

Prediction and rate of infections in diabetes mellitus patients with diabetes ketoacidosis in Penang, Malaysia

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ABSTRACT

Study aimed to determine the rate and prediction of infection in diabetes mellitus patients ≥ 18 year, with diabetic ketoacidosis (DKA). Retrospective cohort study design was adopted to achieve the objectives. Universal sampling technique was employed for data collection among Diabetes ketoacidosis patients, over a period of 3 years (Jan 2008-Dec 2010). Statistical package for social sciences used to analyze data. Over a 3-year period, total of 967 admissions were identified. Of it, 112 (11.6%) with no infection, 679 (70.2%) with bacterial infection and 176 (18.2%) with presumed viral infection. The mean WBC for all the patients was 18,177 (± 9431). 721 (74.6%) had leukocytosis, as defined by a WBC $\geq 15,000/\text{mm}^3$. WBC, differential, leukocytosis, as well as sex, temperature were not significant predictors ($p > 0.05$) of bacterial infection. There was significant ($p < 0.05$) difference of age between the 3 groups, age above 57 years have high rate of infection as compared to age below and equal 57 years. The infection rate in elderly patients with DKA was high and majority of them had lack of clinical evidence. Major bacterial infections with potential serious sequel were particularly common (33.3%), among every third patient being presumed to have serious consequences.

Keywords: Diabetes Mellitus; Diabetes Ketoacidosis; Infections; Predictors; Rate of Infection

1. INTRODUCTION

It is commonly believed that acute infectious illness can precipitate episodes of ketoacidosis in patients with diabetes mellitus. For this reason, a diligent search for bacterial infection is considered essential in the initial evaluation of patients with diabetes ketoacidosis (DKA). Together with hyperglycemic coma, diabetes ketoacidosis

(DKA) is the most severe acute metabolic complication of diabetes mellitus [1]. Defined by the triad hyperglycemia, acidosis, and ketonuria, DKA can be inaugural or complicate diabetes [2]. Although DKA is the evidence of poor metabolic control and usually indicates an absolute or relative imbalance between the patient's requirements and the treatment, DKA-related mortality is low among patients who received standardized treatment, which includes administration of insulin, correction of hydroelectrolytic disorders, and management of the triggering factor (which is often cessation of insulin therapy, an infection, or a myocardial infarction) [3-8].

Unfortunately, the sign and symptoms associated with the ketoacidotic state often make the search for potential infections quiet difficult. These patients often ill appearing, and may have nonspecific symptoms including malaise, headache, abdominal pain, vomiting and altered mental status [9]. Consequently, investigators have searched for predictors of infection, such as the presence of leukocytosis or abnormal differential, in patients with DKA. Slovis *et al.* [9] reported that an elevated band neutrophil count could reliably predict the existence of serious occult bacterial infections in adults with DKA. However, the majority of adult studies have failed to show a clear association between the presence of leukocytosis and the existence of infections in the patient population [6,7].

Although there is no proof that diabetics are more susceptible to infection, but they seem to have more difficulty in the management of infection once it occur [10,11]. Indeed, several aspects of immunity are altered in diabetic patients: polymorphonuclear leukocyte function is depressed, particularly when acidosis is present, and leukocyte adherence, chemotaxis, phagocytosis and bactericidal activity may also be impaired respectively [12-16]. Joshi *et al.* [11] reported that the lack of clinical evidence onwards that diabetic patients are more susceptible to infection than nondiabetic patients. Nevertheless, infection is a well-recognized trigger of DKA. For instantly studies on nondiabetic patients have shown a relationship between the presence of leukocytosis and the existence of

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bacterial infections [17,18]. Probably no large scale study regarding DKA and infection in the diabetic population have been reported till date, the objective of this study is to determine the rate of infection in diabetic adults in ketoacidosis and evaluate presenting clinical features as predictors of infection.

Specifically, the absolute leukocyte count, cell differential, and the presence of leukocytosis were selected as the primary variables of interest. In addition, age, sex, temperature and new onset were evaluated as potential predictors of infection.

2. METHODOLOGY

The study was conducted in an urban, Governmental hospital in the state of Penang, Malaysia. The medication records of patients' age more than and equal to age 18 years and who were admitted the diagnosis of DKA (with diabetes mellitus) between Jan 1, 2008 and December 31, 2010 were reviewed. The charts were identified by the ICD-9 admission and/or discharge codes of "diabetes ketoacidosis" and "diabetes mellitus". In this review process, DKA was defined by an elevated serum glucose ≥ 250 mg/dL, a serum bicarbonate ≤ 15 meq/L and pH ≤ 7.35 .

The entire medical record was reviewed for each hospital admission. Clinical evaluations, including a search for potential infections, as well as all treatment decision, were conducted at the discretion of the admitting physicians. Demographic characteristics were recorded on each patient in addition to the initial maximum temperature, serum glucose, serum bicarbonate, venous or arterial pH, total leukocyte count and cell differential. Fever was defined as a temperature $\geq 38^{\circ}\text{C}$; the method by which temperature was measure was not recorded. Leukocytosis was defined as a total white blood cell count $\geq 15,000/\text{mm}^3$. All admissions were included in the analysis, including those with missing data.

The following are a priori definitions regarding infection: patients with no history (e.g., respiratory symptoms, diarrhea), physical examination (e.g., otitis media, cellulitis), rapid streptococcal testing, culture and/or radiographs, during the entire hospital course, were defined as having no infection. Patients with the documentations of symptoms, signs and/or radiographs consistent with upper and/or lower respiratory tract infections, for which no antibiotics were given, were defined as having presumed viral infection. Patients treated with antibiotics, as deemed necessary by the treating physicians, were defined as having bacterial infection. So patients were categorized into 3 groups based on these definitions; 1) no infection; 2) presumed viral infection; and 3) bacterial infection. Comparison was made between these groups and are stated as "intergroup comparisons".

For primary purpose of descriptive analysis, the pa-

tients with bacterial infection were further divided into minor and major infection categories based on the likelihood of serious sequel as evidenced in the diabetes literature. Statistical analysis were performed using SPSS version 17®. Analyses included the use of student t-test and ANOVA for the normally distributed data, the Mann-Whitney U rank sum and Kruskal-Wallis tests for continuous, nonnominal data and chi-square for dichotomous variables. When comparisons were made between continuous predictive variables, including age, temperature, white blood cell count and cell differential and the dichotomous outcome variables of infection, bacterial infection, and "Occult" infection, stepwise logistic regression analysis for parametric data was performed. When evaluating an association between 2 continuous variables, such as total white blood cell count and pH, a Pearson's correlation test was applied.

All reported p-values are 2-tailed and significance was established at $p \leq 0.05$. Data is presented as mean \pm standard deviation (SD) unless otherwise indicated. Odds ratios with 95% confidence intervals (CI) are presented when applicable. Power calculations using measured proportions were made using Sample Power Version 1.00 (SPSS, Chicago, IL). This Study is approved by the hospitals "Clinical Research Committee (CRC)" as well as "Ministry of Health Malaysia (MOH)".

3. RESULTS

During the time period of January 2008 through December 2010, there were total 2174 diabetes patients admitted; 2174 (100%) patients' charts were reviewed. Of these 967 (44.5%) admission were for DKA. The mean age of the patients was 37.9 ± 5.7 years; 48.9% were male. The mean admission glucose was 551 ± 170 mg/dL whereas the mean bicarbonate was 8.5 ± 3.7 meq/L and mean pH 7.15 ± 0.14 . The mean admission white blood cell count was $18,177 (\pm 9431)$; 721 (74.6%) had leukocytosis. The mean maximum temperature was $37.2 \pm 4.0^{\circ}\text{C}$; 57.1% had fever.

Table 1 summarizes the demographic characteristics of the 3 groups. Among the 967 admissions, 112 (11.6%) had no evidence of infection. There were 176 with presumed viral infection (18.2%), and 679 with bacterial infection (70.2%). Of those with bacterial infection, 453 had minor infection (66.7%), and 226 had major infection (33.3%). Minor bacterial infection included otitis media, streptococcal pharyngitis, sinusitis, and bronchitis. Major bacterial infection included pneumonia, septicemia, cellulitis (leg) and urinary tract infection. The demographic characteristics of those with major bacterial infection are shown in **Table 2**.

There were no significant intergroup different in age, sex, temperature, new onset, total white blood cell count,

Table 1. Presenting clinical symptoms for infection category among patients with DKA.

Category	None Inf	Viral Presumed	Bacterial Inf	Total
Patients	112 (11.6%)	176 (18.2%)	679 (70.2%)	967 (100%)
Age (years)	32.1 (\pm 3.2)	35.7 (\pm 4.6)	42.1 (\pm 7.5)	37.9 (\pm 5.7)
Temperature ($^{\circ}$ C)	37.2 (\pm 4.7)	37.4 (\pm 0.97)	37.1 (\pm 0.84)	37.2 (\pm 4.0)
Glucose mg/dL	571 (\pm 147)	640 (\pm 168)	627 (\pm 197)	551 (\pm 170)
HCO ₃ meq/L	8.7 (\pm 3.5)	8.4 (\pm 3.3)	8.5 (\pm 3.8)	8.5 (\pm 3.7)
pH	7.15 (\pm 0.13)	7.16 (\pm 0.15)	7.16 (\pm 0.11)	7.15 (\pm 0.14)
WBC/mm ³	17,964 (\pm 10,104)	17,773 (\pm 8420)	17,291 (\pm 9724)	18,177 (\pm 9431)
ANC/mm ³	13,781 (\pm 9457)	12,645 (\pm 8974)	11,964 (\pm 7990)	13,249 (\pm 8000)
ABC/mm ³	747 (\pm 1345)	661 (\pm 1397)	793 (\pm 2343)	741 (\pm 1574)
ALC/mm ³	3038 (\pm 2921)	3455 (\pm 2752)	2,990 (\pm 1,737)	3227 (\pm 2771)
New DM	60 (53.6%)	73 (41.5%)	221 (32.5%)	416 (43.0%)
%male:%female	48.2%:51.8%	47.3%:52.7%	51.2%:48.8%	48.9%:51.1%

Abbreviations: WBC, White blood cell count, ANC, Absolute neutrophil count; ABC, Absolute band count; ALC, Absolute lymphocyte count. *Mean with standard deviations in parenthesis.

Table 2. Severe bacterial infections in adult DKA.

N(%) Patients*	Age (mean)	WBC/mm ³ (Mean)	Infection*
245 (36.1)	47.6 (\pm 3.1)	31,200 (\pm 5678)	Septicemia
212 (31.2)	41.7 (\pm 4.5)	25,712 (\pm 5310)	Community acquired pneumonia
117 (17.2)	39.2 (\pm 2.9)	15,180 (\pm 6873)	Hospital acquired pneumonia
198 (29.2)	41.5 (\pm 4.7)	14,890 (\pm 4790)	Ecoli urinary tract infection
359 (52.9)	49.1 (\pm 5.6)	18,310 (\pm 7851)	Cellulitis of leg (toe)

*Majority of patients have multiple infections. So the total number of patients will exceed the 100% (679).

total neutrophil count, total band count and total lymphocyte count. Comparing those with leukocytosis ($n = 721$) versus those without ($n = 246$), there was also no significant intergroup differences. Furthermore, when attempting to use leukocytosis as a predictor of bacterial infection, no significant differences could be found. The power of the analytical comparison of bacterial infection and leukocytosis was 47% (based on the sample size of 721 and 246 for the 2 groups and the measured difference in proportions of 0.07). Notably, of the 80 patients with initial white blood cell counts greater than 40,000/mm³, only 27 (33.8%) had a documented evidence of infection during the hospital course (**Table 2**). None of the variables of interest, including white blood cell count, differential, and leukocytosis, were predictive of major infection. The power of the analysis of major bacterial infection and leukocytosis was 17% (based on the measured difference in proportions of 0.02). Finally, when com-

paring those with leukocytosis to those with any infection, viral or bacterial, no significant association could be found. The power of this analysis was 15% (based on measured difference in proportions of 0.05).

Using the same analytical approach as above, no significant relationship could be found between any category of the cell differential and bacterial infection (**Table 1**). Furthermore, when comparing the categories of the cell differential to the presence or absence of any infection, no significant relationship could be found.

There was significant ($p < 0.05$) difference in age between the 3 groups, age above 57 years have high rate of infection as compared to age below and equal 57 years. When age was compared with those with and without bacterial infections, only a trend towards significance could be found ($p = 0.1$). further analysis showed that 70.8% (481/679) of the patients less than or equal to 57 years of age had bacterial infections compared with 29.1% (198/

679) of the patients greater than 57 years; the odds ratio for this comparison was 2.5 (95% CI = 1.48 to 4.31, $p = 0.03$).

Between the three groups, there was no significant difference in maximum temperature. The presence of fever, however, was a significant predictor of infection 70% of those with fever had infection whereas 25% without fever had infection ($p < 0.001$). On the other hand, fever was not a significant predictor of bacterial infection. In reviewing the data, a significant correlation was found between the total white blood cell count and the pH ($r = -0.57$, $p < 0.001$). There was also a significant correlation comparing the WBC with serum bicarbonate ($r = -0.44$, $p < 0.001$). Furthermore, when dichotomizing pH around the mean pH (*i.e.*, $\text{pH} \leq 7.15$ compared $\text{pH} > 7.15$), a significant association was found between leukocytosis and pH; the odd ratio of this comparison was 2.67 (95% CI = 1.85 to 3.19, $p < 0.001$). Finally, when comparing those with serum bicarbonate above and below the mean bicarbonate of 8.6 meq/L, a significant relationship could also be found between leukocytosis and bicarbonate (odds ratio = 1.97, 95% CI = 1.47 to 2.51, $p < 0.001$).

4. DISCUSSION

Early detection of bacterial infection in patients with diabetes mellitus is a clinical priority. This need is based on the higher morbidity associated with infections in adults with diabetes. Impaired host responses may be responsible for this increased severity of infection. For example, it has been shown that polymorphonuclear leukocytes in diabetic patients, particularly when acidosis is present, may have defects in adherence, chemotaxis, phagocytosis and antioxidant activity involved in bactericidal function [12]. Moreover, diabetic patients with ketoacidosis have alterations in monocyte receptor functions [19]. Finally, a decreased responsiveness of T-cell lymphocytes to mitogenic stimulation had been shown [20].

Despite these concerns, studies have failed to identify reliability predictors of infection in the most severe diabetics, namely those with ketoacidosis. Campbell *et al.* [21] evaluated 140 adults with DKA and concluded that total WBC, blood glucose and bicarbonate had little or no value in predicting infection. Slovis *et al.* [9] attempted to identify adults with occult bacterial infections by examining the records of 169 patients with DKA. He found that 30 (21%) of the patients admitted had occult infections (11 minor infections and 19 major infections) that were not diagnosed initially but within the first 48 hours of administration. He concluded that, of all the variables examined, only a band neutrophil counter greater than 10% could reliably predict major occult bacterial infections in adult patients with DKA.

On the other hand, the association between DKA and

leukocytosis in the absence of infection, predominantly in adult patients, is described in the literature. Zieve *et al.* [22] described 124 patients, aged 14 - 75 years, with moderate to severe DKA, noting that the total WBC ranged from 4200 to 48,000. Cohen *et al.* [23] found that the WBC count ranged from 5100 to 43,000 in patients with severe DKA. Our study showed a range of 8100 to 51,000.

The origin of the leukocytosis observed in adult patients with DKA is unknown but has been attributed, in part, to increased catecholamine release from the adrenal gland in response to stress; marked dehydration and resulting hemoconcentration may also play a role [23-24]. On the other hand, kayashima *et al.* [25] found that granulocyte colony-stimulating factor does not appear to be a mediator in this response.

This retrospective study attempted to identify the frequency of infection and then ascertain whether predictors of infection could be easily identified based on presenting data. Specifically, the patients were categorized into 3 groups based on infection type with high sample size so that comparison could be made with previously published studies on adult diabetes patients. We found that the majority of patients 69.5% had no clinical evidence of infection. Although 70.2% (679/967) of the patients were treated with antibiotics, major bacterial infections were common, representing every third patient with severity of infection load (226, 33.3%) of the adults with DKA. As shown in our power calculation, this high rate of bacterial infection, particularly of the major type, may have created a type I error in our analysis.

Our findings of leukocytosis counts in the range of 4720 to 53,100 is inconsistent with other previous studies, possibly with increase number of sample size and also high mean age value. We found no relationship, however, between leukocytosis or cell differential and infection in adults with DKA. Furthermore, 47 cases (17 major bacterial infections, 30 minor bacterial infections) of bacterial infections were not initially recorded by the admitting physician but noted within the first 48 hours; assuming that these were truly "occult", they represented only 4.9% of the admission of the study which descriptively lower with the study done by Slovis *et al.* [9] reported 21% occult bacterial infections. Furthermore, a band neutrophil count greater than 10%, or any other portion of the cell differential, were not significant predictors of bacterial infection, including these occult infections, in our population. Again, the low prevalence of these infections is meaningful, but resulted in an underpowered analysis.

There are other potential limitations of our study based on the design. Most importantly, a possible bias may be found in any retrospective chart review, particularly when identified dependent variable such as infection. As previously stated, the definitions of infection were applied as priori so as to capture every patient with a possible

viral or bacterial infection. For instance, the presence of upper respiratory tract symptoms was taken as evidence of a presumed viral infection. This, in turn, may have resulted in an overestimation of the total number of viral infections in our analysis. On the other hand, because cultures, rapid streptococcal testing and chest radiographs were not performed on every patient, it is possible that we underestimated the prevalence of bacterial infections. Still it is more likely we overestimated the prevalence of bacterial infections because we included all patients treated with antibiotics in the bacterial infection category. Furthermore, it seems unlikely that a significant number of major bacterial infections were not appropriately identified (*i.e.*, missed) when all 967 patients in our study were admitted and the entire hospital course was reviewed.

Perhaps these same limitations in retrospectively identifying infections account for the wide range of infections rates as described in adults with DKA in previously published studies. For instance, Cohen *et al.* [23] stated that infection, either major or minor, is listed as the cause of DKA in 15% to 50% of the cases. Our findings of 47.7% (n = 461) infection rate is within the wide range reported.

5. CLINICAL IMPLICATION

Of clinical importance, we found the patients more 57 years of age in DKA were more likely to have bacterial infection than those below or equal to 57 years. Yet, major infections were not more common in this group. In addition, statistically significant relationship between the pH, the serum bicarbonate and the WBC were revealed in our post hoc analysis. This suggests that the observed leukocytosis may be another indicator of the severity of the ketoacidosis state rather than a predictor of infection.

6. LIMITATIONS

1) High rate of bacterial infection, particularly of the major type, may have created a type I error in our analysis.

2) The Occult infections with low prevalence are meaningful, but resulted in an underpowered analysis.

3) This study presents the findings of single-centre outcomes, probably will be deferred with multi-centre study.

7. CONCLUSION

The infection rate in Elderly patients in DKA is high and majority of them have lack of clinical evidence. Major bacterial infections with potential serious sequel are particularly common (33.3%), as every third patient being presumed to have serious consequences. Age has a significant effect on the rate and prediction of infection. Leukocytosis is commonly found but more likely reflects the severity of ketoacidosis rather than the presence of infec-

tion. It is also found that the initial evaluation by the admitting physician, followed by an age appropriate work-up as clinically indicated, is the preferred approach to elderly patients presenting in DKA.

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