REVIEW

Hyperglycaemic crises and lactic acidosis in diabetes mellitus

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Postgrad Med J 2004;**80**:253–261. doi: 10.1136/pgmj.2002.004291

Diabetic ketoacidosis, hyperglycaemic hyperosmolar state, and lactic acidosis represent three of the most serious acute complications of diabetes. There have been some advances in our understanding of the pathogenesis of these conditions over the last three decades, together with more uniform agreement on their treatment and innovations in technology. Accordingly their incidence, morbidity, and mortality are decreasing, but at rates that fall short of our aspirations. Hyperglycaemic crises in particular remain an important cause of morbidity and mortality in diabetic populations around the world. In this article, understanding of these conditions and advances in their management, and the available guidelines for their treatment, are reviewed. As far as is possible, the recommendations are based on clear published evidence; failing that, what is considered to be a common sense synthesis of consensus guidelines and recommendations is provided.

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Submitted
12 September 2003
Accepted 1 October 2003

Hyperglycaemic crises are discussed together followed by a separate section on lactic acidosis.

DIABETIC KETOACIDOSIS (DKA) AND HYPERGLYCAEMIC HYPEROSMOLAR STATE (HHS)

Definitions

DKA has no universally agreed definition. Alberti proposed the working definition of ''severe uncontrolled diabetes requiring emergency treatment with insulin and intravenous fluids and with a blood ketone body concentration of >5 mmol/l''.[1] Given the limited availability of blood ketone body assays, a more pragmatic definition comprising a metabolic acidosis (pH <7.3), plasma bicarbonate <15 mmol/l, plasma glucose >13.9 mmol/l, and urine ketostix reaction ++ or plasma ketostix ⩾ + may be more workable in clinical practice.[2] Classifying the severity of diabetic ketoacidosis is desirable, since it may assist in determining the management and monitoring of the patient. Such a classification is based on the severity of acidosis (table 1). A caveat to this approach is that the presence of an intercurrent illness, that may not necessarily affect the level of acidosis, may markedly affect outcome: a recent study showed that the two most important factors predicting mortality in DKA were severe intercurrent illness and pH <7.0.[3]

HHS replaces the older terms, ''hyperglycaemic hyperosmolar non-ketotic coma'' and ''hyperglycaemic hyperosmolar non-ketotic state'', because alterations of sensoria may be present without coma, and mild to moderate ketosis is commonly present in this state.[4 5]

Definitions vary according to the degree of hyperglycaemia and elevation of osmolality required. Table 1 summarises the definition of Kitabchi *et al*.[5]

Epidemiology

The annual incidence of DKA among subjects with type 1 diabetes is between 1% and 5% in European and American series[6–10] and this incidence appears to have remained relatively constant over the last decade in Western countries. Episodes of DKA are more common in younger than older subjects and are twice as common in females than males.[11] Mortality rates are reportedly less than 5% in experienced centres,[5 10 12–15] but increase with age, approaching 50% in those over the age of 80.[11]

The incidence of HHS is more difficult to determine since there are few population based studies, and the frequent presence of complicating illnesses may lead to this diagnosis not being entered in discharge coding. HHS admission rates appear to be lower than those for DKA and account for <1% of admissions primarily related to diabetes.[16 17] Mortality rates are, however, much higher at around 15%,[14 16–19] perhaps reflecting the severity of the associated illnesses and the greater age of many of these patients.

Precipitants

The commonest identified precipitant of DKA and HHS is infection (see table 2), though the fact that DKA *per se* causes a raised white blood cell count, vasodilatation, and polyuria may lead to over diagnosis of infection as a precipitant (see box 2). The other principal precipitant is insulin error, whether accidental or due to non-concordance, and failure to increase insulin during intercurrent illness. Other factors include myocardial infarction, stroke, new onset of type 1 diabetes, pancreatitis, pulmonary embolism, excess alcohol ingestion, and drugs that alter carbohydrate metabolism such as corticosteroids, sympathomimetic agents, α-adrenergic and β-adrenergic blockers, and diuretics. It is worth noting that although DKA is most likely to occur in individuals with type 1 diabetes, it is also well described in individuals with type 2 diabetes and

Abbreviations: DKA, diabetic ketoacidosis; FFA, free fatty acids; HHS, hyperglycaemic hyperosmolar state

Table 1 Diagnostic criteria for diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state (HHS)

	DKA			
	Mild	**Moderate**	**Severe**	**HHS**
Plasma glucose (mmol/l	⩾14	⩾14	⩾14	⩾30
Arterial pH	7.25–7.35	7.0–⩽7.24	<7.0	>7.3
Serum bicarbonate (mmol/l)	15–18	10–14	<10	>15
Urine ketones	⩾++	⩾++	⩾++	⩽+
Plasma ketones	⩾++	⩾++	⩾++	⩽+
Total osmolality (mOsm/kg)*	Variable	Variable	Variable	⩾340
Anion gap†	>10	>12	>12	<12
Level of consciousness	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

*Formula: $2\times\{[Na^+]+[K^+]\}+[urea]+[glucose]$.
†Formula: $[Na^+]-([Cl^-]+[HCO_3^-])$ (mmol/l). Table largely adapted from Kitabchi *et al*.[5]

severe precipitating illness, who may be able to return to therapy with oral hypoglycaemic agents once the acute illness and hyperglycaemic crisis have been treated. DKA has also been increasingly described in obese African Americans with type 2 diabetes, sometimes at diagnosis and sometimes after relatively minor or undiagnosed precipitants in individuals with reasonable baseline control.[16 20] Characteristically these individuals return to oral hypoglycaemic therapy or diet control after resolution of the acute episode.

Recurrent episodes of DKA account for 15% of cases and are more common in those who are female, socially deprived, and of lower educational status. Psychological problems complicated by eating disorder are associated with deliberate omission or under-dosing with insulin and may contribute to 20% of these recurrent admissions in young type 1 diabetic patients.[2]

Pathogenesis

The primary mechanism for the development of ketoacidosis and HHS is a reduction in the effective levels and/or action of circulating insulin with a concomitant elevation of the counter-regulatory hormones: glucagon, catecholamines, cortisol, and growth hormone (fig 1), due to insulin deficiency *per se* and intercurrent illness.

Box 1: Useful equations

In DKA the accumulation of anionic ketones and the consumption of bicarbonate as a buffer lead to an ''anion gap'' acidosis. The anion gap can be calculated by considering the usual major cations (K^+ is not used because of its alterations in acid-base disturbances) and major anions in plasma using the formula:

$[Na^+]-([Cl^-]+[HCO_3^-])$, and should be less than 7–9 mmol/l using current laboratory methods for chloride concentrations.[5]

Hyperglycaemia is restricted to the extracellular space so water moves from the intracellular to the extracellular compartment initially, diluting plasma sodium. During the accompanying osmotic diuresis, water is generally lost in excess of sodium until eventually the loss of water is similar for both extracellular and intracellular compartments. Therefore, in DKA, which is usually of relatively brief duration (<24 hours), plasma sodium concentrations may be artificially lowered and can be corrected using the formula:

Corrected $[Na^+]$ mmol/l = [plasma Na^+] mmol/l + $(1.6\times\{(\text{plasma glucose}-5.6)/5.6\})$.[5 26 27]

Footnote: HCO_3^-, bicarbonate; Cl^-, chloride; Na^+, sodium.

Hyperglycaemia

Insulin deficiency and raised catecholamines, cortisol, and glucagon increase hepatic gluconeogenesis and enhance glycogenolysis. Hypercortisolaemia also increases protein breakdown, providing increased amino acid precursors for gluconeogenesis. Glucose production is thus increased, while glucose disposal in peripheral tissues is decreased as a result of both insulin deficiency and the insulin resistance induced by the raised levels of plasma catabolic hormones and free fatty acids (FFA). Blood glucose levels rise, leading to glycosuria, osmotic diuresis and dehydration, which decreases renal perfusion and renal glucose clearance (especially in HHS), further exacerbating hyperglycaemia.

Hyperketonaemia and acidosis

Hormone sensitive lipase mediates the breakdown of stored triglycerides in adipose tissue. It is exquisitely sensitive to inhibition by insulin, while its activity is increased by the counter-regulatory hormones (especially catecholamines and cortisol). In DKA, profound insulin deficiency and elevated levels of counter-regulatory hormones activate hormone sensitive lipase, increasing lipolysis and releasing large amounts of glycerol and FFA into the portal circulation.[21–24] Glycerol is a precursor for gluconeogenesis in both liver and kidneys while the hepatic mitochondria oxidise FFA to the ketone bodies acetoacetate and 3-hydroxybutyrate. Ketone bodies are strong organic acids and their rapid increase outstrips the bodies buffering capacity (provided by bicarbonate) leading to acidosis.

Why ketoacidosis does not occur in HHS is unknown; current theories draw attention to the lower levels of FFA and growth hormone, and the higher portal vein insulin concentrations.[4 5 25–29]

Fluid and electrolyte losses

Hyperglycaemia and ketonaemia cause an osmotic diuresis with dehydration and loss of electrolytes, particularly the cations: sodium, potassium, and magnesium (table 3). Sodium loss is worsened by insulin deficiency and glucagon

Table 2 Precipitating factors for DKA

Precipitating condition	**Cases (%)**
Infections	19–56
Cardiovascular disease	3–6
Inadequate insulin/non-compliance	15–41
New onset diabetes	10–22
Other medical illness	10–12
Unknown	4–33

Table derived from references Kitabchi *et al*,[5] Bagg *et al*,[12] and Lebovitz.[27]

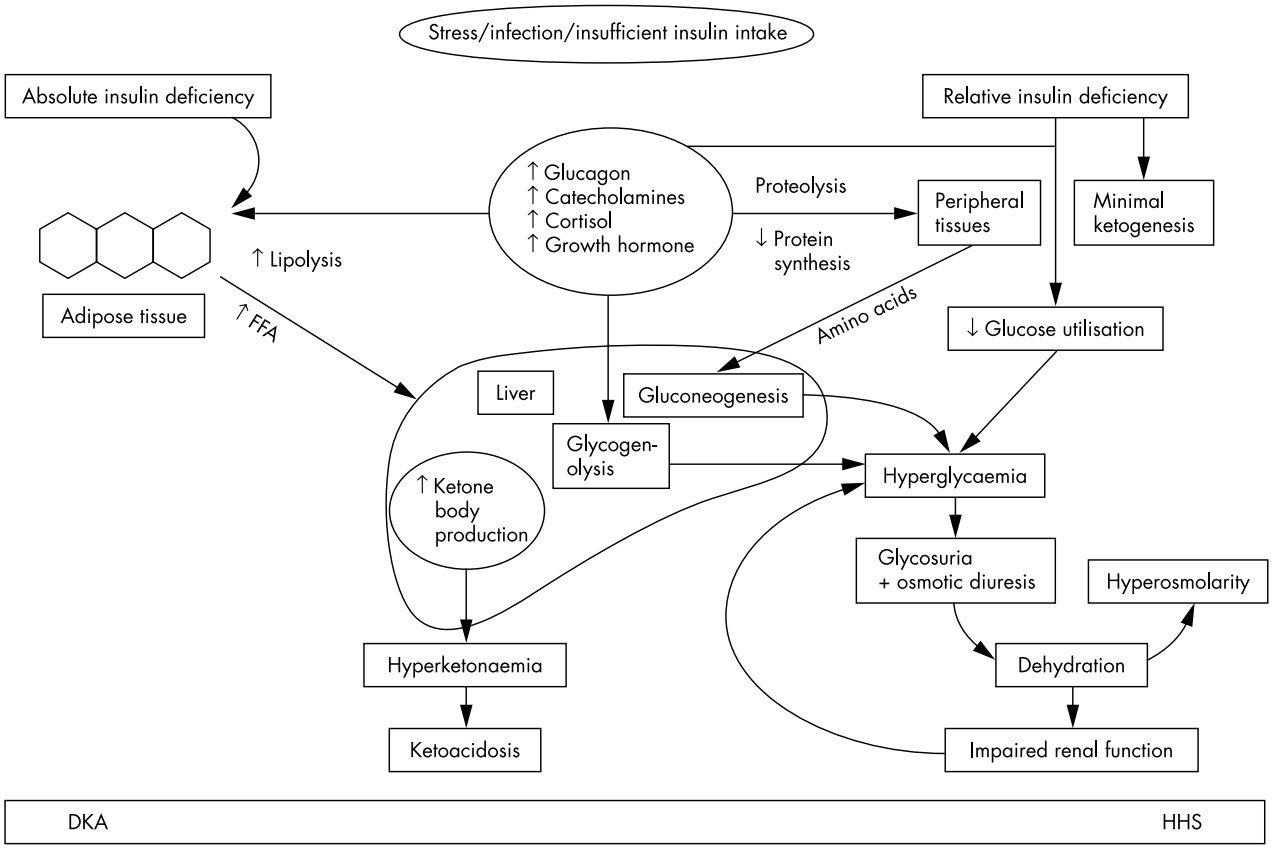

Figure 1 Pathogenesis of diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state (HHS) (FFA, free fatty acids).

excess. Potassium loss is exacerbated by acidosis, which leads to the displacement of this largely intracellular cation into the extracellular space from where it may be excreted in urine or lost in vomit. Furthermore, insulinopenia promotes intracellular proteolysis and also impairs potassium entry into cells, further enhancing the above shifts. Thus plasma potassium concentrations rise although whole body potassium levels fall, and this can lead to cardiac and skeletal muscle toxicity. This process is reversed rapidly on institution of appropriate therapy with insulin and fluid, leading to dramatic counter shifts in potassium and rapid falls in plasma potassium concentrations that are also potentially arrhythmogenic and demand close monitoring (see ''Management''). Phosphate and magnesium are also depleted in DKA, the effects of hypomagnesaemia potentially exacerbating the effects of hyper/hypokalaemia. Hyperventilation, fever, and increased sweating all contribute to further fluid losses and the fluid deficit averages six litres or more at presentation in adults.[4 5 26 27]

Table 3 Typical water and electrolyte deficits at presentation in diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state (HHS)

	DKA*	HHS*
Water (ml/kg)	100 (7 litres)	100–200 (10.5 litres)
Sodium (mmol/kg)	7–10 (490–700)	5–13 (350–910)
Potassium (mmol/kg)	3–5 (210–300)	5–15 (350–1050)
Phosphate (mmol/kg)	1–1.5 (70–105)	1–2 (70–140)
Magnesium (mmol/kg)	1–2 (70–140)	1–2 (70–140)

*Values in parentheses represent the total body deficit for a 70 kg patient. Table largely drawn from Lebovitz[27].

Presentation

DKA and HHS generally present in different ways, evolving over different time periods. DKA usually develops over a short time frame (<24 hours) in individuals with type 1 diabetes, although symptoms of poor diabetes control may have been present for several days. When DKA occurs in individuals with type 2 diabetes, then the precipitating illness is usually severe, although there are exceptions (see ''Precipitants''). The clinical picture commonly includes polyuria, polydipsia, dehydration, weakness, weight loss, and nausea and vomiting. Abdominal pain, potentially mimicking an acute abdomen, is a less common feature, occurring in approximately 46% of patients with DKA[30] but has not been reported in HHS; it is possibly related to dehydration of muscle tissue, delayed gastric emptying, and ileus resulting from acidosis and electrolyte imbalances. It is more common in those with more profound acidosis and typically resolves with resolution of DKA. Abdominal pain that fails to resolve within the first 24 hours should be investigated further.[30] Clouding of consciousness, which may progress to coma is also present in a number of cases, though loss of consciousness is reported to be present in <20% of those with HHS or DKA.[4 14 16 19] Physical examination may reveal Kussmaul respirations (rapid and deep respiration), tachycardia, hypotension, shock, and altered sensorium. The breath may have the odour of nail varnish remover, the result of acetone produced by the decarboxylation of acetoacetate in the liver.

HHS typically presents in overweight subjects with type 2 diabetes and has a more insidious onset with polyuria, polydipsia, and weight loss of several days or even weeks' duration. Mental obtundation and coma are more frequent[4] because of hyperosmolarity, and focal neurological signs (mimicking stroke) and seizures have also been described.[31–33]

Infection is a common precipitant of DKA and HHS, and a history of an infective illness may be obtained. An appropriate history should also pick up any of the other precipitants for DKA or HHS listed in table 2, with particular attention paid to cardiac causes and omission of medication.

The extreme metabolic disturbance of DKA can lead to laboratory and physical findings that may mislead the unwary and it is important to be aware of these pitfalls, which are summarised in box 2.

Management

The aims of DKA management are to correct the acidosis, hyperglycaemia, dehydration and electrolyte disturbance associated with the condition and to identify and treat any associated comorbid events. This requires appropriate and rapid clinical assessment and frequent monitoring of the patient; this demands regular review by the responsible doctors as well as other trained personnel.

After initial assessment, plasma glucose, urea, creatinine, and electrolytes; urinary ketones; arterial blood gases; and full blood count should be obtained, and intravenous fluid and insulin started. An electrocardiogram will be required in most cases, either to exclude a cardiac precipitant of DKA, if appropriate, or because of the potential for cardiac arrhythmias secondary to the large shifts in electrolytes, particularly potassium, with moderate or severe DKA. Blood and urine cultures and chest radiography should be performed as clinically indicated, though the fact that infection is a common precipitant and difficult to exclude (see box 2), particularly in moderate or severe DKA, means that they are frequently required. Urea, creatinine, electrolytes, and plasma glucose should be repeated two hourly for the first four hours and 2–4 hourly subsequently, depending on the patient's progress, with particular attention to potassium concentrations.

There is broad agreement across published guidelines for the management of DKA and HHS covering the above measures and including suggested rates of intravenous insulin infusion. However, there are some clear differences, notably among the suggested protocols for intravenous fluid administration.[5 26 27 34 35] We suggest a compromise between these positions.

Box 2: Diagnostic pitfalls in DKA

Sodium: whole body sodium is depleted but may appear:
- Raised due to dehydration.
- Normal.
- Low (see useful equations).

Potassium: whole body potassium depleted but may appear:
- Raised due to acidosis.
- Normal.
- Occasionally low.

Creatinine: ketone bodies interfere with some assays

White cell count
- Raised with DKA *per se* and thus not necessarily an indicator of infection.

Temperature
- Vasodilated (feel warm).
- Reduced core temperature.
- Cannot interpret temperature as marker of infection (or lack of infection).

Amylase
Pancreatitis can precipitate DKA but amylase is raised in the absence of pancreatitis in DKA (?salivary origin).

Triglycerides
Grossly raised triglycerides can cause pancreatitis and thus DKA but triglycerides are raised in DKA (FFA not taken up by liver $\pm$ adipose breakdown).

Urinary ketones
3-hydroxybutyrate concentrations in plasma are 2–3 times those of acetoacetate but in acidotic states this ratio is increased further.[5 26 81] As therapy improves acidosis, levels of acetoacetate rise and methods that measure only acetoacetate concentration is urine may therefore suggest that ketonaemia is worsening.

Intravenous fluid therapy

An average adult patient in DKA will have a deficit of 5–7 litres of water, 500–700 mmol of sodium, 200–350 mmol of potassium, 350–500 mmol of phosphate, and 200–350 mmol of chloride.[5 26] Intravenous fluid therapy should aim to correct these water and electrolyte deficits over the first 24–48 hours, expanding the intravascular and extravascular volume and restoring renal perfusion. The speed of replacement will depend on the patient's haemodynamic and cardiovascular status. This is assessed using clinical evaluation of jugular venous pressure and postural changes in blood pressure and heart rate. These changes, however, are difficult to interpret in the presence of suspected autonomic neuropathy (which is common in poorly controlled diabetes) or when the patient is using cardioactive or vasoactive medication (a common scenario in older diabetic subjects). This means that in most adults with moderate or severe DKA it is appropriate to assume a deficit of approximately five litres (three litres in mild DKA) and to be guided by the response to therapy. If the patient has significant cardiac disease, then central venous pressure monitoring is required in moderate/severe DKA.

Calculating plasma osmolality ($2\{[Na^+]+[K+]\}+[glucose]+[urea]$) can also be useful: plasma sodium >140 mmol/l and osmolality >340 mOsm/kg are associated with large fluid deficits, and plasma osmolality can be correlated with mental status. As stupor and coma are unusual with a plasma osmolality of <340 mOsm/kg,[5 36] another cause for altered conscious level should be sought if osmolality is below this level.

Infusion of 1–1.5 litres of 0.9% saline in the first hour is appropriate in most cases, though colloid should be considered if the systolic blood pressure is <100 mm Hg. Rates can be adjusted according to requirements subsequently (hydration status, electrolytes, urinary output) but will usually be in the region of 250–1000 ml/hour for the next four hours (4–14 ml/kg/hour). If corrected sodium concentrations are high (>155 mmol/l) after the initial 1–2 litres of 0.9% saline, then 0.45% saline should be considered with close monitoring of electrolytes.[5 37] European guidelines[34] are more circumspect about the use of hypo-osmolar solutions than the new American Position Statement and Technical Review[5 35] and recommend that, if used at all, no more than one litre of 0.45% saline should be given over eight hours.[34] Once plasma glucose falls to <14 mmol/l then 5% dextrose (10% dextrose if less fluid/more insulin required) should be started at 100–125 ml/hour and 0.9% saline continued at a slower rate to complete rehydration and electrolyte replacement. The recommendations of the American Diabetes Association[2] suggest that effective serum osmolality should not change by >3 mOsm/kg/hour and, although this may be hard to ensure, osmolality should be monitored regularly.

Although controversy persists over the speed of fluid replacement, these suggestions broadly fit those guidelines that are available,[5 34] those protocols used in trials with low mortality rates,[15] and even cover the suggestions for lower rate infusions put forward.[38 39] The key to management remains the accurate assessment of circulatory status and fluid losses, and close monitoring.

Potassium

Potassium replacement should commence as soon as hyperkalaemia is excluded or has disappeared with rehydration and insulin therapy. If potassium levels are between 3.3–5.5 mmol/l then give 20 mmol/hour of potassium[5 34] initially (this will equate to between 20–40 mmol potassium/litre of infused fluid in early stages of treatment). Aim to keep potassium >4.0 mmol/l by adjusting the infusion rate accordingly, and consider that 20–30 mmol potassium are likely to be needed in each litre of intravenous fluid. If potassium levels are <3.3 mmol/l at presentation then the patient is at risk of cardiac arrhythmia and respiratory muscle weakness with institution of insulin therapy. This should be withheld until plasma potassium has been corrected by infusion of potassium at 40 mmol/hour.[5] If potassium is >5.5 mmol/l then potassium should be omitted until plasma concentrations are within the target range.[34] Continuous electrocardiographic monitoring should be instituted with therapy.

Insulin therapy

Insulin therapy should be started as a continuous intravenous infusion of six units per hour of fast acting insulin as soon as the diagnosis is made (see fig 2). If there is to be any significant delay in instituting this infusion and potassium levels are >3.3 mmol/l, then 10 units (or less if hyperglycaemia is not marked) of fast acting insulin, injected intravenously or intramuscularly, is appropriate initial therapy. The aim is to bring plasma glucose concentrations down by 3–5 mmol/l/hour. If plasma glucose does not fall by 3 mmol/l in the first hour, then infusion lines and hydration status should be checked. If the lines are patent and the hydration status appropriately treated, then the dose of insulin may be doubled. When plasma glucose levels are ⩽14 mmol/l the rate of insulin infusion may be decreased (we suggest to three units an hour) and intravenous dextrose started as outlined above. Insulin and glucose infusions should be adjusted to maintain plasma glucose between 8–12 mmol/l until the acidosis has resolved when regular insulin therapy may start if the patient is able to eat and drink. Intravenous insulin should continue for 30 minutes after the administration of the first dose of subcutaneous insulin.

If working in a location where continuous intravenous insulin infusion cannot be administered the American Diabetes Association position statement suggests that 0.4 units of fast acting insulin/kg body weight be given, half as an intravenous bolus, half subcutaneously or intramuscularly, and then that 0.1 units/kg are given intramuscularly each hour until plasma glucose is less than 14 mmol/l. At this stage 5–10 units of fast acting insulin are administered every two hours, with concomitant dextrose infusion, until normal insulin can be started.[35] It should be stressed, however, that the studies with the lower mortality rates have all been conducted in centres using intravenous insulin infusion.

Bicarbonate

Bicarbonate remains a controversial treatment in DKA. Those studies of bicarbonate therapy performed in individuals with pH >6.9 have failed to demonstrate any benefit.[40–42] No prospective randomised studies of patients with pH ⩽6.9 have been performed and some still advocate its use in this situation because of theoretical benefits on cardiac and respiratory function.[5] However, there is little clinical evidence to support this approach and one study performed on acidotic patients (due to differing causes) on an intensive care unit demonstrated no haemodynamic improvement, despite increases in blood pH with bicarbonate therapy.[43] Disadvantages include an increased incidence of hypokalaemia,[44 45] hypocalcaemia, paradoxical cerebrospinal fluid acidosis,[44 46 47] worsening intracellular acidosis,[11 48 49] and hypoxia.[44 50] More sinister is an association between bicarbonate use and cerebral oedema outlined in a recent study.[51] Furthermore, there is evidence that bicarbonate therapy augments ketone production and can actually delay the improvement in ketosis produced by appropriate insulin and fluid administration. It might therefore be best reserved for those with impending cardiovascular or respiratory collapse, and prospective randomised trials are long overdue in this area. If administered in a patient with pH <6.9, 100 mmol of sodium bicarbonate infused with 20 mmol potassium chloride over 30 minutes is the recommended dose,[5 34] with serial monitoring of calcium and potassium.

Phosphate

Enhanced urinary phosphate excretion in DKA commonly leads to hypophosphataemia. Complications related to hypophosphataemia are rare unless the condition is severe (phosphate <0.35 mmol/l) but include respiratory and skeletal muscle weakness, haemolytic anaemia, and reduced cardiac systolic function. Routine phosphate replacement has not been shown to be clinically beneficial[52–54] and so replacement should only be considered in those with anaemia, cardiac dysfunction or respiratory depression and hypophosphataemia, or those with severe hypophosphataemia. If phosphate is administered, replacement with 20 mmol phosphate added to one litre of replacement fluid is appropriate, while care is taken to avoid hypocalcaemia.

General measures

General measures to be taken are:

- Passage of a nasogastric tube if the patient is unconscious or drowsy and vomiting.
- Passing a urinary catheter if the patient has not passed urine for more than three hours or is obtunded.
- Heparinisation for those who are hyperosmolar or comatose,[34] although there is a lack of formal studies on this issue.

There are no randomised studies assessing the impact of the location of care (intensive care unit, high dependency unit, emergency medical unit, diabetes specialty ward, or general medical ward) on the outcome of DKA or HHS. Accordingly this choice must be based on the available hospital resources and known prognostic indicators. Patients with DKA need intensive monitoring, and therapy with prompt access to diagnostic and laboratory services and these must be available whichever management site is chosen. Interestingly, the use of standardised written guidelines appear to be more important in determining outcome than the type of hospital or the specialty of the attending physician,[9 14 18 55–58] though implementation of the guidelines may not always be as straightforward as it sounds.[59] In these studies,[9 14 18 55–58] and in a UK study[13] mortality rates for DKA were <5% and those for HHS ≈15%; most deaths occurred in patients over 50 years of age and were secondary to severe concomitant illnesses. Increasing age, severity of concomitant illness, severity of acidosis, or the presence of HHS are persuasive factors in arguing for management on an intensive care or high dependency unit.

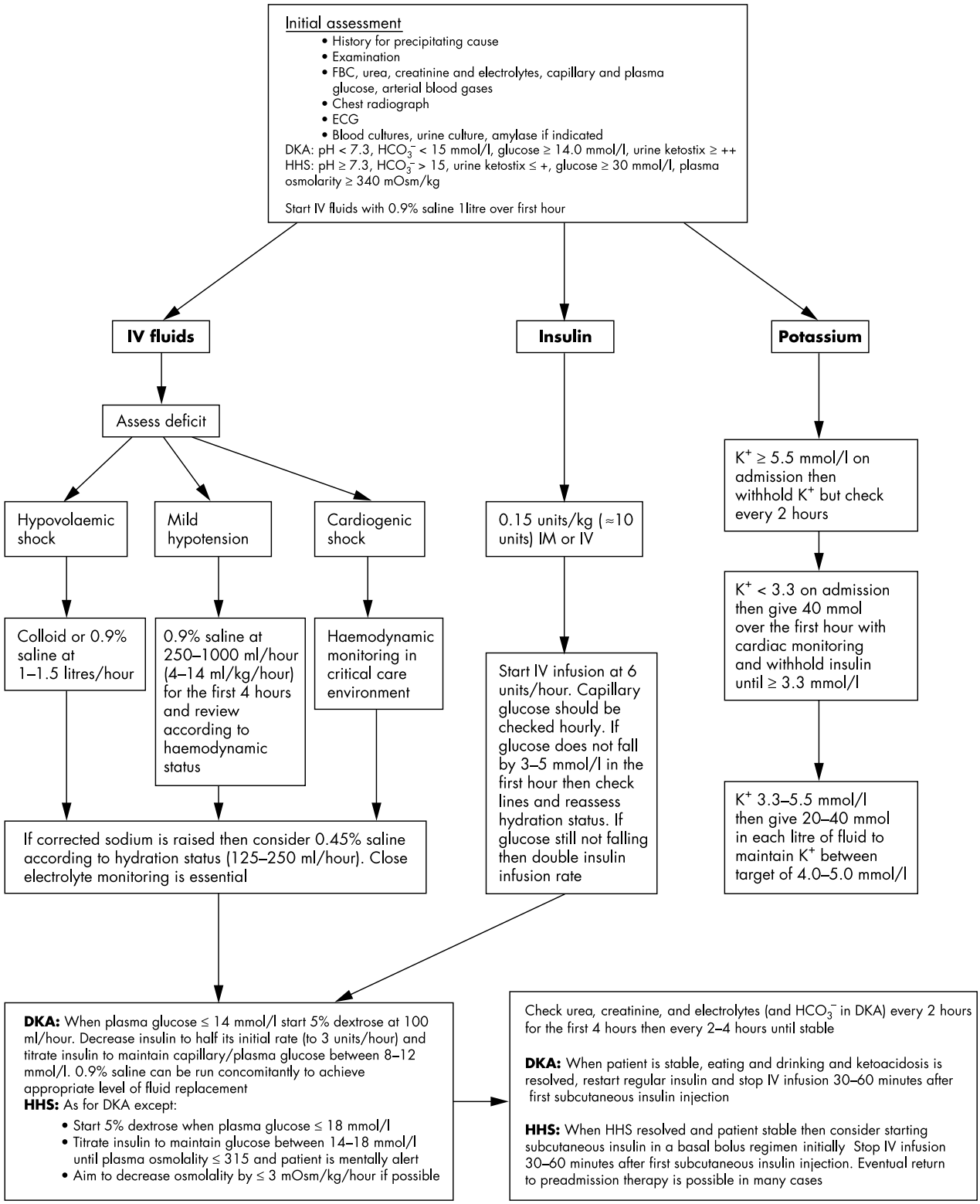

Figure 2 Treatment algorithm for patients admitted with diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state (HHS) (ECG, electrocardiogram; FBC, full blood count; HCO_3^-, bicarbonate; K^+, potassium; IM, intramuscular; IV, intravenous).

Complications

Cerebral oedema is an uncommon but devastating complication of DKA, which primarily occurs in children and adolescents. It occurs in approximately 1% of childhood DKA episodes and has a mortality of 20%–90%.[51 60–64] It usually presents in the 2–24 hours after the start of therapy with headache, incontinence, and behavioural changes followed by abrupt neurological deterioration and coma. The aetiology is still unclear though recent hypotheses suggest that, as extracellular fluid hyperosmolarity and dehydration increase, the brain accumulates intracellular, osmotically active molecules (including glucose and unidentified molecules collectively

termed "idiogenic osmoles") that maintain cellular volume.[65–67] In addition intracellular acidosis (possibly exacerbated by the passage of ketone bodies into cells as well as hypoxia) leads to intracellular sodium accumulation as hydrogen is extruded from the cells by the sodium/hydrogen membrane pump. If extracellular osmolarity falls at a rate exceeding that at which the brain can excrete its accumulated idiogenic osmoles, then oedema occurs.[65–67]

The idea that the treatment of DKA itself might be the cause of cerebral oedema has gained support over the years, but no single aspect of therapy has been implicated in studies to date and cerebral oedema has been shown to be present before treatment even begins.[51 68] Low partial pressures of arterial carbon dioxide, high serum urea, and bicarbonate therapy are the risk factors most predictive of cerebral oedema,[51] though these may merely reflect the severity and duration of DKA in those who subsequently develop this complication.[66] Management is by prompt recognition and the use of intravenous mannitol, though the available data suggest that this treatment fails to reverse neurological dysfunction before the development of coning and subsequent respiratory arrest in 50% of patients and is nearly 100% unsuccessful after respiratory arrest.[62]

Hypoxaemia attributed to a reduction in colloid osmotic pressure and a subsequent increase in lung water content and decrease in lung compliance may complicate therapy of DKA and may precede pulmonary oedema or the development of adult respiratory distress syndrome.

The most common complications, however, remain hypoglycaemia and hypokalaemia as a result of therapy, though these should be only temporary if appropriate monitoring is in place.

Prevention

Improved education and effective communication with those with diabetes is essential in preventing admissions with DKA/HHS. Individuals should be taught about sick day management with information provided as to:

(1) When to contact a health care provider.
(2) Blood glucose goals and use of supplemental insulin during intercurrent illness. Everyone should be told that they should never discontinue their insulin and that they should contact a health professional early in the course of an illness. Insulin requirements may be increased in ill people with diabetes, even if they are not eating very much.
(3) Initiation of an easily digestible liquid diet containing carbohydrates and salt when usual intake is not possible.
(4) When to increase the frequency of blood glucose monitoring (monitoring up to seven times a day is recommended in acute illness).

Caregivers will also need education on these matters in many instances.

As mortality rates from DKA are declining with increasing availability of high quality healthcare, incidence rates remain at 4.6–8 episodes per 1000 patients with diabetes per year[17]; improved preventative measures will hopefully reduce the impact of this serious and life threatening complication.

LACTIC ACIDOSIS

Definition

Severe lactic acidosis is defined as a high anion gap metabolic acidosis (anion gap $\geq$10, as calculated using equation in box 1) with a blood lactate concentration $>$5.0 mmol/l (normal 0.4–1.2 mmol/l). The pathological elevation of lactate and hydrogen ions may result from overproduction or delayed clearance of lactate, or a combination of both.

Box 3: Useful websites

- http://www.diabetes.org—American Diabetes Association (detailed guidelines for management of hyperglycaemic crises available on this site).
- http://www.diabetes.org.uk—Diabetes UK.
- http://www.joslin.harvard.edu/—Joslin diabetes centre.
- http://www.staff.ncl.ac.uk/philip.home/guidelines—Transnational diabetes guidelines from the International Diabetes Federation (European Region) on behalf of the St Vincent Declaration Initiative of IDF (Europe)/WHO (Regional Office for Europe), including guidelines for management of diabetic ketoacidosis.

Pathogenesis

Anaerobic glycolysis results in the production of lactate and hydrogen ions, which are extracted by the liver, kidneys, and heart under normal aerobic conditions, and either oxidised completely to carbon dioxide and water, or entered into the gluconeogenic pathway. Lactic acidosis may be classified according to the presence or absence of hypoxia (see table 4).

Type A lactic acidosis (anaerobic/hypoxic) occurs in states of profound tissue hypoxia such as myocardial infarction, cardiogenic shock, or profound sepsis. In this situation, anaerobic metabolism produces excess lactate that swamps the body's capability to clear it and clearance of lactate may also be decreased. This situation is not peculiar to diabetes but people with diabetes (particularly type 2 diabetes) are at increased risk of hypoxic cardiovascular complications.

Type B lactic acidosis (aerobic) is rarer and is associated with a number of systemic diseases (including diabetes), drugs, toxins, and inborn errors of metabolism. The biguanides metformin and phenformin, used in the treatment of type 2 diabetes, have both been associated with the development of type B lactic acidosis. Phenformin was withdrawn from the market because of this complication; the incidence of lactic acidosis is much lower with metformin, with an estimated incidence of 0.03 episodes per 1000 patient years.[69]

Metformin associated lactic acidosis may be either type A lactic acidosis, where the acidosis is the result of concurrent complicating illness without the accumulation of metformin; type B arising from marked metformin accumulation without concurrent hypoxic factors; or mixed, resulting from a combination of the above factors. Ninety percent of absorbed

Table 4 Causes of lactic acidosis

Type A (anaerobic/hypoxic)	Type B (aerobic)
Shock:	Systemic disease:
Cardiogenic	Diabetes
Endotoxic	Neoplasia
Hypovolaemic	Liver disease
Cardiac failure	Drugs/toxins:
	Biguanides
Asphyxia	Ethanol
	Methanol
Carbon monoxide poisoning	Salicylates
	Inborn errors of metabolism:
	Type 1 glycogen storage disease
	Fructose 1,6-diphosphatase deficiency

Adapted from Stacpoole *et al*.[80]

Box 4: Top five articles in last five years

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metformin is excreted unchanged by the kidneys[69 70] and so it is renal function that determines metformin clearance. The principal contraindication to using metformin is renal impairment: the American Diabetes Association recommends avoiding metformin use if serum creatinine concentration exceeds 125 μmol/l.[71]

Because of the accumulation of lactate in hypoxia, metformin is also contraindicated in conditions such as uncontrolled heart failure that predispose to lactic acidosis.[72]

Presentation

Clinical presentations of lactic acidosis are non-specific, and include hyperpnoea (Kussmaul respiration), nausea, vomiting, diarrhoea, epigastric pain, anorexia, lethargy, thirst, and decreased level of consciousness. Hypotension, hypothermia, cardiac dysrhythmias, and respiratory failure may also occur in severe metformin-associated lactic acidosis.[73–75] Blood glucose levels may be low, normal, or high in diabetic subjects and lactic acidosis may also accompany ketoacidosis.

Management

Treatment of lactic acidosis includes appropriate supportive care (usually on an intensive care unit), treatment of any concomitant condition and elimination of any offending drug by renal excretion or dialysis. Bicarbonate therapy is still one of the principal management modalities for lactic acidosis[70 76] despite conflicting reports as to its efficacy and even reports of potential adverse consequences[77] including the lowering of mixed venous pH and intracellular pH when it is used to treat metabolic acidosis associated with concurrent tissue hypoxia.[48 49 78] Metformin is a dialysable drug and the use of bicarbonate in combination with haemodialysis has been successful in the management of metformin associated lactic acidosis.[70 73 77] Other experimental approaches include the use of dichloroacetate, which activates pyruvate dehydrogenase, reducing intracellular lactate formation and increasing lactate disposal. Unfortunately, despite initially promising results,[79] controlled trials have shown no improvements in haemodynamics or survival in acidotic patients treated with this drug.[80] The use of Carbicarb (sodium bicarbonate and sodium carbonate in equimolar mixture) and THAM (an amino alcohol) is similarly experimental.[77] Despite these management measures the prognosis in lactic acidosis of all causes is poor with only between 12%–17% of patients surviving to discharge in one well conducted study.[80]

In summary, general management of the underlying condition, appropriate supportive care, bicarbonate therapy and haemodialysis are the key approaches to the management of severe lactic acidosis but further trials are needed before we can be clear as to what represents optimum care.

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