further our understanding of the factors which control and influence the development of both health and disease in the human.

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MANAGEMENT OF HYPERGLYCAEMIC EMERGENCIES*

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Acute metabolic decompensation of diabetes leading to life-threatening hyperglycaemia and dehydration with or without ketoacidosis continues to occur commonly despite higher awareness amongst the general public, health care professionals and people with diabetes. Data from the USA suggests an annual incidence of diabetic ketoacidosis (DKA) of 3 to 8 episodes per 1000 patients with 20–30 per cent of new cases presenting in ketoacidosis.[1] A rate of 1.3–2 episodes per 100 patient years was reported by the Diabetes Control and Complications Trial Research Group.[2] The frequency of hyperosmolar non-ketotic coma is about 10 per cent that of ketoacidosic coma. Mortality remains considerable at 5–10 per cent and has changed little over the last 20 years. A significant proportion of deaths are avoidable with careful and experienced management.[3] Some deaths particularly in non-ketotic hyperglycaemic emergencies, are due to the underlying precipitating illness rather than the metabolic upset and there is considerable increase in mortality in the elderly.[4]

PATHOPHYSIOLOGY

The hallmark of diabetic ketoacidosis and non-ketotic hyperglycaemia is an absolute or relative deficiency of circulating insulin. In C-peptide negative diabetic patients, lack of insulin leads to a rapid rise in hepatic glucose output,[5] with an initial fall in insulin-dependent peripheral glucose uptake due to a failure to mobilise GLUT-4 glucose transporters.[6] Blood glucose concentrations rise until glucose disposal again equals glucose input.[5] This occurs at around 16 mmol/l. The fall in insulin-dependent glucose utilisation is compensated for by concentration driven glucose uptake which is insulin-independent and by glycosuria. Further rises in blood glucose concentration occur due to the stimulation of gluconeogenesis and inhibition of peripheral glucose uptake by cortisol, the catecholamines and glucagon acting as counter-regulatory hormones. Glucagon is of particular importance; circulating levels rise in insulin deficiency despite hyperglycaemia,[7] the rises in cortisol and catecholamines occur later. Hyperglycaemia *per se* decreases peripheral glucose utilisation[8,9] and residual insulin secretion,[10] creating a vicious cycle of increasing plasma glucose concentration. Hyperglycaemia leads to dehydration, and eventually hypotension, as well as loss of electrolytes through osmotic diuresis. The dehydration further worsens the hyperglycaemia through poor tissue perfusion, reducing glucose uptake further, and delaying absorption of any remaining subcutaneous insulin.

Insulin deficiency coupled to high circulating levels of counter-regulatory hormones results in unrestrained lipolysis, with a large increase in the supply of non-esterified fatty acids (NEFA) to the liver. Lack of insulin and high glucagon levels combine to switch NEFA metabolism from re-esterification to oxidation,

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with a subsequent rise in ketone body production. Insulin withdrawal studies have demonstrated a continuous rise in plasma ketone levels for 10 h,[11] the level of ketone bodies and NEFA correlating with glucagon concentration.[7,11] It is unclear why ketoacidosis is not a prominent feature of non-ketotic hyperglycaemia, as most report that circulating levels of insulin and glucagon are similar to those observed in ketoacidosis.[12] Malchoff *et al.*[13] suggests that small but finite concentrations of circulating insulin are sufficient to damp down lipolysis. It is possible that the extreme hyperglycaemia and hyperosmolality commonly seen in non-ketotic hyperglycaemia *per se* inhibit lipolysis and ketogenesis.[14] It is worth commenting that non-ketotic and ketotic hyperglycaemia form a continuum with ketone body levels above normal even in the 'non-ketotic' form. It could be that in non-ketotic hyperglycaemia there is a much more rapid rise in glucose levels because of poor renal function or continued high carbohydrate intake, thus representing an earlier stage of metabolic decompensation.

PRESENTATION

Symptoms and signs. In their extreme forms, diabetic ketoacidosis and non-ketotic hyperglycaemia progress to altered consciousness and eventually coma, but less than 10 per cent of patients now present in coma. The majority have symptoms of polyuria, nocturia, thirst and polydipsia and marked signs of dehydration. Ketoacidosis often results in nausea, vomiting and sometimes severe abdominal pain, particularly in the young, whilst the breathing is generally deep and rapid, with the characteristic odour of acetone. There is often hypotension with a tachycardia and a warm skin but decreased core temperature. This is secondary to the acidaemia which has a negative inotropic effect and at the same time causes peripheral vasodilation. Particularly in older patients, symptoms and signs of the underlying precipitating cause may over-ride those of the metabolic upset, or the presentation may be one of a non-specific general deterioration of health. Occasionally in hyperosmolar non-ketotic states, focal neurological signs may be present which resolve completely as the metabolic state returns to normal.

Precipitating factors. The importance of the most common precipitating factors of the hyperglycaemic emergencies, namely infection, other intercurrent illness and failure of insulin delivery, varies with the population studied. World-wide, infection remains the commonest underlying cause.[1,15] Any intercurrent illness, particularly vascular events in older patients, may lead to metabolic decompensation, while problems post-operatively, in pregnancy and with particular drugs are occasional causes. Malfunction of a mechanical insulin-delivery device may precipitate hyperglycaemia, particularly if the problem is not recognised early.[16,17] A significant proportion of cases are accounted for by a small number of patients with repeated episodes.[18,19] These are either young, generally female, patients with severe psychological problems who omit insulin, or elderly, infirm patients who lack appropriate supervision.

Diagnosis. In the classical picture of diabetic ketoacidosis, the diagnosis is obvious but a high index of suspicion is necessary particularly in the elderly and in the non-ketotic, who may present with non-specific symptoms. Euglycaemic keto-acidosis is possible[20] and is associated with fasting in the prodromal period.[21] The diagnosis can be made rapidly by measuring capillary blood glucose concentration at the bedside and testing plasma or urine, if available, for ketones with a dipstick. Laboratory confirmation of hyperglycaemia and acidosis should be sought quickly, together with measurement of serum electrolytes, bicarbonate, and creatinine and arterial or capillary pH, pO_2 and PCO_2. Serum osmolality can be calculated from the formula: $2 \times [Na^+ + K^+] + \text{glucose} + \text{urea} = \text{mOsm/l}$. A search for any precipitating cause should be undertaken (Table 1).

TABLE 1
Initial investigations to identify a precipitating cause of metabolic decompensation

Throat swab
Urine microscopy and culture
Blood culture
Chest X-ray
Electrocardiogram

MANAGEMENT

The main requirements in the treatment of hyperglycaemic emergencies are rehydration, correction of the electrolyte imbalance and steady reversal of the disturbed intermediary metabolism. Assiduous attention to detail is vital. In the early days of insulin treatment, constant medical attendance at the bedside was deemed necessary.[22] Today, no-one would demand such dedication, but the principle of frequent medical review by experienced staff remains paramount.

Fluids

The water deficit is on average 5 to 8 l but may be more, particularly in hyperosmolar non-ketotic coma. In the osmotic diuresis, more free water is lost than sodium, but none-the-less, the average loss of sodium is 400–800 mmol. Despite this, serum sodium is commonly low at presentation. The concentration is artefactually lowered by haemodilution associated with the rising serum glucose, a 3 mmol/l rise in glucose above 5 mmol/l resulting in an apparent lowering of the serum sodium by 1 mmol/l.[23] Thus in a subject with a blood glucose concentration of 56 mmol/l and a measured sodium of 130 mmol/l, the 'true' sodium will be 147 mmol/l.

Adequate, prompt rehydration is vital. This will raise blood pressure, improve blood flow to peripheral tissues such as muscle, allowing even low levels of circulating insulin to have an effect in promoting glucose uptake, reduce the level of circulating counter-regulatory hormones and re-establish the renal circulation, Effective rehydration without insulin treatment lowers serum glucose concentrations significantly, with as much glucose being lost in the urine as is metabolised,[23] but without affecting the acidosis[25,26]

There is still controversy over the type and rate of fluid administration. Over the last 30 years, the emphasis has been on rapid rehydration with isotonic fluids, guidelines suggesting that 8 l of fluid should be administered in the first 24 h, with half this amount being given within the first 4 h.[27] However, recent concerns over complications, which may be related to rapid fluid delivery, especially cardiac failure, hypernatraemia, cerebral oedema and adult respiratory distress syndrome (ARDS), have lead to reappraisal. In a comparison of 2 fluid

regimens, one giving 1 l isotonic saline per hour for 4 h followed by 500 ml/h for 4 h, the second giving fluid at half these rates, plasma glucose fell at the same rate in the two groups, whilst plasma bicarbonate and the anion gap recovered more rapidly with the slower infusion rate, and predictably, sodium and chloride concentrations rose less.[28] Thus more cautious fluid replacement than has previously been recommended may be beneficial, particularly in the elderly where congestive cardiac failure is commonly encountered with standard therapy.[29].

Perhaps more controversial has been the type of fluid infused. On the grounds that more water than sodium is lost in the osmotic diuresis, it has been argued that hypotonic saline reduces the risks of worsening hypernatraemia and hyperosmolality seen with infusion of isotonic saline. However, isotonic saline is hypotonic to the hyperosmolar plasma in DKA and there are risks of circulatory collapse, cerebral oedema and ARDS if the serum osmolality falls rapidly and water is lost from the intravascular space. Conflicting studies on the relationship of the rate and type of fluid replacement to the development of cerebral oedema continue to appear.[30,33] Of note is the fact that hypotonic and uneven fluid administration, particularly rapid early rehydration[33] was associated with a persistently low sodium which in turn was associated into cerebral oedema.

On balance we feel there is enough evidence to suggest that initial resuscitation should be carried out with isotonic and not hypotonic fluid. The exception is when the initial plasma sodium concentration exceeds 150 mmol/l, which occurs particularly in hyperosmolar non-ketotic coma. In such cases 0.045 molar saline should be given, but slowly. If the plasma sodium rises to 155 mmol/l this can be safely replaced with 5 per cent dextrose in water. The rate of replacement should not exceed 500 ml/h unless the patient is shocked (Table 2).

TABLE 2
Guidelines for fluid replacement in hyperglycaemic emergencies

First hour	1 l isotonic saline
Second hour	500 ml isotonic saline
Third hour	500 ml isotonic saline
Thereafter	250 ml isotonic saline per hour until rehydration complete

If persistently hypotensive or oliguric, give colloid or blood.
If serum sodium >150 mmol/l initially, or rises to >155 mmol/l during treatment, use hypotonic fluid (0·045 mmol/l saline or 5 per cent dextrose in water).

Insulin

Historical aspects. Before the advent of insulin, ketoacidosis was almost invariably fatal, although spontaneous recovery following treatment with fluids, alkali, cardiac stimulants and dietary restriction was occasionally reported.[34,35] Initially, the doses of subcutaneous insulin given were governed by its availability.[36] With free supply doses increased rapidly. In his report of 15 cases in 1923, Foster described a dosage range of 70 U in 6 h to 180 U in 12 h.[36] In the fear that continuing high mortality was due to 'insulin resistance' and inadequate treatment, doses continued to escalate through the 1930's and 1940's; 'fearless use of large doses of insulin' was recommended.[37] Standard initial doses of 25–100 U were given, depending on the patient's age, severity of acidosis, previous insulin administration, the degree of coma and presence of infection. In severely ill patients, this large dose was repeated every half hour until clinical and biochemical improvement was observed. Thereafter, doses of 10–20 U were given one to two hourly depending on the degree of glycosuria. Doses given in the first 24 h ranged from 154 U in 1923–1925 to around 200 U in the 1930's and over 600 U in the 1950's.[22,38–43] However, much larger doses, several thousand U in the first 24 h, were recommended in extremely ill 'insulin resistant' patients.[22,41] When intravenous therapy became commonplace, doses rose even higher, initial amounts of 200–400 U followed by 50 U every 30 min, with large amounts of intravenous fluids, apparently improving outcome.[44,45]

Advent of low-dose therapy. Despite the above dogma, several early authors tempered their enthusiasm for vast doses, reporting that frequent, smaller doses of around 50 U were equally effective as larger doses given at longer intervals.[46] A group in Germany from 1946 onwards showed good results with very frequent SC, IM and IV boluses of 4–10 U,[47,48] but no controlled comparisons were performed. In 1954, a randomised study showed no difference in mortality rate or in rates of improvement of biochemical indices in groups given 80, 160 or 240 U insulin subcutaneously every 2 h,[49] In a later paper, 'smaller' doses given by intravenous infusion, 50 U priming followed by 50 U/h, were successfully used.[50] However, this work was largely ignored until the early 1970's. In 1972, in work done primarily to observe the effects of insulin on serum growth hormone, Sonksen *et al.*[51] demonstrated that variable rates of continuous intravenous infusion of insulin, chosen to produce serum levels of 20–180 μU/ml, resulted in similar rates of fall of blood glucose. This lead to the use of low dose intramuscular injection therapy as a 'poor man's' IV infusion, based on the known absorption kinetics of insulin.[50] This proved strikingly effective. An initial loading dose of 10–20 U followed by hourly doses of 5–10 U produced a predictable fall in plasma glucose of around 5 mmol/l/h and a satisfactory rate of recovery from keto-acidosis. Confirmation of the effectiveness of this treatment quickly followed.[53] A randomised trial confirmed that low-dose intermittent intramuscular injection therapy corrected hyperglycaemia as quickly as high-dose combined subcutaneous and intravenous injection therapy, with less hypokalaemia and hypoglycaemia.[54]

Three papers then quickly appeared to attest to the success of low-dose continuous intravenous insulin therapy in diabetic ketoacidosis, with doses ranging from 2·4 to 7·2 U/h.[55–57] Despite many reports, albeit uncontrolled, of successful management using low-dose therapy, doubts persisted, especially about the efficacy of low-dose insulin in the face of 'insulin resistance' and calls came for controlled trials. A prospective study confirmed that low-dose (6 U loading dose, followed by 6 U/h) intravenous infusion gave similar results in terms of reduction of hyperglycaemia as high-dose intravenous/subcutaneous injection therapy, but was easier to use, gave a predictable fall in glucose and could be stopped abruptly if hypoglycaemia developed.[58] In children, low-dose continuous intravenous insulin infusion (0·1 U/kg/h) corrected hyperglycaemia more slowly but keto-acidosis at a similar rate, and results in less hypoglycaemia and hypokalaemia than high-dose (1·0 U/kg/h) infusion.[59] Low dose IM insulin is also effective in children.[60]

Further work confirmed the effectiveness of low-dose insulin given by the intravenous, intramuscular or subcutaneous routes, but demonstrated that, as one might expect, the fall in blood glucose and ketone bodies was faster in the first

two hours of treatment with intravenous insulin in ketoacidotic[61] and non-ketotic hyperglycaemic patients.[62] In all other respects, low-dose intramuscular insulin and continuous low-dose intravenous infusion, both preceded by loading doses, are equally effective in treating ketoacidosis.[63] The loading dose is almost certainly unnecessary with the IV regime. The amount of insulin given is of the order of 6–12 U/h. In several large series, this dose has been sufficient to treat almost all patients, only a small minority requiring larger doses. Even in severely ill, comatose patients with extreme hyperglycaemia, the rate of decline in plasma glucose with low-dose therapy is generally satisfactory, as are other responses to therapy.[64] A poor response is as likely to be due to inadequate rehydration and tissue perfusion as insufficient insulin.

Current practice. Where facilities are available, it is our practise to use intravenous insulin, initially at 6 U/h, without a loading dose. Initial rehydration is in any case the main factor in lowering the blood glucose in the first hour. This rate of infusion is continued until the blood glucose reaches 13–14 mmol/l, at which point the infusion rate is reduced to 4 U/h and infusion of 10 per cent glucose in water, 80 ml/h, is begun. Saline may be continued if the patient is still very dehydrated. The use of 10 per cent rather than 5 per cent dextrose is associated with more rapid clearing of ketones and restoration of pH to normal.[65] It must be appreciated that hyperglycaemia may resolve rapidly eg in 3–6 h whilst metabolism of ketone bodies may take 15 h or more,[66] thus necessitating continued infusion of insulin, to allow utilisation of ketone bodies, covered with glucose to prevent hypoglycaemia. If an infusion pump is not available, the intramuscular route is used, with an initial loading dose of 20 U followed by 6 U/h. Again, when the blood glucose falls to around 13–14 mmol/l, the dose of insulin is reduced to 5 U IM every hour and infusion of 10 per cent glucose begun as above. Thereafter, the rate of glucose infusion is kept constant and the insulin dose adjusted to maintain blood glucose between 10–12 mmol/l. Striving for normoglycaemia within the first 24 h is not necessary and may be dangerous (Table 3).

TABLE 3
Insulin administration regimens for hyperglycaemic emergencies

Diabetic Ketoacidosis	
Adults	
Intravenous	6–8 U/h as 1 U/ml in saline pump or paediatric giving set
Intramuscular	20 U loading dose then 6 U/h
Children	
0·1 U/kg body weight/h either as continuous IV infusion of IM injection	
Hyperosmolar non-ketotic coma	
Intravenous	3–4U/h
Intramuscular	10 U loading dose, then 4 U/h

If blood glucose does not begin to fall within 2 h of starting treatment, the general condition of the patient should be reviewed, particular care being taken to assess circulatory status, hydration and presence of infection. In addition, the infusion system should be carefully examined. If all of these are satisfactory, the insulin dose should be doubled. If IM insulin is being used a switch to IV insulin should be made. The successful use of insulin-like growth factor 1 (IGF-1) for the treatment of severe insulin-resistant DKA has been reported, although it is very rarely likely to be necessary.[67]

In non-ketotic hyperglycaemia, less insulin is said to be required, although we use the same amounts as for DKA.

Transfer to subcutaneous insulin. When the patient begins to feel like eating, fluids and light solids should be given with continuation of intravenous or intramuscular insulin. If this has no adverse effects, subcutaneous insulin should be given before the next full meal and the intravenous infusion of insulin stopped 30 min later. This overlap allows time for absorption of the subcutaneous dose to begin. It is best to begin subcutaneous insulin as short-acting insulin before each of the three main meals, with intermediate-acting insulin in the evening, thus allowing more frequent dosage adjustment. Initial doses are in the range 6–12 U before meals and 10–20 U before bed. Many patients who present with non-ketotic hyperglycaemia may manage without insulin in the long-term, but it is safer to continue insulin for several weeks after the acute event.

Potassium

Despite the large total body deficit of 500–1000 mmol of potassium, the initial serum potassium may be high, normal or low. Those with low or normal levels have probably managed to maintain hydration and therefore renal flow, thus allowing continued loss of potassium in the urine. The cause of the intracellular potassium depletion has been blamed on the acidosis, as well as on insulin deficiency *per se*, although this may be too simplistic a view. Infusion of mineral acids causes potassium displacement from cells[68] but infusion of organic acids does not.[69] It may be that organic acids diffuse into cells readily, so that potassium exchange is not required to maintain ionic balance.[70] In a large study analysing the factors determining initial plasma potassium concentration in ketoacidosis, plasma glucose, pH and anion gap had independent effects.[70] Thus ketoacidaemia and hyperglycaemia, both obviously secondary to insulin deficiency, are the main determinants of plasma potassium, with pre-renal azotaemia contributing by preventing potassium loss in urine. Intracellular fluid loss will also contribute greatly to the total body potassium loss.

Whatever the initial potassium concentration, it invariably falls rapidly when treatment is begun, due to intra and extracellular rehydration, continued loss in the urine, reversal of acidaemia and to direct action of insulin on potassium transport into cells. Effective management of hyperglycaemia therefore requires adequate potassium replacement. Provided renal function is normal, the risk of hypokalaemia far outweighs the risk of hyperkalaemia. It is therefore sensible to begin cautious potassium replacement, 20 mmol/h of potassium chloride, at the time of beginning insulin and rehydration. It can be stopped if the first laboratory value comes back at 5·5 mmol/l or greater, or there are obvious signs of hyperkalaemia on the ECG. Thereafter, the rate of replacement is governed by the serum level, electrocardiographic monitoring and urine output. It may be necessary to infuse as much as 40–80 mmol/h, well diluted in large volumes of rehydrating fluid. It is probably wise to continue oral supplementation for several days after intravenous therapy has ceased.

Bicarbonate

In diabetic ketoacidosis the presence of high concentrations of acetoacetate and 3-hydroxybutyrate imply that there is a large load of potential alkali awaiting metabolism with effective treatment. This, plus the potentially detrimental effects of giving bicarbonate, namely local irritation, hypokalaemia, paradoxical worsening of CSF acidosis, rebound alkalosis and impaired oxyhaemoglobin dissociation, have restricted bicarbonate therapy to patients with severe ketoacidosis. A prospective study[71] and a retrospective, uncontrolled study[72] suggested that infusing bicarbonate did not alter rates of clinical or biochemical recovery, and indeed may have slowed the rate of fall of hyperglycaemia. A randomised, prospective study demonstrated a more rapid rise in pH and capillary blood bicarbonate in those given bicarbonate, but no change in the rate of fall of blood glucose and a delay in the fall of lactate and ketone bodies.[73] In another controlled trial, there was again no change in the rate of fall of glucose and hypokalaemia developed.[74] In animal studies we found that bicarbonate appeared to promote glycolysis but not glucose oxidation with a rise in lactate.[75] Thus metabolically at least, bicarbonate is not advantageous, although its value in protecting against cardiac arrhythmias and improving cardiac function remains unclear. Currently we do not administer bicarbonate unless pH is 6·95 or less, at which stage there can be depression of brain function, when 100 mmol is infused over 45 min, together with 20 mmol KCl, and the arterial pH remeasured 45 min later, and further bicarbonate given if the pH still <6·95. Small doses of bicarbonate (25 mmol) may also be given if the patient is distressed by hyperventilation.

Other electrolytes

It is well recognised that serum phosphate levels fall rapidly with effective treatment of ketoacidosis. In theory, low serum phosphate levels could slow the recovery of red cell 2,3-diphosphoglycerate levels, thus impairing oxygen delivery to the tissues. However, in practice, clinical signs of phosphate deficiency are extremely rare and phosphate replacement does not speed biochemical or clinical recovery,[76] nor elevate red cell 2,3-diphosphoglycerate or impair oxyhaemoglobin dissociation.[77] Thus it seems unnecessary to administer phosphate routinely.

Hypomagnesaemia is common during poor diabetic control and at presentation of and recovery from ketoacidosis, when it may be associated with hypocalcaemia and hypophosphataemia.[78] As with phosphate, replacement is not routinely recommended.

GENERAL MEASURES

Management on the intensive care unit is not generally necessary, provided nursing staff familiar with the condition and trained in its management are available. Attention to detail and regular assessment by experienced clinical staff are probably more important than high technology.[79] Pulse, blood pressure, respiratory rate and temperature should be recorded half hourly for the first 6 h, hourly for the next 6 h and then 2–4 hourly. An accurate record of fluid intake and output is vital. If the patient is elderly or has cardiovascular disease, more careful monitoring of fluid balance should be undertaken using central pressure measurement. If the patient is unconscious, a naso-gastric tube should be passed to

prevent aspiration of gastric contents. Urinary catheterisation is necessary if there has been no urine flow for the first 4 hours. If the patient is found to be oliguric IV furosemide (40 mg) is useful.

Signs of infection are misleading in ketoacidosis. Thus leucocytosis is commonly found but correlates with ketone body levels not infection,[80] whilst body temperature remains normal or low even in the presence of infection. In view of the fact that infection is a common precipitating cause, broad-spectrum antibiotics should be given early if there is any suspicion of infection. Hyperglycaemia, especially non-ketotic hyperglycaemia, is a hypercoaguable state, and pulmonary embolism may occur. Low-dose subcutaneous heparin should therefore be used unless contraindicated, and full-dose intravenous anticoagulation given to those patients who are comatose or have serum osmolality >350 mOsm/l.

Capillary blood glucose concentration should be measured hourly and all urine voided tested for glucose and ketones. Laboratory measurement of blood glucose, plasma sodium and potassium and blood gases (arterial or capillary) should be performed at presentation and at 2, 5 and 12 h of treatment, or more often if clinically indicated. Results should be recorded sequentially on a flow sheet.

COMPLICATIONS OF TREATMENT (Table 4)

Fluid overload. Rapid fluid replacement may induce congestive cardiac failure, especially in older patients[29] and careful monitoring of fluid balance and status is vital, including measuring central venous pressure in the elderly or very ill.

TABLE 4

Complications of hyperglycaemic states

Metabolic	Possibly fluid-related
Hypoglycaemia	Fluid overload
Hypokalaemia	Cerebral oedema
Hyperkalaemia	Adult respiratory distress syndrome
Hyperchloraemic acidosis	
Hypomagnesaemia	Thromboembolic
Hypophosphataemia	Deep venous thrombosis
Rhabdomyolysis	Pulmonary embolism

Cerebral oedema. Classically, cerebral oedema presents suddenly in a patient who is ostensibly making a good biochemical and clinical recovery. The outcome is very poor, a substantial number of cases dying acutely and survivors having significant persistent neurological deficits.[31] The incidence is unknown, but one study reported clinically apparent signs or symptoms in 9 per cent of cases,[33] whilst the incidence of sub-clinical brain swelling is much higher.[81] The relationship of the development of cerebral oedema to fluid administration has been discussed above. It may also be relevant that cerebral oedema does not appear to occur if the blood glucose concentration remains above 14 mmol/l[82] hence the rationale for not striving to reach normoglycaemia too quickly. It is noteworthy, however, that cerebral oedema has been demonstrated at presentation of ketoacidosis, before treatment was begun[81,83] and may worsen with treatment. It is also intriguing that it has been reported much more frequently in children than adults.

The cause of cerebral oedema is unclear. Recently, a role for the Na^+/H^+ cell

membrane ion transporter has been suggested.[84] Activation of the transporter by acidification of the intracellular pH results in expulsion of H^+ and transport of Na^+, and hence water, into the cell, with subsequent cell swelling. In developing ketoacidosis, the extracellular and intracellular concentration of organic acids is roughly equal, with little activation of the Na^+/H^+ transporter and only minimal cell swelling. However, with treatment, the extracellular concentration of acids falls much more rapidly than the intracellular concentration, the exchanger is activated, sodium is taken into the cells and cell swelling results. If correct, this hypothesis would explain the initial minor degree of cerebral oedema at presentation and the worsening with treatment.

Treatment of clinically significant cerebral oedema is not very effective. High doses of mannitol with monitoring of the intra-cranial pressure have been tried.

Adult respiratory distress syndrome. Fortunately, this is a rare although well-recognised complication of ketoacidosis, characterised by the sudden onset of dyspnoea, hypoxaemia, decreasing lung compliance and diffuse pulmonary infiltrates on chest X-ray. Mortality is high,[85] and whilst ventilatory support reduces the death rate from respiratory failure it does not influence the overall mortality. The mechanism is debated, but like cerebral oedema, may be linked to rapidly falling oncotic pressure following rapid infusion of large quantities of hypotonic fluid.[83] Alternatively, it has been postulated that there is a specific alveolo-capillary permeability defect, induced by acidosis and hyperventilation.[86]

Hypoglycaemia. In the early studies of low-dose insulin therapy the incidence of hypoglycaemia during treatment approached zero. Indeed this was cited as one of the main advantages of such regimes. Few reports have appeared since that time until the work of Malone et al.[87] in 1992 which showed an alarming rate of 30 per cent during the first 14 days of admission in 3 private hospitals in the USA. In the first 24 h 6 per cent developed hypoglycaemia (serum glucose $<2{\cdot}7$ mmol/l) and 7 per cent in the next 24 h. Thus hypoglycaemia remains a real risk but should be avoidable with adequate monitoring and an early switch to fluid replacement using glucose-containing solutions.

CONCLUSIONS

The continued high incidence of and mortality from hyperglycaemic emergencies despite more public health-care and professional awareness is disappointing. Further patient and professional education on early recognition of hyperglycaemic emergencies and their effective management is necessary. Although the broad principles of management with fluid and electrolyte replacement and insulin therapy have been recognised for many years, the safest type and rate of fluid administration remains unclear. Controlled studies comparing biochemical, clinical and neurological outcomes with different fluid regimes are required.

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