



GUIDELINES UPDATE: DIABETES MELLITUS EMERGENCY MANAGEMENT

The number of people living with diabetes is increasing globally. The WHO estimates that by 2030, 366 million worldwide will have diabetes. In Sub-Saharan Africa, the incidence of diabetes is expected to increase by 160% from 7 million in 2000 to 20 million in 2030. There are estimated to be over 45000 people living with Diabetes in Botswana by 2030.

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS, also known as non ketotic hyperglycemia) are two of the most serious acute complications of diabetes. They are part of the spectrum of hyperglycemia and each represents an extreme in the spectrum.

Given the high mortality associated with DKA and HHS, there is an urgent need to ensure that clinicians are able to manage patients presenting with 'Diabetic Emergencies.' In this

edition of Tlaleletso we describe how Diabetic Ketoacidosis (DKA) and Hyperosmolar Hyperglycemic Syndrome (HHS) should be managed.

Diabetic Emergencies in Adults

HHS and DKA are conditions on a spectrum. Both conditions present with hyperglycemia, hypovolemia, and certain electrolyte abnormalities.

Although these conditions share as much as 33% of presenting symptoms², the capable health care worker should be able to ascertain the differences between the two entities and begin appropriate treatment.

DKA – Typically younger patients with Type I diabetes present with DKA. They often present with rapid onset of symptoms. The mortality rate with DKA is around a 5% at experienced centers, but is probably much higher in Africa.

HHS – This condition is more common in the elderly and glucose levels are often much higher than in DKA (>30 mmol/l). The mortality rate is also higher, at about 15%.

The prognosis of both conditions is substantially worse at the extremes of age and in the presence of coma and hypotension.^{3,4}

Hypoglycemia can also present as a diabetic emergency (not the focus of this edition of Tlaleletso). Typically it presents with tremor, hunger and perspiration, leading to lightheadedness, seizures and even coma. Management involves treating with 200-300ml of 10% dextrose. Glucagon can also be used but will not work in drunk patients. Dextrose infusion maybe necessary for severe prolonged hypoglycemia.

Pathophysiology of DKA & HHS

Both HHS and DKA result from an increase in circulating glucose and hyper-osmolarity of the blood causing severe dehydration. There are several common causes for HHS/DKA. These include³:

1. Infections (pneumonia, UTI, etc)
2. Dehydration and lack of access to water
3. Stress (either social stress or physiologic stress (stroke, heart attack, etc)
4. Inadequate insulin therapy (or non-adherence)
5. Alcohol
6. Trauma

Presentation of HHS and DKA typically involves polyuria (frequent urination) and polydipsia (excessive thirst), nausea and vomiting. Both can also present with weight loss, clouding of sensoria and finally coma. Although infection is a common precipitating factor in both DKA and HHS, patients can have a normal temperature. Hypothermia is a poor prognostic sign.⁴

HHS – Presents in older patients, often with prodromal illness for previous days and weeks. Precipitating factors include infection, stroke, MI, renal failure. Medications such as beta-blockers, steroids and thiazide diuretics (e.g., HCTZ) can also trigger HHS. Patients present with significant water deficit (up to 8 liters). Mental status can vary from full alertness to profound lethargy and coma, with the latter more common in HHS.

DKA – Presents in younger patients. 20-25% of the time it is the first presentation of Diabetes Mellitus⁶. DKA often also presents in diabetic patients who are non-compliant with their insulin. Patients typically present with a short prodromal illness.

DKA is commonly triggered by acute infection (30-40%). Patients may also present with abdominal pain which can be misdiagnosed as an ‘acute surgical abdomen.’

HIV & DIABETES

Diabetes can present as a new diagnosis in patients with HIV. When diabetes develops, it is typically related to insulin resistance (type II) rather than insulin deficiency (type I).

A recent study at Princess Marina found that 5% of ART-naïve patients had diabetes. The prevalence was higher (>10%) in those patients older than 40 years⁶. The majority of HIV patients that develop diabetes do so as a result of medication side effects. Older NRTIs, such as d4t, ddI, and AZT, are associated with diabetes (d4t, ddI, AZT)⁷. This is likely related to insulin resistance, lipodystrophy, and mitochondrial dysfunction. Lopinavir/ritonavir (Aluvia) increases fatty acids and triglycerides but has little effect on insulin resistance.⁸

HIV infected patients with stable diabetes should be managed cautiously. Metformin is typically the first-line treatment, but in patients with HIV metformin may lead to lactic acidosis, especially in patients with renal failure. Sulfonylureas are typically safe, although should also be used cautiously in patients with impaired renal function. Insulin is typically well tolerated in HIV-positive diabetics.

Often patients have deep rapid breathing (respiratory compensation for metabolic acidosis) and the smell of acetone on their breath. This fruity smell is pathognomonic for DKA!

Laboratory Findings

In Botswana, the essential first tests to get are serum glucose, U&Es, urine ketones by dipstick. Full blood count, blood, CXR, ECG and urine cultures can also be very useful. Pregnancy testing and HIV testing should also be performed as appropriate.

Typical laboratory findings include:

1. **Glucose** (elevated)
2. **Sodium** (usually decreased initially) – glucose levels can affect measurement of sodium. To get an accurate level, it is necessary to calculate the **corrected sodium** (add 1.6 mmol/L sodium for every 5.6 mmol/L glucose over 5.6 mmol/L)
3. **Potassium** (usually low, even if the initial

4. **Ketones** (urine or serum) – mildly elevated or absent in HHS, elevated in DKA. Ketonuria is *less* useful in accurately determining whether DKA has resolved, since ketones can remain in the urine long after serum ketonemia has resolved. Nevertheless, where serum ketones cannot be measured, we strongly recommended serial urine testing for ketones for those patients diagnosed with DKA
5. **HbA1C** –this is not required for emergency management. But the result will indicate whether the patient had well-controlled sugars before developing DKA/HHS. It is performed at Princess Marina and can be ordered at all facilities in Botswana.

	DKA			HHS
	Mild	Moderate	Severe	
Glucose	> 13.9	> 13.9	> 13.9	>33.3
Urine ketones	Positive	Positive	Positive	Small /Negative
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

Symptoms suggestive of DKA or HHS

Look for thirst, polyuria, hyperventilation and abdominal pain. In patients without ketonuria, particularly older patients, consider Hyperosmolar hyperglycemic state (HHS).

Urgent Investigations:

Urinalysis (ketones in urine), Blood glucose, Renal function tests (especially K^+)

Other Investigations:

CXR, ECG, Amylase, blood & urine MCS and other swabs as indicated.

Immediate Management in A&E:

IV access
Start iv fluids, K^+ and insulin
Monitor BP and ECG, Weigh patient (or estimate weight)
Give oxygen if O_2 sats < 95%

INSULIN DOSING		
	DKA	HHS
Initial dose	10 u of actrapid or 0.1U/kg (im, stat)	
Until glucose < 15 mmol/L	Administer 0.2U/kg (im) every 2 hours Increase by 1 unit/hr q 2 hours if < 10% drop in glucose over the first 2 hours	
	Administer 0.1 U/kg (im) every 2 hours until no more ketones in urine	If glucose doesn't drop, increase to 0.4 U/kg (im) every 2 hours until normoglycemic

IV FLUIDS		
	DKA	HHS
1L NaCl 0.9%	Over 1 hr	Over 1 hour
1L NaCl 0.9%	Over 2 hrs	Every 2 hours for 4 hours
1L NaCl 0.9%	Over 4 hrs	Every 6 hours until hydrated
When glucose < 15 mmol/l start alternative liters of 5% dextrose and Ringers Lactate, monitor glucose and stop 2 hourly insulin dosing		

POTASSIUM		
	DKA	HHS
1 st liter	No KCL	Potassium replacement is required when potassium concentration is low. Potassium requirements are less in HHS
2 nd liter	Serum Potassium Replacement:	
3 rd liter	< 3.0 mmol/l 40 mmol	
4 th liter	3.0-5.5 mmol/l 20 mmol	
5 th liter	>5.5mmol/l None	

DKA & HHS INITIAL MANAGEMENT

- Stabilize:** Airway, Breathing, Circulation (ABC). Give oxygen if O_2 sat < 95%
- Access.** Obtain large-bore IV access (16 gauge)
- NPO.** Keep the patient NPO for at least 6 hours while hourly insulin is administered and until patient is awake and alert
- Fluids.** Aggressively rehydrate with intravenous fluids – **give 1 liter of normal saline straight away, followed by further fluid as per protocol** (see above). Every patient with DKA and HHS is volume depleted by at least 3 liters. Patients with HHS are sometimes as much as 8 liters volume depleted. Replace fluids cautiously in patients with cardiac or renal problems; all patients with severe CHF or end stage

renal disease should be discussed with a specialist. Volume expansion with IV fluids alone will lower blood sugar by 2-4 mmol/L/hr. To assess effectiveness of rehydration frequent checks of blood pressure, pulse, urine output and clinical examinations and are essential. Patients receiving normal saline are at risk for hypernatremia. Therefore, once the glucose level has dropped below 15mmol/l consider switching IV fluids to ringers lactate and 5% dextrose

- Insulin.** Administer a bolus of actrapid insulin (0.1 units/kg, IM) after fluids have been commenced. Continuous (IV) infusion of insulin with syringe pump is preferable. Where infusion pumps are not available, actrapid should be administered at least every two hours on a weight based schedule (0,2u/kg/every two hours). This dosing schedule insulin usually decreases glucose at a rate of 2.7 - 4.2 mmol/l/hr.

NOTE: sliding scales are no longer recommended for either HHS or DKA.

- Potassium.** Provide potassium supplementation. Once (IV) fluids and insulin have been administered administered, serum K^+ levels fall very rapidly. Therefore every patient needs potassium supplementation. Where potassium cannot be checked rapidly, supplementation with 20-30 mmol/l potassium in each liter of infusion should be sufficient to maintain serum potassium concentration within the normal range of 4-5 mmol/l.
- Treat infections** – since DKA and HHS are often triggered by infections, look for infection and treat appropriately.
- Consider DVT prophylaxis** – Patients with DKA and HHS are high risk for DVT. Consider starting clexane (40mg OD) or unfractionated heparin.

ONCE THE PATIENT STABILIZED

Post –DKA:

Once the patient is hemodynamically stable and has no further ketones in the blood/ ketonuria, they can then be returned to their prior insulin regimen. Where available, serum bicarbonate levels can be used to establish if the metabolic acidosis has resolved.

If the patient's glycemic control (HbA1c>7%) was poor before, re-evaluate the prior regimen inadequate and consider increasing the insulin dose.

For patients new to insulin consider actophane (daily dose 0.2-0u/Kg in two divided doses, 2/3 in am, 1/3 in pm). As an inpatient consider using a sliding scale as well as this weight base dose until normoglycemia is achieved.

Post-HHS:

Once the patient is stabilized, alert and able to eat they can resume their prior insulin regimen. Alternatively re-evaluate dose if the prior regimen was inadequate.

For patients new to insulin who require >20 units/day to control hyperglycemia: consider actophane (daily dose 0.2-0.1u/Kg in two divided doses, 2/3 in am, 1/3 in pm).

For patients new to insulin who require < 20 units/day to control hyperglycemia resume oral hypoglycemic or (if new diagnosis) consider initiating metformin and titrating dose to glycemic control over the following weeks. Metformin is contraindicated in people with elevated creatinine (>140) or hepatitis.

DIABETES IN CHILDREN

DKA in children usually presents with the following: nausea, vomiting, abdominal pain, dehydration (up to 10% of body weight), shortness of breath (Kussmaul respirations), and progressive decrease in consciousness. Management of children is similar to adults **except** for their rehydration, which requires more careful fluid calculations and monitoring (see below). This is because the major mortality associated with DKA in infants, children, and adolescents is cerebral oedema, which affects 0.5-1.5% of children presenting with DKA yet accounts for 60-90% of DKA-related deaths.

Practical Points – Ask for help! Always consider calling PMH Pediatrician on call

- Weigh the child! This will affect all your calculations for fluids and insulin.
- Rehydrate with NS—start with 10 ml/kg/h over 1-2 hours, and repeat if necessary, to assure a stable circulatory status. Continue with NS for 4-6 hours, then fluid can be switched to 0.45 NS with KCL or LR and given over the ensuing 48 hours at a rate of maintenance + 10% fluid deficit (See below)
- SC insulin dose: 0.1 unit/kg every 1-2 hours.
- When IV fluids are unavailable, arrange urgent transport to a facility that can provide them.
- Giving insulin before intravenous fluid treatment has been started may precipitate shock, and increases the risk of hypokalemia and cerebral oedema.

Example of volumes of maintenance + 10% deficit, to be given evenly over 48 hours.

Weight (kg)	Infusion rate (ml/kg/h)
4 - 9	6
10 - 19	5
20 - 39	4
40 - 59	3.5
60 - 80	3

Example: A 6 year old boy weighing 20 kg will be given 80 ml per hour or a total volume of 1920 ml per 24 hours for two days.



DIABETES & TUBERCULOSIS

Diabetic patients are 3 times more likely to develop TB than non-diabetics^{9,10}. Those at particular risk are patients requiring insulin and those with poorly controlled diabetes, with Hemoglobin A1C >7%.¹¹

Diabetic patients infected with TB on treatment with antituberculous medications may also take longer to convert from sputum positivity to negativity.⁹ They also have an increased risk of death: 6 times greater than that of non-diabetics.¹⁰ Drugs taken by diabetics (especially sulfonylureas) also interact with drugs taken during TB treatment, and this may result in worse glycemic control.

Patients with pulmonary TB may be at increased risk of developing diabetes. Studies have shown that glucose tolerance may be impaired in pulmonary TB patients.

SUMMARY

1. Both DKA and HHS are true metabolic emergencies. Both can present to health care as the initial manifestation of diabetes.
2. HHS is typically a manifestation of type II diabetes. DKA is generally associated with type I diabetes.
3. Always being resuscitation with ABCs
4. Prompt fluid resuscitation is necessary, given that patients may require between 3 and 8 liters. Initially administer normal saline, however, once the glucose level has dropped below 15mmol/l consider switching to ringers lactate and 5% dextrose.
5. An insulin bolus, followed by a weight based hourly or two hourly schedule is necessary. In patients with DKA this should be continued after normoglycemia has been achieved and until there are no further ketones in the urine.
6. There is no role for insulin sliding scale in the initial management of DKA/HHS.
7. Potassium replacement should be started once iv fluids have been started. If serum K^{+1} cannot be measured, giving 20mmol KCl with every bag of fluid for the first 24 hours *may* be adequate. Use oral supplementation if (iv) unavailable.
8. Treat infections! It remains important to correct the precipitating factor of the diabetic emergency such as treating the infectious process, addressing issues of adherence, etc.

UPCOMING LECTURES

- | | |
|------|---------------------------------|
| May | Topics in HIV:
Mental Health |
| June | Guidelines
Update: Overdose |

Got a clinical question about a complicated medical patient or a patient with HIV?

Call Mike Reid -267 724 78 777 **OR** Miriam Haverkamp 267 76516520

BOTSWANA UPENN PARTNERSHIP

214, Independence Avenue

Gaborone, Botswana, PO Box AC 157 ACH

Want to read more about how to manage Diabetic Emergencies?

1. WHO, 2011. (Accessed at http://www.who.int/topics/diabetes_mellitus/en/.)
2. Kitabchi AE, Umpierrez GE, Fisher JN, Murphy MB, Stentz FB. Thirty years of personal experience in hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. *J Clin Endocrinol Metab* 2008;93:1541-52.
3. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care* 2001;24:131-53.
4. Matz R. Hypothermia in diabetic acidosis. *Hormones* 1972;3:36-41.
5. Hatsu I, Marianna K Baum, Fatma Huffman, Hermann Bussmann, Priti Dusara, Joe Makhema, Patricia J Burns, Sabrina Sales, Adriana Campa and Richard Marlink. Diabetes in HIV Positive Adults in Botswana: Nutritional and Demographic Characteristics *The FASEB Journal* 2009;547.15.
6. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med* 2008;5:e152.
7. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. *Lancet Infect Dis* 2009;9:737-46.
8. Liu Z, Fu C, Wang W, Xu B. Prevalence of chronic complications of type 2 diabetes mellitus in outpatients - a cross-sectional hospital based survey in urban China. *Health Qual Life Outcomes* 2010;8:62.
9. Harries AD, Lin Y, Satyanarayana S, et al. The looming epidemic of diabetes-associated tuberculosis: learning lessons from HIV-associated tuberculosis. *Int J Tuberc Lung Dis* 2011;15:1436-44, i.
10. Baker MA, Harries AD, Jeon CY, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC Med* 2011;9:81.
11. Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W. Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. *Am J Trop Med Hyg* 2009;80:634-9.