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Review Article

Management of Diabetic Ketoacidosis and Hyperglycaemic Hyperosmolar States

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ABSTRACT

Introduction: The global rise in diabetes mellitus prevalence has implications for Africa, with diabetic ketoacidosis (DKA) being its most severe acute complication. In Sub-Saharan Africa, DKA rates at first diagnosis among children and adolescents range from 24%-82% constituting 76% of paediatric endocrine admissions. DKA and hyperglycaemic hyperosmolar state (HHS) result in significant morbidity and mortality. Yet, healthcare disparities and unique issues such as severe malnutrition challenge African Management in Africa. **Methodology**: Diagnosis criteria for DKA include symptoms like polyuria, polydipsia, and weight loss combined with hyperglycaemia (>11 mmol/L), venous pH <7.3, and ketonemia (blood ß-hydroxybutyrate ≥3 mmol/L) or significant Ketonuria. Emergency management prioritizes restoring circulation, obtaining relevant laboratory samples, and initiating fluid and insulin therapy. Special attention is given to unique considerations, like administering oral rehydration solution (ORS) without IV fluids or handling severe malnutrition with RESOMAL. **Treatment**: Fluid therapy involves administering deficit replacement plus maintainance. Based on clinical conditions, potassium is added, and bicarbonate is reserved for severe cases. Insulin, vital for treatment, is introduced an hour after fluid therapy. Monitoring for cerebral oedema, especially in high-risk groups, is critical. Following the acute treatment phase, preventative measures are underscored to mitigate recurrence. For HHS, a subset of patients with particular diagnostic criteria, including elevated plasma glucose (>33.3 mmol/L) and higher pH levels, management focuses on restoring volume, renal perfusion, and a steady decline in serum sodium concentration and osmolality. The approach diverges from DKA regarding fluid volume, insulin timing, and monitoring specifics. **Conclusion**: Effective diagnosis and Management of DKA and HHS are pivotal in the African context, considering healthcare limitations and unique challenges. Guidelines that consider these intricacies ensure comprehensive care for affected individuals.

INTRODUCTION

Epidemiology

Diabetes mellitus is a chronic metabolic disorder caused by the body's inability to produce (absolute insulin deficiency) or utilize insulin (relative deficiency) [1]. Insulin deficiency results in an inability to utilize glucose for cellular functions with resultant hyperglycaemia, glycolysis, and gluconeogenesis[1]. The latter, gluconeogenesis, leads to increased production of ketoacids as an alternative source of energy for the brain and cellular functions. Annually, Type 1 diabetes, an

absolute insulin deficiency state, affects an estimated > 65,000 children and adolescents aged <15 years worldwide[2]. Untreated children and adolescents with diabetes may develop diabetic ketoacidosis (DKA). DKA is the most common hyperglycaemic emergency of Type 1 diabetes mellitus (T1D) and sometimes Type 2 diabetes mellitus (T2DM) [3]. It is characterized by hyperglycaemia, Ketonuria or ketonemia, and acidosis[4].

Globally, an estimated 15% to 89% of DKA occurs among newly diagnosed T1 diabetes[5,6]. In developed countries, 6% - 44% of children younger than 15 years with T1D present with DKA at diagnosis[7]. In Sub-Saharan Africa, the rates of DKA at first diagnosis of T1 diabetes among children and adolescents range from 24% to 82%. Diabetic ketoacidosis also constitutes 76% of endocrine admissions among children in developing countries[8]. The incidence rate of DKA is highest among adolescent girls and boys[9]. The population-based lifetime DKA incidence rate in 2018 was estimated at 9.49 per 100,000 person-years[9]. In established diabetes, the lifetime risk of DKA varies between 1% and 10%[10]. Left untreated, DKA is associated with a 3% to 24% (high) mortality risk among children and adolescents with T1D[11]. According to the Global Burden of Disease (GBD) 2019 Diabetes Mortality Working Group, an estimated 16,300 global diabetes-attributable deaths occurred among people younger than 25 years worldwide (12). A total of 15,900 (97·5%) of these deaths occurred in low to high-middle socio-demographic index (SDI) countries. Approximately, 73.7% of these deaths were classified as Type 1 diabetes GBD 2019 Diabetes Mortality Collaborators [12]. With improvements in diabetes care and access to insulin across the globe, there has been a marked decline in mortality due to T1 diabetes among young people[12].

DKA is also associated with complications such as the increased risk of intensive care admission and prolonged hospital stay, cerebral oedema, seizures, renal failure, and hypoglycaemia.

PATHOGENESIS AND PATHOPHYSIOLOGY OF DKA.

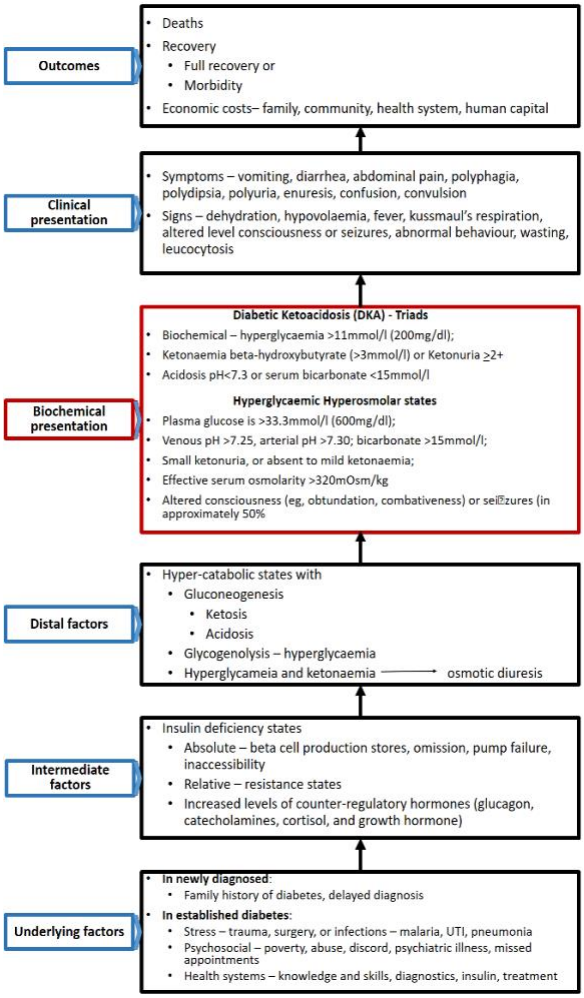
Pathogenesis

Insulin is an important hormone in the physiology of the liver, skeletal muscles and adipose tissue. Insulin is secreted from β cells in the pancreas, and thereafter, it binds to its receptors (IRs) on target cell membranes. In the liver, insulin accelerates the movement of glucose from the blood to the hepatocytes to form glycogen. Insulin helps in the transportation of glucose from the bloodstream to the skeletal muscle. It also stimulates the conversion of fatty acids to triglycerides in adipose tissue as long-term energy stores [13].

When there is insulin deficiency, there is decreased glucose uptake in the tissues, increased breakdown of glycogen stores, and increased gluconeogenesis in both the liver and kidney, reducing the anabolic to catabolic state. There is a breakdown of proteins to form amino acids needed for gluconeogenesis. This leads to hyperglycemia, which is worsened by a stressed state as a result of increased levels of adrenaline, growth hormone and cortisol, which block the action of the little insulin that may be there and trigger the production of glucagon. [14,15]

Insulin normally plays a role in the production and use of ketones by inhibiting the breakdown of lipid and fatty acid oxidation. Insulin promotes the oxidation of ketones in the peripheral tissues. Without insulin, there is both increased production and reduced utilization of ketones[15]. With low glucose in the cells, there is increased glucagon release that stimulates hormone-sensitive lipase, an enzyme that catalyzes the transformation of triglycerides into free fatty acids.[14] Through the mitochondrial membrane, the free fatty acids are carried to be used for the synthesis of ketone bodies, which are acetoacetic acid, betahydroxybutyrate or acetone. However, the peripheral tissues are unable to utilize the excess ketones, and ketosis ensues[16] Hyperglycemia and ketonemia lead to diabetic ketoacidosis.

Figure 1 Conceptual framework of the pathways to DKA and HHS and outcomes



Pathophysiology of DKA

Diabetes ketoacidosis occurs as a result of insulin deficiency in an undiagnosed patient, a missed insulin dose or increased insulin demand due to increased counter-regulatory hormones in a diabetic patient with a fever, infection or surgery. [17] With hyperglycemia, increased plasma osmolarity leads to the movement of water from the intracellular space to the extracellular space, causing dilutional hyponatremia in the extracellular fluid. Normal or hypernatremia in the presence of a high blood glucose is an indication of a clinically significant total body water deficit.[13]

Potassium is an intracellular electrolyte; however, insulin deficiency pushes it into the extracellular fluid, it is excreted in the urine. Patients with DKA may have low or normal serum potassium levels, but the total body potassium is low. If the patient has hyperkalemia, then that implies renal hypoperfusion [18]. Lack of Insulin leads to hyperglycemia above the renal threshold of glucose of 11.1 mmol/l, causing glycosuria. The patient develops thirst with increased fluid loss and high plasma osmolarity, resulting in polydipsia. When the body is stressed, there are increased levels of the counterregulatory hormones, adrenaline, cortisol, and growth hormone. These hormones are thought to help keep the blood pressure in the normal range despite the fluid loss but cause insulin resistance worsening hyperglycemia. [19,20]

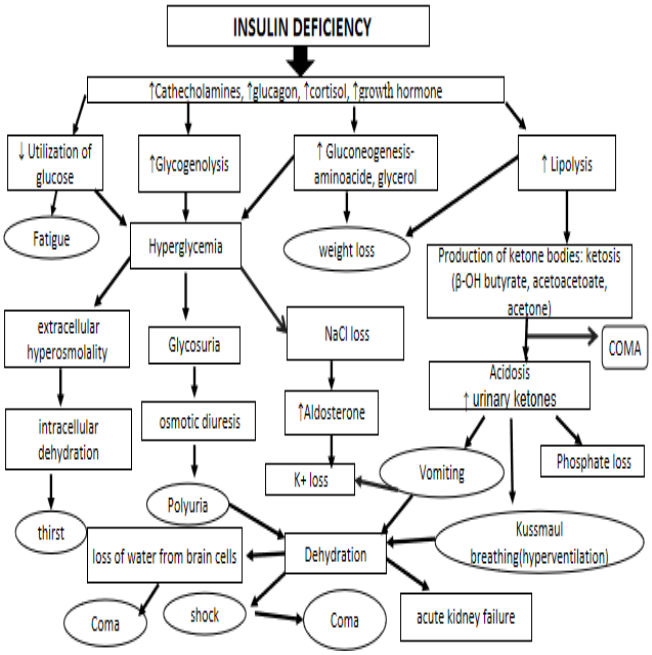
In a patient with ketoacidosis, hydrogen ions accumulate in the extracellular space, leading to the breakdown of bicarbonate into carbon dioxide and water, causing reduced bicarbonates. This worsens the acidosis and leads to Kussmaul breathing seen in diabetic patients. If kidney function is normal, there is increased acid excretion, which is manifested by high levels of urinary ammonium. [21]

Patients with sustained hyperglycemia may present with signs of infection or an opportunistic infection. High blood sugar stimulates the production of adhesion molecules that mediate tissue inflammation. Defects in chemotaxis, phagocytosis, and intracellular killing also complicate the course of the infection. The patients have reduced leucocyte recruitment and pathogen recognition, impaired macrophage glucose metabolism, depletion and malfunction of memory cells. [13]

Diabetic ketoacidosis (DKA) is characterized by severe depletion of water and electrolytes from both the intra- and extracellular fluid compartments; the typical range of losses is shown in Table 1. Despite substantial dehydration, children generally continue to maintain normal blood pressure or even high blood pressure, [7,8] possibly due to elevated plasma catecholamine concentrations, increased release of antidiuretic hormone (ADH) in response to hyperosmolality (which increases blood pressure via vasopressin two receptors), increased osmotic pressure from marked hyperglycemia, or other factors. [7,8] Considerable urine output persists because of glucosuria until extreme volume depletion leads to a critical decrease in renal blood flow and glomerular filtration. At presentation, the specific deficits in an individual child vary depending upon the duration and severity of illness, the extent to which the child could maintain fluid and electrolytes intake, and the content of food and fluids consumed before coming to medical attention. Consumption of fluids with a high-carbohydrate content (fruit juices or sugar-containing soft drinks) may exacerbate hyperglycemia. Clinical manifestations of diabetic ketoacidosis include:

- Dehydration
- Tachypnea: deep, sighing (Kussmaul) respiration
- Nausea, vomiting, and abdominal pain that may mimic an acute abdominal condition
- Confusion, drowsiness

Figure 2.0: Pathophysiology of DKA flow chart



CAUSES OF DKA

Relative or absolute insulin deficiency is the underlying cause of DKA. Several risk factors for insulin deficiency states leading to diabetic ketoacidosis in sub-Saharan Africa have been described and listed in Box1.0 [13].

DIAGNOSIS OF DKA

According to the International Society for Paediatric and Adolescent Diabetes (ISPAD) (4), the diagnosis of DKA is clinically based on the biochemical TRIAD of Diabetes (Hyperglycaemia) >11mmol/l(200mg/dl
Ketonaemia with a ß-hydroxybutyrate concentration of >3mmol/l or moderate or large Ketonuria >2+ .
Acidosis (Venous pH) <7.3 or serum bicarbonate <18mmol/. In resource-limited sub-Saharan Africa (SSA), where there may be no facilities for laboratory analysis and diagnosis of ketonaemia and metabolic acidosis, DKA diagnosis is based on history, clinical

examination, and limited laboratory blood and urine tests or urine for ketones.
The severity of DKA can be categorized into three based on the metabolic acidosis and dehydration level [22]:

- Milld: venous pH 7.2 to <7.3 or serum bicarbonate 10 to <18mmol/L.
- Moderate: pH 7.1 to <7.2 or serum bicarbonate 5 to <10mmol/L.
- Severe: pH <7.1 or serum bicarbonate <5mmol/L

Box 1: Risk factors for Diabetic ketoacidosis in sub-Saharan Africa
Delayed or undiagnosed T1 DM There is a lack of insulin in treated patients for several reasons. Psychosocial – intentional insulin omission or reduction Insulin inaccessibility Insulin unavailability and unaffordability and poor storage or transportation Missed clinic visits. Perceived ill-health and alternative therapies such as herbs, prayers, and rituals Infections – gastroenteritis, malaria, urinary tract infections (UTI), tuberculosis (TB), and pneumonia Ill-equipped and understaffed healthcare systems with little or no knowledge to care for diabetes. Poverty – poor nutrition, low human development index Pubertal growth spurt

DKA Management

In Sub-Saharan Africa, there are two types of health systems: six-tire and three-tire systems. However, in this guideline, care levels will be classified as primary, secondary, and tertiary. Three-tire and six-tire systems will be divided into these levels as follows:

Immediate management at a PHC facility (while arranging the referral to a second or third level)
Diabetic ketoacidosis (DKA) is very difficult to manage at a primary health care (PHC) facility, yet a lot can be done to save lives while arranging for the referral. Once the patient is diagnosed as having DKA, the following should be first evaluated and done.

- Assess the level of consciousness using the Glasgow Coma Scale and make sure that the patient is breathing well. If the patient is not responding, insert an NG tube and put in a lateral position or raise the head of the bed. If not breathing well, try to open the airway using a head tilt manoeuvre, remove any vomitus, make sure the tongue is not blocking the airway, and give oxygen and auscultate the chest to assess air entry.
- Secure an intravenous (IV) line (two if possible) and draw blood for blood sugar. Do not waste a lot of time inserting the line. If difficult, insert an interosseous to resuscitate. In an unconscious patient, an NG tube can also be used to rehydrate, but with caution. If the patient is febrile, check the blood film for malaria, do a septic workup, and do a complete haemogram (CBC), if available. Give an antipyretic and use tepid sponges.
- Weigh the caregiver and then weigh the caregiver with the patient and get the difference, which is the patient's weight.
- Assess the level of dehydration. Check pulse, capillary refill time (CRT) and blood pressure using an appropriate cuff size (whenever possible, if only adult size is available, check blood pressure in the thighs). If the pulse is weak or hard to appreciate, consider this as a hypovolemic shock and manage accordingly:
- Give a bolus of normal saline (NS) or Lactated Ringer's (LR) solution, 20ml/Kg, over 30 minutes if the patient is in shock. This can be repeated as long as the circulation has not been restored yet. Document the starting time and amounts of fluids infused in the referral **note**; this is very important information.
- If the patient is severely dehydrated (not in shock), can start infusing 10ml/Kg over 1 hour and re-assess the circulation again.

NOTE*: Level 1 – in the 6-tire health system is the Community-Village health committees, household, family and individuals*

Levels of care	Equivalent in 3 tire health system	Equivalent to 6 tire health system	Service provided
PRIMARY	Primary health centers, sub-centers, health posts,	Health Centre, Level 2 (Dispensaries), Level 3 (Health/Medical centers), Level- 4 (Primary referral health facility)	Provide immediate care/health education.
SECONDARY	Community Health centers District hospitals, General hospitals	District Hospital, Level 5 (Secondary Referral Health facility)	Specialized care and capacity building
TERTIARY	Regional Hospitals, medical colleges, tertiary hospitals	Regional, Zonal Hospitals, National and Specialized Hospitals Level-6 National Tertiary Referral Health facilities	Specialized care, Capacity building centers, Mentorship and Research

- If the patient is not in shock and not severely hypotensive, dehydrated DON'T give bolus. Assess and start replacement fluids and maintenance (see below). If

Figure 3.0: A sample for a referral note

Name	
Age	
Diabetic for (new/weeks/months/years)	
Using insulin (type) at a dose of	
Estimated/actual weight	
Presented at (time)	
Main complaints	
Vital signs	Pulse:
	CRT:
	BP:
	Temp:
	RR
	GCS
From the assessment:	The patient was shocked The patient was severely dehydrated The patient was moderately dehydrated
Fluids given (type & amount)	Normal Saline/Lactated Ringer's/ORS -------ml/kg over ------- minutes Was it repeated? Yes/No If yes, how many times
Insulin	Not given Regular, -----units, SC/IM Analogue, ---- units, SC/IM
Initial blood sugar	initial--------mg/dl (-------mmol/L) last
Urine for ketones	Not checked Didn't pass urine Positive (how many?): Negative
BFFM, CBC	Not done Attached
Other blood tests	
At the time of referral, the patient is	Stable Sick but stable Critically ill/comatose

not sure about assessment, give the 10ml/Kg N.S or LR over 2 hours while preparing to refer the patient.

- If unable to secure an IV line, insert an interosseous (IO) and follow the same steps from (i). If not possible, insert a nasogastric tube (NGT) and infuse sugar-free Oral Rehydration Solution (ORS), 5ml/kg/hour and quickly refer. A nurse should accompany and be giving the fluid.
- Insert a Foley catheter for urine testing for ketones and collection. If unavailable, we can use an external urine collector to check urine ketones and ensure the patient is passing urine, for infants can squeeze the diaper to test the urine.
- After restoring the circulation (about 1-2 hours from the starting time), give subcutaneous (SC) or intramuscular (IM) short-acting insulin (regular/Humulin R) at a dose of 0.05-0.1 u/kg. Reduce the dose to 0.05U/Kg for infants and children below the age of 5 years. If insulin analogues (lispro/aspart/glulisine) are available, either can be used subcutaneously instead of regular insulin at the same dose. This should be repeated hourly while monitoring the blood sugar and arranging for a transfer. NEVER use IV insulin at a PHC facility. For any help, communicate with the nearest higher centre.

IMPORTANT: write a clear referral note about timing, amounts of fluids infused, initial vital signs, etc. and communicate with the available hotline in the location for safe transportation (Figure 3). DO NOT stop fluid infusion during the transfer.**DKA management at secondary and tertiary healthcare facilities.**

Assessment (all levels of care) Clinical assessment, including history and physical examination, should go on concurrently with Management:

- Assess level of dehydration, (If not sure assume 10%)
- Assess the level of consciousness Using the GCS
- Measure weight (kg)
- take capillary blood for blood glucose and ketones.
- Check Urine for Ketones
- Take blood for the following investigations:
- Blood glucose
- Urea and electrolytes (sodium, potassium, and chloride)
- Full Blood picture (CBC)
- CRP
- Glycated haemoglobin (HbA1c)
- Blood gases if possible
- ECG (for monitoring of potassium disorders), if available
- If an infection is suspected, samples should be taken for culture and sensitivity. Or BF for malaria
- If the laboratory is not available, samples should be sent with the patient to the next level of care.

Resuscitation (when there is shock, this should be done at all levels of care)

- put an intra-osseous access or put in a nasogastric tube.
- Refer to a site with IV facilities.
- Treat shock with IV fluids at 20mls/kg over 30 minutes; this bolus can be repeated.
- Use normal saline (0.9%), or Ringer lactate Categorize and treat shock urgently.
- Support airway and breathing.

- Give oxygen when there is impaired circulation and/or shock.
- Put in a large IV cannula. If the IV line is not accessible for initial resuscitation use IO route
- If the only access is via nasogastric tube, replace the same amount of fluid over 60 minutes.
- Once circulation is restored, give fluids as below.

NOTE: Resuscitate the child adequately before proceeding with these steps:
Fluid Replacement (when not in shock)

Fluid replacement is the total of:

- The volume used to treat shock (bolus over the 1st hour of admission)
- Deficit plus maintenance fluid is given over 48 hours.
- All children not in shock, moderate and severe DKA should receive 10 ml/kg of NS or RL bolus, depending on availability.
- The bolus will be subtracted from the deficit. However, the shock reversal fluid shouldn't be subtracted. Example: If the Patient weighs 20kg, Give 10mls x body weight over one hour, thus 200mls of normal saline over one hour
- Once the patient is stable, refer to the nearest highest level of care, depending on your facility. Document all you have given.
- Fluid deficit (Amount of fluid loss/% dehydration)
- Clinically assess dehydration and measure blood gas (if available). Clinically, the best parameters of dehydration are pulse volume, skin turgor, sunken eyes and mucosa.

Mild Dehydration
1. pH 7.2 to 7.3, bicarbonate 10 to 18mmol/l
2. Mild DKA: assume 5% dehydration (50mls/kg)

Moderate Dehydration
1. pH 7.1 to 7.2, bicarbonate 5 to 10
2. Moderate DKA assume 7 % dehydration (70mls /kg)

Severe Dehydration
1. pH <7.1, bicarbonate <5mmol/l
2. Severe DKA assume 10% dehydration (100mls/Kg)

Important:

When not sure of the severity of dehydration, use 10% dehydration in a significantly ill patient.

DKA:

Example:

- Patient (weighs 20 kg) with severe DKA (100 ml/ kg)

Fluid deficit

- Start with calculating the fluid loss, which is 100mls X body weight = 2000mls
- Deduct the bolus fluid (2000mls -200mls)
- The fluid deficit here is 1800mls (to be run over 48 hours)

Maintenance Fluid
Daily fluid needed by the body (Daily maintenance fluid)

Weight	Daily fluid needed by the body.
Under 10kg.	100ml/kg 10 kg
10 - 20 kg.	100/kg for the 1st 10kg + 50 mls/kg, for each 1kg body weight over 10kg
Over 20 kg.	100ml/kg for the 1st 10kg+50mls/kg (for each 1kg body weight between 10-20kg) + 20mls /kg for each 1kg body weight over 20kg (maximum 2litres in females and 2.5litres in males)

Therefore, maintenance for the patient in the first 24 hours will be 100mls x10 + 50mls x10 = 1500mls, and maintenance for the next 24 hours will be the same amount of 1500. Therefore total maintenance for 48 hours will be 1500 x 2= 3000mls (Over 48 hours), or use the simplified Holliday-Segar formula for fluid maintenance: up to 10kg 4ml/kg/hr. up to 20 kg 40mlplus 2ml/kg, more than 20kg 60 plus 1ml/kg/hr

Total fluid requirement

- Fluid deficit + Maintenance fluid
- 1800mls + 3000 =4800mls to run over 48 hours
- So, in 24 hours, the fluid to be given will be 2400 mls, and for one hour, it will be 100 mls/hour (see **table**)
- If Intravenous/osseous access is not available – use oral rehydration solution (ORS) by NGT if not available, give ORS by oral sips at a rate of 1ml/kg every 5 minutes.
- Once the blood glucose is < 17mmol/l, add dextrose to the saline (use 5% dextrose saline (DNS) or 5%dextrose with 0.45N saline.
- If IV access or NGT is not accessible, refer to the next closer lever of care -depending on where you are.
- Don't give insulin without initial restoration of circulation as this will cause shock.

Insulin therapy (Optimum care after 1st hour of admission)

- Begin insulin therapy when circulation has been restored, mostly 1 to 2 hours after fluid resuscitation)
- Give an insulin infusion of rapid or short-acting insulin (e.g., actrapid). (Infusion rate of 0.05 to 0.1 unit/kg/hr or 0.05unit/kg/hr for children below five years)
- If IV administration is NOT possible, give Insulin SC/IM 0.05-0.1 unit/kg every 1 hour. Or 0.1-.15 units/kg sc two-hourly.

  NOTE: IM insulin injection if patient has poor tissue perfusion

Example:

- Patient (4 years, 20 kg): give Actrapid (0.05 U/kg/hr): 1 unit/ hr
- Patient Y (6 years, 40 kg): give Actrapid (0.1 U/kg/hr): 4 units/ hr.

NOTE: NEVER give insulin as a bolus

- Aim at a glucose reduction of about <5 mmol/l (90mg) per hour.
- A more rapid decline in blood glucose may contribute to the development of cerebral oedema.
- If glucose declines rapidly (more than 100mg) per hour give 5%dextrose saline or decrease the insulin delivery rate.

Potassium replacement:

- Potassium Replacement should be done at the secondary/Tertiary level), if available.
- Potassium replacement is needed for most of children with DKA: Patients with acute kidney failure will not need potassium at the beginning.
- Measure blood potassium when doing the initial assessment.
- If the results take longer than 4 hours or you cannot measure potassium at all, use Electrocardiogram or check urine output.
- Hypokalaemia will be shown by flattening the T wave, widening the QT interval, and the appearance of U waves.
- Tall will show hyperkalaemia, peaked, symmetrical T waves and shortening of the QT interval.
- Start replacing potassium when the value of potassium is below 5mmol/ or there is documented urine output.
- If there is Hyperkalaemia, refer to the next level, waiting until the patient is passing adequate urine and or potassium level less than 5,5mmol/l
- In facilities where electrolytes cannot be checked, potassium chloride 20mmol/l is added to the IV fluid being run when the patient passes adequate urine until laboratory potassium is ready.
- If intravenous Potassium is not available, use oral fruit juice or banana juice through an NG tube and slow the rate of insulin to less than 0.1u/kg/hr.
- If using ORS, no potassium is needed as ORS contains potassium, and the patient is referred to the next level.
- Avoid using bicarbonate in a secondary care set-up unless PH is less than 6.9 with compromised cardiac function.

Monitoring during management

Patients aged less than five years, with severe acidosis or high urea, should be admitted to intensive care or ward with experienced nurses and one-to-one nursing (**see fig 4 for DKA flow sheet**)

Hourly Monitoring

a. clinical parameters (heart rate, Blood Pressure, Respiratory rate, Level of consciousness)
b. Glucose level
c. fluid intake,
d. Insulin therapy and
e. urine output

Four to Six Hourly Monitoring

a. Urea and electrolytes
b. Urine or serum ketones

NOTE*: When the blood glucose reaches less than 15 mmol/l*

- Replacing fluid orally: make sure the child has ORS or Fruit Juice.

Managing problems that occur during treatment.

Blood glucose:

- When blood glucose (BG) drops to < 14-17 mmol/l (250-300 mg/dl), or dropping at a rate more than 100mg/hour add Dextrose 5% to 0.9% or 0.45 Saline,
- When BG drops to < 8 mmol/l (≈ 140-150 mg/dl) change to D10% dextrose with normal saline/half normal saline
- This can be increased to max D12.5% .
- If acidosis is not improving inspite of low blood glucose (may decrease insulin to 0.05 u/kg/hr or even down to 0.03 u/kg/hr but do not stop insulin unless there is severe hypoglycemia inspite of the above measures
- Hypoglycemic attack < 4 mmol/ (≈ 72mg/dl): Give 2-5 ml/kg D10% bolus, hold insulin for 15-30 min, then.
- Repeat blood Glucose till becomes normal then resume insulin.

Potassium Adjustment

- Potassium > 5.5 mmol/l, Hold Potassium, repeat level in 2 hrs.
- Potassium < 3.5 mmol/l Increase KCl to 60 mmol/l (need good peripheral IV or Central Line
- Potassium <2.5 mmol/l Monitored administration of extra one mmol/kg KCL over 2 hours.

Phosphorus *Replacement (based on level or symptomatic hypophosphatemia)*

- Phosphorus < 0.5 mmol/l (1.5 mg/dl): Replace ½ of KCl with Potassium Phosphate

1. If acidosis is not correcting (assess bicarbonate change more than pH), consider:
2. Inadequate fluid resuscitation
3. Wrong insulin dose or preparation
4. Hyperchloremic metabolic acidosis
5. Sepsis (usually with lactic acidosis)

6. Recalculate and assess intake/output every four hrs
7. Recheck all preparation.
8. Measure chloride and anion gap* =(Na-(Cl+HCO3) Normal is 12+/-2
9. If anion gap is normal and patient looks acidotic, measure lactate level. High chloride indicates hyperchloremic acidosis, use half or one fifth normal saline instead of normal saline.

DKA Resolution and Shifting to Daily Insulin Therapy

Consider changing the hourly IV or SC insulin when the DKA has resolved, as shown by the following:

Clinical signs: the patient is fully conscious, not nauseated or vomiting, drinking and eating well and hydrated.

Biochemically,

- blood PH >7.3, HCO3 more than 18mmol/l, no ketonemia, no or mild Ketonuria (in the absence of facility for serum ketones or blood gases as Ketonuria without acidosis can continue for a long time
- The best time to change to SC insulin is just before mealtime.
- Rapid-acting insulin analogues are given 15-30 minutes before DC infusion.
- Short-acting insulin is given 30 minutes to one hour before DC infusion.
- Long-acting analogues e.g., glargine, are given 4-6 hours before stopping the infusion; the same applies to NPH.
- Premixed human insulin can be given 30 minutes before stopping the infusion.
- Meal should be given 15 to 30 minutes before SC insulin.

Insulin Doses and regimen:

Insulin Dose:

- If the patient is known to DM1 on appropriate treatment, then resume the patient's previous doses.
- If new DM1 with DKA start at 0.75 unit/Kg /day, the Basal Bolus regime is divided into:
- 40-50 % long-acting - Basal (e.g., Levemir or Glargine or Degludec)
- 50-60 % as rapid-acting insulin pre or post meals
- Use glargine (Lantus) as long-acting insulin If age above three years and Levemir as basal insulin if age < 3 years.
- Rapid-acting insulin analogues like Aspart, lispro, and Humalog can be given 15-30 minutes before stopping insulin infusion.
- Monitor blood sugar by glucose-check six times daily (Before meals and 2 hours post-meals) and adjust the insulin dose according to blood sugar result.
- Consult a paediatric endocrinologist if available. ‣ Diabetic educators and dietitians should be involved early to educate patients and caregivers
- If insulin analogue is not available, you might use two-dose insulin regimens as shown in the next table:
- Two doses of insulin regimens for newly diagnosed diabetes after resolution of DKA

Total daily Dose

1. Pre-pubertal: 0.5-1.0 unit/kg
2. Pubertal: 1.0-1.2 unit/kg
3. Before breakfast, Two-thirds of total daily dose (TDD)
4. One-third rapid-acting insulin
5. Two-thirds of intermediate-acting insulin (e.g., NPH)

- Before dinner, One-third of TDD ‣ One-third rapid acting & two-third intermediate-acting insulin OR
- In the absence of a long-acting analogue, NPH can be given as basal twice a day, 50-60% in the morning and 40-50% in the evening, with regular or rapid-acting insulins given before each meal.
- Monitor blood sugar by glucometer four times Daily (before meals and at bedtime)

COMPLICATIONS OF DIABETIC KETOACIDOSIS

Diabetic ketoacidosis is fraught with many life-threatening complications either as a continuum of the initial process or following treatment or Management (23, 24) (A). Most of these complications are seen mainly in children but also occur in adults. They are also seen mainly in newly diagnosed diabetes patients or patients with poor glycemic control (25). The incidence of these complications varies from study to study, and different criteria for diagnosis are used in different countries. However, the commonest complications are cerebral oedema, acute kidney injuries, shock, cardiac arrhythmias, encephalopathy, rhabdomyolysis[13].

CEREBRAL OEDEMA

Cerebral oedema is the most severe complication of diabetic keto acidosis globally, and it arises from the condition itself or inappropriate management protocols. It is seen in newly or previously diagnosed diabetes patients with long-duration symptoms and those with severe acidosis, high urea and hypocapnia with no sex predilection. It is common in younger patients than adolescents but can occur at any age. It occurs in about of children with DKA, but the mortality rate is about 25% in various literature [13].

The cause of cerebral oedema in DKA is not fully understood. Still, proposed theories include a rapid rise in the cerebral osmotic pressure following hyperglycaemia with fluid shift into the cerebral tissue [26]. During the

hyperosmolar state of DKA, the brain cells accumulate intracellular osmolytes, pulling fluid into them [27,28]. As treatment starts with saline, the fluid in the intravascular space enters the interstitium through osmosis, worsening cerebral oedema [29]. Other theories include cerebral hypoperfusion causing hypoxic-ischaemic injury as shown in some rat models and also human clinical studies where factors affecting cerebral blood flow during DKA are most strongly associated with risks of life-threatening or subtle cerebral injuries [30,31]. Some researchers have found marked cerebral inflammatory responses acting synergistically with the cerebral hypoperfusion or reperfusion process, thereby increasing the vulnerability to cerebral injury. In Africa, there are possibilities of other parasitic and bacterial infections compounding the process in the brain, with reports of malaria, meningitis, tuberculosis and streptococcus species [23]

Cerebral injuries and oedema manifest in many diverse forms, including but not limited to headaches, hyperventilation, vomiting, irritability, elevated blood pressure, and, when severe enough, low blood pressure, confusion states, abnormal pupillary reflexes, etc. When these are present, it is expedient to rule out raised intracranial pressure using set criteria [13,32,33] Clinically, cerebral oedema is diagnosed if there is one diagnostic criteria, two primary criteria or one major and two minor criteria.

Diagnostic criteria

1. Abnormal motor or verbal response to pain
2. Decorticate or decerebrate posture.
3. Cranial nerve palsy (especially III, IV, and VI)
4. Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea,
5. Cheyne-Stokes respiration, apneusis)

Major criteria

- Altered mentation, confusion, fluctuating level of consciousness
- Sustained heart rate deceleration (decrease more than 20 beats
- per minute) not attributable to improved intravascular volume or
- sleep state
- Age-inappropriate incontinence

Minor criteria

- Vomiting
- Headache
- Lethargy or not easily arousable
- Diastolic blood pressure > 90 mmHg
- Age <5 years

Detecting cerebral oedema using imaging such as brain MRI should not delay treatment. It is also important to note that signs of cerebral oedema in imaging occur late. Imaging is indicated later for those having a neurological sign and if cerebral haemorrhage and thrombosis are suspected.

Prevention of cerebral oedema is better than treating it, as the high mortality rate is associated with the condition. Management of cerebral oedema is initiated immediately, and symptoms and signs start to manifest. Using intravenous mannitol at 1 gram/kilogramme over 10 -15 minutes can be repeated after 30 minutes to 1 hour. Adjust fluid regimen based on blood pressure and cerebral perfusion optimization. Mannitol causes osmotic diuresis; hypoperfusion may occur, leading to reduced cerebral pressure, so the patient should be under constant monitoring. Some patients may need intubation and ventilatory support to protect the airway. Hyperventilation is contraindicated as it reduces the cerebral perfusion pressure below minimal acceptable limits.

Hypertonic saline, 3% sodium chloride at 2.5 – 5 ml/kg over 10 – 15 minutes can be used if the initial treatment with mannitol is not effective or if mannitol is not available or if there is severe hyponatraemia at presentation [29].

Other brain insults include affection of mentation and judgement as well as microinfarcts. Focal cranial nerve palsies, particularly 3,4 and 6, can occur.

Acute Kidney Injury (AKI) in DKA

Acute kidney injury (AKI) has been reported in 40-60% of children with diabetes in DKA, mainly of pre-renal origin, due to extracellular volume depletion or glucotoxicity. It is defined as a high serum creatinine compared to the age with decreased urine output and signs of fluid overload (i.e., oedema and hypertension) by any of the following criteria according to the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline:

⇒ Increase in serum creatinine by≥ 0.3mg/dl within 48 hours.
⇒ Increase in serum creatinine to ≥1.5 times the baseline.
⇒ Urine volume <0.5ml/kg/hour for 6 hours

AKI is divided into three stages according to severity:

- Stage 1: 25% decrease in estimated GFR
- Stage 2: 50% decrease of estimated GFR
- Stage 3: 75% decrease of estimated GFR

Although it is usually mild, reversible, and occurs secondary to hypo-perfusion, it has been postulated that survivors might be prone to having chronic kidney disease in the future. Another pathogenesis behind developing AKI is metabolic dysfunction in DKA patients, including hyperglycemia and metabolic acidosis, both of which cause kidney damage. Therefore, adequate therapy should be targeted to prevent the development of AKI, and if already encountered, kidneys should be properly handled for a better outcome.

The whole idea in managing such a scenario is to properly hydrate the patient by calculating the fluids

meticulously, including the daily maintenance and the deficit over 48 hours.

If the patient was initially anuric or oliguric (urine output is <1 ml/kg/hr for neonates and less than 0.5mlml/kg/hr for children) a challenge test with normal saline bolus should be done provided that blood pressure is not high and the patient is not edematous (i.e., not retaining fluids). This is usually done by infusing 10ml/kg over 30 minutes and checking whether urine output has improved. The test can be repeated twice, and urine output is checked. Diuretics have been proven to be non-beneficial in the acute phase of AKI and should only be reserved to control fluid overload. In patients who develop oedema with reduced urine output, fluid restriction and or fluid removal with dialysis or hemofiltration should be instituted if the patients don't respond to IB diuretics.

For managing severe hypertension, intravenous labetalol or sodium nitroprusside is indicated. If not available, intravenous hydralazine can be used as well. Some studies have suggested the efficacy of sublingual nifedipine. Once blood pressure has been controlled, the patient should be shifted to a longer-acting anti-hypertensive such as amlodipine.

After the initial fluid resuscitation of a DKA patient, one should check the renal profile, including serum creatinine, urea and serum electrolytes. An estimated GFR is to be calculated using the full age-specific equation (FAS) as follows:

eGFRFAS= 107.3/(SCr/Q)

Where SCr: is the serum creatinine and Q: median serum creatinine in mg/dl according to height-specific healthy population.

If the patient is hyperkalemic or anuric, no K+ is added till it drops to below 5mmol/L. If serum K+ is normal with raised serum creatinine, the proper fluid amount should be calculated with close monitoring to input/output, blood pressure and presence of oedema. If the output is lower than the input while maintaining normal blood pressure, fluids should be recalculated to provide urine output plus the insensible losses (400ml/M^2/day). In a hot climate, the insensible losses can be more than that, so it is advisable to decide how much fluids to give based on the urinary output and signs of fluid overload. Electrolyte disturbances such as hypo natremia, hypernatremia, hypocalcemia (due to acidosis), which can present with seizures and hyperkalemia (that can cause cardiac conduction defect), can ensue and should be tackled aggressively. Hyperkalemia is defined as a serum level >6-7 mmol/L. Proper management should be guided to correct electrolytes gradually. Metabolic acidosis and hyperkalemia are combined findings for both DKA and AKI. This might need correction using intravenous or even oral HCO3 bicarbonate, which might be required at a dose of 0.5 - 1mEq/kg over one hour. Acidosis treatment can cause a decrease in the ionized calcium, precipitating the patient to tetany/seizures. Therefore, if it is necessary to use HCO3 for correcting both hyperkalemia and acidosis, it is wise to start 10% calcium gluconate simultaneously at a dose of 100mg/kg up to the maximum of 1 g, or 1ml/kg up to the maximum of 10 ml over 30-60 minutes and then maintain with the same dose over the coming 48 hours. AKI in a child with diabetes in DKA might be resistant to treatment, and such patients might require higher insulin doses and more extended hospital stays. The decision to increase insulin doses is adjusted according to blood sugar levels and the rate of its drop. Attention should also be paid to nephrotoxic medications in dose calculations in children with AKI.

Cardiac arrhythmias

Cardiac arrhythmias are usually from complications of electrolyte imbalance (of potassium or calcium) that occur rarely but can be fatal if not recognized early (34). Hypokalaemia is a major manifestation of untreated and poorly treated DKA where some authors have reported total serum potassium as low as 2.5mEq/L, which can cause major changes in the electrocardiograph (35, 36). Hypokalaemia and, thus, cardiac arrhythmias usually occur in diabetes when potassium shifts from the intracellular compartment to the extracellular compartment to balance the ionic changes that occur with acidosis and sodium loss from dehydration. Cardiac cells lacking potassium have reduced activities which lead to premature atrial and ventricular complex beats, sinus bradycardia, paroxysmal atrial and junctional tachycardia, fibrillations etc. The ECG changes associated with hypokalaemia include prolonged PR interval, flattened T waves, and ST depressions [33].

Cardiac arrhythmia complicating DKA should be prevented as the associated mortality rate is high. Many clinical guidelines recommend commencing potassium replacement immediately after the bolus treatment with saline and insulin infusion has commenced [33, 37] This causes potassium to shift into the intracellular compartment and will not cause a rapid drop in circulating potassium. The recommended infusion dose of potassium chloride is 0.5 – 1mEq/kg/hour or, more conveniently, 40mEq/ 1L of intravenous fluid, except when hypokalaemia is severe and should be corrected as it is depleted using the correction factors. The goal is to increase the potassium by 0.3 – 0.5mEq/L [13]

Other complications of DKA

Metabolic

- Hypoglycemia
- Hypocalcemia,
- Hypomagnesemia
- Severe hypophosphatemia
- Hyperchloremic acidosis
- Hypochloremic alkalosis

Central nervous system complications including cerebral venous sinus thrombosis, basilar artery thrombosis, intracranial haemorrhage, cerebral infarction.

Others

- Deep venous thrombosis
- Pulmonary embolism
- Rhinocerebral or pulmonary mucormycosis
- Aspiration pneumonia
- Pulmonary edema
- Adult respiratory distress syndrome (ARDS)
- Prolonged QTc
- Pneumothorax, pneumomediastinum and subcutaneous emphysema
- Rhabdomyolysis
- Ischemic bowel necrosis
- Acute pancreatitis

DKA IN SPECIAL SITUATIONS:

Neonatal Diabetes/DKA

Neonatal diabetes (ND) is defined as the development of diabetes before the age of 6 months. Symptoms can be very vague and non-specific and overseen as a case of neonatal sepsis. ND can be either transient or permanent. Babies usually present with the following features:

- Remarkable weight loss after birth or not gaining weight.
- Irritability is not easy to control.
- Excessive urination (diapers are always heavy and frequently changed; ants and insects are attracted to the diapers). Mothers of neonates with diabetes always describe the urine as a sticky one.
- Eager to breastfeed and not feeling satisfied easily. If not noticed or diagnosed, they can present with breathlessness (acidotic breathing) decreased arousal and sluggish primitive reflexes.
- Malabsorptive diarrhoea can present when the exocrine function of the pancreas is impaired (associated with GATA6, EIF2AK3 and PTF1A mutations).

  Such babies usually do not have risk factors for sepsis-like prematurity, intra-uterine growth retardation (IUGR), premature rupture of the membranes (PROM), maternal infection in the last trimester, etc. Babies at risk for infection are usually oliguric with floppiness, refusing to feed with bulging anterior fontanel +/- spasticity.
- Blood sugar is usually more than 600mg/dl (35mmol/L) with ketones in urine.

Other features that can help in the suspicion of neonatal diabetes are Polycystic kidney disease, skeletal abnormalities, hepatic dysfunction, and cardiac function, in addition to the history of consanguinity and unexplained neonatal deaths in the family.

So, it is mandatory to check blood sugar in each sick neonate/infant and think of neonatal diabetes because the second differential diagnosis is the sepsis-like picture. A full screening workup should be done to rule out sepsis in a sick neonate.

In both cases, one should do the following:

- Assess the level of consciousness and make sure that the baby is breathing well. Manage accordingly. Check the weight of the baby.
- Secure an IV line (two if possible), draw a blood sample for sugar, and insert a Foley catheter for urine testing and monitoring. If not readily available, do a suprapubic tap and check urine for ketones.
- Assess the level of circulation. If the baby is in shock, restore circulation by giving a bolus of 10ml/kg over 30 minutes and re-assess thereafter. This can be repeated till restoration is attained. If the baby is not responding, start inotropes and put the possibility of a septic shock and manage accordingly. If the baby is severely dehydrated and hypotensive, give a bolus of 10ml/kg over one hour and assess thereafter.
- After restoring the circulation, calculate the replacement fluids amount and infuse over 24 hours as follows: daily maintenance fluids + half the deficit (considering a 10% deficit) over 24 hours.

Maintenance fluid rates for term neonates according to their age	
Age	ml/kg/day
Birth to day 1	50-60
Day 2	70-80
Day 3	80-100
Day 4	100-120
Days 5-28	120-150

Example:

A 6-day-old term neonate presented in shock with a history suggestive of neonatal diabetes. Blood sugar was 760mg/dl. His weight was 2.5 Kg. he was given a bolus of 50 ml of normal saline over 20 minutes, after which circulation was restored. This amount will NOT be subtracted from the replacement fluids amount. Fluid replacement is to be calculated as follows:

24-hour maintenance fluids = 150ml/kg, i.e., 357 ml/24 hours + Half the deficit (5%) = 50ml/kg, i.e., 125 ml
357+125ml= 480ml/24 hours (rate: 20ml/hour)

This same amount will be infused over another 24 hours. So, a total of 48 hours (full deficit + daily maintenance fluids)

NB: Do not divide the amount of calculated fluids 8 hourly. it should be infused continuously (using pumps or micro-droppers)

Type of fluids to be used:

- Normal saline till blood sugar is between 250-300mg/dl (14-17mmol/L), or blood glucose is dropping at rate of more than 100mg/hr then shift to dextrose 5% with 0.45 normal saline. The typical

target of blood glucose drop is 80-90 mg/dl/hour (4-5mmol/l/hour).

- If blood sugar drops suddenly to the level of hypoglycaemia, correct with dextrose 10% and shift fluids again to 5% with 0.45 normal saline.
- After ensuring that the baby has passed urine and that serum potassium (K+) is below five mmol/L, add potassium (K+). 40mmol K+ per litre of fluids (in each 500ml drip, add 20 mmol (one ampoule) of K+. If serum K+ is above 6mmol/l, withhold it till it drops down, and the baby passes adequate urine.
- Breastfeed as soon as the baby can tolerate it.

Insulin therapy: Both intravenous and subcutaneous routes can be used to deliver short-acting insulin. If there is no proper monitoring for blood sugar, SC route would be a better option. The dose ranges from 0.02 to 0.05 units/kg/hour. Insulin infusion rates should be adjusted in a small increment of 0.01 units/kg/hours when blood sugars are less than 100mg/dl or more than 200 mg/dl. Once feeding has been well established (breast milk contains about 2.1 g carbohydrate per 30 ml breast milk), the baby can be shifted to fixed SC insulin doses. Multiple daily injections is the recommended regimen to be used. Although readily available in Africa, it would be better to avoid NPH insulin in ND because of its high risk of hypoglycemia. Therefore, Glargine is a better option at a dose of 0.2-0.4 units/kg/day divided into two injections per day. Regarding the bolus, rapid-acting Insulin-like Aspart, Lispro and Glulisine are recommended since short-acting insulin before each meal may result in stacking of insulin and serious hypoglycemia with a deleterious effect on the growing brain. The recommended starting dose is 0.1-0.15 u/kg/dose if the pre-prandial blood glucose is 200-250 mg/dl. Initial frequent pre-prandial monitoring is crucial since the baby might only need 3-4 doses per day. The smallest dose that can be administered subcutaneously without dilution is 0.5 units. Smaller doses as low as 0.1 units are possible using dilution of the U-100 insulin (100 units of insulin per 1 ml) to up to one-tenth of the original concentration. Dilution should be made using specific insulin diluents (distilled water or normal saline). The shelf life of the diluent should be taken into consideration when decision is made to dilute insulin. Although it is not recommended to dilute glargine, this is practised on the ground when badly needed with good results. The total daily insulin requirements can vary from 0.29 units/kg to 1.4 units/kg/day.

Continuous SC insulin infusion (CSII) can be used whenever available. The initial basal insulin is 0.1 to 0.3 units/kg/day, and the minimum rate is 0.025 – 0.05 units/hour. This can be adjusted to maintain blood glucose between 100 and 200 mg/dl. A correction dose should be given if blood glucose is above 250 mg//dl.

For dilution: Add five units (2.5 lines) of 100 units/mL soluble insulin to sodium chloride 0.9% (to give a total volume of 1mL). The resulting solution contains five units/mL of insulin (in the insulin syringe). Each line contains 0.1 units. The diluent can last for 48 hours in the fridge. Gentle rolling should be done every time before use.

Dose	0.05 units	0.1 units	0.2 units	0.3 units	0.4 units	0.5 units
Volume	0.5 line	1 lines	2 lines	3 lines	4 lines	5 lines

Insulin preparation 100unit/ml for continuous infusion

Insulin 0.05 units/mL

- Double dilution to make 50mL syringe:

Step one:

- Dilute 0.5mL of 100 unit/mL soluble insulin with 9.5mL of compatible fluid (total of 10mL). The resulting solution contains five units/mL insulin.
- Step two: Dilute 0.5mL Insulin (5 units/mL) with 49.5mL of compatible fluid (total of 50mL).

Fluid/Insulin Recommended for neonates <1kg:

Rate ml/hr	0.2	0.4	0.6	0.8	1	Rate ml/hr
Weight (Kg)	Approximate units/kg/hr					Weight (Kg)
0.5	0.02	0.04	0.06	0.08	0.1	0.5
1	0.01	0.02	0.03	0.04	0.05	1
1.5	0.007	0.01	0.02	0.03	0.03	1.5
2	0.005	0.01	0.02	0.02	0.03	2
2.5	0.004	0.008	0.01	0.02	0.02	2.5
3	0.003	0.007	0.01	0.01	0.02	3

Insulin 0.1units/mL

Double dilution to make 50mL syringe:

- Step one: Dilute 0.5mL of 100 unit/mL soluble insulin with 9.5mL of compatible fluid (total of 10mL). The resulting solution contains five units/mL of insulin.
- Step two: Dilute 1mL Insulin (5 units/mL) with 49mL of compatible fluid (total of 50mL).

Fluid/insulin recommended for neonates weighing 1kg - 3kg

Rate ml/hr	0.2	0.4	0.6	0.8	1	Rate ml/hr
Weight (Kg)		Approximate units/kg/hr				Weight (Kg)
1	0.02	0.04	0.06	0.08	0.1	1
1.5	0.01	0.03	0.04	0.05	0.07	1.5
2	0.01	0.02	0.03	0.04	0.05	2
2.5	0.008	0.02	0.02	0.03	0.04	2.5
3	0.007	0.01	0.02	0.03	0.03	3
3.5	0.006	0.01	0.02	0.02	0.03	3.5

Insulin 0.2 units/mL

To make 50mL syringe:

- Step one: Dilute 0.5mL of 100 unit/mL soluble insulin with 9.5mL of compatible fluid (total of

10mL). The resulting solution contains five units/mL of insulin.

- Step two: Dilute 2mL insulin (5units/mL) with 48mL of compatible fluid (total of 50mL)

To calculate infusion rate (mL/hr):

- Rate (mL/hour) = dose (units/kg/hour) x weight (kg)
- Infusion Strength (units/mL)
- To calculate the dose (units/kg/hour):
- Dose (units/kg/hour) = Rate (mL/hour) x Strength (units/mL)
- Weight (kg)

Management of DKA in a severely malnourished child (SMC)

Confirm diagnosis with history and clinical features of severe malnutrition such as oedema in both feet or weight-for-height/length <-3SD or mid-upper arm circumference < 115 mm for children under 5 years, < 135 mm for children between 5 to 9 years and 160 mm for children between 10 years and 14 years and signs of wasting and body mass index below 3rd percentile in older children and adolescents or BMI less than 16kg/m2 in young adults. [38-40]

Fluid/insulin recommended for neonates weighing >3kg

Rate ml/hr	0.2	0.4	0.6	0.8	1	Rate ml/hr
Weight (Kg)	Approximate units/kg/hr					Weight (Kg)
2	0.02	0.04	0.06	0.08	0.1	1
2.5	0.02	0.03	0.05	0.06	0.08	1.5
3	0.01	0.03	0.04	0.05	0.07	2
3.5	0.01	0.02	0.03	0.05	0.06	2.5
4	0.01	0.02	0.03	0.04	0.05	3
4.5	0.01	0.02	0.03	0.04	0.04	3.5

- From history, the patient may have been diagnosed with type 1 diabetes and may not be compliant with insulin treatment. The child may be neglected, an orphan, a refugee, their family may be facing severe economic difficulties or may be mismanaged by diet restrictions. Ask for clinical features of diabetes such as polyuria, polynocturia and enuresis in children who have attained continence although these features of diabetes may be absent in SMC as most of them have infections and so may rather have nausea and poor feeding. [39-41]
- Assess for consciousness and hydration status (they are usually severely dehydrated). However, dehydration may be masked in those who have kwashiorkor by oedema or may be overestimated in those with marasmus. Assess respiratory rate, pulses, blood pressure, auscultate lung bases to rule out respiratory diseases, examine ear, nose and throat, look for signs of wasting such as prominent ribs, scapula, clavicles, loss of subcutaneous tissue, loose skin, loose hanging skin of buttocks.
- Check blood glucose, urine ketones, nitrite and leucocytes, urea and creatinine, blood film for malaria parasites, blood culture, do complete blood count, stool RE for worm and protozoa infestations. Do blood gases if possible.
- If there is hyperglycaemia (blood glucose ≥ 11.1mmol/l), venous blood pH <7.3 or bicarbonate ≤18 mmol/l, blood ketones > 3mmol/l or Ketonuria>2+, the child has DKA. In hospitals without or with poor laboratory support, blood glucose and urine ketones are enough to diagnose DKA. The patient should be admitted to the ward and managed as such.
- In some cases, SMC can present with euglycaemic diabetic ketoacidosis (EuDKA) where the blood glucose is normal (< 11 mmol/L) with significant ketonuria (urine ketone of ≥ 2+). [42]
- If patient is admitted in shock characterised by rapid respiration, tarchycardia, slow weak pulses, lethargy or unconsciousness, give IV half strength normal saline or half-strength Darrow's solution 15 ml/kg/hour. Another bolus of 15 ml/kg/hour may be given if the in initial bolus does not improve peripheral circulation (40). Review patient every 5 to 10 minutes.
- After two hours of IV fluid administration, switch to oral or nasogastric hydration using ReSoMal 10ml/kg/hour for up to 10 hours. ReSoMal should be given in smaller volumes at regular intervals. For example, a child who weighs 18 kg with severe malnutrition in DKA will need 180 ml of ReSoMal every hour. This could be given 30 ml every 10 minutes orally or via NG tube. Patients should be reviewed every 30 minutes. If there is an improvement in peripheral circulation, give short acting insulin intravenously using an infusion pump or purfuser at a rate of 0.05-0.1 unit/kg/hr. The lower dosage (0.05 U/kg/h) can be considered for children with pH > 7.15 or ketonuria of 4+.
- In health facilities without access to perfusers and insulin pumps short acting insulin can also be given 0.15 unit/kg every 2 hours, subcutaneously. If blood glucose drops more than 5 mmol/hour give 0.1 unit/kg every 2 hours[33].
- If patient is admitted in conscious state and can drink give oral rehydration solution for the malnourished (RESOMAL) 5 mL/kg/hr for 4 to 10 hours and then change to 1.5L/m2/day. [40] After rehydration for 2 hours, assess for improvement in peripheral circulation and then start iv soluble insulin.
- After starting soluble insulin, start IV potassium 40 mmol/L potassium. Review the patient 30 minutes for respiration and pulse rate. Check and record blood glucose every hour, urine ketones every 2 hours and electrolytes every 4 hours.
- If blood glucose falls to between 14 and 17 mmol/L, add 5% dextrose to ReSoMal and continue with iv insulin till all ketones clear from urine. [43] After ketones have cleared and the patient looks well, iv soluble insulin can be changed to subcutaneous multiple-dose regimen.

- All children and adolescents with severe malnutrition have infection, mostly bacterial (such as otitis media, tonsilitis, urinary tract infection, pneumonia or septicaemia). So, they should be treated with appropriate antibiotics according to culture and sensitivity or local sensitivity pattern [41]. Malnourished children may also have fungi infections, tinea on the skin and/or scalp, and candidiasis on mucosal surfaces, and they should be treated appropriately.
- Children with severe malnutrition should be fed cautiously with F75 for the first three days and then continued with F100. For adolescents, feeding can be started with F100 and then to ready to use therapeutic food (RUTF). They should be given vitamin A 100,000 units of (for children under 12 months) and 200,000 units of (for children above 12 months) on days 1, 2, and 14. They should also be given zinc, folic acid, and multivitamin supplementation.
- After the patient has fully recovered from DKA, and infections effectively treated, patient feeding well and on RUTF and home-based food can be discharged and have a discharge and be followed up in paediatric diabetes clinic.

Table 1.0: shows approximate 24 hours fluid requirement in DKA (maintenance plus half deficit) and volume (in ml) to be given per hour is shown in Brackets.

Wt (kg)	Mild (5%)	Moderate (7%)	Severe (10%)
10	1200 (50)	1320 (55)	1440 (60)
15	1560 (65)	1680 (70)	2040 (85)
20	1920 (80)	2160 (90)	2400 (100)
25	2160 (90)	2400 (100)	2760 (115)
30	2400 (100)	2760 (115)	3240 (135)
35	2640 (110)	3000 (125)	3600 (150)
40	2880 (120)	3360 (140)	3840 (160)
45	3120 (130)	3600 (150)	4320 (180)
50	3360 (140)	3840 (160)	4560 (190)
55	3600 (150)	4080 (170)	4800 (200)
60	3840 (160)	4320 (180)	5280 (220)

Table 2.0: shows comparison of formulation of oral rehydration solution (ORS)

Mmol/l	Old WHO ORS	Standard Hypo-osmolar WHO ORS	ReSoMal
Osmolarity	311	245	300
Sodium	90	75	45
Potassium	20	20	40
Chloride	80	65	76
Glucose	111	75	125



DATE .....

TIME												
Hours since admission	ER											
Weight (Daily)												
Mental status												
Temperature												
Pulse												
Respiration Depth												
Blood Pressure												
Dextrostic												
Urine Ketones												
Blood Ketones												
ELECTROLYTES												
Na+ mmol/L												
K mmol/L												
CL mmol/L												
HCO3 mmol/L												
Urea mmol/L												
Creatinine mmol/L												
Blood gulcose												
Effective osmolality (2 x Na mmol) (glucose mmol)												
Phosphate mmol/L												
Calcium mmol/L												
Blood Gases												
PH												
HCO3												
B.E												
O2 sat												
PO2												
PCO4												
INSULIN												
Units/HOUR												
Route												
INTAKE												
I.V (volume type)												
P.O (volume type)												
Dextrose												
Saline KCl												
Phosphate												
Bicarbonate												
OUTPUT												
Urine (ml)												
Others												

With Complements of

Sudan Childhood Diabetes Association World Diabetes Foundation

Figure 4.0 DKA Follow up sheet.

Conflicts of Interest: The authors declare no conflicts of interest regarding the publication of this paper.

Author Contributions.

All the authors contributed to this guideline. Dr Lucy Mungai Lead the team and Prof Mohamed edited and made sure all the information was correct.

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