First Line Management of Adult Diabetic Ketoacidosis Patients

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ABSTRACT

Background: Diabetic Ketoacidosis (DKA) is a hyperglycemic crisis that can occur in patients with both type 1 and 2 diabetes mellitus. It is a medical emergency with a significant morbidity and mortality. It is however a potentially reversible condition in case an emergency and immediate medical attention, prompt recognition, diagnosis and treatment were provided.

Aim of the Study:was to leverage the current research data in order to construct a treatment guideline for diabetic ketoacidosis in the emergency department.

Methods:A literature search was carried out on MEDLINE (including MEDLINE in-process), CINAHL,Embase and the Cochrane Library. Databases using "diabetic ketoacidosis" as a MeSH heading and as textword. High yield journals were also hand searched.

Findings: The initial treatment phase aims to restore circulating volume, reduce blood glucose levels, to correct any electrolyte imbalances and to reduce ketone levels which in turn corrects the acidosis. Evidence also showed that there is no need for insulin bolus prior to starting an insulin drip in the treatment of diabetic ketoacidosis. Also, using beta-hydroxybutyrate at presentation can expedite diagnosis and therefore treatment. Implementing treatment guidelines into the emergency department may help expedite diagnosis and treatment.

Conclusion: Prompt first line management of DKA is the most critical stage to profoundly reduce morbidity and mortality rates of this potentially fatal crisis. It's therefore crucial to follow the evidence-based guidelines and DKA protocol in the emergency department to expedite diagnosis, guide treatment, and improve continuity of care between the emergency department and the ICU as well as improving the clinical outcomes of patients with DKA. Initially, this will improve outcomes by decreasing the delay until treatment is initiated andprovide a continuum of treatment between the emergency department and the intensive care unit.

Furthermore, the healthcare providersmust ensure that they have the ability to provide support and education to people at risk of developing DKA and those that have had an episode of DKA by spreading awareness and education to help reduce both the initial occurrence and recurrence of this often preventable life-threatening condition.

Keywords: Diabetes complications, DKA, Ketosis, Diagnosis, Pathogenesis Type 1 diabetes Type 2 diabetes.

INTRODUCTION

Diabetic ketoacidosis (DKA) is a serious medical emergency resulting from relative or absolute insulin deficiency and the unopposed action of counter-regulatory hormones, such as glucagon, cortisol, and catecholamines[1].Omission of insulin is the most common precipitant of DKA[2]. Infections, acute medical illnesses involving the cardiovascular system (myocardial infarction, stroke) and gastrointestinal tract (bleeding, pancreatitis), diseases of the endocrine axis (acromegaly, Cushing's syndrome), and stress of recent surgical procedures can contribute to the development of DKA by causing dehydration, increase in insulin counter-regulatory hormones, and worsening of peripheral insulin resistance. Medications such as diuretics, beta-blockers, corticosteroids, antipsychotics, and/or anticonvulsants may affect carbohydrate metabolism and volume status and, therefore, could precipitate DKA. Other factors that may contribute to DKA include psychological

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problems, eating disorders, insulin pump malfunction, and illegal substance use[3].It is now recognized that new-onset type 2 diabetes mellitus can manifest with DKA[4]. These patients are obese, mostly African Americans or Hispanics, and extremely insulin resistant on presentation[5].

Experimental studies suggest that metabolic acidemia can impair myocardial contractility, reduce cardiac output, affect oxyhemoglobin dissociation and tissue oxygen delivery, inhibit intracellular enzymes, such as phosphofructokinase, alter cellular metabolism, and result in vital organ dysfunction [6].Thus, the target of therapy in DKA has historically placed importance on the rapid reversal of acidemia, in addition to the correction of dehydration and insulin deficiency[7].

DKA is a complex medical emergency with several stages to the treatment, involving reassessment at every stage. Upon initial treatment of DKA in the emergency department, there are varying methods regarding insulin management. Practice differs from some using old guidelines published by the American Diabetes Association (ADA), some adhere to the most recent Consensus Statement from the ADA, while others do not follow any guidelines at all [8]. Currently, there is not a treatment protocol regarding the initial treatment of DKA in the Intermountain Urban Central Region. Treatment varies in the amount of insulin given as well as fluid replacement. Implementation of a DKA protocol reduces practice variation and has been associated with a short length of stay and a trend toward decreased cost[9].The clinical significance of following a protocol is to standardize evidence-based treatment of DKA patients, therefore improving clinical outcomes and decreasing cost. Improving emergency department treatment will also be done by staff training and expediting treatment.

Diabetic ketoacidosis (DKA) can be preventable, however remains a frequent and life threatening complication of type 1 diabetes. Unfortunately, errors in its management are common and importantly are associated with significant morbidity and mortality. Most acute hospitals have guidelines for the management of DKA but it is not unusual to find these out of date and at variance to those of other hospitals[10]. Even when specific hospital guidelines are available audits have shown that adherence to and indeed the use of these is variable amongst the admitting teams.

The presentreview explores the first line ofassessment,optimal treatments, and the importance of communication with adult DKA patients.

MATERIALS AND METHODS

Literature search

Data Sources:electronic databases were searched: MEDLINE (including MEDLINE in-process), CINAHL, Embaseand the Cochrane Library (from 1980).

Internetsearch engines such as Google Scholar and EMGoogle, a focused emergency medicine search engine were also explored.

Search terms diabetic ketoacidosis (DKA), insulin therapy, bolus, adult, treatment guideline, and beta-hydroxybutyrate +/complications

Data extraction

Study selection and eligibility criteria

- Full text articles and studies conducted in English language.
- Abstracts were also be included to assess variety of treatment guidelines and outcomes.
- Study Type: Meta-analysis, practice guidelines, systematic review, and randomized control trials in line with the study end point.
- Population: Adults > 18 years old as this protocol will primarily be used for adults.

Pathophysiology

DKA is a state which can occur in those with diabetes, particularly type I diabetes; where the destruction of beta cells causes a complete deficiency of insulin. It is common in patients with newly diagnosed type I diabetes or may be the event which leads to the diagnosis of the common long term condition[11]. DKA can also occur at any time if triggered by another factor, most commonly poor insulin control or infection. Less frequent causes include myocardial infarction, pulmonary embolism, cerebral accidents or protractedvomiting[12], as well as pancreatitis and drugs [13].

DKA occurs when three events take place within the body; hyperglycemia, ketosis and acidosis. Hyperglycemia occurs as a result of the deficiency of insulin apparent in type I diabetes in combination with an increase in hormones released in response to stress, such as glucagon, cortisol, catecholamine, epinephrine and growth hormone[14].Deficiency of Insulin prevents glucose being utilized by tissues within the body and also increases gluconeogenesis in the liver, both resulting in hyperglycaemia[11].

Insulin deficiency and the increased production of hormones also cause lipolysis to occur. This is the breakdown of fatty acids in the body and results in the release of Acetyl-coA, which in turn, is converted into ketones; acetone, acetoacetate and most importantly beta-hydroxybutyrate. This is ketosis and is what causes acidosis to occur. Beta-hydroxybutyrate can initially be present in the body without the presence of acidosis as the acidity is buffered by bicarbonate in the body, resulting in low bicarbonate in the blood until reserves become depleted and acidosis takes over [12].

In order to deal with hyperglycemia, the body attempts to excrete the excess glucose in the urine along with water, causing polyuria and resulting in dehydration. UK research has found that patients in a state of DKA can experience up to six litres of fluid loss[15]. This in turn causes an electrolyte imbalance in the body which also later needs to be addressed once the immediate threat to life has been removed[16].

KETONES AND ACIDOSIS

Until recently, management of DKA has focused on lowering the elevated blood glucose with fluids and insulin, using arterial pH and serum bicarbonate to assess metabolic improvement. This is based on the assumption that this would efficiently suppress ketogenesis and reverse acidosis. This strategy recognized that blood glucose is only a surrogate for the underlying metabolic abnormality. Recent developments now allow us to focus on the underlying metabolic abnormality (ketonaemia) which simplifies treatment of those who present with modest elevation of blood glucose but with acidosis secondary to ketonaemia 'euglycaemic diabetic ketoacidosis' [17]. This clinical presentation is being encountered more frequently. Improved patient education with increased blood glucose and ketone monitoring has led to partial treatment of DKA prior to admission with consequent lower blood glucose levels at presentation.

DKA DIAGNOSIS and Assessment.

Table 1: Diagnostic criteria for diabetic ketoacidosis (DKA)[18]

Measure	Mild	Moderate	Severe
Plasma glucose level, mmol/l	13.9	13.9	13.9
Arterial or venous pH	7.25–7.30	7.00–7.24	<7.00
Bicarbonate level, mmol/l	15–18	10–14	<10
Urine or blood acetoacetate (nitroprusside reaction)	Positive	Positive	Positive
Urine or blood β-hydroxybutyrate, mmol/l	>3	>3	>3
Effective serum osmolality, mmol/kg*	Variable	Variable	Variable
Anion gap, mmol/l	>10	>12	>12
Alteration in sensorium	Alert	Alert or drowsy	Stupor or coma

*Defined as 2[measured Na^+ (mEq/l)] + [glucose (mmol)].

DKA TREATMENT

Fluid Resuscitation

Fluid resuscitation is one of the key elements in the treatment of DKA as intravascular, intracellular, and interstitial volumes are all reduced in hyperglycemic crisis.The aim to treatment of DKA is to restore circulating volume, reduce blood glucose levels, correct any electrolyte imbalances and to reduce ketone levels therefore correcting acidosis. The following interventions should take place within the first hour following admission[19].

The ADA recommends initial fluid resuscitation with 0.9% normal saline, a crystalloid fluid, which will be recommended in the treatment guidelines[2].Different authors recommend varying approaches to the initial fluid resuscitation goal[2],recommend initial fluid

replacement at 15-20 mL / kg body weight within the first hour, or 1-1.5 liters within the first hour followed by 0.45% NaCl at 250-500 mL/hr, with 0.9% NaCl used in cases with hyponatremia. Another regimen of 500 ml/hr of 0.9% saline for the first four hours in DKA has been recommended [20]. Another study reported that an initial infusion of 1-1.5 liters of 0.9% saline is appropriate in most cases. In a prospective, randomized trial involving patients with no associated illness[21], while Caputo et al.[22] found no significant difference between fluid administration rates of 500 mL/hr and 1000 mL/hr on outcomes regarding morbidity, mortality, ketoacidosis correction, or anion gap closure.

According to these results, emergency guidelines will recommend initial fluid resuscitation of 1.5 liters 0.9% normal saline bolus within the first hour, following recommendations from the ADA Consensus Statement[2]. Also, according to Caputo *et al.*[22], administration of moderate fluids also helps to reduce cost. Further fluid replacement is dependent upon hemodynamics, state of hydration, urinary output, and serum electrolyte levels[2]. Aggressive fluid resuscitation should be utilized in hypotensive patients with isotonic saline until blood pressure normalizes [23].
English & Williams (2004) recommend that colloid fluid should be considered for initial fluid management if the systolic blood pressure is<100 mmHg.

On the contrary, Conversely, Savage *et al.*[24] recommends against colloid because the hypotension that results in DKA is from a loss of electrolyte solution, and it is more physiological to replace with crystalloid fluid. A Cochrane review did not support the use of colloid in preference to crystalloid fluid [25].

Maintenance Fluid

Recommendations on fluid maintenance varied among authors. Chaithongdi et al.[23] has recommended that the fluid replacement goal should be met within 12-24 hours, while Kitabchi et al.[2] similarly recommends goals for fluid replacement should correct estimated deficits within the first 24 hours. Kitabchi recommends that 0.45% normal saline infused at 250-500 ml/hr is appropriate if corrected serum sodium is normal or elevated; 0.9% normal saline at a similar rate if corrected serum sodium is low (2009). Similarly, once glucose has fallen below hyperglycemic levels, intravenous infusion is switched to a solution containing glucose to facilitate the closure of the anion gap, such as D5W to avoid hypoglycemia[2]. Since the maintenance fluid phase of DKA typically occurs in the ICU setting, the current ICU protocol will be implemented in the treatment guidelines.

Insulin

Treatment of hyperglycemia in DKA through an insulin drip is a well-established treatment practice. In a Cochrane review, Fisher, Shahshahani, &Kitabchi[26] established that insulin falls fastest in the first two hours in DKA with insulin given intravenously, and that this is the preferred route. The data also confirmed the efficacy of low-dose insulin therapy for DKA[26]. Wagner et al. [27] established the use of very low dose insulin treatment for DKA. The results of their study indicated that very low dose insulin was useful to prevent the rapid fall in blood glucose or rapid electrolyte displacement[27]. Regular and glusiline insulin have been found to be equally effective during the treatment of DKA [28].

Insulin bolus vs. continuous insulin infusion

As a general practice, Insulin treatment has been initiated with an insulin bolus in adult patients with DKA. In 1980, a Cochrane review showed that an insulin bolus was not necessary in the treatment of DKA in children[29]. Although pediatric guidelines have not recommended treating DKA with an insulin bolus for quite some time, this change has lagged behind in the treatment of the adult population. The most recent ADA Guidelines from 2004 recommend an insulin bolus to begin insulin therapy (ADA, 2004). However, a consensus statement from the ADA in 2009 recommended that an insulin bolus is no longer necessary[2]. It was found that there was no significant difference between receiving an insulin bolus and no insulin bolus in regards to hypoglycemia, rate of glucose change, or length of stay in the emergency department or hospital [30].

Table 2:DKA Treatment recommendation guidelines and doses by the included studies.

Authors	Study Type	Study year	Initial Bolus	Maintenance Fluid
Caputo et al.[22]	Prospective Randomized Study	1997	Found nodifference between 500mL/hr and 1000mL/hr	Not included
Hardern& Quinn[20]	Review	2003	500 ml/hr for first 4 hrs	250 ml/hr for the next 4 hrs
Kitabchi et al.[2]	Review	2009	15-20 ml/kg within first hr, or 1-1.5 L NS	250-500 ml/hr
Savage et al.[24]	Review	2011	Replace fluid deficit	deficit Caution overhydration d/t risk of cerebal edema
Chaithongdi et al.[23]	Review	2011	1-2 Liters in the first hour, additional liter in 2nd hour	3-5th hr: 500-1000 mL/hr 6th-12th hr: 250-500 ml/hr

Sodium Bicarbonate

Due to the extreme acidosis that can result in metabolic pathways in DKA, sodium bicarbonate has been considered in treatment to correct this pH abnormality. Jearreat[31] reported that sodium bicarbonate in DKA is controversial, and not usually used. In a study done comparing sodium bicarbonate for metabolic acidosis in DKA, the authors showed that the patients who received sodium bicarbonate did not have improved glycemic control or clinical efficacy. There was also evidence that the bicarbonate administration prolonged hospitalization, as well as increased the risk for cerebral edema. The researchers concluded that there is no evidence to justify the administration of bicarbonate in the emergent treatment of DKA, due to the lack of benefits as well as the possibility for clinical harm [32]. These results were in line with a previous randomized control study done in 1991 that showed no improvement in outcomes in patients treated with sodium bicarbonate [33]. In a review done by Kitabchi*et al.*, it was reported that multiple studies done have not shown any beneficial effects of using sodium bicarbonate, and they do not recommend it in pH >6.9. However, in extreme acidosis with pH values.

Communication

Guidelines recommend that following admission with DKA, the diabetes specialist team are contacted as soon as possible, ideally within the first hour[19] and that they are seen by the team within 24 hours[34]. Poor insulin control was one of the most common causes of DKA and is most likely the cause of patients' admission with DKA. Research has found that adherence is lowest in certain health conditions, of which one is diabetes [35]. Therefore it is important to investigate why some patients, do not adhere to the recommended insulin regime prescribed by medical specialists. Communication with patients has been proven to be essential for patient education and therefore compliance [36].

A meta-analysis of research into the impact of socio-economic status (SES) of the patient on patient-physician communication has found that patients with lower SES experience less effective communication. Physicians often assume that patients of lower SES have less desire for information or less understanding and therefore physicians are less informative; however, ineffective communication is not entirely the fault of the health care professionals. Patients with lower SES often have a more passive communication style, meaning they ask fewer questions, express less opinions and less desire to make decisions [37].This emphasises the need for two way communication and encouraging patients to express their needs, opinions and to make fully informed decisions about their own care. A study into communication between physicians and patients with diabetes found that those with poor functional health literacy, often linked to lower SES, were more likely to be under informed about their condition and how to manage it

[38].This suggests that physicians need to tailor their communication to individual patients, taking into consideration their literacy levels in order to optimise patient understanding and therefore compliance.

DKA Protocol

Researchers found that using a protocol reduced the DKA resolution time and hypoglycemic events. In a retrospective chart review of an algorithm-based protocol for the management of DKA (in which the protocol was not provided), researchers found that using a protocol reduced the DKA resolution time and hypoglycemic events. Use of the protocol was also associated with improved clinical measures of DKA management[39]

Also, there was no increased rate of electrolyte imbalance. Use of the protocol was associated with improved clinical measures of DKA management [39].Therefore, implementing an evidence-based guideline for the treatment of DKA to be initiated in the emergency department may improve the clinical outcomes of DKA. Initially, this will improve outcomes by decreasing the delay until treatment is initiated. Also, a treatment guideline will help to address gaps in practice and provide a continuum of treatment between the emergency department and the intensive care unit.

CONCLUSION

Timely first line management of DKA is very critical to save patients' lives. It's crucial to follow the correct guidelines in the emergency department is to expedite diagnosis, guide treatment with evidence-based rationale, and improve continuity of care between the emergency department and the ICU. A strong body of evidence suggests that following the guideline for the treatment of DKA -to be initiated in the emergency department- may significantly improve the clinical outcomes of patients with DKA. Initially, this will improve outcomes by decreasing the delay until treatment is initiated. Also, a treatment guideline will help to address gaps in practice and provide a continuum of treatment between the emergency department and the intensive care unit.

Furthermore, a combination of communication techniques should be used and factors such as socioeconomic status and level of heath literacy should be taken into account to ensure the best outcome for the patient, and to prevent future readmissions with DKA. The healthcare professional should ensure that they have the ability to provide support and education to people at risk of developing DKA and those that have had an episode of DKA; it is important to re-enforce the ongoing education to help reduce both the initial occurrence and recurrence of this often preventable life-threatening condition.

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