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Guidelines and controversies in the management of diabetic ketoacidosis – A mini-review

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Abstract

Diabetic ketoacidosis (DKA) is a complication seen in patients with both type 1 and type 2 diabetes. Due to its large, growing economic impact with associated morbidity, closer look at proper management is important. Factors involved in appropriate management involves fluid resuscitation, insulin regimen, and electrolyte replacement including types of fluid and insulin treatment. The caveat with generalized protocol is application to special populations such as renal or heart failure patients the sequelae of complications due to pathophysiology of the disease processes. This leads to complications and longer length of stay in the hospital, therefore, possibly increased cost and resource utilization during the hospitalization. This review takes a closer look at current guidelines of DKA management and resource utilization, the drawbacks of current management protocols and the cost associated with it. Therefore, a need for amendment to existing protocol or initiation of a newer guideline that properly manages DKA should incorporate special populations and appropriate regimen of fluid resuscitation, insulin therapy and electrolyte management.

Key words: Diabetic ketoacidosis management; Fluid resuscitation; Insulin regimen; Electrolyte replacement

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Core tip: Diabetic ketoacidosis (DKA) management in both type 1 and type 2 has been in practice for many years, yet the complications and cost associated with it is ever increasing. Treatment with proper resource utilization is the key to appropriate management of DKA, decreased complications and length of stay, therefore, decreased cost of treatment. This review aims to review previous guidelines, choice of therapy, cost

associated with it and need for amendments to existing protocols to increase efficacy of DKA treatment, decrease complications and decrease economic burden due to mismanagement of DKA.

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INTRODUCTION

Diabetic ketoacidosis (DKA) is a metabolic disorder that is common but preventable complication of diabetes often, as a result of insulin deficiency^[1]. The metabolic disorder itself is hyperglycemia with increase in ketones circulating in the body leading to ketoacidosis^[2]. DKA is a significant contributor of mortality and morbidity in type 1 diabetes mellitus (T1DM) patients and most common reason for hospitalization of T1DM patients and therefore contributes significantly to hospital costs. Healthcare costs in events of ketosis are high in patients with T1DM patients, adults and children alike. The number of hospital admissions secondary to DKA have steadily increased worldwide with a decrease in total length of stay^[3]. The in-hospital mortality has decreased, however the cost of hospitalizations has increased significantly^[4]. This literature review focuses to analyze the current practice and guidelines followed for the management of DKA.

SEARCH

MEDLINE (*via* PubMed) and EMBASE databases were searched for articles published between 1 January 2000 and 31 December 2017 (date of search execution) by a single review author. The terms used to search the databases for relevant articles were - "Management of DKA", "Guidelines for DKA" and "Cost/Burden of DKA". Only human studies published in English were included.

TREATMENT STRATEGY FOR DKA

Management of DKA includes optimizing volume status, glucose levels, ketoacidosis, electrolyte abnormalities and precipitating factors. The current protocols for DKA management calls for fluid resuscitation with goal of volume repletion within 24-36 h with 50% of resuscitation fluid administered within first 8-12 h of presentation^[5]. Protocols are in place to optimize DKA management. Prior to protocol implementation, the mean intensive care unit (ICU) unit stays were 44+/-28 h, and hospital lengths of stay were 91+/-73 h. After implementation of protocols, ICU stays have decreased

23% to 34+/-18 h. and mean hospital lengths of stay have decreased 30% to 64+/-41 h of stay^[6].

Current guidelines recommend initiating volume repletion with isotonic saline (0.9% NaCl). Further volume repletion with the type of IV fluid is based on corrected serum sodium. To manage hyperglycemia, current guideline has options for insulin use either *via* intravenous or Subcutaneous/Intramuscular route. The other focus of therapy is to correct electrolytes (particularly sodium, potassium, phosphorus and magnesium) as necessary and avoid over correction. With management of DKA comes management of acid/base level as well. Bicarbonate supplementation is recommended only for pH < 6.9.

CONTROVERSIES

Although the mainstay in DKA management is regular insulin either *via* either IV continuous infusion or frequent subcutaneous or intramuscular injections, the question remains regarding the bolus dose of insulin, ideal route of insulin therapy and the cost associated with it. According to current guidelines of DKA management, an IV insulin bolus dose is recommended followed by continuous infusion. However, in a prospective observational study it was observed that administration of an initial bolus dose of insulin was not associated with significant benefit to DKA patients and was noted to be on similar efficacy and results when compared to patients who were not administered bolus dose of insulin^[7]. On the other hand, for most practicing clinicians and experts, IV regular insulin after initial bolus dose of insulin still remains the preferred route due to delayed onset of action^[8]. Although treating patients with IV insulin causes rapid decline in plasma glucose and ketone levels, the cost of DKA treatment with IV insulin is higher due to management of DKA requiring ICU admission or specialized care unit requiring continuous IV insulin infusion^[9]. In a recent small randomized study including 3 studies in adults and 1 study including pediatric population, it was observed, patients with mild-to-moderate DKA, SC insulin lispro every 1 to 2 h conferred an alternative to continuous IV regular insulin^[10].

EFFICACY OF PROTOCOL DRIVEN TREATMENT

Studies have shown that protocol driven management of DKA is safe and efficient with decreased length of stay^[11]. In a retrospective study, the efficacy of protocol driven management of DKA was studied in teaching hospital in the United States based on 2009 American Diabetes Associations guidelines. Patients undergoing this protocol had resolution of DKA within approximately 10 h^[12]. However, the protocol driven care of DKA differs based on different institutions. For example,

retrospective study in the United Kingdom showed that universal protocol was not adhered to for reasons including patient and clinician factors^[13]. Other studies revealed that low adherence was prevalent as a result of discontinuation of medical care, staffing issues^[14].

SPECIAL POPULATION

Another deficit of following current protocols is the failure to address DKA management in special patient populations such as patient with chronic kidney disease or congestive heart failure or both. For example, in chronic kidney diseases (CKD) patients, osmotic diuresis due to hyperglycemia fails to occur, therefore leading to extracellular volume expansion. If according to current protocol fluid resuscitation is undertaken fatal consequences can pursue. Similarly, potassium replacement is vital in management of DKA. Potassium excretion is often impaired in patients with renal injury or failure. Therefore, potassium supplementation according to current protocol can result in life-threatening hyperkalemia. In addition, insulin is renally excreted, therefore, dose adjustment of insulin is needed in CKD patients^[15]. Application of general DKA protocol to all patient populations can be dangerous to patients leading to complications and longer hospital stays. General DKA protocol in renal or heart failure patients can be detrimental due to over treatment with fluids and exacerbating fluid status and the sequelae associated in such fluid sensitive patient populations. Therefore, increasing costs of for hospitalization and treatment of DKA.

NEW GUIDELINES/RECONSIDERATION

In a review study of efficacy of DKA treatment according to Joint British Diabetes Society protocol, it was revealed that guideline adherence in DKA management is of benefit in the immediate stage of treatment. But inadequate fluid or electrolyte management, inadequate metabolic monitoring, iatrogenic hypoglycemia continues to be area of concern^[16]. This often precludes to avoidable consequences that leads to longer duration of hospital course, cost, both health and economic, associated with mismanagement of DKA for patients. Therefore, it seems appropriate to highlight the need for nursing education on timely administration of fluids, hourly laboratory draws, and administration of insulin.

Due to hyperglycemia in DKA causing osmotic diuresis and severe dehydration, the mainstay of treatment is rehydration. Traditional treatment as mentioned above is "one bag protocol (1 liter/bag)" with normal saline and supplemental electrolytes vs "two bag protocol (1 liter/bag)" that includes two bags of fluids, one containing saline and supplemental electrolytes and another bag containing same solution with additional 10% dextrose. Closure of anion gap was noted to be

earlier (10 h) with "two bag protocol" compared to "one bag protocol" (14 h). Hyperglycemia was also noted to improve faster in "two bag protocol" (7 h) compared to "one bag protocol" (9 h)^[17]. Whether or not this affects length of hospital stay in the long term is difficult to assess but should be explored in future prospective studies. Similarly, prospective studies on efficacy and cost effect on treatment of DKA with subcutaneous insulin vs IV insulin infusion need to be pursued.

CONCLUSION

Given the increasing cost burden on management of diabetes, with large proportion attributed to DKA management and hospitalization, it is appropriate to readdress guidelines for management of DKA. While current protocol for DKA management has been standard use, it is important to address the efficacy of it. Therefore, there is a need for new protocol where treatment with subcutaneous insulin vs IV insulin infusion, "one bag protocol" vs "two bag protocol," and management of DKA in special populations should be addressed.

REFERENCES

1. Seth P, Kaur H, Kaur M. Clinical Profile of Diabetic Ketoacidosis: A Prospective Study in a Tertiary Care Hospital. *J Clin Diagn Res* 2015; **9**: OC01-OC04 [PMID: 26266145 DOI: 10.7860/JCDR/2015/8586.5995]
2. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2017
3. Maldonado MR, Chong ER, Oehl MA, Balasubramanyam A. Economic impact of diabetic ketoacidosis in a multiethnic indigent population: analysis of costs based on the precipitating cause. *Diabetes Care* 2003; **26**: 1265-1269 [PMID: 12663608 DOI: 10.2337/diacare.26.4.1265]
4. Dhatariya KK, Skedgel C, Fordham R. The cost of treating diabetic ketoacidosis in the UK: a national survey of hospital resource use. *Diabet Med* 2017; **34**: 1361-1366 [PMID: 28727175 DOI: 10.1111/dme.13427]
5. Rosival V. Management of adult diabetic ketoacidosis. *Diabetes Metab Syndr Obes* 2014; **7**: 571-573 [PMID: 25489249 DOI: 10.2147/DMSO.S73896]
6. Bull SV, Douglas IS, Foster M, Albert RK. Mandatory protocol for treating adult patients with diabetic ketoacidosis decreases intensive care unit and hospital lengths of stay: results of a nonrandomized trial. *Crit Care Med* 2007; **35**: 41-46 [PMID: 17095944 DOI: 10.1097/01.CCM.0000249825.18677.D2]
7. Goyal N, Miller JB, Sankey SS, Mossallam U. Utility of initial bolus insulin in the treatment of diabetic ketoacidosis. *J Emerg Med* 2010; **38**: 422-427 [PMID: 18514472 DOI: 10.1016/j.jemermed.2007.11.033]
8. Fisher JN, Shahshahani MN, Kitabchi AE. Diabetic ketoacidosis: low-dose insulin therapy by various routes. *N Engl J Med* 1977; **297**: 238-241 [PMID: 406561 DOI: 10.1056/NEJM197708042970502]
9. Vincent M, Nobécourt E. Treatment of diabetic ketoacidosis with subcutaneous insulin lispro: a review of the current evidence from clinical studies. *Diabetes Metab* 2013; **39**: 299-305 [PMID: 23642642 DOI: 10.1016/j.diabet.2012.12.003]
10. Kearney T, Dang C. Diabetic and endocrine emergencies. *Postgrad Med J* 2007; **83**: 79-86 [PMID: 17308209 DOI: 10.1136/

- pgmj.2006.049445]
- 11 **Waller SL**, Delaney S, Strachan MW. Does an integrated care pathway enhance the management of diabetic ketoacidosis? *Diabet Med* 2007; **24**: 359-363 [PMID: 17298587 DOI: 10.1111/j.1464-5491.2007.02102.x]
 - 12 **Hara JS**, Rahbar AJ, Jeffres MN, Izuora KE. Impact of a hyperglycemic crises protocol. *Endocr Pract* 2013; **19**: 953-962 [PMID: 23807521 DOI: 10.4158/EP13077.OR]
 - 13 **Devalia B**. Adherence to protocol during the acute management of diabetic ketoacidosis: would specialist involvement lead to better outcomes? *Int J Clin Pract* 2010; **64**: 1580-1582 [PMID: 20846206 DOI: 10.1111/j.1742-1241.2010.02348.x]
 - 14 **Agarwal A**, Yadav A, Gutch M, Consul S, Kumar S, Prakash V, Gupta AK, Bhattacharjee A. Prognostic Factors in Patients Hospitalized with Diabetic Ketoacidosis. *Endocrinol Metab* (Seoul) 2016; **31**: 424-432 [PMID: 27586452 DOI: 10.3803/EnM.2016.31.3.424]
 - 15 **Varma R**, Karim M. Lesson of the month 1: Diabetic ketoacidosis in established renal failure. *Clin Med (Lond)* 2016; **16**: 392-393 [PMID: 27481389 DOI: 10.7861/clinmedicine.16-4-392]
 - 16 **Sidana JK**, Phillips C, Sinha A, Levy N. Therapeutic challenges in the management of diabetic ketoacidosis. *J Intensive Care Soc* 2016; **17**: 353-355 [PMID: 28979521 DOI: 10.1177/1751143716638376]
 - 17 **Munir I**, Fargo R, Garrison R, Yang A, Cheng A, Kang I, Motabar A, Xu K, Loo LK, Kim DI. Comparison of a 'two-bag system' versus conventional treatment protocol ('one-bag system') in the management of diabetic ketoacidosis. *BMJ Open Diabetes Res Care* 2017; **5**: e000395 [PMID: 28878933 DOI: 10.1136/bmjdr-2017-000395]

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