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DKA/HHS Protocol: (Adult)

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Introduction and aim of the protocol:

Diabetes Mellitus (DM) is one of most common endocrine disease in Saudi Arabia which affects both children and adults[1]. It is a chronic metabolic disorder that affects metabolism of all major macronutrients including proteins, fats and carbohydrates[2].

Diabetes prevalence is increasing worldwide at an alarming rate due to modernization, urbanization, socio-economic development, obesity and increased physical inactivity[3]. The International Diabetes Federation (IDF) estimated that diabetes mellitus worldwide will rise from 171 million in 2000 to 366 million by 2030. But in 2011, it already reached 366 million[4]. As per new estimates in 2013, 8.3% of world population (382 million) suffer from DM at present and will rise to 592 million in less than 25 years[5].

According to World Health Organization (WHO) report in 2014, Saudi Arabia ranks 2nd in the region in diabetes prevalence and 7th in the world. As per report, out of 33.3million population, 7 million have diabetes and 3 million have pre diabetes[6]. A study from central region especially Riyadh reported that among adults of age 30-70 years, 23.7% have Diabetes Mellitus and 14.1% have impaired fasting glucose and the incidence rate in urban region was more than rural with 25.5% to 19.5%[7]. Another study in 2014, reported that in adults with age 30 and above, 25.4% have diabetes and another 25.5% had pre diabetes[8]. And if current trend is followed, by 2030, 50% of population will be diabetic[9].

In Saudi Arabia both type 1 and Type 2 DM in Adults are present. But as we know that type 1 is more common in children and adolescents and type 2 DM is more common in adults and there is an overlap too. Both types of DM are rising at an alarming rate and as per current data Type 1 DM has an annual incidence of 3-4% worldwide[10]. And with an annual incidence of 33.5%, Saudi Arabia stands at number 4 world-wide in Type 1 DM. Total number of type 1 DM is Saudi Arabia are more than 35000 with annual addition of 3900 new cases

per year[11]. In Saudi Arabia, Type 1 DM prevalence is highest in Riyadh region with rates as high as 126/100,000 and mostly urban in origin[12,13].

This very high incidence and prevalence of diabetes in Saudi Arabia is a major reason for more and more patients presenting in Emergency departments with diabetes related complications which may be life threatening like DKA and HHS[14,15]. About DKA in Saudi Arabia, over last 3 decades, there have been many studies on epidemiology and clinical characteristics of DKA and HHS[16]. These studies have shown that DKA has a very high incidence at the time of 1st presentation in Saudi Arabia as compared to developed countries[17,18].

So, keeping in view the disease burden in the form of high incidence and prevalence of diabetes and diabetes related acute complications with high morbidity, high mortality, very high cost and importance of protocol implementation, and the fact that we don't have a unified protocol of Diabetes Ketoacidosis in adults the aim of this protocol is to unify the management protocol of DKA throughout the Kingdom of Saudi Arabia, and we aim to reduce the length of stay and hence to reduce the cost of management and reduce morbidity and mortality of the DKA in concomitant of Saudi vision 2030.

Methodology:
Development of DKA protocol went through 4 steps as follows:

Phase 1: review the literature of Diabetic Ketoacidosis with special attention to the world wide protocols and guidelines in this regard including the existing protocols and their effect in managing patients with diabetic ketoacidosis, this phase has been done by experts in adult Endocrinology and Diabetes. The outcome of this phase is unified DKA management protocol according the best evidence based practice.

Phase 2: the panel of experts has been extended to including adult Emergency Medicine and intensive care units whom they reviewed the protocol developed by the endocrinologist and diabetologists and put their input according to their specialty

Phase 3: the protocol has been reviewed and amended by another panel of experts from nurses, pharmacists, lab experts as well as quality improvement experts

Phase 4: experts from the different specialties including (adult endocrinology and diabetology, adult emergency medicine, and adult intensive care) from the 20 regions of Saudi Arabia whom they reviewed the protocol and shared their opinion.

Literature Review:

DKA is related with another similar condition called hyperosmolar hyperglycemic state (HHS). The hospitalization rate in HHS is less than DKA and its less than 1% of all diabetes related admissions worldwide[19]. But admission with HHS in Saudi Arabia are significantly higher than the world[20]. One study from Jeddah in adults with diabetes mellitus has shown that out of all patients with hyperglycemic crisis, 82.9% had DKA and 17.1% had HHS. And More patients with type 1 DM patients presented with DKA (87.5%) than with HHS (12.5%). Similarly, in patients with Type 2 DM more patients presented with HHS than DKA[20].

Both of these conditions (DKA and HHS) differ in many aspects, which include more severe hyperglycemia, absence of ketosis and metabolic acidosis. There are many clinical characteristics including presence of more

co morbidities, longer duration of diabetes, presence of more severe dehydration, reduced level of consciousness, and more chances of renal impairment at presentation in HHS. Therefore, it is necessary to address this clinical entity separately and to write a separate protocol HHS management.

Similarly, the acute complications of Diabetes like DKA and HHS are associated with high morbidity and mortality if not treated properly. In Children and adolescents with Type 1 DM, DKA is a cause of mortality in almost 50% of patients[21]. Mortality is variable depending on region and the health care facility. Over last 3 decades, worldwide mortality from DKA has reduced from 8% to less than 1% [22].

One of study from USA in 2018 showed that DKA mortality has been reduced from 2000-2014 from 1.1% to 0.4% [23]. Similarly, in United Kingdom, Adult DKA mortality has been reported to be less than 0.16%. And a single episode of DKA was associated with 5.2% risk of death, while recurrent DKA admissions were associated with 23.4% risk of death. Also, those patients with more than 5 DKA admissions died over a period of 2.4 years[24]. DKA mortality in adults in Italy is 7.4%[25]. And one study from Denmark showed that mortality was 4% with most of patients age 50 years and above and having type 2 DM and co morbidities[26]. In Australia and New Zealand, the DKA mortality in adults is 1.4%[27]. In China, one study of adult DKA showed that mortality is 0.67% [28]. Recently in 2016, one study from India reported very high inpatient mortality of 30% and most of these patients who died were above the age of 20 years (81.5%)[29].

In Middle Eastern North African (MENA) Region, there are many studies on epidemiological and clinical characteristics of patients with DKA and HHS but very few studies on mortality from these conditions. In Kenya, mortality from DKA was 30% and most of patients in this study were adults and half of these patients were newly diagnosed with co morbidities presenting with altered mental status and coma due to late presentation[30]. In Libya one study showed that the overall mortality among adults and children with DKA is 11.7% and all patients who died were adults with co morbidities and increased duration of diabetes especially type 2 DM[31].

In Saudi Arabia the documented mortality from DKA is 3.5% and 2.9% in two different studies[32,33]. Another study by Al Rubeaan in 2011 reported zero mortality in patients with DKA at tertiary hospital in Riyadh for 240 patients admitted between 1985-2005[34]. Similar results with zero mortality were shown by Faiza Qari in a study of 60 patients with DKA at a university hospital ICU[35]. And these results may be due to highest level of care provided at university hospital.

The mortality is almost 10 times higher in HHS than in DKA and it ranges between 5-16%. This high mortality is mostly due to presentation in old age, presence of co morbidities, and lack of early recognition of this life threatening condition[36-38].

Another important issue in management of diabetes, diabetes related complications including acute emergencies, is high cost. In 2011, worldwide total healthcare related cost for diabetes and related complications amounted to 465 billion US$. And this cost is expected to rise to 595 billion US$ in 2030[39]. In Saudi Arabia, in 2010, out of total health expense of 9.4 billion US$, 0.9 billion US$ was spent only on diabetes related costs, which means out of each 11 $ spent, 1 $ was spent on Diabetes[40]. Similarly, the cost of managing acute diabetes emergencies is huge due to its life-threatening nature. In USA, the cost of management of one DKA patient is around 17500 US$.[41].

With better understanding of pathophysiology and development of evidence based DKA and HHS guidelines and implementation of care pathways, Mortality in DKA /HHS reduced substantially in recent years throughout world[42,43]. Worldwide, it has been a standard practice to have national level evidence-based guidelines and hospital protocols for acute diabetes emergencies. The implementation of such standard order set and protocols improve quality of care, reduce morbidity, improve time to DKA and HHS resolution, reduce length of stay and improved compliance in shifting to sub cut insulin.

One study from USA in 2017 showed that DKA protocol implementation by computerized orders set in ICU improved time to resolution of DKA[44]. In Saudi Arabia, there is no data on diabetes emergencies protocols implementation in adults. Only one study in 2017 reported that implementation of clinical practice guidelines at a university hospital reduced the length of stay in children and adolescents with DKA[45].

Diabetic ketoacidosis management protocol for adults (>14 years)

Diabetic ketoacidosis (DKA) is defined by the biochemical triad of ketonemia, hyperglycemia and acidemia. The main treatment of DKA is rehydration, insulin administration and electrolytes balance, mainly potassium, together with identification and treatment of the precipitating factor. Type 1 diabetes mellitus (T1DM) subjects are at risk of developing DKA if they acquire infection, secondary to frequently missed insulin doses or due to marked stress. Furthermore, subjects with newly diagnosed T1DM often present with DKA. Also, subjects with T2DM may present with DKA if they have persistent hyperglycemia for long period of time or they become under the effect of a stressor. Diagnosis of DKA is not difficult and depends on the finding of acidemia, ketonemia or significant ketonuria and hyperglycemia. Treatment of DKA mandates good monitoring of fluid status, electrolytes, acidosis and blood sugar. This is a simplified protocol for management of DKA prepared after extensive review of the available evidence based medicine and clinical practice. Most importantly, this protocol provides general guidance; however, it may not suit all patients and will not replace the clinical judgment of the treating physicians.

Clinical presentation

The commonest clinical presentation of DKA and HHS is due to hyperglycemia and include polyuria, polydipsia, weight loss, weakness, and physical signs of dehydration such as dry buccal mucosa, sunken eye balls, poor skin turgor, tachycardia, hypotension and shock in severe cases. Kussmaul respiration, acetone breath, nausea, vomiting and abdominal pain may also occur primarily in DKA. Abdominal pain correlates with the severity of acidosis (3).

Diagnosis

Diagnostic Criteria for DKA:

- Plasma glucose (PG) more than or equal to 200 mg/dl (11.1 mmol/L) or known diabetes;
- Positive serum ketones or significant ketonuria (more than or equal to 2+ urine ketone) and;
- Venous or arterial HCO3 less than 15 mmol/L and/ or pH less than 7.3.

(All 3 biochemical criteria are required for the diagnosis)[1]

Investigations

should be directed towards finding the precipitating factors and should be ordered by the treating physician whenever it is appropriate.

Markers of severity (Manage in HDU/ICU):

- GCS less than 12
- pH less than 7.1
- Serum ketones more than 6 mmol/L
- HCO3 less than 5 mmol/L
- K^+ less than 3.3 or more than 6.0 mmol/L
- SBP less than 90 mmHg
- SpO2 less than 92% in room air and pulse rate more than 100 or less than 60 bpm
- Urine output less than 0.5 ml/kg/hr or evidence of acute kidney injury

Treatment of DKA:

Fluid therapy

Subjects with DKA usually present with variable degrees of dehydration (up to 6 litres) and will require gentle and well monitored fluid replacement. The initial fluid of choice is isotonic saline at the rate of 15–20 ml /kg body weight per hour or 1–1.5 L during the first hour. The choice of fluid for further repletion depends on the hydration status, serum electrolyte levels, and urinary output. In patients who are hypernatremic , 0.45% NaCl infused at 4–14 ml/kg/hour is appropriate, and 0.9% NaCl at a similar rate is preferred in patients with eunatremia or hyponatremia. The goal is to replace half of the estimated water deficit over a period of 12- 24 hours. In patients with hypotension, aggressive fluid therapy with isotonic saline should continue until blood pressure is stabilized (2). The protocol is not designed for subjects who are hemodynamically unstable and those will require management by the ICU team. Quick and over-replacement of fluids is associated with morbidities in DKA subjects e.g. cerebral edema therefore, physicians should always pay attention to the amount of fluids given.

Insulin

Treatment with intravenous insulin should be established once the serum potassium level is more than (3.3 meq/l) and should be continued till the patient is out of DKA and can be shifted to subcutaneous insulin. The only indication to stop insulin is when the K level is less than 3.3 meq/l where replacement with KCL should take be done before insulin is started . The initial insulin dose should be 0.1 unit/kg which should be lowered to 0.05 units /kg if the blood sugar is less than 6 mmol/L. As in the order sheet of the protocol, to avoid hypoglycemia 25 cc of D50% saline can be given as a bolus whenever the BS fall below 4 mmol/l. The other option is to add D10%w to the existing fluids to increase and maintain the blood sugar in the target levels.

Potassium Therapy

Most morbidity and mortality in DKA management came from mismanagement of potassium replacement. Although total-body potassium is depleted, mild to moderate hyperkalemia is frequently seen in patients with DKA, due to acidosis, proteolysis and insulinopenia. Insulin therapy, correction of acidosis, and volume expansion decrease serum potassium concentrations. To prevent hypokalemia, potassium replacement is initiated after serum levels fall below the upper limit of normal.

Patients with DKA who had severe vomiting or had been on diuretics may present with significant hypokalemia. In such cases, potassium replacement should begin with fluid therapy, and insulin treatment should be postponed until potassium concentration becomes > 3.3 mEq/L, in order to prevent arrhythmias and respiratory muscle weakness. The order sheet outline few points to take over in case of severe hypokalemia (2). Good monitoring of potassium level is crucial during the management of DKA and the order sheet provides flexibility

for the physician to select the timing of repeating the level however aggressive monitoring might be needed especially for those unusually presenting with hypokalemia.

Bicarbonate: (Not routinely needed only in cases of severe Acidosis {pH less than 6.9} not responding to initial treatment).

- If pH is less than 6.9: NaHCO3 (50 mmol) dilute in 200 ml H2O infuse at 200 ml/hr, hold if K is below 3.3 mmol/l
- Repeat HCO3 infusion every 2 hour until pH is more than 6.9.
- Monitor K+ level every 2 hours while on Bicarbonate infusion.
-

Criteria for switching to subcutaneous Insulin:

Venous HCO3 ≥ 18 mmol/L and/or pH ≥ 7.3, and closed anion gap.
The patient is able to take orally.
Overlap the first dose of rapid acting insulin for one hour with the insulin infusion before stopping.

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Patient:
MRN:

Order Sheet for the Management of Adult Patients (more than 14 years old) with DKA

Please admit the patient to: ☐ General Ward ☐ ICU, as a case of _____ , secondary to _____

under the care of Dr. _____.

Vital Signs: ☐ STAT ☐ Then every_____ **Glasgow coma scale** ☐ STAT ☐ Then every_____

Diet: ☐ Diabetic Diet ☐ NPO **Urinary Catheter:** ☐ Yes ☐No **Nasogastric Tube needed:** ☐ Yes ☐ No

Investigations:

VBG: ☐STAT ☐ Then every _____ **Urea / Electrolytes:** ☐STAT ☐ Then every _____

☐ CBC ☐ Urine Analysis ☐ Urine Ketones ☐ Urine culture/sensitivity ☐ Blood Culture ☐ Random Blood sugar ☐ Serum Ketones

☐ **Phosphorus** ☐ **Ca·** ☐ **Mg**

☐ CXR ☐ ECG ☐ Troponin/CK-MB ☐ Others _____

Monitoring: Check blood sugar, by glucometer (if hourly blood sugar readings are between 5-10 mmol/L for 3 consecutive hours, then the frequency of blood glucose checking can be reduced to 2 hourly).

☐ Input/Output Chart ☐ Daily Weight

Fluids: (If the patient is hemodynamically unstable, **DON'T** use this protocol)

☐ **If Systolic BP is more than or equal to 90 mmHg,** please use the algorithm below: Be cautious with elderly patients, very young patients, and patients with compromised cardiac status due to risk of fluid overload.

Weight at presentation more than 50 kg
☐ 0.9% NaCl 1L over 1st hour (no added potassium chloride)
☐ 0.9% NaCl 1L over next 2 hours (no added potassium chloride)
☐ 0.9% NaCl 1L over next 4 hours (with potassium chloride as per potassium replacement algorithm)

Weight at presentation less than or equal to 50 kg
Do not use this protocol.

☐ Continue NS fluid at a rate of (100 – 250 ml/hr)……..ml/hour with potassium as in potassium algorithm.

☐ When blood sugar is less than13 mmol/L, change to D5 NS at a rate (100 – 250 ml/hr)……ml/hour.

☐ **If blood sugar is less than 4.0 mmol/L, give a bolus of 25 ml of Dextrose 50%.**

Insulin: (Don't start insulin till K level is available)

☐ Mix 50 units human regular insulin with 50 ml with 0.9% NaCl solution.

☐ Infuse insulin at a fixed rate (0.1 unit/kg/hr) _____units/hour. (No bolus)

☐ Check blood sugar hourly by glucometer.

☐ When the blood sugar is less than 6 mmol/L, decrease insulin infusion to (0.05 unit/kg/hr) _____ units/hour.

☐ If the patient is using Levemir/ Glargine continue same dose at the same time _____units at _____daily (optional)

❖ **Potassium Chloride Replacement** (make sure the patient is passing urine and has a normal renal function)
Starting potassium should be:

☐ more than 5.2 mmol/L	☐ 3.3 to 5.2 mmol/L	☐ less than 3.3 mmol/L (call the doctor immediately)
☐NIL	☐ 40 mmol/L To be added to IV fluid, don't exceed the maximum rate of 10 meq/potassium chloride per hour	• Hold insulin infusion for 2 hours or until serum potassium is more than or equal to 3.3 meq/L • **Perform ECG** • **Apply cardiac monitor to patient** • Increase the rate of potassium chloride infusion but don't exceed the maximum rate of 10 meq/potassium chloride per hour. • Request a higher potassium chloride concentration infusion from pharmacy. • Once ready, give 40 meq of potassium chloride in 500 ml 0.9 % normal saline to run over 4 hours. • Resume insulin infusion when serum potassium is more than or equal to 3.3 mmol/L.

❖ **Potassium drip concentration** should be changed whenever the serum potassium level is checked as per potassium chloride replacement algorithm. Insulin infusion should be resumed after correction of potassium level

Physician's Name and Stamp: _____ **Date:** _____

Signature: _____ **Time:** _____

Nurse's Name: _____ **Date:** _____

Signature: _____ **Time:** _____

- For subjects who presented with unexplained hypoglycemia (either on using insulin or oral hypoglycemic agents) a reduction in the insulin dose and/or OHA (10-25%) should be considered
- For individuals who presented with explained hypoglycemia, consider lowering the dose.
- Enhance DM related education

Order Sheet for the Management of Adult Patients (more than 14 years old) with DKA

Confirm DKA Diagnosis (All 3 biochemical criteria are required for the diagnosis):

- Plasma glucose (PG) more than or equal to 200 mg/dl (11.1 mmol/L) or known diabetes;
- Positive serum ketones or significant ketonuria (more than or equal to 2+ urine ketone) and;
- Venous or arterial HCO3 less than 15 mmol/L and/ or pH less than 7.3.

Bicarbonate: (Not routinely needed only in cases of severe Acidosis {pH less than 6.9} not responding to initial treatment).

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- Repeat HCO3 infusion every 2 hour until pH is more than 6.9.
- Monitor K+ level every 2 hours while on Bicarbonate infusion.

Criteria for switching to subcutaneous Insulin:

- Venous HCO3 more than 18 mmol/L and/or pH more than 7.3, and closed anion gap.
- The patient is able to take orally.

Overlap the first dose of rapid acting insulin for one hour with the insulin infusion before stopping.

Markers of severity (Manage in HDU/ICU):

- GCS less than 12
- pH less than 7.1
- Serum ketones more than 6 mmol/L
- HCO3 less than 5 mmol/L
- K^+ less than 3.3 or more than 6.0 mmol/L
- SBP less than 90 mmHg
- SpO2 less than 92% in room air and pulse rate more than 100 or less than 60 bpm
- Urine output less than 0.5 ml/kg/hr or evidence of acute kidney injury

Definition: Diabetic ketoacidosis is defined by the biochemical triad of ketonemia, hyperglycemia and acidemia. The main treatment of DKA is rehydration, insulin administration and electrolytes balance, mainly potassium, together with identification and treatment of the precipitating factor.

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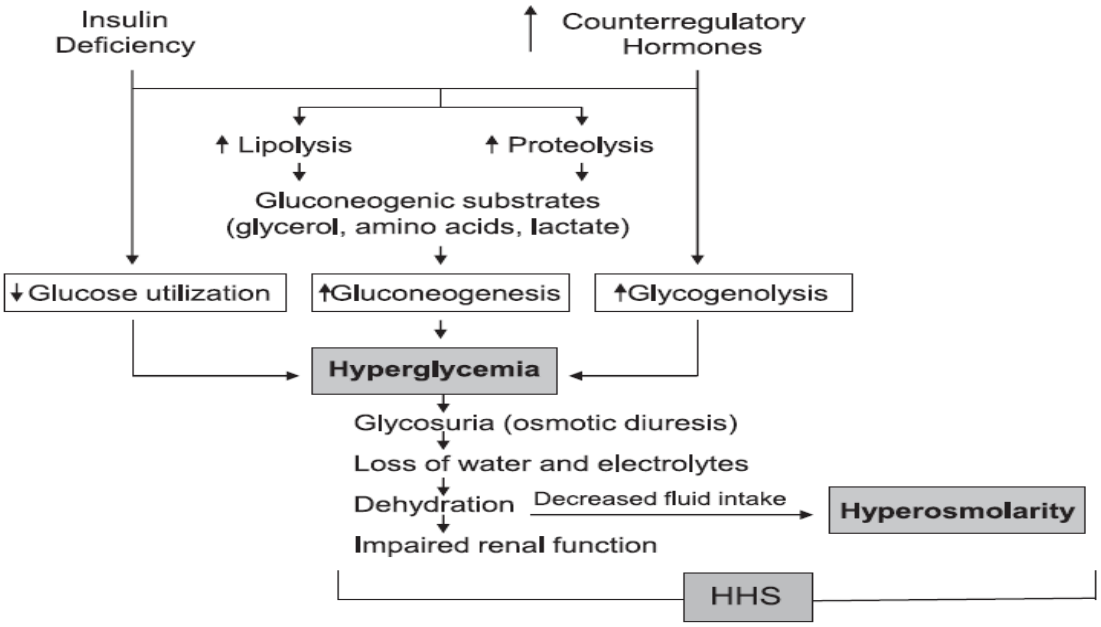
Protocol for diagnosis and management of adults with hyperglycemic, hyperosmolar state

Introduction:

The hyperosmolar hyperglycemic state (HHS) is a syndrome characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of ketoacidosis. The estimated incidence account for <1% of hospital admissions in patients with diabetes. Most cases of HHS are seen in elderly patients with type 2 diabetes; however, it has also been reported in children and young adults. The overall mortality rate is estimated to be as high as 20%, which is about 10 times higher than the mortality in patients with diabetic ketoacidosis (DKA). The prognosis is determined by the severity of dehydration, presence of comorbidities, and advanced age. Treatment of HHS is directed at replacing volume deficit and correcting hyperosmolality, hyperglycemia, and electrolyte disturbances, as well as management of the underlying illness that precipitated the metabolic decompensation. Low-dose insulin infusion protocols designed for treating DKA appear to be effective; however, no prospective randomized studies have determined best treatment strategies for the management of patients with HHS.

Pathophysiology:

HHS is characterized by extreme elevations in serum glucose concentrations and hyperosmolality without significant ketosis. These metabolic derangements result from synergistic factors including insulin deficiency and increased levels of counter regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) . Hyperglycemia develops because of an increased gluconeogenesis and accelerated conversion of glycogen to glucose (glycogenolysis) and by inadequate use of glucose by peripheral tissues, primarily muscle. From the quantitative standpoint, increased hepatic glucose production represents the major pathogenic disturbance responsible for hyperglycemia in DKA. As the glucose concentration and osmolality of extracellular fluid increase, an osmolar gradient is created that draws water out of the cells. Glomerular filtration is initially increased, which leads to glycosuria and osmotic diuresis. The initial glycosuria prevents the development of severe hyperglycemia as long as the glomerular filtration rate is normal. However, with continued osmotic diuresis, hypovolemia eventually occurs, which leads to a progressive decline in glomerular filtration rate and worsening hyperglycemia.



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Diagnostic Criteria of HHS :

- **Marked Hyperglycemia** (> plasma glucose > 30 mmol/L, **without significant hyperketonemia**(negative urine ketones or trace) **or acidosis** (PH > 7.3, serum Bicarbonate > 15)
  plus
- **Serum Osmolality > 320 mOsmol/kg)** [β]
  β Formula for calculating serum Osmolality={ 2X (Na) + Glucose(mmol/L) + Urea (mmol/L)

Precipitating factors:

- New diagnosis of T2DM
- Infection
- High dose steroids
- Myocardial infarction
- Vomiting
- Stroke
- Thromboembolism
- Poor treatment compliance
- Impaired sense of thirst

Presentation:

- Patients with HHS may present with :
- Confusion
- Coma
- Seizures
- Vomiting
- Features of the precipitating factor

Physical examination findings:

- Dehydration
- Hypotension
- Coma
- Confusion
- Focal neurology
- Features of the precipitating factor

Investigations:

- Laboratory glucose
- Urea & electrolytes
- Venous blood gas (VBG) to rule out DKA (unless hypoxic, then do arterial blood gas or ABG)
- Urine analysis
- Serum osmolality (if difficult to obtain, then use calculated osmolality).
- Further tests:
- Chest X Ray
- ECG, CBC, CRP, Troponin, CK-MB, Amylase
- Consider CT Brain if obtunded.

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Management:

Treatment Goals:

The goals of treatment of HHS are to treat the underlying cause and to gradually and safely
Normalize the plasma osmolality
Replace fluid and electrolyte losses
Normalize blood glucose
Other goals include prevention of arterial or venous thrombosis, cerebral edema, central pontine myelinolysis and foot ulceration.
Immediate Management:
Make sure the patient has intact airway, breathing and circulation and support as indicated
Cardiac monitor
Urinary catheter (if indicated)
Consider central venous pressure and nasogastric tube if there is a necessity.

Intravenous fluid

If the patient is hemodynamically unstable, aggressive resuscitation should be done initially to stabilize the patient first until Systolic BP is > 90 then follow this fluid replacement policy). Be cautious with elderly patients, and patients with compromised cardiac and renal status due to risk of fluid overload.

- Patients with HHS often have fluid deficit of over 8 liters (10-22 ml/kg). Fluid resuscitation is the main stay of treatment together with a small dose of insulin, however, it's important not to correct the fluid and electrolytes abnormalities too quickly as this could precipitate cerebral edema and heart failure.
- Aim to replace 4 liters of the fluid losses in the first 12 hours starting with 0.9 % N.S
- Start a liter of 0.9 % N.S over one hour with no added potassium while waiting for the lab result of serum potassium.
- Give 3 more liters of 0.9 % NS over the next 11 hours with added potassium as detailed in the potassium section.
- If the blood glucose is < 13 mmol/L, change to D5 0.9% NS at the same rate.
- Monitor therapy by measuring/calculating serum osmolality(Osmolality={ 2X (Na) + Glucose(mmol/L) + Urea (mmol/L)} at time : 0 hours, 3 hours, 6 hours, 12 hours and then 12 hourly until resolution of metabolic abnormalities. If serum osmolality is falling too quickly (i.e. > 5 mOsmol/kg/hr) , reduce the rate of intravenous fluids.
- Aim to reduce serum osmolality by about 5 mOsmol/kg per hour.
- Expect an initial rise in serum sodium after initiation of treatment, however, as far as serum osmolality is falling, continues with 0.9 % N.S. However, if serum osmolality is not declining by > 5 mOsmol/kg per hour despite adequate positive fluid balance and /or serum Na > 150) , then change fluid to 0.45 % N.S.
- The rate of fall in serum sodium should not exceed 10 mmol/L over 24 hours.

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Potassium

Aim to keep serum potassium levels in the normal range. Make sure the patient has good urine output and has normal renal function. Be cautious as most patients with HHS may have a degree of renal impairment due to severe dehydration.

☐ more than 5.2 mmol/L	☐ 3.3 to 5.2 mmol/L	☐ less than 3.3 mmol/L
☐NIL	☐40 mmol/L	☐ Hold insulin for 2 hours or until potassium more than or equal to 3.3 mmol/L ☐ Increase the rate of the fluid replacement not more than or equal to 10 meq/potassium chloride per hour *or* ☐ Give potassium chloride 40 meq in 500 ml normal saline to run over 4 hours
		☐ Apply cardiac monitor to patient
		☐ Perform ECG

Insulin

Mix 50 units of regular insulin in 50 ml of 0.9 % N.S In a syringe. Use intravenous route for insulin infusion as per the following sliding scale. Patients with HHS need half the dose of insulin that is used to Treat DKA. Make sure the patient has received reasonable amount of fluid (at least 1 Liter of I.V fluid) before insulin is started due to the risk of circulatory collapse in case of sudden reduction of plasma glucose without enough intravascular volume repletion. Please do not exceed a maximum of 0.05 units/kg/ hour (e.g. 4 units in an 80 kg patient).

Blood glucose level	Insulin infusion rate
If blood sugar ≥ 13 mmol/	IV insulin (0.05/kg/hr)……Units/hr
If blood sugar <13 mmol/l	IV insulin 0.025/kg/hr……..Units/hr
If blood sugar is < 5mmol/l	Start D10 as in the fluid algorithm

Time line for interventions :

First Hour:

Start 1 Liter of 0.9% N.S over one hour

Only commence i.v insulin infusion (0.05 units/kg/hour) if there is significant ketonemia or ketonuria 2+ (Mixed DKA and HHS). Remember, i.v fluid alone can result in significant drop in plasma glucose in patients with HHS. The earliest start of i.v insulin infusion should be after the patient has received at least one liter of i.v fluid.

Clinical assessment including foot exam

Investigations:

(VBG, U&E, Lactate, CBC, CRP, Measured/calculated plasma osmolality, ECG, CXR, urine analysis and culture, blood cultures).

Monitoring:

Hourly blood sugars

Serum osmolality, serum sodium, serum potassium at time zero and then 3 hourly (or more frequent if needed)
Hourly Urine out put
Pulse oximetry, cardiac monitor (if available)
Prophylactic Low molecular weight heparin.
Decide about anti biotic need.

60 minutes-6 hours:

Aims:
To achieve gradual decline in osmolality (by ~ 5 mosmol/kg/hour)

- Use 0.9 % N.S and target 2-3 liters positive fluid balance by 6 hours (be careful with cardiac patients)
- Observe goals regarding osmolality, and glucose fall
- Aim for target plasma glucose between 10-15 mmol/L

If the glucose is not falling less than 5 mmol/L

- If fluid balance is inadequate, increase fluid rate
- If already in positive fluid balance, commence low dose i.v insulin (0.05 units/kg/hour).

Aim to maintain potassium in the normal reference rate.

6 hours -12 hours

- Aim to achieve a fluid balance of 3-6 liters by 12 hours
- Make sure clinical an biochemical paramerts are met
- Assess for occurrence of complications
- Continue to treat the precipitating factor
- Avoid hypoglycemia (change fluid to D5 0.9 % NS if glucose falls below 13 mmol/L)

12-24 hours:

- Ensure continuous improvement in clinical and biochemical parameters
- Continue i.v fluid to replace the remaining balance of fluid loss within the next 12 hours.
- Continue insulin as per sliding scale in the insulin algorithm
- Assess for complications.

Further management

Full anticoagulation with low molecular weight heparin and TED stockings should be considered in all patients unless contraindicated
Broad spectrum antibiotics should be stated if there is evidence of infection.
Treat precipitating factor as appropriate.

Foot protection:

These patients are at very high risk of developing foot ulceration, therefore, an initial foot examination and assessment must be done, together with application of heel protectors for those at risk of ulceration such as patients with neuropathic feet, foot deformities and peripheral vascular disease.

Anti-infective agents:

An infective source should be sought on clinical history and physical examination and CRP may be helpful. Antibiotics should be given when there are clinical signs or imaging and /or laboratory evidence of its presence.

Recovery phase

Complete correction of electrolytes and osmolality abnormalities may take more than 24 hours (unlike DKA). Therefore, too aggressive correction could prove harmful. Recovery in most of these patients, who are usually elderly, will be determined by their previous functional status.
I.V insulin can be discontinued once they are eating and drinking normally but i.v fluids may be required for longer if oral intake is poor.

Most patients should be transferred to subcutaneous insulin (regime should be individualized). Newly diagnosed patients with diabetes or well controlled patients on oral agents could be considered for oral agents after their condition becomes stable. All patients need to be seen by diabetes educators to education.

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Patient:
MRN:

Order Sheet for the Management of Adults with Hyperosmolar Hyperglycemic State

Please admit the patient to: ☐ General Ward ☐ ICU, as a case of _____, secondary to _____

under the care of Dr. _____

Vital signs : ☐ **Stat** ☐ **Then every** ----------

Investigations:

VBG(to rule out DKA) : ☐ STAT

Serum Urea, Electrolytes and serum Osmolality : ☐STAT ☐ 3 hours ☐ 6 hours ☐ 12 hours ☐ Then every _____

☐ CBC ☐ Blood Culture ☐Urine Culture& Microscopy ☐ Random Blood sugar ☐ Serum Ketones ☐ Urine Ketones

☐ CXR ☐ ECG ☐ Troponins/CK-MB ☐ Amylase ☐ Lactate

☐ Check blood sugar, by glucometer, every hour (if hourly readings are between 5-10 mmol/L for 3 consecutive hours, then the frequency of blood glucose checking can be reduced to 2 hourly)

Diet: ☐ Diabetic Diet ☐ NPO ☐ Input/Output Chart ☐ Daily Weight

Urinary Catheter: ☐ Yes ☐No **Thrombophylaxis** Given ? ☐ Yes ☐ NO (give all patients unless contraindicated)

Fluids: (If the patient is hemodynamically unstable, **DON'T** use this protocol)

☐ **If Systolic BP is more than or equal to 90 mmHg,** please use the algorithm below: Be cautious with elderly patients, and patients with compromised cardiac and renal status due to risk of fluid overload.

Order	Instruction
☐ Over the 1st hour, Start a liter of 0.9 % N.S (without KCl). Then, ☐ Over the next twelve hours, give 0.9%NS at a rate of 250 ml/hour **(with KCl as indicated in the potassium algorithm). Then,** ☐ Decrease IVF to 0.9%NS at a rate of (100-250 ml /hour……ml/hour **(with KCl as indicated in the potassium algorithm)** ☐ whenever blood sugar is less than 13mmol/L please change IVF to D5 0.9NS and change insulin as in insulin algorithm ☐ If blood sugar is ≤ 5 mmol/l add D10% W to run at a rate of …… (50-100 ml/Hr) till blood sugar reaches 10 mmol/l	• Always refer to corrected sodium when calculating the osmolality • Monitor therapy by measuring/calculating serum osmolality(Osmolality={ 2X (Na) + Glucose(mmol/L) + Urea (mmol/L)} at time : 0 hours, 3 hours, 6 hours, 12 hours and then 12 hourly until resolution of metabolic abnormalities. • Aim to reduce serum osmolality by 5 mOsmol/kg per hour. If serum osmolality is falling by > 5 mOsmol/kg/hour , reduce the rate of intravenous fluids by 50 %. • if serum osmolality is not declining by > 5 mOsmol/kg per hour despite adequate positive fluid balance and /or corrected serum Na > 150) , then change fluid to 0.45 % N.S at the same rate. • The rate of fall in corrected serum sodium should not exceed 10 mmol/L over 24 hours. • **The total fluid infusion rate shouldn't exceed 250 cc/hr at any time.**

Potassium :

Aim to keep serum potassium levels in the normal range. Make sure the patient has good urine output and has normal renal function. Be cautious as most patients with HHS may have a degree of renal impairment due to severe dehydration.

☐ more than 5.2 mmol/L	☐ 3.3 to 5.2 mmol/L	☐ less than 3.3 mmol/L
☐NIL	☐ 20 mmol/L ☐ 30 mmol/L ☐ 40 mmol/L	• Hold insulin infusion for 2 hours or until serum potassium is more than or equal to 3.3 meq/L • Perform ECG • Apply cardiac monitor to patient • Increase the rate of potassium chloride infusion but don't exceed the maximum rate of 10 meq/potassium chloride per hour. • Request a higher potassium chloride concentration infusion from pharmacy. • Once ready, give 40 meq of potassium chloride in 500 ml 0.9 % normal saline to run over 4 hours. • Resume insulin infusion when serum potassium is more than or equal to 3.3 mmol/L.

Insulin

Mix 50 units of regular insulin in 50 ml of 0.9 % N.S (1 ml=1 unit). Use intravenous route for insulin infusion as per the following sliding scale
Make sure the patient has received reasonable amount of fluid before insulin is started due to risk of circulatory collapse and cerebral edema.

Capillary Blood Glucose mmol/L	Intravenous Insulin Infusion Rate (Unit/hr)
If blood sugar ≥ 13 mmol/	IV insulin (0.05/kg/hr)……Units/hr
If blood sugar <13 mmol/l	IV insulin 0.025/kg/hr……Units/hr
If blood sugar is < 5mmol/l	Add D10% W as in the fluid algorithm (***Do not stop insulin***)

Physician's Name and Stamp: _____ **Date:** _____

Signature: _____ **Time:** _____

Nurse's Name : _____ **Date:** _____

Signature: _____ **Time:** _____

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References:

1- Mohammad Zubair et al, Clinical, demographic, and biochemical profile of pediatric diabetic ketoacidosis patients in King Khalid Civilian Hospital, Tabuk. Medical Sciences; 22(89), January - February, 2018.

2- American Diabetes Association (2010) Diagnosis and Classification of diabetes mellitus. Diabetes Care 33: S62-S69.

3- Whiting DR, Guariguata L, Clara Weil, Jonathan Shaw. Global estimates of the prevalence of diabetes for 2011 and 2030. Diab Res Clin Pract., 2011; 94: 311-321.

4- Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Dia- betes Care. 2004; 27: 1047-53.

5- Forouhi NG, Wareham NJ. Epidemiology of diabetes. Medicine [Abingdon]. 2014; 42: 698-702.

6- World Health Organization 2014.

7- Al-Nozha MM, Al-Maatouq MA, Al-Mazrou YY, et al. Diabetes mellitus in Saudi Arabia. Saudi Med J. 2004; 25: 1603-10.

8- Al-Rubeaan K, Al-Manaa HA, Khoja TA, et al. Epidemiology of abnormal glucose metabolism in a country facing its epidemic: SAUDI-DM study. J Diabetes. 2014 Sep 30.

9- Al Dawish MA et al. Diabetes Mellitus in Saudi Arabia: A Review of the Recent Literature. Curr Diabetes Rev. 2016;12(4):359-368.

10- J. Tuomilehto, "The emerging global epidemic of type 1 diabetes," Current Diabetes Reports, vol. 13, no. 6, pp. 795–804, 2013.

11- Asirvatham Alwin Robert, Abdulrahman Al-Dawish, Muhammad Mujammami, and Mohamed Abdulaziz Al Dawish, Type 1 Diabetes Mellitus in Saudi Arabia: A Soaring Epidemic. International Journal of Pediatrics Volume 2018, 9 pages.

12- A. Al-Herbish, M. El-Mouzan, A. Al-Salloum, M. M. AlQurachi, and A. A. Al-Omar, "Prevalence of type 1 diabetes mellitus in Saudi Arabian children and adolescents," Saudi Medical Journal, vol. 29, no. 9, pp. 1285–1288, 2008.

13- K. Al-Rubeaan, "National surveillance for type 1, type 2 diabetes and prediabetes among children and adolescents: a population-based study (SAUDI-DM)," Journal of Epidemiology and Community Health, vol. 69, no. 11, pp. 1045–1051, 2015.

14- Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009; 32: 1335-43.

15- Dhatariya K, Savage M, Claydon A, et al. Joint British Diabetes Societies Inpatient Care Group. The management of diabetic ketoacidosis in adults. 2nd edn. 2013. Update: September 2013, http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_DKA_ Adults_Revised.pdf [Last accessed 5th September 2018].

16- Zayed H. Epidemiology of diabetic ketoacidosis in Arab patients with type 1 diabetes: a systematic review. Int J Clin Pract. 2016 Mar;70(3):186-95.

17- J. A. Usher-Smith, M. Thompson, A. Ercole, and F. M. Walter, "Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: a systematic review," *Diabetologia*, vol. 55, no. 11, pp. 2878–2894, 2012.

18- Dabelea D, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. Pediatrics [Internet] 2014 Apr;133(4). p938-45.

19- Pasquel FJ, Umpierrez GE. Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatment. Diabetes Care. 2014 Nov; 37 (11): 3124-31.
20- Maimoona Mushtaq Ahmed. Clinical presentation of diabetic emergencies in university hospital. Global Advanced Research Journal of Medicine and Medical Science, Vol. 3(10) pp. 308-314, October 2014.
21- Basu, A. et al. Persisting mortality in diabetic ketoacidosis. Diabet Med. 10, 282-284 (1993)
22- Umpierrez G1, Korytkowski M2. Diabetic emergencies - ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol. 2016 Apr; 12(4): 222-32.
23- Benoit SR, Zhang Y, Geiss LS, Gregg EW, Albright A. Trends in diabetic ketoacidosis hospitalizations and in-hospital mortality - United States, 2000-2014. MMWR Morb Mortal Wkly Rep 2018;67: 362–365.
24- Gibb FW, Teoh WL, Graham J, Lockman KA. Risk of death following admission to a UK hospital with diabetic ketoacidosis. Diabetologia 2016;59: 2082–2087
25- Lombardo F, Maggini M, Gruden G, Bruno G.Temporal trend in hospitalizations for acute diabetic complications: a nationwide study, Italy, 2001-2010. PLoS One 2013;8
26- Svendsen OL. Diabetic ketoacidosis in Denmark: incidence and mortality estimated from public health registries. Diabetes Res Clin Pract 2007; 76:51–56.
27- Venkatesh B, Pilcher D, Prins J, Bellomo R, Morgan TJ, Bailey M. Incidence and outcome of adults with diabetic ketoacidosis admitted to ICUs in Australia and New Zealand. Crit Care 2015; 19:451.
28- Lin SF1, Lin JD, Huang YY. Diabetic ketoacidosis: comparisons of patient characteristics, clinical presentations and outcomes today and 20 years ago. Chang Gung Med J. 2005 Jan;28(1):24-30.
29- Agarwal A, Yadav A, Gutch M, et al. Prognostic factors in patients hospitalized with diabetic ketoacidosis. Endocrinol Metab (Seoul) 2016;31: 424–432.
30- Mbugua PK1, Otieno CF, Kayima JK, Amayo AA, McLigeyo SO. Diabetic ketoacidosis: clinical presentation and precipitating factors at Kenyatta National Hospital, Nairobi. East Afr Med J. 2005 Dec; 82(12 Suppl): S191-6.
31- Rafik R. Elmehdawi, Mohammad Ehmida, Hanan Elmagrehi, and Ahmad Alaysh. Incidence and Mortality of Diabetic Ketoacidosis in Benghazi-Libya in 2007. Oman Med J. 2013 May; 28(3): 178–183.
32- Yousuf M CS (1994). Diabetic ketoacidosis in Saudi Arabia. Saudi. Med. J. 15:295-296.
33- Qari FA. Precipitating factors for diabetic ketoacidosis. Saudi Med J 2002 Feb; 23(2): 173-176.
34- Al-Rubeaan KA, Aftab SA, Alotaibi MS, Alghamdi AA, Rafiullah MR. Clinico-laboratory characteristics of diabetic keto acidosis in adults in a tertiary hospital in Saudi Arabia. Eur Rev Med Pharmacol Sci. 2011 Oct;15(10):1202-6.
35- Faiza Qari. Clinical characteristics of patients with diabetic ketoacidosis at the Intensive Care Unit of a University Hospital. Pak J Med Sci. 2015 Nov-Dec; 31(6): 1463-66
36- Bhowmick SK1, Levens KL, Rettig KR. Hyperosmolar hyperglycemic crisis: an acute life-threatening event in children and adolescents with type 2 diabetes mellitus. Endocr Pract. 2005 Jan-Feb; 11(1): 23-9.
37- Fadini GP, de Kreutzenberg SV, Rigato M, et al. Characteristics and outcomes of the hyperglycemic hyperosmolar non-ketotic syndrome in a cohort of 51 consecutive cases at a single center. Diabetes Res Clin Pract 2011;94: 172–179
38- Pasquel FJ, Umpierrez GE. Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatment. Diabetes Care. 2014 Nov; 37 (11): 3124-31.
39- Global Diabetes Plan 2011-2021, International Diabetes Federation.
40- Sherif S, Sumpio BE. Economic development and diabetes preva- lence in MENA countries: Egypt and Saudi Arabia comparison. World J Diabetes. 2015 Mar 15; 6: 304-11.

41- Centers for Disease Control and Prevention. Diabetes data & trends. [online], http://www.cdc.gov/nchs/fastats/inpatient-surgery.htm (2015)
42- Dhatariya KK, Nunney I, Higgins K, Sampson MJ, Iceton G.A national survey of the management of diabetic ketoacidosis in the UK in 2014. Diabetic Med 2016; 33: 252-60.
43- Scott A, Claydon A, Brennan G, et al. The management of the hyperosmolar hyperglycaemic state (HHS) in adults with diabetes. The Joint British Diabetes Societies Inpatient Care Group. 2012, http://www.diabetologists abcd.org.uk/JBDS/JBDS_IP_HHS_ Adults.pdf [Last accessed 5th September 2018].
44- Laliberte B, Yeung SYA, Gonzales JP. Impact of diabetic ketoacidosis management in the medical intensive care unit after order set implementation. Int J Pharm Pract. 2017 Jun;25(3):238-243.
45- Abdulrahman Al Nemri, et al. Substantial reduction in hospital stay of children and adolescents with diabetic ketoacidosis after implementation of Clinical Practice Guidelines in a university hospital in Saudi Arabia. Journal of Evaluation in Clinical Practice. 23(1):173–177, Feb 2017.