Current Treatment of DKA
A Review and Approach to Establishing a Best Practice Protocol

Max Qually
Dr. Ricardo Lebato de Faria
5/6/2015

A capstone project submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements for the degree of MASTER OF PHYSICIAN ASSISTANT STUDIES.
# Table of Contents

ABSTRACT .............................................................................................................................. 3  
INTRODUCTION ...................................................................................................................... 4  
BACKGROUND ....................................................................................................................... 5  
METHODS .................................................................................................................................. 6  
RESULTS AND RECOMMENDATIONS ...................................................................................... 7  
  DKA MANAGEMENT STRATEGIES ....................................................................................... 7  
  DIAGNOSIS, MONITORING, AND BETAHYDOXYBUTERATE ................................................. 12  
  USE OF PROTOCOLS ............................................................................................................... 15  
  DKA TEAMS .......................................................................................................................... 17  
DISCUSSION ............................................................................................................................ 17  
CONCLUSION ............................................................................................................................ 19  
ACKNOWLEDGMENTS .............................................................................................................. 19  
APPENDIX A ............................................................................................................................ 21  
APPENDIX B ............................................................................................................................ 22  
BIBLIOGRAPHY ....................................................................................................................... 26
Abstract
Diabetic ketoacidosis (DKA) is a life threatening complication of diabetes, with profound implications for patients and the healthcare system\(^1\). Effective treatment of DKA depends on early diagnosis and initiation, followed by timely and accurate monitoring of the disease process\(^1\). Emphasis was placed on how to manage DKA efficiently, to decreased patient length of stay, without compromising patient safety. This article addresses the underutilization of point of care beta-hydroxybuteric acid (βOHB) meters for diagnostic and treatment guidance. The use, and safety, of point of care βOHB meters for diagnostic and treatment guidance are examined. Improved utilization of such devices may present an opportunity to improve patient outcomes and decrease patient lengths of stay\(^2\).

Methods: Using Scopus, PubMed, and Google Scholar search engines, a review of English, peer reviewed literature of the past 10 years on the diagnosis and management of DKA was constructed. Careful consideration has allowed recommendations presented here to be in agreement with the Canadian Diabetic Association's Clinical Practice Guidelines\(^3,4\). A best practice protocol order set was produced; ready for implementation at WRHA community hospitals.

Results and Recommendations: Effective treatment of DKA requires early diagnosis, fluid and electrolyte repletion, insulin therapy, and constant monitoring. Treatment strategies have been researched with the goal of diminishing patient length of stay without compromising patient safety.

Conclusion: Recommended DKA treatments presented here are optimized when such treatments involve the use βOHB meters for diagnosis and management of DKA. As well it is recommended that treatment strategies be directed via up to date best evidence protocol order sets. There is evidence that such order sets in conjunction with the use of such meters will provide a cost and safety benefit to hospitals and patients respectively\(^5\).
Introduction

The worsening diabetes epidemic has caused diabetic ketoacidosis (DKA) to become a growing problem in Canadian healthcare. According to the Canadian Medical Association Journal, the incidence of DKA is between 4.6 and 8.0 per 1000 person-years among patients with diabetes. These numbers have increased 30% in the past decade and continue to climb today. It is now estimated that up to 10,000 Canadians are admitted to hospital with DKA yearly. In 2009, the American Diabetic Association reported DKA to be responsible for an estimated 500,000 days of inpatient care in the United States alone. This has allowed annual national health care cost to balloon to estimates as high as $2.5 billion USD.

The commonality of DKA makes diagnosis and treatment a routine and common skill amongst emergency room doctors and staff. However, the risk of significant morbidity and mortality increases with delays in treatment initiation and monitoring. Thus, it is imperative that patients are treated quickly using the best available evidence. Treatment until resolution can be a labour intensive process requiring close monitoring and careful fluid administration, often necessitating high acuity unit (ACU) or intensive care unit (ICU) stays. This results in a substantial labour costs per patient; considerably higher than on general medicine wards. Reducing the treatment complications and patient length of stay can turn into significant savings to the health region while improving patient access to these vital resources.

The treatment process is vulnerable to delays in initiation due to logistic delays in reporting blood chemistry, miscommunication between staff, and poor compliance resulting in less than optimal outcomes. By placing treatment strategies into protocols, such delays can theoretically be decreased. A best practice protocol consisting of our recommendations was designed and proposed for possible implementation into emergency room practice in Seven Oaks General Hospital (SOGH). Herein currently available evidence concerning the optimal treatment of patients presenting with DKA is reviewed.
Background

Since 1985 there has been a tenfold increase in worldwide cases of diabetes mellitus (DM), a disease which is now regarded as a pandemic of global proportion\(^3\). In Canada it is estimated that 6.8% of the population, or 2.4 million people, had DM in 2009; this number far surpassed projected estimates made in 1998. It is expected that by 2019, 3.4 million people will have a diagnosis of DM in Canada, with an estimated $16.9 billion economic burden placed on the Canadian healthcare system\(^3\). Genetic susceptibility, environment, and socioeconomic status each present as risk factors for the disease\(^3\). As healthcare costs continue to rise, health authorities are looking for cost effective strategies for the management of DM and its many complications.

DKA is a state of life threatening hyperglycemia and metabolic acidosis is found in uncontrolled diabetic patients. Classically, DKA is thought of as a complication of T1DM, in which the patient is unable to produce insulin at all. However, given the increased prevalence of T2DM, these patients now make up one third of all DKA admissions\(^2\). Current estimates suggest that for every 1,000 admissions of patients with DM, 4 to 8 of them will be for DKA\(^1,11\). Current estimates place the average hospital stay at 3.6 days in Canada, with cerebral edema, particularly in children, being the most common cause of all case mortality\(^7\). DKA occurs primarily as a result of insufficient endogenous insulin, due to decreased secretion. In those with T2DM, increased peripheral insulin resistance also plays a role\(^11\). Peripheral tissues begin signaling pathways which send the body into a state of hyperglycemic fasting fat metabolism\(^1\). The liver then begins producing glucose via gluconeogenesis, glycogenolysis, and oxidation of fatty acids into ketone bodies including acetoacetate, acetone, and βOHB. The hyperglycemia combined with the ketonemia result in osmotic imbalance favoring a fluid shift toward the intravascular space pulling electrolytes such as potassium, sodium, chloride, phosphate, calcium and magnesium out of the intracellular environment\(^11\). DKA only takes hours to days to develop. Often there is an underlying etiology precipitating the attack\(^1\).
The rapid accumulation of high levels of βOHB allows clinicians the opportunity to use it as biochemical marker for DKA. Recently use of point of care serum βOHB meters, for diagnosis and management decisions has been shown to provide treatment benefit and reduction in hospital length of stay. While guidelines recommend the use of such devices, they appear to remain underutilized throughout Canada.

Methods

A review of current literature on the diagnosis and management of DKA was conducted. Scopus, PubMed, and Google Scholar were used to conduct searches of peer reviewed journal articles. Care was taken to ensure the recommendations within the Canadian Diabetes Association (CDA) recommendations on hyperglycemic emergencies are in accordance with recommendations presented here.

Within the guidelines the use of point of care βOHB meters and best practice protocol implementation are mentioned and recommended but poorly expanded upon. A literature search has allowed for a more in depth analysis of these recommendations.

Our treatment recommendations are then constructed into an up to date order set similar to order sets already in practice in hospitals. The design of our protocol is inspired by several available resources. The order and content are reflective of the WRHA Standard Reference Order Set for SOGH. Using documents from ThinkResearch.com as a guide and a template we established a new order set consisting of recommended practices in each area discussed above for the management of DKA. From these templates we were able to combine the already existing ER Diabetic Ketoacidosis (DKA) Order Set with the Transition from IV Insulin Infusion to Subcutaneous Insulin Post Diabetic Ketoacidosis (DKA) Episode Order Set into one seamless protocol. We also included some steps from the already existing and in practice Nurse Initiated Hyperglycemic Order Set from SOGH and added them in to the nursing section of our protocol. In addition we added recommendations of our own, when necessary, to ensure that our protocol was in agreement with the evidence presented above. Including recommendations
regarding insulin infusion rates, switch to subcutaneous insulin, and the use of βOHB meters. The final product, presented in Appendix B, is a pre-formatted draft that is subject to further refinement by any site looking to implement the guidelines it recommends.

Results and Recommendations

**DKA Management Strategies**

Definitive criteria for the diagnosis of DKA has not yet been established. The CDA suggests that correlation of acidemia (pH ≤7.3), decreased serum bicarbonate (≤15 mmol/L), an elevated anion gap (>12 mmol/L), with positive serum and or urine ketones, is diagnostic for DKA. High blood glucose readings are becoming less sensitive as the prevalence of euglycemic DKA appears to be rising. Management of DKA focuses on resolution of ketoacidosis, correction of electrolyte and glycemic imbalances, and investigations for, and treatment of, precipitating cause. Ideally patient will be admitted to an ACU or ICU as initial physical exams and blood testing as constant as every two hours is required. Patients require fluid and electrolyte replacement as well as insulin infusion. Careful monitoring of electrolytes, osmolality, and ketonemia is required to ensure patient safety. Serial venous blood gases are used to monitor pH and changing concentrations of electrolytes. In a typical DKA patient, sodium and water deficits can be as great as 7-10 mmol/L and 100mL/Kg respectively, with variable levels of serum osmolality, which can be as high as 320 mOsm/kg. Volume contraction is responsible for many symptoms of DKA, and must be addressed as quickly as possible.

Fluid repletion is an important step in the treatment of DKA as corrected fluid volumes improve tissue perfusion and increase glucose losses via increased diuresis. Although DKA treatment requires insulin infusion, fluid repletion alone, using crystalloid solutions, has been shown to reduce severity of hyperglycemia, decrease counter regulatory hormone production, and decrease peripheral insulin resistance. Care should be given, particularly in children, that hyperosmolarity not be corrected faster than 3 mOsm/L, as rapid correction has been associated with cerebral edema, one of the leading causes of
mortality in those with DKA\textsuperscript{4}. Patients presenting in shock should be given 1-2 litre intravenous boluses of isotonic saline\textsuperscript{7} over one hour\textsuperscript{4}. Once tissue perfusion is adequate, this rate should be slowed to 500 mL/hr for four hours, then reduced again to 250 mL/hr\textsuperscript{4}. For dehydrated patients with mild hypotension, hyponatremia should be assessed by using a corrected sodium level. Studies have shown that a correction factor of 2.4 is more accurate than traditional formulas which use 1.6\textsuperscript{1,17}. If the corrected sodium is in normal or hypernatremic range, switch to a reduced sodium fluid as indicated\textsuperscript{17}. Often half normal saline will be used once volume re-expansion has occurred. This is signified via hypo-osmotic diuresis. This strategy is intended to replace approximately 50\% of the fluid deficit in the first 12 hours safely\textsuperscript{1}.

Potassium levels are typically elevated at presentation as potassium exits the cell in exchange for hydrogen, a compensatory response to the worsening acidemia\textsuperscript{1,4}. These levels must be monitored closely as they are not a reflection of total body potassium\textsuperscript{1}. Potassium replacement in DKA patients has not been extensively studied. Those presenting with potassium $>$5.0 mmol/L should have potassium added to fluid only once potassium levels have normalized and diuresis has been re-established. This typically occurs during the second liter of fluid\textsuperscript{4}. Patients receiving potassium through IV should also have continuous cardiac monitoring\textsuperscript{17}. Short acting IV insulin administration, used to correct acidosis, should be withheld until potassium levels have been checked, as insulin administration will worsen an already existing hypokalemia. Patients found to be hypokalemic ($<$3.3 mmol/L), require IV potassium infusion before insulin can be administered\textsuperscript{4}. Those who present with normokalemia or hypokalemia should have 20-40 mEq/L of potassium added to initial boluses with an intended target of 4-5.5 mmol/L in the blood\textsuperscript{4,17}. In the event of renal failure with associated oliguria, potassium replacement should not occur with serum readings $>$4 mmol/L in the absence of hypokalemic pathology on EKG\textsuperscript{1}.

In the event of severe acidemia (pH $<$7.0), one ampoule of bicarbonate administered with 250 mL of D5W is recommended. This is to be repeated if pH does not rise above 7.0 after administration\textsuperscript{4,7}. There is no indication for phosphate supplementation unless phosphate levels fall below 0.05 mmol/L\textsuperscript{1,17}. 
Insulin infusion is a necessary second step in reversal of DKA, but always follows volume repletion therapy, and electrolyte monitoring in order to avoid potentially lethal complications due to sudden electrolyte shifts\textsuperscript{1}. Administration of insulin will inhibit lipolysis, ketogenesis, and glucagon secretion while increasing glucose uptake from the blood stream into peripheral tissues\textsuperscript{1}. Insulin given intravenously is most common as it provides the benefit of faster decline in glycemia, acidemia, ease of titration, short half life and physician comfort\textsuperscript{1,18}. The role for subcutaneous insulin administration using short acting analogues remains unclear and will be discussed briefly later.

Recommendations for the rate of insulin administration are varied and focus on the advantages of initial boluses versus continuous infusions without bolus. Few studies have shown any benefit to giving initial insulin boluses, with some studies showing significant increases of hypoglycemia in patients treated with boluses\textsuperscript{4,7}. Others have found administration of insulin boluses have resulted in increases in cerebral edema in pediatric populations\textsuperscript{4}. Although the topic of considerable study, no consensus has been reached on ideal insulin management\textsuperscript{1,4,16,19}. Another topic of controversy concerns the rate at which insulin should be given. The potential advantages and disadvantages of low verses high dose insulin administration have been compared in a randomized control trial. Those receiving high doses did not experience a significant increase in the rate of resolution, but were found to be at a much higher risk of hypoglycemic events\textsuperscript{20}. This has lead most guidelines to endorse a low rate of insulin infusion. A recent review suggests either giving a 0.1 U/Kg bolus followed by initiation of 0.1 U/Kg/hr infusion, or simply starting the patient on a 0.14 U/Kg/hr infusion without bolus, as acceptable options\textsuperscript{1}. The CDA recommends starting patients on 0.1 U/Kg/hr without a initial bolus, and adjustment based on response to therapy by measuring acidosis\textsuperscript{4}. The CDA recommendation is in line with national guidelines in place in Great Britain and are ultimately what shall be advocated for here\textsuperscript{16}. Regardless of the initial rate of insulin infusion, agreement has been made that hyperglycemia should be corrected at a rate of 2.8-4.2 mmol/L/hr\textsuperscript{1,4,7,16}. Failure to reach this goal may indicate the need for adjustment as peripheral insulin resistance may be a factor, especially in the growing number of type 2 DM patients experiencing DKA.
The CDA guidelines do not address this concern, however a 0.14 U/kg bolus of insulin followed by
continuation of previous insulin infusion rate has been suggested. A different review recently suggested
that a doubling of the continuous infusion serially every hour until hyperglycemia begins to correct at a
rate of 2.8-4.2 mmol/L/h is indicated. Regardless of insulin infusion rate, serial plasma glucose
measures are essential to avoid hypoglycemia, which can cause a rebound ketosis due to increases in
counter regulatory hormones, lengthening hospital stay. Severe complications of hypoglycemia include
cardiac arrhythmias, brain injury, and death. Once levels have reached 14.0 mmol/L, IV 5% dextrose
should be administered along with insulin. Studies have identified that using 10% dextrose can
significantly reduce ketonemia, but failed to confer advantage to resolution of acidemia. 10% dextrose
solutions should be used if blood glucose levels continue to fall after 5% dextrose infusions have been
applied. If serum osmolarity begins to drop too quickly, practitioners should consider increasing the
sodium concentration of the IV fluid.

There is yet a clear role for short and longer acting subcutaneous insulins in the treatment of
DKA. It has been shown that in mild cases of DKA, these analogs may reduce the amount of insulin used,
time to resolution of ketoacidosis, hypoglycemic events, and length of hospital stay. There is a cost
benefit to the hospital as patients on these regimes can avoid ICU stay. However, unpredictable rates of
absorption and distribution following administration in patients experiencing volume depletion and or
vasoconstriction, combined with delayed onset, and physician discomfort have made subcutaneous insulin
administration difficult when resources for IV administration are available. The evidence for
subcutaneous administration as a sole insulin source during treatment is based on a few small studies and
will not be considered within the protocol (Appendix B) at this time.

Resolution of DKA has occurred once acidosis has been neutralized (pH >7.3), anion gap has
normalised, lost fluid volume has been replenished, electrolyte and serum osmolality levels have
stabilized at physiologic values (HCO3 >15.0 mmol/L), ketosis has reduced (capillary βOHB levels <0.5
mmol/L) and hyperglycemia has returned to our goal range (12-14 mmol/L). These physiological
markers, in an alert and oriented patient capable of full per os diet, indicate discontinuation of IV infusion. Transfer of the patient from the ICU may also be considered. The CDA does not make any recommendations regarding the method in which IV insulin is discontinued. This step can be difficult as improper discontinuation of IV insulin can result in a sharp rebound of hyperglycemia and metabolic acidosis. Administration of longer acting basal insulin 30 minutes before a meal, and 1-2 hours before discontinuation of IV insulin, may provide a smoother transition and reduce the occurrence of rebound acidosis. Discontinuation of IV glucose administration should only occur once patients are able to tolerate a full oral diet. Patients who were previously on a subcutaneous insulin regime may be restarted on their previous dose, with consideration for close in and outpatient follow up by a DKA team to monitor adequate glycemic control, especially in the setting of idiopathic DKA. Those without previous insulin regimes may be started on 0.5 - 0.8 U/Kg/day. Half this dose should be given as an intermediate acting basal insulin with the rest divided evenly and administered with meals. A variation of this strategy is suggested by the American Diabetes Association in which it is suggested that 75-80% of the total daily dose of IV insulin is split, as above, between basal and prandial doses. In each case, care must be taken, especially in insulin naive patients, as insulin sensitivity is a potential complicating factor. Management that is too aggressive could result in a hypoglycemic event. Therefore, it is also common practice to consider starting these patients on 0.3-0.5 U/Kg/day and titrating up if necessary.

Once they have started their subcutaneous regimens, it is important to start these patients on a regular regimen as soon, and safely, as possible. In many hospital wards it is common for physicians, residents, and students to prescribe insulin sliding scales (ISS) as a sole means of glycemic control. An ISS is an insulin regimen in which only short acting insulin is prescribed at a dose relative to the degree of hyperglycemia. This provides poor glycemic control, does not mimic physiological insulin administration, and therefore must be avoided. This is especially pertinent to patients recovering from DKA whom typically suffer from T1DM. In these patients, ISS are more likely to result in hyper- or
hypoglycemia, ketosis, and acidosis\textsuperscript{21}. Further discussion on ISS is beyond the scope of the paper and will distract from our main point. Thus the reader is pointed toward some relevant literature on the topic\textsuperscript{21–27}.

**Diagnosis, Monitoring, and Betahydroxybuterate**

Diagnosis can become more difficult in the setting of mixed acid base disorders, osmotic diuresis which can lower the anion gap to physiologic ranges, or redox potentials which favor the formation of βOHB. This last point highlights an important concept currently under study. βOHB levels are not detected in classic serum and urine ketone tests. This has lead to studies which use point of care devices that measure capillary βOHB levels at triage, which may expedite diagnosis and treatment initiation\textsuperscript{4}. Faster diagnosis of DKA in the emergency department can, in turn, lead to shorter ICU stays and reduced morbidity and mortality.

As mentioned above, during DKA the accumulation of ketones including acetoacetate (AcAc) and βOHB, byproducts of lipolysis, are largely responsible for the underlying metabolic and acidic-base changes which occur. Often a rise in βOHB can be detected in the blood before DKA is clinically apparent\textsuperscript{8}. Diagnosis of DKA traditionally focuses on correlation of hyperglycemia, blood bicarbonate concentration, and acid base status\textsuperscript{28}. Conventionally, qualitative urine dipstick analysis, which tests urine for the presence of AcAc and acetone via nitroprusside assay, is used to screen for DKA, while laboratory measure of pH or bicarbonate is used to confirm diagnosis\textsuperscript{29}. This method presents several problems regarding utility for early diagnosis, reliable sample production, and real time evaluation of treatment\textsuperscript{28}. Recent technological advancements have allowed for the production of laboratory assays and point of care meters, which can detect and analyze ketone levels in blood quantitatively by measuring βOHB. Research has focused on the utility of these assays and meters in the early diagnosis, tracking of treatment, and resolution of ketonemia in those with DKA\textsuperscript{1}.

It has been found that during DKA the body produces βOHB in concentrations up to ten times that of AcAc\textsuperscript{28,30}. Rises in βOHB can be detected in blood sooner than in urine. DKA patients may be unable to produce urine due to volume depletion, and with AcAc there is a paradoxical rise in urine
ketones during DKA resolution, as AcAc is a metabolic byproduct of βOHB metabolism\textsuperscript{28}. βOHB can be measured in the laboratory by analysis of whole blood, serum, and plasma as well as in a point of care fashion with fingerstick samples, which use capillary blood. It has been hypothesized that quantitative results may be used to guide and monitor treatment. One study found the fingerstick test for βOHB in capillary blood to be as sensitive and much faster than conventional indicators of DKA. This suggests that use at triage can provide benefit through quick diagnosis and faster treatment initiation for DKA patients in the emergency department\textsuperscript{2}. Some studies have also identified possible benefit to self management and DKA prevention in children, with at home monitoring of capillary blood βOHB levels. Use of such meters for early identification may reduce children’s hospital ICU stays\textsuperscript{30}. One such study reported a 50\% decrease in hospitalizations in children whose ketones were measured as part of a sick day management protocol\textsuperscript{8}. This same study also reported patient preference for the capillary blood test rather than urine tests\textsuperscript{8}. Klocker \textit{et. al}, conducted a review that concluded blood βOHB testing to be more effective than urine testing by reducing emergency department assessment time, number of patients hospitalized, and the length of time for patient recovery. Although the papers reviewed were focused on children and adolescents, it is considered likely that these results can be generalized to adult populations\textsuperscript{29}. However, the authors determined this evidence only to be supported at level C, or satisfactory. Within its conclusions the authors noted that there needs to be more research done on the topic as the articles it included were heterogeneous in design and objectives\textsuperscript{28,29}. Research on the topic remains controversial, as there is no homogeneity between studies, type of tests used, comparison of models, patient populations, and outcomes tested\textsuperscript{28}. This confusion, along with logistic impediments, have resulted in many hospitals being slow to adopt routine βOHB as a safe and effective tool in the identification and treatment of DKA.

Currently published guidelines suggest that there is a role for βOHB monitoring, but there is some controversy as to when and what methods should be used. The CDA clinical practice guidelines state that blood βOHB is sensitive and specific for the diagnosis of DKA and should be used as a
screening tool, if available, to allow for more rapid diagnosis in those at risk for DKA. It is suggested that those presenting with type 1 diabetes and capillary glucose >14.0 mmol/L should be checked with point of care capillary βOHB meters\(^4\). A reading >1.5 mmol/L of βOHB warrants further investigation for the presence of DKA\(^4\). At this cut off concentration, measurement of βOHB has been found to be as sensitive and more specific than urine ketone testing\(^30,31\). The Joint British Diabetes Society recommends the use of bedside capillary ketone meters for diagnostic and treatment management purposes. The suggestion is that monitoring levels of ketones allows for adequate planning and treatment of those patients reporting with only modest hyperglycemia and high metabolic acidosis caused by rampant ketonemia. This is seen in a condition known as euglycemic DKA, which is on the rise with increased diabetes patient education, and may account for approximately 10% of DKA cases\(^16\). The American Diabetes Association also recommends the use of urine or serum and direct ketone monitoring, but does not elaborate as to what method is recommended\(^28\).

It appears as though uncertainty about the effective parameters in which these meters can be used safely has been, and continues to be, a barrier to their acceptance into common practice. A recent review points out that although there is gathering evidence supporting the use of point of care serum ketone measurements for the diagnosis and prevention of DKA, caution should be applied as it is not yet clear under what circumstances these measures are accurate\(^28\). Operational parameters outlined by the manufacturers typically report these meters as accurate up to 6.0-8.0 mmol/L. However, papers examining their operational utility have concluded that this range is not practical, as deviation from gold standard tests have been shown above 3.0 mmol/L\(^32-34\). Others have reported that βOHB readings >5.0 mmol/L in whole blood can differ from readings collected from plasma\(^29\), with most organizations supporting the use of readings up to 3.0 mmol/L\(^4,16\). Interestingly, manufacturers caution users not to use ketone meters as a diagnostic tool for DKA\(^35\). Some models have parameters which exclude patients with hematocrits greater than 60%, a common case in volume depleted patients\(^28\). Ceriotti \textit{et al.}, found significant differences in hematocrit interference between models, and recommended careful selection of
instruments. The authors encouraged health care teams to choose meters not sensitive to these changes\textsuperscript{36}. Several papers have looked at the accuracy of individual meters, but methods and results tend to differ from one research group to another. Appendix A shows a list of different studies and their recommended βOHB concentration parameters for safe and effective use. The variation in recommended use parameters has frustrated reviewers who are calling for more standardized testing to ensure adequate reproducibility\textsuperscript{28}.

On the contrary, it may be noted that readings greater than 3.0 mmol/L may be irrelevant to emergency room staff who are able to diagnose DKA and initiate treatment based on readings approaching, but below, this level. Further controversy regarding point of care meters is derived from the intention of using these meters to guide insulin therapy decisions. The literature offers weak support for serial measurements to be a practical method of assessing the severity or monitoring the resolution of the disease. These problems have led to the suggestion that meters should be set to show a "High" reading at any concentration above 3.0 mmol/L\textsuperscript{32}. Given that diagnosis of DKA can be made with good sensitivity and specificity $\geq$1.5 mmol/L, and that these meters have been shown to be highly accurate up to 3.0mmol/L, it stands to reason that readings higher than 3.0 are irrelevant for treatment and diagnostic decisions. The switch from IV to subcutaneous insulin is advised only once ketonemia has resolved below 0.5 mmol/L, well within the proven range of accurate measure\textsuperscript{35}, making readings higher than 3.0 mmol/L irrelevant for guiding insulin therapy. Thus, it appears that even though these meters become unreliable at the high physiologic concentrations of βOHB one might expect to find in DKA, they do produce accurate results at low concentrations and can be safely used to diagnose DKA and guide insulin management.

**Use of Protocols**

The complexity of DKA, especially in the context of a considerable amount of new and ongoing research, makes it difficult for health care providers to stay current with recommended guidelines. The relatively low incidence, and complex management of DKA makes it difficult for healthcare teams in the emergency department to ensure the best evidence based management is provided to patients\textsuperscript{37,38}. Several
organizations have released guidelines which promote implementation and compliance with best practice protocols\textsuperscript{4,16,19,39}. These protocols focus on early diagnosis, intervention, and close monitoring, with the eventual goal of faster resolution in DKA. Simply implementing such can improve DKA management outcomes without increasing the incidence of hypoglycemia, hypokalemia, or cerebral edema\textsuperscript{40}. Studies on the efficacy and safety of protocol directed DKA treatment have returned promising results with reduced ICU stays as high as 23\%\textsuperscript{5}, and up to a 30\% reduction in length of hospital stays, with reduced rates of hypoglycemic and hypokalemic events\textsuperscript{40}. More recent studies, using protocols based on the American Diabetes Association's recommended guidelines\textsuperscript{39} have reported 9.2 hour decrease in time to ketonemia resolution, a reduced time anion gap closure, dextrose administration, and potassium repletion, without compromising patient safety\textsuperscript{41,42}. Implementation of these protocols into our emergency rooms and inpatient wards has appears to be a necessary step to improve patient care and reduce hospital expenditures.

Protocol implementation is only the first step to improved outcomes. Staff compliance appears to be a common problem, which may hinder potentially positive results. In the UK, a retrospective study examined the adherence to an already implemented protocol for DKA. Researchers found awareness of the protocol was good, and that initial management of DKA patients was adequate with appropriate fluid therapy started within one hour as per protocol recommendation, but after the first hour adherence to the protocol dropped. There was poor compliance with recommended testing at set intervals during treatment. Less than 50\% of patients requiring ICU stay as per protocol recommendations actually were admitted. Little evidence has been gathered on why protocol compliance decreases as treatment continues. The authors suggest that advising clinical judgment within the protocol, poor communication during staff hand over, and the need for further training all contribute to decreased compliance. It has not been made clear which, if any, of these reasons is the largest barrier\textsuperscript{43}. Implementation of protocols appear to provide a therapeutic and financial advantage, though further research needs to be done in order to understand the best way to encourage their proper use throughout the entire management of DKA.
**DKA Teams**

It has been reported that, up to 25% of patients are readmitted multiple times for DKA, indicative of poor compliance with their anti-hyperglycemic medications. It has been suggested that the implementation of a DKA team may provide a therapeutic benefit and improved DKA treatment outcomes. Teams typically consist of an endocrinologist or diabetes specialist and support staff. They focus their efforts on searching for and treating precipitating factors, following the management of DKA, discharge planning and follow up, as well as monitor hospital performance in treating DKA. With emphasis placed on education and follow up repeated admissions by the same patient may decrease. Studies have shown improved patient education and reduced readmission for diabetes related morbidity in those followed by a diabetes specialist team. Although there is little evidence suggesting improved outcomes when these teams are consulted early in management, there appears to be a role for education of medical staff and patients, ensuring proper protocol compliance, as well as conducting audits on outcomes, equipment, and staff performance to ensure better patient care.

**Discussion**

Although the introduction of a DKA protocol is not a novel idea, it is an important step that all hospitals need to acknowledge in order to provide best evidence care. Quick diagnosis and early initiation of safe and effective treatment is critical to provide adequate patient care. Seven Oaks General Hospital is one of several hospitals within the WRHA that has adopted electronic patient records allowing for easy access to patient data sets. Using SOGH as a pilot project to launch a new strategy across Manitoba, once successfully adopted, it is planned that protocols similar to this one can be implemented at several rural sites with the hope of improving outcomes outside of the WRHA. This may provide a unique opportunity for research as DKA treatment in the rural setting presents challenges not commonly encountered in Winnipeg.

Our protocol is designed to ensure that each patient presenting to the emergency department with DKA on the differential diagnosis will be screened using point of care capillary βOHB meters. If found to
be positive, treated appropriately. However, implementation of protocols such this is not the only step that can be taken toward improving DKA patient care. Dr. Ricardo de Faria, Director of the SOGH emergency department, reports that an estimated 120 patients are seen every day in the emergency department. This suggests that there are approximately 53 cases of DKA which could require admission each year. Bed pressure and available resources have resulted in many of these patients being kept in and treated at the emergency department. Last year only 15 of these patients were admitted to the hospital from the emergency department to inpatient wards with ICD codes for DKA. This problem ties up emergency beds and makes adherence to established treatments more difficult. Eventual transfer from emergency department to inpatient wards leaves patients vulnerable to missed blood work, assessment, and thus adherence to protocol standards. This fact, combined with the reality some DKA patients are already inpatients within hospitals, adds further complications in providing adequate treatment of the entire patient population. This has led us to the conclusion that implementation of our protocol is much more likely to succeed with the hiring or appointment of staff charged with ensuring optimal protocol utilization.

Implementation of this protocol provides opportunities for further research. As it remains unclear exactly what dose and rate of insulin patients with DKA should receive, it is obvious that further research on the treatment of DKA will prove valuable. Simply auditing the local effects and benefits pre- and post-implementation, may contribute to the growing body of evidence in the field. Such audits may also highlight certain areas that are in need of improvement locally, as well as nationally. As discussed previously, more research regarding point of care βOHb meters may be required before they can be universally accepted. There does not appear to be any published studies comparing the success of protocols that use βOHb point of care meters with those that do not. There may be benefit from studying the efficacy of different DKA teams, especially in a rural setting, where access to endocrinologists and diabetologists is very limited and whose roles may be filled by other members of the health care team.
In Manitoba, genetic and environmental factors place First Nations populations at greater risk of developing DM\textsuperscript{46}. In many northern Manitoba communities there is a relatively large First Nations population, thus having safe, ready, and effective diagnostic and treatment strategies available is critical. Devices such as point of care meters provide quick and reliable results affordably. Strategies proven to be effective at larger centers may not translate well to underserved areas where medical resources can often be scarce. Examining effectiveness of the strategies discussed above in these remote settings may prove beneficial to providing improved care across Manitoba.

**Conclusion**

With DM becoming an increasingly common problem worldwide, efficient and effective treatment strategies for DKA are essential. The literature on DKA management has shed light on how to reduce patient time to DKA clearance, hospital length of stay, and recurrence rates, without sacrifice of patient safety. Quick diagnosis, and proper insulin administration are rudimentary however require close monitoring. By providing optimal treatment the risks of death and long term mortality are greatly reduced. The proven safety, reliability, and effectiveness of point of care βOHb meters makes their current underutilization a questionable flaw in current practice, which requires change. Evidence of improved patient outcomes by simple protocol implementation and staff compliance highlights the importance of such protocols. Implementation of recommendations presented here allows for research opportunities.

**Acknowledgments**

I would like to thank Dr. Ricardo Lobato de Faria for his knowledge, guidance, time, and effort put towards helping me complete this project. I would also like to thank the friendly and helpful staff of Seven Oaks General Hospital including Anne Hakansson, Trevor Strome, and Linda Codville. Special thanks go to Tina Ly for your tireless editing efforts. Thank you to the faculty of the University of
Manitoba Master of Physician Assistant Studies who have provided valuable feedback and editing and have encouraged and supported my continuous effort throughout the year.
### Appendix A

<table>
<thead>
<tr>
<th>Authors</th>
<th>Device</th>
<th>Method of Comparison</th>
<th>Recommended Range</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byrne <em>et al.</em> 47</td>
<td>Precision Xtra (MediSense/Abbott Laboratories)</td>
<td>Urine nitroprusside</td>
<td>0.0-6.0 mmol/L</td>
<td>Sensor tends to overestimate blood βOHB concentrations slightly; Accuracy was similar for capillary and venous blood samples; βOHB measurement unaffected by presence of acetone or AcAc.</td>
</tr>
<tr>
<td>Janssen <em>et al.</em> 32</td>
<td>Precision Xceed (Abbott Diabetes Care)</td>
<td>Liquid chromatography tandem mass spectrum</td>
<td>0.0-3.0 mmol/L</td>
<td>Inter-individual variation while approaching the saturation level (6.0mmol/L) is large; All readings &gt;3.0 mmol/L should be reported simply as 'high'.</td>
</tr>
<tr>
<td>Dhatariya, 2014 35</td>
<td>GlucoMen LX Plus (A Manarini Diagnostics)</td>
<td>Review</td>
<td>0.0-5.0 mmol/L</td>
<td>Precision Xceed should not be used when measuring concentrations &gt;5.0mmol/L; GlucoMen LX Plus and Free Style OPtimum Neo are the most commonly used devices in the UK.</td>
</tr>
<tr>
<td></td>
<td>Free Style Optimum Neo (Abbott Diabetes Care)</td>
<td>Nil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yu <em>et al.</em> 33</td>
<td>Precision Xceed (Abbott Diabetes Care)</td>
<td>Standbio reagent</td>
<td>0.0-3.0 mmol/L</td>
<td>Reliable for diagnosis of DKA; Physiological levels of AcAc found in DKA can interfere with βOHB measurement.</td>
</tr>
<tr>
<td>Ham <em>et al.</em> 48</td>
<td>Precision Xtra (MediSense/Abbott Laboratories)</td>
<td>GDS reagent/COBAS FARAS II centrifugal analyzer</td>
<td>0.0-4.0 mmol/L</td>
<td>With a βOHB cut off value of 1.5 mmol/L, this meter has a positive predictive value of 0.85 and a negative predictive value of 1.0 for DKA.</td>
</tr>
<tr>
<td>Turan <em>et al.</em> 30</td>
<td>Optium (Medisense)</td>
<td>Urine nitroprusside</td>
<td>0.0-6.0</td>
<td>Concluded that the βOHB meter was superior to the urine assay for early detection and treatment monitoring.</td>
</tr>
<tr>
<td>Loh <em>et al.</em> 49</td>
<td>Precision Xtra (MediSense/Abbott Laboratories)</td>
<td>Review</td>
<td>0.0-3.0 mmol/L</td>
<td>The bedside ketone meter is useful for monitoring the resolution of DKA; Limitations include decreased accuracy due at high βOHB and interference from AcAc.</td>
</tr>
<tr>
<td>Chiu <em>et al.</em> 34</td>
<td>Optium Neo (Abbott Diabetes Care)</td>
<td>Procedure 310-UV (Sigma Diagnostics)</td>
<td>0.0-6.0 mmol/L</td>
<td>Precision was poorer at the lower end of the range of detection; AcAc resulted in minor negative interference.</td>
</tr>
</tbody>
</table>

* denotes industry sponsored study
Appendix B

Admission

Admit to Inpatient for Diabetic Ketoacidosis

Admitting Provider: ____________________ □ Teaching □ Non-Teaching

☐ Admit to inpatient ward _______
☐ Admit to ICU
☐ Emergency Department Observation
☐ Other ___________________________________________

Discharge Planning

Goals of Therapy: pH > 7.3, anion gap < 12, Euvolemic, HCO₃ > 15.0 mmol/L, serum βOHB < 0.5 mmol/L, Blood glucose well controlled, patient is alert and oriented, tolerating full PO diet.

Estimated Length of Stay: 72 hours

Advance Care Plan

☐ ACP- R □ M □ C

IV Access

☐ IV Access Peripheral □ IV Access Saline Lock
☐ Central Venous Access - Advised for administration of IV Potassium > 20mEq/L

IV Therapy

Severe Volume Deficit (shock)

IV fluid resuscitation goal: All 3 of the following:

- Heart Rate less than 100 beats/minute
- Systolic blood pressure greater than 90
- Urine output greater than/equal to 0.5 mL/kg/h

☒ When resuscitation goal achieved, follow Mild to Moderate Volume Deficit orders
☒ If resuscitation goal has not been achieved, notify MD to reassess patient

*** MD to consider fluid resuscitation with 0.9% NaCl 1-2L/h to correct hypotension/shock
☐ 0.9% NaCl 500 mL IV bolus over 15 minutes
   Then ☒ 0.9% NaCl 500 mL IV bolus q15minutes until resuscitation goal has been achieved
   ☒ 0.9% NaCl 500 mL IV bolus q15minutes until a total of 2,000mL has been administered
☐ 0.9% NaCl at 1,000 mL/h for 2 hours

Mild to Moderate Volume Deficit

*** Note that hyperomolarity should not be corrected faster than 3 mmol/kg/h to avoid complications of cerebral edema

☐ 0.9% NaCl at 500 mL/h IV for 4 hours
   Then ☒ 0.9% NaCl at 500 mL/h IV for 4 hours
   Then ☒ notify MD for further IV fluid orders

Euvolemic

*** MD to consider changing IV fluid solution based on corrected sodium levels calculated using conversion factor of 2.4 and/or rate of fall of effective plasma osmolality.

☐ 0.9% NaCl at 250 mL/h hyponatremic
☐ 0.45% NaCl at 250 mL/h for those found to be eunatremic or hypernatremic
Potassium Replacement

*** Do not start insulin therapy until potassium levels have been checked. Patients receiving potassium therapy should be on continuous cardiac monitor. Serum potassium less than 3.3 mmol/L require replacement. Those found to have potassium levels greater than 5.0 mmol/L should have potassium withheld from IV fluids until levels drop to less than or equal to 5.0 mmol/L and diuresis is established.

- Do not administer potassium until potassium is less than/equal to 5 mmol/L and there is urine output
- If serum potassium is less than 3.3 mmol/L or greater than/equal to 6 mmol/L notify MD STAT
- If renal failure is present with associated oliguria, do not give potassium if serum potassium is greater than 4 mmol/L
- If serum potassium is less than 3.3 mmol/L and urine output is present, change IV maintenance fluid to include 40 mmol KCl/L
- If serum K is 3.3-5.0 mmol/L and urine output is present, change IV maintenance fluid to include 20 mmol KCl/L
- OR
- If serum potassium is 3.3-5.0 mmol/L and urine output is present, change IV maintenance fluid to include 40 mmol KCl/L

Acidosis Management

*** Sodium bicarbonate administration is only indicated in severe acidemia (pH < 7.0)

- One ampoule of sodium bicarbonate in 250 mL of 5% dextrose in water

Insulin Infusion

*** Do not start insulin until a serum potassium level greater than 3.3 mmol/L has been verified. Use prepared IV insulin regular solution:

- insulin regular 100 units in 100 mL 0.9% NaCl. Concentration = 1 unit per 1 mL

- Run first 20 mL insulin regular solution through IV tubing and discard (repeat flush with each IV tubing change)
- Insulin regular IV infusion ran at 0.1 units/kg/hour
- Reassess and titrate initial doses of insulin to correct hyperglycemia at a rate of 2.8-4.2 mmol/L/h
- Reassess insulin orders once anion gap is less than/equal to 12 mmol/L

Ongoing IV Fluid and Glycemic Management

*** Do not allow serum osmolarity to drop at a rate faster than 3 mmol/kg/h

- When serum glucose level is less than/equal to 14 mmol/L, continue ordered IV maintenance fluid
- If serum osmolarity is decreasing too quickly, switch to hyponatremic solution at a rate equal to previously ordered maintenance.
  - Serum Glucose 10.1 - 14 mmol/L
    - IV 5% Dextrose at 50 mL/h in addition to ordered IV maintenance fluid
      - And Resume insulin regular IV infusion to 50% of starting rate
    - *** If serum glucose values continue to fall consider switch to 10% Dextrose at 50 mL/h
    - Serum Glucose 4.1 - 10.0 mmol/L
    - IV 10% Dextrose at 75 mL/h in addition to ordered IV maintenance fluid
      - And Reduce insulin regular IV infusion to 50% of starting rate
    - Serum Glucose less than 4.1 mmol/L
      - *** Notify MD to reassess
    - IV 10% Dextrose at 100 mL/h in addition to ordered IV maintenance fluid
      - And 50% Dextrose 50 mL/IV push over 1-3 minutes
      - And Hold insulin regular IV infusion for 15 minutes
      - Then Resume insulin regular IV infusion after rate has been reassessed by MD

Transition to Subcutaneous Insulin

Criteria for transition from IV insulin infusion to subcutaneous insulin therapy include:
- Blood glucose less than 14 mmol/L
- Capillary βOHB less than 0.5 mmol/L
- Arterial pH greater than 7.3
- Bicarbonate greater than/equal to 15 mmol/L
- Anion gap less than 12 mmol/L
- Patient is able to tolerate PO intake

- Administer long or medium acting basal insulin

*** Give patient previously prescribed home dose of basal insulin. If patient did not have a previous regimen begin patient on 0.5-0.8 U/Kg divided equally so that half of this dose is given as basal bolus of medium or long acting insulin and the other half is given as a three separate bolus doses of rapid or short acting insulin with meals.
30 minutes after administration of basal allow patient to eat a meal
- Discontinue IV insulin 2 hours after administration of basal insulin
- Complete Diabetes Management Order Set as applicable
  - Refer to Diabetes Management Order Set (Patient eating meals)
  - Refer to Diabetes Management Order Set (Tube feeding/Total parenteral nutrition)
- Discontinue 5% dextrose IV infusion
- Other ________________________________
  - Transition to subcutaneous insulin pump
  - Reinitiate patient's subcutaneous insulin pump only if patient is alert and oriented
    - Then Discontinue IV insulin infusion 2 hours after subcutaneous insulin pump is reinitiated
    - Patient to manage own insulin pump and administration
- Discontinue maintenance IV when tolerating fluids and food
- Discontinue 5% Dextrose IV infusion
- Other ________________________________
  - Capillary Blood Glucose Monitoring
    - *** In appropriate discontinuation of IV insulin may result in rebound hyperglycemia and metabolic acidosis
    - Capillary blood glucose at time of first subcutaneous insulin administration, then as per applicable Diabetes Management Order Set
    - Other ________________________________

**Nausea Management**
- Dimenhydrinate _____ mg PO/NG/IV/PR q4h PRN (12/5-50 mg) [caution-Beers]
- Ondansetron 4 mg PO/IV q____h PRN (q8-12h)
- Maxeran 10 mg PO/IV q6h PRN

**Medications Reconciliation**
- Complete attached medication reconciliation
- Discontinue home antihyperglycemic medications
- When stable and ready to come off IV insulin patient may be restarted on home insulin doses and assessed for adequacy of blood glucose control.

**Laboratory**
- Notify MD to reassess if:
  - Arterial pH is less than 7.1 -- Consider Bicarbonate Therapy
  - Blood Glucose has not fallen by 10% in the first hour of treatment
  - Sodium is less than/equal to 130 mmol/L
- When capillary βOHB is less than 0.5 mmol/L, notify MD to reassess insulin and IV therapy orders

**Hematology and Coagulations**
- CBC
- APTT
- INR
- Other ________________________________

**Chemistry**
- Electrolytes
- Lactic Acid
- Ca
- Albumin
- A1C
- Creatinine
- VBG
- Mg
- ALT, ALP, Bilirubin
- Serum βHCG
- Glucose
- ABG
- Phosphate
- Lipase
- Urine βHCG
- BUN
- Serum βOHb
- Capillary βOHb
- CK
- Serum Ketones
- Anion Gap
- Serum Osmolality
- UA
- Troponin
- Serum Drug Screen
- Other ________________________________

**Microbiology**
- Blood C+S x 2
- Urine R+M
- Sputum C+S
- Urine C+S

**Follow-up Lab Investigations**
- Capillary Blood Glucose q1h
- Capillary βOHb q1h
- Electrolytes, Glucose, Creatinine, Anion Gap, q2h, the anion gap is less than 12 mmol/L, and/or until βOHb is less than/equal to 0.5 mmol/L, with serum potassium greater than/equal to 3.4 mmol/L
  - Then Electrolytes, Glucose, Creatinine, Capillary βOHb, and Anion Gap q4h
- Serum Osmolality q2h x 4
- Other ________________________________
Diagnostics

*** All patients receiving potassium through the IV should be on continuous heart monitoring

☐ Telometry
☐ CXR portable
☐ ECG
☐ Other ______________________________________________________________________________

Nursing

☐ Establish above ordered IV access
☐ If patient is wearing an insulin pump, remove pump upon arrival
☐ Do capillary βOHB (results greater than 1.5 mmol/L are concerning for DKA)
☐ Do capillary blood glucose
☐ Administer O₂ - Titrate to achieve minimum O₂ SAT at 92%

Diet
☐ NPO

Activity
☐ Ambulation as tolerated

Vitals/Monitoring
☐ Weight
☐ Vitals q1h
☐ Neurovitals q1h
☐ If ordered, start patient on continuous cardiac/SpO₂ monitoring
☐ Accurate Ins/Outs
☐ Serial βOHB until resolution (<0.5 mmol/L)
☐ Serial blood glucose q1h until IV insulin is discontinued

Notify MD when:
- New adventitious breath sounds develop
- Patient is anuric
- Blood results have returned
- No improvement in hyperglycemia after initiation of insulin
- Changes in patient status

Tubes
☐ NG tube to straight drainage
☐ NG tube to intermittent low suction
☐ Other gastric tube ______________________________________________________________________
☐ Insert folley catheter
☐ Other urinary catheter __________________________________________________________________

Consults

☐ DKA Team - Endocrinologist/diabetologist
☐ Pharmacy
☐ ICU
☐ Internal Medicine
☐ Other ________________________________________________________________________________

Additional Orders
______________________________________________________________________________________
______________________________________________________________________________________
______________________________________________________________________________________
______________________________________________________________________________________
______________________________________________________________________________________
______________________________________________________________________________________
______________________________________________________________________________________
______________________________________________________________________________________
Bibliography


15. Winnipeg Regional Health Authority, Seven Oaks General Hospital. ER Nurse Initiated Hyperglycemic Order Set. 2013:2.


45. Lobato De Faria R. Personal Correspondence. 2015.


