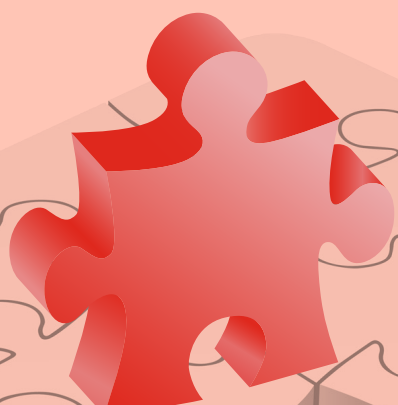


The Management of Hyperosmolar Hyperglycaemic State (HHS) in Adults*

February 2022



*For 16-18 year olds
Use this guideline if the person aged 16 – 18 is being managed by the adult diabetes team. If they are managed by the paediatric team, they should follow the following guideline: <http://www.a-c-d-c.org/wp-content/uploads/2012/08/Practical-Management-of-Hyperglycaemic-Hyperosmolar-State-HHS-in-children-8.pdf>



Royal College
of Physicians



The Association for
Clinical Biochemistry &
Laboratory Medicine



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

Other JBDS documents:

<i>The hospital management of hypoglycaemia in adults with diabetes mellitus</i>	<i>JBDS 01</i>
<i>The management of diabetic ketoacidosis in adults</i>	<i>JBDS 02</i>
<i>Management of adults with diabetes undergoing surgery and elective procedures: improving standards</i>	<i>JBDS 03</i>
<i>Self-management of diabetes in hospital</i>	<i>JBDS 04</i>
<i>Glycaemic management during the inpatient enteral feeding of stroke patients with diabetes</i>	<i>JBDS 05</i>
<i>The management of the hyperosmolar hyperglycaemic state (HHS) in adults with diabetes</i>	<i>JBDS 06</i>
<i>Admissions avoidance and diabetes: guidance for clinical commissioning groups and clinical teams</i>	<i>JBDS 07</i>
<i>Management of hyperglycaemia and steroid (glucocorticoid) therapy</i>	<i>JBDS 08</i>
<i>The use of variable rate intravenous insulin infusion (VRII) in medical inpatients</i>	<i>JBDS 09</i>
<i>Discharge planning for adult inpatients with diabetes</i>	<i>JBDS 10</i>
<i>Management of adults with diabetes on the haemodialysis unit</i>	<i>JBDS 11</i>
<i>Managing diabetes and hyperglycaemia during labour and birth</i>	<i>JBDS 12</i>
<i>The management of diabetes in adults and children with psychiatric disorders in inpatient settings</i>	<i>JBDS 13</i>
<i>A good inpatient diabetes service</i>	<i>JBDS 14</i>
<i>Inpatient care of the frail older adult with diabetes</i>	<i>JBDS 15</i>
<i>Diabetes at the front door</i>	<i>JBDS 16</i>
<i>The management of glycaemic control in people with cancer</i>	<i>JBDS 17</i>

These documents are available to download from the ABCD website at <https://abcd.care/joint-british-diabetes-societies-jbds-inpatient-care-group> , the Diabetes UK website at www.diabetes.org.uk/joint-british-diabetes-society

These guidelines can also be accessed via the [Diabetologists \(ABCD\)](#) app (need ABCD membership to access the app)



[@JBDSIP](#)



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Statement for Inpatient Guidelines

These guidelines have been developed to advise the treatment and management of hyperosmolar hyperglycaemic state in adults.

The guideline recommendations have been developed and reviewed by a multidisciplinary team led by the Joint British Diabetes Societies (JBDS) for Inpatient Care and a number of organisations with an understanding of HHS which have endorsed this guideline.

It is intended that the guideline will be useful to clinicians and service commissioners in planning, organising and delivering high quality diabetes inpatient care. There remains, however, an individual responsibility of healthcare professionals to make decisions appropriate to the circumstance of the individual, informed by them and/or their guardian or carer and taking full account of their medical condition and treatment.

When implementing this guideline full account should be taken of the local context and in line with statutory obligations required of the organisation and individual. No part of the guideline should be interpreted in a way that would knowingly put staff, those with diabetes or anyone else at risk.

Copyright statement

These guidelines are free for anyone to distribute, amend and use. However, we would encourage those who use them to acknowledge the source of the document and cite the Joint British Diabetes Societies for Inpatient Care.

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Disclaimer

The information contained in this guidance is a consensus of the development and consultation groups' views on current treatment. It should be used in conjunction with any local policies/procedures/guidelines and should be approved for use according to the trust clinical governance process. Care has been taken in the preparation of the information contained in the guidance. Nevertheless, any person seeking to consult the guidance, apply its recommendations or use its content is expected to use independent, personal medical and/or clinical judgement in the context of the individual clinical circumstances, or to seek out the supervision of a qualified clinician. The group makes no representation or guarantee of any kind whatsoever regarding the guidance content or its use or application and disclaim any responsibility for its use or application in any way.

To enable the guideline to stay relevant, it is envisaged that all of the JBDS guidelines will be updated or reviewed each year. As such these are 'living' documents – designed to be updated based on recently published evidence or experience. Thus, feedback on any of the guidelines is welcomed. Please email christine.jones@nnuh.nhs.uk with any comments, suggestions or queries.

Conflict of interest statement

The authors declare no conflicts of interest

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Young Diabetologists & Endocrinologists' Forum (YDEF)

The writing process

During the writing of this guideline available literature was reviewed and general areas for consideration were discussed within the JBDS-IP care group including conflicts of interest (of which there were none). A draft version was written and initially sent to the writing and review group; changes were discussed and incorporated as appropriate. This process was repeated several times until there was good consensus within the writing group. The guideline was subsequently sent to the full JBDS group and the process was repeated. Finally all the multi-professional endorsing groups received the document and their comments were considered and incorporated.

This guideline will be freely and widely available to all trusts with no copyright restrictions. It is hoped that it will be a useful resource for all healthcare professionals involved in discharge planning. However, as with all the JBDS guidelines, the authors welcome any comments, criticisms, or suggestions for future reviews. If you have any comments please email christine.jones@nuh.nhs.uk

Abbreviations

BG	Blood glucose
bpm	Beats per minute
BW	Body weight
CBG	Capillary blood glucose
CKD	Chronic kidney disease
CPM	Central pontine myelinolysis / Osmotic demyelination syndrome
CRP	C-reactive protein
DISN	Diabetes inpatient specialist nurse
DKA	Diabetic ketoacidosis
ECG	Electrocardiogram
FRIII	Fixed Rate Intravenous Insulin Infusion
HF	Heart failure
HHS	Hyperosmolar Hyperglycaemic State
hr	Hour
ICU	Intensive Care Unit
IV	intravenous
kg	kilograms
LMWH	Low molecular weight heparin
NEWS	National Early Warning Score
T1 DM	Type 1 diabetes mellitus
T2 DM	Type 2 diabetes mellitus
VBG	Venous blood gas
VRIII	Variable Rate Intravenous Insulin Infusion
VTE	Venous thromboembolism

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Foreword

The incidence of hyperosmolar hyperglycaemic state (HHS) has been reported as occurring up to 7 times less frequently than the other hyperglycaemic emergency, diabetic ketoacidosis (DKA). However, it has a greater mortality associated with it. This is likely to be due to the population who are at greatest risk of developing the condition – older individuals with multiple co-morbidities.

The previous version of this guideline recognised that the management of HHS was more complex than that of DKA and laid out a pathway of care. As with other diabetes related emergencies, the initial management is often carried out by non-specialists. Thus, the guideline needed to be relatively straightforward and easy to follow. The fact that the document was rapidly adopted by almost all hospitals in the UK and, in a survey of hospital diabetes teams, was thought to be safe and of good quality is a testament to the original author.

This updated document now includes more of the recently published evidence on how this hyperglycaemic emergency should be managed. The core of the document – the 'How To' guide, remains essentially unchanged but it now more closely resembles some of the newer JBDS documents. It also includes a new definition of resolution, as well as new audit standards to allow individual teams to benchmark themselves over time.

As with all of the other JBDS documents, these are always in a state of evolution. If new data are published, the document will be updated to reflect that. As always, if you feel something could be done differently, please feel free to contact us.



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[Signature]

The Management of the Hyperosmolar Hyperglycaemic State (HHS) in Adults with Diabetes

Executive Summary

The Hyperosmolar Hyperglycaemic State (HHS) is a medical emergency. It occurs much less frequently than the other hyperglycaemic emergency, diabetic ketoacidosis (DKA), and its treatment requires a different approach. HHS usually affects those with pre-existing type 2 diabetes mellitus (T2DM) but may sometimes be the first presentation of this condition. Typically HHS occurs in those aged over 45 years old, but it can affect younger adults and teenagers (1; 2). HHS often develops over several days, and consequently the dehydration and metabolic disturbances are more extreme. The predominant cause of HHS is usually a chest or urinary tract infection (3). HHS has a high mortality because it may be due to, or complicated by, vascular events such as myocardial infarction, stroke or peripheral arterial thrombosis (3; 4). Neurological complications, such as cerebral oedema and central pontine myelinolysis (CPM) / osmotic demyelination syndrome are uncommon but can be seen as a complication of the rapid changes in osmolality during treatment of HHS (5; 6).

Fluid Replacement

Fluid losses in HHS are estimated to be between 100 – 220 ml/kg (i.e. 10 – 22 litres in a person weighing 100 kg) (7). 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:

- use intravenous (IV) 0.9% sodium chloride solution as the principle fluid to restore circulating volume and reverse dehydration
- measure or calculate osmolality $[(2Na^+) + \text{glucose} + \text{urea}]$ every hour for the first 6 hours, then 2 hourly for the next 6 hours to monitor the response to treatment and to avoid sudden osmotic shifts
- 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 due to the reversal of relative pseudohyponatraemia in the context of hyperglycaemia and is not itself an indication for hypotonic fluids. The rate of change of serum sodium should not exceed 10 mmol in 24 hours (8; 9)
- underlying precipitants of HHS must be identified and treated

- the fall in osmolality should not be more than 3.0-8.0 mOsm/kg/hr to minimise the risk of neurological complications
- the fall in glucose should not be more than 5.0 mmol/L/hr
- ONLY commence insulin infusion quickly in the following circumstances:
 - o If there is HHS and ketonaemia (blood ketones 3 β -hydroxybutyrate >1.0 - \leq 3.0 mmol/L or urine ketones \geq 2+) and not acidotic (venous pH >7.3 and bicarbonate >15.0 mmol/L) then use 0.05 units/kg/hr OR
 - o If there is significant ketonaemia (3 β -hydroxybutyrate >3.0 mmol/L) or ketonuria (\geq 2+) with a pH <7.3 and bicarbonate <15 mmol/L (i.e. mixed DKA and HHS) then use the DKA guidelines at 0.1 units/kg/hr
 - o Treat as mixed DKA/HHS if the following criteria are met. Start FRIII and IV fluids immediately and treat according to DKA pathway using 0.1 units/kg/hr
 - o marked hypovolaemia
 - o marked hyperosmolality
 - o pH <7.3 and
 - o blood ketones >3.0 mmol/L
 - o IV fluid replacement should aim to achieve a positive balance of 3-6 litres during the first 12 hours and the remaining replacement of estimated fluid loss during the following 12 hours, although complete normalisation of biochemistry may take up to 72 hours
- the individual 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 of complications of treatment e.g. fluid overload, cerebral oedema or CPM / osmotic demyelination syndrome (as indicated by a deteriorating conscious level) must be undertaken frequently (every 1-2 hours).
- prophylactic LMWH is required in most people
- everyone should be assumed to be at high risk of foot ulceration, particularly if obtunded or uncooperative. The heels should be appropriately protected and daily foot checks undertaken (10)
- HHS can be considered to be resolved when the following criteria are met: when measured or calculated serum osmolality falls to <300 mOsm/kg, hypovolaemia has been corrected (urine output \geq 0.5 ml/kg/hr), cognitive status has returned to the pre-morbid state and blood glucose <15 mmol/L

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

Changes since the original guideline

This document has been significantly updated. Where new evidence has emerged, this has been cited. The document now also emphasises that because more children and young people are being diagnosed with T2DM, and also presenting with HHS, that there is a separate guideline for those under 18 years old, who are managed by paediatric teams. This can be found at <http://www.a-c-d-c.org/wp-content/uploads/2012/08/Practical-Management-of-Hyperglycaemic-Hyperosmolar-State-HHS-in-children-8.pdf>.

The bedside monitoring chart found at the end of this document, and available separately on line, has been updated. We have also introduced a formal definition of resolution of HHS and audit standards.

There are now a lot of data on the impact of COVID-19 infection on people with diabetes. Whilst these data are important, the presence of COVID-19 infection as a cause of HHS does not change how it is managed, and thus is not dealt with separately.

Who should read this guideline?

- All members of the hospital multidisciplinary Diabetes Specialist Team (DST)
- All medical and nursing staff and allied healthcare professionals looking after people with diabetes in hospital
- The single point of assessment discharge coordinator for each acute area
- All members of the community diabetes care provider team
- Hospital and ward managers
- Local clinical commissioning groups

HHS Care Pathway in Adults*

*For 16-18 year olds

Use this guideline if the person aged 16 – 18 is being managed by the adult diabetes team. If they are managed by the paediatric team, they should use the following guideline: <http://www.a-c-d-c.org/wp-content/uploads/2012/08/Practical-Management-of-Hyperglycaemic-Hyperosmolar-State-HHS-in-children-8.pdf>

The Hyperosmolar Hyperglycaemic State (HHS) is a medical emergency. HHS is associated with a significant morbidity and mortality and must be diagnosed promptly and managed intensively. The diabetes specialist team should be involved as soon as possible after admission.

Diagnosis

Definition and Diagnosis

A precise definition of HHS has not been agreed, but there are characteristic features that differentiate it from other hyperglycaemic states such as DKA.

The characteristic features of a person with HHS are:

- marked hypovolaemia
- measured or calculated serum osmolality usually ≥ 320 mOsm/kg
- marked hyperglycaemia (≥ 30 mmol/L)
- without significant hyperketonaemia (ketones ≤ 3.0 mmol/L)
- without significant acidosis (pH ≥ 7.3 and blood or serum bicarbonate ≥ 15.0 mmol/L)

N.B. A mixed picture of HHS and DKA occurs relatively frequently (4).

Assessment of severity

Care for people with HHS can be complex because they often have multiple co-morbidities and may require intensive monitoring.

The presence of one or more of the following should prompt discussion because they indicate the need for admission to a High-Dependency Unit / Level 2 environment:

- | | |
|---|--|
| <ul style="list-style-type: none">• Measured or calculated Osmolality >350 mOsm/kg• Sodium >160 mmol/L• Venous/arterial pH <7.1• Hypokalaemia (<3.5 mmol/L) or hyperkalaemia (>6 mmol/L) on admission• Glasgow Coma Scale (GCS) <12 or abnormal AVPU (Alert, Voice, Pain, Unresponsive) scale | <ul style="list-style-type: none">• 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/hr• Serum creatinine >200 µmol/L and/or acute kidney injury• Hypothermia• Macrovascular event such as myocardial infarction or stroke• Other serious co-morbidity |
|---|--|

Goals of Treatment

HHS is associated with a significant morbidity and higher mortality than DKA and must be diagnosed promptly and managed intensively (11; 12). The goals of treatment of HHS are to treat the underlying cause and to gradually and safely:

- | |
|---|
| <ul style="list-style-type: none">• normalise the osmolality• replace fluid and electrolyte losses• normalise blood glucose |
|---|

Other goals include prevention of:

- | |
|---|
| <ul style="list-style-type: none">• arterial or venous thrombosis• other potential complications e.g. cerebral oedema/ central pontine myelinolysis / osmotic demyelination syndrome• foot ulceration |
|---|

Management timeline:

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.

Intravenous fluid

Commence IV 0.9% sodium chloride – 1 litre to run over 1 hour

- Consider more rapid replacement if systolic blood pressure (SBP) < 90 mmHg
- Caution in the elderly where too rapid rehydration may precipitate heart failure but insufficient may fail to reverse acute kidney injury

Intravenous insulin

ONLY commence insulin infusion quickly in the following circumstances:

- If there is HHS and ketonaemia (blood ketones 3 β -hydroxybutyrate >1.0 - \leq 3.0 mmol/L or urine ketones < 2+) and not acidotic (venous pH >7.3 and bicarbonate >15.0 mmol/L) then use 0.05 units/kg/hr

OR

- If there is significant ketonaemia (3 β -hydroxybutyrate >3.0 mmol/L) or ketonuria (\geq 2+) with a pH <7.3 and bicarbonate <15 mmol/L (i.e. mixed DKA and HHS) and use the DKA guideline at 0.1 units/kg/hr

https://abcd.care/sites/abcd.care/files/site_uploads/JBDS_02%20DKA_Guideline_amended_v2_June_2021.pdf

Assessment

Clinical assessment:

- 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
- Mini Mental State assessment for cognitive assessment
- Assess for contraindications of low molecular weight heparin (LMWH)

Assess foot risk score – assume high risk if the person is obtunded or uncooperative

- Ensure heels are off-loaded
- Ensure daily foot checks

Investigations

- Capillary blood glucose (BG) (finger prick point of care)
- Venous plasma BG (blood in a fluoride bottle)
- Urea and electrolytes
- Measured or calculated serum osmolality $[(2 \times \text{Na}^+) + \text{glucose} + \text{urea}]$. Until the urea is available, calculate using $(2 \times \text{Na}^+ + \text{glucose})$. Recalculate osmolality once urea is available, and then use $(2 \times \text{Na}^+ + \text{glucose} + \text{urea})$.
- Venous blood gas (VBG) for: pH, bicarbonate, lactate, and electrolytes
- Capillary blood ketones (finger prick point of care)
- Full blood count
- Blood cultures
- ECG
- Chest x-ray
- Urinalysis and culture
- CRP (if indicated)

Monitoring

Establish monitoring regime appropriate to the individual – generally hourly blood glucose, Na^+ , K^+ , urea and calculated osmolality $[(2 \times \text{Na}^+) + \text{glucose} + \text{urea}]$ for the first 6 hours, then 2 hourly osmolality if the response is satisfactory (i.e. a fall of 3.0-8.0 mOsm/kg/hr).

- Chart measured or calculated osmolality / glucose / sodium
- Continuous pulse oximetry
- Consider continuous cardiac monitoring

60 minutes to 6 hours

Aims

- Treat underlying cause if known
- To achieve a gradual decline in osmolality (i.e. 3.0-8.0 mOsm/kg/hr)
 - Using 0.9% sodium chloride solution aim to give a further 0.5-1 litre/hr depending on clinical assessment of dehydration vs. risk of precipitating heart failure. The target is to achieve positive fluid balance of 2-3 litres by 6 hours
 - Measure glucose, urea and electrolytes hourly and calculate osmolality $[(2 \times \text{Na}^+) + \text{glucose} + \text{urea}]$
- 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 3.0 mOsm/kg/hr), check fluid balance. If positive balance is inadequate, then increase the rate of infusion of 0.9% sodium chloride solution
- If the osmolality is increasing and fluid balance adequate, then consider switching to 0.45% sodium chloride at same infusion rate
- If osmolality falling at rate exceeding 8.0 mOsm/kg/hr consider reducing infusion rate of IV fluids and/or insulin (if already commenced)
 - If glucose falling less than 5.0 mmol/L per hour check fluid balance
- If positive balance inadequate, increase rate of infusion of 0.9% sodium chloride
- Fluid replacement should be adjusted for those who are <50 kg in body weight or with pre-existing heart and renal disease. More cautious fluid replacement is necessary e.g. 0.25 ml/kg/hr as recommended by NICE (13)
- **ONLY** start IV insulin once fluid replacement is adequate and glucose concentrations have plateaued. Starting an IV insulin infusion too early could result in circulatory collapse
- If positive fluid balance is adequate, commence low dose IV insulin as a fixed rate intravenous insulin infusion (FRIII) at 0.05 units/kg/hr or if already running, increase rate to 0.1 units/kg/hr if glucose concentrations are not falling
- Maintain potassium in the normal range
 - Hypokalaemia (<3.5 mmol/L) and hyperkalaemia (>6.0 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 concentration in first 24h (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 BG 10-15 mmol/L in first 24 hours
 - If BG 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 National Early Warning Score (NEWS)
- Check ketone concentrations hourly until HHS resolution
- Maintain accurate fluid balance chart (minimum urine output 0.5 ml/kg/hr)
- Heel protectors and an appropriate mattress should be provided for those with immobility, neuropathy, peripheral vascular disease or lower limb deformity.

6 to 12 hours

Aims

- Ensure that clinical and biochemical parameters are improving
 - Continue charting BG 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, cerebral pontine myelinolysis (e.g. deteriorating conscious level)
- Continue treatment of any underlying precipitant(s).
 - If the person is not improving, seek senior advice
- Avoid hypoglycaemia
 - Aim to keep BG 10-15 mmol/L in first 24 hours
 - If BG 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 the diabetes team

12 to 24 hours

Aims

- Ensure continuing improvement of clinical and biochemical parameters
 - 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 normalised by 24 hrs (sodium and osmolality are likely to be raised)
 - Take appropriate action as outlined above (in time 60 min to 6 hours) depending on results
- Check ketones hourly until HHS resolution
- Continue IV fluid replacement to achieve remaining replacement of estimated fluid losses within next 12 hrs. 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 BG 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, central/extra pontine myelinolysis/osmotic demyelination syndrome (e.g. deteriorating conscious level)
- Continue treatment of any underlying precipitant(s)
 - If the person is not improving seek senior advice

24 hours to day 3

Expectations

- The individual should be steadily recovering, beginning to eat and drink, and the biochemistry is as it was prior to the acute episode
- 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 https://abcd.care/sites/abcd.care/files/resources/JBDS_IP_VRIII.pdf
 - Convert to appropriate subcutaneous insulin regime when biochemically stable
 - Encourage early mobilisation
 - Daily urea and electrolytes
 - Remove urinary 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 those deemed very high risk. This may require specialist advice)
- Ensure that the person has been reviewed by diabetes team

After Care

Most people should go home on subcutaneous insulin (the regime being determined by their circumstances). For those 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. How long this will be for is dependent on the person with diabetes and local circumstances. Ensure the individual has appropriate diabetes education prior to discharge and arrange follow-up by diabetes team.

See Care Pathway on pages 19 and 20

Hyperosmolar Hyperglycaemic State (HHS) care pathway in adults

Clinical features (all the below)	Aims of therapy	Criteria for resolution of HHS: Holistic assessment of the following:
1) Marked hypovolaemia 2) Osmolality ≥ 320 mOsm/kg 3) Marked hyperglycaemia (≥ 30 mmol/L) 4) Without significant ketonaemia (≤ 3.0 mmol/L) 5) Without significant acidosis (pH ≥ 7.3) and bicarbonate ≥ 15 mmol/L	A mixed picture of HHS and DKA occurs relatively frequently 1) Improvement in clinical status and replacement of all estimated fluid losses by 24 hours 2) Gradual decline in osmolality: drop of 3-8 mOsm/kg/hr 3) Blood glucose: aim to keep to 10-15 mmol/L in the first 24 hours 4) Avoid hypoglycaemia and hypokalaemia 5) Prevent harm: VTE, osmotic demyelination, fluid overload, foot ulceration	1) Clinical and cognitive status is back to the pre-morbid state 2) Osmolality < 300 mOsm/kg 3) Hypovolaemia has been corrected (urine output ≥ 0.5 ml/kg/hr) 4) Blood glucose < 15 mmol/L

Theme	Time	0-60 minutes	60 minutes - 6 hours	6-12 hours	12-24 hours	24-72 hours
Clinical assessment and monitoring						
Clinical status / NEWS		History/Examination, NEWS, cardiac monitoring, urine output Establish adequate intravenous lines (preferably 2 large bore IV cannulas) Discuss with outreach/ICU team early if there are markers of high severity (see Table 1 overleaf)			Check for continuing improvement	
Precipitating cause(s)		Assess for precipitating cause(s): sepsis, diabetic foot infection, treatment omissions, vulnerable adult, vascular event (myocardial infarction, stroke)			Ongoing management of the precipitating cause(s)	Expect steady recovery, patient eating and drinking, and biochemistry as it was prior to HHS
Osmolality (VBG/blood) Measure/calculate ($2 \times \text{Na}^+$) + Glucose + Urea Aim for gradual decline of 3-8 mOsm/kg/hr		Check every hour for 6 hours Until the urea is available, calculate using ($2 \times \text{Na}^+$ + glucose). Recalculate osmolality once urea is available, and then use ($2 \times \text{Na}^+$ + glucose + urea)		Check every 2 hours	Check every 4 hours (if no clinical improvement then check every 2 hours)	Ongoing management of the precipitating cause(s) Replacement of all estimated fluid losses by 24 hours Individual BG target 6-10 mmol/L
How to interpret osmolality results		Check Figure 1 overleaf	Check Figure 1 overleaf	Check Figure 1 overleaf	Check Figure 1 overleaf	
Blood glucose (BG) (Aim for 10-15 mmol/L in the first 24 hours)		Check every hour Fall in BG should be up to 5.0 mmol/L per hour (check Figure 2 overleaf for details)		Check every hour (check Figure 2 overleaf for details)	Check every hour (check Figure 2 overleaf for details)	
Interventions						
Intravenous fluids (0.9% saline) (In IV line 1) (caution in HF/CKD/BW < 50 kg)		1 litre over 1 hour (caution in HF/CKD/BW < 50 kg)	Aim for 2-3 litres positive balance by 6 hours	Aim for up to 6 litres positive balance by 12 hours	Reassess fluid balance to plan fluids replacement for the next 12 hours	Can be stopped if patient is eating and drinking
Insulin infusion (FRIII 0.05 units/kg/hr using Actrapid®) (In IV line 2)		Use DKA guidelines if ketonaemia (> 3.0 mmol/L) or ketonuria ($\geq 2+$) Start FRIII if ketonaemia ($> 1.0 - \leq 3.0$ mmol/L) or ketonuria ($< 2+$)	Only commence if positive fluid balance and BG plateaued on repeated measurements (> 2 occasions)		Rate may need adjustment to 1 unit/hr to achieve BG target 10-15 mmol/L	VRIII if not eating and drinking Otherwise convert to subcutaneous insulin
Glucose infusion: 5% or 10% @ 125ml/hr (In IV line 2)		Not required at this stage	Only initiate if BG < 14 mmol/L		Continue infusion at 125 ml/hr	Can be stopped if patient is eating and drinking
Potassium		Senior review / ICU outreach if potassium < 3.5 or > 6.0 mmol/L	Check Table 2 overleaf for potassium replacement guidelines	Check Table 2 overleaf for potassium replacement guidelines	Check Table 2 overleaf for potassium replacement guidelines	Check U&Es daily
Assessments and prevention						
Prevent harm		VTE prophylaxis (low molecular weight heparin) Assess for complications e.g. fluid overload, cerebral oedema, osmotic demyelination (deteriorating conscious level)				VTE prophylaxis until discharge Daily feet checks
Prevent hypoglycaemia		Glucose 5% or 10% at 125 ml/hr if BG < 14 mmol/L				Target BG 6-10 mmol/L
Prevent foot ulceration		Daily foot checks				Daily foot checks
Refer to the inpatient diabetes team early. Escalate management if there is clinical deterioration.						Review by inpatient diabetes team before discharge

Abbreviations: BG=blood glucose; BW=body weight; CKD=chronic kidney disease; FRIII=fixed rate intravenous insulin infusion; HF=heart failure; hr=hour; ICU=intensive care unit; IV=intravenous; kg=kilograms; NEWS=national early warning score; U&Es=urea and electrolytes; VBG=venous blood gas analysis; VRIII=variable rate intravenous insulin infusion; VTE=venous thromboembolism

Hyperosmolar Hyperglycaemic State (HHS) care pathway in adults

Figure 1: Managing osmolality changes during treatment of HHS

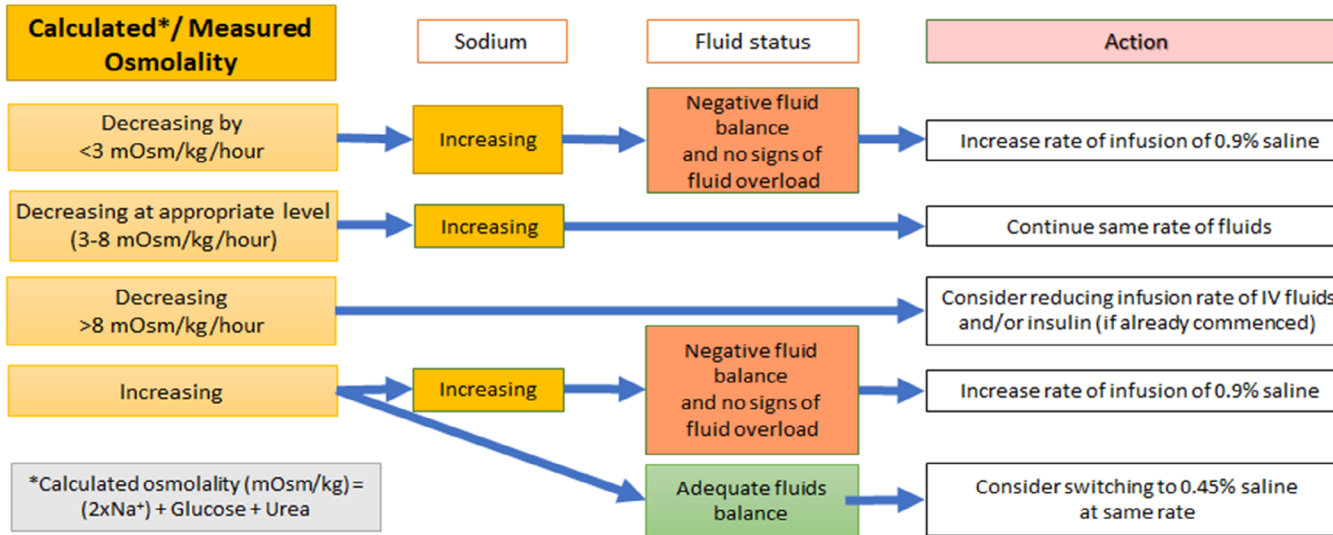
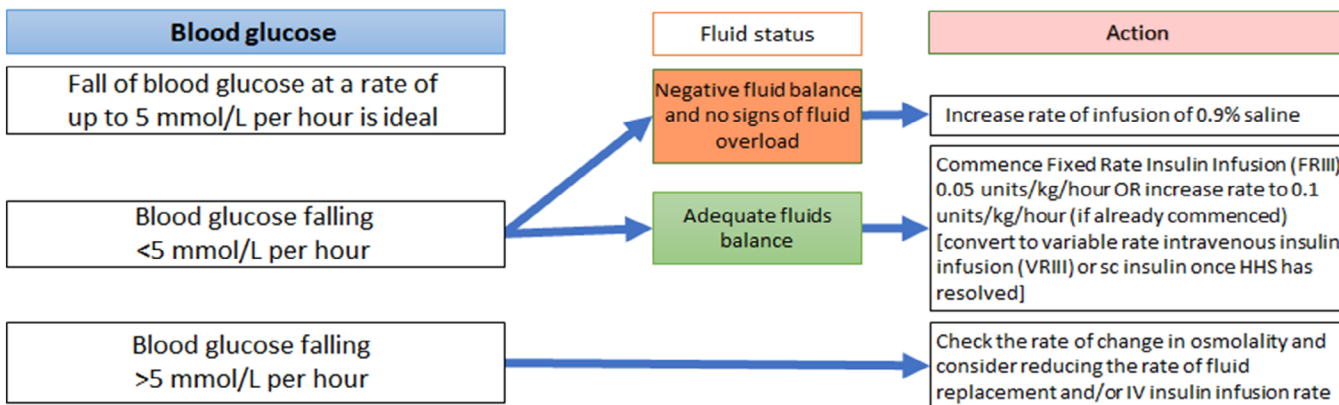


Figure 2: Managing glucose changes during treatment of HHS



If the parameters in Figures 1 and 2 above are not met, seek specialist input early to help tailor the management according to the individual's need

Table 1: Escalate to ICU/outreach if any of the following is present:

- Osmolality >350 mOsm/kg
- Sodium >160 mmol/L
- Venous/arterial pH <7.1
- Hypokalaemia (<3.5 mmol/L) or hyperkalaemia (>6 mmol/L) on admission
- Glasgow Coma Scale (GCS) <12 or abnormal AVPU (Alert, Voice, Pain, Unresponsive) scale
- Oxygen saturation <92% on air (assuming normal baseline respiratory function)
- Systolic blood pressure <90 mmHg
- Pulse >100 or <60 beats per minute
- Urine output <0.5 ml/kg/hour
- Serum creatinine >200 µmol/L and/or Acute kidney injury
- Hypothermia
- Macrovascular event such as myocardial infarction or stroke
- Other serious co-morbidity

Table 2: Potassium replacement guidelines

Potassium level in first 24 hours (mmol/L)	Potassium replacement in infusion solution
≥6.0	Senior review ICU/outreach
5.5-5.9	Nil
3.5-5.5	40 mmol/L
<3.5	Senior review ICU/Outreach. Additional potassium is required

Guideline for the Management of the Hyperosmolar Hyperglycaemia State (HHS) in Adults

Introduction

Until the publication of the first edition of this document, national guidelines on the management of hyperosmolar hyperglycaemic state (HHS) in adults had been uncommon. As is now well recognised, HHS is different to diabetic ketoacidosis (DKA), and treatment requires a different approach. Although typically occurring in those aged over 45 (1; 2), HHS can present in children and younger adults (1; 14; 15), often as the initial presentation T2DM (1; 16).

HHS is uncommon, in the USA accounting for only 13% of hyperglycaemia related emergency admissions (2), but has a higher mortality than DKA (4; 17-19). There are no recent publications from the UK on mortality in HHS, but reported series suggest mortality may have improved though remains high at between 15-20% (20-24).

HHS often develops over many days, and consequently the dehydration and metabolic disturbances are usually more extreme. Many people with diabetes have severe but transient elevations of BG – 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 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. There were controversies that persisted around the speed and type of fluid replacement and when insulin should be introduced. However, the use of the previous edition of this guideline has standardised practice across many parts of the UK, with most teams feeling they were of good quality and safe (25).

These guidelines are evidence 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 (18). 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 health care professional that manages HHS in adults.

Definition and Diagnosis

Characteristics of a person with HHS:

Hypovolaemia
+
Osmolality ≥ 320 mOsm/kg
+
Marked hyperglycaemia (≥ 30.0 mmol/L)
+
Without significant hyperketonaemia (≤ 3.0 mmol/L)
Without significant acidosis ($\text{pH} \geq 7.3$)
and bicarbonate ≥ 15.0 mmol/L

Osmolality (mOsm/kg) = $(2 \times \text{Na}^+) + \text{glucose} + \text{urea}$

International guidelines vary as to the precise definition of HHS (18), 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.

Previously called HyperOsmolar Non Ketotic (HONK) coma it was apparent that most of these people were not comatosed, but were extremely ill. Changing the name to Hyperosmolar Hyperglycaemic State (HHS) allows for the fact that some people with severely raised BG may also be mildly ketotic and acidotic. Whilst the reasons why these people do not become ketoacidotic are not fully understood, hyperglycaemia and hyperosmolality without evidence of significant dehydration are insufficient to make the diagnosis (26).

People with HHS are generally older than those with DKA, but increasingly, as the diabetes pandemic crosses generational boundaries, it may be seen in young adults and even children as the first presentation of newly diagnosed diabetes (1; 14; 15). HHS has a slower onset than DKA. This is important because the brain tissue of those who typically develop HHS, particularly in those who are older, are at higher risk of injury due to rapid shifts in sodium, water and glucose. Therefore, to prevent significant neurological damage, HHS requires less aggressive fluid resuscitation and slower glucose-lowering than DKA. In HHS there is usually no significant ketosis/ketonaemia (≤ 3.0 mmol/L), although a mild acidosis ($\text{pH} > 7.3$, bicarbonate > 15.0 mmol/L) may accompany those affected by acute kidney injury or severe sepsis. Some people have severe hypertonicity and ketosis and acidosis (mixed DKA and HHS) (4). This situation is likely to reflect a relative insulin deficiency due to beta cell exhaustion as a result of temporary glucotoxicity and excess counter-regulatory hormone production. These individuals may require a modification of this treatment guideline to take into account which aspect predominates. If a predominant diagnosis is unclear (HHS vs mixed HHS/DKA), early specialist input should be sought to help tailor management according to the individual's need. However, if ketone concentrations are high, then the local DKA protocol may be appropriate.

There remain many aspects of care that are unanswered. An example is venous-thromboembolism prophylaxis. Whilst thrombotic complications such as myocardial infarction, stroke or peripheral arterial thrombosis occur more frequently in HHS, it is not known whether or not these can be prevented by prophylaxis with low dose LMWH or anti-platelet therapy, or if a full therapeutic dose should be used (27; 28).

Initial Assessment

Hyperglycaemia results in an osmotic diuresis and renal losses of water in excess of sodium and potassium (29). Fluid losses in HHS can be significant and have been estimated to be between 100 – 220 ml/kg (10 -22 L in a person weighing 100 kg) – Table 1

Table 1- Typical fluid and electrolyte losses in HHS

		For a 60 kg individual	For a 100 kg individual
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 cognitive impairment is not necessarily present and may be associated with dehydration but is not specific to the condition. Alterations in cognitive status are more common when the osmolality rises above 330 mOsm/kg. The constellation of sunken eyes, longitudinal furrows on the tongue and extremity weakness correlates well with raised blood urea (30; 31). Severe hypovolaemia may manifest as tachycardia (pulse >100 bpm) and/or hypotension (systolic blood pressure <100 mmHg) (17; 32; 33). People will usually be identified as being at high risk by use of a validated triage system e.g. NEWS (34).

However, despite these severe electrolyte losses and total body volume depletion, often the person 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 spaces – see Figure 1) (35-37).

Biochemical

HHS should not be diagnosed using biochemical parameters alone. However, the blood glucose is markedly raised (usually ≥ 30 mmol/L), as is the osmolality (usually ≥ 320 mOsm/kg).

As described in Appendix 2, osmolality is useful as an indicator of severity and for monitoring the rate of change with treatment. Serum osmolality is often provided in biochemistry reports, either calculated or measured, but can be calculated using the formula $[(2 \times \text{Na}^+) + \text{glucose} + \text{urea}]$. (Note the laboratory calculation may use a different formula and that laboratory measurement is a batched procedure i.e. run once a day, so not usually available for rapid repeat measurements unless you discuss it with the laboratory.)

This formula gives the best approximation to measured osmolality, although a more accurate formula has been derived (37). *(For the sake of clarity, calculated osmolality and measured osmolality is referred to as osmolality in this document)*. 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 Cognitive Performance during HHS

HHS can have marked effects on cerebral function and be associated with transient changes in cognitive performance and also with longer-term effects. This may be due to a number of things, including but not limited to: cerebral oedema in severe cases, presence of significant electrolyte disturbances, acute changes in osmolality, dehydration, infection/sepsis, hypoglycaemia during treatment, or kidney injury. A daily assessment of cognition during admission with a comparison to the pre-morbid state should accompany the full history, physical examination and review of drug therapy on admission.

Goals of Treatment of HHS

The goals of treatment of HHS are to address the underlying cause(s) 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 / osmotic demyelination syndrome
- foot ulceration

General Treatment Principles and Controversial Areas

Early senior review by a clinician familiar with the management of HHS is essential to confirm the treatment plan and review progress. The diabetes inpatient specialist team should be involved in their care as soon as possible.

Point of Care vs Laboratory Testing

Blood gas machines are readily available in almost all UK emergency departments. These are able to produce reliable measurements of pH, electrolytes, glucose etc., and should be used to frequently monitor progress and calculation of osmolality. 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, usually using VBG and point of care testing. The former can indicate lactic acidosis related to e.g. sepsis, and the latter will exclude significant ketonaemia (β -hydroxybutyrate <1.0 mmol/L).

Markers of Severity Indicating the Need for High Dependency / Level 2 Care

Care for people with HHS can be complex, they often have multiple co-morbidities and may require intensive monitoring. The presence of one or more of the following should prompt discussion because they indicate the need for admission to a High-Dependency Unit /Level 2 environment. Immediate senior review by a clinician skilled in the management of HHS should be considered:

- Measured or calculated Osmolality >350 mOsm/kg
- Sodium >160 mmol/L
- Venous/arterial pH <7.1
- Hypokalaemia (<3.5 mmol/L) or hyperkalaemia (>6 mmol/L) on admission
- Glasgow Coma Scale (GCS) <12 or abnormal AVPU (Alert, Voice, Pain, Unresponsive) scale
- 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/hr
- Serum creatinine >200 µmol/L and/or acute kidney injury
- 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. There are almost no data on the benefits or risks of particular fluid replacement regimens in HHS. Controversies persist around the speed and type of fluid replacement, and a systematic review is being undertaken (38). However, a Cochrane review recommended use of crystalloid fluids rather than colloid in critically ill individuals because use of crystalloids is associated with less need for further interventions (39).

As the majority of electrolyte losses are sodium, chloride and potassium, the initial fluid replacement of choice should be 0.9% sodium chloride solution with potassium added as required (40).

Osmolality, Sodium and Glucose

The key parameter in HHS that needs to be taken into account is osmolality. Sodium and glucose are the main contributors to this, and too rapid changes are dangerous because large fluid shifts can lead to neurological complications, in particular cerebral oedema and CPM/osmotic demyelination. Because these parameters are inter-related we advise that they are plotted on a graph or tabulated to permit appreciation of the rate of change (See Appendices 1 and 2).

Osmolality can be calculated using the formula $[(2 \times \text{Na}^+) + \text{glucose} + \text{urea}]$ (41).

Use of the previous version of this guideline has confirmed that fluid replacement alone will lower glucose concentrations. A FRIII should **NOT** be started as part of the initial treatment unless significant ketonaemia is present – i.e. > 3.0 mmol/L or urine ketones $> 2+$. In all other circumstances, intravenous fluids should be administered first, and an FRIII only started once the glucose has stopped falling. The risk of adding insulin at the start of treatment is that this will lead to larger osmotic shifts leading to neurological complications. In addition, adding IV insulin too early will also potentially lead to circulatory collapse. Appendix 3 outlines when and how insulin should be started.

If the IV fluids and FRIII are managed appropriately, the fall in measured or calculated serum osmolality should be within the target range of 3.0-8.0 mOsm/kg/hr. If the rate is faster than this, it increases the risk of neurological complications such as cerebral oedema and CPM/osmotic demyelination.

Potassium

People with HHS are usually potassium depleted but potassium shifts are less pronounced than those with DKA because they are less acidotic. The differences are driven largely by the lack of insulin in DKA. In addition, the FRIII rate is lower, and there is often co-existing renal impairment. However, hyperkalaemia can be present with acute kidney injury. In addition, those on diuretics may be profoundly hypokalaemic. Potassium should be replaced or omitted as required (see Table 2).

Table 2- Suggested potassium replacement regimen in HHS

Potassium level during the first 24h (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)

Isotonic versus Hypotonic Fluid Replacement

- rapid changes in osmolality may be harmful. 0.9% sodium chloride solution should be used as the principle fluid to restore circulating volume and reverse dehydration because it is relatively hypotonic compared to 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 glucose concentrations which will lower measured or calculated serum osmolality by 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
- a rising sodium is only a concern if the osmolality is NOT declining concurrently. If the inevitable rise in serum sodium is much greater than 2.4 mmol/L for each 5.5 mmol/L fall in BG this would suggest insufficient fluid replacement (42)
- the rate of fall of serum sodium should not exceed 10 mmol/L in 24 hours (43)
- a safe rate of fall of plasma glucose is between 4.0 and 6.0 mmol/hr
- 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. However, 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
- an initial target glucose of between 10-15 mmol/L is a reasonable goal until the person is eating and drinking normally, and then an individual target glucose (if appropriate 6–10 mmol/L) should be set by the diabetes specialist team and the person with diabetes
- complete normalisation of electrolytes and osmolality may take up to 72 hours

Hypotonic Fluid Replacement

Ideally, people will recover quickly enough to replace the water deficit themselves by taking fluids orally. 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. There are no data to justify using fluids that are less hypotonic than 0.45% sodium chloride solution.

Insulin Dose and Timing

- if significant ketonaemia is not present do NOT start an intravenous insulin infusion
 - **ONLY** commence insulin infusion quickly in the following circumstances:
 - If there is HHS and ketonaemia (blood ketones 3 β -hydroxybutyrate >1.0 - \leq 3.0 mmol/L or urine ketones < 2+) and not acidotic (venous pH >7.3 and bicarbonate >15.0 mmol/L) then use 0.05 units/kg/hr
- OR
- If there is significant ketonaemia (3 β -hydroxybutyrate >3.0 mmol/L) or ketonuria (\geq 2+) with a pH <7.3 and bicarbonate <15 mmol/L (i.e. mixed DKA and HHS) and use the DKA guideline at 0.1 units/kg/hr https://abcd.care/sites/abcd.care/files/site_uploads/JBDS_02%20DKA_Guideline_amended_v2_June_2021.pdf
- fluid replacement alone with 0.9% sodium chloride solution will result in a falling blood glucose and because most people with HHS are insulin sensitive there is a risk of lowering the osmolality precipitously. To prevent the measured or calculated serum osmolality falling too quickly, the plasma glucose should ideally fall by no more than 5 mmol/L/hr
 - insulin treatment prior to adequate fluid replacement may result in cardiovascular collapse because water will move out of the intravascular space, resulting in a reduction in intravascular volume (a consequence of insulin-mediated glucose uptake and a diuresis from urinary glucose excretion) (see Figure 1)
 - the recommended insulin dose is a FRIII given at 0.05 units/kg/hr
 - a fall of glucose at a rate of up to 5.0 mmol/L per hour is ideal
 - once the 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 1.0 unit/hr. As with DKA, a FRIII is preferred, though generally lower doses are required
 - Appendix 2 outlines when and how insulin should be started

Clinical Scenarios and Interpretation of Serum Sodium, Osmolality and Glucose Concentrations

- if the serum sodium is increasing but the osmolality declining at an appropriate rate, continue 0.9% sodium chloride solution
- if serum sodium is increasing AND the osmolality is increasing (or declining at < 3.0 mOsm/kg/hr), then check the fluid balance. If it is inadequate, then increase the infusion rate of 0.9% sodium chloride solution
- if the osmolality is increasing and the fluid balance is adequate, consider switching to 0.45% sodium chloride solution given at the same rate
- if osmolality is falling at a rate exceeding 8.0 mOsm/kg/hr (or > 3 mOsm/kg/hr in those at high risk of developing cerebral oedema), then consider reducing the infusion rate of IV fluids and/or insulin (if already commenced)
- if the blood glucose is falling at < 5.0 mmol/L per hour, then check fluid balance. If the fluid balance is inadequate, then increase the rate of infusion of 0.9% sodium chloride solution. If the fluid balance is adequate, then commence an FRIII at 0.05 units/kg/hr, or if already running, increase the rate to 0.1 units/kg/hr
- if the blood glucose is falling at over 5.0 mmol/L/hr, then check the rate of change in osmolality and consider reducing the rate of fluid replacement and / or intravenous insulin infusion rate

Antibiotic Therapy

As with all acutely ill people, sepsis may not be accompanied by pyrexia. An infective source should be sought on clinical history and examination. Antibiotics should be given when there are clinical signs, and / or laboratory or radiological evidence of infection.

Anticoagulation

Having diabetes is associated with an increased risk of developing venous thromboembolic disease (VTE) (44). People with HHS have an increased risk of arterial and VTE (45; 46). A study of hyperglycaemia (not necessarily with HHS) during COVID-19 admissions suggested that the risk of arterial and VTE was three times higher than those without hyperglycaemia (47). Other work has estimated that people with diabetes and hyperosmolality have a risk of VTE similar, or only marginally above those with acute renal failure, acute sepsis or acute connective tissue disease (48; 49). The risk of venous thromboembolism is greater than in diabetic ketoacidosis (45; 50; 51). Other factors, such as hypernatraemia and increasing vasopressin concentrations can promote thrombogenesis by producing changes in haemostatic function consistent with a hypercoagulable state (52).

Everyone with HHS should receive prophylactic low molecular weight heparin (LMWH) for the full duration of admission unless contraindicated. There are no data to recommend that this advice be extended to therapeutic anticoagulation. Full, therapeutic anticoagulation should only be considered in those with suspected thrombosis or acute coronary syndrome.

Other Electrolyte Imbalances and Complications Associated with HHS

Hypophosphataemia and hypomagnesaemia are common in HHS. There are no data looking at the use of replacement of either of these in HHS. It is likely that this represents an epiphenomenon, particularly for magnesium where protein binding is affected by the change in the extracellular milieu and that therefore tissue status is likely normal. Many studies in ICU settings demonstrate no evidence of tissue deficiency nor any benefit from magnesium replacement in acutely ill patients with hypomagnesaemia. If low concentrations persist beyond the acute phase of treatment and the patient is apparently symptomatic with good risk factors for long term magnesium deficiency, oral replacement may be considered (IV is associated with high urinary excretion therefore very little of the infusion remains in the circulation so should only be considered if severely deplete and symptomatic e.g. ECG changes or neurological manifestations); see local magnesium replacement guidelines for further advice. Proton pump inhibitor use is common in the same population who develop HHS and the use of these drugs has been associated with hypomagnesaemia.

Foot Protection

People with HHS are at high risk of pressure related foot ulceration. An initial foot assessment should be undertaken on admission and daily during admission (53). Heel protectors and an appropriate mattress should be provided for those with immobility, neuropathy, peripheral vascular disease or lower limb deformity. If the individuals are too confused or sleepy to cooperate with assessment of sensation assume they are at high risk.

Definition of Resolution of HHS

Because the precise definition of HHS has not been agreed, it is difficult to give a precise definition of when HHS has resolved. Different authors have used different criteria for resolution, with some using osmolality as the criteria, others using volume status or cognitive status. It is important to remember that a normal glucose or sodium concentration in isolation is not sufficient to say that the episode has resolved. It can also be difficult to gauge the degree of dehydration at the bedside. However, we propose that a holistic approach be used, so resolution can be defined when measured or calculated serum osmolality falls to <300 mOsm/Kg, hypovolaemia has been corrected (urine output ≥ 0.5 ml/kg/hr), cognitive status is back to the pre-morbid state and blood glucose <15 mmol/L. At that point we consider that HHS is no longer present.



Recovery Phase

Complete correction of electrolyte and osmolality abnormalities may take up to 72 hours. Because many of these individuals are elderly with multiple co-morbidities, recovery will largely be determined by their previous functional status and the underlying precipitant(s) of HHS. Early mobilisation is essential, as is the need for good nutrition.

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 people should be transferred to subcutaneous insulin (the regimen being determined by their circumstances). For those with previously undiagnosed diabetes or who were well controlled on oral agents, switching from insulin to the appropriate oral or subcutaneous glucose lowering drugs should be considered after a period of stability. This may take weeks or months.

Everyone with HHS will require diabetes education to reduce the risk of recurrence and prevent long-term complications. Where applicable, holistic multiple cardiovascular risk factor optimisation should also occur.

FIGURE 1. Fluid balance in HHS

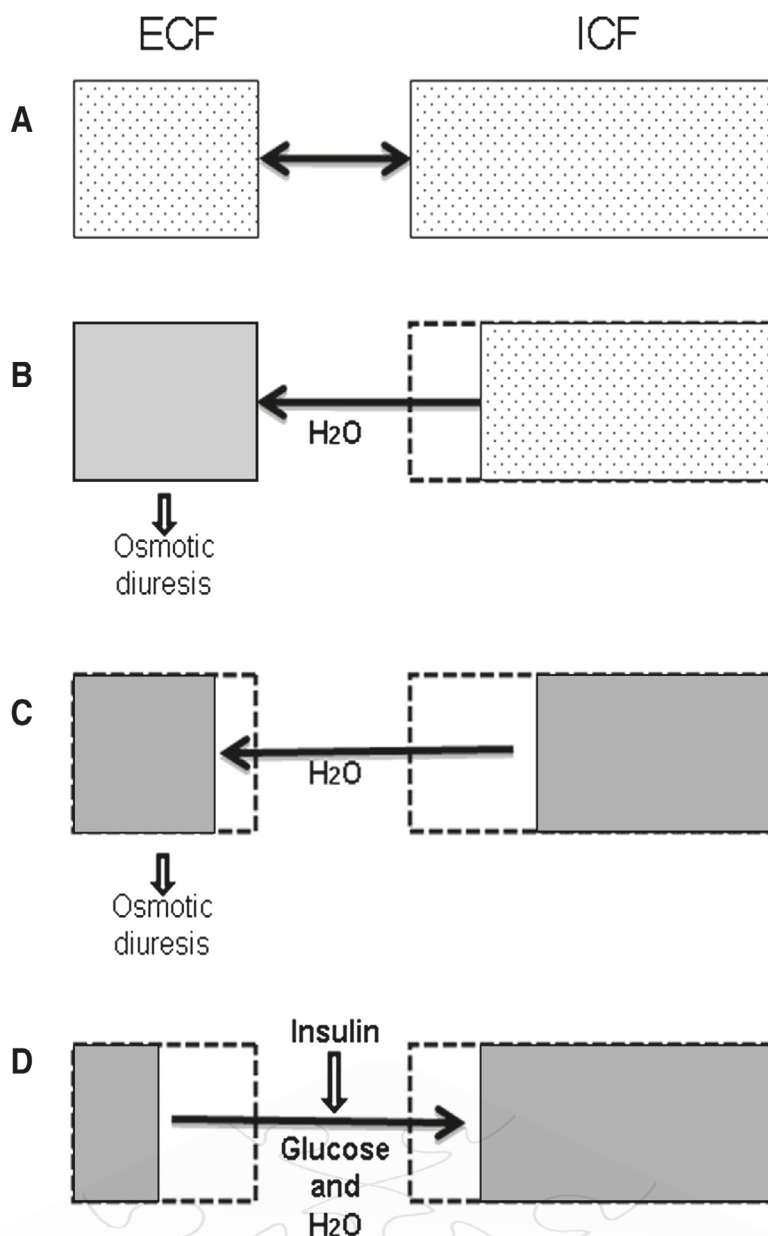
(Adapted from reference (15))

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




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Appendix 1

Sample Insulin and Fluid Prescription Chart Intravenous Insulin Prescription and Fluid Protocol FOR HYPEROSMOLAR HYPERGLYCAEMIC STATE (HHS)

<p>For use for ALL ADULT (over 18 years) patients with a diagnosis of HHS NOT FOR USE IN CHILDREN ALWAYS draw up insulin using an insulin syringe NEVER use an IV syringe to draw up insulin ALWAYS continue subcutaneous intermediate* or basal insulin** *Intermediate: Insulatard[®], Humulin I[®], Insuman Basal[®] **Basal: Lantus[®], Semglee[®] or Abasaglar[®] (all glargine), Levemir[®] (detemir), Tresiba[®] (degludec), Toujeo[®] (long acting glargine) Doctor: All prescriptions for insulin and fluids must be signed Nurse: All entries must be signed</p>	Ward	Consultant	Admission Date:	
			Discharge Date:	
	Surname		First Name	
	Hospital Number		Date of Birth / Age	
	NHS Number			
Address				

ENTRY (diagnostic) CRITERIA (ALL must be ticked to establish diagnosis)	
Significant hypovolaemia	<input type="checkbox"/>
Elevated osmolality ≥ 320 mOsm/kg - Calculate osmolality using the equation: $(2 \times \text{Na}^+) + \text{glucose} + \text{urea}$	<input type="checkbox"/>
Marked hyperglycaemia (≥ 30.0 mmol/L) without significant ketonaemia (blood ketones ≤ 3.0 mmol/L; urine ketones $< 2+$) or acidosis ($\text{pH} \geq 7.3$; venous bicarbonate > 15.0 mmol/L)	<input type="checkbox"/>
If patient satisfies all ENTRY CRITERIA, commence intravenous fluid management (see ACTION 1) ONLY commence intravenous insulin therapy IF patient has significant ketonaemia (blood ketones > 3.0 mmol/L or ketonuria (urine ketones $> 2+$) (see ACTION 3)	

ACTION 1: INTRAVENOUS FLUID MANAGEMENT (Saline regime) CAUTION: Slower in young people aged 18-25 years, elderly, pregnant, heart or renal failure		ACTION 2: INTRAVENOUS FLUID MANAGEMENT (Glucose regime) Once CBG < 14.0 mmol/L	
0.9% sodium chloride 1 litre (no KCl)	Over 1 st hour	Give 10% Glucose to run at 125 ml/hr AND	
0.9% sodium chloride 1 litre (check K ⁺)	Over next 2 hours	Continue Saline as per Saline regime (see ACTION 1)	
0.9% sodium chloride 1 litre (check K ⁺)	Over next 2 hours	Run through Saline and Glucose regime in 2 separate lines at the SAME time	
0.9% sodium chloride 1 litre (check K ⁺)	Over next 4 hours	Run Glucose regime and insulin therapy in the same line via a three way non-return valve	
0.9% sodium chloride 1 litre (check K ⁺)	Over next 4 hours		
Anticipate a fall in potassium and replace (see BOX 4)			
Re-assessment of cardio-vascular status at 12 hours is mandatory, further fluid may be required			

ACTION 3: INTRAVENOUS INSULIN THERAPY AND PRESCRIPTION						Weight/insulin dose reference Guide					
A Fixed Rate Intravenous Insulin Infusion (FRIII) calculated on 0.05 units/kg body weight is recommended (see Weight/insulin dose Reference Guide) It may be necessary to estimate the weight of the patient						Weight (in Kg)	Insulin dose/hr (Units)	Weight (Kg)	Insulin dose/hr (Units)		
Patient's Weight: _____ kg (Actual/Estimated)						50-59*	2.5	100-109	5		
Insulin dose per hour: _____ units Date: _____						60-69	3	110-119	5.5		
Print Name: _____ Signature: _____						70-79	3.5	120-129	6		
						80-89	4	130-139	6.5		
						90-99	4.5	>140	*		
Date	Time	Adjusted dose (units/hr)	Prescriber Name	Prescriber Signature	Bleep	* < 50 kg or > 140 kg: seek senior advice or advice from the Diabetes Specialist Team					
Drug (approved name)		Dose	Volume		Route	Prescriber's Signature	Prescriber Print name		Date		
Actrapid [®]		50 UNITS	Made up to 50 ml with NaCl 0.9% (1 unit per mL)		IV						

SYRINGE PREPARATION				ACTION 4: POTASSIUM REPLACEMENT	
Prepared and administered by	Date	Time started	Time stopped	Add potassium as per guidance below EXCEPT for the first Saline (1 hour) bag ONLY use pre-prepared bags	
				> 5.5 mmol/L	None
				$3.5 - 5.5$ mmol/L	40 mmol KCl per litre
				< 3.5 mmol/L	40 mmol KCl per litre (senior review as additional potassium needs to be given)
Insert catheter and monitor fluid balance (input/output); Check pulse, BP, saturations, urine output and CBG hourly. Check GCS every 1-2hrs					
Aim for positive balance of 3-6 litres by 12hr; fluid replacement alone will lower CBG and reduce osmolality					
An initial increase in serum sodium is expected and is not an indication for hypotonic fluids ONLY Use 0.45% N/Saline if osmolality is not falling despite adequate fluids					

BOX 5: INTRAVENOUS FLUID PRESCRIPTION

For information on dilutions, infusion rates, compatibilities and monitoring parameters, consult the: Injectable Medicines Guide or contact Medicines Information

CAUTION: Slower in young people aged 18-25 years, elderly, pregnant, heart or renal failure

Date	Solution	Volume	Additives and dose Check potassium Refer to BOX 4 [0.15% = 20mmol/L]		Rate	Duration	Route	Prescriber Signature & Bleep	Batch No.	Given by 2 nd check	Time started	Time stopped	Pharm and supply notes
	0.9% NaCl	1 litre	KCl	None	1000 ml/hr	1 hr	IV						
	0.9% NaCl	1 litre	KCl		500 ml/hr	2 hr	IV						
	0.9% NaCl	1 litre	KCl		500 ml/hr	2 hr	IV						
	0.9% NaCl	1 litre	KCl		250 ml/hr	4 hr	IV						
	0.9% NaCl	1 litre	KCl		250 ml/hr	4 hr	IV						
	0.9% NaCl	1 litre	KCl		166 ml/hr	6 hr	IV						
	10% Glucose	1 litre			125 ml/hr	8 hr	IV						
	10% Glucose	500 ml	KCl	0.15%	125 ml/hr	4 hr	IV						
	10% Glucose	500 ml	KCl	0.15%	125 ml/hr	4 hr	IV						

Switch from FRIII to VRIII with 10% Glucose with 0.15% KCl (i.e. 20 mmol/l) at 125 ml/hr IF Biochemical markers have normalised (osmolality <300 mOsm/kg) and STILL not eating and drinking				Bedside and laboratory results Check creatinine, electrolyte and venous bicarbonate and pH at 1-2 hours then 2 to 4 hourly until osmolality normalised							EXIT CRITERIA (ALL must be ticked)				
PRESCRIPTION: If IV insulin requirements have exceeded 1 unit per hr on VRIII, then start subcutaneous basal insulin at 0.2 (or 0.1) units per kg body weight and refer to specialist diabetes team				Date	Time	Ketones	Na ⁺	K ⁺	Creatinine	HCO ₃	pH	Osmolality	Signature	Clinical/cognitive status back to pre-morbid state <input type="checkbox"/>	
														Osmolality normalised (<300 mOsm/kg) <input type="checkbox"/>	
														hypovolaemia corrected (UOP ≥0.5 ml/kg/hr) <input type="checkbox"/>	
														Blood glucose <15 mmol/L <input type="checkbox"/>	
														<i>Transfer to subcutaneous insulin regime</i>	
CBG mmol/L	Insulin units/hr	Insulin units/hr	Insulin units/hr											Notes: Maintain IV insulin infusion for 30 minutes after re-starting original insulin regime- IV insulin has a 5 minute half-life	
> 14	6													ALWAYS continue subcutaneous basal insulin	
12.1 – 14	4													All patients are at high risk of foot ulceration. Protect heels and perform daily foot checks.	
10.1 - 12	3													Refer to the Diabetes Specialist Team	
7.1 – 10	2													Seek and treat precipitating factors	
4 - 7	1													Prophylactic low molecular weight heparin	
< 4	0.5													Other issues:	
Signature															
Bleep No.															
Date / Time															

INTRAVENOUS INSULIN, CBG AND KETONES MONITORING RECORD SHEET

Guide:

Only use for patients on intravenous insulin regimen (use different chart for patients on subcutaneous insulin)

Make sure the patient's hands are clean

Check CBG hourly

Check capillary blood ketone hourly until HHS resolved

ADDRESSOGRAPH
LABEL

DATE	Time	Blood glucose (mmol/L)	Blood ketones (mmol/L)	Hourly infusion rate (units/hr)	Volume left in syringe (ml)	Volume infused in one hour (ml)	Total volume infused (ml)	Signatures		KEY EVENTS / NOTES

Appendix 2

Rational 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 because they are able to freely move across cell membranes they play no role in the distribution of free water (36; 54).

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, e.g.:

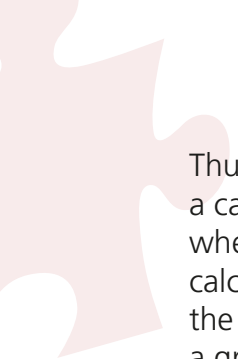
$[(2 \times \text{Na}^+) + \text{glucose} + \text{urea}]$

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

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

The best approximation to measured osmolality can be calculated using the formula $[(2 \times \text{Na}^+) + \text{glucose} + \text{urea}]$, though a more accurate formula has been derived (41). 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. hypo-osmolality.



Thus an individual with a Na^+ 122 mmol/L, glucose 13.0 mmol/L, urea 23 mmol/L has a calculated osmolality of 280 mOsm/kg and an effective osmolality of 257 mOsm/kg, whereas a person with a Na^+ 122 mmol/L, glucose 30.0 mmol/L, urea 4 mmol/L has a calculated osmolality of 278 mOsm/kg and an effective osmolality of 274 mOsm/kg. So the person with the raised urea has a much lower effective osmolality and is therefore at a greater risk of osmotic demyelination should correction of the hyponatraemia be too fast.

The hyponatraemia in an individual with a BG of 30 mmol/L is largely dilutional and will correct as the glucose falls (corrected $\text{Na}^+ = 122 + (2.4 \times 4) = 131.6$) (42).

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 Na^+) + glucose + urea].

Appendix 3

When and How to Start Fixed-Rate Intravenous Insulin Infusions (FRIII) in HHS

Scenario 1 - HHS and blood ketones <3.0 mmol/L and not acidotic (venous pH >7.3 and bicarbonate >15.0 mmol/L)

- Do not start FRIII immediately
- Continue to monitor hourly capillary glucose during IV fluid replacement (use laboratory venous glucose if capillary reading '>28 mmol/L' or 'Hi')
- Once glucose plateaus with fluid replacement alone, commence FRIII at rate of 0.05 units/kg/hr, aiming for a target glucose of 10.0 – 15.0 mmol/L

Scenario 2 – HHS and blood ketones >1.0 mmol/L (urine ketones >2+) and not acidotic (venous pH >7.3 and bicarbonate >15.0 mmol/L)

- Start FRIII immediately at rate of 0.05 units/kg/hr (correct to nearest whole unit)
- Continue to monitor hourly capillary glucose during IV fluid replacement (use laboratory venous glucose if capillary reading '>28 mmol/L' or 'Hi')
- Continue to monitor capillary ketones hourly
- If glucose is dropping too quickly (i.e. by >5.0 mmol/L/hr), then reduce the FRIII rate by 50%
- Repeat the glucose and blood ketones hourly and, if necessary, adjust the insulin infusion rate to ensure the ketones are clearing and the glucose is falling in a controlled manner. Aim for a target glucose of 10.0 – 15.0 mmol/L

Scenario 3 – Significant hypovolaemia, hyperosmolality and pH<7.3 and ketones >3.0 mmol/L

- This suggests a mixed picture of HHS/DKA
- In this circumstance the DKA pathway should be followed (https://abcd.care/sites/abcd.care/files/site_uploads/JBDS_02%20DKA_Guideline_amended_v2_June_2021.pdf)
- Commence IV fluids and FRIII of 0.1 units/kg/hr

Appendix 4

Audit Standards

Institutional standards:	
Indicator:	Standard:
Access:	
Has the Trust either adopted these national guidelines or has their own alternative, evidence based and audited internal guidelines for the management of any person admitted with HHS under an adult medical team?	Yes
Does the Trust collect data about the outcomes for those admitted with HHS?	Yes
Does the Trust have the services of a dedicated Diabetes Inpatient Specialist Nurse (DISN) at staffing levels most recently recommended by the Diabetes UK?	Yes
Institutional accountability and integrity:	
Does the Trust have a 'clinical lead' for the management of those admitted with HHS / hyperglycaemic emergencies under an adult team who has responsibility for implementation of the HHS guidelines?	Yes
NPSA standards (55; 56)	
Indicator:	Standard:
All regular and single insulin (bolus) doses are measured and administered using an insulin syringe or commercial insulin pen device. Intravenous syringes must never be used for insulin administration	100%
The term 'units' is used for insulin measure in all contexts. Abbreviations such as 'U' or 'IU' are never used	100%
All clinical areas and community staff treating people with diabetes with insulin have adequate supplies of insulin syringes and subcutaneous needles which staff can obtain at all times	100%
An insulin syringe must always be used to measure and prepare insulin for an intravenous infusion	100%
A training programme should be put in place for all healthcare staff (including medical staff) expected to prescribe, prepare and administer insulin (e.g. the safe use of insulin and the safe use of intravenous insulin e-learning packages from NHS Improving Quality)	100%
Policies and procedures for the preparation and administration of insulin and insulin infusions in clinical areas are reviewed to ensure compliance with the above	100%
Department of Health 'Never Event' standard:	
Indicator:	Standard:
Death or severe harm as a result of maladministration of insulin by a health professional	Never

Additional standards	
Indicator:	Standard:
People admitted to hospital with HHS should be referred to the diabetes specialist team on admission	100%
People admitted to hospital with HHS should be seen by member of the diabetes specialist team within 1 working day of admission	100%
People with diabetes should have access to the specialist diabetes team	100%
Where clinically appropriate, people with diabetes should have the choice to self-monitor their condition	80%
<p>People admitted to hospital with HHS receive educational support from a member of the diabetes specialist team prior to discharge. This education should include:</p> <ul style="list-style-type: none"> • Review of usual glycaemic control • Review of injection technique/blood glucose monitoring/ equipment/sites • Discussion of sick day rules • Assessment of the need for home ketone testing (blood or urinary) with education to enable this • Provision of contact telephone numbers for the diabetes specialist team including out of hours 	100%
Those admitted with HHS are seen by a diabetologist or DISN prior to discharge	100%
People admitted to hospital with HHS receive follow up by a diabetes specialist team or their primary diabetes care provider	100%
People admitted to hospital with HHS should be discharged with a written care plan: a process that allows the person with diabetes to have active involvement in deciding, agreeing and owning how their diabetes is managed. This should be copied to the GP	100%
Percentage of people admitted with HHS where discharge is delayed because of diabetes related problems	0%
Institutional accountability and integrity:	
Percentage of people with diabetes identified as such on hospital patient administration system	95%
Percentage of clinical coding that identifies people with diabetes correctly	100%
Patient and staff satisfaction:	
Percentage of staff who feel that they have sufficient levels of appropriate and timely support from the Diabetes Inpatient Specialist Team	100%
Percentage of people with diabetes who express satisfaction with their inpatient journey, using validated tools such as the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the Diabetes Treatment Satisfaction Questionnaire for Inpatients (DTSQ-IP)	80%

Appendix 5

JBDS IP Group

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