Diabetic ketoacidosis in children: diagnosis and management

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Diabetic ketoacidosis (DKA) still remains an important cause of diabetes-related deaths in children despite frequent updates of internationally agreed guidelines. The majority of guidelines are consensus rather than evidence based. However, knowledge of the pathophysiology and evidence based management strategies help to understand the rationale behind the consensus guidelines of DKA[1].

Definition[2]

The biochemical criteria for diagnosis of DKA are:

- Hyperglycaemia (blood glucose >11mmol/L or >200mg/dL)
- Venous pH <7.3 or bicarbonate < 15mmol/L
- Ketonaemia and ketonuria

DKA is most frequent in children less than 5 years old and becomes less common with increasing age. In a carefully analyzed cohort of paediatric patients who had new onset diabetes mellitus (DM) with DKA, 23% of the children presented with DKA. Thirty six percent of children below 5 years of age presented with DKA as the initial diagnosis compared to 16% of children older than 14 years of age. In children with established DM, the risk of DKA is 1-10% patients per year[3].

Although DKA is commonly associated with Type 1 DM (TIDM), there has been an increased incidence of DKA reported among patients with type 2 DM (T2DM), associated with increased rate and severity of obesity, in some centres now accounting for as much as one half of newly diagnosed patients in children[4].

A family history of DM reduces the risk whereas vulnerability increases with poor metabolic control, peripubertal girls and those with difficult family and social circumstances (social class 3-5 increases risk).

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The majority of DKA episodes are thought to be due to insulin omission or treatment error. The other causes include inadequate insulin therapy during intercurrent illness, alcohol, and technical errors, e.g. a malfunctioning pen, leaking cartridge or insulin pump failure[5,6].

Pathophysiology

DKA results from absolute or relative deficiency of circulating insulin and the combined effects of increased levels of counter regulatory hormones viz. catecholamines, glucagon, cortisol, and growth hormone[7,8].

Insulin is required for the active movement of glucose into cells as a source of energy. In the absence of insulin, the body goes into a catabolic state with breakdown of glycogen, protein and fat in muscles, liver, and adipose tissue. Counter regulatory hormones stimulate glycogenolysis, gluconeogenesis, proteolysis, lipolysis and ketogenesis in an attempt to provide more fuel to cells. Despite an excess of extracellular glucose, the cells sense a deficiency of fuel for metabolic needs[9].

An impaired peripheral glucose utilization results in hyperglycaemia and hyperosmolality, increased lipolysis and ketogenesis causing ketonaemia and metabolic acidosis. Hyperglycaemia that exceeds the renal threshold and hyperketonaemia causes osmotic diuresis, dehydration, and obligatory loss of electrolytes, often aggravated by vomiting. These changes stimulate further stress hormone production, inducing more severe insulin resistance and worsening hyperglycaemia and hyperketonaemia[10].

Ketoacidosis may be aggravated by lactic acidosis secondary to anaerobic glycolysis from poor tissue perfusion or sepsis. Lactic acidosis shifts acetoacetate towards beta-hydroxybutyrate, reducing the body's ability to eliminate ketoacids by the acetone route[9]. The ketone bodies are weak acids that dissociate completely and give rise to a large hydrogen ion load that rapidly exceeds normal buffering capacity.

Kussmaul respiration develops and despite this effort metabolic acidosis ensues[1]. If this cycle is not interrupted with exogenous insulin, fluid and electrolyte therapy, fatal dehydration and metabolic acidosis will ensue.

Clinical presentation and evaluation

The cardinal symptoms of diabetes (thirst, polyuria and weight loss) are often not complained of by patients and families. They are much more likely to complain about vulvo-vaginitis or balanitis, secondary enuresis, vomiting and abdominal pain. It is always helpful to ask about thirst, polyuria and weight loss directly to avoid any delay in diagnosis[11].

The length of history is very important in determining the severity of DKA, particularly with respect to the symptom of deep breathing, drowsiness, and vomiting. Symptoms that suggest a precipitating cause, such as infections, should also be sought. Examination should focus on signs that help to determine the severity of DKA, and those that suggest a precipitating cause. The typical child who has DKA is about 5-10% dehydrated [12,13].

Assessment of the degree of dehydration can be difficult with a tendency to overestimate the severity, probably because weight loss precedes dehydration. Most of the time degree of dehydration is estimated based on physical findings which are based on extracellular fluid volume. However, the extracellular fluid volume is maintained by plasma hyperosmolality till the last moment and it is not a very accurate measurement[9].

DKA is characterized by severe depletion of water and electrolytes from both the intra- and extracellular fluid compartments; the range of losses is shown in Table 1.

Table 1[10]
Losses of fluids and electrolytes in DKA and maintenance requirements in normal children

Fluid/Electrolyte	Average (range) losses per kg	24-hour maintenance requirements
Water	70 ml (30–100)	*≤10 kg 100 ml/kg/24 hr 11–20 kg 1000 ml + 50 ml/kg/24 hr for each kg from 11–20 >20 kg 1500 m + 20 ml/kg/24 hr for each kg >20
Sodium	6 mmol (5–13)	2–4 mmol
Potassium	5 mmol (3–6)	2–3 mmol
Chloride	4 mmol (3–9)	2–3 mmol
Phosphate	(0.5–2.5) mmol	1–2 mmol

the Holiday-Segar formula

Despite their dehydration, patients continue to maintain normal blood pressure and have considerable urine output until extreme volume depletion and shock supervene. This eventually causes severe impairment of renal excretory function such as excretion of glucose, ketones and hydrogen irons. This leads to rapid rise of glucose and blood urea nitrogen (BUN) levels resulting in extreme hyperosmolality.

Osmolality = 2 (Na + K) + (glucose)/18 + (BUN)/ 2.8 mOsm/kg

Sodium and potassium concentrations are expressed in mEq/L and glucose and BUN are expressed in mg/dl. In a typical child who has DKA, glucose is elevated just above 400 mg/dl, and the BUN is elevated by about 15mg/dl[9].

At presentation the magnitude of specific deficits in an individual patient varies depending on the duration and severity of illness, the extent to which the patient was able to maintain intake of fluids and electrolytes and content of food and fluids consumed before seeking medical attention[14].

Early Kussmaul breathing can be easily missed as it is the depth rather than the rate of breathing that is striking. The level of consciousness needs to be assessed by using the Glasgow Coma Score (Table 2) and fundi need to be examined.

Table 2
Glasgow Coma Scale

Best Motor Response	1 = none
	2 = extensor response to pain
	3 = abnormal flexion to pain
	4 = withdraws from pain
	5 = localises pain
	6 = responds to commands
Eye Opening	1 = none
	2 = to pain
	3 = to speech
	4 = spontaneous
Best Verbal Response	1 = none
	2 = incomprehensible sounds
	3 = inappropriate words
	4 = appropriate words but confused
	5 = fully orientated

Maximum score 15, minimum score 3

Modification of verbal response score for younger children

2-5 years	**< 2 years**
1 = none	1 = none
2 = grunts	2 = grunts
3 = cries or screams	3 = inappropriate crying or unstimulated screaming
4 = monosyllables	4 = cries only
5 = words of any sort	5 = appropriate non-verbal responses (coos, smiles, cries)

The patients have to be screened for possible sepsis as a precipitating cause, both clinically and with the help of laboratory investigations. Fever is an unreliable indicator of infection as it is commonly absent in DKA. Its presence, however, is indicative of infection. Overall, it is wise to have a low threshold to treat very sick patients with antibiotics[1]. It is also very important to weigh patients if possible, even if they are very sick. This allows accurate calculations for fluid and insulin administration.

The severity of DKA is categorized by the degree of acidosis[15].

- Mild : venous pH< 7.3 or bicarbonate <15mmol/L
- Moderate: pH <7.2,bicarbonate <10 mmol/ L
- Severe : pH <7.1, bicarbonate <5 mmol/L

It is also important to recognize that overlap between the characteristic features of hyperglycaemic hyperosmolar state (HHS) and DKA may occur. Some patients with HHS, when there is severe dehydration, have mild to moderate acidosis, conversely some children with type I DM may have features of HHS if high carbohydrate containing beverages have been used prior to diagnosis[16].

The criteria for HHS[16] are:

- Plasma glucose concentration >33.3 mmol/L (600mg/ dl)
- Arterial pH >7.3
- Serum bicarbonate >15 mmol /L
- Small ketonuria, absent to mild ketonaemia.
- Serum osmolality >320 mOsm/kg
- Stupor or coma.
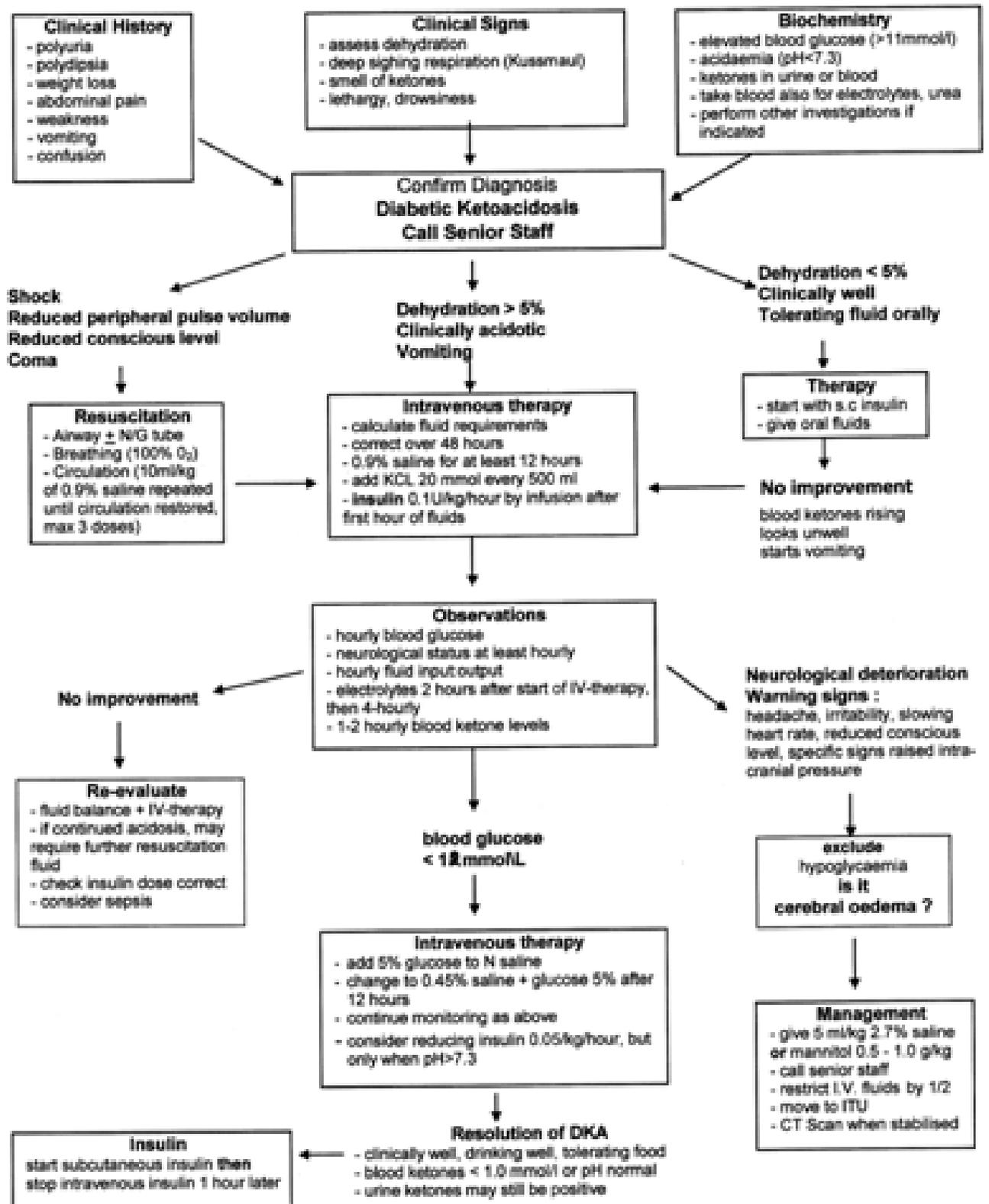
Management of DKA (Figure 1)[17]

Clinical History
- polyuria
- polydipsia
- weight loss
- abdominal pain
- weakness
- vomiting
- confusion

Clinical Signs
- assess dehydration
- deep sighing respiration (Kussmaul)
- smell of ketones
- lethargy, drowsiness

Biochemistry
- elevated blood glucose (>11mmol/l)
- acidaemia (pH<7.3)
- ketones in urine or blood
- take blood also for electrolytes, urea
- perform other investigations if indicated

Confirm Diagnosis
Diabetic Ketoacidosis
Call Senior Staff

Shock
Reduced peripheral pulse volume
Reduced conscious level
Coma

Dehydration > 5%
Clinically acidotic
Vomiting

Dehydration < 5%
Clinically well
Tolerating fluid orally

Resuscitation
- Airway ± N/G tube
- Breathing (100% O₂)
- Circulation (10ml/kg of 0.9% saline repeated until circulation restored, max 3 doses)

Intravenous therapy
- calculate fluid requirements
- correct over 48 hours
- 0.9% saline for at least 12 hours
- add KCL 20 mmol every 500 ml
- Insulin 0.1U/kg/hour by infusion after first hour of fluids

Therapy
- start with s.c insulin
- give oral fluids

No improvement
blood ketones rising
looks unwell
starts vomiting

Observations
- hourly blood glucose
- neurological status at least hourly
- hourly fluid input output
- electrolytes 2 hours after start of IV-therapy, then 4-hourly
- 1-2 hourly blood ketone levels

No improvement

Neurological deterioration
Warning signs :
headache, irritability, slowing heart rate, reduced conscious level, specific signs raised intra-cranial pressure

Re-evaluate
- fluid balance + IV-therapy
- if continued acidosis, may require further resuscitation fluid
- check insulin dose correct
- consider sepsis

blood glucose
< 12mmol/L

exclude
hypoglycaemia
is it
cerebral oedema ?

Intravenous therapy
- add 5% glucose to N saline
- change to 0.45% saline + glucose 5% after 12 hours
- continue monitoring as above
- consider reducing insulin 0.05/kg/hour, but only when pH>7.3

Management
- give 5 ml/kg 2.7% saline or mannitol 0.5 - 1.0 g/kg
- call senior staff
- restrict I.V. fluids by 1/2
- move to ITU
- CT Scan when stabilised

Insulin
start subcutaneous insulin then stop intravenous insulin 1 hour later

Resolution of DKA
- clinically well, drinking well, tolerating food
- blood ketones < 1.0 mmol/l or pH normal
- urine ketones may still be positive

Figure 1: *Algorithm for the management of DKA*[17]

Perform clinical evaluation to confirm diagnosis. Always consult with a more senior doctor on call as soon as you suspect DKA even if you feel confident of your management. Remember that children can die from DKA.

Goals of therapy

1. General resuscitation: A,B.C
2. Correct dehydration.
3. Correct acidosis and reverse ketosis.
4. Restore blood glucose to near normal.
5. Avoid complications of therapy.
6. Identify and treat any precipitating event.

Airway: Secure airway. If the child is comatose insert an airway. If consciousness is reduced or child has recurrent vomiting, insert nasogastric (NG) tube, aspirate and leave on open drainage.

Breathing: Give 100% oxygen via face mask. This should be given to all and should be continued during the first hour of management, even if oxygen saturation is 100% in air. This is important because patients with DKA suffer intracellular phosphate depletion and changes in serum phosphate. This may result in reduced levels of 2, 3-DPG in red cells. This results in a shift of the oxygen–haemoglobin dissociation curve to the left, causing reduced oxygen availability to the tissues [1,18].

Circulation: Monitor BP, pulse volume and rate, skin turgor, capillary refill. Insert at least two IV cannulae and take blood samples for blood glucose, serum electrolytes, blood urea nitrogen, calcium, magnesium, phosphorus, blood gas, lactate, white cell count (leukocytosis is a feature of DKA and not always suggestive of an infection), haematocrit, Hb%, HbA1C, blood ketones (if available more superior)[19] and urinary ketones, serum osmolality. These should be repeated two hourly for the first 12 hours.

In addition, the following should be done.

Septic screen: (blood and urine culture, chest x-ray)[9]

Calculation of anion gap: Anion gap = Na - (Cl + HCO3). Normal is 12±2 mmol/L. In DKA the anion gap is typically 20-30 mmol/L. Anion gap >35 mmol/L suggests concomitant lactic acidosis.

Continuous cardiac monitoring to assess T waves for evidence of hyper or hypokalaemia is also very important[20,21].

Assess degree of dehydration[22]

Mild (3%)   : only just clinically detectable
Moderate (5%): dry mucous membranes, reduced
                 skin turgor.
Severe (8%)   : those above + sunken eyes, poor
                 capillary return
Shock   : poor perfusion, thready rapid pulse
                 (reduced BP is a late sign)

Only if in shock give 10ml/kg 0.9% saline as a bolus over 30 minutes and repeat as necessary to a maximum of 30ml/kg. Shock with haemodynamic compromise is rare in paediatric DKA. Very sick patients should be catheterized for accurate monitoring of urine output but it should not be done as a routine procedure.

Over-estimation of the degree of dehydration is dangerous. The clinical estimates of volume deficit are subjective and inaccurate. Therefore in moderate DKA use 5-7% and in severe DKA 7-10% dehydration[10]. (Do not use more than 8% dehydration in calculations. BSPED-2009)[17].

Conscious level

An hourly neurological observation including Glasgow Coma Score (Table 2) should be monitored for early recognition of cerebral oedema as this can cause death.

Fluid calculation (Table 1)

No treatment strategy can be definitively recommended as being superior to others based on evidence. The principles described below were developed after a comprehensive review of the literature and were accepted by Lawson Wilkins Paediatric Endocrine Society, (LWPES) the European Society for Paediatric Endocrinology (ESPE) and ISPAD[2,22]. There are no data to support the use of colloid in preference to crystalloid in the treatment of DKA.

Requirement = Maintenance + deficit – resuscitation fluids already given.

Maintenance requirement- uses the Holliday Segar formula[24,25].

100 ml/kg for first 10kg
50 ml/kg for second 10kg
20ml/kg for subsequent kilograms

Deficit (litres) = % of dehydration x body weight in kg

Add calculated maintenance (for 48 hours) and estimated deficit, subtract the amount already given as resuscitation fluid, and give the total volume evenly over 48 hours[1, 17, 26].

Hourly rate = 48 h maintenance + deficit – resuscitation fluid
                                    48

Type of fluid

Initially use 0.9% saline with 20 mmol KCL in 500ml, and continue this for at least 12 hours until blood glucose falls to 12mmol/l, then if plasma sodium level is stable change to 500ml bags of 0.45% saline /5%glucose/20mmol KCL. If the plasma corrected sodium level falls during treatment, then continue with normal saline with or without added dextrose depending on blood sugar level[17].

Corrected sodium = measured Na + (2 x (blood glucose- 5.5) /5.5)

Serum sodium usually rises as the blood glucose falls and this may be associated with increased risk of cerebral oedema. Theoretically serum sodium should rise by 2mmol for every 5.5 mmol fall in blood glucose[10].

During initial fluid resuscitation if plasma glucose concentration falls steeply >5mmol/L/h, consider adding glucose even before plasma glucose has decreased to 12mmol/L[27]. In addition to clinical assessment of dehydration calculation of osmolality may be valuable to guide fluid and electrolyte therapy.

Insulin therapy

Once dehydration fluids and potassium are running, blood glucose levels will start to fall. Therefore do not start insulin until intravenous fluids have been running for at least an hour. There is now evidence that too early insulin treatment has been found to be a risk factor for the development of cerebral oedema[28]. However, insulin therapy is essential thereafter to correct hyperglycaemia, inhibit lypolysis, ketogenesis, and glycogenolysis and to counteract the excessive levels of stress hormones[29].

Continuous low dose intravenous infusion is the preferred method. Because insulin is adsorbed to the plastic IV tubing, a volume (about 50ml) of infusion should be run through the tubing before initiating therapy. There is no need for an initial bolus. Make up a solution of 1 unit per ml, of human soluble by adding 50 unit (0.5ml) insulin to 50ml of 0.9% saline in a syringe pump. Do not add insulin directly to the fluid bag. The solution should then run at 0.1unit/kg/hour. There are some who believe that 0.05unit/kg/hour is an adequate dose. There is no firm evidence to support this .The aim of treatment is to achieve a gradual fall in blood glucose, which does not exceed 5mmol/l/h. If blood glucose falls too rapidly insulin dose can be reduced to 0.05U/kg/h[17].

Once blood glucose reaches 12mmol/l, the intravenous fluids should be changed to 0.45% saline and 5% dextrose. It is very important that insulin is not stopped and the dose is not reduced below 0.05U/kg/h because only insulin can switch off ketone production. Some suggest also adding glucose if the initial rate of fall of blood glucose is greater than 5-8 mmol/l per hour, to protect against cerebral oedema. There is no good evidence for this practice, and blood glucose levels will often fall quickly purely because of rehydration[17]. If blood glucose falls below 4mmol, give a bolus of 2 ml/kg of 10% dextrose and increase the glucose concentration of the infusion. If needed, solution of 10% glucose wit 0.45% saline can be made up by adding 50ml of 50% glucose to a 500ml bag of 0.45% saline /5% glucose with 20mmol KCL.

If biochemical parameters of DKA (pH, anion gap) do not improve, reassess the patient, review insulin therapy, and consider other possible causes of impaired response to insulin; e.g.

- Insufficient insulin to switch off ketones.
- Inadequate resuscitation.
- Sepsis
- Hyperchloraemic acidosis due to excess 0.9% saline
- Salicylate or other drugs.

In circumstances where continuous IV administration is not possible, hourly or two hourly SC or IM administration of short or rapid acting insulin analog (insulin lispro or insulin aspart) is safe and may be as effective as IV regular insulin infusion[30-35] but should not be used in subject whose peripheral circulation is impaired. Initial dose SC: 0.3unit/kg, followed one hour later by SC insulin lispro or aspart at 0.1 unit/kg/h or 0.15-0.2 units/kg every two hours.

Potassium replacement

Total body potassium is always substantially depleted in DKA, and the major loss is from the intracellular pool as a result of hypertonicity, insulin deficiency and exchange for hydrogen ions with in the cell. Intravenous fluids and insulin administration will drive potassium back into the cells resulting in a rapid fall in serum potassium. Therefore potassium replacement should be started as soon as resuscitation is completed provided anuria is not reported by the family and the ECG does not show elevated T waves. Ensure that every 500ml bag of fluid contains 20mmol KCL and check BUN and electrolytes 2 hourly after initial resuscitation[1].

Bicarbonate

There is no evidence that bicarbonate treatment is either necessary or safe in DKA and it should not be used in the initial resuscitation. Bicarbonate should only be considered in children who are profoundly acidotic (pH 6.9) and shocked with circulatory failure due to decrease cardiac contractility and peripheral vasodilatation resulting in further impairment of tissue perfusion. Dose if decided to treat is 1-2mmol/kg over 60 minutes[17,36].

Phosphate

There is no evidence in adults or children that phosphate replacement has any benefit. Phosphate administration may lead to hypocalcaemia[17,37].

Introduction of oral fluids and regular SC insulin

Oral fluids should only be introduced when substantial clinical improvement has occurred and change over to subcutaneous insulin once blood ketone levels are below 1.0 mmol/l, although urinary ketones may not have disappeared completely.

The most convenient time to change to subcutaneous insulin is just before a mealtime. To prevent hyperglycaemia the first SC injection should be given 60 minutes before discontinuing the insulin infusion if using soluble or long acting insulin or 10-15 minutes before with rapid acting insulin.(Novorapid or Humalog)[20,38].

Insulin dosage: Total daily dose (TDD) for prepubertal children is 0.75-1.0 unit/kg and for pubertal patients 1.0-1.2 unit/kg[38].

Thrice daily administration
Before breakfast: two third of TDD (1/3 as rapidly acting insulin; 2/3 as intermediate acting insulin)
Before lunch: One third to one half of the remainder of the TDD as rapid acting insulin.
Before dinner: One half to two thirds of the remainder of the TDD as intermediate-acting insulin.

Blood sugar should be monitored two hourly to prevent hypoglycaemia or hyperglycaemia. Supplemental rapid acting insulin is given at four hourly intervals to correct blood glucose levels that exceed 200mg/dl[9].

Or

Subcutaneous insulin should be started according to local protocols for newly diagnosed diabetes or child should be started back on to their usual insulin regimen at an appropriate time[17].

Complications

Cerebral oedema, hypoglycaemia, hypokalaemia, infections and aspiration pneumonia are the main complications.

Cerebral oedema

The signs and symptoms are:

- Headache and slowing of heart rate and rising blood pressure - late sign
- Change of neurological status. (restlessness, irritability, drowsiness, incontinence)
- Specific neurological signs (cranial nerve palsies)
- Rising BP, decrease SaO_2
- Abnormal posturing.

Convulsions, papilloedema, respiratory arrest are late signs and are associated with a very poor prognosis.

Management[17, 39,40]

Inform senior staff immediately and arrange transfer to PICU.

1. Exclude hypoglycaemia.
2. Give hypertonic (3%)5-10 ml over 30 minutes or mannitol 0.5-1.0 g/kg over 20 minutes.
3. Restrict intravenous fluids to 2/3 maintenance and replace over 72 hours rather than 48 hours.

4. Intubation and ventilation may be required whilst awaiting transfer to PICU.
5. Repeat dose of mannitol may be required after 2 hours if no response.
6. Documentation of all events in medical records is important.

Continuing abdominal pain is common and may be due to liver swelling, gastritis, bladder retention, ileus. A raised serum amylase is common in DKA[41].

Prevention

Increasing public awareness of the symptoms and signs of diabetes is the most important way to achieve early diagnosis. Patients with established diabetes and their families need clear guidelines for management of illness and high blood glucose.

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