DOI: 10.1111/dme.12757

Diabetes UK Position Statement

Management of hyperosmolar hyperglycaemic state in adults with diabetes

A. R. Scott on behalf of the Joint British Diabetes Societies (JBDS) for Inpatient Care* and the JBDS hyperosmolar hyperglycaemic guidelines group†

Sheffield Teaching Hospitals NHS Trust, Sheffield, UK

Accepted 19 March 2015

Abstract

Hyperglycaemic hyperosmolar state (HHS) is a medical emergency, which differs from diabetic ketoacidosis (DKA) and requires a different approach. The present article summarizes the recent guidance on HHS that has been produced by the Joint British Diabetes Societies for Inpatient Care, available in full at http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_HHS_Adults.pdf. HHS has a higher mortality rate than DKA and may be complicated by myocardial infarction, stroke, seizures, cerebral oedema and central pontine myelinolysis and there is some evidence that rapid changes in osmolality during treatment may be the precipitant of central pontine myelinolysis. Whilst DKA presents within hours of onset, HHS comes on over many days, and the dehydration and metabolic disturbances are more extreme. The key points in these HHS guidelines include: (1) monitoring of the response to treatment: (i) measure or calculate the serum osmolality regularly to monitor the response to treatment and (ii) aim to reduce osmolality by 3–8 mOsm/kg/h; (2) fluid and insulin administration: (i) use i.v. 0.9% sodium chloride solution as the principal fluid to restore circulating volume and reverse dehydration, (ii) fluid replacement alone will cause a fall in blood glucose (BG) level, (iii) withhold insulin until the BG level is no longer falling with i.v. fluids alone (unless ketonaemic), (iv) an initial rise in sodium level is expected and is not itself an indication for hypotonic fluids and (v) early use of insulin (before fluids) may be detrimental; and (3) delivery of care: (i) The diabetes specialist team should be involved as soon as possible and (ii) patients should be nursed in areas where staff are experienced in the management of HHS.

Diabet. Med. 32, 714–724 (2015)

Introduction

Unlike diabetic ketoacidosis (DKA), guidelines on the management of hyperglycaemic hyperosmolar state (HHS) in adults are uncommon and often there is little to differentiate them from the management of DKA, but HHS *is* different and treatment requires a different approach [1]. Although typically occurring in the elderly, HHS is presenting in ever younger adults and teenagers [2,3], often as the initial presentation of Type 2 diabetes mellitus [4].

In those previously diagnosed, the disease may have been managed by diet, oral hypoglycaemic agents or insulin. It is an uncommon condition, but has a higher mortality rate than DKA [5]. There are no recent publications from the UK of mortality rates for HHS, but reported series suggest mortality may have improved, despite remaining high, at between 15 and 20% [6–10].

Whilst DKA presents within hours of onset, HHS comes on over many days, and consequently the dehydration and metabolic disturbances are more extreme. Although many definitions of HHS can be found in the world literature, they are invariably contradictory and arbitrary. Previously called hyperosmolar non-ketotic (or HONK) coma it was apparent that most of these patients were not comatosed but were extremely ill. Changing the name to HHS allows for the fact that some people with severely raised blood glucose (BG) levels may also be mildly ketotic and acidotic. Whilst the reasons why these patients do not develop DKA are not fully understood, hyperglycaemia and hyperosmolality are insufficient to make the diagnosis of HHS [11]. Many people with diabetes have severe but transient elevations of BG level, the difference between this and HHS being the duration of hyperglycaemia and the accompanying dehydration.

Correspondence to: Adrian Roy Scott. E-mail: Adrian.Scott@sth.nhs.uk
*For core membership see Appendix 1.
†For full membership see Appendix 2.
Diabetes UK and the Association of British Clinical Diabetologists (ABCD) contributed to the development of this guideline. Accordingly, a summary of the guideline will appear both in Diabet Med (the journal of Diabetes UK) and Br J Diabetes Vasc Dis (the journal of ABCD).

As with many serious but rare metabolic emergencies the evidence base for treatment is based more on common sense and clinical experience than randomized controlled trials. What is clear is that the greater mortality and morbidity in HHS is only in part related to age and comorbidities. Controversies persist around the speed and type of fluid replacement [12,13]. As a general rule of thumb in medicine, rapid metabolic changes can be corrected rapidly, but otherwise the correction rate needs to take into account the physiological protective mechanisms induced by the metabolic decompensation. Seizures, cerebral oedema and central pontine myelinolysis are uncommon but well described complications of HHS [14,15]. There is some evidence that rapid changes in osmolality during treatment may be the precipitant [16]. Although thrombotic complications such as myocardial infarction, stroke or peripheral arterial thrombosis occur more frequently, it is not known whether or not these can be prevented by prophylaxis with low molecular weight heparin or antiplatelet therapy.

The present guidelines are evidenced-based as far as that evidence exists; otherwise they reflect a consensus derived from an analysis of the published literature in English and the views of specialist diabetes clinicians in the UK. The emphasis throughout is on ensuring that biochemical evaluation must go hand in hand with clinical evaluation. Correction of the former does not guarantee a good outcome. They are intended for use by any healthcare professional who manages HHS in adults.

Even when specific hospital guidelines are available, adherence to and the use of these is variable amongst the admitting teams. In many hospitals, patients with HHS are managed by non-specialist teams, and it is not uncommon for the most junior member, who is least likely to be aware of the hospital guidance, to be given responsibility for the initial management of this complex and challenging condition. Diabetes specialist teams are rarely involved at an early stage and sometimes never at all.

To address these issues, the Joint British Diabetes Societies for Inpatient Care, has produced up-to-date guidance developed by a multidisciplinary group of practising specialists with considerable experience in this area. Where possible, the guidance is evidence-based but it also draws from accumulated professional experience. A number of new recommendations have been introduced, including the use of serial calculations of serum osmolality to monitor response to treatment to avoid over-rapid corrections of the biochemical derangements. These rapid shifts in osmolality have been implicated in often fatal neurological complications such as central pontine myelinosis and cerebral oedema. For similar reasons we advocate that initial treatment is with 0.9% sodium chloride solution alone, and that insulin is only introduced when the rate of fall of BG has plateaued. The first 24 h or so of treatment are very labour-intensive and we strongly suggest that this treatment is undertaken either on a medical intensive care unit or monitored bed on a well-staffed acute admissions ward. At all times, if the patient is not improving, senior advice should be sought.

Definition and diagnosis

A precise definition of HHS does not exist and would be inappropriate, but there are characteristic features that differentiate it from other hyperglycaemic states such as ketoacidosis. Defining HHS by osmolality alone is inappropriate without taking into account other clinical features.

A survey of hospital guidelines in the UK (unpublished data) suggests the following would be reasonable:

- high osmolality, often ≥ 320 milli Osmol (mOsmol)/kg;
- high BG level, usually ≥ 30 mmol/l;
- severe dehydration and feeling unwell.

People with HHS are generally older, but increasingly, as the diabetes pandemic crosses generational boundaries, it may be seen in young adults and even children, as the first presentation [17]. In HHS there is usually no significant ketosis/ketonaemia (3b-hydroxy butyrate < 3 mmol/l), although a mild acidosis (pH > 7.3, bicarbonate > 15 mmol/l) may accompany the prerenal failure. Some patients have severe hypertonicity and ketosis and acidosis (mixed DKA and HHS). This presumably reflects insulin deficiency caused by β-cell exhaustion as a result of temporary glucotoxicity. Such patients may require a modification of this treatment guideline to take into account which aspect predominates.

Initial assessment

Hyperglycaemia results in an osmotic diuresis and renal losses of water in excess of sodium and potassium [18]; thus in managing HHS there is a requirement to correctly identify and address both dehydration and extracellular volume depletion, depending on the degree of free water and sodium deficit as assessed in any individual case. Fluid losses in HHS are estimated to be between 100 and 220 ml/kg (10–22 l in a person weighing 100 kg; Table 1).

Acute impairment in cognitive function may be associated with dehydration but is not specific to the condition and is not necessarily present. Alterations in mental status are common with osmolalities > 330 mOsmol/kg. The constellation of sunken eyes, longitudinal furrows on the tongue and extremity weakness correlates well with raised blood urea [19,20]. Severe hypovolaemia may manifest as tachycardia (pulse > 100 bpm) and/or hypotension (systolic blood pressure < 100 mmHg) [5,21,22]. Patients will usually be identified as being at high risk by use of a validated triage early warning scoring system.

Despite these severe electrolyte losses and total body volume depletion, the typical patient with HHS may not look as dehydrated as they are, because the hypertonicity leads to preservation of intravascular volume (causing movement of water from intracellular to extracellular compartments; (Fig. 1) [23–25].

Table 1 Typical fluid and electrolyte losses in hyperglycaemic hyperosmolar state

		For patient weighing 60 kg	For patient weighing 100 kg
Water	100–220 ml/kg	6–13 litres	10–22 litres
Na^+	5–13 mmol/kg	300–780 mmol	500–1300 mmol
Cl^-	5–15 mmol/kg	300–900 mmol	500–1500 mmol
K^+	4–6 mmol/kg	240–360 mmol	400–600 mmol

HHS should not be diagnosed from biochemical markers alone; however, blood glucose is markedly raised (usually ≥ 30 mmol/l), as is the osmolality, in patients with HHS.

Osmolality is useful, both as an indicator of severity and for monitoring the rate of change with treatment. As frequent measurement of osmolality is not usually available in UK hospitals, osmolarity should be calculated as a surrogate using the formula 2Na + glucose + urea. This gives the best approximation to measured osmolality, although a more accurate formula has been derived [26]. (For the sake of clarity, calculated osmolarity and measured osmolality will be referred to as osmolality in the rest of this paper). Urea is not an effective osmolyte but including it in the calculation is important in the hyperosmolar state, as it is one of the indicators of severe dehydration.

HHS and DKA can have marked effects on cerebral function and can be associated with transient changes in mental performance and also with longer-term effects. This may be attributable to cerebral oedema in severe cases or to the presence of significant electrolyte disturbances, changes in osmolality, dehydration, infection and sepsis, hypoglycaemia during treatment and renal failure. Some authors [27,28] have suggested that changes in mental performance correlate with the severity of hyperosmolality and confusion is common with an osmolality > 330 mOsmol/kg. An assessment of cognition should accompany a full history, physical examination and review of drug therapy. Of course, tests of cognition, must be viewed in comparison with the

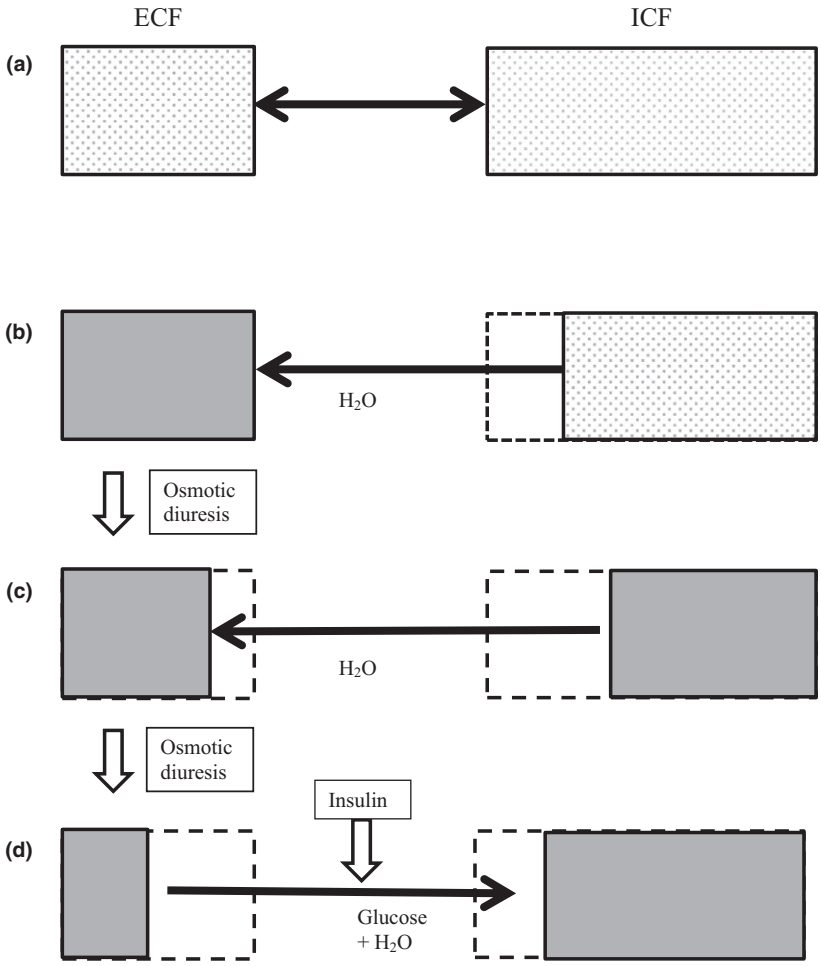

FIGURE 1 Fluid balance in hyperglycaemic hyperosmolar state (adapted from Zeitler 2011 [3]). (a) Normoglycaemia and normal hydration. (b) Early – extracellular fluid (ECF) is hyperosmolar causing water to shift from intracellular (ICF) into ECF. (c) Late – continued osmotic diuresis causes dehydration, volume loss and hyperosmolality in both ICF and ECF. (d) Insulin therapy without adequate fluid replacement shifts glucose and water from ECF to ICF causing vascular collapse and hypotension.

pre-morbid state, but this information in the elderly inpatient is often lacking.

The goals of treatment of HHS are to treat the underlying cause and to gradually and safely:

- normalize the osmolality;
- replace fluid and electrolyte losses;
- normalize BG.

Other goals include prevention of:

- arterial or venous thrombosis;
- other potential complications, e.g. cerebral oedema/ central pontine myelinolysis;
- foot ulceration.

Early senior review by a clinician familiar with the treatment of HHS is essential to confirm the treatment plan and review progress

Monitoring

Most hospitals in the UK now have ready access to blood gas analysis that allows reliable measurements of pH, urea, electrolytes and glucose. After the initial laboratory diagnostic sample, use of the blood gas analysis for frequent monitoring of progress and calculation of osmolality may be more convenient than sending repeated samples to the laboratory. Unless it is necessary to measure oxygen saturation as well, venous rather than arterial samples are sufficient. Local facilities will determine which mechanism is the most safe and efficient.

Serum lactate and ketones must also be checked; the former can indicate type 1 lactic acidosis related to sepsis and the latter will exclude significant ketonaemia if 3β-hydroxy butyrate is < 1 mmol/l. BG and ketone measurement should be checked with a laboratory quality-controlled device meeting appropriate standards; procedures for checking the glucose must be strictly followed [29]. Periodic, simultaneous, laboratory measurements of glucose may be necessary to confirm that there is minimal discrepancy between the two methods.

Rationale for measurement and calculation of osmolality/osmolarity

Total body water is divided between the intra- and extracellular fluid spaces, and its distribution is determined by the presence of osmotically effective substances on either side of the cell membrane. Intracellular osmotic pressure is exerted principally by potassium, chloride and phosphate ions while extracellular osmotic pressure is primarily dependent upon sodium, chloride and bicarbonate ions. These osmoles play a critical role in the movement of free water across the cell membrane, as they are themselves unable to pass freely between the intra- and extracellular compartments. Glucose, lipids and proteins also exert an osmotic pressure, being largely confined to the extracellular space, while urea and ethanol are termed ineffective osmoles, which recognizes that they are able to freely move across cell membranes and thus play no role in the distribution of free water within the body [24,30]. Serum sodium, a close approximation to osmolality in the absence of hyperglycaemia, may be reassuringly normal or even low in the presence of hyperglycaemia. The addition of glucose to the extracellular space causes an osmotic shift of free water into the extracellular fluid and a resultant dilution of serum sodium. The literature is scattered with conflicting definitions of HHS, compounded by the fact that there are many different formulae to calculate osmolality:

- 2Na+ + glucose + urea
- 2(Na+ +K+) + glucose
- 2Na+ + glucose

The best approximation to measured osmolality can be calculated using the formula 2Na+ + glucose + urea, although a more accurate formula has been derived [26]; however, as urea is an ineffective osmolyte it can be omitted from the equation to allow calculation of tonicity (or effective osmolality). This is of greatest importance when someone is hyponatraemic as tonicity indicates risk of cerebral oedema, i.e. hyposmolality.

A patient with sodium 122 mmol/l, glucose 13 mmol/l and urea 23 mmol/l has a calculated osmolality of 280 and an effective osmolality of 257, whereas a person with sodium 122 mmol/l, glucose 30 mmol/l and urea 4 mmol/l has a calculated osmolality of 278 and an effective osmolality of 274. So the patient with the raised urea level has a much lower effective osmolality and is therefore at a greater risk of cerebral oedema, should correction of the hyponatraemia be too fast. The hyponatraemia in the patient with a blood glucose of 30 mmol/l is largely dilutional and will correct as the glucose falls (corrected sodium = 122 + (2.4 × 4) = 131.6) [31].

We did consider using effective osmolality (2Na + glucose) but in a survey of British diabetes specialists (Adrian Scott, personal communication) the difference between this and osmolality (2Na + glucose + urea) was not well understood.

The key variable is osmolality, to which glucose and sodium are the main contributors; too rapid changes in osmolality are dangerous. As these variables are inter-related we advise that they are plotted on a graph or tabulated to permit appreciation of the rate of change.

High dependency/level 2 care

Patients with HHS are complex to treat and often have multiple comorbidities, therefore, they require intensive monitoring. The Joint British Diabetes Societies (JBDS)

suggest that the presence of one or more of the following may indicate the need for admission to a high-dependency unit/level 2 environment, where the insertion of a central venous catheter to aid assessment of fluid status and immediate senior review by a clinician skilled in the management of HHS should be considered:

- osmolality > 350 mOsmol/kg;
- sodium level > 160 mmol/l;
- venous/arterial pH < 7.1;
- hypokalaemia (< 3.5 mmol/l) or hyperkalaemia (> 6 mmol/l) on admission;
- Glasgow Coma Scale score < 12 or abnormal Alert, Voice, Pain, Unresponsive (AVPU) scale score;
- oxygen saturation < 92% on air (assuming normal baseline respiratory function);
- systolic blood pressure < 90 mmHg;
- pulse > 100 or < 60 bpm;
- urine output < 0.5 ml/kg/h;
- serum creatinine level > 200 μmol/l;
- hypothermia;
- macrovascular event such as myocardial infarction or stroke;
- other serious comorbidity.

Treatment

The goal of the initial therapy is expansion of the intravascular and extravascular volume and to restore peripheral perfusion. Controversies persist around the speed and type of fluid replacement necessary [12,13,32,33]. A Cochrane Review [34] recommended the use of crystalloid fluids rather than colloid in ill patients.

There is no evidence for the use of Ringer's Lactate (Hartmann's solution) in HHS, and a recent study failed to show benefit from using Ringer's lactate solution compared with 0.9% sodium chloride solution in patients with DKA [35].

As the majority of electrolyte losses are sodium, chloride and potassium, the base fluid that should be used is 0.9% sodium chloride solution with potassium added as required [36].

Existing guidelines encourage vigorous initial fluid replacement and this alone will result in a decline in plasma glucose. Although for practical and safety reasons an infusion of insulin is often commenced simultaneously, rapid falls in blood glucose are not desirable (see below).

We advise using 0.9% sodium chloride solution as the principle fluid to restore circulating volume and reverse dehydration (in this situation, even 0.9% saline will be relatively hypotonic compared with the serum in someone with HHS). Measurement or calculation of osmolality should be undertaken every hour initially and the rate of fluid replacement adjusted to ensure a positive fluid balance sufficient to promote a gradual decline in osmolality.

Fluid replacement alone (without insulin) will lower blood glucose, reducing osmolality and causing a shift of water into the intracellular space. This inevitably results in a rise in serum sodium level (a fall in BG level of 5.5 mmol/l will result in a 2.4 mmol/l rise in sodium level). This is not necessarily an indication to give hypotonic solutions. A rising sodium level is only a concern if the osmolality is NOT declining concurrently. Rapid changes must be avoided – a safe rate of fall of BG level of between 4 and 6 mmol/h is recommended [12]. If the inevitable rise in serum Na is significantly greater than 2.4 mmol/l for each 5.5 mmol/l fall in BG [31], this would suggest insufficient fluid replacement. Thereafter, the rate of fall of plasma sodium level should not exceed 10 mmol/l in 24 h [37]. The aim of treatment should be to replace ~50% of estimated fluid loss within the first 12 h and the remainder in the following 12 h, although this will in part be determined by the initial severity, the degree of renal impairment and comorbidities such as heart failure, which may limit the speed of correction. A target BG of between 10 and 15 mmol/l is a reasonable goal. Complete normalization of electrolytes and osmolality may take up to 72 h.

Ideally patients will recover quickly enough to replace the water deficit themselves by taking fluids orally. There is no experimental evidence to justify using hypotonic fluids < 0.45% sodium chloride solution; however, if the osmolality is no longer declining despite adequate fluid replacement with 0.9% sodium chloride solution AND an adequate rate of fall of BG is not being achieved, then 0.45% sodium chloride solution should be substituted.

Insulin dose and timing

- If significant ketonaemia is present (3β-hydroxy butyrate is > 1 mmol/l) this indicates relative hypoinsulinaemia and insulin should be started at time zero.
- If significant ketonaemia is not present (3β-hydroxy butyrate is < 1 mmol/l) do NOT start insulin.
- Fluid replacement alone with 0.9% sodium chloride solution will result in a falling BG level and because most patients with HHS are insulin-sensitive there is a risk of lowering the osmolality precipitously. Insulin treatment before adequate fluid replacement may result in cardiovascular collapse as water moves out of the intravascular space, with a resulting decline in intravascular volume (a consequence of insulin-mediated glucose uptake and a diuresis from urinary glucose excretion; Fig. 1).

- The recommended insulin dose is a fixed rate i.v. insulin infusion given at 0.05 units per kg per h (e.g. 4 units/h in a man weighing 80 kg) is used. A fall of glucose at a rate of up to 5 mmol/l per h is ideal and, once the BG has ceased to fall after initial fluid resuscitation, reassessment of fluid intake and evaluation of renal function must be undertaken. Insulin may be started at this point, or, if already in place, the infusion rate increased by 1 unit/h. As with DKA, a fixed rate i.v. insulin infusion is preferred, although generally lower doses are required.

Patients with HHS are potassium deplete but less acidotic than those with DKA so potassium shifts are less pronounced, the dose of insulin is lower, and there is often co-existing renal failure. Hyperkalaemia can be present with acute kidney injury and patients on diuretics may be profoundly hypokalaemic. Potassium should be replaced or omitted as required (Table 2).

Anti-infective therapy

As with all acutely ill patients, sepsis may not be accompanied by pyrexia. An infective source should be sought on clinical history and examination and measurement of C-reactive protein may be helpful [38]. Antibiotics should be given when there are clinical signs of infection or imaging and/or laboratory tests suggest its presence.

Anticoagulation

Patients with HHS have an increased risk of arterial and venous thromboembolism [39,40]. Previous studies have estimated that patients with diabetes and hyperosmolality have an increased risk of venous thromboembolism similar to patients with acute renal failure, acute sepsis or acute connective tissue disease [41,42]. The risk of venous thromboembolism is greater than in patients with DKA [43]. Hypernatraemia and increasing arginine vasopressin (AVP) concentrations can promote thrombogenesis by producing changes in haemostatic function consistent with a hypercoagulable state [44].

All patients should receive prophylactic low molecular weight heparin for the full duration of admission unless contraindicated. In a survey of UK hospitals (unpublished) of guidelines for the treatment of HHS, some have recommended the use of full treatment dose anticoagulation; however, patients with HHS are often elderly and at increased risk of haemorrhage and we could not find evidence to support this approach. Full anticoagulation should only be considered in patients with suspected thrombosis or acute coronary syndrome. One study has suggested that patients with HHS have an increased risk of venous thromboembolism for 3 months after discharge [42]. Consideration should be given to extending prophylaxis beyond the duration of admission in patients deemed to be at high risk.

Hypophosphataemia and hypomagnesaemia are common in HHS. As with the management of DKA there is no evidence of benefit of treatment with phosphate infusion, but these patients are often elderly and may be malnourished, and the re-feeding syndrome could be precipitated once the person begins to eat. If hypophosphataemia persists beyond the acute phase of treatment of HHS, oral or i.v. replacement should be considered. Magnesium replacement has also not been shown to be beneficial so should only be considered if the patient is symptomatic or has symptomatic hypocalcaemia.

Table 2 Potassium replacement in hyperglycaemic hyperosmolar state

Potassium level in first 24 h	Potassium replacement in infusion solution
> 5.5 mmol/l	Nil
3.5–5.5 mmol/l	40 mmol/l
< 3.5 mmol/l	Senior review as additional potassium required (via central line in high-dependency unit)

Foot protection

Patients with HHS are at high risk of pressure ulceration. An initial foot assessment should be undertaken and heel protectors applied in those with neuropathy, peripheral vascular disease or lower limb deformity. If patients are too confused or sleepy to cooperate with assessment of sensation, it should be assumed that they are at high risk. The feet should be re-examined daily [45,46].

Recovery phase

Unlike DKA, complete correction of electrolyte and osmolality abnormalities is unlikely to be achieved within 24 h and too rapid correction may be harmful. As many patients with these abnormalities are elderly with multiple comorbidities, recovery will largely be determined by their previous functional level and the underlying precipitant of HHS. Early mobilization is essential, as is the need for good nutrition and, where indicated, multivitamins and phosphate (to prevent re-feeding syndrome).

Intravenous insulin can usually be discontinued once they are eating and drinking but i.v. fluids may be required for longer if intake is inadequate.

Most patients should be transferred to s.c. insulin (the regime being determined by their circumstances). For patients with previously undiagnosed diabetes or diabetes well controlled on oral agents, switching from insulin to the appropriate oral hypoglycaemic agent should be considered after a period of stability (weeks or months). People with HHS should be referred to the specialist diabetes team as soon as practicably possible after admission. All patients will require diabetes education to reduce the risk of recurrence and prevent long-term complications.

In summary, the management of HHS is different from that of DKA, and treatment requires a different approach. This HHS management guideline summarizes the core issues in the management of HHS, and proposes new principles in HHS treatment that are summarized in Fig.1 and Appendix 3.

Acknowledgements

We would like to especially thank Christine Jones (DISN UK Group administrator, Norwich) for her administrative work and help with these guidelines and with the JBDS Inpatient Care Group.

References

1 Savage MW, Dhatariya KK, Kilvert A, Rayman G, Rees JAE, Courtney CH *et al*. Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. *Diabet Med* 2011; **28**: 508–515.
2 Rosenbloom AL. Hyperglycemic Hyperosmolar State: an emerging pediatric problem. *J Pediatr* 2010; **156**: 180–184.
3 Zeitler P, Haqq A, Rosenbloom A, Glaser N for the Drugs and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Hyperglycemic Hyperosmolar Syndrome in Children: Pathophysiological considerations and guidelines for treatment. *J Pediatr* 2011; **158**: 9–14.
4 Ekpebergh CO, Longo-Mbenza B, Akinrinmade A, Blanco-Blanco E, Badri M, Levitt NS. Hyperglycaemic crisis in the Eastern Cape province of South Africa: High mortality and association of hyperosmolar ketoacidosis with a new diagnosis of diabetes. *S Afr Med J* 2010; **100**: 822–826.
5 Delaney MF, Zisman A, Kettyle WM. Diabetic ketoacidosis and hyperglycaemic, hyperosmolar non-ketotic syndrome. *Endocrinol Metab Clin North Am* 2000; **29**: 683–705.
6 Piniés JA, Cairo G, Gaztambide S, Vazquez JA. Course and prognosis of 132 patients with diabetic non ketotic hyperosmolar state. *Diabetes Metab* 1994; **20**: 43–48.
7 Rolfe M, Ephraim GG, Lincoln DC, Huddle KR. Hyperosmolar non-ketotic diabetic coma as a cause of emergency hyperglycaemic admission to Baragwanath Hospital. *S Afr Med J* 1995; **85**: 173–176.
8 Kitabchi AE, Nyenwe EA. Hyperglycemic crises in diabetes mellitus: diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Endocrinol Metab Clin North Am* 2006; **35**: 725–751.
9 MacIsaac RJ, Lee LY, McNeil KJ, Tsalamandris C. Jerums G Influence of age on the presentation and outcome of acidotic and hyperosmolar diabetic emergencies. *Intern Med J* 2002; **32**: 379–385.
10 Chung ST, Perue GG, Johnson A, Younger N, Hoo CS, Pascoe RW, Boyne MS. Predictors of hyperglycaemic crises and their associated mortality in Jamaica. *Diabetes Res Clin Pract* 2006; **73**: 184–190.
11 English P, Williams G. Hyperglycaemic crises and lactic acidosis in diabetes mellitus. *Postgrad Med J* 2004; **80**: 253–261a.
12 Kitabachi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycaemic Crises in adult Patients with Diabetes. *Diabetes Care* 2009; **32**: 1335–1343.
13 Milionis HJ, Liamis G, Elisaf MS. Appropriate treatment of hypernatraemia in diabetic hyperglycaemic hyperosmolar syndrome. *J Int Med* 2001; **249**: 273–276.
14 Cokar O, Aydin B, Ozer F. Non-ketotic hyperglycaemia presenting as epilepsia partialis continua. *Seizure* 2004; **13**: 264–269.
15 Raghavendra S, Ashalatha R, Thomas SV, Kesavadas C. Focal neuronal loss, reversible subcortical focal T2 hypointensity in seizures with a nonketotic hyperglycemic hyperosmolar state. *Neuroradiology* 2007; **49**: 299–305.
16 O'Malley G, Moran C, Draman MS, King T, Smith D, Thompson CJ, Agha A. Central pontine myelinolysis complicating treatment of the hyperglycaemic hyperosmolar state. *Ann Clin Biochem* 2008; **45**: 440–443.
17 Fourtner SH, Weinzimer SA. Levitt Katz LE. Hyperglycemia, hyperosmolar non-ketotic syndrome in children with Type 2 diabetes. *Paediatr. Diabetes* 2005; **6**: 129–135.
18 Arrief AI, Carroll HJ. Nonketotic Hyperosmolar Coma with hyperglycaemia: clinical features, pathophysiology, renal function, acid base balance, plasma cerebrospinal fluid equilibria and the effects of therapy in 37 cases. *Medicine* 1972; **51**: 73–94.
19 Sinert R, Spektor M. Clinical assessment of hypovolaemia. *Ann Emergency Med* 2005; **45**: 327–329.
20 Gross CR, Lindquist RD, Woolley AC, Granieri R, Allard K, Webster B. Clinical indicators of dehydration severity in elderly patients. *J Emerg Med* 1992; **10**: 267–274.
21 Lapides J, Bourne RB, Maclean LR. Clinical signs of dehydration and extracellular fluid loss. *JAMA1965*; **191**: 141–143.
22 Kavouras SA. Assessing hydration status. *Curr Opin Clin Nutr Metab Care* 2002; **5**: 519–524.
23 Coller FA, Maddock WG. A study of dehydration in adults. *Annals of Surgery* 1935;947–960.
24 Mange K, Matsuura D, Cizman B, Soto H, Ziyadeh FN, Goldfarb S *et al*. Language guiding therapy: the case of dehydration versus volume depletion. *Ann Intern Med* 1997; **127**: 848–852.
25 Bartoli E, Bergamaco L, Castello L, Sainaghi PP. Methods for the quantitative assessment of electrolyte disturbances in hyperglycaemia. *Nutr Metab Cardiovasc Dis* 2009; **19**: 67–74.
26 Bhagat CI, Garcia-Webb P, Fletcher E, Beilby JP. Calculated vs measured osmolality revisited. *Clin Chem* 1984; **30**: 1703–1705.
27 Kitabchi AE, Fisher JN. Insulin therapy of diabetic ketoacidosis: physiologic vs pharmacologic doses of insulin and their routes of administration. In: Brownlee M ed. *Handbook of Diabetes Mellitus*. New York: Garland ATPM, 1981: 95–149.
28 Daugiradis JT, Kronfol NO, Tzamaloukas AH, Ing TS. Hyperosmolar coma: cellular dehydration and the serum sodium concentration. *Ann Intern Med* 1989; **110**: 855–857.
29 Bektas F, Fray O, Sari R, Akbas H. Point of care testing of diabetic patients in the emergency department. *Endo Res* 2004; **30**: 395–402.
30 Bhave G, Neilson EG. Volume depletion versus dehydration: How understanding the difference can guide therapy. *Am J Kidney Dis* 2011; **58**: 302–309.
31 Katz MA. Hyperglycemia-induced hyponatremia: calculation of expected serum sodium depression. *N Engl J Med* 1973; **289**: 843–844.
32 Hillman K. Fluid resuscitation in diabetic emergencies: a reappraisal. *Intensive Care Med* 1987; **13**: 4–8.
33 Matz R. Hyperosmolar nonacidotic diabetes (HNAD). In: Porte D Jr, Sherwin RS eds. *Diabetes Mellitus: Theory and Practice*, 5th ed. Amsterdam: Elsevier, 1997: 845–860.
34 Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2013; **2**. Art. No.: CD000567.
35 Van Zyll DG, Rheeder P, Delport E. Fluid management in diabetic-acidosis—Ringer's lactate versus normal saline: a randomized controlled trial. *QJM* 2012; **105**: 337–343.
36 NPSA Patient Safety Alert. *Potassium solutions: risks to patients from errors occurring during intravenous administration*. London: NPSA, 2002.
37 Adrogue HJ, Madias NE. Hypernatremia. *N Engl J Med* 2000; **342**: 1493–1499.

38 Gogos CA, Giali S, Paliogianni F, Dimitracopoulos G, Bassaris HP, Vagenakis AG. Interleukin-6 and C-reactive protein as early markers of sepsis in patients with diabetic ketoscidosis or hyperosmosis. *Diabetologia* 2001; **44**: 1011–1114.
39 Whelton MJ, Walde D, Havard CWH. Hyperosmolar Non-Ketotic Diabetes Coma – with particular reference to vascular complications. *BMJ* 1971; **1**: 85–86.
40 Keller U, Berger W, Ritz R, Truog P. Course and prognosis of 86 episodes of diabetic coma. *Diabetologia* 1975; **11**: 93–100.
41 Paton RC. Haemostatic changes in diabetic coma. *Diabetologia* 1981; **21**: 172–177.
42 Keenan CR, Murin S, White RH. High risk for venous thromboembolism in diabetics with hyperosmolar state: comparison with other acute medical illnesses. *J Thrombosis Haemostasis* 2007; **5**: 1185–1190.
43 Petrauskiene V, Falk M, Waernbaum I, Norberg M, Eriksson JW. The risk of venous thromboembolism is markedly elevated in patients with diabetes. *Diabetologia* 2005; **48**: 1017–1021.
44 Carr ME. Diabetes mellitus: a hypercoagulable state. *J Diabetes Complications* 2001; **15**: 44–54.
45 NICE CG10 2004. Available at http://www.nice.org.uk/guidance/cg10/resources/guidance-type-2-diabetes-foot-problems-pdf.
46 Putting Feet First. Available at http://www.diabetes.org.uk/Get_involved/Campaigning/Putting-feet-first/ 2012.

Appendix 1

Joint British Diabetes Societies Inpatient Care Group

Dr Belinda Allan, Hull and East Yorkshire Hospital NHS Trust

Dr Ketan Dhatariya, Norfolk and Norwich University Hospital NHS Foundation Trust

Dr Daniel Flanagan, Plymouth Hospitals NHS Trust

Dr Maggie Hammersley, Oxford University Hospitals NHS Trust

Dr Rowan Hillson, MBE, National Clinical Director for Diabetes

June James, University Hospitals of Leicester NHS Trust

Dr Johnny McKnight, NHS Lothian

Dr Rif Malik, King's College Hospital NHS Foundation Trust

Dr Gerry Rayman, The Ipswich Hospitals NHS Trust

Dr Kate Richie, Southern Health and Social Care Trust, Northern Ireland

Dr Aled Roberts, Cardiff and Vale University NHS Trust

Professor Mike Sampson (Norwich), JBDS Inpatient Care Group Chair

Dr Mark Savage, The Pennine Acute Hospitals NHS Trust

Debbie Stanisstreet, East and North Hertfordshire NHS Trust

Dr Louise Stuart, The Pennine Acute Hospitals NHS Trust

Esther Walden, Norfolk and Norwich University Hospital NHS Foundation Trust

Dr Chris Walton, Hull and East Yorkshire Hospital NHS Trust

Dr Peter Winocour, East and North Hertfordshire NHS Trust

Appendix 2

Writing group

Dr Geraldine Brennan, NHS Tayside

Dr Peter Carey, City Hospitals Sunderland NHS Foundation Trust

Dr Ketan Dhatariya, Norfolk and Norwich University Hospital NHS Foundation Trust

Dr Maggie Hammersley, Oxford University Hospitals NHS Trust

Dr Philippa Hanson, Barts Health NHS Trust

Dr Stuart Ritchie, NHS Lothian

Dr Mark Savage, The Pennine Acute Hospitals NHS Trust

Professor Alan Sinclair, Luton & Dunstable Hospital NHS Foundation Trust and Dean of Beds and Herts Postgraduate Medical School

Appendix 3

Hyperglycaemic hyperosmolar state care pathway

HHS is a medical emergency. In the UK it is less common than DKA, although in areas with a high proportion of patients of African origin this may not be the case. HHS is associated with a significant morbidity and higher mortality than DKA and must be diagnosed promptly and managed intensively. The diabetes specialist team should be involved as soon as possible after admission.

For young people under the age of 16 years contact your paediatric diabetes service and refer to published paediatric guidelines for the management of HHS such as those by Zeitler *et al.* 2011 [3] .

Diagnosis

The characteristic features of a person with HHS are:

- Hypovolaemia
- Marked hyperglycaemia (≥ 30 mmol/l) **without** significant hyperketonaemia (< 3 mmol/l), ketonuria (2 + or less) or acidosis (pH > 7.3, bicarbonate > 15 mmol/l)
- Osmolality usually 320 mmol/kg or more

N.B. A mixed picture of HHS and ketoacidosis DKA may occur.

Assessment of severity

Patients with HHS are complex and often have multiple comorbidities so require intensive monitoring. Consider the need for admission to a level 2 / high-dependency unit environment, when one or more of the following are present:

- osmolality > 350 mOsm/l;
- sodium > 160 mmol/l;
- venous / arterial pH < 7.1;

- hypokalaemia (< 3.5 mmol/l) or hyperkalaemia (> 6 mmol/l) on admission;
- Glasgow Coma Scale score < 12 or abnormal AVPU (Alert, Voice, Pain, Unresponsive) scale score;
- oxygen saturation below 92% on air (assuming normal baseline respiratory function);
- systolic blood pressure < 90 mmHg;
- pulse > 100 or < 60 bpm;
- urine output < 0.5 ml/kg/h;
- serum creatinine > 200 μmol/l;
- hypothermia;
- macrovascular event such as myocardial infarction or stroke;
- other serious comorbidity.

Goals of treatment

The goals of treatment of HHS are to treat the underlying cause and to gradually and safely:

- normalize the osmolality;
- replace fluid and electrolyte losses;
- normalize BG.

Other goals include prevention of:

- arterial or venous thrombosis;
- other potential complications, e.g. cerebral oedema/ central pontine myelinolysis;
- foot ulceration.

New principles

- Measure or calculate osmolality (2Na + Glucose + Urea) frequently to monitor treatment response.
- Use i.v. 0.9% sodium chloride solution as the principle fluid to restore circulating volume and reverse dehydration. Only switch to 0.45% sodium chloride solution if the osmolality is not declining despite adequate positive fluid balance.
- An initial rise in sodium is expected and is not itself an indication for hypotonic fluids. Thereafter, the rate of fall of plasma sodium should not exceed 10 mmol/l in 24 h.
- The fall in BG should be no more than 5 mmol/l/h. Low-dose i.v. insulin (0.05 units/kg/h) should be commenced once the BG is no longer falling with i.v. fluids alone OR immediately if there is significant ketonaemia (3β-hydroxy butyrate > 1 mmol/l).
- Assess foot risk score on admission.

A. **Hour 1: Immediate management upon diagnosis: 0 to 60 min**

T = 0 at time i.v. fluids are commenced. If there is a problem with i.v. access, critical care support should be requested immediately.

- Commence i.v. 0.9% sodium chloride – 1 litre to run over 1 h
  - Consider more rapid replacement if systolic blood pressure < 90 mmHg
  - Caution in the elderly where too rapid rehydration may precipitate heart failure but insufficient may fail to reverse acute kidney injury
- Only commence insulin infusion (0.05 units/kg/h) **IF** there is significant ketonaemia (3β-hydroxy butyrate greater than 1 mmol/l) or ketonuria 2 + or more (i.e. mixed DKA and HHS)
- Clinical assessment of the patient
  - Does the history suggest sepsis/vascular event or a recent change in medication?
  - Assess the degree of dehydration
  - Examine for a source of sepsis or evidence of vascular event
  - Mental state assessment
- Assess foot risk score – assume high risk if patient obtunded or uncooperative
  - Ensure heels are off-loaded
  - Ensure daily foot checks
- Investigations
  - Capillary BG
  - Venous plasma blood glucose
  - Urea and electrolytes
  - Measured and calculated osmolality (2Na + glucose + urea)
  - Venous blood gas
  - Blood ketones and lactate
  - Full blood count
  - Blood cultures
  - ECG
  - Chest X-ray

    Urine analysis and culture
  - C-reactive protein (if indicated)

- Establish monitoring regime appropriate to patient – generally hourly BG, Na^+, K^+, urea and calculated osmolality (2 × Na + glucose + urea) for the first 6 h then 2-hourly osmolality if response satisfactory (a fall of 3–8 mOsmol/kg/h)
    - Chart osmolality/glucose/sodium
    - Continuous pulse oximetry
    - Consider continuous cardiac monitoring
- Insert urinary catheter to monitor hourly urine output and calculate fluid balance
- Ensure early senior review and/or inform specialist diabetes team
- Commence prophylactic low molecular weight heparin
- Consider i.v. antibiotics if sepsis identified or suspected

B. **60 min to 6 h**
Aims

- To achieve a gradual decline in osmolality (3–8 mOsmol/kg/h)
    - Using 0.9% normal saline aim to give a further 0.5 to 1 litre/h depending on clinical assessment of dehydration/risk of precipitating heart failure and fluid balance (target is to achieve positive fluid balance of 2–3 litres by 6 h)
    - Measure glucose, urea and electrolytes hourly and calculate osmolality (2Na + glucose + urea)
        - If plasma Na^+ increasing but osmolality declining at appropriate rate, continue 0.9% sodium chloride
        - If plasma Na^+ increasing AND osmolality increasing (or declining at less than 3 mOsm/kg/h) check fluid balance. If positive balance inadequate increase rate of infusion of 0.9% sodium chloride
        - If osmolality increasing and fluid balance adequate, consider switching to 0.45% sodium chloride at same rate
        - If osmolality falling at rate exceeding 8 mOsmol/kg/h consider reducing infusion rate of i.v. fluids and/or insulin (if already commenced).
    - If blood glucose falling < 5 mmol/l per h check fluid balance.
        - If positive balance inadequate, increase rate of infusion of 0.9% sodium chloride
        - If positive fluid balance adequate, commence low-dose i.v. insulin (0.05 units/kg/h) or if already running, increase rate to 0.1 units/kg/h
- To maintain potassium in the normal range
    - Hypokalaemia (< 3.5 mmol/l) and hyperkalaemia (> 6 mmol/l) are life-threatening conditions and warrant senior review. They are less common in HHS than in DKA but monitoring and replacement are essential

Potassium level in first 24 h	Potassium replacement in infusion solution
> 5.5 mmol/l	Nil
3.5–5.5 mmol/l	40 mmol/l
< 3.5 mmol/l	Senior review as additional potassium required

- Avoidance of hypoglycaemia
    - Aim to keep BG 10–15 mmol/l in first 24 h
    - If BG falls below 14 mmol/l commence 5% or 10% glucose at 125 ml/h AND CONTINUE 0.9% sodium chloride solution
- Monitor vital signs and chart Early Warning Score (EWS)
- Maintain accurate fluid balance chart (minimum urine output 0.5 ml/kg/h)

C. **6 to 12 h**
Aims

- Ensure that clinical and biochemical variables are improving
    - Continue charting BG hourly; sodium and calculated osmolality 2-hourly
    - Take appropriate action (as outlined in time 60 min to 6 h) above
- Continue i.v. fluid replacement to achieve positive balance of 3–6 l by 12 h
    - Maintain an accurate fluid balance chart
- Assess for complications of treatment e.g. fluid overload, cerebral oedema, extra pontine myelinolysis (e.g. deteriorating conscious level)
- Continue treatment of any underlying precipitant
    - If patient not improving seek senior advice
- Avoid hypoglycaemia
    - Aim to keep BG 10–15 mmol/l in first 24 h
    - If BG falls below 14 mmol/l commence 5 or 10% glucose at 125 ml/h AND CONTINUE 0.9% sodium chloride solution
- Ensure referral has been made to diabetes team

D. **12 to 24 h**
Aims

- Ensure continuing improvement of clinical and biochemical variables
    - Continue charting BG hourly. Measurement of sodium and calculated osmolality can be reduced to 4 hourly if improvement maintained (if not continue 2-hourly)
    - Do not expect biochemistry to have normalized by 24 h (sodium level and osmolality are likely to be raised)
    - Take appropriate action (as outlined in time 60 min to 6 h) depending on results
- Continue i.v. fluid replacement to achieve remaining replacement of estimated fluid losses within next 12 h – this will be dependent on factors such as initial degree of dehydration / body weight etc and MOST IMPORTANTLY the response to treatment so far. Therefore,
    - Continue maintaining accurate fluid balance chart, plotting osmolality and make appropriate adjustments to fluid replacement rates
- Continue i.v. insulin with or without 5 or 10% glucose solution to maintain blood glucose 10–15 mmol/l
    - Adjust insulin infusion rate hourly by 1 unit/h increments or decrements to achieve desired blood glucose
- Assess for complications of treatment e.g. fluid overload, cerebral oedema, extra pontine myelinolysis (e.g. deteriorating conscious level)
- Continue treatment of any underlying precipitant
    - If patient not improving seek senior advice

E. **24 h to day 3**
Expectation: patient should be steadily recovering, beginning to eat and drink, biochemistry back to normal.

- Ensure that clinical and biochemical variables are improving or have normalized
    - Continue i.v. fluids until eating and drinking normally
    - Variable rate insulin if not eating and drinking
    - Convert to appropriate s.c. regime when biochemically stable
    - Encourage early mobilization
    - Daily urea and electrolytes
    - Remove catheter when clinically appropriate
- Assess for signs of fluid overload or cerebral oedema
- Assess for evidence of continuing sepsis
- Daily foot checks
- Continue low molecular weight heparin until day of discharge (consider extended treatment in very high risk patients)
- Ensure patient has been reviewed by diabetes team

After care

Most patients should go home on s.c.insulin (the regime being determined by their circumstances). For patients with previously undiagnosed diabetes or well controlled on oral agents, switching from insulin to the appropriate oral hypoglycaemic agent should be considered after a period of stability (weeks or months). Ensure patient has appropriate diabetes education before discharge and arrange follow-up by diabetes team.