Paediatric diabetic ketoacidosis

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Key points

Diabetic ketoacidosis (DKA) is the leading cause of morbidity and mortality in children with diabetes. Cerebral oedema is the most common cause of death and a high index of suspicion is always required.

Cerebral oedema may be exacerbated by factors related to both DKA presentation and therapy.

I.V. fluid boluses should be given cautiously.

Always use low-dose insulin regimes and avoid insulin boluses.

Misinterpretation of acid–base abnormalities is avoided when changes in pH and base deficit are viewed in conjunction with the anion gap (the latter being a better representation of resolution of ketoacidosis).

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Diabetic ketoacidosis (DKA) can occur with both types 1 and 2 diabetes mellitus,[1] and is the leading cause of morbidity and mortality in children with diabetes.[2] Unlike the adult population, paediatric mortality is mainly due to the development of cerebral oedema.[1] This article will review the pathophysiology and complications of paediatric DKA and discuss the principles behind current treatment strategies.

Pathophysiology

Incidence

The incidence of DKA is generally higher for type 1 diabetes, both at presentation and in the setting of established disease. Studies from Europe and the USA have estimated an incidence of DKA at first diabetic presentation of 15–70% for type 1 diabetes (with patients under 5 yr of age being at highest risk), and 5–25% for type 2.[1, 3] It is thought that the wide variation in incidence within both sub-types is influenced by the availability of healthcare and frequency of diabetes in a given population.[3] In established type 1 diabetes, the risk of DKA is 1–10% per patient per year,[3] with a considerably lower incidence in type 2 diabetes.[1]

Aetiology

DKA is the result of an absolute or relative lack of insulin in combination with the effects of increased levels of counter-regulatory hormones, including catecholamines, glucagon, cortisol, and growth hormone. Absolute insulin deficiency is observed in newly diagnosed type 1 diabetes and in insulin-treated diabetics where insulin is omitted. A relative insulin deficiency results in patients who have some circulating insulin; however, levels of the catabolic counter-regulatory hormones are increased in response to various stress conditions such as obesity, trauma, sepsis, and gastrointestinal illness, and outweigh the anabolic effects of any insulin present.

It is the resulting accelerated catabolic state that gives rise to the classical picture of DKA with: *hyperglycaemia, hyperketonaemia, and hyperosmolality*.[3] Hyperglycaemia is due to impaired peripheral uptake of glucose with increased hepatic gluconeogenesis and glycogenolysis, whereas ketonaemia occurs secondary to increased lipolysis; both contribute to the ensuing hyperosmolar state. The resultant osmotic diuresis leads to dehydration and loss of total body electrolytes; if this is severe, the glomerular filtration rate will decrease, exacerbating the hyperosmolar state through inability to excrete glucose and ketones.[3] This is further compounded by release of counter-regulatory stress hormones.

The metabolic acidosis at DKA presentation is almost exclusively ketonaemic; lactic acidosis is uncommon, unless DKA has been triggered by a secondary phenomenon, such as sepsis.[4]

However, with treatment the aetiology of the acidosis may change, with hyperchloraemia (secondary to resuscitation/rehydration fluid), becoming predominant.[4]

The pathophysiology of DKA is summarized in Figure 1.

Diagnosis

The diagnosis of diabetes mellitus is often delayed in younger children (particularly infants); this is because the classic 'adult' triad of *polyuria, polydipsia, and weight loss* is frequently absent. This may partially explain the increased severity of first presentation of DKA in this age group.[5]

The *biochemical criteria* for the diagnosis of DKA are as follows:[2]

- hyperglycaemia (blood glucose >11 mmol litre^{-1});
- venous pH <7.3 or bicarbonate <15 mmol litre^{-1};
- ketonaemia.

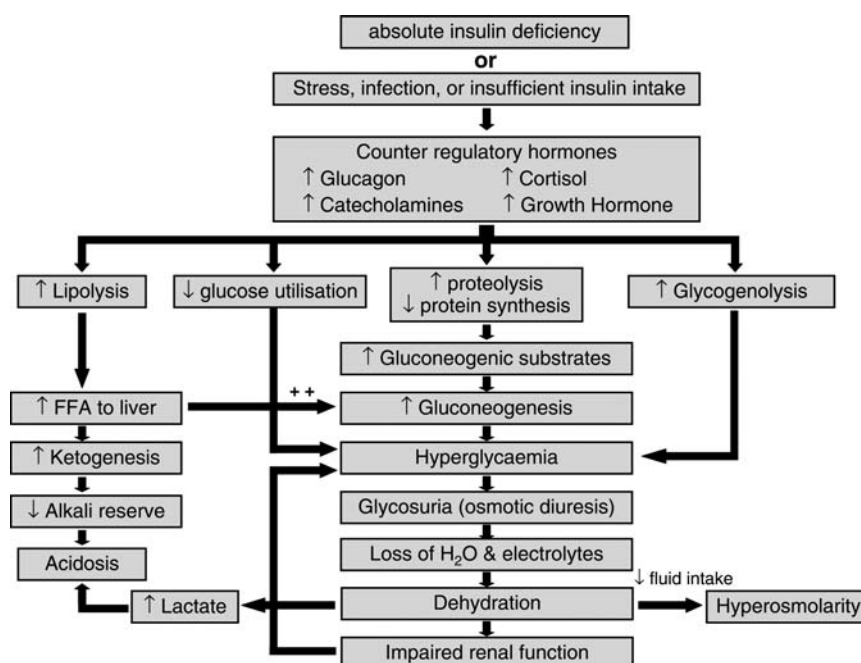Euglycaemic ketoacidosis is rarely seen, but can be present in children who are partially

Fig. 1 Pathophysiology of DKA (reprinted from Diabetes Care®, Vol. 29, 2006; 1150−9 with permission from *The American Diabetes Association*). Copyright © 2006 American Diabetes Association.[3]

treated or who have had minimal carbohydrate intake.[3]

Severity is classified as follows:[3]

Severity	Venous pH	Plasma bicarbonate (mmol litre^{-1})
Mild	7.2−7.3	10−15
Moderate	7.1−7.2	5−10
Severe	<7.1	<5

Several risk factors related to age and severity at presentation have been associated with the development of cerebral oedema and death; these are elaborated in 'Mortality and cerebral oedema'.

Management

The management considerations for paediatric DKA are broadly similar to those for adults, namely:

1. exogenous insulin;
2. i.v. fluid therapy;
3. replacement of electrolytes.

However, several important differences between adult and paediatric DKA exist, which may impact on treatment:

- paediatric DKA often presents with greater severity;
- children are more prone to the development of cerebral oedema;

- development of cerebral oedema may, in part, be exacerbated by treatment.

General considerations

ABC approach

Give oxygen. Failure to adequately protect the airway due to drowsiness is an ominous sign and likely due to cerebral oedema. Drowsiness should be treated urgently with i.v. osmotherapy (either hypertonic saline, 3% at 3−5 ml kg^{-1} over 10 min, or mannitol 0.5 g kg^{-1}), in conjunction with standard airway positioning manoeuvres. If the patient is *in extremis*, tracheal intubation may be required; however, hyperventilation should be avoided, regardless of the patient's spontaneous Pa_{CO_2}.[6] A nasogastric tube should be inserted to reduce the risk of pulmonary aspiration of stomach contents. Ensure secure peripheral i.v. access with two cannulae. The decision to give a fluid bolus should be based upon objective signs of inadequate intravascular volume: extreme tachycardia, hypotension and elevated blood lactate (>3 mmol litre^{-1}). Capillary refill alone is an inadequate sign in this setting. Fluid boluses should be given with caution, and in 10 ml kg^{-1} aliquots only (see 'Fluid therapy').

Assess the level of consciousness

Cerebral oedema can occur at presentation, but may initially produce minimal changes to the sensorium.[3, 6] Marcin and colleagues[6] have published a neurological symptom score which is

Table I Neurological symptom score to grade severity of cerebral oedema (adapted from Wolfsdorf and colleagues[3])

Score	Clinical correlate	GCS range
1	Irritable, disorientated, confused	13–15
2	Lethargic, somnolent	11–12
3	Stuporous, purposeful response to pain	8–10
4	Abnormal response to pain	6–7
5	Focal neurology, fixed and dilated pupil(s), resp. arrest	3–5

quick to perform, reproducible, and corresponds to discrete intervals of the Glasgow coma score (Table 1). This score can be used as an early warning sign of cerebral oedema. Any signs of cerebral oedema must be treated promptly and aggressively.

Weight of the patient

This is essential for calculating fluid therapy and drug dosing.

Give antibiotics if febrile

An increased white blood cell count is often seen in DKA without infection;[2] however, if the child is febrile, it is sensible to commence broad-spectrum antibiotics empirically after taking cultures.

Specific considerations

Insulin therapy

Insulin is essential in switching off lipolysis and ketogenesis. Physiological studies suggest that low-dose insulin ($0.1 \text{ unit kg}^{-1} \text{ h}^{-1}$) achieves steady-state plasma levels of $100–200 \text{ } \mu\text{U ml}^{-1}$ within 60 min.[2] These plasma levels are sufficient to overcome insulin resistance, inhibiting lipolysis and ketone production while exerting near maximal effects on gluconeogenesis suppression and peripheral glucose uptake.[2] I.V. bolus doses of insulin at the start of therapy are unnecessary and may increase the risk of developing cerebral oedema,[3] possibly due to activation of membrane Na^+/H^+ exchangers leading to increased intracellular Na^+ with associated osmotic fluid shifts.[7] Recent guidelines have suggested avoiding insulin boluses, and delaying commencement of insulin infusion until after 1–2 h of fluid therapy.[3]

Fluid therapy

The goals of fluid therapy are two-fold: (i) to resuscitate, if intravascular volume is inadequate (see 'ABC approach') and (ii) to replace fluid deficit secondary to dehydration.

Fluid resuscitation

Shock with haemodynamic compromise is uncommon in DKA[2] and judicious use of fluid boluses is advised. When fluid boluses are required to restore intravascular volume (i.e. in the tachycardic, hypotensive patient), the current recommendation is to use saline 0.9%, $10–20 \text{ ml kg}^{-1}$ given in the first 1–2 h, repeated as necessary.[3] Our own experience and current practice is based upon a restrictive view, aiming to give a maximum bolus of 20 ml kg^{-1} in the first 4 h, and if the patient remains hypotensive, then early consideration is given to commencing inotropes. Ongoing signs of intravascular deficit should raise the suspicion of sepsis.

Rehydration

Always rehydrate over a minimum of 48 h. Replacement fluid comprises normal maintenance plus estimated dehydration. Never give hypotonic solutions as they may increase the risk of cerebral oedema; thus standard therapy should comprise saline 0.9%, with added glucose (5–10%) when the plasma glucose decreases to $\sim 15 \text{ mmol litre}^{-1}$.[7] Urinary losses should not be included routinely in the calculation for fluid replacement.[3] The clinical assessment of dehydration in children with DKA is inaccurate when using standard clinical assessment tools such as capillary refill time, skin turgor, sunken eyes, sunken fontanelle, and dry mucus membranes;[8] thus a recent pre-morbid weight (if available) may be helpful. A recent prospective study of children presenting to an emergency department with DKA yielded a median calculated measure of dehydration of $\sim 9\%$;[8] it therefore seems reasonable to assume 10% dehydration for children presenting with severe DKA, and 5% for those with moderate severity (see 'Diagnosis').

Electrolytes

DKA is associated with major perturbations in plasma electrolytes; primarily sodium, potassium, and phosphate.[2]

Sodium

In health, sodium is the most important extracellular cation influencing intracellular volume. Several factors in DKA may cause an apparent lowering of the plasma sodium, making it an unreliable estimator of both intracellular volume and the degree of extracellular volume contraction.[3] First, total body sodium may be depleted in tandem with water loss as a consequence of the osmotic diuresis secondary to hyperglycaemia and ketonaemia. Secondly, the increased concentration of extracellular glucose (due to insulin deficiency) produces an osmotic movement of water from the cells, leading to a pseudohyponatraemia. The measured sodium will thus invariably increase as plasma glucose decreases with fluid and insulin therapy; however, this can occur in the face of dramatic decreases in effective osmolality (primarily due to glucose no longer being an extracellular osmole). Thus, it is mandatory to calculate the corrected sodium to provide a more accurate estimate of changes in effective osmolality.

$$\text{Corrected sodium} = \text{measured } Na^+ + 0.4[\text{glucose}(\text{mmol litre}^{-1}) - 5.5]$$

The importance of maintaining an adequate effective osmolality during DKA treatment was underlined by Hoorn and colleagues,[7]

who demonstrated that cerebral oedema is less likely to occur when the reduction in effective osmolality is minimized, either via smaller decreases in plasma glucose or via larger increases in plasma sodium. Our local protocol utilizes changes in corrected sodium as the trigger for adjustments in fluid volume (http://www.strs.nhs.uk).

Potassium

Total body potassium deficits in children presenting with DKA are estimated at between 3 and 6 mmol kg^{-1}, mostly from intracellular stores. The serum potassium levels may be normal, increased, or decreased,[3] but this is simply a reflection of how long the DKA process has been continuing for before treatment is commenced. There are several causes of potassium loss including insulin deficiency, metabolic acidosis, vomiting, losses due to an osmotic diuresis and secondary hyperaldosteronism as a result of volume depletion.[3]

Potassium replacement is required in all patients; however, if the serum potassium is >5.5 mmol $litre^{-1}$, defer giving potassium until it begins to decrease or you have a documented urine output.[3] Once treatment with insulin is started, the serum potassium concentration can decrease abruptly.

Phosphate

Intracellular phosphate depletion also occurs in DKA. Clinically significant hypophosphataemia, however, tends to occur only when the resumption of food intake is prolonged beyond 24 h.[3] Studies have not shown phosphate replacement to be beneficial. In addition, i.v. phosphate administration can induce hypocalcaemia; however, this may be considered in cases of muscular weakness.

Metabolic acidosis and anion gap

Appropriate monitoring of acid–base status during DKA treatment is essential. A primary goal of therapy is resolution of ketoacidosis; this can only be quantified *directly* by measurement of blood ketones (which is now possible at the bedside)[9] or *indirectly* via calculation of the anion gap.

$$Anion\ gap = (Na + K) - (Cl + HCO_3)$$
$$normal\ value < 18 mmol\ litre^{-1}$$

In clinical practice, however, ketoacidotic resolution is commonly inferred via blood gas analysis using pH and base deficit. A major limitation of this approach is that confounding factors (notably hyperchloraemia secondary to fluid therapy) may supervene during treatment, attenuating the resolution of metabolic acidosis. A recent study in severe DKA showed that metabolic acidosis persisted 20 h after commencement of treatment (mean pH 7.31, base deficit 10 mmol $litre^{-1}$), despite resolution of

ketoacidosis. Over the same time period, the relative contribution of chloride to the base deficit increased from 2% to 98%.[4]

Monitoring

The management of DKA requires frequent monitoring of both the clinical status of the patient and physiochemical changes that occur during treatment. In addition to the routine observation chart documenting vital signs and neurological status hourly, it is helpful to have a flow chart to record all electrolyte and blood gas results over each 24 h period. An example is given in Figure 2.

Mortality and cerebral oedema

Cerebral oedema occurs in up to 1% of all paediatric DKA episodes with two-thirds of cases presenting within the first 6–7 h after treatment has started.[1] Cerebral oedema is the most common cause of mortality in children with DKA, accounting for 60–90% of all paediatric DKA deaths.[5] Other causes of mortality include hypokalaemia and hyperkalaemia (with associated arrhythmias), sepsis (including mucormycosis), aspiration pneumonia, acute pancreatitis, intracranial venous thrombosis, and rhabdomyolysis.[1]

The aetiology of cerebral oedema is poorly understood, although there are likely to be multiple processes involved with vasogenic, osmotic, and ischaemic mechanisms being implicated.[1] There are several risk factors associated with the development of cerebral oedema, including:[2, 3, 5–7, 10, 11]

- younger age;
- newly diagnosed diabetes;
- longer duration of symptoms;
- raised serum urea;
- initial pH <7.1;
- extreme hypocapnia (P_{CO_2} <2 kPa) at presentation;
- hypocapnia in association with mechanical ventilation;
- >40 ml kg^{-1} total fluid given in first 4 h;
- bicarbonate therapy;
- an attenuated increase, or a decrease in *corrected* plasma sodium during treatment;
- bolus insulin therapy.

Cerebral oedema is a clinical diagnosis with varying signs and symptoms including alteration in neurological status, headache, cranial nerve palsies, bradycardia, and hypertension. This can be subtle, and may have a worse prognosis if diagnosed later after presentation.[6]

If cerebral oedema is suspected then treatment should begin *immediately* using either hypertonic saline (saline 3%, 3–5 ml kg^{-1}) or mannitol (0.5 g kg^{-1}=2.5 ml kg^{-1} of 20% solution) while arranging for a computed tomography scan. This should be repeated until a clinical improvement in neurological status is seen (this may require achievement of plasma sodium levels of 150–158 mmol $litre^{-1}$).[7]

Fig. 2 Sample monitoring record for DKA.

We recommend hypertonic saline as the preferred osmotherapy, for several reasons:

(i) Plasma sodium is the most important variable influencing effective osmolality, and hence intracellular volume in DKA (after insulin therapy has commenced); it is also easily measurable (particularly out-of-hours) in all hospital laboratories.

(ii) Hypernatraemia ($150-158$ mmol litre^{-1}) is effective at both avoiding and reversing the clinical manifestations of cerebral oedema; this appears most pronounced in patients who demonstrate the largest decreases in plasma glucose.[7]

(iii) Mannitol induces an osmotic diuresis and is rapidly excreted, meaning that its effect may be short-lived. In addition, rapid swings in osmolality may be more harmful. Lastly, plasma corrected sodium can now no longer be used as an estimate of effective osmolality, owing to the presence of another osmole (mannitol).

Summary

DKA is a life-threatening condition that requires specific management and monitoring to be instituted early if serious morbidity and mortality are to be avoided. Full treatment guidelines can be found at the websites by following the link: http://www.strs.nhs.uk or alternatively http://www.ispad.org.

References

1. Rosenbloom AL. Hyperglycemic crises and their complications in children. *J Pediatr Endocrinol Metab* 2007; **20**: 5–18

2. Dunger DB, Sperling MA, Acerini CL *et al.* ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. *Arch Dis Child* 2004; **89**: 188–94

3. Wolfsdorf J, Craig ME, Daneman D *et al.* Diabetic ketoacidosis, ISPAD Clinical Practice Consensus Guidelines 2006–2007. *Pediatr Diabetes* 2007; **8**: 28–43

4. Taylor D, Durward A, Tibby SM *et al.* The influence of hyperchloraemia on acid–base interpretation in diabetic ketoacidosis. *Intensive Care Med* 2006; **32**: 295–301

5. Wolfsdorf J, Glaser N, Sperling MA. Diabetic ketoacidosis in infants, children and adolescents. *Diabetes Care* 2006; **29**: 1150–9

6. Marcin JP, Glaser N, Barnett P *et al.* The Pediatric Emergency Medicine Collaborative Research Committee. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. *J Pediatr* 2002; **141**: 793–7

7. Hoorn EJ, Carlotti A, Costa L *et al.* Preventing a drop in effective plasma osmolality to minimize the likelihood of cerebral edema during treatment of children with diabetic ketoacidosis. *J Pediatr* 2007; **150**: 467–73

8. Koves IH, Neutze J, Donath S *et al.* The accuracy of clinical assessment of dehydration during diabetic ketoacidosis in childhood. *Diabetes Care* 2004; **27**: 2485–7

9. Noyes KJ, Crofton P, Bath LE *et al.* Hydroxybutyrate near-patient testing to evaluate a new end-point for intravenous insulin therapy in the treatment of diabetic ketoacidosis in children. *Pediatr Diabetes* 2007; **8**: 150–6

10. Mahoney CP, Vlcek BW, DelAguila M. Risk factors for developing brain herniation during diabetic ketoacidosis. *Pediatr Neurol* 1999; **21**: 721–7

11. Glaser N, Barnett P, McCaslin I *et al.* Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. *N Engl J Med* 2001; **344**: 264–9

Please see multiple choice questions 13–15