Q J Med 2004; **97**:773–780
doi:10.1093/qjmed/hch132

Review

QJM

Recent advances in the monitoring and management of diabetic ketoacidosis

T.M. WALLACE and D.R. MATTHEWS

From the Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK

Summary

Diabetic ketoacidosis (DKA) is still a major contributor to morbidity and mortality in diabetes. The triad of hyperglycaemia, ketosis and acidosis can be diagnosed within a few minutes of the patient presenting, by measuring blood glucose and ketones using a meter, and venous blood pH on a blood gas analyser. Quantifying ketosis allows accurate distinction between simple hyperglycaemia and metabolic decompensation. We review the management of DKA, and the emerging role of near-patient testing in diagnosing ketosis and monitoring its resolution.

Background

Diabetic ketoacidosis (DKA) is an acute and potentially fatal complication of diabetes typically characterized by hyperglycaemia, ketone body formation and metabolic acidosis. Over the past 20 years, there has been no reported reduction in mortality rates, which remain between 3.4 and 4.6%.[1] Mortality is predominantly due to underlying morbidity, such as sepsis or acute myocardial infarction, but deaths also occur as a result of hypokalaemia-induced arrhythmias and cerebral oedema.

Diagnosis

The incidence of DKA is difficult to ascertain, as definitive criteria for the diagnosis have not been agreed, and there is no national register for recording cases. The diagnosis is based on the clinical features of uncontrolled diabetes in the presence of ketosis and acidosis (i.e. arterial blood pH <7.3), although in practice patients with a bicarbonate <15 mmol/l in the presence of a normal pH are often classified as having ketoacidosis. The presence of ketones can now be established by finger-prick testing, results being available within 30 s. We review the advantages of using such a system in the diagnosis and management of decompensated diabetes.

Pathophysiology

The pathology is invariably the result of relative or absolute insulin deficiency which, in combination with increased levels of stress hormones, stimulates lipolysis resulting in the production of acetylCoA from fatty acid. This acts as the substrate for hepatic synthesis of ketone bodies (acetoacetate, beta-hydroxybutyrate and acetone) (Figure 1). In addition to increased lipolysis, the relative lack of insulin in DKA results in decreased glucose utilization and increased gluconeogenesis.

Address correspondence to Professor D.R. Matthews, Oxford Centre for Diabetes, Endocrinology and Metabolism, The Churchill Hospital, Old Road, Oxford OX3 7LJ. e-mail: david.matthews@ocdem.ox.ac.uk

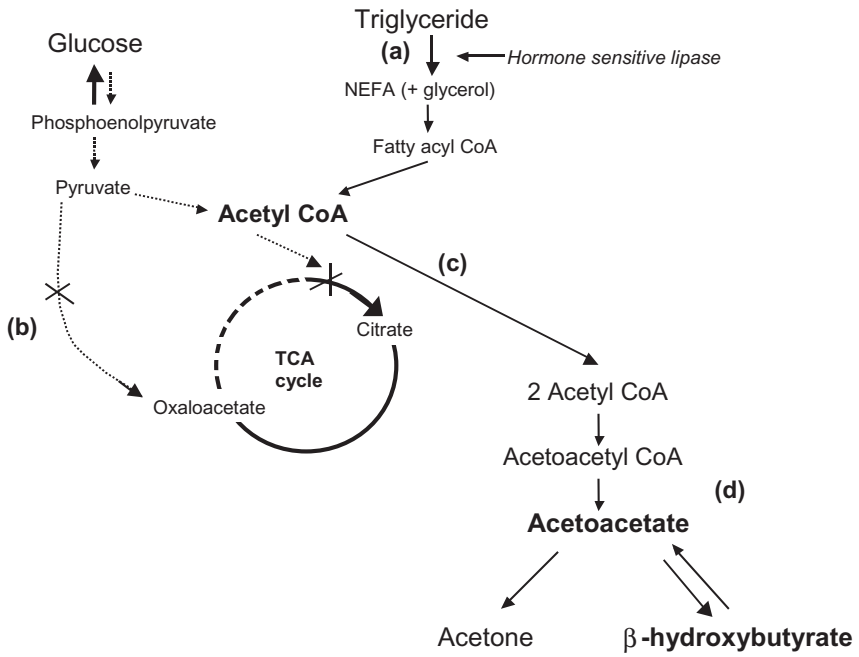

Figure 1. (**a**) Increased lipolysis results in the production of acetylCoA from fatty acids which acts as the substrate for hepatic synthesis of ketone bodies (acetoacetate, beta-hydroxybutyrate and acetone). A lack of insulin results in decreased glucose utilization and a reduction in oxaloacetate production. (**b**) The amount of oxaloacetate available for condensation with acetylCoA is reduced; and (**c**) acetylCoA is thus diverted from entering the tricarboxylic acid cycle and (**d**) undergoes condensation to form acetoacetate followed by reduction to beta-hydroxybutyrate.

Measurement of ketones

The commonly used urine dipstick tests are based on the use of a nitroprusside reaction (Ketostix, Acetest) and give a semi-quantitative measure of acetoacetate, react weakly with acetone but do not register the presence of beta-hydroxybutyrate (β-OHB). Acetone is responsible for the characteristic 'pear-drop' smell present in DKA, but does not contribute to acidosis. In DKA, the ratio of β-OHB to acetoacetate increases from 1:1 to as much as 5:1 and thus β-OHB is the predominant ketone body contributing to the acidosis.[2] When acidosis resolves with treatment, β-OHB is oxidized to acetoacetate. Under these circumstances, urine tests may give the misleading impression that ketosis is not improving, and from a practical point of view there can be a problem obtaining urine samples from severely dehydrated patients at the time of presentation. Blood ketones can now be measured directly with a hand-held sensor (Optium meter, Medisense/Abbott) which measures β-OHB in 30 s using blood from a fingerprick test.[3] The meter has been shown to be reliable, with accuracy and precision that is well within acceptable clinical limits.[3,4] The use of blood ketone tests based on the measurement of β-OHB, rather than urine ketone tests, for diagnosis and monitoring of DKA, is now recommended by the American Diabetes Association.[5]

Distinction between ketosis and acidosis

Ketosis and acidosis are not synonymous, because the increase in H^+ concentration resulting from the production of ketone acids is initially buffered by bicarbonate. As the concentration of H^+ exceeds the buffering capacity of bicarbonate, bicarbonate reserves become depleted and are no longer able to compensate for the excess production of H^+ ions and acidosis results. During the initial compensated phase of a metabolic acidosis, the usual picture is of low bicarbonate and normal pH, the latter being maintained at the expense of bicarbonate loss. Thus it is essential to measure blood pH, and a venous sample is adequate for this purpose.[6]

Special situations

In a small percentage of cases of DKA, the glucose levels are not elevated at presentation—'euglycaemic DKA'. This usually occurs in association with excessive vomiting and continued insulin administration. The role of monitoring β-OHB is particularly

valuable in euglycaemic (or near-euglycaemic) DKA, as the relatively low blood glucose levels in this state are a poor guide to the underlying metabolic derangement, and can result in inadequate insulin replacement. Euglycaemic DKA has been reported to occur in 10% of cases of DKA complicating pregnancy. Although there is no increase in maternal mortality in DKA during pregnancy, fetal mortality is high, and is reported to be in the region of 35%.[7] African-Americans[8] and black South Africans[9] with type 2 diabetes may present with diabetic ketoacidosis, but following acute treatment with insulin they often revert to good control with oral hypoglycaemic agents.

Precipitants and clinical features of DKA

The most common identifiable causes of DKA are infection in 28–43% of cases and inadequate insulin doses in 13–45% (Table 1).[10–13] The most frequently diagnosed infections are pneumonia and urinary tract infections.[14] Other acute medical illnesses may precipitate DKA including pulmonary embolism, myocardial infarction, cerebrovascular accidents and protracted vomiting.

Patients typically present with a short history of symptoms developing over a few days. The cardinal symptoms are increasing polyuria and polydipsia, variable weight loss and weakness, followed by drowsiness, decreased level of consciousness and eventually coma (in 10%) (Table 2). Signs of dehydration and hypovolaemia (reduced skin turgor, hypotension and tachycardia) are common. Other features include the presence of Kussmaul ventilation (hyperventilation due to respiratory compensation for a metabolic acidosis) and a detectable odour of acetone on the patient's breath. DKA may be associated with nausea, vomiting or abdominal pain: an 'acute abdomen' may precipitate DKA, or the abdominal pain may be due to the metabolic acidosis; in the latter case, the pain will improve as the acidosis resolves.[15]

Table 1 Precipitating causes of DKA

Precipitating factor	% of cases
Infection	28–43%
Omission/reduction of insulin dose	13–45%
1st presentation of diabetes	10–20%
Myocardial infarction	1%
No cause identified	<40%

Data from references 10–14.

Investigations in DKA

The triad of hyperglycaemia, ketosis and acidosis can be diagnosed within a few minutes of the patient presenting by measuring blood glucose and ketones using a meter and venous blood pH on a blood gas analyser. Baseline investigations required in DKA are shown in Table 3. The differential diagnosis of marked hyperglycaemia with dehydration is the hyperosmolar non-ketotic state (HONK), which is characterized by hyperosmolarity in the absence of ketones.

Some blood results may be misleading in the presence of DKA: transaminases are raised in 25–50% of cases with no evidence of hepatocellular disease, and creatine kinase is elevated in 25–40% of cases in the absence of any evidence of myocardial infarction.[16,17] Amylase and lipase levels are elevated in 16–25% of cases in the absence of any clinical evidence of pancreatitis; although acute pancreatitis may accompany or precipitate DKA, the diagnosis should not be based solely on the finding of elevated amylase or lipase levels, which may be increased by threefold.[17] A full blood count often shows a non-specific leukocytosis. A raised creatinine may reflect dehydration and/or pre-renal renal failure, but may also be falsely elevated due to interference from acetoacetate with some automated creatinine assays.[18]

Management of DKA

Fluid replacement

The aim is to replace the fluid deficit (average 6 l) over approximately 24 h, but the rate of replacement depends on medical co-morbidity. Rehydration should initially be with intravenous 0.9% saline at a rate of the order of 1 litre over 30 min followed by 1 litre over 2 h, 1 litre over 4 h, 1 litre over 6 h and then 1 litre 6-hourly. An accurate record of fluid balance is essential. As the glucose falls, intravenous

Table 2 Clinical features of DKA

Clinical features	Pathophysiology
Infection	Hyperglycaemia (gluconeogenesis)
Weight loss, muscular weakness	Tissue breakdown (lipolysis, proteolysis)
Polyuria, nocturia, thirst	Osmotic diuresis
Blurred vision	Osmotic changes in the eye
Hyperventilation, abdominal pain, nausea, vomiting	Ketogenesis → ketoacidosis

Table 3 Baseline investigations required in DKA

	Measurement	Comments
Diagnostic investigations		
Meter readings	Capillary glucose	
	Capillary beta-hydroxybutyrate	If not elevated then look for alternative cause for acidosis e.g. lactate. Should fall by 1mmol/l per hour with adequate treatment.
Blood gas and pH analyser	Venous blood pH	A heparinized venous sample is adequate unless pO_2 is needed
Initial investigations		
Biochemistry	U&E, creatinine, bicarbonate	
	Plasma glucose	To confirm capillary result but do not await result to start treatment
	CRP and troponin	If clinically indicated
Haematology	Full blood count	Neutrophil count may be non-specifically raised
Urine tests	Dipstick test for protein, nitrites, leucocytes, blood	
Microbiology	MSU	
	Blood cultures and additional microbiology	If clinically indicated
Cardiovascular	ECG	Increased risk of silent MI in patients with diabetes
Radiology	CXR	If clinically indicated. Consolidation may not show on CXR in dehydrated patients.

U&E, urea and electrolytes; CRP, C-reactive protein; MSU, mid-stream urine specimen; ECG, electrocardiogram; CXR, chest X-ray.

dextrose (5–10%) may be required. With prolonged use of dextrose, there is potential for hyponatraemia and if the sliding scale needs to be continued for several days after the biochemistry has corrected (e.g. if patient is not eating), then it may be appropriate to switch to using 5% dextrose alternating with 0.9% saline.

Insulin replacement

The aim of therapy is to switch off ketogenesis and to correct the metabolic derangement smoothly and the evidence supporting the use of low-dose intravenous insulin infusion is well established.[19–21] Treatment should aim to reduce glucose levels by 5–6 mmol/l per hour.

Sliding scale regimen: soluble insulin (e.g. 50 units Actrapid in 50 ml N saline) is usually given by continuous intravenous infusion according to a sliding scale (Table 4). Capillary glucose and ketones should be measured hourly and the insulin infusion rate adjusted accordingly. If the glucose and ketones do not fall by at least 5 mmol/l per hour and 0.5 mmol/l per hour, respectively, the fluid regimen and sliding scale should be reviewed.

If an infusion pump is not available for the administration of insulin, an intramuscular regimen[22] can be used: 20 units soluble insulin (e.g. Actrapid) is given intramuscularly initially, followed by 5 units hourly until the blood glucose falls below 15 mmol/l. Once the glucose is <15 mmol/l, the route of administration is switched from intramuscular to subcutaneous.

Table 4 Example of an intravenous sliding scale insulin regime

Capillary glucose (mmol/l)	Soluble insulin (units/h)
0–4.0*	0.5
4.1–7.0	1
7.1–11.0	2
11.1–14.0	3
14.1–17.0	4
17.1–20.0	5
>20	6

*If glucose <2.5 mmol/l, treat for hypoglycaemia.

Potassium replacement

Regular monitoring of electrolytes (at baseline, 2 h, 6 h and further as indicated) should guide potassium replacement. However plasma potassium is not a reliable indicator of total body potassium, which is usually depleted. No potassium is required in the first litre of fluid unless K^+<3.5 mmol/l. A guide to potassium replacement thereafter is suggested in Table 5.

Table 5 A guide to intravenous potassium replacement in DKA

Plasma potassium (mmol/l)	KCl to be added from 2nd litre onwards
<3.5	40 mmol/l
3.5–5.5	20 mmol/l
>5.5	Not required

Other measures

Continuous ECG monitoring is recommended in view of the risk of hypo- or hyperkalaemia and consequent arrhythmias. A nasogastric tube should be inserted if the patient has an impaired level of consciousness, because of the risk of gastroparesis and aspiration. Urinary catheterization should be considered if there is impaired level of consciousness, or if the patient has not passed urine 4 h after treatment is commenced. The need for central venous monitoring should be assessed on an individual basis, but may be required in elderly patients or those with pre-existing cardiac failure. The administration of sodium bicarbonate is virtually never indicated.

Consideration should be given to antibiotic therapy if there is evidence of infection, but white cell count is often spuriously raised in DKA and does not confirm infection (history, examination, the presence of pyrexia and elevated C-reactive protein are more helpful markers).

Interpretation of capillary ketone levels

Under normal circumstances, β-OHB concentrations do not exceed 1 mmol/l in type 1 diabetic subjects.[4,23] In patients presenting with DKA, mean β-OHB is about 7 mmol/l but can range between 4 and 12 mmol/l.[2,4,24–26] With optimal treatment of DKA, β-OHB would be expected to fall by 1 mmol/l per hour;[4] failure to do so suggests inadequate treatment, and insulin and fluid infusion rates should be reviewed.

Monitoring the resolution of DKA

The aim of treatment in DKA is to switch off ketogenesis, with consequent resolution of acidosis. The measurement of capillary glucose levels have to some degree been used as surrogate markers of the resolution of metabolic derangement. However, glucose levels are often not particularly stable on a sliding scale, and if hyperglycaemia occurs, it is important to know whether this is accompanied by ketosis, implying metabolic decompensation, or not. Figure 2 shows data from two patients admitted with DKA (from reference 4) in whom the measurement of β-OHB helped to distinguish between the recurrence of ketosis requiring the reinstatement of intravenous insulin therapy (Figure 2a) and simple hyperglycaemia (Figure 2b).

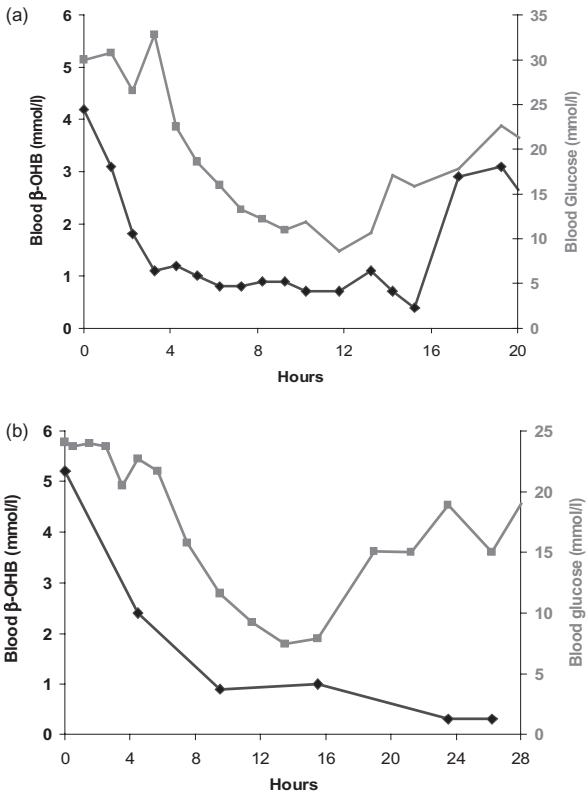

Figure 2. Glucose and β-OHB profiles in two patients admitted with DKA. There is an initial reduction in β-OHB and glucose with treatment. When glucose levels rise at 14–16 h, it is important to know whether this is accompanied by ketosis (**a**), implying metabolic decompensation, or not (**b**).

The recent introduction of a blood ketone meter allows insulin administration to be titrated against falling ketone levels rather than glucose levels. Obviously, it remains important to continue to monitor glucose levels in order to minimize the risk of hypoglycaemia. But if hypoglycaemia is a problem in the face of continuing ketosis, insulin administration should be continued with the addition of glucose infusion, e.g. 10–20% dextrose. Monitoring capillary ketone levels has the advantage of being much less invasive than arterial blood gas monitoring, and is a more appropriate measure than plasma bicarbonate levels as the replenishment of bicarbonate stores lags behind the resolution of the metabolic acidosis. The time course of bicarbo-

nate and β-OHB in a patient admitted with DKA are illustrated in Figure 3 (from reference 4).

Long-term management

The patient should be switched to subcutaneous insulin when the ketone reading is <1.0 mmol/l, the blood glucose is reasonably controlled, and the patient is clinically well and eating normally. Intravenous insulin should be discontinued 1 h after the first subcutaneous dose. Patients admitted with DKA should be referred to a diabetes team for education and follow-up.

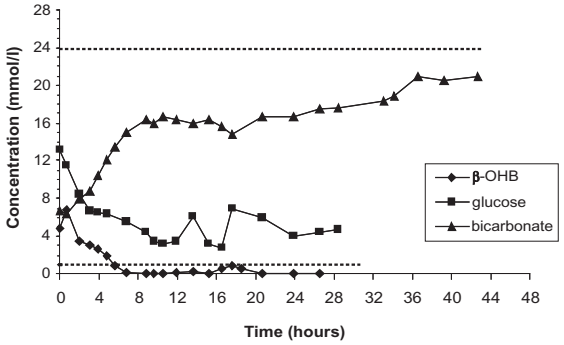

Figure 3. The time course for blood glucose (squares), β-hydroxybutyrate (β-OHB, diamonds) and bicarbonate (triangles) in hours from initiation of treatment. The lower dotted line represents the upper limit of normal for β-OHB, and the higher dotted line represents the lower limit of normal for bicarbonate.

Prevention of DKA

Education aimed at raising the awareness of the symptoms of diabetes is essential in order to prevent DKA in newly presenting type 1 diabetes.[27] For prevention of DKA in established type 1 diabetes, the primary issue is that of early detection and prompt intervention in cases of metabolic decompensation. Although home blood glucose monitoring is well established in diabetic patients, the development of high glucose levels (>15 mmol/l) can create a dilemma for patients and healthcare professionals managing type 1 diabetes, as rising levels are associated with an increasing risk of developing ketoacidosis. The availability of point-of-contact testing by patients and healthcare professionals should reduce unnecessary visits to hospital and avoid the need for more invasive tests. β-OHB levels do not normally exceed 1 mmol/l in patients with type 1 diabetes who have no evidence of metabolic decompensation, irrespective of the prevailing glucose concentration.[4] Figure 4 shows guidelines for the use of the meter in out-patients.

Financial cost of DKA

The average cost of treating a single episode of DKA in the US is $6500–$7500, which represents about 25% of the total spent on the care of patients with type 1 diabetes.[28,29] These figures do not take into account any costs arising from time off work.

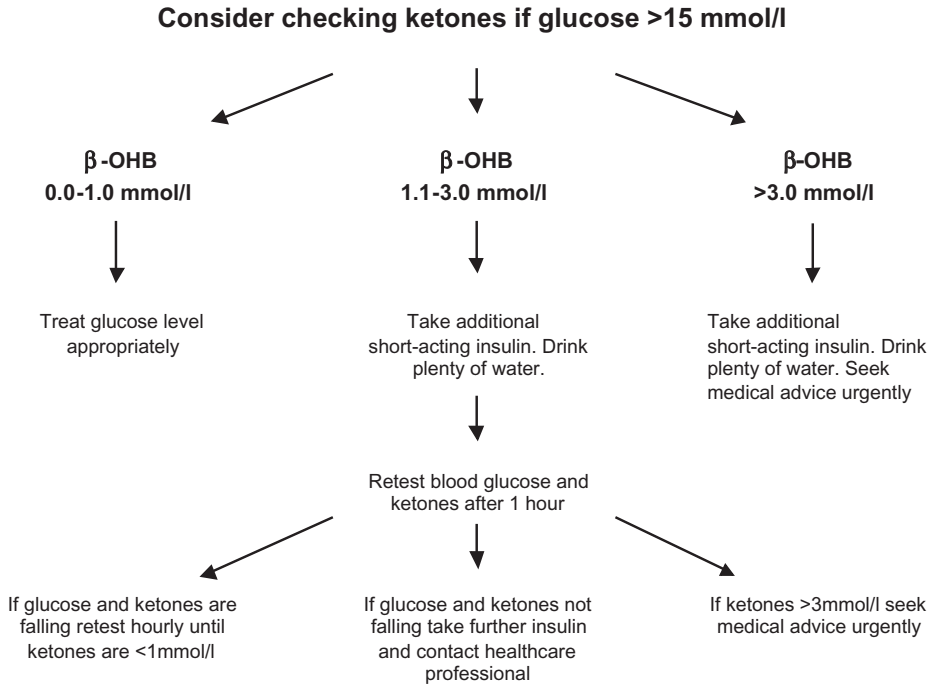

Figure 4. Guidelines for the use of the ketone meter in out-patients.

Monitoring β-OHB levels in children with DKA reduces the length of stay on the intensive care unit, with an average saving of $163[30] or €184 per patient.[31] We suggest that the introduction of routine β-OHB monitoring could not only reduce the duration of hospital admission, but may also help to prevent episodes of DKA, with a consequent reduction in healthcare expenditure.

Conclusion

In summary, blood ketone testing is a useful adjunct to glucose monitoring and allows clinicians and patients to distinguish between simple hyperglycaemia and a potentially life-threatening ketotic state. The facility to measure blood ketones should be available in A&E departments, GP surgeries, diabetes centres, and for self-monitoring in patients with type 1 diabetes. Monitoring ketones is also clinically useful in the management of DKA in children.[32] Further studies on the impact of measuring ketones on the management and prevention of DKA are needed; in particular, there are no randomized controlled trials of the use of routine ketone monitoring in DKA, although the logistics and ethics of establishing such a trial would be problematic.

Although there has been no *reported* reduction in mortality rates in DKA over the past 20 years, it is difficult to ascertain the incidence of DKA and its mortality, due to the lack of a national reporting system. The introduction of a national register would allow accurate statistics on incidence, complications, mortality and treatment to be collected. This would allow a structured audit of the management to be undertaken, which could form the basis for multi-centre or national prospective studies to determine the optimal management strategy.

Acknowledgments

TMW is the Oxford Servier Clinical Diabetes Research Fellow.

References

1. Basu A, Close CF, Jenkins D, Nattrass, Wright AD. Persisting mortality in diabetic ketoacidosis. *Diab Med* 1993; **10**:282–4.
2. Stephens JM, Sulway MJ, Watkins PJ. Relationship of blood acetoacetate and 3-hydroxybutyrate in diabetes. *Diabetes* 1971; **20**:485–9.
3. Byrne HA, Tieszen KL, Hollis S, Dornan TL, New JP. Evaluation of an electrochemical sensor for measuring blood ketones. *Diabetes Care* 2000; **23**:500–3.
4. Wallace TM, Meston NM, Gardner SG, Matthews DR. The hospital and home use of a 30-second hand-held blood ketone meter: guidelines for clinical practice. *Diabet Med* 2001; **18**:640–5.
5. American Diabetes Association: clinical practice recommendations 2004. *Diabetes Care* 2004; **27(Suppl. 1)**:S94–102.
6. Brandenburg MA, Dire DJ. Comparison of arterial and venous blood gas values in the initial emergency department evaluation of patients with diabetic ketoacidosis. *Ann Emerg Med* 1998; **31**:459–65.
7. Montoro MN, Myers VP, Mestman JH, Xu Y, Anderson BG, Golde SH. Outcome of pregnancy in diabetic ketoacidosis. *Am J Perinatol* 1993; **10**:17–20.
8. Umpierrez GE, Casals MM, Gebhart SP, Mixon PS, Clark WS, Phillips LS. Diabetic ketoacidosis in obese African-Americans. *Diabetes* 1995; **44**:790–5.
9. Rheeder P, Stolk RP, Grobbee DE. Ethnic differences in C-peptide levels and anti-GAD antibodies in South African patients with diabetic ketoacidosis. *Q J Med* 2001; **94**:39–43.
10. Chapman J, Wright AD, Nattrass M, Fitz Gerald M. Recurrent diabetic ketoacidosis. *Diab Med* 1988; **5**:659–61.
11. Faich GA, Fishbein HA, Ellis S. The epidemiology of diabetic acidosis: a population-based study. *Am J Epidemiol* 1983; **117**:551–8.
12. Umpierrez GE, Kelly JP, Navarrete JE, Casals MM, Kitabchi AE. Hyperglycemic crises in urban blacks. *Arch Intern Med* 1997; **157**:669–75.
13. Dissanayake AM, Gamble G, Baker JR, Reed L. Diagnostic delays of adult patients admitted to hospital with diabetic ketoacidosis. *Diabet Med* 2004; **21**:290–1.
14. Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, *et al*. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care* 2001; **24**:131–53.
15. Umpierrez G, Freire AX. Abdominal pain in patients with hyperglycemic crises. *J Crit Care* 2002; **17**:63–7.
16. Kreisberg R. Diabetic ketoacidosis: new concepts and trends in pathogenesis and treatment. *Ann Intern Med* 1978; **88**:681–95.
17. Yadav D, Nair S, Norkus EP, Pitchumoni CS. Nonspecific hyperamylasemia and hyperlipasemia in diabetic ketoacidosis: incidence and correlation with biochemical abnormalities. *Am J Gastroenterol* 2000; **95**:3123–8.
18. Kemperman FA, Weber JA, Gorgels J, van Zanten AP, Krediet RT, Arisz L. The influence of ketoacids on plasma creatinine assays in diabetic ketoacidosis. *J Intern Med* 2000; **248**:511–17.
19. Alberti KG. Low-dose insulin in the treatment of diabetic ketoacidosis. *Arch Intern Med* 1977; **137**:1367–76.
20. Page MM, Alberti KG, Greenwood R, Gumaa KA, Hockaday TD, Lowy C, *et al*. Treatment of diabetic coma with continuous low-dose infusion of insulin. *Br Med J* 1974; **2**:687–90.
21. Burghen GA, Etteldorf JN, Fisher JN, Kitabchi AQ. Comparison of high-dose and low-dose insulin by continuous intravenous infusion in the treatment of diabetic ketoacidosis in children. *Diabetes Care* 1980; **3**:15–20.
22. Alberti KG, Hockaday TD, Turner RC. Small doses of intramuscular insulin in the treatment of diabetic 'coma'. *Lancet* 1973; **2**:515–22.

23. Foster KJ, Alberti KGMM, Hinks L, Lloyd B, Postle A, Smythe P, *et al*. Blood intermediary metabolite and insulin concentrations after an overnight fast: reference ranges for adults, and interrelations. *Clinical Chemistry* 1978; **24**:1568–72.
24. Umpierrez GE, Watts NB, Phillips LS. Clinical utility of b-hydroxybutyrate determined by reflectance meter in the management of diabetic ketoacidosis (Letter). *Diabetes Care* 1995; **18**:137–8.
25. Luzi L, Barrett EJ, Groop LC, Ferrannini E, DeFronzo RA. Metabolic effects of low-dose insulin therapy on glucose metabolism in diabetic ketoacidosis. *Diabetes* 1988; **37**:1470–7.
26. Sulway MJ, Malins JM. Acetone in diabetic ketoacidosis. *Lancet* 1970; **2**:736–40.
27. Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacalone T, Chiarelli F. Effectiveness of a prevention program for diabetic ketoacidosis in children. An 8-year study in schools and private practices. *Diabetes Care* 1999; **22**:7–9.
28. Javor KA, Kotsanos JG, McDonald RC, Baron AD, Kesterson JG, Tierney WM. Diabetic ketoacidosis charges relative to medical charges of adult patients with type I diabetes. *Diabetes Care* 1997; **20**:349–54.
29. Maldonado MR, Chong ER, Oehl MA, Balasubramanyam A. Economic impact of diabetic ketoacidosis in a multiethnic indigent population: analysis of costs based on the precipitating cause. *Diabetes Care* 2003; **26**:1265–9.
30. Vanelli M, Chiari G, Capuano C. Cost effectiveness of the direct measurement of 3-beta-hydroxybutyrate in the management of diabetic ketoacidosis in children. *Diabetes Care* 2003; **26**:959.
31. Vanelli M, Chiari G, Capuano C, Iovane B, Bernardini A, Giacalone T. The direct measurement of 3-beta-hydroxy butyrate enhances the management of diabetic ketoacidosis in children and reduces time and costs of treatment. *Diabetes Nutr Metab* 2003; **16**:312–16.
32. Ham MR, Okada P, White PC. Bedside ketone determination in diabetic children with hyperglycemia and ketosis in the acute care setting. *Pediatr Diabetes* 2004; **5**:39–43.