Original Article

Presentation and management of diabetic ketoacidosis in adults in Malta

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Abstract

Aim: The aim of this audit was to assess adherence to local guideline in the management of Diabetic Ketoacidosis (DKA).

Method: Patients admitted with DKA between April 2013 and March 2015 were identified and data was retrospectively collected from patients' confidential files and Isoft®. Data collected included initial parameters recorded and biochemical investigations taken (initial and subsequent assessment of pH, HCO^{3-}, blood glucose, potassium levels and urinary ketones), insulin regime started and intravenous fluid administered.

Results: During the established time period 40 cases of DKA were identified in 18 patients. Median age was 33 years with a female preponderance of 60%. Six patients had newly diagnosed diabetes mellitus while 8 patients had more than one admission of DKA. All cases had capillary blood glucose monitoring (BGM) and/or venous random blood (plasma) glucose (RBG) checked and pH and HCO^{3-} recorded on admission. 0.9% sodium chloride was the intravenous fluid started in all cases (as recommended by the guideline) and a median of 6.75L was prescribed during the first 24 hours. The median time spent on intravenous insulin infusion was 42.7 hours while the median time to pH >7.30, HCO^{3-} >15mmol/L and negligible urinary ketones were 6.88, 12.83 and 34.5 hours respectively. Subcutaneous insulin was started at a median time of 48.21 hours from initiation of DKA protocol.

Conclusion: This audit showed good adherence to local guideline. The great discrepancy between the time to pH >7.3 and the time to negligible urinary ketones highlights the need to introduce tools to measure systemic ketone production in the management of DKA with an update in the current local clinical practice guideline.

Keywords
Diabetes type 1, Diabetic Ketoacidosis, Complications, Mater Dei Hospital

Introduction

Diabetic ketoacidosis (DKA) is defined by the biochemical triad of ketone production, hyperglycaemia and acidaemia. Although not common, mortality from DKA is approximately 2%,[1] however, each death is potentially avoidable. Increasing patient and healthcare professional education and awareness of DKA and its management, has led to a decline in mortality over recent years.

The current audit aimed to assess the management of patients with DKA and compare these practices with the local DKA guideline issued in 2007.[3] Changes in current practice that could improve patient care and shorten hospital stay will be identified and instituted.

Methods

All adult patients (>16years of age) admitted with DKA to Mater Dei Hospital (MDH) over a two year period, between April 2013 and March 2015 were identified. These were identified from the Accident and Emergency (A&E) admission book and the Electronic Case Summary system. Patients' confidential files and Isoft® investigations were analysed in detail and predefined data sets obtained, in line with Data Protection Act. Only patients with parameters fulfilling the biochemical triad of DKA: 1) blood glucose > 11.0mmol/L or known to have diabetes mellitus, 2) metabolic acidosis with HCO_3^- <15.0mmol/L and/or venous pH < 7.3 and 3) significant ketonuria > 2+ on standard urine sticks, were included in the study.[4] The identified patients had their DKA management analysed in detail and compared to the current DKA guideline[3] available at MDH. All data was recorded on Microsoft Excel spreadsheet and analysis of data was then performed using IBM SPSS® version 22. Kolmogorov–Smirnov test was carried out to determine the normal distribution of the data and then either T-Test / ANOVA (for parametric data) or Mann-Whitney U / Kruskal–Wallis or $\chi 2$ (for non-parametric data) tests were used as appropriate. Correlation analyses were carried out using Spearman correlation.

Results

1. Demographics

Using the criteria above to define DKA, 40 cases (n = 40) were identified in a total of 18 different patients, during the study period. In the cases studied the median age was 33 years (IQR 24 – 52.25) with a female predominance of 60%. Six patients (33.3%) had newly diagnosed diabetes. 8 patients (44.4%) had more than one admission with DKA during the studied period.

2. Initial Assessment and investigations

Vital parameters (temperature (T), systolic blood pressure (SBP), Glasgow coma scale (GCS), oxygen saturation (SO_2%) and pulse (P)) at presentation, as documented in casualty were analysed (Table 1).

On admission all patients had recorded bedside capillary blood glucose monitoring (BGM). BGM was recorded as 'HI' in 7 cases, while the median reading in 32 cases was 25.7mmol/L (IQR 23.48 – 30). Venous random blood (plasma) glucose (RBG) was documented in 29 cases and the median was 33.6mmol/L (IQR 25.2 – 37.4). All 40 cases had pH and HCO_3^- levels checked, in 33 cases by an arterial blood gas (ABG) and 7 cases by a venous blood gas (VBG) analysis. The median pH of the study population at presentation was 7.18 (IQR 7.11 – 7.24) while the median value for HCO_3^- was 7.4 (IQR 5.4 – 11.45). A urine sample confirming ketonuria was obtained in 22 cases in the A&E Department.

Additional investigations recommended by the current DKA guideline[3] include a complete blood count (CBC), renal profile (U&E, Cr), arterial blood gases (ABG), urinalysis, pregnancy test in female patients, ECG and chest x-ray (CXR). An amylase level is recommended in patients with abdominal pain. The frequency and results of these tests in concordance to the local guideline is illustrated in Table 1.

All cases were admitted to Mater Dei Hospital, with 4 cases requiring admission to intensive therapy unit (ITU).

***Table 1**: Parameters and investigations with respective median results measured at admission*

Parameters and investigations on admission	Frequency (*n*)	Median (Interquartile Range)
Temperature (°C)	38	36.4 (36 - 36.8)
GCS	40	15
Oxygen saturation (%)	37	99 (98 - 99)
SBP (mmHg)	39	121 (107 - 134.5)
Pulse rate (/min)	39	103 (93 - 120)
White cell count (x10^9/L)	40	13.55 (8.78 - 19.98)
Creatinine (µmol/L)	40	104 (94.75 - 120.5)
eGFR (mls/min/1.73m^2)	40	60.5 (48.25 - 71.25)
Amylase (U/l)	24	39 (35 - 76.75)
ECG	39	n/a
CXR	33	n/a

Table 2: Frequency of ABG/VBG testing with median results for pH and HCO_3^-

Time of ABG/VBG (hrs from start of protocol)	Frequency (*n*)	Percentage (%)	Median pH (mmHg) (IQR)	Median HCO^{3-} (mmol/L) (IQR)
0	40	100	7.19 (7.11 - 7.25)	7.4 (5.4 - 11.45)
2	33	82.5	7.22 (7.18 - 7.27)	8.7 (5.4 - 13.2)
4	29	72.5	7.27 (7.22 - 7.31)	8.6 (7.2 - 13.7)
8	35	87.5	7.33 (7.28 - 7.37)	14 (12.2 - 16.6)
12	33	82.5	7.36 (7.34 - 7.40)	16.6 (15.4 - 19.0)
24	14	35	7.42 (7.36 - 7.43)	18 (16.6 - 20.5)

***Table 3**: Frequency of K level checked and median level at time interval 0, 2, 4, 8, 12 and 24 hours from start of DKA protocol*

Time of K (hrs from start of protocol)	Frequency of K level checked *n* (%)	Median K level (mmol/L) (IQR)
0	40 (100)	4.7 (4.2 – 5.1)
2	31 (78)	4 (3.4 - 4.4)
4	29 (73)	4.3 (3.9 - 4.5)
8	35 (88)	3.8 (3.5 - 4.4)
12	32 (80)	3.9 (3.5 - 4.1)
24	22 (55)	3.7 (3.2 - 4.1)

3. ABGs/VBGs

According to current local DKA guideline, pH and HCO_3^- should be measured at 2, 4, 8, 12 hours after starting the protocol or until normalisation of metabolic acidosis. All patients had ABGs/VBGs repeated until pH and HCO_3^- levels had normalised but not necessarily within the stipulated time intervals (see table 2).

4. Ketones

The current DKA guideline recommends measuring urinary ketones every 4 hours until clearance is achieved. Ketones were checked regularly in 38 cases (95%) during the first 24 hours, while 29 patients still required urinary ketone testing for more than 24 hours after starting DKA treatment protocol. In the initial 24 hours after starting treatment the median number of times urinalysis was performed was 4 times (IQR 3 – 5.75) with a median of 2 times (IQR 1 – 3) at 24 – 48 hours.

5. BGM

Hourly BGM checks are recommended in the current local DKA guideline, for patients on intravenous insulin infusion. The median number of BGM checked was 17.5 times (IQR 9.75 – 22.25) during the first 24 hours and 4 times (IQR 3 – 5.75) at 24 – 48 hours from admission.

6. Insulin administration

All cases studied were treated with a variable-rate insulin infusion (VRIII) of short-acting insulin (Actrapid®). Long-acting basal insulin together with intravenous Actrapid® was co-administered in 4 cases (10%). The median time spent on Actrapid® infusion was 42.7 hours (IQR 27.9 – 65.75). During this period of time the median number of units of insulin required was 89Units (IQR 65 – 114) in the first 24 hours of protocol and 66Units (IQR 54.5 – 83) at 24 – 48 hours. Total insulin dose in the first 24 hours was positively correlated with initial RBG (ρ=0.381, P= 0.024). In 7 cases (18%), a further increase in insulin was required to reach target BGM.

7. Intravenous fluids

All patients were started on 0.9% of sodium chloride in concordance with the local guideline. The patients received a median of 6.75L (IQR 6.11 – 7.45L) during the first 24 hours. 10 cases (25%) did not require intravenous fluid for more than 24 hours, while 30 cases (75%) received a median of 2L (IQR 0.5 – 2.72L) at 24 – 48 hours from starting DKA protocol.

Intravenous fluids are to be changed to 5% dextrose in normal saline if BGM is less than 11mmol/L and to 10% dextrose if BGM is less than 5mmol/L in the current local DKA guideline. Intravenous fluids were correctly changed in 36 cases when BGM fell below 11mmol/L. In 10 cases BGM fell less than 5mmol/L during the initial 24 hours and 9 of these cases had the intravenous fluid correctly changed to 10% dextrose.

Table 4: *Correlation between different parameters in DKA management*

		Initial pH	Initial RBG	Age	Systolic BP on admission	Initial Potassium	WCC on admission	eGFR on admission	Total Insulin given in 1st 24 hrs	Time Period till pH.>7.3	Time Period till HCO^{3-} >15	Time Period till urine Ketones -ve	Hours on Actrapid pump
HCO^{3-}	ρ	**0.560**	-0.323	-0.500	**-0.386**	0.070	**-0.630**	**0.487**	-0.296	**-0.396**	**-0.0630**	**-0.444**	**-0.497**
	P	**<0.001**	0.058	0.764	**0.017**	0.672	**<0.001**	**0.002**	0.071	**0.014**	**<0.001**	**0.023**	**0.001**
Initial pH	ρ		-0.041	0.304	-0.231	0.002	-0.253	0.200	0.072	**-0.579**	**-0.520**	-0.141	0.026
	P		0.814	.056	0.158	0.991	0.115	0.216	0.662	**<0.001**	**0.001**	0.483	0.872
Initial RBG	ρ			0.475	-0.309	**0.406**	**0.419**	**-0.747**	**0.381**	0.108	0.140	**0.409**	**0.544**
	P			0.003	0.066	**0.014**	**0.009**	**<0.001**	**0.024**	0.530	0.429	**0.038**	**0.001**
Age	ρ				0.074	**0.314**	0.194	**-0.325**	0.244	-0.046	-0.150	-0.090	**0.333**
	P				0.655	**0.049**	0.231	**0.041**	0.134	0.781	0.370	0.654	**0.036**
Systolic BP on admission	ρ					-0.236	0.028	0.181	-0.080	0.237	0.200	-0.302	0.020
	P					0.148	0.865	0.271	0.633	0.152	0.235	0.125	0.905
Initial Potassium	ρ						0.288	-0.191	-0.036	-0.127	0.017	-0.039	0.104
	P						0.072	0.238	0.825	0.441	0.919	0.849	0.523
WCC on admission	ρ							**-0.406**	**0.349**	0.224	**0.500**	**0.545**	**0.566**
	P							**0.009**	**0.029**	0.170	**0.001**	**0.003**	**<0.001**
eGFR on admission	ρ								**-0.328**	-0.264	-0.309	-0.325	**-0.589**
	P								**0.041**	0.105	0.059	0.098	**<0.001**
Total Insulin given in 1st 24 hrs	ρ									-0.050	0.182	0.091	**0.403**
	P									0.767	0.281	0.658	**0.011**
Time Period till pH.>7.3	ρ										**0.544**	0.015	0.165
	P										**0.001**	0.941	0.315
Time Period till HCO^{3-} >15	ρ									**0.544**		**0.494**	**0.390**
	P									**0.001**		**0.010**	**0.015**
Time Period till urine Ketones -ve	ρ									0.015	**0.494**		**0.436**
	P									0.941	**0.010**		**0.023**
Hours on Actrapid pump	ρ									0.165	**0.390**	**0.436**	
	P									0.315	**0.015**	**0.023**	

Results in bold are statically significant (P<0.05) p: Spearman rank-order correlation coefficient; P: Significance (two-tailed)

8. *Potassium supplementation*

The current guideline suggests checking potassium (K) levels at 2, 4, 8, and 12 hours and to add supplemental potassium chloride into the intravenous fluid solution according to results. Table 3 shows frequency and results of K level at the time intervals recommended. Correlation analysis showed K levels at presentation to be positively correlated with increasing age and RBG (ρ=0.314, P=0.049 and ρ=0.406, P=0.014 respectively). (Table 4)

9. *Additional management*

In 7 cases insulin was infused via pump at a higher rate than recommended by protocol while in 2 cases the intravenous fluids prescribed after admission differed by both rate (infused at a standard rate of 128mL/min) and type (Hartmann's solution) respectively from what is recommended in the guideline. Furthermore, 2 patients were prescribed sodium bicarbonate.

Antibiotics were prescribed in 23 patients. 10 patients had no documented source of infection, 5 patients had documented respiratory tract infection, 4 patients had a urinary tract infection, 2 patients had gastroenteritis while one patient had antibiotics started for pelvic inflammatory disease. White cell count on admission was found to be negatively correlated with initial HCO_3^- and eGFR (ρ=-0.630, P=<0.01 and ρ=-0.406, P=0.009 respectively), but positively correlated with initial RBG levels (ρ=0.419, P=0.009) and time to resolution of DKA (ρ=0.545, P=<0.01) (Table 4).

Urinary catheterisation was performed in 11 cases during admission. Reason for catheterisation was documented as haemodynamic instability in 5 cases, acute kidney injury in 4 cases and in 2 cases this was undocumented.

10. *Time to resolution of DKA*

According to our local guidelines, DKA is considered resolved and fixed doses of subcutaneous insulin are recommended to be restarted once pH and bicarbonate are normal, normoglycaemia is achieved, urine is free of ketones and patient is eating normally. Using these criteria time to resolution of DKA and time spent on DKA protocol (taken as the time to subcutaneous insulin) were determined. These results are shown in Figure 1. Most of the 4 variables which were taken as indicative of resolution of DKA correlated positively with each other as shown in Table 4.

Discussion

The main aim of this audit was to assess adherence of current practices to the local guidelines and identify areas for improvement in the management of DKA.

From the whole cohort, 8 patients had more than one admission. Seven patients had 2 admissions and one patient had 11 admissions. Recurrent admissions with DKA is associated with multiple factors including poor control, noncompliance and nonattendance to outpatient clinic, female gender, presence of co-morbidity and psychological problems.[2] From the cohort of patients with readmissions, 6 patients were females, 4 patients were non-compliant to treatment, 1 patient had underlying pancreatic tumour and 1 patient had steroid-induced DKA. The patient with 11 admissions with DKA had an underlying psychological disorder.

All patients had BGM checked on admission. Median RBG was noted to be significantly higher than median BGM (33.6mmol/L and 25.7mmol/L respectively). In 7 cases (17.5%) the BGM value was unrecordable as point of care machines are not able to give a numerical reading at very high levels. The median BGM was therefore underestimated as these 7 cases were excluded from the calculated BGM median.

Deviation from protocol was noted in some cases. All 40 cases had pH and bicarbonate levels measured. 33 cases (82.5%) had an ABG measurement, whilst 7 cases (17.5%) had a VBG measurement on admission. Current local guideline recommends taking ABGs until normalisation of pH and taking VBGs in difficult cases if general condition is improving.[3] Guidelines issued by the Joint British Diabetes Societies (JBDS) Inpatient Care Group[4] suggest measuring venous rather than arterial bicarbonate and pH as the difference between venous and arterial pH is 0.02 – 0.15 pH units and the difference between arterial and venous bicarbonate is 1.88mmol/L. This negligible difference will neither impact diagnosis nor management of DKA.[5]

In 18 cases (45%) a urine sample was not available for measuring urinary ketones at the A&E department for various reasons including inability of patients to pass urine, dehydration and low GCS.

According to the JBDS guidelines one of the criteria defining DKA is a serum ketonaemia of ≥ 3.0mmol/L or significant ketonuria of ≥ 2+ on standard urine sticks.[4] Locally ketone meters are not available yet and this may delay the detection of ketones in patients who are unable to provide a urine sample at A&E. Ketone meters detect β-hydroxybutyrate which is the main type of ketone produced in DKA as opposed to acetoacetate detected by the standard urine dipsticks. The latter also sometimes gives false positive results and the presence of acetoacetate in urine lags behind the actual systemic ketone production, therefore delaying both diagnosis and resolution of DKA.[6]

Local guideline recommends use of a VRII and in 7 cases (18%), a further increase in insulin treatment recommended. Updates in JBDS guideline suggest using a fixed-rate insulin infusion (FRII) rather than VRII. FRII consists of prescribing a fixed insulin regime according to weight, thus partially accommodating for the very obese patients[4] and enabling rapid ketone clearance. In 4 cases (10%) long-acting insulin (glargine) was continued together with intravenous short-acting insulin infusion. Continued use of background insulin avoids rebound hyperglycaemia when intravenous insulin is stopped and should also shorten duration of inpatient stay.[7]

Initial intravenous fluid recommended in current guideline is 0.9% NaCl, which is to be changed to 5% dextrose in 0.9% NaCl if BGM < 11mmol/L and to 10% dextrose if BGM <5mmol/L[3]. This recommendation was adhered to in 36 cases (90%). This represents a significant improvement from observations in a previous audit, in which correct change in intravenous fluids was observed in 71.4% of cases.[8] Patients in DKA often have mild to moderate hyperkalaemia at diagnosis, despite a total body deficit of potassium. The initiation of insulin further lowers circulating potassium as it shifts potassium intracellularly, potentially resulting in severe hypokalaemia.[9] Hence close attention needs to be given to potassium levels, in order to avoid complications associated with hypokalaemia, including cardiac arrhythmias, arrest and respiratory muscle weakness.[4] Data on potassium supplementation differs. The American Diabetes association guidelines suggest the addition of 20-30mmol of potassium in each litre of infusion fluid to maintain a potassium level between 4 and 5mmol/l,[10] whereas the JBDS guidelines[4] recommend replacing with a dose of 40mmol/L of potassium if serum level is less than 5.5mmol/l.

An elevated WCC was negatively correlated with HCO^{3-} and pH levels, although the latter did not reach statistical significance (p = <0.001 and p = 0.115 respectively). DKA is associated with an elevated level of proinflammatory cytokines, reactive oxygen species, and adhesion molecules which all contribute to the increased WCC.[11]

Assessment of resolution of DKA was based on normalisation of pH, HCO^{3-} and urinary ketones level. From our results, pH levels returned to normal at the shortest time interval, followed by HCO^{3-} and urinary ketones respectively (Fig. 1). From our data HCO_3^- correlated well with the 2 other variables measured for the resolution of DKA. However JBDS guidelines recommend not using HCO^{3-} as the only variable due to possible hyperchloraemia secondary to large volumes of 0.9% sodium chloride solution used as fluid replacement. Consequent hyperchloraemic acidosis may lower HCO^{3-} levels and lead to difficulty in assessing for resolution of ketosis.[4]

The limitations of this audit include missing data from files and observation charts. Unclear and incomplete documentation also limited extraction of relevant data for this audit. Nonetheless, the audit performed showed numerous strengths including correct diagnosis of patients on presentation to A&E, accurate assessment of fluid balance and BGM management, accurate documentation of time at which subcutaneous insulin was restarted and of resolution of DKA.

Conclusion

In the current local guideline the diagnosis and resolution of DKA is based on pH, bicarbonate and detection /lack of ketones in the urine. Results from our audit for resolution of DKA have highlighted the great discrepancy between the time taken to achieve a pH >7.3mmHg (7.38hrs) and the time taken to achieve negative ketones in the urine (26.25hrs). The difficulty in obtaining a urine sample to test for ketones early on presentation and the persistent detection of ketones in the urine after suppression of ketonaemia contribute to the delay in diagnosing DKA and in identifying resolution of DKA respectively. This might result in potentially harmful delays in initiating treatment of DKA and subsequent unnecessary prolonged treatment with

insulin infusion. The introduction of ketone meters to measure ketones in the blood would expedite DKA diagnosis, facilitate monitoring of the patient admitted with DKA and accurately identify resolution of DKA early while the administration of insulin infusion at a fixed rate, tailored to the individual patient according to the patient's weight, would contribute to rapid ketone clearance thus improving the overall management of the patient admitted with DKA.

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