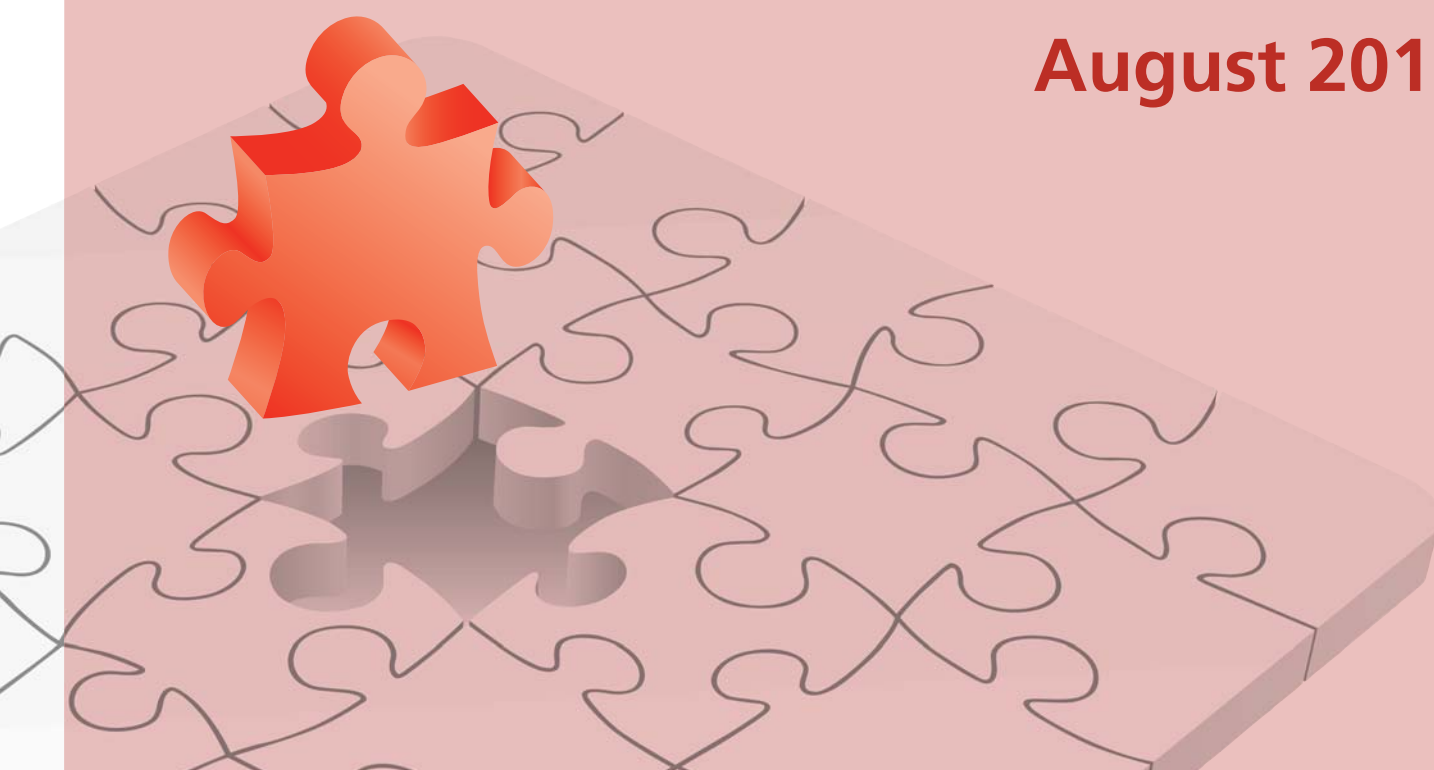


The management of the hyperosmolar hyperglycaemic state (HHS) in adults with diabetes

Joint British Diabetes Societies
Inpatient Care Group

August 2012



This document is coded JBDS 06 in the series of JBDS documents:

Other JBDS documents:

Glycaemic management during the inpatient enteral feeding of stroke patients with diabetes JBDS 05

Self-Management of Diabetes in Hospital March 2012 JBDS 04

The Management of Adults with Diabetes undergoing Surgery and Elective Procedures: improving standards April 2011 JBDS 03

The Hospital Management of DKA in Adults March 2010 JBDS 02

The Hospital Management of Hypoglycaemia in Adults with Diabetes Mellitus March 2010 JBDS 01

All of these publications can be found on the NHS Diabetes website at www.diabetes.nhs.uk

Contents

Foreword	5
List of authors	6
Executive summary	8
Introduction	10
• Definition and diagnosis	11
Initial assessment of fluid volume status	12
• Clinical	12
• Biochemical	12
• Changes in mental performance during HHS	13
Treatment of HHS	14
• Treatment goals	14
General treatment principles and controversial areas	15
• Point of care testing	15
• Calculation of Osmolality	15
• High-dependency / level 2 care	15
• Type of fluid	16
• Osmolality, sodium and glucose	16
• Isotonic versus hypotonic fluid replacement	16
• Water replacement and hypotonic fluid	17
• Insulin dose and timing	17
• Potassium	18
• Anti-infective therapy	18
• Anticoagulation	18
• Other electrolyte imbalances and complications associated with HHS	19
• Foot protection	19
• Recovery phase	19
References	20
FIGURE 1: Fluid balance in HHS	23
FIGURE 2: Change in osmolality during treatment of HHS	24
HHS care pathway	25
Appendix 1: Rationale for measurement and calculation of osmolality/osmolarity	31

Insert

Summary HHS management guideline

Foreword

Unlike the other common diabetes emergency, diabetic ketoacidosis (DKA), guidelines on the management of the hyperglycaemic hyperosmolar state (HHS) in adults are uncommon and often there is little to differentiate them from the management of DKA. However, HHS **is** different and treatment requires a different approach.

The person with HHS is often elderly, frequently with multiple co-morbidities but always very sick. Even when specific hospital guidelines are available, adherence to and use of these is variable amongst the admitting teams. In many hospitals these patients 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 (JBDS) for inpatient care, supported by NHS Diabetes, has produced up-to-date guidance developed by a multidisciplinary group of practicing specialists, with considerable experience in this area. Where possible, the guidance is evidence based but 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 the 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 glucose has plateaued.

The first 24 hours or so of treatment are very labour intensive and we strongly suggest that this is undertaken either in a medical intensive care unit or monitored bed in a well-staffed acute admissions ward.

Finally, we propose that adherence to the guideline should be audited after every admission with HHS. In conjunction with the Association of British Clinical Diabetologists (ABCD) we hope to undertake a prospective audit of the outcomes of care of people admitted with HHS to hospitals in the UK.

Dr Adrian Scott
Chair of HHS writing group
August 2012



List of Authors

Lead authorship

Dr Adrian Scott, Sheffield Teaching Hospitals NHS Foundation Trust

Anne Claydon, Barts Health NHS Trust

Supporting organisations

Tracy Kelly, Diabetes UK

Professor Mike Sampson (Norwich), Joint British Diabetes Societies (JBDS) Inpatient Care Group Chair

Esther Walden (Norwich), Diabetes Inpatient Specialist Nurse (DISN) UK Group Chair

Dr Chris Walton (Hull), Association of British Clinical Diabetologists (ABCD) Chair

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

JBDS IP Review Group

Dr Belinda Allan, Hull and East Yorkshire Hospital NHS 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), Joint British Diabetes Societies (JBDS) Inpatient Care Group Chair

Dr Mark Savage, The Pennine Acute Hospitals NHS Trust

Debbie Stanisstree, 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



Thanks also to comments from Dr Carl Waldmann on behalf of the Faculty of Intensive Care Medicine Professional Standards Committee and Dr Steve Ball, Senior Lecturer Newcastle University & Newcastle Hospitals NHS Trust

With special thanks to Christine Jones (DISN UK Group administrator, Norwich) for her administrative work and help with these guidelines and with JBDS – IP

Executive Summary

The hyperglycaemic hyperosmolar state (HHS) is a medical emergency. HHS is different from diabetic ketoacidosis (DKA) and treatment requires a different approach. Although typically occurring in the elderly, HHS is presenting in ever younger adults and teenagers, often as the initial presentation of type 2 diabetes mellitus (T2DM). It has a higher mortality than DKA and may be complicated by vascular complications such as myocardial infarction, stroke or peripheral arterial thrombosis. Seizures, cerebral oedema and central pontine myelinolysis (CPM) are uncommon but well-described complications of HHS. There is some evidence that rapid changes in osmolality during treatment may be the precipitant of CPM. Whilst DKA presents within hours of onset, HHS comes on over many days, and consequently the dehydration and metabolic disturbances are more extreme.

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 DKA. These are:

- Hypovolaemia
- Marked hyperglycaemia (30 mmol/L or more) without significant hyperketonaemia (<3 mmol/L) or acidosis ($\text{pH} > 7.3$, bicarbonate > 15 mmol/L)
- Osmolality usually 320 mosmol/kg or more

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

Goals of treatment

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

- Normalise the osmolality
- Replace fluid and electrolyte losses
- Normalise blood glucose

Other goals include prevention of:

- Arterial or venous thrombosis
- Other potential complications e.g. cerebral oedema/ central pontine myelinolysis
- Foot ulceration

Principles of treatment

HHS is associated with a significant morbidity and higher mortality than DKA and must be diagnosed promptly and managed intensively (Savage 2011). The diabetes specialist team should be involved as soon as possible after admission. Fluid losses in HHS are estimated to be between 100 -220 ml/kg (10-22 litres in a person weighing 100 kg) (Kitabachi 2009). The rate of rehydration will be determined by assessing the combination of initial severity and any pre-existing co-morbidities. Caution is needed, particularly in the elderly, where too rapid rehydration may precipitate heart failure but insufficient may fail to reverse acute kidney injury.



The principles of HHS treatment recommended in these guidelines are:

- Measure or calculate osmolality (2Na^+ + glucose + urea) frequently to monitor the response to treatment.
- Use intravenous (IV) 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. The rate of fall of plasma sodium should not exceed 10 mmol/L in 24 hours.
- The fall in blood glucose should be no more than 5 mmol/L/hr. Low dose IV insulin (0.05 units/kg/hr) should only be commenced once the blood glucose is no longer falling with IV fluids alone OR immediately if there is significant ketonaemia (3β -hydroxy butyrate greater than 1 mmol/L or urine ketones greater than 2+).
- IV fluid replacement aims to achieve a positive balance of 3-6 litres by 12 hours and the remaining replacement of estimated fluid losses within next 12 hours though complete normalisation of biochemistry may take up to 72 hours.
- The patient should be encouraged to drink as soon as it is safe to do so and an accurate fluid balance chart should be maintained until IV fluids are no longer required.
- Assessment for complications of treatment e.g. fluid overload, cerebral oedema or central pontine myelinosis (as indicated by a deteriorating conscious level) must be undertaken frequently (every 1-2 hours).
- Underlying precipitants must be identified and treated.
- Prophylactic anticoagulation is required in most patients.
- All patients should be assumed to be at high risk of foot ulceration if obtunded or uncooperative - the heels should be appropriately protected and daily foot checks undertaken (NICE 2004).

At all times, if the patient is not improving, senior advice should be sought.

Introduction

Unlike the other common diabetes emergency, 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. However, HHS **is** different and treatment requires a different approach. Although typically occurring in the elderly, HHS is presenting in ever younger adults and teenagers (Rosenbloom 2010, Zeitler 2011), often as the initial presentation of type 2 diabetes mellitus (T2DM) (Ekpebergh 2010).

In those previously diagnosed, the disease may have been managed by diet, oral hypoglycaemic agents or insulin. It is uncommon, but has a higher mortality than DKA (Delaney 2000). There are no recent publications from the UK of mortality in HHS, but reported series suggest mortality may have improved though remains high at between 15-20% (Piniés 1994, Rolfe 1995, MacIsaac 2002, Kitabachi 2006, Chung 2006).

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 international literature, they are inevitably contradictory and arbitrary. Previously called hyperosmolar non ketotic (HONK) coma, it was apparent that most of these patients were not comatose but were extremely ill. Changing the name to hyperosmolar hyperglycaemic state (HHS) allows for the fact that some people with severely raised blood glucose may also be mildly ketotic and acidotic. Whilst the reasons why these patients do not become ketoacidotic are not fully understood, hyperglycaemia and hyperosmolality are insufficient to make the diagnosis (English 2004). Many people with diabetes have severe but transient elevations of blood glucose – the difference between this and HHS, being the duration of hyperglycaemia and the accompanying dehydration.

As with many serious but rare metabolic emergencies, the evidence base for treatment is based more on common sense and clinical experience than randomised controlled trials. What is clear is that the greater mortality and morbidity in HHS is only in part related to age and co-morbidities. Controversies persist around the speed and type of fluid replacement (Milionis 2001, Kitabachi 2009). 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 (Cokar 2004, Raghavendra 2007). There is some evidence that rapid changes in osmolality during treatment may be the precipitant (O'Malley 2008). Whilst 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 anti-platelet therapy.

These 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.

Definition and Diagnosis

Characteristic features of a person with HHS:

Hypovolaemia

+

Marked hyperglycaemia (>30 mmol/L) without significant hyperketonaemia (<3.0 mmol/L) or acidosis ($\text{pH} > 7.3$, bicarbonate >15 mmol/L)

+

Osmolality >320 mosmol/kg

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 DKA. Defining HHS by osmolality alone is inappropriate without taking into account other clinical features.

A survey of hospital guidelines in the UK suggests the following would be reasonable:

- high osmolality, often 320 mosmol/kg or more
- high blood glucose, usually 30 mmol/L or more
- severely dehydrated and 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 (Fournier 2005). In HHS there is usually no significant ketosis/ketonaemia (less than 3 mmol/L), though a mild acidosis (pH greater than 7.3, bicarbonate greater than 15 mmol/L) may accompany the pre-renal failure. Some patients have severe hypertonicity and ketosis and acidosis (mixed DKA and HHS). This presumably reflects insulin deficiency, due to beta cell exhaustion as a result of temporary glucotoxicity. These patients may require a modification of this treatment guideline to take into account which aspect predominates.

Initial Assessment of fluid volume status

Hyperglycaemia results in an osmotic diuresis and renal losses of water in excess of sodium and potassium (Arrieff 1972). Thus in managing HHS there is a requirement to correctly identify and address both dehydration and extracellular volume depletion, depending upon the degree of free water and sodium deficit as assessed in any individual case. Fluid losses in HHS are estimated to be between 100-220 ml/kg (10-22 litres in a person weighing 100 kg) – Table 1.

Table 1 – Typical fluid and electrolyte losses in HHS (Kitabachi 2009)

		For 60 kg patient	For 100 kg patient
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

Clinical

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 over 330 mosmol/kg. The constellation of sunken eyes, longitudinal furrows on the tongue and extremity weakness correlates well with raised blood urea (Gross 1992, Sinert 2005). Severe hypovolaemia may manifest as tachycardia (pulse >100 bpm) and/or hypotension (systolic blood pressure <100 mmHg), (Lapides 1965, Delaney 2000, Kavouras 2002). Patients will usually be identified as being at high risk by use of a validated triage Early Warning Scoring systems (EWS).

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 – see Figure 1 (Coller 1935, Mange 1997, Bartoli 2009).

Biochemical

HHS should not be diagnosed from biochemical parameters alone. However, the blood glucose is markedly raised (usually 30 mmol/L or more), as is the osmolality.

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, osmolality should be calculated as a surrogate using the formula $2\text{Na}^+ + \text{glucose} + \text{urea}$.

This gives the best approximation to measured osmolality, though a more accurate formula has been derived (Bhagat 1984). *(For the sake of clarity, calculated osmolality and measured osmolality will be referred to as osmolality in the rest of this guideline).* 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.



Changes in mental performance during HHS

HHS and DKA can have marked effects on cerebral function and be associated with transient changes in mental performance and also with longer term effects. This may be due 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 (Kitabachi 1981, Daugiradis 1989) have suggested that changes in mental performance correlates with the severity of hyperosmolality, confusion common with an osmolality greater than 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 to the pre-morbid state which in the elderly inpatient is often lacking.



Treatment of HHS

Treatment goals

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

- Normalise the osmolality
- Replace fluid and electrolyte losses
- Normalise blood glucose

Other goals include prevention of:

- Arterial or venous thrombosis
- Other potential complications e.g. cerebral oedema/ central pontine myelinolysis
- Foot ulceration

General treatment principles and controversial areas

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

Point of care vs laboratory testing

Most hospitals in the UK now have ready access to blood gas machines that are able to produce reliable measurements of pH, urea, electrolytes, glucose etc. After the initial laboratory diagnostic sample, use of the blood gas machine 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 also measure oxygen saturation, 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 3 β -hydroxy butyrate is less than 1 mmol/L.

Capillary blood glucose and ketone measurement should be checked with a laboratory quality-controlled device meeting appropriate standards; procedures for checking the glucose must be strictly followed (Bektas 2004). Periodic, simultaneous, laboratory measurements of glucose may be necessary to confirm that there is minimal discrepancy between the two methods.

Calculation of osmolality

We did consider using effective osmolality ($2\text{Na}^+ + \text{glucose}$) but in a survey of British diabetes specialists, the difference between this and osmolality ($2\text{Na}^+ + \text{glucose} + \text{urea}$) was not well understood. (Appendix 1 for rationale)

High-dependency / level 2 care

Patients with HHS are complex and often have multiple co-morbidities so require intensive monitoring. The 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 greater than 350 mosmol/kg
- Sodium above 160 mmol/L
- Venous/arterial pH below 7.1
- Hypokalaemia (less than 3.5 mmol/L) or hyperkalaemia (more than 6 mmol/L) on admission
- Glasgow Coma Scale (GCS) less than 12 or abnormal AVPU (Alert, Voice, Pain, Unresponsive) scale
- Oxygen saturation below 92% on air (assuming normal baseline respiratory function)
- Systolic blood pressure below 90 mmHg
- Pulse over 100 or below 60 bpm

- 
- Urine output less than 0.5 ml/kg/hr
 - Serum creatinine > 200 µmol/L
 - Hypothermia
 - Macrovascular event such as myocardial infarction or stroke
 - Other serious co-morbidity

Type of fluid

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 (Hillman 1987, Matz 1997, Milionis 2001, Kitabachi 2009,). A Cochrane review (Perel 2011) recommended 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 to 0.9% sodium chloride solution in patients with DKA (Van Zyll 2011).

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 (NPSA 2002).

Osmolality, sodium and glucose

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

As frequent measurement of osmolality is not usually available in UK hospitals, osmolality should be calculated, as a surrogate, using the formula $2Na^+ + \text{glucose} + \text{urea}$ (Bhagat 1984). 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).

Isotonic versus hypotonic fluid replacement

- Rapid changes in osmolality may be harmful. Use 0.9% sodium chloride solution as the principle fluid to restore circulating volume and reverse dehydration.
- 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 which will reduce osmolality causing a shift of water into the intracellular space. This inevitably results in a rise in serum sodium (a fall in blood glucose of 5.5 mmol/L will result in a 2.4 mmol/L rise in sodium). This is not necessarily an indication to give hypotonic solutions.

- Isotonic 0.9% sodium chloride solution is already relatively hypotonic compared to the serum in someone with HHS.
- Rising sodium is only a concern if the osmolality is NOT declining concurrently. Rapid changes must be avoided – a safe rate of fall of plasma glucose of between 4 and 6 mmol/hr is recommended (Kitabachi 2009). If the inevitable rise in serum Na⁺ is much greater than 2.4 mmol/L for each 5.5 mmol/L fall in blood glucose (Katz 1973) this would suggest insufficient fluid replacement. Thereafter, the rate of fall of plasma sodium should not exceed 10 mmol/L in 24 hours (Adroque 2000).
- The aim of treatment should be to replace approximately 50% of estimated fluid loss within the first 12 hours and the remainder in the following 12 hours though this will in part be determined by the initial severity, degree of renal impairment and co-morbidities such as heart failure, which may limit the speed of correction.
- A target blood glucose of between 10 and 15 mmol/L is a reasonable goal. Complete normalisation of electrolytes and osmolality may take up to 72 hours.

Water replacement and hypotonic (0.45% sodium chloride solution) fluid

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 less than 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 plasma glucose is not being achieved then 0.45% sodium chloride solution should be substituted.

Insulin dose and timing

- If significant ketonaemia is present (3 β -hydroxy butyrate is more than 1 mmol/L) this indicates relative hypoinsulinaemia and insulin should be started at time zero.
- If significant ketonaemia is not present (3 β -hydroxy butyrate is less than 1 mmol/L) do NOT start insulin.
- Fluid replacement alone with 0.9% sodium chloride solution will result in falling blood glucose and because most patients with HHS are insulin sensitive there is a risk of lowering the osmolality precipitously. Insulin treatment prior to 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) (see Figure 2).
- The recommended insulin dose is a fixed rate intravenous insulin infusion (FRIII) given at 0.05 units per kg per hour (e.g. 4 units/hr in an 80 kg man) is used. A fall of glucose at a rate of up to 5 mmol/L per hour is ideal and once the blood glucose has ceased to fall following 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/hr. As with DKA, a FRIII is preferred, though generally lower doses are required.

Potassium

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 (see Table 2).

Table 2 – Potassium replacement in HHS

Potassium level in first 24 hr (mmol/L)	Potassium replacement in infusion solution
Over 5.5	Nil
3.5 – 5.5	40 mmol/L
Below 3.5	Senior review as additional potassium required (via central line in HDU)

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 C-reactive protein may be helpful (Gogos 2001). Antibiotics should be given when there are clinical signs of infection or imaging and/or laboratory tests suggest its presence.

Anticoagulation

Patients in HHS have an increased risk of arterial and venous thromboembolism (Whelton 1971, Keller 1975). Previous studies have estimated that patients with diabetes and hyperosmolality have an increased risk of venous thromboembolism (VTE) similar to patients with acute renal failure, acute sepsis or acute connective tissue disease (Paton 1981, Keenan 2007). The risk of venous thromboembolism is greater than in DKA (Petrauskiene 2005). Hypernatraemia and increasing antidiuretic hormone concentrations can promote thrombogenesis by producing changes in haemostatic function consistent with a hypercoagulable state (Carr 2001).

All patients should receive prophylactic low molecular weight heparin (LMWH) 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 VTE for three months after discharge (Keenan 2007). Consideration should be given to extending prophylaxis beyond the duration of admission in patients deemed to be at high risk.



Other electrolyte imbalances and complications associated with HHS

Hypophosphataemia and hypomagnesaemia are common in HHS. As with the management of DKA there is no evidence of benefit of treatment with phosphate infusion. However, 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 IV 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.

Foot protection

These patients 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 assume they are at high risk. **Re-examine the feet daily** (NICE 2004, *Putting Feet First* 2012).

Recovery phase

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

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

Most patients should be transferred to subcutaneous 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). People with HHS should be referred to the specialist diabetes team as soon as practically possible after admission. All patients will require diabetes education to reduce the risk of recurrence and prevent long-term complications.

References

- Adroque HJ, Madias NE. Hyponatremia. *N Engl J Med*. May 18 2000;342:1493-9
- Arrieff 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;73-94.
- Bartoli E, Bergamaco L, Castello L, Sainaghi PP. Methods for the quantitative assessment of electrolyte disturbances in hyperglycaemia. *Nutrition, Metabolism & Cardiovascular Diseases* 2009;19:67-74.
- 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.
- Bhagat CI, Garcia-Webb P, Fletcher E, Beilby JP. Calculated vs measured osmolality revisited. *Clin Chem* 1984; 30(10):1703-5.
- Bhave G, Neilson EG. Volume depletion versus dehydration: How understanding the difference can guide therapy. *Am J Kidney Disease* 2011: 302-309.
- Carr ME. Diabetes mellitus: a hypercoagulable state. *J Diabetes Complications* 2001; 15: 44–54.
- 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 Aug;73(2):184-90.
- Cokar O, Aydin B, Ozer F. Non-ketotic hyperglycaemia presenting as epilepsia partialis continua. *Seizure* 2004;13:264-69.
- Coller FA, Maddock WG. A study of dehydration in adults. *Annals of Surgery* 1935;947-960.
- Daugiradis JT, Kronfol NO, Tzamaloukas AH, Ing TS. Hyperosmolar coma: cellular dehydration and the serum sodium concentration. *Ann Intern Med* 1989;110:855-57.
- Delaney MF, Zisman A, Kettyle WM. DKA and hyperglycaemic, hyperosmolar non-ketotic syndrome. *Endocrinol Metab Clin North Am* 2000; 29:683-705.
- 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;100:822-26.
- English P, Williams G. Hyperglycaemic crises and lactic acidosis in diabetes mellitus. *Postgrad.Med.J.* 2004;80:253-261a.
- Fourtner SH, Weinzimer SA, Levitt Katz LE. Hyperglycemia, hyperosmolar non-ketotic syndrome in children with Type 2 diabetes. *Paediatr Diabetes* 2005;6:129-35.
- 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 ketoacidosis or hyperosmosis. *Diabetologia* 2001;44:1011-14.
- Gross CR, Lindquist RD, Woolley AC, Granieri R, Allard K, Webster B. Clinical indicators of dehydration severity in elderly patients. *The Journal of Emergency Medicine* 1992;267-274.
- Hillman K: Fluid resuscitation in diabetic emergencies: a reappraisal. *Intensive Care Med* 1987;13:4–8.

Katz MA. Hyperglycemia-induced hyponatremia: calculation of expected serum sodium depression. *N Engl J Med* 1973;289:843-4.

Kavouras SA. Assessing hydration status. *Current Opinion in Clinical Nutrition and Metabolic Care* 2002;519-524.

Keenan CR., Murin S, White RH. High risk for venous thromboembolism in diabetics with hyperosmolar state: comparison with other acute medical illnesses. *J of Thrombosis and Haemostasis* 2007;5(6):1185-90.

Keller U, Berger W, Ritz R, Truog P. Course and prognosis of 86 episodes of diabetic coma. *Diabetologia* 1975;11:93-100.

Kitabchi AE, Fisher JN. Insulin therapy of diabetic ketoacidosis: physiologic vs pharmacologic doses of insulin and their routes of administration. In *Handbook of Diabetes Mellitus*. Brownlee M, Ed. New York, Garland ATPM 1981:95-149.

Kitabchi AE, Nyenwe EA. Hyperglycemic crises in diabetes mellitus: DKA and hyperglycemic hyperosmolar state. *Endocrinol Metab Clin North Am.* 2006;35(4):725-51.

Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycaemic Crises in adult Patients with Diabetes. *Diabetes Care* 2009 ;32:1335-1343.

Lapides J, Bourne RB, Maclean LR. Clinical signs of dehydration and extracellular fluid loss. *JAMA* 1965;141-143.

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(8):379-85.

Mange K, Matsuura D, Cizman B, Soto H, Ziyadeh FN, Goldfarb S, Neilson EG. Language guiding therapy: the case of dehydration versus volume depletion. *Ann Intern Med,* 1997;848-852.

Matz R. Hyperosmolar nonacidotic diabetes (HNAD). In *Diabetes Mellitus: Theory and Practice*. 5th ed. Porte D Jr, Sherwin RS, Eds. Amsterdam, Elsevier, 1997, 845–860.

Milionis HJ, Liami G, Elisaf MS. Appropriate treatment of hypernatraemia in diabetic hyperglycaemic hyperosmolar syndrome. *J Int Med* 2001;249:273-76.

NICE CG10 2004 <http://www.nice.org.uk/nicemedia/Live/10934/29241/29241.pdf>.

NPSA Patient Safety Alert: Potassium solutions: risks to patients from errors occurring during intravenous administration. London 2002.

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;45:440-3.

Paton RC. Haemostatic changes in diabetic coma. *Diabetologia* 1981;21:172-177.

Perel P, Roberts J. Colloids vs crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database of Systematic Reviews* 2011, Issue 3 Art. No.: CD000567. DOI: 10.1002/14651858.CD000567.pub4.

Petruskiene V, Falk M, Waernbaum I, Norberg M, Eriksson JW. The risk of venous thromboembolism is markedly elevated in patients with diabetes. *Diabetologia* 2005; 48: 1017–21.



Piniés JA, Cairo G, Gaztambide S, Vazquez JA. Course and prognosis of 132 patients with diabetic non ketotic hyperosmolar state. *Diabete Metab.* 1994 Jan -Feb;20(1):43-8.

Putting Feet First. http://www.diabetes.org.uk/Get_involved/Campaigning/Putting-feet-first/ 2012.

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.

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 Mar; 85(3):173-6.

Rosenbloom AL. Hyperglycemic Hyperosmolar State: an emerging pediatric problem. *J of Pediatrics.* 2010;156(2):180-84.

Savage MW, Dhatariya KK, Kilvert A, Rayman G, Rees JAE, Courtney CH, Hilton L, Dyer PH, Hamersley MS, for the Joint British Diabetes Societies, Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. *Diabetic Medicine* 2011;28(5):508-15.

Sinert R, Spektor M. Clinical assessment of hypovolaemia. *Annals of Emergency Medicine* 2005; 327-329.

Van Zyll DG, Rheeder P, Delport E. Fluid management in diabetic-acidosis - Ringer's lactate versus normal saline: a randomized controlled trial. *QJM* 2011 doi: 10.1093/qjmed/hcr226. First published online: November 22, 2011

Whelton MJ, Walde D, Havard CWH. Hyperosmolar Non-Ketotic Diabetes Coma – with particular reference to vascular complications. *BMJ* 1971;1:85-86.

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 of Pediatrics* 2011;158(1):9-14.

FIGURE 1: (Adapted from Zeitler 2011)

Fluid balance in HHS:

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

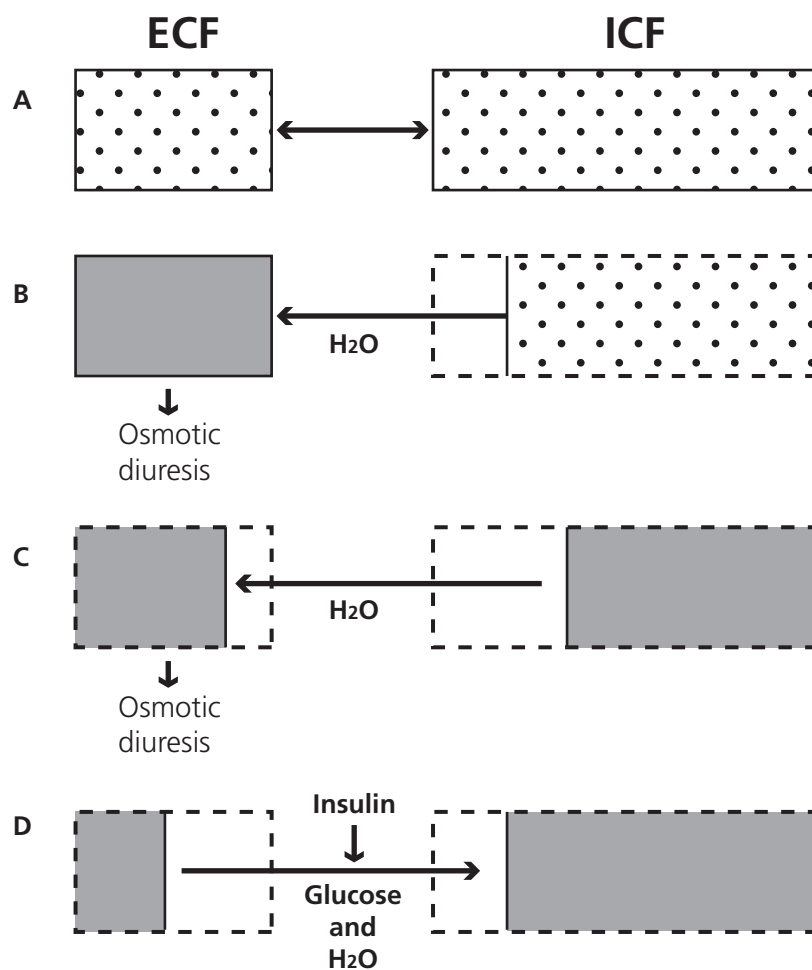
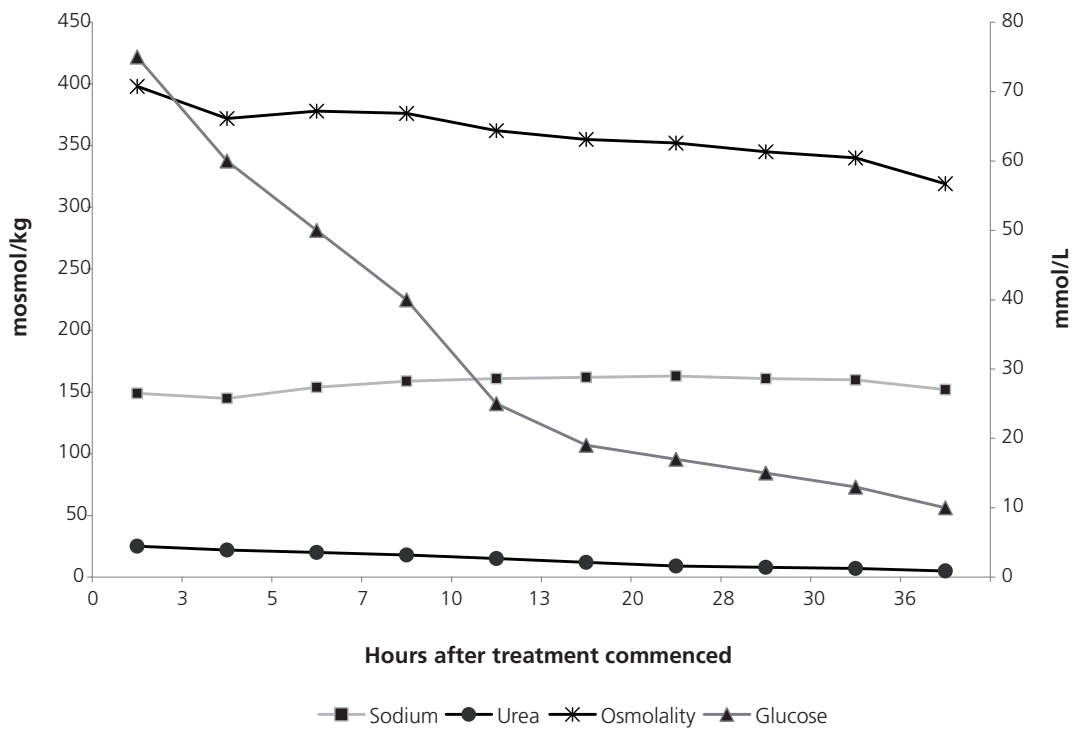


FIGURE 2:

Figure showing the change in osmolality during treatment of HHS with 0.9% sodium chloride solution. Note the fall in blood glucose (initially at 5 mmol/L per hr) and urea accompanied by a rise in sodium is nevertheless associated with a slow but steady fall in (calculated) osmolality.



HHS care pathway

The Hyperglycaemic Hyperosmolar State (HHS) is a medical emergency. In the UK it is less common than diabetic ketoacidosis (DKA), though 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 (2011).

Diagnosis

The characteristic features of a person with HHS are:

- Hypovolaemia
- Marked hyperglycaemia (30 mmol/L or more) **without** significant hyperketonaemia (less than 3 mmol/L), ketonuria (2+ or less) or acidosis (pH greater than 7.3, bicarbonate greater than 15 mmol/L)
- Osmolality usually 320 mosmol/kg or more

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

Assessment of severity

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

- osmolality greater than 350 mosmol/kg
- sodium above 160 mmol/L
- venous/arterial pH below 7.1
- hypokalaemia (less than 3.5 mmol/L) or hyperkalaemia (greater than 6 mmol/L) on admission
- Glasgow Coma Scale (GCS) less than 12 or abnormal
- AVPU (Alert, Voice, Pain, Unresponsive) scale
- oxygen saturation below 92% on air (assuming normal baseline respiratory function)
- systolic blood pressure below 90 mmHg
- pulse over 100 or below 60 bpm
- urine output less than 0.5 ml/kg/hr
- serum creatinine >200 µmol/L
- hypothermia
- macrovascular event such as myocardial infarction or stroke
- other serious co-morbidity.



Goals of treatment

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

- normalise the osmolality
- replace fluid and electrolyte losses
- normalise blood glucose.

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 ($2\text{Na}^+ + \text{glucose} + \text{urea}$) frequently to monitor treatment response.**
- **Use IV 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 in itself an indication for hypotonic fluids. Thereafter, the rate of fall of plasma sodium should not exceed 10 mmol/L in 24 hours.**
- **The fall in blood glucose should be no more than 5 mmol/L/hr. Low dose IV insulin (0.05 units/kg/hr) should be commenced once the blood glucose is no longer falling with IV fluids alone OR immediately if there is significant ketonaemia (3β -hydroxy butyrate greater than 1 mmol/L).**
- **Assess foot risk score on admission.**

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

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

- Commence IV 0.9% sodium chloride – 1 litre to run over 1 hour
 - Consider more rapid replacement if SBP below 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/hr) **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 BG
 - Urea and electrolytes
 - Measured or calculated osmolality (2Na^+ + glucose + urea)
 - Venous blood gas
 - Blood ketones and lactate
 - Full blood count
 - Blood cultures
 - ECG
 - CXR
 - Urinalysis and culture
 - CRP (if indicated)
 - Establish monitoring regime appropriate to patient – generally hourly blood glucose (BG), Na^+ , K^+ , urea and calculated osmolality (2Na^+ + glucose + urea) for the first 6 hours then 2 hourly if response satisfactory (a fall of 3-8 mosmol/kg/hr).
 - 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 LMWH
 - Consider IV antibiotics if sepsis identified or suspected

B. 60 minutes to 6 hours

Aims

- To achieve a gradual decline in osmolality (3-8 mosmol/kg/hr)
 - Using 0.9% normal saline aim to give a further 0.5 – 1 L/hr depending on clinical assessment of dehydration / risk of precipitating heart failure and fluid balance (target is to achieve positive fluid balance of 2-3 L by 6 hours)
 - 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 mosmol/kg/hr) 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/hr consider reducing infusion rate of IV fluids and/or insulin (if already commenced).
- If blood glucose falling less than 5 mmol/L per hour check fluid balance.
 - If positive balance inadequate, increase rate of infusion of 0.9% sodium chloride
 - If positive fluid balance adequate, commence low dose IV insulin (0.05 units/kg/hr) or if already running, increase rate to 0.1 units/kg/hr
- To maintain potassium in the normal range
 - Hypokalaemia (less than 3.5 mmol/L) and hyperkalaemia (greater than 6 mmol/L) are life-threatening conditions and warrant senior review. They are less common in HHS than DKA but monitoring and replacement are essential

Potassium level in first 24 hr (mmol/L)	Potassium replacement in infusion solution
Over 5.5	Nil
3.5 - 5.5	40 mmol/L
Below 3.5	Senior review as additional potassium required

- Avoidance of hypoglycaemia
 - Aim to keep blood glucose 10-15 mmol/L in first 24 hours
 - If blood glucose falls below 14 mmol/L commence 5% or 10% glucose at 125 ml/hr 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/hr)

C. 6 to 12 hours

The aim within this time period is to:

- Ensure that clinical and biochemical parameters are improving
 - Continue charting blood glucose hourly; sodium and calculated osmolality 2 hourly
 - Take appropriate action (as outlined in time 60 minutes to 6 hours) above
- Continue IV fluid replacement to achieve positive balance of 3-6 litres by 12 hours
 - 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 blood glucose 10-15 mmol/L in first 24 hours
 - If blood glucose falls below 14 mmol/L commence 5% or 10% glucose at 125 ml/hr AND CONTINUE 0.9% sodium chloride solution
- Ensure referral has been made to diabetes team

D. 12 to 24 hours

Aim:

- Ensure continuing improvement of clinical and biochemical parameters
 - Continue charting blood glucose 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 normalised by 24 hr (sodium and osmolality are likely to be raised)
 - Take appropriate action (as outlined in time 60 minutes to 6 hours) as outlined above depending on results
- Continue IV fluid replacement to achieve remaining replacement of estimated fluid losses within next 12 hours – 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 IV 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/hr increments or decrements to achieve desired BG
- 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 hours to Day 3

Expectation: patient should be steadily recovering, beginning to eat and drink, biochemistry back to normal.

- Ensure that clinical and biochemical parameters are improving or have normalised
 - Continue IV fluids until eating and drinking normally
 - Variable rate insulin if not eating and drinking
 - Convert to appropriate subcutaneous regime when biochemically stable
 - Encourage early mobilisation
 - 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 LMWH 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 subcutaneous 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 prior to discharge and arrange follow-up by diabetes team.

Appendix 1 Rationale for measurement and calculation of osmolality/osmolarity

Hyperosmolality

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 since 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, recognising that they are able to freely move across cell membranes and thus play no role in the distribution of free water within the body (Mange 1997, Bhavé 2011).

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:

$2\text{Na}^+ + \text{glucose} + \text{urea}$

$2(\text{Na}^+ + \text{K}^+) + \text{glucose}$

$2\text{Na}^+ + \text{glucose}$

The best approximation to measured osmolality can be calculated using the formula $2\text{Na}^+ + \text{glucose} + \text{urea}$, though a more accurate formula has been derived (Bhagat 1984). 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 since tonicity indicates risk of cerebral oedema i.e. hyposmolality.

Thus a patient with a Na^+ 122 mmol/L, glucose 13 mmol/L, urea 23 mmol/L has a calculated osmolality of 280 and an effective osmolality of 257, whereas a person with a Na^+ 122 mmol/L, glucose 30 mmol/L, urea 4 mmol/L has a calculated osmolality of 278 and an effective osmolality of 274. So the patient with the raised urea 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 $\text{Na}^+ = 122 + (2.4 \times 4) = 131.6$) (Katz 1973).

In the hyperosmolar state, osmolality is useful as an indicator of severity and for monitoring the rate of change with treatment. If frequent *measurement* of osmolality is not practical, osmolality should be made calculated using the formula $2\text{Na}^+ + \text{glucose} + \text{urea}$. This gives the best approximation to measured osmolality, though a more accurate formula has been derived (Bhagat 1984). 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.

www.diabetes.nhs.uk

Further copies of this publication can be ordered from Prontaprint, by emailing diabetes@leicester.prontaprint.com or tel: 0116 275 3333, quoting DIABETES 184