THE NORTHERN HOSPITAL

HYPEROSMOLAR HYPERGLYCEMIC STATE

Design for Acanthus chintz wallpaper, William Morris 1876.

"Have nothing in your home that
you do not know to be useful
or believe to be beautiful".

William Morris, 1882.

"Either that wallpaper goes, or I do".

Oscar Wilde, last dying words to his friend Claire de Pratz,
October 1900.

As Oscar Wilde lay dying in a drab Parisian apartment in October 1900, he was not cheered by his wallpaper! He would have much preferred a more beautiful vision as his last conscious sight in this world. It would have eased his passing no end had he been surrounded by a wallpaper designed by William Morris. Morris was one of the foremost wallpaper designers of the late Nineteenth century. His African acanthus chintz design seen above demonstrates his astonishing talent in sketching out the basic pattern, then filling in the color working ever outwards from the center. In the words of Fiona McCarthy, "it can be seen from this design sketch that the apparent spontaneity of pattern is arrived at with enormous technical exactitude".

It is a pity that the interior decorator of Oscar's apartment had not heeded the wise words of William Morris himself, "Have nothing in your houses that you do not know to be useful or believe to be beautiful". Therefore in the sprit of Mr. Morris, it is to be hoped that by the provision of his acanthus above, and the guidelines of the British Diabetes Society, sketched out with "enormous technical exactitude", will prove not only useful, but beautiful as well!

Left: William Morris, oil on canvas, late 19th century, William Blake Richmond. Right: Portrait of Oscar Wilde, albumen photographic print, New York 1882, Napoleon Sarony.

HYPEROSMOLAR HYPERGLYCEMIC STATE

Introduction

The **hyperglycaemic hyperosmolar state (HHS)** is a medical emergency.

HHS is a *different* entity to diabetic ketoacidosis (DKA) and treatment requires a **different approach**.

HHS is associated with a significant morbidity and higher mortality than DKA and must be diagnosed promptly and managed intensively

Although *typically* occurring in the elderly, HHS is presenting in ever younger adults and even teenagers, often as the *initial presentation* of **type 2** diabetes mellitus.

There is **no** precise definition of HHS and indeed a strict definition would be inappropriate, however *characteristic features* that differentiate it from other hyperglycaemic states (such as DKA) include the following:

1. Hypovolaemia:

    - Note that HHS should not be diagnosed from biochemical parameters *alone*, the clinical parameter of dehydration/ hypovolemia is also important in making the diagnosis.

2. Marked hyperglycaemia (**> 30 mmol/L**) *without* significant:

    - Hyperketonaemia (**< 3 mmol/L**)

    Or

    - Acidosis (i.e. **pH >7.3** / **bicarbonate >15 mmol/L**)

3. Osmolality **> 320 mosmol/kg**

In general terms therefore. When compared to DKA, there is a greater degree of dehydration, and relatively less ketosis and acidosis.

Note, however that a *mixed* picture of HHS and DKA may also occur as some patients have severe hypertonicity and ketosis and acidosis. This presumably reflects insulin deficiency, due to beta cell exhaustion as a result of temporary glucotoxicity. These patients may require a modification of treatment guideline to take into account which aspect predominates.

The principal goals of treatment of HHS are to treat the **underlying cause** and to **gradually** (**over 48 - 72 hours**) replace fluid and electrolyte losses and normalize osmolality.

All cases should have early consultation with the endocrine unit and the ICU

Definitions

In strict terms:

- **Osmolality** is the number of osmoles of solute in a *kilogram* of solvent
- **Osmolarity** is the number of osmoles of solute in a *litre* of solution.

Osmolality is a *laboratory measured* parameter and is useful, both as an **indicator of severity** and for **monitoring the rate of change** with treatment.

If laboratory measured osmola**l**ity is not available, then calculated osmola**r**ity can be used as a surrogate using the following formula:

Osmolarity = 2xNa^+ + glucose + urea.

In strict terms urea is not actually 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.**

(Urea is "ineffective" with regard to osmoles, as it is freely able move across cell membranes and thus plays no role in the distribution of free water within the body).

History

Hyperglycaemic hyperosmolar state (HHS) was traditionally called hyperosmolar non ketotic (HONK) coma, however it was apparent that most of these patients were not comatose though they could be extremely ill.

Changing the name to hyperosmolar hyperglycaemic state (HHS) allowed 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 of themselves are insufficient to make the diagnosis.

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.**

Epidemiology

Although typically occurring in the **elderly**, HHS is now presenting in ever younger adults and even teenagers.

Often it presents as the *initial* presentation of **type 2** diabetes mellitus.

Pathophysiology

The pathogenesis of HHS is complex and incompletely understood.

One theory is as follows:

- The quantity of insulin required to inhibit lipolysis in adipose tissue (and hence ketogenesis) is less than the quantity required to promote utilization of glucose by the peripheral tissues.

- Therefore ketoacidosis does not occur, as there is enough insulin to inhibit lipolysis, but not enough to prevent hyperglycemia.

- There is a slowly developing hyperglycemia and severe dehydration, without the accompanying effects of acidosis, (which is present to a much greater degree in DKA and makes the patient present earlier).

Complications:

HHS is associated with a significant morbidity and has a higher mortality than DKA.

Complications include:

1. Severe dehydration with hypovolemic shock

    - Fluid losses in HHS at presentation are estimated to be between **100 - 220 ml/kg** (compared to around 100 mls/kg for DKA at presentation).

2. Severe electrolyte disturbances:

    Hyperglycaemia results in an osmotic diuresis and renal losses of water *in excess* of sodium and potassium.

    Typical fluid and electrolyte losses in HSS are as follows:

Parameter	**Degree of loss**	**For 60 kg patient**	**For 100 kg patient**
Water	100 - 220 ml/kg	6 - 13 liters	10 - 22 liters
Sodium	5-13 mmol/kg	300 - 780 mmol	500 - 1300 mmol
Chlorine	5-15 mmol/kg	300 - 900 mmol	500 - 1500 mmol
Potassium	4-6 mmol/kg	240 - 360 mmol	400 - 600 mmol

3. Vascular thrombotic events, including:

- Myocardial infarction
- Stroke
- Peripheral arterial thrombosis
- DVT

4. CNS:

   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.

Clinical features

Important points of history:

1. Whilst DKA presents within *hours* of onset, HHS typically comes on over **many days**, and consequently the dehydration and metabolic disturbances are more extreme.

2. Hyperosmolar hyperglycaemic state (HHS) most commonly occurs in elderly patients, however, it is increasingly being seen in younger adults, and even occasionally in teenagers.

3. It is seen most commonly in type II diabetics, and may in fact be the first presenting problem of type II diabetes.

4. There may be s precipitating illness, most commonly infection or ACS.

Important points of examination:

1. Assess vital signs

   - Tachycardia / hypotension (with circulatory compromise):

     ♥ Severe hypovolaemia manifests as circulatory shock with tachycardia (pulse >100) and/or hypotension (systolic blood pressure < 90 mmHg).

     *Note however, that despite severe electrolyte losses and total body volume depletion, the typical patient with HHS, may not look as dehydrated as they actually are, because the hypertonicity leads to some **preservation of intravascular volume**, causing movement of water from the intracellular to extracellular space, (see Appendix 1 below).*

   - Fever or hypothermia with concurrent sepsis

- Altered conscious state:
    - ♥ Acute impairment in cognitive function may be associated with dehydration but is not specific to the condition and is *not necessarily* present.
    - ♥ Alterations in mental status are common with osmolalities > **330 mosmol/kg.**

2. Assess hydration status

3. Immediate bedside capillary blood testing for **glucose** and **ketones.**

Assessment of HSS severity:

Patients with HHS are complex and often have multiple co-morbidities so require intensive monitoring.

The Joint British Diabetes Society have suggested that the presence of one or more of the following may indicate severe illness that may need admission to a HDU/ICU:

1. Clinical features:
    - Pulse over 100 or below 60 bpm
    - Systolic blood pressure below 90 mmHg
    - Oxygen saturation below 92% on air (assuming normal baseline respiratory function)
    - Glasgow Coma Scale (GCS) less than 12 or abnormal AVPU (Alert, Voice, Pain, Unresponsive) scale
    - Hypothermia
    - Macrovascular event such as myocardial infarction or stroke
    - Other serious co-morbidity
    - Urine output less than 0.5 ml/kg/hr
2. Biochemical features:
    - 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
- Serum creatinine > 200 µmol/L

Investigations

Blood tests:

1. FBE
2. CRP:
   - 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 CRP may be helpful.
3. U&Es
4. Glucose / ketones:
   - Both these parameters can be quickly checked at the bedside, by **capillary blood testing devices.**
5. Osmolality / osmolarity:

   Osmolality is a *laboratory measured* parameter and is useful, both as an **indicator of severity** and for **monitoring the rate of change** with treatment.

   If laboratory measured osmola**l**ity is not available, then calculated osmola**r**ity can be used as a surrogate using the following formula:

   - **Osmolarity = $2xNa^+$ + glucose + urea.**
6. Beta HCG - for women of child bearing age.
7. Blood gases/ lactate:

   Venous blood gas analysis (as opposed to arterial) is sufficient for the urgent measurement of:

   - pH
   - Bicarbonate
   - Potassium:

   The difference between arterial and venous values for these parameters is minor (for pH is it is 0.02 - 0.15 pH units and for bicarbonate it is 1.88 mmol/L) and will not

alter management decisions. This allows for easier blood sampling and also saves patients from a degree of distress associated with arterial sampling.

An arterial line may be required in the very unwell, where frequent assessment of oxygenation is required or real time monitoring of blood pressure is desirable.

Serum lactate should also be checked; this can indicate type 1 lactic acidosis related to **sepsis**

8. Blood cultures:

    - These are often done as a screen for occult sepsis.

Ongoing monitoring:

After the initial laboratory diagnostic sample, use of a blood gas analysis machine for frequent monitoring of progress and **calculation of osmolarity**, 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.

Frequency of blood testing will depend to a large extent on how unwell the patient is.

In general terms for the average presentation it is reasonable to do **hourly** measurements for the first **6 hours** on:

1. Glucose
2. Blood ketones
3. Venous pH
4. Bicarbonate
5. Potassium
6. Osmolality (or calculate the osmolarity).

If response is satisfactory after the first 6 hours, then **2 hourly** blood tests can be done after that.

ECG:

As for any unwell patient.

Look in particular for:

- Possible precipitating acute coronary syndrome.
- Potassium abnormalities: hypokalemia / hyperkalemia

CXR:

Exclude pneumonia (possible precipitating cause for HSS)

Urine:

Take urine for microscopy and culture (possible precipitating cause for HSS) .

CT scan brain:

A CT scan of the brain should be considered for any patient who presents with an altered conscious state.

Management

1. Immediate attention to ABC issues, assess and treat as clinically indicated.

2. Establish IV access and commence **initial fluid resuscitation**:

    - Preferably large bore and with "pump set" line.
    - Patients may require initial fluid resuscitation to restore a compromised circulation.

      Normal saline should be used to achieve a blood pressure of at least 90 mmHg systolic.

      As a *general guide*, 250 - 500 mls of 0.9% sodium chloride solution may be given over 10 - 15 minutes.

      If systolic blood pressure remains below 90 mmHg this may be repeated.

      In practice most patients will respond to between 500 -1000 ml given rapidly.

      Colloid solutions are *not* recommended.

3. Establish monitoring:

    - Continuous **ECG** monitoring.
    - Continuous **pulse oximetry** monitoring.
    - IDC:
        - ♥ In the unwell.

If not unwell, consider if the patient is incontinent or anuric (i.e. not passed urine by 60 minutes)

Aim for at least **0.5 mls/kg/hr** is a minimum desired urine output.

- Consider arterial line and CVC, according to how unwell the patient is.

4. Fluid replacement:

Normal Saline:

Normal saline (i.e. 0.9% sodium chloride) solution is the solution of choice for the initial treatment of HSS.

Normal saline replacement **alone** (i.e. **without insulin**) will lower blood glucose which will reduce osmolality causing a shift of water into the intracellular space.

This inevitably results in an initial 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) and 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 - 6 mmol/hr** is recommended.

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.

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.

Generally fluids is given at **1 liter per hour** for the first few hours and the patient is reassessed regularly.

This will however, 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 - 15 mmol/L is a reasonable goal.

Complete normalisation of electrolytes and osmolality may take up to 72 hours.

Use of hypotonic saline (i.e. 0.45% saline):

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.

5. Potassium replacement:

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.

Potassium level in first 24 hours	**Rate of Potassium Administration**
Potassium > 5.5 mmol/L	Withhold potassium
Potassium 4.0 - 5.5 mmol/L	10 mmol KCl / hour.
Potassium < 4.0 mmol/L	20 mmol KCl / hour
10-20 mmol KCl may be added to *hourly* one liter normal saline bags. **If additional potassium needs to be given then 10 - 20 mmols can be given in *separate* bags of 100 mls normal saline over one hour.**	

In **severe hypokalaemia**, rates higher than 20 mmol/hr (via a central line) may be appropriate.

6. Insulin therapy:

Usually patients with hyperosmolar hyperglycaemia are more sensitive to insulin than is the case with DKA and so they require **lower doses.**

It is not advisable to lower the blood glucose too rapidly in HHS, due to the (possible) risk of CNS complications

If significant ketonaemia is present (i.e. **3β-hydroxy butyrate is > 1 mmol/L on capillary testing**) this indicates relative hypoinsulinaemia and insulin should be started at **time zero.**

If significant ketonaemia is not present (3β-hydroxy butyrate is < 1 mmol/L) insulin should **not** be commenced.

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, as a consequence of insulin-mediated glucose uptake and a diuresis from urinary glucose excretion. (**See Appendix 2 below**).

The recommended insulin dose is a fixed rate intravenous insulin infusion given at:

- **0.05 units per kg per hour (e.g. 4 units/hr in an 80 kg man)**

  (*So half the usual starting rate that is used in DKA*).

A fall of glucose at a rate of up to 5 mmol/L per hour is ideal.

Once the **blood glucose has ceased to fall** following initial fluid resuscitation, **insulin infusion can be started at this point.**

If an insulin infusion is already in place, and the **glucose level is not falling**, then infusion rate may be increased by **1 unit/hr.**

IV insulin can usually be discontinued once the patient is 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).

Therapeutic targets:

The goals of treatment of HHS are to treat the **underlying cause** and to **gradually** (**over 48 - 72 hours**) and safely:

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

The main contributors to plasma osmolality are sodium and glucose.

There can be an initial rise in serum Na+ of 2.4 mmol/L for each 5.5 mmol/L fall in blood glucose Thereafter, the rate of fall of plasma sodium should not exceed **10 mmol/L in 24 hours.**

A safe rate of fall of plasma glucose is between **4 - 6 mmol/hour.**

Osmolality is useful, both as an indicator of severity and for *monitoring the rate of change* with treatment. If measurement of osmolality is not available, osmolarity should be calculated as a surrogate using the formula $2xNa^+$ + glucose + urea.

Summary of fluid and insulin therapy:

Measure glucose, urea and electrolytes hourly and calculate osmolality ($2xNa^+$ + 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 the blood glucose is 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

7. Commencement of IV glucose/ avoidance of hypoglycaemia:

If blood glucose falls below 14 mmol/L:

- Commence 5% or 10% glucose at 125 mls/kg

And continue:

- Normal saline.

8. Antibiotics:

Antibiotics should be given when there are clinical signs of infection or imaging and/or laboratory tests suggest its presence.

9. Anticoagulation:

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.

The risk of venous thromboembolism in HSS is greater than that seen in DKA.

Hypernatraemia and increasing antidiuretic hormone concentrations can promote thrombogenesis by producing changes in haemostatic function consistent with a hypercoagulable state.

All patients should receive **prophylactic** low molecular weight heparin (LMWH) for the full duration of admission **unless contraindicated.**

Some have recommended the use of full treatment dose anticoagulation. However, patients with HHS are often elderly and at increased risk of haemorrhage and there is no evidence to support this approach.

Full anticoagulation should only be considered in patients with confirmed or 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.

It should be noted that it is not definitely known whether prophylaxis with low molecular weight heparin (or anti-platelet therapy) can prevent HSS induced vascular thrombosis.

10. Phosphate:

Hypophosphataemia is common in HHS, however 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.

11. Hypomagnesaemia:

Hypomagnesaemia is also common in HHS.

Magnesium replacement has also not been shown to be beneficial so should only be considered if the patient is symptomatic or has symptomatic hypocalcaemia.

12. Foot protection:

HSS 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.

13. Precipitating factors:

Precipitating factors should always be considered

Possible precipitating illnesses can include:

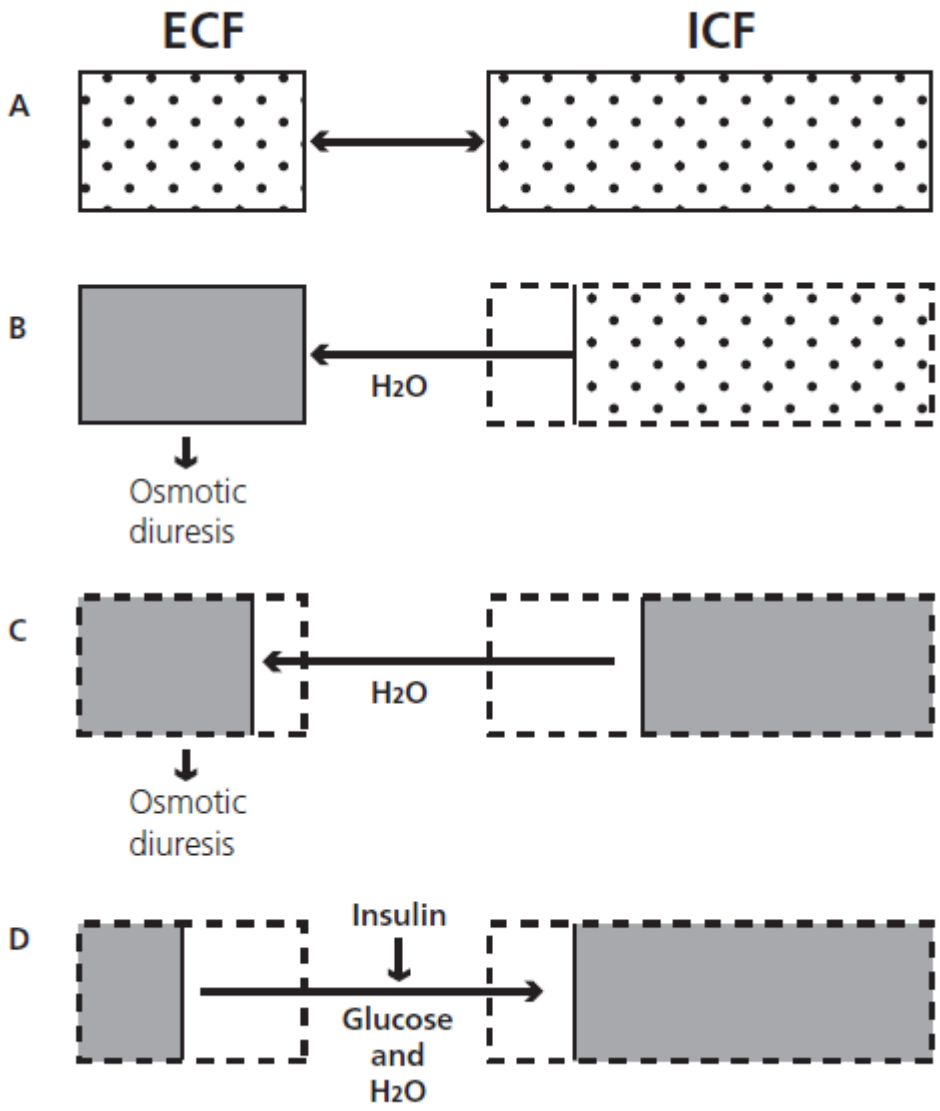
- Acute coronary syndrome.
- Sepsis (UTI, chest infection, cellulitis)
- Occult surgical conditions
- Pancreatitis
- Stroke

Disposition:

All cases should have early consultation with:

- **The endocrine unit**
- **ICU - especially if criteria for very serious illness is met (see above)**
- **Once recovered all patients will require diabetes education to reduce the risk of recurrence and prevent long-term complications.**

Appendix 1 - *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*

Appendix 2

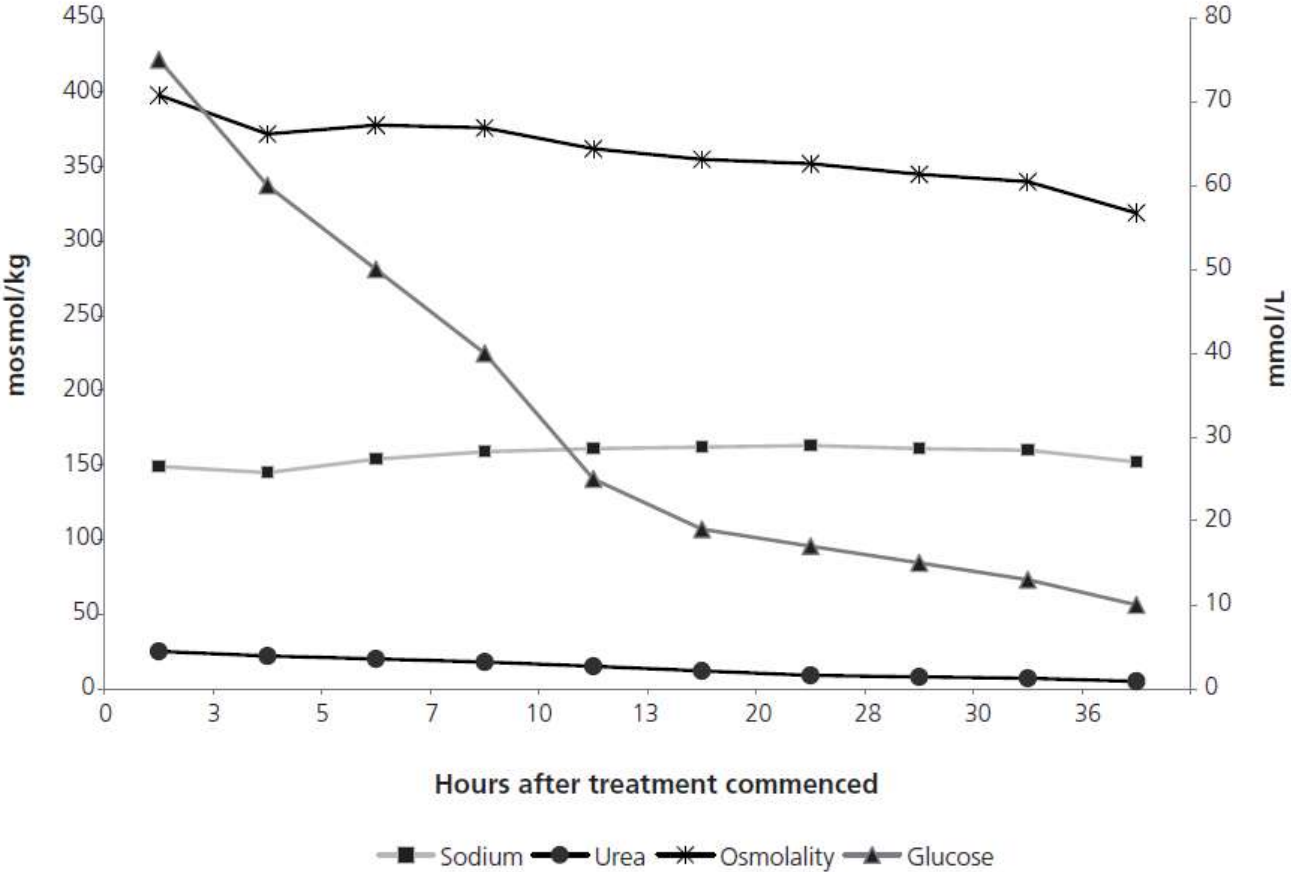


Figure showing the change in osmolality during treatment of HHS with 0.9% sodium chloride solution. Note the fall in blood glucose (initially at 5 mmol/L per hr) and urea accompanied by a rise in sodium is nevertheless associated with a slow but steady fall in (calculated) osmolality.

Appendix 3

Parameter	DKA	HSS
Dehydration	Relatively less than HSS (*Around 100 mls/kg of water loss*)	Relatively more than DKA (*Around 100 - 220 ml/kg of water loss*)
Onset	Presents within **hours** of onset	Develops more slowly over **many days.**
Age Group	Any age group	More commonly in the elderly, but increasingly is seen in younger adults as well.
Ketosis	Can be severe	Normal or mild only (ketones < 3 mmol/L)
Acidosis	Can be severe	Normal or mild only (pH >7.3 / bicarbonate >15 mmol/L)
Hyperglycaemia	Ranges from almost normal ("euglycemic") to high	Always high (> 30 mmols/L)
Osmolality	High	High to very high (> 320 mosmol/kg)

References

1. The Management of the Hyperosmolar Hyperglycaemic State (HHS) in Adults with Diabetes Joint British Diabetes Societies Inpatient Care Group August 2012.

- www.diabetes.nhs.uk

Dr J. Hayes
Reviewed June 2017.