Complete Summary

GUIDELINE TITLE

Hyperglycemic crises in diabetes.

BIBLIOGRAPHIC SOURCE(S)

Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, Wall BM. Hyperglycemic crises in diabetes. Diabetes Care 2004 Jan;27(Suppl 1):S94-102. [38 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

The guideline was originally approved in October 2000; the most recent review/revision was completed in 2001.

American Diabetes Association (ADA) position statements are reissued annually.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Type 1 diabetes mellitus
- Type 2 diabetes mellitus
- Diabetic ketoacidosis (DKA)
- Hyperosmolar hyperglycemic state

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Prevention
Treatment

CLINICAL SPECIALTY

Emergency Medicine
Endocrinology
Family Practice
Internal Medicine
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To outline precipitating factors and recommendations for the diagnosis, treatment, and prevention of diabetic ketoacidosis and hyperosmolar hyperglycemic state

TARGET POPULATION

- Adults and children with type 1 diabetes mellitus
- Adults and children with type 2 diabetes mellitus

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Rapid, careful history and physical examination, with special attention to:
    - Patency of airway
    - Mental status
    - Cardiovascular and renal status
    - Sources of infection
    - State of hydration
2. Diagnostic tests:
    - Plasma glucose
    - Blood urea nitrogen (BUN)/creatinine
    - Serum ketones
    - Electrolytes (with calculated anion gap)
    - Osmolality
    - Urinalysis, urine ketones by dipstick
    - Initial arterial blood gases
    - Complete blood count with differential

- Bacterial cultures of urine, blood, and throat, etc. (if infection is suspected)
- Glycated hemoglobin
- Chest x-ray (if indicated)
- Electrocardiogram

Treatment and Management

1. Fluid therapy
2. Insulin therapy
3. Potassium
4. Bicarbonate
5. Phosphate

Prevention

1. Education of patients and caregivers:
    - Knowledge regarding conditions, procedures, and medications that worsen diabetes control
    - Glucose monitoring
2. Sick-day management:
    - When to contact the health care provider
    - Blood glucose goals and use of supplemental short-acting insulin during illness
    - Means to suppress fever and treat infection
    - Initiation of an easily digestible liquid diet containing carbohydrates and salt
    - Patient advisement never to discontinue insulin and to seek professional advice early in the course of the illness
    - Involvement by the patient and/or a family member
    - Accurate measurement and recording of blood glucose and urine or blood ketone
    - Measurement of temperature, respiratory and pulse rate, and body weight and communication to a health care professional

MAJOR OUTCOMES CONSIDERED

- Incidence rates of diabetic ketoacidosis and hyperosmolar hyperglycemic state
- Morbidity and mortality associated with diabetic ketoacidosis and hyperosmolar hyperglycemic state
- Efficacy of treatment
- Health care costs

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Recommendations have been assigned ratings of A, B, or C, depending on the quality of evidence (see table below). Expert opinion (E) is a separate category for recommendations in which there is as yet no evidence from clinical trials, in which clinical trials may be impractical, or in which there is conflicting evidence. Recommendations with an "A" rating are based on large, well-designed clinical trials or well done meta-analyses. Generally, these recommendations have the best chance of improving outcomes when applied to the population to which they are appropriate. Recommendations with lower levels of evidence may be equally important but are not as well supported.

American Diabetes Association's evidence grading system for clinical practice recommendations:

A

Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered including:

- Evidence from a well-conducted multicenter trial
- Evidence from a meta-analysis that incorporated quality ratings in the analysis
- Compelling non-experimental evidence, i.e., "all or none" rule developed by the Center for Evidence Based Medicine at Oxford*

Supportive evidence from well-conducted randomized trials that are adequately powered including:

- Evidence from a well-conducted trial at one or more institutions
- Evidence from a meta-analysis that incorporated quality ratings in the analysis

**Either all patients died before therapy and at least some survived with therapy, or some patients died without therapy and none died with therapy. Example: use of insulin in the treatment of diabetic ketoacidosis*.

B

Supportive evidence from well-conducted cohort studies, including:

- Evidence from a well-conducted prospective cohort study or registry
- Evidence from a well-conducted meta-analysis of cohort studies

Supportive evidence from a well-conducted case-control study

C

Supportive evidence from poorly controlled or uncontrolled studies:

- Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results
- Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls)
- Evidence from case series or case reports

Conflicting evidence with the weight of evidence supporting the recommendation

E

Expert consensus or clinical experience

COST ANALYSIS

Significant resources are spent on the cost of hospitalization. Based on an annual average of 100,000 hospitalizations for diabetic ketoacidosis in the U.S., with an

average cost of $13,000 per patient, the annual hospital cost for patients with diabetic ketoacidosis may exceed $1 billion per year.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This document was peer-reviewed, modified, and approved by the Professional Practice Committee and the Executive Committee, October 2000. The paper was most recently revised in 2001.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Excerpted by the National Guideline Clearinghouse (NGC)

The evidence grading system (A through C, E) is defined at the end of the "Major Recommendations" field.

Diagnosis

History and Physical Examination

The first approach to patients suspected of diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS) consists of a rapid but careful history and physical examination with special attention to (1) patency of airway, (2) mental status, (3) cardiovascular and renal status, (4) sources of infection, and (5) state of hydration. These steps should allow determination of the degree of urgency and priority with which various laboratory results should be obtained so that treatment can start without delay. Please refer to the original guideline document for signs and symptoms associated with diabetic ketoacidosis and hyperosmolar hyperglycemic state.

Laboratory Evaluation

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. Glycated hemoglobin (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. Table 1 (reproduced below) and Table 2 titled "Typical Total Body Deficits of Water and

Electrolytes in DKA and HHS" in the original guideline document depict typical laboratory findings in patients with DKA or HHS.

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 to 7.30	7.00 to 7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15 to 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	Variable
Alteration in sensorium or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

*Nitroprusside reaction method

**Calculation: 2[measured Na (mEq/)] + glucose (mg/dL)/18

***Calculation: $(Na^+) - (Cl^- - HCO_3^-)$ (mEq/L). See the text of the original guideline document for details.

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 ($\geq$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 are distinguished by clinical history and by plasma glucose concentrations that range from mildly elevated (rarely >250 mg/dL) to hypoglycemia. In addition, although alcoholic ketoacidosis can result in profound acidosis, the serum bicarbonate concentration in starvation ketosis is usually not lower than 18 mEq/L. Diabetic ketoacidosis 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.

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 Figures 1, 2, and 3 of the original guideline document. Table 3 in the original guideline document includes a summary of major recommendations and evidence gradings.

Fluid Therapy

Initiate fluid replacement therapy based on recommendations in the original guideline document. (*Grade A*)

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% sodium chloride) is infused at a rate of 15 to 20 mL/kg body weight per hour or greater during the 1st hour (approximately 1 to 1.5 liters in the average adult). Subsequent choice for fluid replacement depends on the state of hydration, serum electrolyte levels, and urinary output. In general, 0.45% sodium chloride infused at 4 to 14 mL/kg per hour is appropriate if the corrected serum sodium is normal or elevated; 0.9% sodium chloride at a similar rate is appropriate if corrected serum sodium is low. Once renal function is assured, the infusion should include 20 to 30 mEq/L potassium (2/3 potassium chloride and 1/3 potassium phosphate) 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 hours. The induced change in serum osmolality should not exceed 3 mOsm/kg H_2O per hour. 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.

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 first hour of fluids should be isotonic saline (0.9% sodium chloride) at the rate of 10 to 20 mL/kg per hour. 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 hours of therapy. Continued fluid therapy is calculated to replace the fluid deficit evenly over 48 hours. In general, 0.45 to 0.9% sodium chloride (depending on serum sodium levels) infused at a rate of 1.5 times the 24-hour maintenance requirements (approximately 5 mL/kg per hour) will accomplish a smooth rehydration, with a decrease in osmolality not exceeding 3 mOsm/kg H_2O per hour. Once renal function is assured and serum potassium is known, the infusion should include 20 to 40 mEq/L potassium (2/3 potassium chloride or potassium-acetate and 1/3 potassium phosphate). Once serum glucose reaches 250 mg/dL, fluid should be changed to 5% dextrose and 0.45 to 0.75% sodium chloride, with potassium as described above. Therapy should include monitoring mental status to rapidly identify changes that might indicate iatrogenic fluid overload, which can lead to symptomatic cerebral edema.

Insulin Therapy

Initiate insulin therapy according to the recommendations in the original guideline document. (*Grade A*)

Unless the episode of DKA is mild (see Table 1, above), regular insulin by continuous intravenous infusion is the treatment of choice (*Grade B*). In adult patients, once hypokalemia (K^+ <3.3 mEq/L) is excluded, an intravenous bolus of regular insulin at 0.15 units/kg body weight, followed by a continuous infusion of regular insulin at a dose of 0.1 unit/kg per hour (5 to 7 units per hour 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 per hour may be started in these patients. This low dose of insulin usually decreases plasma glucose concentration at a rate of 50 to 75 mg/dL per hour, similar to a higher-dose insulin regimen. If plasma glucose does not fall by 50 mg/dL from the initial value in the first hour, check hydration status; if acceptable, the insulin infusion may be doubled every hour until a steady glucose decline between 50 and 75 mg/hour 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 to 0.1 unit/kg per hour (3 to 6 units per hour), and dextrose (5 to 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 beta-hydroxybutyric acid in the blood is the preferred method for monitoring DKA. The nitroprusside method only measures acetoacetic acid and acetone. However, beta-hydroxybutyric acid, the strongest and most prevalent acid in DKA, is not measured by the nitroprusside method. During therapy, beta-hydroxybutyric acid 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 to 4 hours for determination of serum electrolytes, glucose, blood urea nitrogen, creatinine, osmolality, and venous pH (for DKA). Generally, repeat arterial blood gases are unnecessary; venous hydrogen ion concentration (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. Patients with mild diabetic ketoacidosis should first receive a "priming" dose of regular insulin of 0.4 to 0.6 units/kg body weight, half as an intravenous bolus and half as a subcutaneous or intramuscular injection. Thereafter, 0.1 unit/kg per hour of regular insulin should be given subcutaneously or intramuscularly.

Criteria for resolution of DKA includes a glucose <200 mg/dL, serum bicarbonate $\geq$18 mEq/L, and a venous pH of >7.3. Once DKA is resolved, if the patient is nothing by mouth, continue intravenous insulin and fluid replacement and supplement with subcutaneous regular insulin as needed every 4 hours. 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 $\geq$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 to 2 hours 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 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 approximately 0.5 to 1.0 units/kg per day, 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 to 30 mEq potassium (2/3 potassium chloride and 1/3 potassium phosphate) in each liter of infusion fluid is sufficient to maintain a serum potassium concentration within the normal range of 4 to 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

Assess need for bicarbonate therapy and, if necessary, follow treatment recommendations in the original guideline document: bicarbonate may be beneficial in patients with a pH <6.9; no bicarbonate is necessary if pH is >7.0. (*Grade C*)

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/hour. In patients with a pH of 6.9 to 7.0, 50 mmol sodium bicarbonate is diluted in 200 mL sterile water and infused at a rate of 200 mL/hour. 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 Figure 1 in the original guideline document.) Thereafter, venous pH should be assessed every 2 hours until the pH rises to 7.0, and treatment should be repeated every 2 hours if necessary.

In the pediatric patient, there are no randomized studies in patients with pH <6.9. If the pH remains less than 7.0 after the initial hour of hydration, it seems prudent to administer 1 to 2 mEq/kg sodium bicarbonate over the course of one hour. This sodium bicarbonate can be added to sodium chloride, with any required potassium, to produce a solution that does not exceed 155 mEq/L sodium. No bicarbonate therapy is required if pH is $\geq$7.0.

Phosphate

Prospective randomized studies have failed to show any beneficial effect of phosphate replacement on the clinical outcome in DKA, and overzealous phosphate therapy can cause hypocalcemia with no evidence of tetany. 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 less than 1.0 mg/dL. (*Grade A*) When needed, 20 to 30 mEq/L potassium phosphate can be added to replacement fluids. No studies are available on the use of phosphate in the treatment of hyperosmolar hyperglycemic state. Continuous monitoring using a flowsheet (see Figure 4 in the original guideline document) aids in the organization of recovery parameters and treatment interventions.

Complications

Complications of DKA and HHS, including hypoglycemia, hypokalemia, hyperglycemia, hyperchloremia, cerebral edema, hypoxemia, and non-cardiogenic pulmonary edema are discussed in the original guideline document.

Studies of cerebral edema in DKA are limited in number. Therefore, to avoid the occurrence of cerebral edema, follow the recommendations in the original guideline document 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 state of the patient. (*Grade C*)

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/kg H_2O per hour) and the addition of dextrose to the hydrating solution once blood glucose reaches 250 mg/dL. In HHS, a glucose level of 250 to 300 mg/dL should be maintained until hyperosmolarity and mental status improves and the patient becomes clinically stable.

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 is disturbing and underscores the need for 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 provider, (2) blood glucose goals and 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 hyperosmolar hyperglycemic state 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 hyperosmolar hyperglycemic state.

Because repeated admissions for DKA are estimated to drain approximately one out 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.

Definitions:

American Diabetes Association's evidence grading system for clinical practice recommendations:

A

Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered including:

- Evidence from a well-conducted multicenter trial
- Evidence from a meta-analysis that incorporated quality ratings in the analysis
- Compelling non-experimental evidence, i.e., "all or none" rule developed by the Center for Evidence Based Medicine at Oxford*

Supportive evidence from well-conducted randomized trials that are adequately powered including:

- Evidence from a well-conducted trial at one or more institutions
- Evidence from a meta-analysis that incorporated quality ratings in the analysis

**Either all patients died before therapy and at least some survived with therapy, or some patients died without therapy and none died with therapy. Example: use of insulin in the treatment of diabetic ketoacidosis*.

B

Supportive evidence from well-conducted cohort studies, including:

- Evidence from a well-conducted prospective cohort study or registry
- Evidence from a well-conducted meta-analysis of cohort studies

Supportive evidence from a well-conducted case-control study

C

Supportive evidence from poorly controlled or uncontrolled studies:

- Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results
- Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls)
- Evidence from case series or case reports

Conflicting evidence with the weight of evidence supporting the recommendation

E

Expert consensus or clinical experience

CLINICAL ALGORITHM(S)

The original guideline document contains clinical algorithms for:

- Management of Adult Patients with Diabetic Ketoacidosis
- Management of Adult Patients with Hyperosmolar Hyperglycemic State
- Management of Pediatric Patients (<20 years) with Diabetic Ketoacidosis or Hyperosmolar Hyperglycemic State

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for select recommendations (see the "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate management (diagnosis, treatment, and prevention) of hyperglycemic crises in patients with diabetes
- Decreased incidence and severity of diabetic ketoacidosis and hyperosmolar hyperglycemic state
- Decreased morbidity and mortality associated with diabetic ketoacidosis and hyperosmolar hyperglycemia
- Decreased health care costs

POTENTIAL HARMS

- Severe hypocalcemia is associated with phosphate therapy.
- Hypoglycemia or hypokalemia are associated with insulin administration.
- Hypokalemia is associated with bicarbonate.
- Hyperchloremia and transient non-anion gap metabolic acidosis are associated with saline for fluid and electrolyte replacement. These biochemical abnormalities are transient and are not clinically significant except in cases of acute renal failure or extreme oliguria.
- Fatalities can be associated with the treatment of diabetic ketoacidosis or hyperosmolar hyperglycemic state. Cerebral edema is a rare but frequently fatal complication of diabetic ketoacidosis. Fatal cases of cerebral edema have also been reported with hyperosmolar hyperglycemic state. 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 diabetic ketoacidosis or hyperosmolar hyperglycemic state.

Subgroups Most Likely to be Harmed

Patients with acute renal failure or extreme oliguria are most likely to be harmed by saline for fluid and electrolyte replacement.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Bicarbonate use in diabetic ketoacidosis remains controversial. 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 diabetic ketoacidosis patients with pH between 6.9 and 7.1. No prospective randomized studies concerning the use of bicarbonate in diabetic ketoacidosis with hydrogen ion concentration values <6.9 have been reported. In the pediatric patient, there are no randomized studies in patients with pH <6.9.
- No studies are available on the use of phosphate in the treatment of hyperosmolar hyperglycemic state.
- There is a lack of information on the morbidity associated with cerebral edema in adult patients; therefore, any recommendations for adult patients are clinical judgments, rather than scientific evidence.
- Evidence is only one component of clinical decision-making. Clinicians care for patients, not populations; guidelines must always be interpreted with the needs of the individual patient in mind. Individual circumstances, such as comorbid and coexisting diseases, age, education, disability, and above all, patient's values and preferences, must also be considered and may lead to different treatment targets and strategies. Also, conventional evidence hierarchies, such as the one adapted by the American Diabetes Association, may miss some nuances that are important in diabetes care. For example, while there is excellent evidence from clinical trials supporting the importance of achieving glycemic control, the optimal way to achieve this result is less clear. It is difficult to assess each component of such a complex intervention.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, Wall BM. Hyperglycemic crises in diabetes. Diabetes Care 2004 Jan;27(Suppl 1):S94-102. [38 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 Oct (revised 2001; republished 2004 Jan)

GUIDELINE DEVELOPER(S)

American Diabetes Association - Professional Association

SOURCE(S) OF FUNDING

The American Diabetes Association (ADA) received an unrestricted educational grant from LifeScan, Inc., a Johnson and Johnson Company, to support publication of the 2004 Diabetes Care Supplement.

GUIDELINE COMMITTEE

Professional Practice Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Authors of Position Statement, Initial Draft: 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; Barry M. Wall, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

The guideline was originally approved in October 2000; the most recent review/revision was completed in 2001.

American Diabetes Association (ADA) position statements are reissued annually.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Diabetes Association (ADA) Web site.

Print copies: Available from American Diabetes Association, 1701 North Beauregard Street, Alexandria, VA 22311.

AVAILABILITY OF COMPANION DOCUMENTS

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 2001:24:131-53.

In addition, a description of the American Diabetes Association (ADA) clinical practice recommendations and reports and evidence grading system is available in the introduction to the 2003 compilation (Diabetes Care 2003 Jan;25[Suppl 1]:S1-S2).

Print copies: Available from the American Diabetes Association, 1701 North Beauregard Street, Alexandria, VA 22311.

PATIENT RESOURCES

None available

NGC STATUS

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