DIABETIC KETOACIDOSIS AND HYPEROSMOLAR HYPERGLYCAEMIC NON-KETOTIC STATE
Supporting information

This guideline has been prepared with reference to the following:

Mustafa OG, Haq M, Dashora U et al. Management of Hyperosmolar Hyperglycaemic State (HHS) in Adults: An updated guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care Group. Diabet Med. 2023;40:e15005

https://onlinelibrary.wiley.com/doi/10.1111/dme.15005

NICE. Type 1 diabetes in adults: diagnosis and management. 2022. NICE. London

https://www.nice.org.uk/guidance/ng17

Dhatariya K & Joint British Diabetes Societies for Inpatient Care. The management of diabetic ketoacidosis in adults-An updated guideline from the Joint British Diabetes Society for Inpatient Care. Diabet Med. 2022;39:e14788

https://onlinelibrary.wiley.com/doi/10.1111/dme.14788

Immediate Treatment

Initial IV fluid replacement using sodium chloride 0.9% in the regimen described is appropriate in the immediate treatment of diabetic ketoacidosis?
In a prospective study of 23 patients (Adrogue, 1989), 12 patients given isotonic saline at 1000 mL/h for 4 hours and then 500 mL/h for the next 4 hours recovered less quickly than 11 patients given saline at half the rate. On the basis of this study, backed by clinical experience, another suggested regimen for patients who are not shocked or oliguric (<30 ml/h) is 500 ml/h of sodium chloride 0.9% for 4 hours, followed by 250 ml/h for the next 4 hours (Hardern, 2003).
A position statement of the American Diabetes Association (Kitabchi, 2009) recommends sodium chloride 0.9% at a rate of 15-20 mL/kg or greater during the first hour.
The consensus appears to be that 6-10 litres of fluid (which will usually be sodium chloride 0.9%) are required by the average adult patient during the first 24 hours. Considerable caution is advised with elderly patients or those with heart disease.

Adrogue HJ, Barrero J, Eknoyan G. Salutary effects of modest fluid replacement in the treatment of adults with diabetic ketoacidosis: use in patients without extreme volume deficit. JAMA 1989;262:2108-13

Hardern RD, Quinn ND. Emergency management of diabetic ketoacidosis in adults. Emerg Med J 2003;20:210-3 http://emj.bmj.com/content/20/3/210.full

Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in diabetes. Diabetes Care 2009;32:1335-43 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2699725/

Evidence level: V

Administration of insulin via IV syringe pump at 6 units/hour is appropriate for the immediate treatment of diabetic ketoacidosis?
This conforms to the European IDDM Policy Group's (1993) guidelines and is echoed by most textbooks. Kitabchi (1995) recommends 7 units/hour, but anywhere between 5 and 10 units/hour seems to be considered appropriate. A position statement of the American Diabetes Association (Kitabchi, 2009) recommends a bolus of 0.15 units/kg, followed by continuous infusion of 0.1 unit/kg equating to between 5-7 units/hour. If no response, check pump and lines before doubling dose (Hardern, 2003).

European IDDM Policy Group. Consensus guidelines for the management of insulin-dependent (Type 1) diabetes. Diabet Med 1993;10:990-1005

Hardern RD, Quinn ND. Emergency management of diabetic ketoacidosis in adults. Emerg Med J 2003;20:210-3 http://emj.bmj.com/content/20/3/210.full

Kitabchi AE, Wall BM. Diabetic ketoacidosis. Med Clin North Am 1995; 79:9-37

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Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in diabetes. Diabetes Care 2009; 32:1335-43 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2699725/

Evidence level: V

Having initiated an IV infusion of insulin using a syringe pump, if there is no change in the blood glucose after 2 hours, the infusion rate should be doubled repeatedly at hourly intervals until a response occurs?

As mechanical problems are the most common cause of failure to respond, blockages and pump failures should be checked for first (Pickup 1997). Otherwise, advice again corresponds to European IDDM Policy Group (1993) guidelines. In some cases, the advice is to start doubling the infusion rate if no change is observed after 1 hour rather than 2 (Anon, 2003; Chiasson, 2003; Magee, 2001).

Anon. Hyperglycemic crises in patients with diabetes mellitus. Diabetes Care 2003;26:S109-17

Chiasson JL, Aris-Jilwan N, Belanger R, et al. Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. CMAJ 2003;168:859-66 http://www.cmaj.ca/content/168/7/859.long

European IDDM Policy Group. Consensus guidelines for the management of insulin-dependent (Type 1) diabetes. Diabet Med 1993;10:990-1005 https://www.staff.ncl.ac.uk/philip.home/iddmintr.htm

Magee MF, Bhatt BA. Management of decompensated diabetes: diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome. Crit Care Clin 2001;17:75-106

Pickup J, Williams G. Textbook of diabetes, 2nd ed. Oxford: Blackwell Science, 1997. 39.11

Evidence level: V

Pre-mixed bags containing potassium should be used, according to the plasma potassium concentration, giving nil if plasma K >5.5, 20 mmol/hour if plasma K 3.5-5.5, and 40 mmol/hour if plasma K <3.5?

The European IDDM Policy Group (1993) and American Diabetes Association (Kitabchi, 2009) guidelines agree with this; the former also advise checking the plasma K every 1.5-2.0 hours.

European IDDM Policy Group. Consensus guidelines for the management of insulin-dependent (Type 1) diabetes. Diabet Med 1993;10:990-1005

Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in diabetes. Diabetes Care 2009; 32:1335-43 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2699725/

Evidence level: V

Monitoring heart rate and rhythm continuously during infusion of potassium helps to identify cardiac complications and affects the clinical outcome?

Recommended in European guidelines and suggested in earlier papers by Malone (1980) and Soler (1974), to identify electrolyte abnormalities that can cause fatal cardiac arrhythmias. On the other hand, Harrower (1978) and Moss (1987) maintain that routine ECGs may be safely and cost-effectively omitted; in the latter case, without mortality in 250 consecutive patients.

European IDDM Policy Group. Consensus guidelines for the management of insulin-dependent (Type 1) diabetes. Diabet Med 1993;10:990-1005 https://www.staff.ncl.ac.uk/philip.home/iddmintr.htm

Harrower AD, Campbell IW, Ewing DJ, et al. The value of continuous ECG monitoring during treatment of diabetic ketoacidosis. A computer study. Acta Diabetol Latina 1978;15:88-94

Malone JI, Brodsky SJ. The value of electrocardiogram monitoring in diabetic ketoacidosis. Diabetes Care 1980; 3:543-7

Moss JM. Diabetic ketoacidosis: effective low-cost treatment in a community hospital. South Med J 1987; 80:875-81

Soler NG, Bennett MA, Fitzgerald MG, et al. Electrocardiogram as a guide to potassium replacement in diabetic ketoacidosis. Diabetes 1974;23:610-5

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Evidence level: V

Giving IV sodium bicarbonate to correct metabolic acidosis can adversely affect the clinical outcome in patients with diabetic ketoacidosis?

A retrospective study (Duhon 2013) of DKA patients admitted to an Emergency Department between 2007 and 2011 with a ph less than 7 stratified them into 2 groups based on receipt of IV sodium bicarbonate. This also included a subgroup analysis of patients with <6.9 – the American Diabetic Association's recommended PH for sodium bicarbonate use (Kitabchi 2009) The study found that there was no significant difference in time to resolution of acidosis (8 hours vs 8 hours; p = 0.7) or time to hospital discharge (68 hours vs 61 hours; p = 0.3) between patients who received intravenous bicarbonate (n = 44) compared with those who did not (n = 42).

European guidelines (1993) and American Diabetes Association guidelines (Kitabchi, 2009) recommend the use of sodium bicarbonate in these patients.

"The administration of sodium bicarbonate is virtually never indicated" (Wallace, 2004). The use of bicarbonate remains controversial, but "it may be prudent to give 50 mmol of bicarbonate in 200 mL of sterile water with 10 mEq of potassium chloride over 2 hours to maintain the pH at greater than 7.0" in patients with a pH between 6.9 and 7.0 (Kitabchi, 2006).

A double-blind, randomised, placebo controlled trial of 20 patients by Gamba (1991) found sodium bicarbonate produced a small benefit in patients with pH 6.9 to 7.15.

Anon. Hyperglycemic crises in patients with diabetes mellitus. Diabetes Care 2003;26(Suppl 1):S109-17

European IDDM Policy Group. Consensus guidelines for the management of insulin-dependent (Type 1) diabetes. Diabet Med 1993; 10:990-1005
https://www.staff.ncl.ac.uk/philip.home/iddmintr.htm

Duhon B, Attridge RL, Franco-Martinez AC et al. Intravenous sodium bicarbonate therapy in severely acidotic diabetic ketoacidosis. Ann Pharmacother 2013 47 (970-5)

Gamba G, Oseguera J, Castrejon M, et al. Bicarbonate therapy in severe diabetic ketoacidosis. A double blind, randomized, placebo controlled trial. Rev Invest Clin 1991; 43:234-8

Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in diabetes. Diabetes Care 2009; 32(7):1335-1343
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2699725/

Kitabchi AE, Nyenwe EA. Hyperglycemic crises in diabetes mellitus: diabetic ketoacidosis and hyperglycemic hyperosmolar state. Endocrinol Metab Clin N Am 2006;35:725-51

Wallace TM, Matthews DR. Recent advances in the monitoring and management of diabetic ketoacidosis. QJM 2004;97:773-80
http://qjmed.oxfordjournals.org/content/97/12/773.2.long

Evidence level: II

When correcting metabolic acidosis, the appropriate dose of sodium bicarbonate 1.26% if plasma pH is 6.8-6.9 should be 300 ml, accompanied by a premixed bag containing 500 ml sodium chloride 0.9% with 10 mmol of potassium chloride; and that if plasma pH <6.8, double this dose should be given?

European guidelines (1993) agree that nil should be given if pH is above 6.9, but recommend 100 mmol of sodium bicarbonate with 20 mmol of potassium chloride for plasma pH of <= 6.9. Kitabchi (1995) recommends 44 mEq for pH 6.9-7.0 and 88 mmol for pH <6.9.

European IDDM Policy Group. Consensus guidelines for the management of insulin-dependent (Type 1) diabetes. Diabet Med 1993;10:990-1005
https://www.staff.ncl.ac.uk/philip.home/iddmintr.htm

Kitabchi AE, Wall BM. Diabetic ketoacidosis. Med Clin North Am 1995; 79:9-37

Evidence level: V

Inserting a nasogastric tube in unconscious patients with diabetic ketoacidosis, allowing aspiration of the stomach, improves the outcome?

Pickup and Williams (1997) advise this, cautioning that it should be performed by a skilled practitioner because of the risk of precipitating vomiting. Watkins (1996) notes that "the procedure is lifesaving, but a small number of deaths still occur as a result of inhalation of gastric contents."

Pickup J, Williams G. Textbook of diabetes, 2nd ed. Oxford: Blackwell Science, 1997. 39.12

Watkins PJ, Drury PL, Howell SL. Diabetes and its management, 5th ed. Oxford: Blackwell Science, 1996. p.125

Evidence level: V

Giving a broad spectrum antibiotic in patients with diabetic ketoacidosis who are febrile and in whom no obvious cause can be found for fever, improves the clinical outcome?
In Pickup and Williams' (1997) series of 746 episodes of diabetic ketoacidosis, infections were the most common identifiable cause at 28%. Despite this, no specific advice is given about antibiotic treatment. Narrative reviews (Wallace, 2004; Magee, 2001) recommend the use of broad spectrum antibiotics as part of general supportive measures.

Magee MF, Bhatt BA. Management of decompensated diabetes: diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome. Crit Care Clin 2001;17:75-106

Pickup J, Williams G. Textbook of diabetes, 2nd ed. Oxford: Blackwell Science, 1997. 39.2

Wallace TM, Matthews DR. Recent advances in the monitoring and management of diabetic ketoacidosis. QJM 2004;97:773-80
http://qjmed.oxfordjournals.org/content/97/12/773.2.long

Evidence level: V

Patients with hyperglycaemic hyperosmolar nonketotic coma are at increased risk of venous thromboembolism (VTE) and should be treated with prophylactic heparin?
A retrospective study in 2859 patients with diabetes and hyperosmolarity (Keenan, 2007) found that 34 (1.2%) developed VTE during hospitalisation and 14 (0.5%) developed VTE within 91 days after discharge. Compared to uncomplicated diabetes, patients with hyperosmolarity had a significantly higher risk of VTE (HR = 3.0; 95% CI: 2.1–4.5) whereas patients with ketoacidosis were not at higher risk (HR = 1.2; 95% CI: 0.8–1.7).
Although full heparin anticoagulation has been associated with an increased risk of major GI or intracranial bleeding in HONK patients (Kian, 2003), there is no evidence that heparin in doses sufficient for prophylaxis carries a similar risk.

Keenan CR, Murin S, White RH. High risk for venous thromboembolism in diabetics with hyperosmolar state: comparison with other acute medical illnesses. J Thromb Haemost 2007;5:1185-90
http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2007.02553.x/full

Kian K, Eiger G. Anticoagulant therapy in hyperosmolar non-ketotic diabetic coma. Diabet Med 2003;20:603

Evidence Level: IV

Subsequent Management

Once blood glucose has fallen to below 15 mmol/litre, the infusion should be changed from sodium chloride 0.9% to 5% glucose?
Pickup and Williams (1997) recommend that 5% dextrose is introduced when blood glucose has fallen to 15 mmol/litre to avoid hypoglycaemia until the patient is eating again, administered at 250ml/h. Watkins (1996) suggests10% dextrose when blood glucose falls below 10 mmol/l at the rate of 1l 8 hrly. European guidelines (1993) advise 10% dextrose when blood glucose falls below 13 mmol/l.

European IDDM Policy Group. Consensus guidelines for the management of insulin-dependent (Type 1) diabetes. Diabet Med 1993;10:990-1005
https://www.staff.ncl.ac.uk/philip.home/iddmintr.htm

Pickup J, Williams G. Textbook of diabetes, 2nd ed. Oxford, Blackwell Science, 1997. 39.10

Watkins PJ, Drury PL, Howell SL. Diabetes and its management, 5th ed. Oxford, Blackwell Science, 1996. p.124

Evidence level: V

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In patients with diabetic ketoacidosis, the persistence of hypotension beyond 12 hours should raise suspicion of underlying sepsis, myocardial infarction or pancreatitis?
European guidelines (1993) advise checking for other contributory disease in the absence of infection. In Pickup and Williams' (1997) series of 746 episodes, myocardial infarction was responsible for only 1%, while "miscellaneous conditions" accounted for a further 5%. No precipitating cause was identified in 43% of episodes. Plasma expanders were not considered to be necessary to treat persistent hypotension.

European IDDM Policy Group. Consensus guidelines for the management of insulin-dependent (Type 1) diabetes. Diabet Med 1993;10:990-1005
https://www.staff.ncl.ac.uk/philip.home/iddmintr.htm

Pickup J, Williams G. Textbook of diabetes, 2nd ed. Oxford, Blackwell Science, 1997. 39.13

Evidence level: V

Patients who are normoglycaemic and who are eating normally (usually within 48 hours), are appropriately managed using intermittent subcutaneous injections of insulin using a total daily dosage which is two thirds of the previous 24 hour requirement for IV insulin, and given as short-acting insulin in divided doses 8 hourly?
Only general recommendations appear to be available in this area. Pickup and Williams (1997) advise giving the first subcutaneous injection of insulin 1 hour before ending the IV infusion, to allow time for absorption from the subcutaneous depot. Watkins (1996) advocates giving the first injection before breakfast and discontinuing the IV infusion after the meal, again after an hour has elapsed. Neither source advises on the dose as a fraction of the IV requirement, and the implication appears to be that the patient's normal insulin is reintroduced after 24 hours.

Pickup J, Williams G. Textbook of diabetes, 2nd ed. Oxford, Blackwell Science, 1997. 39.11

Watkins PJ, Drury PL, Howell SL. Diabetes and its management, 5th ed. Oxford, Blackwell Science, 1996. p125

Evidence level: V

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