Current Practice

Diabetic ketoacidosis in children

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Introduction

Diabetic ketoacidosis (DKA) is a life-threatening, preventable complication of diabetes mellitus. It is characterized by inadequate insulin action, hyperglycaemia, dehydration, electrolyte loss, metabolic acidosis and ketosis[1]. DKA is the most frequent cause of paediatric intensive care unit (PICU) admissions and deaths in children with type 1 diabetes mellitus (T1DM)[1]. About 15-70% of all DKA occur at the presentation of T1DM[2]. However, children already diagnosed as T1DM can develop DKA due to non-compliance with insulin therapy, insulin pump failure or intercurrent illness[2]. Cerebral oedema is the most serious complication of DKA in children. It is common in young children newly diagnosed as T1DM and is rare in individuals more than 20 years of age[3]. A high index of suspicion is warranted because, although uncommon, it is the major cause of morbidity and mortality in DKA[3].

Diagnosis

The diagnosis of DKA can be missed as it can resemble other more common paediatric illnesses such as severe dehydration and acute severe asthma[1]. DKA should be considered in any child or young adult with respiratory distress, dehydration, acidosis or mental status changes[4]. The presence of DKA is supported by a history of polyuria, polydipsia, vomiting, weight loss and rapid breathing with fruity-smelling breath[1]. The diagnosis of DKA is based on biochemical evidence of hyperglycaemia (serum glucose levels >200mg/dl), acidosis (venous pH <7.3 and/or serum bicarbonate levels <18mEq/l) and ketosis or ketonuria. DKA may be categorized as mild (venous pH of 7.2–7.3), moderate (venous pH 7.1–7.2), or severe (venous pH <7.1) [1].

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Pathophysiology[4,5]

The primary abnormality in DKA is insulin deficiency. It causes hyperglycaemia by increased gluconeogenesis, accelerated glycogenolysis and impaired peripheral glucose utilization[1]. When the serum glucose level exceeds the renal threshold of 180 mg/dl, an osmotic diuresis occurs, resulting in the loss of extracellular water and electrolytes. Furthermore, physiologic stress caused by dehydration and coexistent infection, stimulate the release of counter-regulatory hormones such as glucagon, catecholamines and cortisol. They further exacerbate hyperglycaemia by increasing hepatic glucose production and further impairing peripheral glucose uptake[5].

Counter-regulatory hormones, particularly epinephrine, also promote lipolysis, free fatty acid release, and subsequently, ketoacidosis through the oxidation of free fatty acids to ketone bodies. Accumulation of ketoacids is the primary cause of the metabolic acidosis in DKA. Acetone is also formed and gives a fruity odour to the breath, but it does not contribute to the acidosis. The increasing levels of hyperglycaemia and acidosis contribute to a vicious cycle: osmotic diuresis leads to intravascular volume depletion, which decreases renal blood flow and glomerular perfusion, limiting the body's ability to excrete glucose and worsening the hyperglycaemia. Progressive dehydration and acidosis further stimulate the release of counter-regulatory hormones, which accelerates the production of glucose and ketoacids. More severe dehydration then leads to poor peripheral perfusion, causing lactic acidosis. Abdominal pain and vomiting occur as a result of the intestinal ileus brought on by ketoacids and dehydration, preventing patients from maintaining hydration with oral fluids. In the setting of metabolic acidosis, potassium (K) is transported out of the cell into the plasma in exchange for hydrogen and is lost in the urine. Thus, virtually all patients with DKA develop a deficiency of total body K, regardless of their serum K level. Phosphate,

another predominantly intracellular ion, is handled similarly.

The pathogenesis of cerebral oedema in DKA is not well understood. It has been postulated that certain elements of treatment (high doses of insulin, rapid administration of hypotonic fluid, administration of intravenous bicarbonate) may cause cerebral oedema[6-9]. However, cerebral oedema is evident in many patients even before treatment is initiated[9]. Recent studies suggest that the development of cerebral oedema may be linked to a loss of cerebral autoregulation and a vasogenic mechanism[8,9].

Management[1,4,5,10]

The killer in DKA and its management is cerebral oedema (CE). Thus, the aim of management is correcting metabolic abnormalities while preventing CE. Because common management practices may be linked to the development of cerebral oedema, the use of these interventions must be employed judiciously. Therapy of DKA consists of fluid and electrolyte replacement, insulin administration, and careful ongoing monitoring of clinical and laboratory factors.

The osmotic diuresis and the compromised fluid intake (due to nausea and vomiting) result in a large water and electrolyte deficit so that intravenous fluid replacement should begin as soon as the diagnosis of DKA is established. Initial fluid therapy is aimed at rapid stabilization of the circulation to correct impending shock. However, too rapid fluid administration should be avoided. Fluid replacement in excess of 4 L/m^2/24 hours has been associated with the development of potentially fatal cerebral oedema in DKA[1]. For this reason, an initial fluid bolus (10ml/kg) is usually advised only in vascular decompensation (extreme tachycardia, hypotension, cold extremities, and/or anuria) to expand the vascular compartment and improve peripheral circulation. Once the patient has been stabilized, subsequent rehydration is accomplished with caution. The fluid deficit should be corrected gradually, over 36-48 hours.

Fluid Administration

The degree of dehydration in these patients is frequently overestimated[11]. Deficits should be estimated at 5-7% of body weight unless shock is present when 10-15% loss of body weight is assumed. Rehydration fluids should contain at least 115-135mEq/L of sodium chloride to ensure a gradual decline in serum osmolality (1.5–2mOsm/hour) and prevent excessive free water accumulation. Serial calculations of effective osmolality (2 sodium + glucose) are recommended, as sodium levels that fail to rise with treatment may signify excessive free water accumulation and an increased risk of cerebral oedema)[10]. Generally, fluid replacement with 0.9% normal saline is provided at least during the first 6 hours[1]. Hyponatraemic fluids should be avoided as there is a potential risk of life threatening cerebral oedema[8-10].

Electrolyte Therapy

Potassium[1,4,5]

Although the serum potassium (K) level at presentation is often normal or elevated, the total body K is low and should be replaced. Early K replacement is also important to prevent the K depletion during therapy. With the initiation of insulin therapy and correction of acidosis, serum K levels may drop precipitously as K shifts back from the extracellular to the intracellular compartment. Unless the patient exhibits hyperkalaemia (serum K level >5.5mEq/L) or anuria, K should be added to the intravenous fluids at the beginning of the second hour of therapy. Otherwise K is added as soon as urine output is established or the hyperkalaemia abates. If the patient presents with hypokalaemia, (serum K level <3mEq/L) K replacement is initiated immediately. Most patients require 30 to 40mEq/L of K in the replacement fluids, with adjustment based on serum K concentrations that are measured frequently.

Phosphate

DKA results in significant phosphate depletion. Furthermore, serum phosphate values decrease during treatment. Hypophosphataemia may cause metabolic disturbances. However, clinical studies have not shown benefit from phosphate replacement during the treatment of DKA. Phosphate replacement should be given if the values decrease below 1 mg/dl[4,5].

Bicarbonate

Bicarbonate losses are significant in DKA. However, during the treatment of DKA, the patient can produce bicarbonate. Insulin stimulates the generation of bicarbonate from the metabolism of ketones. Consistent with this, clinical trials have failed to show any benefit of bicarbonate administration. Potential risks of bicarbonate therapy include paradoxical central nervous system acidosis, exacerbation of hypokalaemia and cerebral oedema. Therefore, bicarbonate treatment should be considered only in cases of extreme acidosis (pH<6.9) which impairs cardiovascular stability after

the fluid resuscitation or as treatment of life-threatening hyperkalaemia. If bicarbonate administration is believed to be necessary, 1 to 2mmol/kg (added to 0.9% saline) should be provided over 1 to 2 hours[1,4,5].

Insulin[1,4,5]

Serum glucose concentration often falls significantly with initial rehydration alone due to increased glomerular filtration from improved renal perfusion. Therefore insulin treatment is begun after the initial fluid resuscitation i.e. at the beginning of the second hour of therapy. Insulin is administered as a continuous intravenous infusion of regular insulin at a rate of 0.1units/kg per hour. Early insulin infusion during the initial rehydration and insulin bolus therapy increase the risks of cerebral oedema due to rapid drop of serum osmolality[10]. The aim of insulin therapy is gradual reduction of the blood glucose and suppression of ketoacidosis. However, resolution of the acidosis in DKA invariably takes longer than the time to achieve a normal blood glucose concentration. The temptation to decrease the rate of insulin administration based on glucose values should be resisted because this practice delays resolution of the acidosis.

Dextrose (5% increasing to 12.5% as necessary) should be added to the intravenous solutions when the serum glucose level is <250–300 mg/dl with the goal of keeping the serum glucose level in the range of 150–250 mg/dl to avoid rapid drop in serum osmolality[10]. The insulin dose should be decreased only if hypoglycaemia or a rapid reduction of serum glucose persists despite administration of maximal dextrose concentrations in the intravenous fluid. If the acidosis is not resolving, the insulin dose should be increased to 0.15 or 0.2 units/kg per hour. Insulin should be administered intravenously until the ketosis and acidosis improves. When ketoacidosis has resolved (venous pH >7.3 and serum bicarbonate level >18mEq/L), a short-acting subcutaneous insulin with a longer-acting preparation is given in combination with a snack or meal. Intravenous insulin should be continued, to allow time for the subcutaneous insulin to act. Urine ketones (acetoacetate) will take longer to disappear and do not need to be cleared before starting subcutaneous insulin[1,4,5].

Monitoring[1,4,5]

Successful management of DKA requires meticulous attention to clinical and laboratory changes. Most children with DKA should be treated in a PICU. Clinical monitoring is essential: vital signs, perfusion, input/output balance, and neurologic status should be documented at least hourly. Cardiac monitoring is recommended due to the risk of dysrhythmia. Laboratory monitoring should include venous blood sugar concentrations hourly and electrolytes and venous pH every 2-4 hours until normal. Lack of improvement in clinical and biochemical parameters with time suggests an occult infection or inadequate insulin or fluid replacement.

Cerebral oedema

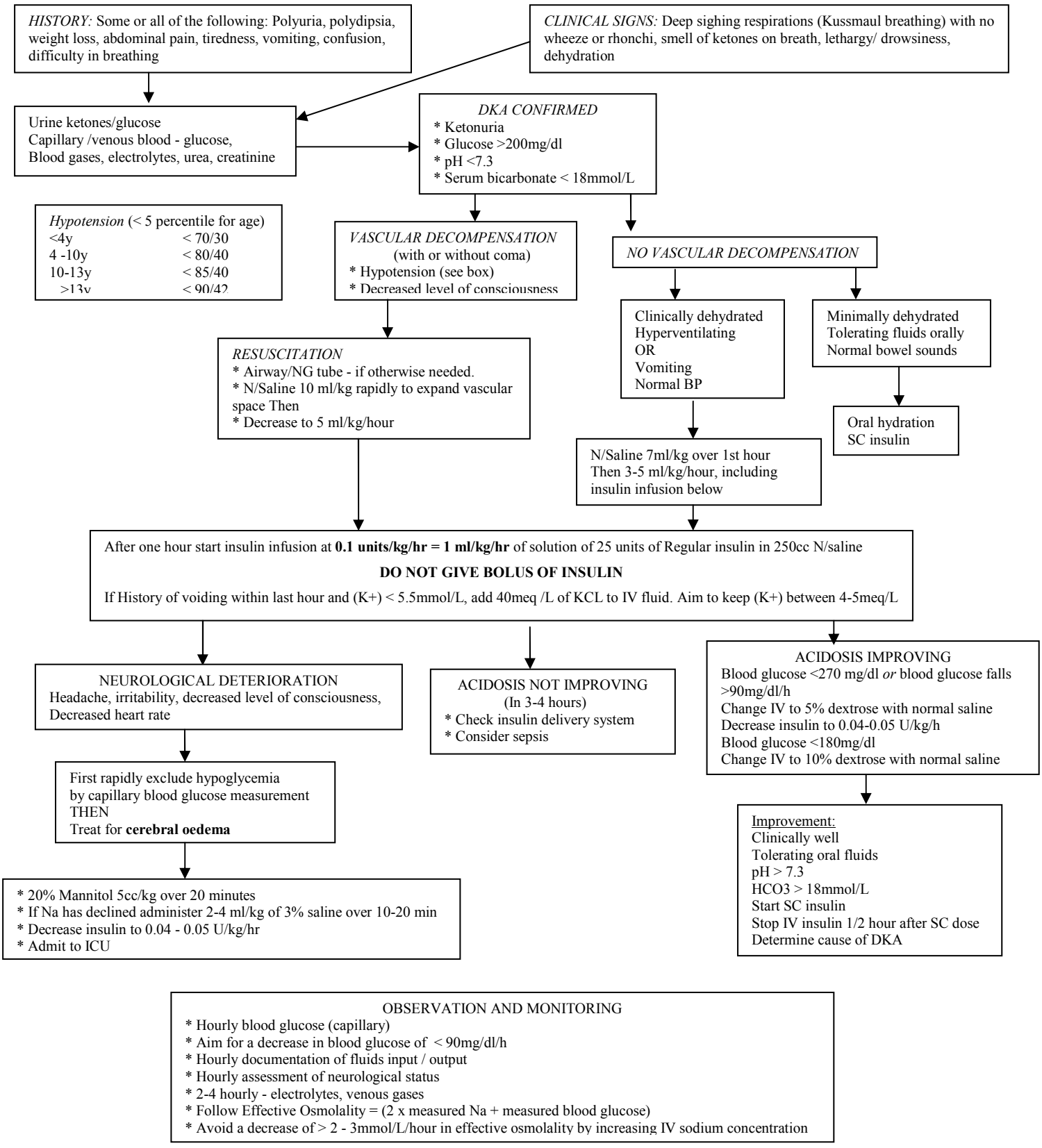
DKA is the most frequent diabetes-related cause of death in children. Acute cerebral oedema, accounts for 75-87% of the mortality in DKA[10]. Cerebral oedema is more likely to occur in patients at the time of first diagnosis of diabetes, younger children, and those presenting with the most severe degree of dehydration and metabolic derangement[7]. It typically develops within the first 24 hours of treatment of DKA[6]. Symptoms and signs include headache, confusion, slurred speech, bradycardia, hypertension and other signs of increased intracranial pressure. A common proposed mechanism of cerebral oedema involves a rapid decline in serum osmolality[10]. Rapid administration of fluid, hypotonic fluids, insulin boluses and rapid drop in blood sugar all can cause a rapid decline in serum osmolality during the treatment of DKA[10].

Management of cerebral oedema should be initiated with clinical suspicion without waiting for a radiological diagnosis. It is aimed at lowering intracranial pressure by prompt administration of IV mannitol or hypertonic saline and preventing rapid drop in serum osmolality by reducing rates of fluid and insulin administration[4,5]. Tracheal intubation to mechanically hyperventilate and surgical decompression with ventriculostomy are less successful at preventing mortality or severe disability. Intracranial imaging to exclude other pathologies, such as cerebral infarction or thrombosis, should be obtained but not at the expense of timely therapeutic interventions[1,5,9].

Conclusion

DKA is the major cause of severe morbidity and mortality in children with T1DM. However they can be managed successfully with minimal complications by early recognition and proper fluid and electrolyte management aimed at avoiding rapid drop in plasma osmolality.

DKA MANAGEMENT ALGORITHM



OBSERVATION AND MONITORING

* Hourly blood glucose (capillary)
* Aim for a decrease in blood glucose of < 90mg/dl/h
* Hourly documentation of fluids input / output
* Hourly assessment of neurological status
* 2-4 hourly - electrolytes, venous gases
* Follow Effective Osmolality = (2 x measured Na + measured blood glucose)
* Avoid a decrease of > 2 - 3mmol/L/hour in effective osmolality by increasing IV sodium concentration

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