Hyperosmolar Hyperglycaemic Non-Ketotic State

Aim(s) and objective(s)

Hyperosmolar, Hyperglycaemic, Non-Ketotic State is a life threatening derangement of metabolism in diabetes which may be insidious in onset, difficult to recognise and challenging to treat. The underlying causes are wide and variable.

This guideline serves to increase knowledge of the features and management of this condition to improve awareness and support prevention through education of both health professionals and people with diabetes.

Author(s)

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User group

Primary Care
Acute physicians including those in Care of the Elderly
A&E clinicians
Scottish Ambulance Service staff
Diabetes specialist staff

This guideline is not intended to serve as a protocol or standard of care. That is best based on all clinical data available for an individual case and may be subject to change as scientific knowledge and technology advances and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should it be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same result. Ultimately a judgement must be made by the appropriate healthcare professional(s) responsible for a particular clinical procedure or treatment plan following discussion with the patient, covering the diagnostic and treatment options available. It is advised that any significant departure from the guideline should be documented in the patient’s medical record at the time the decision is taken.

Guideline

This extreme metabolic derangement in Diabetes occurs through a combination of intercurrent illness, dehydration and an inability to take normal diabetic therapy due to the effect of illness. It is a potentially life-threatening emergency. It is characterised by severe hyperglycaemia with marked serum hyperosmolarity, without evidence of significant ketosis.

Hyperglycaemia causes an osmotic diuresis with hyperosmolarity leading to an osmotic shift of water into the intravascular compartment, resulting in severe intracellular dehydration. Ketosis does not occur due to the presence of basal insulin secretion sufficient to prevent ketogenesis, but insufficient to reduce blood glucose.

Cause

- Intercurrent or co-existing illness
- Medication induced – metformin during intercurrent illness, diuretics, β blockers, H₂ Receptor antagonists, dialysis/total parenteral nutrition/glucose containing fluids, calcium channel blockers, chlorpromazine/other antipsychotics (olanzapine), prednisolone, phenytoin, substance misuse
- Diabetes related – first presentation, poor control or non-compliance
**Risk factors**
- Can affect people of all ages, but is much commoner in older people with Type 2 Diabetes
- Nursing/rest home residents or those that live alone
- Dementia
- Sedative drugs
- Heat waves
- Propensity to infection, e.g. immunosuppressed, corticosteroid users

**Symptoms**
- Patients usually notice early symptoms of generalised weakness, leg cramps or visual impairment
- Nausea and vomiting may occur but this is much less so than for diabetic ketoacidosis.
- As the condition progresses patients may become bed-bound, confused and lethargic
- Focal neurological symptoms such as weakness on one side or hemisensory abnormalities may develop and be easily confused with stroke
- Seizures are present in up to 25% of cases; they can be generalised, focal, movement-induced or myoclonic-jerk type
- Despite the condition’s name, coma is a relatively rare feature affecting only about 10% of those who present with the relevant metabolic abnormalities. Progression to coma represents severe disease

**Signs**
- **General Inspection:** Patients usually appear ill and look exhausted if they are still conscious. There may be evidence of disorientation or confusion. Look for signs of self-neglect due to recent illness or long-standing inability to self-care. Signs of dehydration such as dry mouth, decreased skin turgor or sunken eyes may be visible on general inspection
- **Vital Signs:** Tachycardia is common due to dehydration. Hypotension may be present due to severe fluid depletion or underlying sepsis/cardiac impairment. Postural hypotension is not a specific or sensitive sign due to its high background prevalence in the elderly population. An increased respiratory rate may be found due to compensatory attempt to reduce metabolic acidosis. The temperature may reveal pyrexia or hypothermia. Pulse oximeter measurement may show haemoglobin desaturation, in which case administer oxygen whilst conducting further assessment
- **Skin:** A careful examination of the entire skin surface is needed, looking for rashes and localised sepsis (e.g. cellulitis or leg ulcers). Turgor will be reduced due to dehydration; in patients with infection the skin may feel warm and moist. Severe sepsis can lead to cold, dry mottled skin. Don’t forget the feet.
- **Head:** Check the eyes to see if they are sunken. Look in the mouth for dryness, check the pharynx for inflammation and perform auroscopy, looking for middle ear infection. A quick screening cranial nerve examination may reveal visual field deficits, nystagmus or other cranial nerve palsies
- **Neck:** Check the lymph glands for enlargement and look for goitre due to thyrotoxicosis. Check for neck stiffness due to meningitis
- **Chest examination:** May reveal evidence of pneumonia or acute respiratory distress syndrome (a potential complication of HONK)
- **Cardiac examination:** May reveal evidence of heart failure as the precipitant illness, or give reason to suspect myocardial infarction or infective endocarditis
- **Abdominal examination:** Should look for signs of an acute abdomen. Paralytic ileus or gastroparesis may occur during the acute phase but usually settles when HONK is treated.
Persisting signs of intestinal obstruction should prompt a search for an intra-abdominal cause for HONK. Consider rectal examination if there is reason to suspect GI bleeding, prostatitis or pelvic abscess. Women may need a pelvic examination/swab to exclude infection in the gynaecological tract.

- **Neurological examination**: Check orientation and higher cerebral functions. Kernig's test positive? Cranial nerves and limb tone, power, co-ordination, reflexes and sensation should be assessed.

**Investigations**

- Urinalysis shows marked glycosuria with normal or only slightly elevated ketones.
- Capillary glucose is usually markedly elevated at >27.8 mmol/l. Samples should also be sent for plasma glucose.
- Serum osmolality is usually > 320 mmol/l (normal range is 290 ± 5 mmol/l). Osmolarity can be approximately calculated as:
  
  \[
  \text{Plasma Osmolarity} = 2 (\text{Na mmol/l} + \text{K mmol/l}) + \text{urea mmol/l} + \text{glucose mmol/l}
  \]

  - Hypernatraemia is almost always present.
  - Urea and creatinine are often elevated due to dehydration and pre-renal renal failure.
  - Hyperkalaemia may be present.
  - Arterial blood gases usually show evidence of mild metabolic acidosis with pH < 7.30.
  - The anion gap should be small at 10-12. Higher values indicate a possible alternative cause for metabolic acidosis. The anion gap should be calculated:
    
    \[
    \text{Anion Gap} = (\text{Na mmol/l} + \text{K mmol/l}) - (\text{Cl mmol/l} + \text{HCO}_3^-)
    \]

  - Creatine kinase and cardiac enzymes: Myocardial infarction and rhabdomyolysis can cause the syndrome or arise as a complication.
  - Further investigations to detect the underlying cause should include urine, blood and any other relevant cultures and specific tests directed at detecting the most likely cause in a given case, where relevant to ongoing management, e.g. lumbar puncture for suspected meningitis.

**MANAGEMENT**

**Initial general measures:**

- Resuscitation ABC: Check for and treat any problems with airway, breathing or circulation to buy time.
- Intubate and ventilate patients with deteriorating oxygen saturations (take senior-A&E/medical/anaesthetic advice).
- Obtain large-bore IV access (central line may be needed).
- Connect patient to ECG monitor, SpO2 monitor and BP monitor.
- Give oxygen if needed.
- Catheterise patient to obtain urine and monitor urine output.
- Consider passing nasogastric tube if impaired consciousness and risk of aspiration.
- Arrange transfer to high dependency area as soon as feasible.
- Alert acute medical/diabetic team.

**Intravenous rehydration and electrolyte replacement:**

- Patients will require intravenous fluids. The overall fluid deficit is around 100-200 ml per kg, averaging about 9 litres of intravenous fluid.
- Initially give 1 litre of 0.9% NaCl over first hour.
• Shocked patients may benefit from colloid infusion and/or inotropic support in an intensive care setting
• Further intravenous fluid regimens depend on the patient’s response and continuing assessment of electrolytes:
  o Expert acute-medical/diabetologist input is needed
  o Consider using hypotonic saline (0.45%) if markedly hypernatraemic, otherwise give normal saline (0.9% NaCl)
  o It is important not to correct hypernatraemia too rapidly as it may precipitate cerebral oedema
  o Watch for fluid overload
  o Remember the condition has evolved over days or weeks and this should be reflected in the rate of rehydration
• Glucose: When blood glucose levels are returning to near normal then dextrose infusion will need to be introduced to the regimen to prevent over-rapid fall in blood glucose, leading to hypoglycaemia
• Potassium: Once insulin is given (the next most important arm of therapy), serum potassium can plummet from high to very low levels, as overall potassium depletion has occurred, despite its initial high blood concentration in the dehydrated patient
• Insulin will cause an intracellular shift of potassium, so replacement potassium is usually given in intravenous fluids as soon as levels fall to between 3.5-5.0 mmol/l. This should be done under expert acute-medical supervision with regular electrolyte monitoring
• Levels of phosphate, magnesium and calcium may also be monitored and replaced as appropriate (although trial data to show the efficacy of replacing these electrolytes is currently lacking)

**Insulin therapy**

- Aim to reduce glucose levels slowly, by approximately 3 mmol/hr
- Patients with hyperosmolar, hyperglycaemic, non-ketotic state are often exquisitely sensitive to insulin and require much lower doses than in diabetic ketoacidosis (DKA)
- Fluid replacement must commence first; an initial insulin bolus of 0.15 Units per kg may be given once infusions are under way
- The variable insulin infusion rate below is a guide: glucose must be monitored hourly and the regimen adjusted on an individual basis, depending on response. Other approaches include starting with 6 units per hour and adjust according to response. Advice should be sought from a diabetologist

<table>
<thead>
<tr>
<th>Capillary glucose</th>
<th>Soluble insulin (1f 50 Units in 50ml 0.9% NaCl, U/ hr = ml/ hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 mmol/l</td>
<td>0 Units/hr</td>
</tr>
<tr>
<td>4.1-7.0 mmol/l</td>
<td>1 Units/hr</td>
</tr>
<tr>
<td>7.1-11.0 mmol/l</td>
<td>2 Units/hr</td>
</tr>
<tr>
<td>11.1-17.0 mmol/l</td>
<td>3 Units/hr</td>
</tr>
<tr>
<td>&gt; 17.0 mmol/l</td>
<td>4 Units/hr</td>
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• Treat underlying cause if known
• Antibiotics should not be used routinely but where there are reasonable grounds to suspect sepsis, such as elevated white cell count or a hypotensive patient, have a low threshold for their use
• Review any medications the patient is taking and decide whether they should be discontinued pro-tem or permanently
• Low-molecular weight heparin should be given routinely at prophylactic doses or as formal anticoagulation if there is a significant risk of thromboembolic disease

Complications
• Ischaemia or infarction affecting any organ, particularly myocardial infarction and brain (cerebral infarct)
• Thromboembolic disease, including deep vein thrombosis and pulmonary embolism
• Acute respiratory distress syndrome
• Disseminated intravascular coagulation
• Multi-organ failure
• Rhabdomyolysis
• Cerebral oedema (rare in adults, less so in children)
• Iatrogenic complications due to inexpert rehydration and electrolyte management; over-administration of insulin; fluid overload leading to cardiac failure

Prognosis
Mortality is 10-20%.

Prevention
• Diabetic patients should be well educated about how to manage their condition, particularly when ill
• Awareness in the medical profession that this is a possible presentation of diabetes may lead to earlier recognition of the problem
• Patients who have suffered HONK should receive education and extra support to try and stop this from recurring

Diabetes MCN endorsement
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