SUPPLEMENT TO

MANAGED Care

The Importance of Blood Ketone Testing in Diabetes Management

Based on an online conference, Dec. 17, 2003

HIGHLIGHTS

• Detection of Ketosis and Monitoring of Diabetic Ketoacidosis

• Novel Syndromes of Ketosis-Prone Diabetes:
  Implications for Management and Medical Economics

• Role of Blood Ketone Testing in Sick-Day Management

• Challenges and Opportunities in Diabetes Care:
  Improving Outcomes With Education, DM, and Technology

• ROUNDTABLE DISCUSSION
  Evaluating Tools for Ketosis Assessment in Diabetes Patients

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MANAGED Care

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Optimizing Assessment of Diabetic Ketoacidosis in Diabetes Patients

On Dec. 17, 2003, a select panel of experts convened to discuss the relative benefits of blood- and urine-ketone testing for assessing ketosis in diabetes patients. The discussion that took place elucidates why the American Diabetes Association states that blood-ketone monitoring is preferred over urine-ketone testing for diagnosing diabetic ketoacidosis (DKA) in type 1 diabetes patients. Further, with annual medical costs to treat patients with DKA in excess of $1 billion, the pharmacoeconomic implications of appropriate management of type 1 diabetes were central to the discussion.

Metabolic ketosis and ketoacidosis are ever-present complications for the patient with type 1 diabetes. Prolonged insulin insufficiency from a variety of causes can progress rapidly to serious life-threatening metabolic acidosis. In the emergency room and hospital setting, this is usually confirmed with a battery of laboratory tests, including blood gases, pH, and bicarbonate levels. For confirmation of ketosis and ketoacidosis in the home or the decentralized setting, health care professionals and patients with diabetes have had access to urine-ketone dipstick methods for more than 30 years. Yet, just as with the early measurement of glucose in urine, there are serious limitations to urine-ketone measurements, both in terms of accuracy and predictive value. The advent of the specific measurement of the major ketone in blood, β–hydroxybutyrate, has given us a new option.

This meeting of health care professionals with experience in the assessment of diabetic ketoacidosis (DKA) and its sequelae was assembled to review the state of knowledge on urine- and blood-ketone measurement. The objective was to see whether a consensus on the use of blood-ketone monitoring for sick-day management could be developed.

The important insights that were generated in this unique forum have been effectively captured in this MANAGED CARE supplement. In a review of testing methodologies and practice patterns that begins on page 5, Peter Chase, MD, provides an informative overview of DKA. He describes it as a life-threatening complication of diabetes — one that timely use of blood tests for β-hydroxybutyrate can help to avert.

Beginning on page 15, Lori Laffel, MD, establishes point-of-care testing of β-hydroxybutyrate concentrations as an essential tool for sick-day management of diabetes, whether in the home or the physician's office, to augment blood-glucose monitoring. She makes clear that timely use of β-hydroxybutyrate monitoring may prevent significant morbidity and potential mortality, with an associated reduction in treatment costs.

In an article coauthored by Mario Maldonado, MD, and Ashok Balasubramanyam, MD, on page 7, the focus is on understanding the forms of ketosis-prone diabetes — especially in the context of multiple ethnicities in urban adult populations — and the value of a dedicated diabetes treatment unit to manage diabetes patients.

Finally, on page 11, Marlyn L. Crane, RN, a certified diabetes educator, provides insights into the importance of early at-home blood-ketone testing during sick days. Even before blood glucose begins to rise, blood-ketone levels can signify a change in metabolic status. Early detection of these changes can have a significant impact in preventing the development of DKA.

We hope that you will take advantage of the continuing education opportunity within this supplement, provided through The Chatham Institute. Credit is offered to physicians and pharmacists who read this supplement and successfully complete and mail in the post-test and evaluation form that can be found at the back of this publication.

Continuing Education Section

The Importance of Blood Ketone Testing in Diabetes Management

Continuing education is offered to physicians and pharmacists who read pages 5 through 21 of this publication, complete the post-test on page 22, and fill out the evaluation form on page 23.

PURPOSE AND OVERVIEW

This activity focuses on blood ketone testing in diabetes management. The currently accepted guidelines relative to practice protocols and management of type 1 diabetes patients will be discussed. A review of recent literature on blood ketone and urine ketone testing methodologies and an overview of prevalence and treatment costs associated with diabetic ketoacidosis will allow for a balanced look at approaches to the care of these patients. These articles are derived from "The Importance of Blood Ketone Testing in Diabetes Management: Detection of Ketosis and Monitoring of Diabetic Ketoacidosis," an online symposium on Dec. 17, 2003.

Educational needs assessment

Managed care organizations are seeking cost-effective ways to optimize treatment for type 1 diabetes patients. The two main emergencies that can befall patients with diabetes are hypoglycemia and diabetic ketoacidosis (DKA), both of which can result in death. DKA is the leading cause of death among children known to have diabetes.

Treatment costs for patients with DKA are in excess of $1 billion annually; for patients with type 1 diabetes who develop DKA, treatment costs are approximately double those for a type 1 patient without DKA.

Despite the 2003 American Diabetes Association guidelines that recommend the use of blood ketone testing, a premeeting survey and faculty perceptions of significant trends indicate that health professionals still are seeking information to assist them in differentiating between the relative effectiveness of blood and urine testing of ketone levels. There is, thus, a clear need to educate managed care decision makers about the optimal approach to improving outcomes for these patients.

Educational objectives

After reading this publication, the participant should be able to:

- Discuss current testing methodologies and practice patterns for detecting diabetic ketoacidosis.
- Review the relative benefits of blood and urine ketone testing for detection of ketosis in diabetic ketoacidosis.
- Demonstrate the implications of appropriate management of type 1 diabetes with respect to patient health and pharmacoeconomics.
- Highlight the importance and cost effectiveness of monitoring both blood glucose and blood ketone levels, with daily assessment of ketosis.
- Determine how guidelines might be developed for blood glucose and blood ketone home monitoring for the type 1 diabetes patient.
- Ascertain the potential for managed care organizations to assist in implementing and disseminating such guidelines.
- Discuss the potential avenues for retaining the inclusion of a ketone-level measurement as a data-quality assessment.
- Enhance health care professionals' awareness of the importance of blood ketone testing.

Target audiences

Managed health care professionals, including physicians, pharmacists, medical directors, chief medical officers, pharmacy directors, and other senior managers in managed care organizations.

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Continuing Education

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This activity has been planned and implemented in accordance with the ACCME Essential Areas, Elements, and Policies.

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Continuing Education Section

The Importance of Blood Ketone Testing in Diabetes Management

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Faculty disclosures

H. Peter Chase, MD, acknowledges that he has a consulting relationship with and has received research support from Abbott Laboratories.

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Detection of Ketosis and Monitoring Of Diabetic Ketoacidosis

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The two main emergencies that can befall patients with diabetes are hypoglycemia and diabetic ketoacidosis (DKA), each of which can result in death. Indeed, DKA is the leading cause of death among children known to have diabetes, accounting for about 85 percent of such fatalities. Cerebral edema is associated with approximately 70 percent of these deaths.

Annual medical costs to treat patients with DKA exceed $1 billion, and the annual medical costs for treating a patient with type 1 diabetes who develops DKA are about twice those for a type 1 patient without DKA. (It should be noted that DKA is not restricted to patients with type 1 diabetes, as it is commonly believed (see Laffel's article on pages 15–18).

About 80 to 90 percent of children who are newly diagnosed with diabetes have elevated levels of ketone bodies, and 30 percent present with a blood pH below 7.30 — already in acidosis, by definition. Therefore, the first goal in the treatment of patients who are newly diagnosed with diabetes should be to stop the production of the ketone bodies.

Diabetes Control and Complications Trial

In the Diabetes Control and Complications Trial, the incidence of DKA was 2.8 per 100 patient-years in the intensive-treatment group vs. 4.7 per 100 patient-years in the conventional-treatment group (DCCT 1994). We followed 1,243 children with known type 1 diabetes in metropolitan Denver for 6 years and observed 320 episodes of DKA (defined as a visit to the emergency room [ER] or a hospital admission) during 3,994 patient-years of follow-up, an overall incidence of 8 per 100 patient-years (Rewers 2002). The incidence rate increased with age in girls (4 per 100 patient-years among those below age 7, 8 among those ages 7 to12, and 12 in patients who are at least 13 years old), higher HbA_{1c} levels, higher doses of insulin per kilogram of body weight, the presence of psychiatric diagnoses, and underinsurance.

For these reasons, DKA deserves the attention of managed care organizations and parents of children with diabetes (65 percent of DKA cases occur in patients under the age of 19). Fortunately, the mortality and morbidity associated with DKA are largely avoidable through prudent in-home monitoring of ketone bodies. The education of parents and patients therefore is paramount as soon as diabetes is diagnosed. They must be made aware of why ketone testing is important, when it should be done, and how to interpret the results. They also must remember to have test kits available at home and while traveling (Chase 2002).

Accumulation of ketone bodies

The presence of ketone bodies (Table) in the blood or urine is a sign that the body is breaking down its stores of fat because it lacks access to its normal source of energy — glucose. Starvation is one method by which glucose supplies become depleted, forcing the body to use fatty acids instead.

Under normal conditions, fat is broken down into glycerol and fatty acids, which are converted to acetyl-CoA. If adequate amounts of oxaloacetate are available, then the acetyl-CoA can enter the tricarboxylic acid cycle (also known as the Krebs or citric acid cycle). If supplies of oxaloacetate are inadequate, the liver instead converts

TABLE	Ketone bodies*		
	Acetoacetate	**β-hydroxybutyrate**	**Acetone**
Formula	$CH_3COCH_2COO^-$	$CH_3CHOHCH_2COO^-$	CH_3COCH_3
Where detected	Urine	Blood	Breath
Tests	Chemstrip (Roche)	Precision Xtra	None, other than detecting
	Clinistix (Bayer)	(Abbott/MediSense)	a fruity odor on patient's breath
	Keto-Diastix (Bayer)		
	Ketostix (Bayer)		

*The terminology is traditional, not scientific, as the substances are not "bodies" — and β-hydroxybutyrate is not a ketone (a compound containing a carbonyl functional group in which the carbonyl carbon bears two alkyl groups).

the acetyl-CoA into ketone bodies. In patients without diabetes, ketone production can occur during fasting or when carbohydrates are inadequate, but the amounts of ketones usually are low and the condition does not progress to ketoacidosis.

In people with diabetes, insulin activity is lacking, due to decreased production of insulin (type 1 diabetes) or reduced sensitivity to insulin (type 2 diabetes). A shortage or absence of insulin approximates a state of extreme starvation, because glucose, even if present, is inaccessible as an energy source.

Infection or illness is the primary reason that a person with known diabetes develops ketone bodies. Under these circumstances extra energy is required and, if insulin levels are insufficient, fat will be broken down. Stress from surgery, a myocardial infarction, or an abscess can precipitate DKA. For example, a 15-year-old girl with type 2 diabetes died from DKA subsequent to an abscess under her arm.

Inadequate insulin levels in patients taking insulin also can be the consequence of a missed dose, a dose that is too low, malfunction of an insulin pump, or improper storage of insulin (storing it above 90 degrees Fahrenheit or allowing it to freeze).

An abnormal level of ketone bodies is dangerous, because they circulate as acids (β-hydroxybutyric acid, acetoacetic acid) and alter the pH of the blood — which normally is in the range of 7.35 to 7.45. Many enzymes that govern metabolic processes require a pH within this range, if they are to function properly. Acidosis is defined by a blood pH below 7.30, and in such an acidic environment, enzyme function is blocked.

When blood glucose levels rise due to inadequate or absent insulin, the hyperglycemia induces osmotic diuresis, leading to dehydration. Potassium also is lost, resulting in reduced gastrointestinal motility, vomiting, and loss of other electrolytes.

The only other disease in which a patient presents with dehydration, a dry mouth, and a dry tongue but still is voiding frequently is diabetes insipidus. A blood glucose test and a blood ketone test should be done immediately if a person is dehydrated and still voiding, which may lead to a lifesaving diagnosis.

A fruity odor to the breath is another sign that ketone bodies are accumulating. Acetoacetate spontaneously decomposes into acetone, which is not metabolized further and lends its characteristic odor to exhaled breath. Another important sign of DKA is deep breathing that is known as Kussmaul respiration, the presence of which mandates taking the patient to the ER.

Testing for ketone bodies also is recommended if blood sugar levels are high (>240 mg/dL after fasting,

>300 mg/dL during the day); during illness or infection; subsequent to traumatic stress — especially important in type 2 diabetes — and during pregnancy.

Measuring ketone bodies

Ketone bodies can be measured via dipstick urine tests — which measure acetoacetate , or blood tests — which measure β-hydroxybutyrate. For many years, urine tests were the only tests available. The newer blood test, however, is the one now recommended by the American Diabetes Association for measuring ketone bodies (ADA 2003). Levels of β-hydroxybutyrate are a better indicator than acetoacetate of a patient's metabolic status during the detection and treatment of DKA (Schade 1982). The blood test indicates the patient's status at the time of the test, whereas urine that is tested may have been in the bladder for hours. Second, a urine test may be infeasible, due to the patient's inability to void. In addition, the urine ketone strips degrade over time and must be used within 6 months. If the test strips have had long exposure to air or if the urine specimen is highly acidic, false-negative readings can occur. In addition, sulfhydryl drugs such as captopril can cause false-positive results in test strips using reagents that contain nitroprusside.

A β-hydroxybutyrate level below 0.6 mmol/L is considered normal. If it is between 0.6 and 1.0 mmol/L, the patient should take additional insulin and increase fluid intake to flush out the ketones. In addition to taking these measures, the patient's physician should be called if the β-hydroxybutyrate concentration is between 1.0 and 1.5 mmol/L; if it is between 1.5 and 3.0 mmol/L, the physician should be called immediately. Any level above 3.0 mmol/L warrants a trip to the ER.

In summary, DKA is a life-threatening complication of diabetes that largely can be avoided through the timely use of blood tests for β-hydroxybutyrate.

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Novel Syndromes of Ketosis-Prone Diabetes: Implications for Management And Medical Economics

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Diabetic ketoacidosis (DKA) commonly is regarded as being predominantly a complication of type 1 diabetes. Statements in leading medical textbooks reinforce this notion. For example, Daniel W. Foster, MD, widely regarded as an authority in the field of ketoacidosis, wrote in the 1998 edition of *Harrison's Principles of Internal Medicine*: "Ketoacidosis rarely develops in true non-insulin-dependent diabetes mellitus…." Likewise, Matthew J. Orland, MD, writing in the 1998 edition of the *Washington Manual of Medical Therapeutics*, states that predisposition to DKA is characteristic of type 1 diabetes, but he notes that DKA may develop in any patient with diabetes who is sufficiently stressed. In this article, we present data to suggest that the situation is considerably more complicated, especially in the context of multiple ethnicities in urban adult populations.

Seen from the standard physiologic perspective, ketogenesis is regarded largely as a matter of achieving balance between insulin and counterregulatory hormones (chiefly glucagon, but also cortisol, growth hormone, and catecholamines). If insulin is lacking, as in typical type 1 autoimmune diabetes, the counterregulatory hormones outweigh insulin and tip the seesaw toward ketosis. Even if insulin secretion appears to be normal, severe stress also could lead to the overproduction of counterregulatory hormones, again favoring ketosis.

Case studies

Two case studies (Table 1, page 8) drawn from the hundreds of patients seen in our ketosis-prone diabetes specialty clinic at Ben Taub General Hospital illustrate why this paradigm is wanting. The first patient is a 39-year-old Hispanic male who presents with polyuria/polydipsia of recent onset. There is a strong history of type 2 diabetes in his family, but he has no history of diabetes and no obvious stress. His body mass index (BMI) approaches the obese stage, and he has central obesity, acanthosis nigricans, and extremely high HbA_{1c}. Based on these signs and symptoms, the majority of endocrinologists and other physicians would conclude that this man has classic type 2 diabetes.

Before we consider his case further, it will be helpful to look at the second patient, a 42-year-old black woman, presenting with polyuria/polydipsia of recent onset. Like the first patient, she displays no signs of stress and has no history of diabetes, although there is a strong history of type 2 diabetes in her family. She also has a high BMI, increased abdominal girth, and high HbA_{1c} levels. Most clinicians would conclude that she also is fairly typical of patients presenting for the first time with type 2 diabetes.

In fact, both patients came to the emergency department. The male patient presented with nausea and vomiting, and both patients had a pH in the acidic range, an anion gap, and positive serum ketones. That is, each had bona fide DKA. The conventional wisdom therefore suggests that they have type 1 diabetes. But do they?

After the patients were stabilized, additional tests were ordered. The man's tests were negative for β-cell autoantibodies and his C-peptide concentration suggested some degree of preserved β-cell reserve. The woman tested positive for β-cell autoantibodies, but her fasting C-peptide level was not as low as might be expected for the typical type 1 diabetic patient.

Cases like these defy easy classification, and they are being reported with increasing frequency in many parts of the world. It is time for a systematic investigation to determine if there indeed are novel syndromes of diabetes that might present with such severe β-cell dysfunction that the patient develops DKA.

Study of DKA outpatients

At the Ben Taub General Hospital, we undertook a simple study about 5 years ago, using computer records to identify 181 patients who presented with DKA in 1994 and 1995, following them for 2.5 to 4 years as they received outpatient treatment, usually at community health center clinics. Patients were classified as type 1 or type 2 on the basis of clinical criteria at their initial and follow-up visits (Table 2, page 8). Patients who initially had

TABLE 1   Case studies challenging the DKA paradigm

	Case study #1: 39-year-old Hispanic male	Case study #2: 42-year-old black female
Presented with	Polydipsia/polyuria for 3 weeks	Polydipsia/polyuria for 3 weeks
Personal history of type 2 diabetes	No	No
Family history of type 2 diabetes	Yes, strong	Yes, strong
Stress	Not obvious	Not obvious
Body mass index	29.4 kg/m^2	30.6 kg/m^2
Waist:hip ratio	0.95	0.93
Blood pressure	129/74 mm Hg	143/76 mm Hg
Emergency room findings		
HbA$_{1c}$	12.5%	13.8%
pH	7.23	7.17
HCO$_3$	10.9	9.7
Anion gap	23	24
Serum ketones	1:8	1:8
Tests ordered after stabilization		
β-cell autoantibodies	Negative	Positive
Fasting C-peptide	2.0 ng/mL	1.8 ng/mL

new-onset diabetes were designated as type 1 if they had required continuous insulin therapy since their initial DKA episode or type 2 if they had been able to discontinue insulin completely or for significant periods without recurrence of DKA. The overall distribution of DKA events among ethnic groups reflects the Ben Taub patient population, which is 46 percent black, 34 percent Hispanic, and 18 percent white.

In this analysis, only white patients followed the textbook pattern that links DKA with type 1 diabetes. Hispanic patients were more likely to have type 2 diabetes than type 1 diabetes, and DKA also was observed in a high percentage of black patients with type 2 diabetes. These observations led us to establish a special unit to follow DKA patients prospectively. Since June 1, 1999, we have evaluated, treated, and followed virtually all patients admitted with DKA. In addition to conducting a detailed physical examination, collecting anthropometric information, and obtaining a family history, we also test for β-cell autoantibodies and β-cell functional reserve, and we collect DNA for genetic analysis. The autoantibody testing is done through a special collaboration with Ake Lernmark, MD, PhD, at the University of Washington in Seattle, and the normative base for these data comes from approximately 100 normal, nondiabetic patients in each ethnic group to establish ethnic-specific 95th percentile ranges.

To address the problem of classifying patients who do not have obvious autoimmune type 1 diabetes or classic type 2 diabetes, we prospectively sorted them into four groups based on two markers generally accepted as distinctive for type 1 diabetes. The first of these markers is the presence or absence of antibodies, defined as any of a battery of GAD65, GAD67, IA-2, or islet cell antibodies. The second is β-cell function, defined by either a fasting C-peptide level or glucagon-stimulated C-peptide response.

The four groups generated by these markers are the following: $A+ \beta+$, indicating patients with antibodies but some β-cell functional reserve; $A- \beta+$, indicating patients with no antibodies and some β–cell functional reserve; $A+\beta-$, indicating the classic type 1 patients with antibodies and no β-cell functional reserve; and $A- \beta-$, indicating patients with no evidence of autoimmunity and no β-cell functional reserve. Baseline clinical data and human leukocyte antigen (HLA) genotyping for these groups are presented in Table 3.

Note that the $A- \beta+$ group — patients who might be mistaken for those with type 2 diabetes — accounts for

TABLE 2   Final distribution of DKA patients by diabetic classification and ethnicity

	Black (n=65)	Hispanic (n=43)	White (n=30)	Asian (n=3)
Type 1 diabetes	53% (35)	34% (15)	80% (24)	33% (1)
Type 2 diabetes	44% (28)	47% (20)	17% (5)	67% (2)
Unknown	3% (2)	19% (8)	3% (1)	0% (0)

SOURCE: BALASUBRAMANYAM 1999

TABLE 3 **Baseline clinical and biochemical characteristics and HLA genotyping for patients presenting with DKA**

Clinical and biochemical characteristics

	A+ β+	*A*− β+	*A*+ β−	*A*− β−	*P* value
N (%)	11 (11)	51 (50)	18 (17)	23 (22)	–
Age	43 ± 14	42 ± 13	34 ± 17	38 ± 15	.1000
Age at diagnosis	42 ± 12	39 ± 12	25 ± 17	26 ± 12	<.0001[a]
Male:female ratio	0.6:1	1.7:1	1:1	1.3:1	.4000
Family history of type 2 diabetes	9 (82%)	45 (88%)	9 (50%)	19 (83%)	.0100
Body mass index, kg/m^2	30.6 ± 7.6	29.4 ± 8.3	24.5 ± 3.9	23.0 ± 2.8	.0003[b]
HbA$_{1c}$, %	12.5 ± 2.3	13.8 ± 2.5	13.1 ± 2.3	14.5 ± 2.2	.3000
Fasting C-peptide, ng/dL	1.66 ± 0.31	1.94 ± 0.13	0.14 ± 0.04	0.24 ± 0.06	<.0001[c]

[a] Pair-wise significant differences between A+ β+ and A+ β−; A+ β+ and A− β−; A− β+ and A+ β−; and A− β+ and A− β−.

[b] Pair-wise significant differences between A+ β+ and A− β−; A− β+ and A+ β−; and A− β+ and A− β−.

[c] Pair-wise significant differences between A+ β+ and A+ β−; A+ β+ and A− β−; A− β+ and A+ β−; A− β+ and A− β−; and A+ β+ and A− β+.

Group frequencies of class II HLA alleles associated with type 1 autoimmune diabetes

DQA*03	45%	45%	**89%**	48%	.020
DRB1*15	9%	16%	0%	9%	>.700
DQB1*02	55%	25%	**72%**	26%	.005
DQB1*04	0%	22%	0%	13%	>.700
DQB1*0602	9%	20%	**0%**	9%	>.700

Red=susceptibility allele; green=protective allele

SOURCE: MALDONADO 2003A

half the adult patients in our population presenting with DKA. In addition, the male:female ratio is exactly the reverse of the usual ratio in a population of diabetic patients who are not prone to ketosis.

Differences in patients' ages at the time of diagnosis also are apparent, with the groups having some β-cell function being much older than patients without β-cell function. Patients with some β-cell function also were substantially more overweight, compared with the other groups.

In terms of ethnicities, the greatest differences are seen

TABLE 4 **Ethnic distribution of patients presenting with DKA (N=106)**

	Black (n=41)	Hispanic (n=45)	White (n=18)	Asian (n=2)
A+ β+	10% (4)	9% (4)	17% (3)	0% (0)
A− β+	37% (15)	67% (30)	28% (5)	50% (1)
A+ β−	32% (13)	4% (2)	28% (5)	50% (1)
A− β−	22% (9)	20% (9)	28% (5)	0% (0)

between Hispanic and non-Hispanic groups (Table 4). Differences between blacks and whites are not apparent, possibly due to the low number of patients.

This is an extremely heterogeneous patient population — some with β-cell function at baseline, some with none — but all received essentially the same kind of intensive treatment in our dedicated clinic. Those with some β-cell function (the β+ groups) responded well to intensive treatment (Figure 1), with their HbA$_{1c}$ levels rapidly reaching a level that is consistent with good glycemic control, and remaining so for 12 months. In contrast, the patients without β-cell function (the β− groups) had HbA$_{1c}$ levels that never reached the recommended glycemic goal, despite intensive treatment. Not surprisingly, patients without β-cell function at baseline never were able to come off insulin therapy, but a substantial number of patients with residual β-cell function could do so. Among patients in the *A*+ β+ group, those able to do without insulin treatment appeared to be those carrying protective HLA alleles, perhaps indicating a rationale for HLA testing in select patients who present with DKA.

Four distinct forms of ketosis-prone diabetes

To summarize the information that may be most useful to practitioners, there appear to be at least four distinct forms of ketosis-prone diabetes among urban adults that are phenotypically and potentially genotypically distinguishable. The $A+$ $\beta-$ group is most recognizable, because it comprises those with classic type 1 diabetes. Their disease begins at a young age and is long standing, and they tend to be lean, have a high percentage of susceptibility alleles, and are completely dependent on insulin.
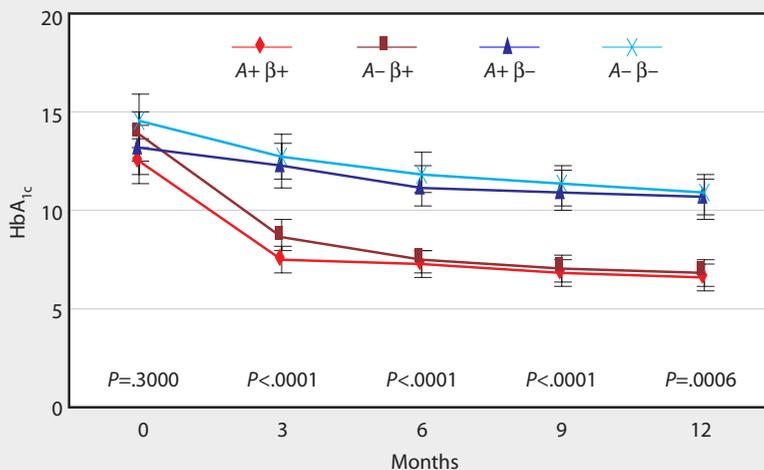
The other three groups are more mysterious. The $A+$ $\beta+$ group represents an unusual subset of patients with autoimmune diabetes. They have evidence of autoantibodies, yet they also have good β-cell function. They have an older age of onset and a shorter duration of diabetes, they tend to be overweight, they have a lower frequency of the high-susceptibility alleles, and they may or may not be insulin-dependent in the long run, depending on their protective allele status.

The remaining two groups without autoimmunity also are extremely interesting, each being likely to represent novel, possibly "nonimmunologic" forms of β-cell dysfunction. Patients in the $A-$ $\beta-$ group resemble type 1 diabetics, being lean and having long-standing disease, yet they lack antibodies and have a low frequency of the high-susceptibility alleles. It is hard to say whether they have genetically based β-cell dysfunction, but from a practical standpoint they are insulin-dependent.

The $A-$ $\beta+$ group represents the largest number of patients in the urban multiethnic population. They tend to be older at the age of diabetes onset, and quite often are found to have new-onset diabetes at the time they present with DKA. They tend be overweight and have a low frequency of susceptibility alleles. They quite often are not insulin-dependent.

Recognizing and closely following patients with these newer forms of ketosis-prone diabetes may prove essential to reducing the morbidity and costs associated with DKA. Nevertheless, even as clinicians increase their level of alertness for novel syndromes of diabetes, they should remember that the leading precipitating cause of DKA appears to be noncompliance (Maldonado 2003b). In a series of patients admitted to our hospital with DKA (N=167) during 1998, noncompliance was the precipitating cause among 59 percent of the patients, while new-onset diabetes and acute illness accounted for 23 and 18 percent, respectively, of DKA admissions. Although

the mean inpatient costs were substantially lower among the noncompliant patients ($7,470) than among patients with new-onset diabetes ($11,863) or acute illness ($20,864), the sheer number of noncompliant patients made them the most costly group to treat.

From a practical standpoint, providing outpatient diabetes care through a dedicated diabetes treatment unit may be the optimal strategy for reducing the readmission rate among indigent patients for DKA (Maldonado 2003c). In summary, understanding the forms of ketosis-prone diabetes and using a specialized program such as a diabetes treatment unit to follow patients closely are essential to reducing morbidity and costs of DKA.

FIGURE 1 Characterization of patients presenting with DKA glycemic control

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Role of Blood Ketone Testing In Sick-Day Management

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Although blood glucose monitoring is generally the most important aspect of care in managing diabetes, blood ketone testing becomes the focus of attention during sick days (Laffel 2000). Even before blood glucose begins to rise, blood ketone levels can signify a change in metabolic status. Patients should be taught to begin blood ketone testing at the first signs and symptoms of a physical change, such as onset of the flu, a cold, a sore throat, or general malaise.

Such changes that occur at home need early evaluation and may warrant treatment by a prepared clinical staff. Physical symptoms and increasing blood glucose that do not resolve with added insulin injections should be reported to the physician or other members of the professional treatment team.

Early at-home treatment

Early at-home sick-day diabetes management strives to prevent diabetic ketoacidosis (DKA). Insulin titration and increased fluid intake are fundamental treatment strategies used on sick days. Instructions for patients who become ill at home include additional insulin injections, blood ketone testing, and an increased intake of sugar-free fluids. Because dehydration can occur in the early stages of DKA, increased fluid intake is important. The adult patient could require an extra liter or more in fluids to keep up with ongoing losses and to maintain normal hydration. If adequate hydration can be maintained, successful treatment of diabetes at home that is aimed at maintaining normal metabolic status and preventing DKA becomes probable. The patient should contact the health care team with the onset of emesis that prevents maintenance of hydration. Blood glucose and blood ketone levels also should be reported to the health care team.

During sick days, nurses in an outpatient treatment center can play a primary role in DKA prevention, particularly because they may be the key contact for patients. They not only educate patients about the importance of blood glucose and blood ketone monitoring, but they also aid in the interpretation of the data. Nurses ensure that patients understand why it is essential to monitor ketones. As changes in blood ketones may precede an increase in blood glucose levels, awareness of these changes can provide the extra time needed to initiate at-home treatment and thus aid in prevention of DKA.

Based on glucose and ketone values reported by the patient (via e-mail or telephone — according to the individual center's protocol), nurses or other trained members of the health care team assign patients the appropriate frequency for retesting.

Testing of ketones and glucose may be warranted every 1 to 2 hours. Until the patient returns to euglycemia or achieves a physician-designated glucose level and normal hydration, titration of additional insulin injections or pump boluses continues, along with increased fluid intake. If these conditions are not achieved, the patient may require medical assessment and referral for possible parenteral treatment.

Morbidity and mortality associated with failed sick-day management of diabetes may be prevented if early treatment is initiated successfully in the home. Furthermore, the health care costs associated with emergency hospital care may be contained. Thus, the potential benefits of early treatment apply both to patients and the health care system.

Early physiologic changes in DKA

When implementing a sick-day protocol, the health care team should ensure that the patient understands how sickness, whether physical or emotional, raises the body's energy requirements. During stressful times, the production of counterregulatory hormones, such as cortisol, growth hormone, glucagon, adrenaline, and other catecholamines, increases. When these hormones are released into the bloodstream, hepatic glycogenolysis (breakdown of stored glycogen), gluconeogenesis (synthesis of glucose), and ketogenesis (production of ketones) are promoted, with resulting increases in blood glucose and ketone levels. If insulin levels are inadequate, as they may be in the patient with diabetes, the glucose released by the liver is not utilized for energy; instead, the counterregulatory stimulus for fuel and energy continues to promote lipolysis and ketogenesis.

As a consequence of the metabolism of fatty acids, ketone bodies (acetoacetate, β-hydroxybutyrate, and acetone) accumulate in the blood. In addition, in the absence of adequate insulin to utilize glucose, an osmotic diuresis ensues — leading to dehydration. Ketogenesis continues, leading to an accumulation of ketones. This increase in ketones coupled with dehydration produces a decrease in blood pH. Decreasing pH inhibits the proper

functioning of cellular enzymes. The patient may steadily progress to DKA and, if the acidosis remains unchecked, significant morbidity and mortality may occur.

Testing of blood ketones in the home environment represents a new paradigm in outpatient diabetes sick-day management. The blood ketone status, more than the blood glucose level, is the line in the sand that represents when a patient's care must be more aggressive and possibly transitioned from the home to the hospital environment. As long as blood ketone tests demonstrate levels of less than 3.0 mmol/L, continued home sick-day management generally is considered safe. This is, however, a clinical decision that the health care team must make for each patient, case by case.

Early at-home treatment is possible when the patient clearly understands the value of early detection of blood ketone elevations and reports the information to the designated clinical provider. Clinicians receiving accurate information from patients using proven self-testing tools can act with confidence and provide earlier treatment for the prevention of DKA. Thus, clinicians and patients need to be fully educated regarding the role of at-home blood ketone testing.

In the past, detection of DKA could start at home, based on the presence of urine ketones or the onset of clinical changes such as vomiting, while treatment took place in the hospital. With the advent of at-home blood testing for ketones, such ketone testing can become the new standard, giving the clinician a greater opportunity to provide patients with effective home management on sick days. Indeed, as of 2000, the American Diabetes Association held the gold standard for ketone testing to be blood, not urine. Thus, DKA, a significant and costly acute complication of diabetes, becomes more easily managed and even preventable.

Inaccuracy of urine testing

Urine-glucose testing became antiquated more than 2 decades ago with the advent of blood glucose monitoring. Yet urine-ketone testing has remained the mainstay of ketone monitoring until recently. In the current era stressing blood glucose monitoring, most patients view urine testing as inconvenient and messy. More importantly, urine-ketone test results can be inaccurate.

First, a urine sample depends on the patient's hydration status and can represent information that is many hours old. Second, urine tests can produce false-positive and false-negative results.

False positives can occur if the patient is taking a drug containing a sulfhydryl group, such as the angiotensin-converting enzyme inhibitor captopril. Highly colored urine also can cause a false-positive result, because urine test strips are interpreted according to a color code. False-negative results can occur if the strips have been exposed to air for prolonged periods, if the urine sample is highly acidic, if the patient has taken high doses of vitamin C, or if microbial action in the urine has reduced the ketone concentration.

Urine-ketone measurements present yet another problem. The dominant ketone body in DKA is β-hydroxybutyrate, but urine ketone tests measure acetoacetate and, to a lesser extent, acetone, which is produced from the spontaneous degradation of acetoacetate. Urine acetoacetate levels are assessed through a reaction with sodium nitroprusside with which β-hydroxybutyrate does not react.

Thus, a blood test for β-hydroxybutyrate, in addition to being more convenient than a urine test, provides a real-time measure of ketonemia by testing for the substance that is most indicative of risk for DKA. Under normal circumstances, the ratio of β-hydroxybutyrate to acetoacetate is 1:1; after prolonged fasting, the ratio can rise to 6:1; and in pathological ketosis, such as DKA, the ratio might exceed 10:1 (Laffel 1999).

Urine testing cannot provide the precision required for at-home prevention, identification, and treatment of DKA. Blood ketone testing offers an accurate and timely method by which treatment at-home can be initiated. With the new standard of blood ketone testing, such management protocols can be successfully implemented.

Initiating blood ketone testing

Any illness, stress, or the presence of persistent hyperglycemia is a signal to initiate blood ketone monitoring. Any condition that leaves the patient unable to perform routine activities suggests that the patient should increase the frequency of blood glucose monitoring and begin testing for blood ketones.

In our center, we also suggest that persistent fasting hyperglycemia greater than 200 mg/dL for several consecutive mornings signals the need to assess blood ketone levels to help ascertain metabolic changes overnight. The presence of early-morning ketones may suggest inadequate nocturnal insulin levels, or more rarely, overnight drops in blood glucose levels with subsequent counter-regulation.

The careful assessment of blood glucose and blood ketone levels overnight and on awakening can help distinguish these different metabolic pathways and direct appropriate treatment, as the former may require additional insulin while the latter will likely respond to decreases in therapy. Blood ketone testing also becomes warranted when daytime blood glucose levels persistently exceed 180 mg/dL or another designated level, such as 250 mg/dL, determined by patient factors and health care team recommendations. Finally, any symptoms of nausea and/or vomiting indicate a need to monitor blood ketones. Knowledge of blood ketone and blood glucose levels helps to determine appropriate insulin dosing (see Laffel, pages 15–18).

Approaches to insulin dosing, based on insulin sensitivity

In calculating supplemental insulin doses needed in the managing sick days, insulin sensitivity (IS) refers to the expected decrement in blood sugar levels following the administration of exogenous insulin, given as fact-acting regular insulin or as one of the rapid-acting insulin analogues — lispro or insulin aspart. Notably, the drop in blood sugar will be greater in a patient who is more insulin-sensitive than in one who is less sensitive, given the same dose of insulin.

There are two approaches to the calculation of a patient's IS; the first is called the "1,500 rule" and the second is the "1,800 rule." The general rule is to divide 1,500 by the patient's average total daily dose of insulin, including the different types of insulins and the various doses given throughout the day. The 1,500 rule often is used when the fast-acting insulin will be regular, while the 1,800 rule may be employed when a rapid-acting insulin analogue — either lispro and insulin aspart — will be used. The number resulting from the calculation is the approximate amount the blood glucose will fall (in mg/dL) following administration of 1 unit of either regular, lispro, or aspart insulin. The 1,800 rule tends to provide less insulin for the anticipated drop in blood glucose and, therefore, may be less likely to induce hypoglycemia. The rate of fall of blood glucose also will depend on the peak-action time of the insulin used.

Sick-day algorithms take into account the blood glucose and blood ketone levels when calculating the supplemental dose of insulin required to reduce blood glucose levels and halt ketone-body formation. The IS can be used to help select the supplemental insulin dose by subtracting a target glucose value, generally between 100 and 150 mg/dL (depending on the patient's individualized treatment goals) from the current blood glucose level. This dose generally suffices when blood ketones are not elevated, generally less than 1.0 mmol/L.

When blood ketones are 1.0 mmol/L or higher, additional insulin may be needed, which can vary from an additional 1 to 2 units to even double the calculated supplemental dose, depending on patient-specific factors. The health care team is best able to calculate the optimal supplemental doses along with the patient, based on past experiences. Additionally, illness and elevated blood glucose levels may cause the patient to become more insulin-resistant and, thus, to require more insulin to prevent progression to DKA. Ongoing dialogue between the patient and health care team, regarding blood glucose, blood ketones, insulin dosing, and hydration status, helps to ensure safe and successful diabetes sick-day management.

It also is necessary to review the timing and amount of previously administered insulin in the calculation of supplemental doses to prevent a "stacking" effect. While the peak time of insulin action may have passed, the downward slope of insulin action may lead to continued insulin effect and the possibility of late hypoglycemia if insulin boosters continue to be administered at the same rate and dose.

For example, when the next dose of insulin is given 2 hours after a previously administered dose, the previous insulin may not be completely gone. The "tail" action of the previously administered insulin continues to accumulate on top of each additional dose. Thus, hypoglycemia may occur, unless supplemental doses are decreased. Again, the health care team can assist the patient in making appropriate treatment adjustments based on the data reported.

The peak action of the insulin also helps to determine the frequency of blood glucose monitoring. If a patient is using regular insulin, blood glucose should be tested every 2 to 3 hours. For lispro or aspart insulins, monitoring may be best at intervals of 1 to 2 hours. The frequency of blood ketone testing can be hourly, as changes in blood ketones occur rapidly and can help direct further management.

At-home treatment protocol suggestions

The health care team should ask questions to assess the patient's status: "How long have you been feeling ill?" "Have you had any recent emotional changes in your life?" "What are your blood sugar and blood ketone levels?" "Are you able to drink extra fluids? If so, what kinds and how much?" "Are you experiencing nausea, with or without vomiting? If so, how many times have you vomited?" Other questions can be tailored to the patient's specific needs.

Once blood glucose and blood ketone levels are known, the clinician implements the insulin titration schedule that was previously designated and is known by the patient. Extra insulin should be available in the form of fast-acting regular or rapid-acting lispro or novolog. Importantly, when patients are well, for example, during their routine health care visits, sick-day rules should be reviewed. It is important that patients be instructed in the use of these fast- and rapid-acting insulins, even if these insulins are not a routine part of the daily treatment.

In addition to extra insulin, the patient must continue drinking as much as a pint of fluids every 30 to 60 minutes, depending on losses. Continuous sipping, rather than large swallows, may offer the patient greater comfort and may help to avert stimulation of the gag reflex, even in a nauseated patient. It is important for patients and families to keep a sick-day cupboard containing the patient's favorite fluids in both sugar-free and sugar-containing varieties. The types and amounts of fluids depend on patient characteristics that include age, weight, body composition, likes and dislikes, culture, and lifestyle. Teaching the patient to have these fluids on hand is critical to successful home management.

Discontinuing at-home management

The treatment team must determine the point at which continuation of at-home management is no longer safe for the patient. There are several criteria to consider, including ongoing vomiting, dehydration, blood glucose levels, blood ketone levels, and any symptoms related to underlying illness or stress. The patient's ability to absorb exogenous insulin is directly related to the dehydration level. If dehydration progresses at a rate that cannot be managed by oral fluid intake, for example, because of continued emesis, the patient will need intravenous fluids. Adequate hydration thus becomes critical for successful at-home treatment. If the patient is drinking a sufficient amount of fluid, either sugared or sugar-free depending on the blood glucose level, the patient's continued management at home seems reasonable. Whether at home or in the hospital, the therapeutic goal remains the same — rehydration, normalization of blood glucose levels, arresting ketone formation, and treatment of any underlying illness.

The superiority of β-hydroxybutyrate blood ketone testing over urine ketone testing provides an opportunity for successful management of sick days at home, resulting in a reduced need for costly emergency department visits or hospitalizations (see Laffel article, pages 15–18). If the blood ketone levels continue to rise and remain above 3.0 mmol/L, home management may have reached its limit. Early identification of progressive metabolic decompensation becomes possible with blood ketone testing followed by appropriate referral to an emergency department. Continued dialogue with the health care team allows for timely transitions to intravenous therapy.

In conclusion, in a forward-thinking organization, nurses, as central members of the health care team, can be important resources for patients with diabetes and their families during sick days. Educating patients about the importance of blood ketone monitoring during sick days provides important opportunities for successful at-home management. Using the β-hydroxybutyrate blood ketone test to help prevent DKA may significantly reduce the frequency of hospital and emergency admissions and help contain costs while ensuring quality of at-home sick-day therapy.

During sick days, nurse case managers can be active members of the health care team by helping to continually review with the patient the results of blood glucose and blood ketone monitoring. With sick-day management utilizing at-home blood ketone testing, the health care team can now provide better treatment at the first point of contact.

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Challenges and Opportunities in Diabetes Care: Improving Outcomes With Education, Disease Management, and New Technologies

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The introduction of blood glucose monitoring in the late 1970s soon led to a revolution in diabetes care. Today, in-home monitoring of blood glucose levels has become part of patients' daily routines. Until recently, however, there was no parallel improvement in ketone monitoring; urine monitoring was the only rapid ketone test that was available. Even in the hospital, measurement of blood ketones was complicated, and it could take weeks to receive results. With the development of new technology, namely β-hydroxybutyrate, that permits blood ketones to be tested easily and rapidly at the point of care, the field of diabetes management is poised for another major advance. Nevertheless, providing patients with the advantages of β-hydroxybutyrate blood testing will necessitate that health care professionals acquire a new body of knowledge. That effort will involve learning new terminology, new definitions of normal and abnormal β-hydroxybutyrate levels, and new markers indicating when a patient requires emergency medical care, and then transmitting this information to patients and their families.

Levels of β-hydroxybutyrate in the blood are measured in mmol/L. These concentrations can be compared with the measurements of urine ketones (composed mainly of acetoacetate), with which patients and clinicians are familiar. The normal level of β-hydroxybutyrate in the blood, in a patient with or without diabetes, is between 0.0 and 0.5 mmol/L; this level corresponds to a negative or trace amount of urine ketones. A reading between 0.6 and 1.0 mmol/L indicates mild elevation and a need to recheck blood ketones; this level corresponds to a small amount of urine ketones. A β-hydroxybutyrate concentration exceeding 1.0 mmol/L is elevated, corresponding to moderate to large amounts of urine ketones, almost always necessitating a change in insulin therapy for patients. Values exceeding 3.0 mmol/L are consistent with developing ketoacidosis and necessitate communication with, and possible assessment by, the health care team.

The measurement of concentrations of blood β-hydroxybutyrate is usually an important adjunct to the measurement of blood glucose and more informative than urinary acetoacetate levels for monitoring diabetes and adjusting treatments. For example, in a study assessing response to stress, such as the induction of a fever, the body releases counterregulatory hormones (Schade 1980). In patients with type 1 diabetes, the first metabolic response to these stress hormones is a rapid elevation in fatty acids and ketone bodies, which may signal the onset of diabetic ketoacidosis (DKA). Only after 60 to 90 minutes have elapsed, following the increases in fatty acids and ketone bodies, will an elevation in blood glucose above baseline become evident. Likewise, if a patient's delivery of insulin via an infusion pump (continuous subcutaneous insulin infusion [CSII]) is interrupted, concentrations of blood β-hydroxybutyrate rise much faster than do concentrations of blood glucose (Guerci 1999). Moreover, once insulin infusion has been restored by CSII, β-hydroxybutyrate levels fall faster than glucose levels.

In addition, in patients with DKA, the total concentration of ketone bodies begins to decrease after treatment of DKA has been initiated. Even as the concentration of β-hydroxybutyrate falls precipitously, however, acetoacetate levels continue to rise for 7 or 8 hours (Schade 1982). Therefore, continued measurement of acetoacetate is useless in the correction of ketosis.

Case studies

Patients and clinicians can exploit β-hydroxybutyrate measurement to improve the management of diabetes, as the following two case studies will illustrate. In the first, a 13-year-old girl with type 1 diabetes of 9 years' duration presented with nausea, vomiting, and possible hypoglycemia. Her daily insulin dose was 0.95 U per kilogram, given as 5 units of regular insulin plus 35 units of NPH insulin in the morning, and 5 units of regular insulin plus 17 units of NPH insulin in the evening. Her family had decreased her insulin dose at home because they had initially identified low blood sugar in association with vomiting and anorexia. The child had never been hospitalized since her diagnosis of type 1 diabetes, and she had no history of DKA. With an HbA_{1c} of 10.8 percent, her diabetes control was suboptimal but not unusual for an adolescent with diabetes. On physical examination, she was found to have Kussmaul respirations

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(rapid, deep, labored breathing), and exudative pharyngitis was evident as the source of her acute illness. Laboratory tests revealed her blood glucose to be greater than 300 mg/dL, serum bicarbonate less than 5 mEq/L, and venous pH of 7.05, with positive urine ketones. Due to her severe DKA, she was admitted to the intensive care unit, where she was treated by standard DKA protocol without major sequelae. Her protracted vomiting, however, had produced esophagitis, a Mallory-Weiss esophageal tear, and hematemesis, thus she was unable to resume her usual oral intake after correction of her acidosis and had to remain hospitalized for more than 10 days.

The patient's pharyngitis was found to be secondary to mononucleosis, but it was more than the acute illness that had produced the metabolic decompensation and need for urgent care. Rather, it was a misunderstanding and failure of sick-day management. She and her family had failed to check blood glucose levels frequently; they did not test for ketones after the initial blood sugar level was relatively low; and, due to their inexperience with sick-day management, they neglected to administer extra insulin or call the health care team in a timely manner. Furthermore, the guidelines of sick-day management necessitate constant reinforcement, as many patients and families find it counterintuitive that a person with diabetes may require more insulin during an acute illness that renders the patient anorexic and may be associated with nausea and vomiting. Frequent monitoring of blood glucose and blood ketone levels, along with supplemental insulin therapy, may have prevented the acute and severe decompensation.

Early contact with the health care team, especially when vomiting persists, is a fundamental component of successful sick-day management. What began as a simple sick-day episode evolved into a situation that caused the patient and her family significant distress and cost the health care system tens of thousands of dollars, along with additional indirect costs associated with her parents' missed work.

The second case study involves a 37-year-old male with type 1 diabetes for 20 years. He had a history of retinopathy, peripheral neuropathy, and erectile dysfunction. He presented with marked dyspnea and dizziness. Thirty-six hours previously, he had mild nausea and no appetite, which was followed by the onset of recurrent vomiting. Because he was vomiting, he omitted his usual morning dose of 20 units of NPH insulin, but he did take 6 units of short-acting lispro. He kept checking his blood sugar levels and found hyperglycemia (200–400 mg/dL). Due to his continued emesis, he presented to a local emergency room where, on examination, he displayed Kussmaul breathing and had ketotic breath, suggestive of ketoacidosis. He also had low blood pressure (90/48 mm Hg) and a rapid heart rate (110 beats per minute), with clear evidence of volume depletion. On examination, he was found to have a low arterial pH (7.21), low bicarbonate (11 mEq/L), elevated blood glucose (389 mg/dL), and elevated serum ketones, confirming the diagnosis of DKA. In the search for the triggers of DKA in a patient with presumed autonomic neuropathy, his chest was found to be clear, his cardiac and abdominal examinations were unremarkable, but an ultrasound revealed multiple gallstones.

The cause of his decompensation was acute cholecystitis. Surgery was needed, but he could not safely undergo anesthesia until the acidosis was corrected and he was metabolically stable. Thus, the missed opportunities to successfully manage rising blood sugar levels and blood ketone levels resulted in the onset of DKA, the need to postpone his surgery, a protracted hospitalization along with a delay in his return to good health, and an increased economic burden on the health care system.

In both cases, the routine home monitoring of β-hydroxybutyrate concentrations as a part of sick-day management could have provided opportunities to prevent the development or reduce the severity of DKA.

Discordant ketone readings between urine and blood tests

To compare data from urine ketone tests with blood ketone results, 174 insulin-treated but otherwise healthy, ambulatory children (n=86) and adults (n=88) were followed prospectively for 1 month at six medical centers across the country (Fineberg 2000, Laffel 2000a). Patients were asked to check their blood glucose and blood ketones three times daily and their urine ketones twice daily. The urine ketone tests were contemporaneous with the blood ketone determinations each morning and evening. Participants were instructed in the use of the Precision Xtra Monitor (Abbott Laboratories/MediSense Products) for the blood ketone measurements, and they were provided with Ketostix (Bayer) for the urine ketone determinations. The Precision Xtra measures β-hydroxybutyrate concentrations in a 5 µL blood sample within 30 seconds. Previous studies have demonstrated the accuracy of the Precision Xtra for β-hydroxybutyrate concentrations of 0 to 6 mmol/L compared with standard laboratory procedures (Byrne 2000, Wallace 2001).

The results revealed that whenever blood ketones were in the normal range (0.0 to 0.5 mmol/L) for both the children and adults, 98 percent of the urine tests were concordant, showing either no ketones or only a trace amount. Nevertheless, 2 percent of the urine tests were discordant, testing positive for small to large amounts of ketones. The latter results could prompt the unnecessary administration of supplemental insulin and increase the risk of hypoglycemia.

When the blood tests yielded elevated β-hydroxybutyrate concentrations of 0.6 mmol/L or higher, only 44

percent of the urine tests in children and 31 percent of the urine tests in adults were concordant with small to large ketone results. The remaining 56 percent and 69 percent of urine tests in children and adults, respectively, revealed negative results. Thus, the majority of urine results remained negative when the blood measurements were showing elevated ketone levels. The negative urine results would fail to signal a need for supplemental insulin for timely intervention to prevent progression of ketosis to ketoacidosis.

This small investigation also demonstrated the ease of blood ketone determinations compared with urine measurements. Even though urine testing has been perceived as easier than blood monitoring, in the current era that stresses frequent blood glucose checking, both the children and adults demonstrated significant nonadherence, missing close to 35 and 30 percent, respectively, of the requested urine testing opportunities. The percentage of missed blood ketone measurements was only 20 percent for both children and adults.

Fewer hospitalizations with blood ketone monitoring

The efficacy of a blood ketone meter recently was evaluated in a randomized, prospective study conducted at two pediatric centers in New England — the Joslin Diabetes Center in Boston and the New England Diabetes and Endocrinology Center in Waltham, Mass. (Laffel 2002). The study enrolled 123 patients, all 22 years old or younger, with confirmed type 1 diabetes treated with either multiple daily insulin injections or continuous insulin infusion pump. Study participants were randomly assigned to either a control group, who checked their blood glucose and urine ketones in conventional ways (Precision QID blood glucose meter, Abbott Laboratories/MediSense; Ketostix, Bayer), or an intervention group, who monitored their blood glucose and blood β-hydroxybutyrate with an integrated device (Precision Xtra). The Precision Xtra measures both blood glucose and blood β-hydroxybutyrate concentrations, although the different tests must be performed serially, each re-

quiring a specific reagent strip inserted into the device's single port.

At study entry, sick-day rules were reviewed, HbA_{1c} was measured, and patients completed questionnaires regarding their routine management of diabetes, including their usual frequency of blood glucose and ketone monitoring. Study participants and families received sick-day treatment algorithms for determining additional boosters of insulin based on both ketone (either urine or blood) and blood glucose concentrations (Laffel 2000b) (Table).

During the 6 months of follow-up, each study group experienced the same number of sick days, defined as self-reported illnesses (about 4 percent of the total study days). Notably, blood ketones were monitored during 91 percent of the sick-day episodes by patients in the intervention group but only during 61 percent of the episodes by patients checking urine tests ($P<.05$). Thus, the common perception that patients are more likely to perform urine ketone tests than blood tests is not supported by actual patient behavior.

The significantly increased monitoring behavior during sick days in the blood ketone group compared with the urine ketone group provided more opportunities to successfully manage the early metabolic derangements of diabetes at home and avoid the need for costly hospital treatments. Indeed, during this 6-month prospective study, there was a significant 50 percent reduction in the rate of hospitalization and emergency room use in the blood ketone group compared with the urine ketone group; the rate of acute complications was 38 per 100 patient-years in the blood ketone group compared with 75 per 100 patient-years in the urine ketone group ($P=.05$). Overall, twice as many acute events necessitating an emergency department visit or hospitalization occurred among the patients using urine ketone tests compared to the group using blood ketone tests.

In-office blood ketone testing speeds recovery

The final case study shows how β-hydroxybutyrate testing can be used in the office to monitor and treat im-

TABLE	Sick-day treatment algorithms for supplemental insulin doses					
	Intervention group (β-hydroxybutyrate, mmol/L)			Control group (urine ketones)		
	<1.0	*1.0–1.4*	*≥1.5*	*Negative to trace*	*Small*	*Moderate to large*
Blood glucose						
<250 mg/dL	No change	0–5%	0–10%	No change	0–5%	0–10%
250–400 mg/dL	5%	10%	15–20%	5%	10%	15–20%
>400 mg/dL	10%	15%	20%	10%	15%	20%

SOURCE: LAFFEL 2000B

pending DKA. A 20-year-old female presents for her routine office visit. She has had type 1 diabetes for 17 years and a history of an eating disorder, insulin omission, and past psychiatric admissions. Her daily diabetes management prescription includes premixed insulin administered by pen, aimed at increasing adherence to a twice-daily injection program. Her prescribed daily insulin dose was 0.95 units per kilogram, given as 35 units 70/30 (NPH/regular) in the morning and 30 units 70/30 in the evening, but her usual daily injected dosage fell between 0.2 and 0.5 units per kilogram. As a consequence of this erratic insulin therapy, the HbA_{1c} usually ranged from 10 to 18 percent (reference range 4 to 6 percent).

At the clinic visit, the patient disclosed that she had taken no insulin for 2 days. She had no history of recent vomiting. Her weight had declined by 5.6 kilograms; her blood pressure was 100/70 mm Hg; and her heart rate was 84 beats per minute. She had ketotic breath but was not in distress. Within seconds, a fingerstick revealed a blood sugar of 492 mg/dL. Additional venous and urine labs were obtained. While the bicarbonate, electrolyte, and urine tests were pending, a capillary blood ketone test indicated a β-hydroxybutyrate concentration of 4.5 mmol/L — a significantly elevated value. Thus, the patient had hyperketonemia and likely early DKA resulting from her eating disorder, with insulin omission as her form of purging.

This patient needed emergency care, but she mainly required a psychiatric admission to manage her underlying mental health condition. Appropriately, no psychiatric hospital would allow admission of a patient who was metabolically unstable to such an extent. Thus, we began her treatment in the ambulatory setting by providing supplemental insulin injections and oral rehydration. At noon, she received 12 units of regular insulin intramuscularly and fluids. We continued to monitor her blood glucose and β-hydroxybutyrate concentrations hourly. By 1:45 PM, her blood glucose had fallen to 381 mg/dL and her β-hydroxybutyrate was down to 2.3 mmol/L. She was given 10 units of NPH subcutaneously. By 2:20 PM, her blood glucose and β-hydroxybutyrate had declined further to 275 mg/dL and 0.9 mmol/L, respectively. Thus, DKA was successfully averted in this young woman with the aid of frequent blood glucose and ketone monitoring, supplemental insulin therapy, and oral hydration. The ability to serially follow her blood glucose and blood ketone levels in the office setting provided a means to titrate her therapy and rapidly correct her ketosis, allowing the team to orchestrate a psychiatric consultation and an admission to a psychiatric hospital the following morning.

Summary

In summary, point-of-care testing of β-hydroxybutyrate concentrations, whether in the home or the physician's office, augments blood glucose monitoring and serves as an important tool for the routine management of diabetes. Through the timely use of β-hydroxybutyrate monitoring, patients may be able to avert episodes of DKA, preventing significant morbidity and potential mortality. Furthermore, health care systems can be spared the substantial expense of hospital treatment of DKA and its consequences. The challenge for diabetes professionals comes with the need to establish blood ketone monitoring as a routine part of diabetes care, similar in importance to blood glucose monitoring for patients with insulin-treated diabetes.

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Evaluating Tools for Ketosis Assessment In Diabetes Patients

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The four preceding articles and the following panel discussion demonstrate that the available tests that specifically measure blood β-hydroxybutyrate can be a major aid to the identification and detection of ketosis and diabetic ketoacidosis (DKA). With appropriate training, the patient can use these tests for successful at-home treatment. This improved management approach has the potential to lead to reduced patient morbidity and an increase in associated cost savings. This is further confirmed by the American Diabetes Association, which highlights the superiority of blood ketone testing for the diagnosis and monitoring of DKA. The consensus from the faculty of the meeting that served as the basis of this supplement suggests an important role for blood ketone monitoring within an integrated strategy for sick-day management for patients with diabetes. Home tests are available, and their wider use should be promulgated through educational and promotional efforts by health care professionals and medical service providers. At a time when health care costs are escalating, this methodology has the potential to lower costs by addressing an expensive complication of type 1 diabetes.

ROBERT S. KLOOS: I have a question for our managed care colleagues. How compelling are the data that Dr. Laffel presented on the sick-day study for health plans that look at their formularies for this testing equipment?

Terry, you mentioned earlier that health plans focus on blood glucose monitoring without taking blood ketone testing into consideration. Will these data be important to health plans?

TERRY K. MAVES, RPh: Yes. It's important to disseminate the information. I recently completed a formulary process throughout our state. We had medical directors representing eight or nine health systems. The subject of blood ketone monitoring was not raised at all. It seems to take a while for some of these guidelines to be accepted and implemented. It's a lack of communication, rather than a lack of caring, or the recognition that we should be doing this to reduce health care costs.

KLOOS: Lori, in addition to the material that is appearing in the MANAGED CARE supplement generated by today's meeting, is

your study going to be published?

LORI M.B. LAFFEL, MD, MPH: Most likely it will be published soon in a diabetes journal; the challenge will still be to get the information out to a larger population of providers and payers.

KLOOS: What is the best way to get this kind of information to health plans and providers?

MICHAEL N. BAXLEY, MD, MPH: The way you disseminate this important message to a wider audience is through medical practice guidelines. This is something that clearly has a benefit for decreasing morbidity and for reducing the cost of managing these patients' complications.

H. PETER CHASE, MD: A very effective strategy is to get to the physician-champions — the pediatric endocrinologists or adult endocrinologists — in this case, because they become very effective communicators within their organizations.

KLOOS: So, again, effective communication is one way to implement the new paradigm that Dr. Chase talked about earlier.

Relative to blood ketone testing versus urine ketone testing, it seems that there is compelling information — in terms of improved outcomes, improved adherence to self-monitoring, and the cost benefits — indicating that blood ketone testing is the direction in which to proceed.

MARLYN L. CRANE, RN, MSN: 100 percent. That's my take.

CHASE: I would agree. It is time to look at blood ketone monitoring as a treatment guideline.

KLOOS: Which patients should be testing? When? How frequently? There seem to be some differences in opinion. I know, Marli, in your practice setting, that you would like to see all your patients avail themselves of blood ketone testing.

LAFFEL: Patients who utilize insulin-pump therapy would benefit from knowing about testing both blood sugar and blood ketones in a timely manner.

CHASE: Let me just say the same. We don't start any patients on a pump now until they've got their Precision Xtra Meter.

LAFFEL: Another vulnerable population includes toddlers with diabetes, particularly if these children cannot control when they're going to the bathroom. Certainly their parents find it exceedingly welcome and reassuring to be able to check blood glucose as well as blood ketones.

The platforms that test blood glucose and blood ketones are even more powerful, because it is difficult to carry everything with you that you may need for diabetes care. When you can have a blood glucose and a blood ketone monitor together, that makes it so much easier to follow the management guidelines. Also, obviously, anyone who has had an episode of ketoacidosis should be provided with a monitor that can measure both blood glucose and blood ketones and should be taught how to use it. Other groups who also benefit are patients with eating disorders, but then we're getting to smaller and smaller numbers in the population.

KLOOS: What about the sick-day patients?

LAFFEL: Patients who are prone to ketosis need to be able to measure blood glucose as well as blood ketones. I'm trying to avoid saying either type 1 or type 2 diabetes patient, because the discussion today is about patients who are ketosis-prone, which crosses the boundaries with respect to the kind of diabetes that a patient has.

KLOOS: Very good.

MAVES: In a guideline, don't you want to focus on the people who are going to get the most benefit? I agree that it crosses the boundaries, but it seems that type 1 diabetics are much more prone to ketosis. Also, what about ethnic groups? Should we be targeting these groups because they're at greater risk?

BOYD E. METZGER, MD: I think that there has been a misinterpretation of the data. That presentation was on individuals in ethnic groups who presented with diabetic ketoacidosis. The vast majority of Hispanic Americans with type 2 diabetes will never experience an episode of DKA in their lifetime. So, yes, once anybody has demonstrated an episode of DKA or very poor β–cell function, whatever their subclassification is, their risk is increased. When we mention ethnic groups, however, we are referring to groups that in the past were thought to be free of the risk of DKA. Today's discussion demonstrated that within the ethnic group, there are some at risk — and they don't fit into our pigeonholes as easily.

LAFFEL: Boyd, I agree with you there. I think that is why we are emphasizing those who have demonstrated their ketosis.

METZGER: Right. I think that's the best way to qualify it.

CHASE: Every clinic that cares for people with diabetes and every emergency room now need to have rapid point-of-care testing for blood β–hydroxybutyrate. I recently saw a child who was newly diagnosed and who has a sibling with diabetes. The check-in person did a urine ketone test and the number was large. I immediately said, "Get me the blood ketones, so I know if I can treat this child here or if I have to send him to the hospital."

KLOOS: Other recommendations?

CRANE: If the cost of the meters was not an issue, that would make a compelling argument that everybody should be able to do this. Because we have the largest African-American and Hispanic population for southern California in our database, I would tend to push for the Precision Xtra Meter for the population that would be more ketosis-prone. Moreover, I would go

forward without waiting to have a ketosis event to consider that potential.

KLOOS: Before we adjourn, I would like to ask each of you to think about everything that has been discussed and presented today. If you had to identify the one or two most important key points, what would they be?

CHASE: I just need help making the case that blood β-hydroxybutyrate measurements need to be approved, so that these families can have insurance coverage.

KLOOS: You are referring to making sure reimbursement is available to remove that barrier for people who need access to this technology.

CHASE: Yes, but I'm being blunt: as a physician, I don't have time to go to HMOs and beg for this. Somebody else has to do that.

KLOOS: Understood. Terry?

MAVES: Being on the other side of that coin, I have no problem covering this. It becomes an issue of getting coverage and then determining which blood glucose monitor should be covered. We also need some guidelines to help us target those patients who need this most. A concise guideline would be a huge help in convincing decision makers to cover this methodology.

BAXLEY: Based on what we've heard today, there is probably a great need for stratification of complicated diabetic patients. A set of criteria regarding the use of blood ketone testing would make it much easier to get beyond medical practice guidelines committees for the more complicated patients, especially if it has been built under a fee-management/case-management rubric.

KLOOS: Very good points. Dr. Davis, from the perspective of the disease management community, what are the key takeaways and recommendations you'd like to make?

JEFFREY M. DAVIS, MD, MPH: The best way to facilitate adoption of improved practice is to share with the providers and managed care communities the information that Lori has presented and to conduct another study replicating her findings.

CHASE: As a matter of fact, we're in the process of replicating some of Lori's data in Denver.

METZGER: Lori's data will help make the case for making blood ketone testing available for sick-day management and people at risk for ketosis. It will take some time for the American Diabetes Association guidelines to be implemented, but they are headed in the right direction.

CRANE: The most important thing I heard today is lead-time: blood ketone testing provides lead-time for treatment. That is probably the bottom line for decreasing hospital care. If we can keep patients out of the hospital, we dramatically reduce the cost of diabetes care. From what I've heard this morning, it does not seem that only type 1 diabetic patients are involved.

KLOOS: We very much appreciate your perspective and contributions, Marli. As a nurse care manager, you have a unique perspective, in that you play an important role with these patients day to day.

Finally, Lori, you have the last word.

LAFFEL: As I began my discussion, I'd say it took many years for blood glucose monitoring to become routine in a culture embedded in urine glucose monitoring. I remain optimistic, but the challenge lies in how to get the message out that blood ketone testing is superior to urine ketone testing in at-risk populations.

KLOOS: That probably underlines one of the key motivators of our sponsor to convene the panel and develop this supplement, which will help disseminate this information to a broader audience.

If I may just wrap things up by summarizing the key takeaways, I think we are in agreement that:

- Blood ketone testing is the new gold standard, and the value in some patient populations is now well established.
- Diabetic ketoacidosis is clearly a major driver of health system costs associated with type 1 diabetes.
- Noncompliance is a major cause of diabetic ketoacidosis.
- Compliance may be improved with adoption of blood ketone monitoring.
- Self-monitoring has been shown to improve outcomes and reduce costs. There are some barriers, however, in some cases linked to patients' comfort with other equipment that they've been using for a number of years, and also relative to reimbursement issues in other patients.
- Good sick-day management includes patient education and training as well as the availability of home blood ketone tests.
- The role of blood ketone testing needs to be better communicated across the board to health care providers, payers, health plans, and decision makers in the plans.

The Importance of Blood Ketone Testing in Diabetes Management

Please tear out the combined answer sheet/evaluation form on page 23. On the answer sheet, place an X through the box of the letter corresponding with the correct response for each question. There is only one correct answer to each question.

1. **Diabetic ketoacidosis is found only in patients with type 1 diabetes.**
   a. True.
   b. False.

2. **The presence of ketone bodies in the blood or urine indicates the metabolism of:**
   a. Glucose.
   b. Fatty acids.
   c. Amino acids.
   d. Carbohydrates.

3. **Which of the following is not among the traditional "ketone bodies?"**
   a. Acetoacetate.
   b. Acetohexamide.
   c. Acetone.
   d. β-hydroxybutyrate.

4. **An abnormal level of ketone bodies in the blood is dangerous because it:**
   a. Blocks the action of insulin.
   b. Blocks the action of glucagon.
   c. Lowers the pH of the blood.
   d. Raises the pH of the blood.

5. **Which ketone test does the American Diabetes Association recommend?**
   a. Urine test for β-hydroxybutyrate.
   b. Urine test for acetoacetate.
   c. Breath test for acetone.
   d. Blood test for β-hydroxybutyrate.
   e. Blood test for acetoacetate.

6. **Which of the following can lead to an elevated level of ketone bodies?**
   a. Surgery.
   b. Infection.
   c. Missed insulin dose.
   d. All the above.

7. **The leading precipitating cause of diabetic ketoacidosis is:**
   a. Fasting.
   b. Infection.
   c. Noncompliance.
   d. Surgery.

8. **A patient with classic type 1 diabetes could be described as having:**
   a. Both β-cell function and autoantibodies.
   b. β-cell function but no autoantibodies.
   c. Neither β-cell function nor autoantibodies.
   d. Autoantibodies but no β-cell function.

9. **In patients with diabetes other than classic type 1 diabetes, stress is necessary to precipitate diabetic ketoacidosis.**
   a. True
   b. False

10. **A urine test can generate a false-positive result if patients are taking:**
    a. Captopril.
    b. Enalapril.
    c. Any ACE inhibitor.
    d. Any ARB.

11. **Stress presents a potential problem for patients with diabetes because it:**
    a. Inhibits the action of insulin.
    b. Inhibits the action of glucagon.
    c. Lowers the body's energy requirements.
    d. Increases the body's energy requirements.

12. **Concentrations of ketone bodies can be elevated even if blood glucose levels are not elevated.**
    a. True.
    b. False.

13. **Which test provides a real-time measure of ketone bodies?**
    a. Urine test for β-hydroxybutyrate.
    b. Urine test for acetoacetate.
    c. Blood test for β-hydroxybutyrate.
    d. Blood test for acetoacetate.

14. **Which primary ketone body is measured by the sodium nitroprusside urine test?**
    a. Acetone.
    b. Acetoacetate.
    c. β-hydroxybutyrate.
    d. Fructose.

15. **Blood levels of β-hydroxybutyrate are measured in:**
    a. mcg/L.
    b. mg/dL.
    c. mmol/L.
    d. mmol/dL.

16. **Patients have been found to be more compliant with urine tests than with blood tests for ketone bodies.**
    a. True.
    b. False.

17. **In patients with type 1 diabetes, the first metabolic response to stress hormones is a:**
    a. Rapid increase in blood glucose.
    b. Gradual increase in blood glucose.
    c. Rapid increase in β-hydroxybutyrate.
    d. Gradual increase in β-hydroxybutyrate.

18. **If a blood test shows that β-hydroxybutyrate levels are 0.5 mmol/L or less, the vast majority of urine tests for ketone bodies will show a correspondingly negative result (zero or trace amounts).**
    a. True.
    b. False.

19. **If a blood test shows that β-hydroxybutyrate levels are 0.6 mmol/L or greater, the majority of urine tests for ketone bodies will be negative.**
    a. True.
    b. False.

20. **The Precision Xtra device provides a measurement of β-hydroxybutyrate blood concentrations in:**
    a. 1 hour.
    b. 3 minutes.
    c. 30 seconds.
    d. 30 minutes.

CONTINUING EDUCATION ANSWER SHEET/CERTIFICATE REQUEST
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EXAMINATION: Place an X through the box of the letter that represents the best answer to each question on page 22. There is only ONE answer per question. Place all answers on this form:

	A.	B.	C.	D.	E.
1.	☐	☐			
2.	☐	☐	☐	☐	
3.	☐	☐	☐	☐	
4.	☐	☐	☐	☐	
5.	☐	☐	☐	☐	☐
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20.	☐	☐	☐	☐	

PROGRAM EVALUATION
So that we may assess the value of this self-study program, we ask that you please fill out this evaluation form.

Have the activity's objectives been met?

Discuss current testing methodologies and practice patterns for detecting diabetic ketoacidosis.   ☐ Yes ☐ No

Review the relative benefits of blood and urine ketone testing for detection of ketosis in diabetic ketoacidosis.   ☐ Yes ☐ No

Demonstrate the implications of appropriate management of type 1 diabetes with respect to patient health and pharmacoeconomics.   ☐ Yes ☐ No

Highlight the importance and cost effectiveness of monitoring both blood glucose and blood ketone levels, with daily assessment of ketosis.   ☐ Yes ☐ No

Determine how guidelines might be developed for blood glucose and blood ketone home monitoring for the type 1 diabetic patient.
   ☐ Yes ☐ No

Ascertain the potential for managed care organizations to assist in implementing and disseminating such guidelines.
   ☐ Yes ☐ No

Discuss the potential avenues for retaining the inclusion of ketone-level measurement as a data quality assessment. ☐ Yes ☐ No

Enhance health care professionals' awareness of the importance of blood ketone testing.   ☐ Yes ☐ No

Was this publication fair, balanced, and free of commercial bias?   ☐ Yes ☐ No

If no, please explain: _____

_____

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Did this educational activity meet my needs, contribute to my personal effectiveness, and improve my ability to:

Strongly agree ... *Strongly disagree*

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5	4	3	2	1	N/A

Communicate with patients?

5	4	3	2	1	N/A

Manage my medical practice?

5	4	3	2	1	N/A

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5	4	3	2	1	N/A

Effectiveness of this method of presentation:

Excellent	Very good	Good	Fair	Poor
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Time spent reading this publication:

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What other topics would you like to see addressed? _____

_____

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