketones, electrolytes (with calculated anion gap), osmolality, urinalysis, urine ketones by dipstick, as well as initial arterial blood gases, complete blood count with differential, and electrocardiogram. Bacterial cultures of urine, blood, and throat, etc., should be obtained and appropriate antibiotics given if infection is suspected. HbA_{1c} may be useful in determining whether this acute episode is the culmination of an evolutionary process in previously undiagnosed or poorly controlled diabetes or a truly acute episode in an otherwise well-controlled patient. A chest X-ray should also be obtained if indicated. Tables 1 and 2 depict typical laboratory findings in patients with DKA or HHS.

The majority of patients with hyperglycemic emergencies present with leukocytosis proportional to blood ketone body concentration. Serum sodium concentration is usually decreased because of the osmotic flux of water from the intracellular to the extracellular space in the presence of hyperglycemia, and less commonly, serum sodium concentration may be falsely lowered by severe hypertriglyceridemia. Serum potassium concentration may be elevated because of an extracellular shift of potassium caused by insulin deficiency, hypertonicity, and acidemia. Patients with low-normal or low serum potassium concentration on admission have severe total-body potassium deficiency and require very careful cardiac monitoring and more vigorous potassium replacement, because treatment lowers potassium further and can provoke cardiac dysrhythmia. The occurrence of stupor or coma in diabetic patients in the absence of definitive elevation of effective osmolality (**≥320 mOsm/kg**) demands immediate consideration of other causes of mental status change. Effective osmolality may be calculated by the following formula: 2[measured Na (mEq/l)] + glucose (mg/dl)/18. Amylase levels are elevated in the majority of patients with DKA, but this may be due to nonpancreatic sources, such as the parotid gland. A serum lipase determination may be beneficial in the differential diagnosis of pancreatitis. However, lipase could also be elevated in DKA. Abdominal pain and elevation of serum amylase and liver enzymes are noted more commonly in DKA than in HHS.

Differential diagnosis

Not all patients with ketoacidosis have DKA. Starvation ketosis and alcoholic ketoacidosis (AKA) are distinguished by clinical history and by plasma glucose concentrations that range from mildly elevated (rarely >250 mg/dl) to hypoglycemia. In addition, although AKA can result in profound acidosis, the serum bicarbonate concentration in starvation ketosis is usually not lower than 18 mEq/l. DKA must also be distinguished from other causes of high–anion gap metabolic acidosis, including lactic acidosis, ingestion of drugs such as salicylate, methanol, ethylene glycol, and paraldehyde, and chronic renal failure (which is more typically hyperchloremic acidosis rather than high–anion gap acidosis). Clinical history of previous drug intoxications or metformin use should be sought. Measurement of blood lactate, serum salicylate, and blood methanol level can be helpful in these situations. Ethylene glycol (antifreeze) is suggested by the presence of calcium oxalate and hippurate crystals in the urine.

Paraldehyde ingestion is indicated by its characteristic strong odor on the breath. Because these intoxicants are low–molecular weight organic compounds, they can produce an osmolar gap in addition to the anion gap acidosis (14–16).

TREATMENT — Successful treatment of DKA and HHS requires correction of dehydration, hyperglycemia, and electrolyte imbalances; identification of comorbid precipitating events; and above all, frequent patient monitoring. Guidelines for the management of patients with DKA and HHS follow and are summarized in Figs. 1, 2, and 3. Table 3 includes a summary of major recommendations and evidence gradings.

Fluid therapy

Adult patients. Initial fluid therapy is directed toward expansion of the intravascular and extravascular volume and restoration of renal perfusion. In the absence of cardiac compromise, isotonic saline (0.9% NaCl) is infused at a rate of 15–20 ml · kg^{-1} body wt · h^{-1} or greater during the 1st hour (~1–1.5 l in the av-

Table 2—*Typical total body deficits of water and electrolytes in DKA and HHS**

Total water (l)	6	9
Water (ml/kg)†	100	100–200
Na^+ (mEq/kg)	7–10	5–13
Cl^- (mEq/kg)	3–5	5–15
K^+ (mEq/kg)	3–5	4–6
PO_4 (mmol/kg)	5–7	3–7
Mg^{++} (mEq/kg)	1–2	1–2
Ca^{++} (mEq/kg)	1–2	1–2

*Data are from Ennis et al. (15) and Kreisberg (8); †Per kilogram of body weight.

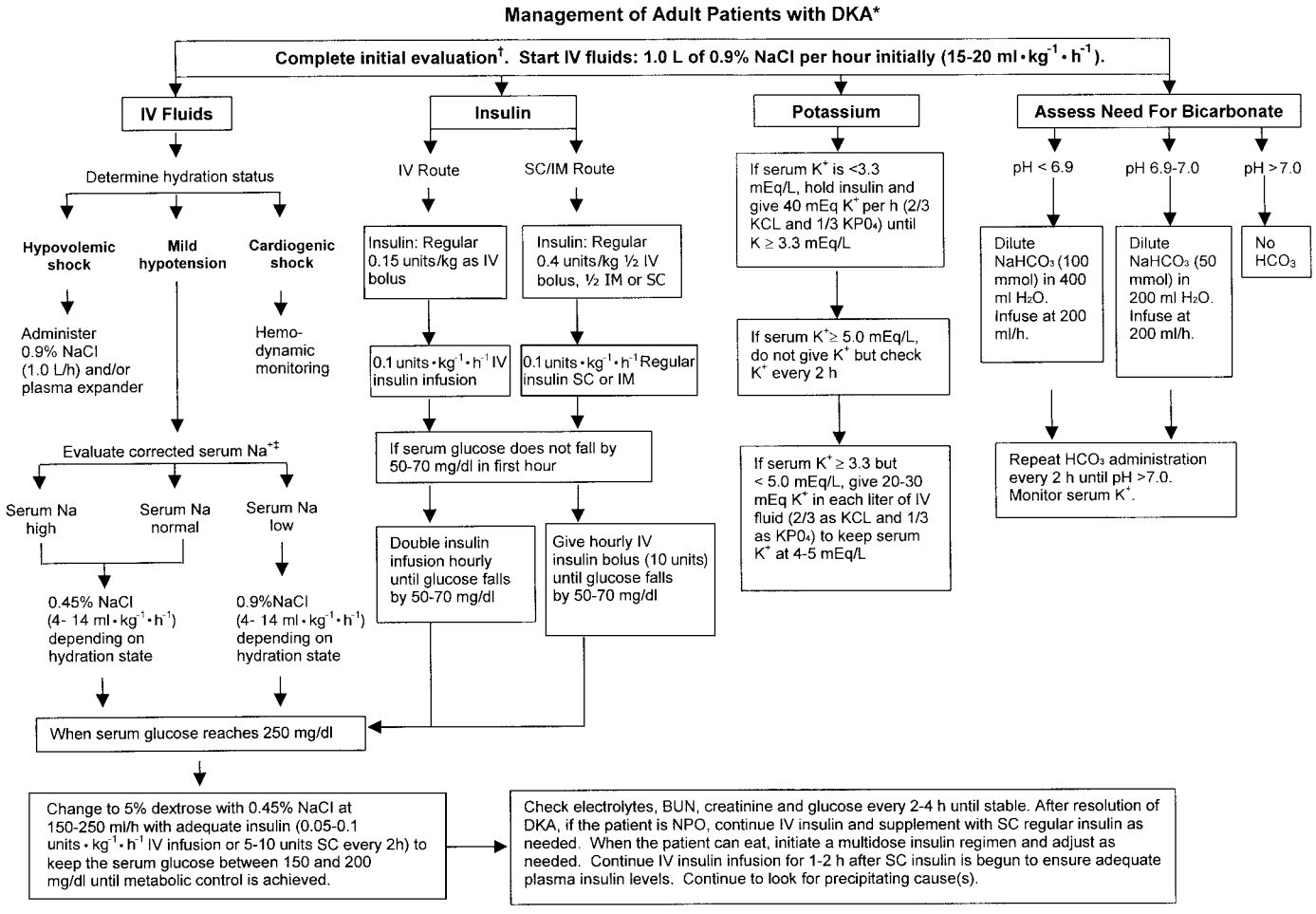

Figure 1—*Protocol for the management of adult patients with DKA. *DKA diagnostic criteria: blood glucose >250 mg/dl, arterial pH <7.3, bicarbonate <15 mEq/l, and moderate ketonuria or ketonemia. †After history and physical examination, obtain arterial blood gases, complete blood count with differential, urinalysis, blood glucose, blood urea nitrogen (BUN), electrolytes, chemistry profile, and creatinine levels STAT as well as an electrocardiogram. Obtain chest X-ray and cultures as needed. ‡Serum Na should be corrected for hyperglycemia (for each 100 mg/dl glucose >100 mg/dl, add 1.6 mEq to sodium value for corrected serum sodium value). IM, intramuscular; IV, intravenous; SC subcutaneous.*

erage adult). Subsequent choice for fluid replacement depends on the state of hydration, serum electrolyte levels, and urinary output. In general, 0.45% NaCl infused at 4–14 ml • kg^{-1} • h^{-1} is appropriate if the corrected serum sodium is normal or elevated; 0.9% NaCl at a similar rate is appropriate if corrected serum sodium is low. Once renal function is assured, the infusion should include 20–30 mEq/l potassium (2/3 KCl and 1/3 KPO_4) until the patient is stable and can tolerate oral supplementation. Successful progress with fluid replacement is judged by hemodynamic monitoring (improvement in blood pressure), measurement of fluid input/output, and clinical examination. Fluid replacement should correct estimated deficits within the first 24 h. The induced change in serum osmolality should not exceed 3 mOsm • kg^{-1} H_2O • h^{-1} (14–20,22). In patients with renal or cardiac compromise, monitoring of serum osmolality and frequent assessment of cardiac, renal, and mental status must be performed during fluid resuscitation to avoid iatrogenic fluid overload (14–20,22).

Pediatric patients (<20 years of age). Initial fluid therapy is directed toward expansion of the intravascular and extravascular volume and restoration of renal profusion. The need for vascular volume expansion must be offset by the risk of cerebral edema associated with rapid fluid administration. The 1st hour of fluids should be isotonic saline (0.9% NaCl) at the rate of 10–20 ml • kg^{-1} • h^{-1}. In a severely dehydrated patient, this may need to be repeated, but the initial reexpansion should not exceed 50 ml/kg over the first 4 h of therapy. Continued fluid therapy is calculated to replace the fluid deficit evenly over 48 h. In general, 0.45–0.9% NaCl (depending on serum sodium levels) infused at a rate of 1.5 times the 24-h maintenance requirements (~5 ml • kg^{-1} • h^{-1}) will accomplish a smooth rehydration, with a decrease in osmolality not exceeding 3 mOsm • kg^{-1} H_2O • h^{-1}. Once renal function is assured and serum potassium is known, the infusion should include 20–40 mEq/l potassium (2/3 KCl or potassium-acetate and 1/3 KPO_4). Once serum glucose reaches 250 mg/dl, fluid should be changed to 5% dextrose and 0.45–0.75% NaCl, with potassium as described above. Therapy should include monitoring mental status to rapidly identify changes that might indicate iatrogenic

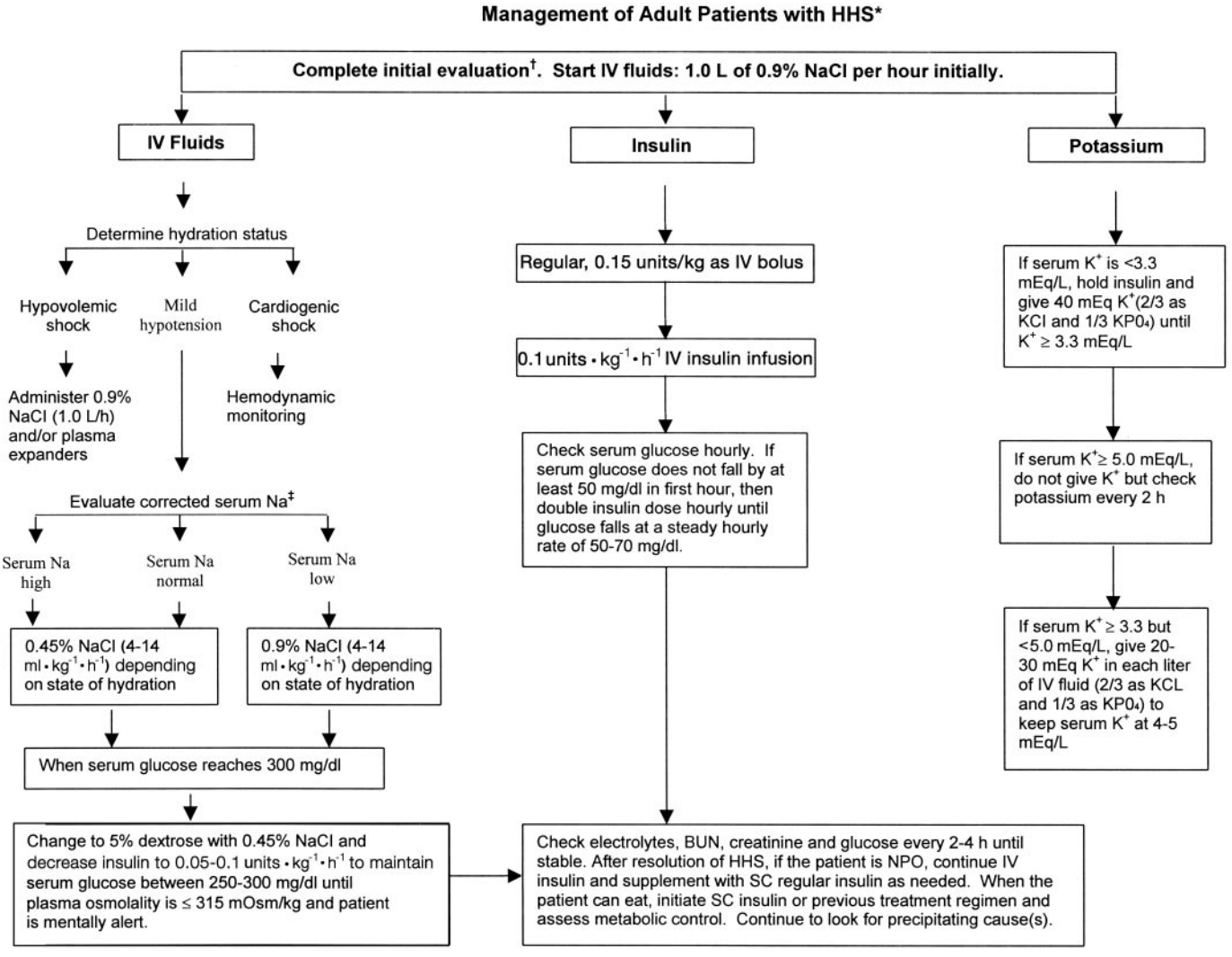

Figure 2—*Protocol for the management of adult patients with HHS. *Diagnostic criteria: blood glucose >600 mg/dl, arterial pH >7.3, bicarbonate >15 mEq/l, mild ketonuria or ketonemia, and effective serum osmolality >320 mOsm/kg H_2O. This protocol is for patients admitted with mental status change or severe dehydration who require admission to an intensive care unit. For less severe cases, see text for management guidelines. Effective serum osmolality calculation: 2[measured Na (mEq/l)] + glucose (mg/dl)/18. †After history and physical examination, obtain arterial blood gases, complete blood count with differential, urinalysis, plasma glucose, blood urea nitrogen (BUN), electrolytes, chemistry profile, and creatinine levels STAT as well as an electrocardiogram. Obtain chest X-ray and cultures as needed. ‡Serum Na should be corrected for hyperglycemia (for each 100 mg/dl glucose >100 mg/dl, add 1.6 mEq to sodium value for corrected serum value). IV, intravenous; SC subcutaneous.*

fluid overload, which can lead to symptomatic cerebral edema (23–25).

Insulin therapy

Unless the episode of DKA is mild (Table 1), regular insulin by continuous intravenous infusion is the treatment of choice. In adult patients, once hypokalemia (K^+ <3.3 mEq/l) is excluded, an intravenous bolus of regular insulin at 0.15 units/kg body wt, followed by a continuous infusion of regular insulin at a dose of 0.1 unit · kg^{-1} · h^{-1} (5–7 units/h in adults), should be administered. An initial insulin bolus is not recommended in pediatric patients; a continuous insulin infusion of regular insulin at a dose of 0.1 unit · kg^{-1} · h^{-1} may be started in these patients. This low dose of insulin usually decreases plasma glucose concentration at a rate of 50–75 mg · dl^{-1} · h^{-1}, similar to a higher-dose insulin regimen (26). If plasma glucose does not fall by 50 mg/dl from the initial value in the 1st hour, check hydration status; if acceptable, the insulin infusion may be doubled every hour until a steady glucose decline between 50 and 75 mg/h is achieved.

When the plasma glucose reaches 250 mg/dl in DKA or 300 mg/dl in HHS, it may be possible to decrease the insulin infusion rate to 0.05–0.1 unit · kg^{-1} · h^{-1} (3–6 units/h), and dextrose (5–10%) may be added to the intravenous fluids. Thereafter, the rate of insulin administration or the concentration of dextrose may need to be adjusted to maintain the above glucose values until acidosis in DKA or mental obtundation and hyperosmolarity in HHS are resolved.

Ketonemia typically takes longer to clear than hyperglycemia. Direct measurement of β-OHB in the blood is the preferred method for monitoring DKA. The nitroprusside method only measures

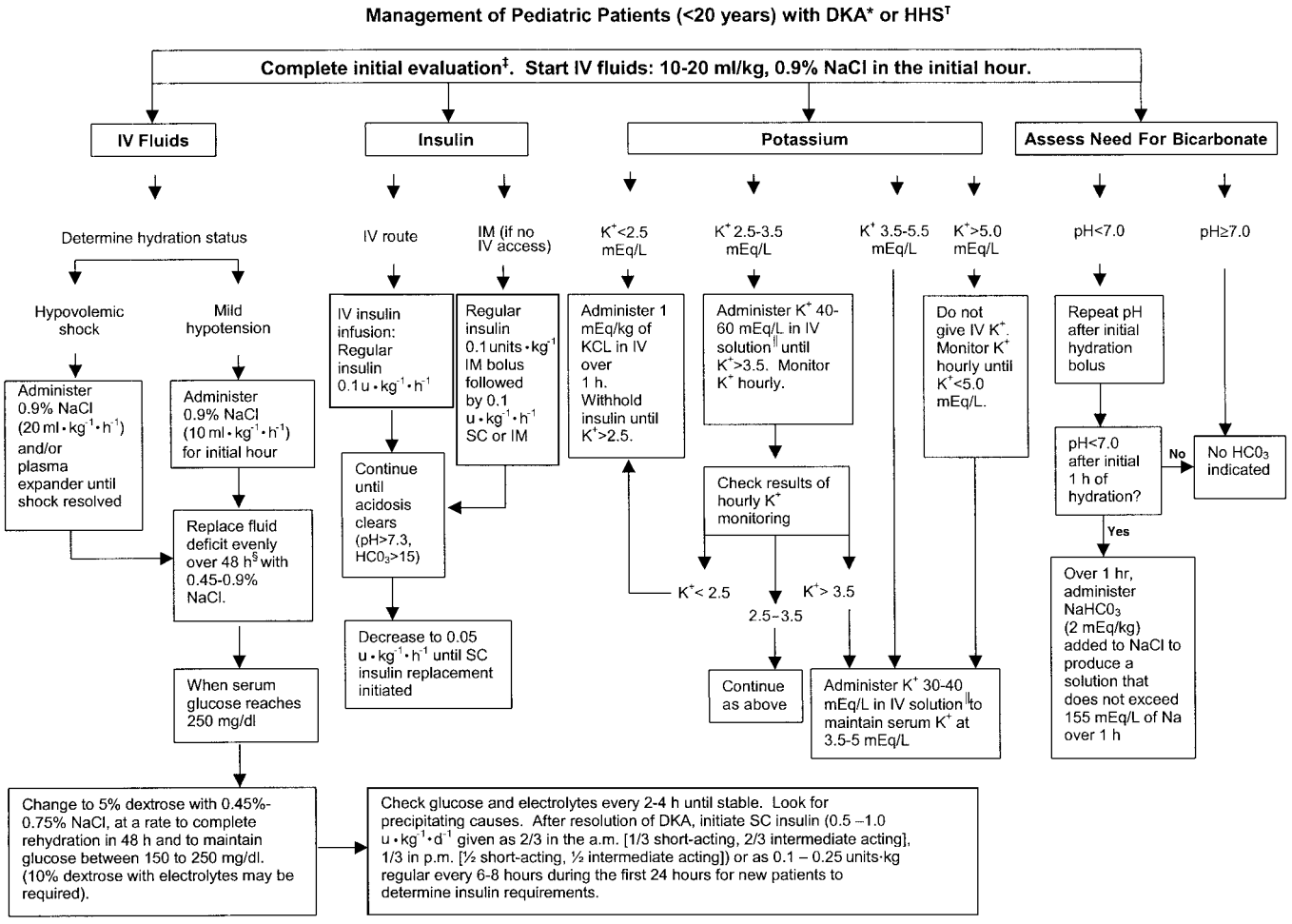

Figure 3—*Protocol for the management of pediatric patients (<20 years) with DKA or HHS. *DKA diagnostic criteria: blood glucose >250 mg/dl, venous pH <7.3, bicarbonate <15 mEq/l, moderate ketonuria or ketonemia.†HHS diagnostic criteria: blood glucose >600 mg/dl, venous pH >7.3, bicarbonate >15 mEq/l, and altered mental status or severe dehydration. ‡After the initial history and physical examination, obtain blood glucose, venous blood gases, electrolytes, blood urea nitrogen (BUN), creatinine, calcium, phosphorous, and urine analysis STAT. §Usually 1.5 times the 24 h maintenance requirements (~5 ml · kg^{-1} · h^{-1}) will accomplish a smooth rehydration; do not exceed two times the maintenance requirement. ‖The potassium in solution should be 1/3 KPO_4 and 2/3 KCl or Kacetate. IM, intramuscular; IV, intravenous; SC subcutaneous.*

acetoacetic acid and acetone. However, β-OHB, the strongest and most prevalent acid in DKA, is not measured by the nitroprusside method. During therapy, β-OHB is converted to acetoacetic acid, which may lead the clinician to believe that ketosis has worsened. Therefore, assessments of urinary or serum ketone levels by the nitroprusside method should not be used as an indicator of response to therapy. During therapy for DKA or HHS, blood should be drawn every 2–4 h for determination of serum electrolytes, glucose, blood urea nitrogen, creatinine, osmolality, and venous pH (for DKA). Generally, repeat arterial blood gases are unnecessary; venous pH (which is usually 0.03 units lower than arterial pH) and anion gap can be followed to monitor resolution of acidosis. With mild DKA, regular insulin given either subcutaneously or intramuscularly every hour is as effective as intravenous administration in lowering blood glucose and ketone bodies (27). Patients with mild DKA should first receive a "priming" dose of regular insulin of 0.4–0.6 units/kg body wt, half as an intravenous bolus and half as a subcutaneous or intramuscular injection (22). Thereafter, 0.1 unit · kg^{-1} · h^{-1} of regular insulin should be given subcutaneously or intramuscularly.

Criteria for resolution of DKA includes a glucose <200 mg/dl, serum bicarbonate ≥18 mEq/l, and a venous pH of >7.3. Once DKA is resolved, if the patient is NPO, continue intravenous insulin and fluid replacement and supplement with subcutaneous regular insulin as needed every 4 h. In adult patients, this can be given in 5-unit increments for every 50 mg/dl increase in blood glucose above 150 mg/dl for up to 20 units for blood glucose of ≥300 mg/dl. When the patient is able to eat, a multiple-dose schedule should be started that uses a combination of short- or rapid-acting and intermediate- or long-acting insulin as needed to control plasma glucose. Continue intravenous insulin infusion for 1–2 h after the split-mixed regimen is begun to ensure adequate plasma insulin levels. An abrupt discontinuation of intravenous insulin coupled with a delayed onset of a subcutaneous insulin regimen may lead to worsened control; therefore, some overlap should occur in intravenous insulin

Table 3—*Summary of major recommendations*

Recommendations	Grading
● Initiate insulin therapy according to recommendations in position statement.	A
● Unless the episode of DKA is mild, regular insulin by continuous intravenous infusion is preferred.	B
● Assess need for bicarbonate therapy and, if necessary, follow treatment recommendations in position statement: bicarbonate may be beneficial in patients with a pH <6.9; not necessary if pH is >7.0	C
● Studies have failed to show any beneficial effect of phosphate replacement on the clinical outcome in DKA. However, to avoid cardiac and skeletal muscle weakness and respiratory depression due to hypophosphatemia, careful phosphate replacement may sometimes be indicated in patients with cardiac dysfunction, anemia, or respiratory depression and in those with serum phosphate concentration <1.0 mg/dl.	A
● Studies of cerebral edema in DKA are limited in number. Therefore, to avoid the occurrence of cerebral edema, follow the recommendations in the position statement regarding a gradual correction of glucose and osmolality as well as the judicious use of isotonic or hypotonic saline, depending on serum sodium and the hemodynamic status of the patient.	C
● Initiate fluid replacement therapy based on recommendations in position statement.	A

Scientific evidence was ranked based on the American Diabetes Association's grading system. The highest ranking (A) is assigned when there is supportive evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered, including evidence from a meta-analysis that incorporated quality ratings in the analysis. An intermediate ranking (B) is given to supportive evidence from well-conducted cohort studies, registries, or case-control studies. A lower rank (C) is assigned to evidence from uncontrolled or poorly controlled studies or when there is conflicting evidence with the weight of the evidence supporting the recommendation. Expert consensus (E) is indicated, as appropriate. For a more detailed description of this grading system, refer to *Diabetes Care* 24 (Suppl. 1): S1–S2, 2001.

therapy and initiation of the subcutaneous insulin regimen. Patients with known diabetes may be given insulin at the dose they were receiving before the onset of DKA or HHS and further adjusted as needed for control. In patients with newly diagnosed diabetes, the initial total insulin dose should be ~0.5–1.0 units · kg^{-1} · day^{-1}, divided into at least two doses in a regimen including short- and long-acting insulin until an optimal dose is established. Finally, some type 2 diabetes patients may be discharged on oral antihyperglycemic agents and dietary therapy.

Potassium

Despite total-body potassium depletion, mild to moderate hyperkalemia is not uncommon in patients with hyperglycemic crises. Insulin therapy, correction of acidosis, and volume expansion decrease serum potassium concentration. To prevent hypokalemia, potassium replacement is initiated after serum levels fall below 5.5 mEq/l, assuming the presence of adequate urine output. Generally, 20–30 mEq potassium (2/3 KCl and 1/3 KPO_4) in each liter of infusion fluid is sufficient to maintain a serum potassium concentration within the normal range of 4–5 mEq/l. Rarely, DKA patients may present with significant hypokalemia. In such cases, potassium replacement should begin with fluid therapy, and insulin treatment should be delayed until potassium concentration is restored to >3.3 mEq/l to avoid arrhythmias or cardiac arrest and respiratory muscle weakness.

Bicarbonate

Bicarbonate use in DKA remains controversial (28). At a pH >7.0, reestablishing insulin activity blocks lipolysis and resolves ketoacidosis without any added bicarbonate. Prospective randomized studies have failed to show either beneficial or deleterious changes in morbidity or mortality with bicarbonate therapy in DKA patients with pH between 6.9 and 7.1 (29). No prospective randomized studies concerning the use of bicarbonate in DKA with pH values <6.9 have been reported. Given that severe acidosis may lead to a myriad of adverse vascular effects, it seems prudent that for adult patients with a pH <6.9, 100 mmol sodium bicarbonate be added to 400 ml sterile water and given at a rate of 200 ml/h. In patients with a pH of 6.9–7.0, 50 mmol sodium bicarbonate is diluted in 200 ml sterile water and infused at a rate of 200 ml/h. No bicarbonate is necessary if pH is >7.0.

Insulin, as well as bicarbonate therapy, lowers serum potassium; therefore, potassium supplementation should be maintained in intravenous fluid as described above and carefully monitored. (See Fig. 1 for guidelines.) Thereafter, venous pH should be assessed every 2 h until the pH rises to 7.0, and treatment should be repeated every 2 h if necessary. (See Kitabchi et al. [11] for a complete description of studies done to date on the use of bicarbonate in DKA.)

In the pediatric patient, there are no randomized studies in patients with pH <6.9. If the pH remains <7.0 after the initial hour of hydration, it seems prudent to administer 1–2 mEq/kg sodium bicarbonate over the course of 1 h. This sodium bicarbonate can be added to NaCl, with any required potassium, to produce a solution that does not exceed 155 mEq/l sodium. No bicarbonate therapy is required if pH is ≥7.0 (30,31).

Phosphate

Despite whole-body phosphate deficits in DKA that average ~1.0 mmol/kg body wt, serum phosphate is often normal or increased at presentation. Phosphate concentration decreases with insulin therapy. Prospective randomized studies have failed to show any beneficial effect of phosphate replacement on the clinical outcome in DKA (32), and overzealous phosphate therapy can cause severe hypocalcemia with no evidence of tetany (17,32). However, to avoid cardiac and skeletal muscle weakness and respiratory depression due to hypophosphatemia, careful phosphate replacement may sometimes be indicated in patients with cardiac dysfunction, anemia, or respiratory depression and in those with serum phosphate concentration <1.0 mg/dl. When needed, 20–30 mEq/l potassium phosphate can be added to replacement fluids. No studies are available on the use of phosphate in the treatment of HHS.

Continuous monitoring using a flowsheet (Fig. 4) aids in the organization of recovery parameters and treatment interventions.

SUGGESTED
DKA/HHS FLOWSHEET

DATE: HOUR:	ER												
Weight (daily)													
Mental Status*													
Temperature													
Pulse													
Respiration/Depth**													
Blood Pressure													
Serum Glucose (mg/dl)													
Serum Ketones													
Urine Ketones													
ELECTROLYTES													
Serum Na^+ (mEq/L)													
Serum K^+ (mEq/L)													
Serum Cl^- (mEq/L)													
Serum HCO_3^- (mEq/L)													
Serum BUN (mg/dl)													
Effective Osmolality													
2[measured Na(mEq/L)]													
+Glucose (mg/dl)/18													
Anion Gap													
A.B.G.													
pH Venous(V) Arterial(A)													
pO_2													
pCO_2													
O_2 SAT													
INSULIN													
Units Past Hour													
Route													
INTAKE FLUID/METABOLITES													
0.45% NaCl(ml) past hour													
0.9% NaCl(ml) past hour													
5% Dextrose(ml) past hour													
KCL (mEq) past hour													
PO_4 (mMOLES) past hour													
Other (e.g., HCO_3^-)													
OUTPUT													
Urine (ml)													
Other													

* A-ALERT D-DROWSY S-STUPOROUS C-COMATOSE
** D-DEEP S-SHALLOW N-NORMAL

Figure 4—*DKA/HHS flowsheet for the documentation of clinical parameters, fluid and electrolytes, laboratory values, insulin therapy, and urinary output. From Kitabchi et al. (14).*

COMPLICATIONS— The most common complications of DKA and HHS include hypoglycemia due to overzealous treatment with insulin, hypokalemia due to insulin administration and treatment of acidosis with bicarbonate, and hyperglycemia secondary to interruption/discontinuance of intravenous insulin therapy after recovery without subsequent coverage with subcutaneous insulin. Commonly, patients recovering from DKA develop hyperchloremia caused by the use of excessive saline for fluid and electrolyte replacement and transient non–anion gap metabolic acidosis as chloride from intravenous fluids replaces ketoanions lost as sodium and potassium salts during osmotic diuresis. These biochemical abnormalities are transient and are not clinically significant except in cases of acute renal failure or extreme oliguria.

Cerebral edema is a rare but frequently fatal complication of DKA, occurring in 0.7–1.0% of children with DKA. It is most common in children with newly diagnosed diabetes, but it has been reported in children with known diabetes and in young people in their twenties (25,33). Fatal cases of cerebral edema have also been reported with HHS. Clinically, cerebral edema is characterized by a deterioration in the level of consciousness, with lethargy, decrease in arousal, and headache. Neurological deterioration may be rapid, with seizures, incontinence, pupillary changes, bradycardia, and respiratory arrest. These symptoms progress as brain stem herniation occurs. The progression may be so rapid that papilledema is not found. Once the clinical symptoms other than lethargy and behavioral changes occur, mortality is high (>70%), with only 7–14% of patients recovering without permanent morbidity. Although the mechanism of cerebral edema is not known, it likely results from osmotically driven movement of water into the central nervous system when plasma osmolality declines too rapidly with the treatment of DKA or HHS. There is a lack of information on the morbidity associated with cerebral edema in adult patients; therefore, any recommendations for adult patients are clinical judgements, rather than scientific evidence. Prevention measures that might decrease the risk of cerebral edema in high-risk patients are gradual replacement of sodium and water deficits in patients who are hyperosmolar (maximal reduction in osmolality 3 $mOsm \cdot kg^{-1}$ $H_2O \cdot h^{-1}$) and the addition of dextrose to the hydrating solution once blood glucose reaches 250 mg/dl. In HHS, a glucose level of 250–300 mg/dl should be maintained until hyperosmolarity and mental status improves and the patient becomes clinically stable (34).

Hypoxemia and, rarely, noncardiogenic pulmonary edema may complicate the treatment of DKA. Hypoxemia is attributed to a reduction in colloid osmotic pressure that results in increased lung water content and decreased lung compliance. Patients with DKA who have a widened alveolo-arteriolar oxygen gradient noted on initial blood gas measurement or with pulmonary rales on physical examination appear to be at higher risk for the development of pulmonary edema.

PREVENTION

Many cases of DKA and HHS can be prevented by better access to medical care, proper education, and effective communication with a health care provider during an intercurrent illness. The observation that stopping insulin for economic reasons is a common precipitant of DKA in urban African-Americans (35,36) is disturbing and underscores the need for our health care delivery systems to address this problem, which is costly and clinically serious.

Sick-day management should be reviewed periodically with all patients. It should include specific information on *1*) when to contact the health care pro-

vider, 2) blood glucose goals and the use of supplemental short-acting insulin during illness, 3) means to suppress fever and treat infection, and 4) initiation of an easily digestible liquid diet containing carbohydrates and salt. Most importantly, the patient should be advised to never discontinue insulin and to seek professional advice early in the course of the illness. Successful sick-day management depends on involvement by the patient and/or a family member. The patient/family member must be able to accurately measure and record blood glucose, urine or blood ketone determination when blood glucose is >300 mg/dl, insulin administered, temperature, respiratory and pulse rate, and body weight and must be able to communicate this to a health care professional. Adequate supervision and help from staff or family may prevent many of the admissions for HHS due to dehydration among elderly individuals who are unable to recognize or treat this evolving condition. Better education of care givers as well as patients regarding signs and symptoms of new-onset diabetes; conditions, procedures, and medications that worsen diabetes control; and the use of glucose monitoring could potentially decrease the incidence and severity of HHS.

The annual incidence rate for DKA from population-based studies ranges from 4.6 to 8 episodes per 1,000 patients with diabetes, with a trend toward an increased hospitalization rate in the past two decades (37). The incidence of HHS accounts for <1% of all primary diabetic admissions. Significant resources are spent on the cost of hospitalization. Based on an annual average of ~100,000 hospitalizations for DKA in the U.S., with an average cost of $13,000 per patient, the annual hospital cost for patients with DKA may exceed $1 billion per year. Many of these hospitalizations could be avoided by devoting adequate resources to apply the measures described above.

Because repeated admissions for DKA are estimated to drain approximately one of every two health care dollars spent on adult patients with type 1 diabetes, resources need to be redirected toward prevention by funding better access to care and educational programs tailored to individual needs, including ethnic and personal health care beliefs. In addition, resources should be directed toward the education of primary care providers and school personnel so that they can identify signs and symptoms of uncontrolled diabetes and new-onset diabetes can be diagnosed at an earlier time. This has been shown to decrease the incidence of DKA at the onset of diabetes (30,38).

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