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Review article

New approaches to the use of insulin in patients with diabetic ketoacidosis

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ABSTRACT

Diabetic ketoacidosis (DKA) is one of the most common and serious acute complications of diabetes and is a significant cause of morbidity and mortality. In the last decade the mortality rate from DKA has declined because of greater recognition and improvements in its management.

The current available guidelines state that the most effective means of insulin delivery during DKA is a continuous infusion of regular insulin, usually referred to as continuous low-dose insulin infusion. However, the cost of this treatment is usually quite high, because patients are required to be admitted to an intensive care unit in order to be monitored closely.

New analogs of human insulin that have a rapid onset of action have become available in the past decade and represent potential alternatives to the use of regular insulin in the treatment of DKA.

In several trials it has been demonstrated that the use of subcutaneous rapid-acting insulin analogs represents a safe, cost-effective and technically simpler treatment that precludes intensive care unit admission without significant differences in outcome in the management of patients with mild to moderate, uncomplicated DKA. The long-acting insulin analog may have a role in facilitating the transition from continuous intravenous insulin infusion to subcutaneous maintenance therapy in patients with DKA. This avoids rebound hyperglycaemia and ketogenesis when intravenous insulin is stopped and may avoid excess length of stay.

1. Introduction: past and present of DKA treatment

Diabetic ketoacidosis (DKA) is a life-threatening acute complication of diabetes. The National Diabetes Surveillance Program of the Center for Disease Control (CDC) estimated that there were 120,000 hospital discharges for DKA in 2005 in the United States [1]. It has been estimated that treatment of DKA episodes represent about one of every four health care dollars spent on direct medical care for adult patients with type 1 diabetes [2].

The mortality for DKA before the discovery of insulin was greater than 90%. This was dramatically reduced in subsequent years to less than 50% and was further reduced to less than 20% with the incorporation of antibiotics and forced hydration [3]. In the 1950s, the mortality of patients with DKA treated with high doses of insulin was reported to be less than 10% [4].

In more recent years, the use of standardized written guidelines for therapy has resulted in a mortality rate less than 5%, with higher mortality observed in elderly subjects and in patients with concomitant life threatening illnesses [4–7].

In the last decade there has been significant improvement of survival among DKA patients in most developed countries and now it reported to be <1% [8,9]. Improved health education of out-patient diabetics and introduction of hospital management guidelines of DKA might explain such an improvement of survival [8]. Moreover, mortality rates from DKA in elderly patients have also declined significantly over the last decade [8].

Although treatment with “low doses” of insulin in the early years of insulin therapy was found to be effective [10], “high-dose” insulin therapy became the standard of care after results from retrospective non-randomized trials in the 1950s and 1960s (“low dose” 40 to 50 units/day, “high dose” of insulin 200 to 300 units/day) [11,12].

As a result, until the early 1970s, insulin doses of 100 units per hour or more were given due to perceived insulin resistance. This approach was later replaced in the light of prospective randomized trials showing no advantage of high-dose insulin, compared with lower doses [13,14].

In 1973, Alberti et al. reported the results of low-dose intramuscular insulin in the management of patients with mild to moderate DKA [15]. They reported that an initial average bolus dose of 16 units followed by 5–10 units of intramuscular regular insulin per hour was effective in correcting hyperglycaemia and metabolic acidosis [16].

In addition the lower-dose therapy led to a decreased incidence of hypoglycaemia and hypokalaemia [17–20]. Thus, low-dose insulin therapy for the treatment of DKA became the standard of care.

Subsequently, Kitabchi and co-authors initiated a series of prospective randomized clinical trials on the management of DKA [17,21–29].

Abbreviations: DKA, Diabetic Ketoacidosis; NPH insulin, Neutral Protamine Hagedorn; DM, Diabetes Mellitus; ICU, Intensive Care Unit.

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In these trials several aspects of DKA treatment were studied: high-dose vs. low-dose insulin in adult DKA, route of insulin administration, loading vs. no-loading insulin, high-dose vs. low-dose insulin in paediatric patients, metabolism of low-dose insulin in DKA, use of phosphate therapy, use of bicarbonate therapy, lipid metabolism and influence of low doses of insulin on leptin level in patients with DKA.

In addition they proposed a new working classification of DKA [30,31]. This classification divided DKA into mild, moderate and severe forms according to clinical and laboratory data (Table 1).

The current available guidelines state that the most effective means of insulin delivery during DKA is a continuous infusion of regular insulin, usually referred to as continuous low-dose insulin infusion [30,31]. Unless the episode of DKA is mild, regular insulin by continuous intravenous infusion is recommended in the management of DKA in adult patients [30].

However, the cost of this treatment is usually quite high, because patients are required to be admitted to an intensive care unit in order to be followed under close monitoring [32–34]. Subcutaneous regular insulin administration might be used in patients with a mild clinical presentation. Nevertheless, delayed onset of action and prolonged activity of subcutaneous regular insulin seems to be a disadvantage for the rapid and proper management of DKA patients [19,22]. Moreover, it had been reported that when treated with intramuscular or subcutaneous regular insulin, 30%–40% of patients did not achieve a significant fall in their plasma glucose levels in the first hour after insulin injection and that the rate of decrease in the concentration of ketone bodies was significantly lower in this group when compared to intravenous treatment [22].

It has also been demonstrated that, in addition to insulin, successful treatment of DKA requires correction of dehydration, and electrolyte imbalances, identification of co-morbid precipitating events and above all frequent and close monitoring of the patients [30,31].

2. New approaches to the treatment of DKA

2.1. Rapid acting insulin analogs

Insulin lispro, a fast acting insulin analog, was first approved for use in the United States in 1996, and insulin aspart that was approved in the United States in 2000 became available for wide clinical use and represent alternatives to the use of regular insulin in the treatment of DKA, but the literature regarding this issue is limited.

Several previous reports reveal equal efficacy and in vivo potency of intravenous rapid-acting insulin analogs (glulisine, aspart, and lispro) when compared to regular insulin in animal and humans, attributable to their similar receptor binding affinity and receptor-mediated clearance [35–37]. Pharmacokinetics and pharmacodynamic trials comparing the intravenous administration of glulisine and regular insulin have shown a similar onset of action (within 20 min), a similar distribution and elimination profile and equivalent glucose utilization and disposal [36,38].

Table 1
Diagnostic criteria for DKA.

	Mild	Moderate	Severe
Plasma glucose (mg/dl)	>250	>250	>250
Arterial pH	7.25–7.30	7.00–7.24	<7.00
Serum bicarbonate (mEq/l)	15–18	10 to <15	<10
Urine ketones[a]	Positive	Positive	Positive
Serum ketones[a]	Positive	Positive	Positive
Effective serum osmolality[b]	Variable	Variable	Variable
Anion gap[c]	>10	>12	>12
Mental status	Alert	Alert/drowsy	Stupor/coma

[a] Nitroprusside reaction method.
[b] Effective serum osmolality: 2[measured Na^+ (mEq/l)] + glucose (mg/dl)/18.
[c] Anion gap: $(Na^+) - [(Cl^- + HCO_3^-$ (mEq/l)]. (Data adapted from Ref. [30].)

Based on these pharmacological similarities, Umpierrez and colleagues conducted a controlled multicenter, open-label prospective and randomized trial of 68 patients with DKA who were assigned to receive intravenous treatment with regular insulin or glulisine insulin until resolution of DKA [39]. After resolution of ketoacidosis, patients treated with intravenous regular insulin were transitioned to subcutaneous NPH and regular insulin twice daily. Patients treated with intravenous glulisine insulin were transitioned to subcutaneous glargine once daily and glulisine before meals. They found no differences in the mean duration of treatment or in the amount of insulin infusion until resolution of DKA between intravenous treatment with regular and glulisine insulin. After transition to subcutaneous insulin, the mean daily blood glucose levels were similar, but patients treated with NPH and regular insulin had a higher rate of hypoglycaemia (blood glucose <70 mg/dl). The authors concluded that regular and glulisine insulin are equally safe and effective during the acute treatment of DKA. However, intravenous regular insulin is more cost-effective and should still be preferred over rapid-acting insulin analogs during the acute intravenous treatment phase of DKA but that a basal-bolus regimen with glargine and glulisine was safer and should be preferred over NPH and regular insulin after the resolution of DKA [39].

Another interesting question that arises in regard to the rapid acting insulin analog is the possibility of using the subcutaneous route of administration, given their shorter onset of action. Following subcutaneous administration, insulin lispro starts acting within 10–20 min, reaches a peak insulin concentration within 30–90 min and has duration of action of approximately 3–4 h [40].

This issue was addressed in a prospective, randomized trial that compared the efficacy and safety of subcutaneous insulin lispro every hour with that of a standard low-dose intravenous infusion protocol of regular insulin in adult patients with uncomplicated DKA [41]. Patients treated with subcutaneous lispro were treated in the regular medicine wards or in the intermediate-care unit and because of hospital regulations intravenously treated patients were managed in the intensive care unit.

The duration of treatment until correction of hyperglycaemia (7 ± 3 h vs. 7 ± 2 h) and resolution of ketoacidosis (10 ± 3 h vs. 11 ± 4 h) in patients treated with subcutaneous lispro was not different than in patients treated with intravenous regular insulin. There were no deaths in either group, and there were no differences in the length of hospital stay, amount of insulin until resolution of diabetic ketoacidosis, or in the rate of hypoglycaemia between treatment groups. Treatment of diabetic ketoacidosis in the intensive care unit was associated with 39% higher hospitalization charges than was treatment with subcutaneous lispro in a non-intensive care setting ($\$14{,}429 \pm \$5243$ vs. $\$8801 \pm \$5549$, $P<0.01$) [41].

Another similar trial by Ersöz and co-authors compared the efficacy and safety of hourly subcutaneous insulin lispro administration to intravenous regular insulin in the treatment of mild and moderate DKA [42]. In this prospective, randomized, open trial of 20 patients, the rate of decline of plasma glucose concentration, capillary blood β-hydroxybutyrate, effective plasma osmolality, urinary ketone excretion and the mean duration of treatment until correction of ketoacidosis were equivalent between the two treatment groups. Furthermore, no serious side effects associated with the treatment protocol in both groups were observed [42].

Treatment with subcutaneous insulin injections on an hourly schedule, however, may be difficult due to the intensity of treatment and shortage of nursing staff on regular wards. Therefore, in order to try to facilitate the management of patients with DKA in medical wards, Umpierrez and colleagues studied whether treatment with subcutaneous rapid-acting insulin analogs, given at different time intervals (1 and 2 h), would be equally effective as the use of intravenous regular insulin in patients with DKA. A total of 45 consecutive patients admitted with DKA without signs of haemodynamic instability or organ failure were randomly assigned to receive subcutaneous aspart insulin every

hour or every 2 h or intravenous infusion of regular insulin. Response to medical therapy was evaluated by assessing the duration of treatment until resolution of hyperglycaemia and ketoacidosis. Similar to previous experience with lispro [41] in this trial there were no differences in the length of hospital stay, total amount of insulin administration until resolution of hyperglycaemia or ketoacidosis or the number of hypoglycaemic events among treatment groups [43]. There was, however, a reduction in treatment costs of approximately 30% in the subcutaneous groups. Based on these trial, the authors concluded that the use of subcutaneous rapid-acting insulin analogs every 1 or 2 h represents a safe and effective alternative to the use of intravenous regular insulin in the management of patients with uncomplicated DKA [43].

2.2. The choice of route of insulin therapy

As Haas and Hoffman have pointed out any method of insulin administration is usually effective in a patient with mild to moderate forms of DKA. However the use of constant intravenous insulin infusions is now generally considered to be the standard of care in most hospitals [44].

The issue of cost effectiveness in the treatment of DKA is also very important as treatment with continuous intravenous insulin infusion is more resource intensive as compared to hourly subcutaneous insulin injection due to the need for treatment in the intensive care unit.

Therefore the choice of route of insulin treatment seems to depend not only on the severity of DKA but also on the cost of treatment. If a hospital allows for intravenous insulin drips on the general medical wards then the cost of intravenous drip therapy would approach that of subcutaneous therapy.

In a large part the choice of route insulin therapy for patients with DKA is institution dependent [44].

2.3. Long acting insulin

The long-acting insulin analog glargine has been developed for once a day application in patients with type 1 and type 2 DM with the objective of providing a basal insulin component [45,46]. Its onset of action is approximately 1 h and its slow release from microprecipitates provides a relatively constant concentration of insulin over 24 h. Due to these pharmacological properties, it has been suggested that this type of insulin may have a role in facilitating the transition from continuous intravenous insulin infusion to subcutaneous maintenance therapy in patients with DKA.

In one trial the authors hypothesized that the initiation of a long-acting insulin therapy concurrently with intravenous insulin infusion would decrease the rate of rebound hyperglycaemia after discontinuation of the insulin infusion. Sixty-one diabetic patients (among them 25 with DKA) receiving intravenous insulin therapy participated in this prospective randomized study. Subjects in the intervention group received daily injections of glargine subcutaneously (0.25 U/kg body weight) starting within 12 h of initiation of intravenous regular insulin infusion. The authors concluded that once-daily subcutaneous insulin glargine administered during intravenous regular insulin infusion is a safe method for preventing future rebound hyperglycaemia, without an increased risk of hypoglycaemia [47].

"The Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis" also recommends continuation of long-acting insulin analog during the initial management of DKA because it provides background insulin when the intravenous insulin is discontinued [48]. According to these guidelines on DKA management, maintaining the normal daily dose of the patients' long acting insulin is unlikely to affect the blood glucose response to the intravenous insulin infusion and should pave the way for a smoother transition from an intravenous route to a subcutaneous delivery of insulin. This potentially avoids rebound hyperglycaemia and ketogenesis when the intravenous insulin is stopped and may decrease length of stay. If the patient is not taking a long-acting analog, background insulin should be reintroduced before the intravenous infusion is stopped [48].

3. Conclusion and perspectives of future clinical researches

Treatment of mild and moderate, non-complicated DKA with subcutaneous administration of rapid acting insulin analog is a safe and effective alternative to traditional use of intravenous regular insulin infusion. Patients with severe or complicated forms of DKA, however, should still be treated with intravenous regular insulin in an intensive care unit setting.

The long-acting insulin analog may have a role in facilitating the transition from continuous intravenous insulin infusion to subcutaneous maintenance therapy in patients with DKA. This avoids rebound hyperglycaemia and ketogenesis when intravenous insulin is stopped and may avoid excess length of stay.

Learning points

- Treatment of mild and moderate, non-complicated DKA both in adults and children with subcutaneous administration of novel rapid acting insulin analog is a safe and effective alternative to traditional use of intravenous regular insulin infusion.

Conflict of interests

The authors have no any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence, their work.

References

[1] http://www.cdc.gov/diabetes/statistics/hospitalization_national.htm. [Accessed on March 02, 2011].
[2] 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.
[3] Bradley RF. Diabetic ketoacidosis and coma. In: Marble A, White P, Bradley RF, Krall LP, editors. Joslin's Diabetic Mellitus. 11th ed. Philadelphia: Lea and Febiger; 1971. p. 361–416.
[4] Kitabchi AE. Low-dose insulin therapy in diabetic ketoacidosis: fact or fiction. In: DeFronzo R, editor. Diabetes metabolism reviews. New York: John Wiley, Sons; 1989. p. 337–63.
[5] 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.
[6] Umpierrez GE, Kelly JP, Navarrete JE, Casals MM, Kitabchi AE. Hyperglycemic crises in urban blacks. Arch Intern Med 1997;157:669–75.
[7] Kitabchi AE, Umpierrez GE, Murphy MB. Diabetes ketoacidosis and hyperglycemic hyperosmolar state. In: DeFronzo RA, Ferrannini E, Keen H, Zimmet P, editors. International textbook of diabetes mellitus. 3rd ed. Chichester, UK: John Wiley, Sons, Ltd.; 2004. p. 1101–19.
[8] Chen HF, Wang CY, Lee HY, See TT, Chen MH, Jiang JY, et al. Short-term case fatality rate and associated factors among inpatients with diabetic ketoacidosis and hyperglycemic hyperosmolar state: a hospital-based analysis over a 15-year period. Intern Med 2010;49:729–37 [Epub 2010 Apr 15].
[9] Umpierrez GE, Smiley D. Diabetic ketoacidosis and hyperglycemia hyperosmolar syndrome. In: Fonseca VA, editor. Clinical Diabetes. Translating Research into Practice. Philadelphia, PA: Saunders Elsevier; 2006. p. 101–18.
[10] Foster NB. The treatment of diabetic coma with insulin. Am J Med Sci 1923;166: 699–709.
[11] Root HF. The use of insulin and the abuse of glucose in the treatment of diabetic coma. JAMA 1945;127:557–64.
[12] Black AB, Malins JM. Diabetic ketosis: a comparison of results of orthodox and intensive methods of treatment based on 170 consecutive cases. Lancet 1949;1:56–9.
[13] Smith K, Martin HE. Response of diabetic coma to various insulin dosages. Diabetes 1954;3:287–95.
[14] Shaw Jr CE, Hurwitz GE, Schumkler M, Brager SH, Bessman SP. A clinical and laboratory study of insulin dosage in diabetic acidosis: comparison with small and large doses. Diabetes 1962;11:23–30.
[15] Alberti KG, Hockaday T, Turner RC. Small doses of intramuscular insulin in the treatment of diabetic "coma". Lancet 1973;5:515–22.
[16] Alberti KG. Comparison of different insulin regimens in diabetic ketoacidosis. Lancet 1976;1:83.

[17] Kitabchi AE, Ayyagari V, Guerra SNO. Efficacy of low dose vs conventional therapy of insulin for treatment of diabetic ketoacidosis. Ann Intern Med 1976;84:633–8.
[18] Gonzalez-Villalpando C, Blachley JD, Vaughan GM, Smith JD. Low- and high-dose intravenous insulin therapy for diabetic ketoacidosis. JAMA 1979;241:925–7.
[19] Alberti KG. Low-dose insulin in the treatment of diabetic ketoacidosis. Arch Intern Med 1977;137:1367–76.
[20] Heber D, Molitch ME, Sperling MA. Low-dose continuous insulin therapy for diabetic ketoacidosis. Prospective comparison with "conventional" insulin therapy. Arch Intern Med 1977;137:1377–80.
[21] Kitabchi AE, Sacks H, Fisher JN. Clinical trials in diabetic ketoacidosis. In: Clarke WL, Larner J, Pohl SL, editors. Methods in diabetes research, vol. 2. New York: Wiley and Sons; 1986. p. 315–28.
[22] Fisher JN, Shahshahani MN, Kitabchi AE. Diabetic ketoacidosis: low doseinsulin therapy by various routes. N Engl J Med 1977;297:238–41.
[23] Sacks HS, Shahshahani MN, Kitabchi AE, Fisher JN, Young RT. Similar responsiveness of diabetic ketoacidosis to low-dose insulin by intramuscular injection and albumin-free infusion. Ann Intern Med 1979;90:36–42.
[24] Burghen GA, Etteldorf JN, Fisher JN, Kitabchi AE. Comparison of high-dose to low-dose insulin by continuous intravenous infusion in the treatment of diabetic ketoacidosis in children. Diabetes Care 1980;3:15–20.
[25] Huffstutter E, Hawkes J, Kitabchi AE. Low dose insulin for treatment of diabetic ketoacidosis in a private community hospital. South Med J 1980;73:430–2.
[26] Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. J Clin Endocrinol Metab 1983;57:177–80.
[27] Morris LR, Murphy MB, Kitabchi AE. Bicarbonate therapy in severe diabetic ketoacidosis. Ann Intern Med 1986;105:836–40.
[28] Weidman SW, Ragland JB, Fisher JN, Kitabchi AE, Sabesin SM. Effects of insulin on plasma lipoproteins in diabetic ketoacidosis: evidence for a change in high density lipoprotein composition during treatment. J Lipid Res 1982;23:171–82.
[29] Kitabchi AE, Umpierrez GE. Changes in serum leptin in lean and obese subjects with acute hyperglycemia crises. J Clin Endocrinol Metab 2003;88:2593–6.
[30] American Diabetes Association. Diabetes Care 2006;29.
[31] Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32:1335–43.
[32] Soler NG, Bennett MA, FitzGerald MG, Malins JM. Intensive care in the management of diabetic ketoacidosis. Lancet 1973;1:951–4.
[33] May ME, Young C, King J. Resource utilization in treatment of diabetic ketoacidosis in adults. Am J Med Sci 1993;306:287–94.
[34] Freire AX, Umpierrez GE, Afessa B, Latif KA, Bridges L, Kitabchi AE. Predictors of intensive care unit and hospital length of stay in diabetic ketoacidosis. J Crit Care 2002;17:207–11.
[35] Gillies PS, Figgitt DP, Lamb HM. Insulin glargine. Drugs 2000;59:253–60.
[36] Plum A, Agerso H, Andersen L. Pharmacokinetics of the rapid-acting insulin analog, insulin aspart, in rats, dogs, and pigs, and pharmacodynamics of insulin aspart in pigs. Drug Metab Dispos 2000;28:155–60.
[37] Hennige AM, Strack V, Metzinger E, Seipke G, Haring HU, Kellerer M. Effects of new insulin analogues HMR1964 (insulin glulisine) and HMR1423 on insulin receptors. Diabetologia 2005;48:1891–7.
[38] Becker RH, Frick AD, Burger F, Scholtz H, Potgieter JH. A comparison of the steadystate pharmacokinetics and pharmacodynamics of a novel rapid-acting insulin analog, insulin glulisine, and regular human insulin in healthy volunteers using the euglycemic clamp technique. Exp Clin Endocrinol Diabetes 2005;113:292–7.
[39] Umpierrez GE, Jones S, Smiley D, Mulligan P, Keyler T, Temponi A, et al. Insulin analogs versus human insulin in the treatment of patients with diabetic ketoacidosis: a randomized controlled trial. Diabetes Care 2009;32:1164–9.
[40] Holleman F, Hoekstra JB. Insulin lispro. N Engl J Med 1997;337:176–83.
[41] Umpierrez GE, Latif K, Stoever J, Cuervo R, Park L, Freire AX, et al. The efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for treatment of diabetic ketoacidosis. Am J Med 2004;117:291–6.
[42] Ersöz HO, Ukinc K, Köse M, Erem C, Gunduz A, Hacihasanoglu AB, et al. Subcutaneous lispro and intravenous regular insulin treatments are equally effective and safe for the treatment of mild and moderate diabetic ketoacidosis in adult patients. Int J Clin Pract 2006;60:429–33.
[43] Umpierrez GE, Cuervo R, Karabell A, Latif K, Freire AX, Kitabchi AE. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. Diabetes Care 2004;27:1873–8.
[44] Haas RM, Hoffman AR. Treatment of diabetic ketoacidosis: Should mode of insulin administration dictate use of intensive care facilities? Am J Med 2004;117:357–8.
[45] McKeage K, Goa KL. Insulin glargine: a review of its therapeutic use as a long-acting agent for the management of type 1 and 2 diabetes mellitus. Drugs 2001;61:1599–624.
[46] Dunn CJ, Plosker GL, Keating GM, McKeage K, Scott LJ. Insulin glargine: an updated review of its use in the management of diabetes mellitus. Drugs 2003;63:1743–78.
[47] Hsia E, Seggelke S, Gibbs J, Hawkins RM, Cohlmia E, Rasouli N, et al. Subcutaneous administration of glargine to diabetic patients receiving insulin infusion prevents rebound hyperglycemia. J Clin Endocrinol Metab 2012;97:3132–7, http://dx.doi.org/10.1210/jc.2012-1244 [Epub 2012 Jun 8].
[48] Savage MW, Dhatariya KK, Kilvert A, Rayman G, Rees JA, Courtney CH, et al. Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. Diabet Med 2011;28:508–15, http://dx.doi.org/10.1111/j.1464-5491.2011.03246.x.