Original Article

# Characteristics and Treatment Outcome of Pediatric Diabetic Ketoacidosis in Mekong Delta, Vietnam: A 5-Year Retrospective Study

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## ABSTRACT

### Background

Diabetic ketoacidosis (DKA), a critical and potentially fatal complication resulting from a lack of insulin, presents with elevated blood sugar, acid-base imbalance, and increased ketone bodies.

### Objectives

Our research was designed to assess the clinical manifestations, laboratory findings, and outcomes of treatment in children diagnosed with DKA over a span of five years in the Mekong Delta region of Vietnam.

### Methods

This study retrospectively analyzed pediatric cases of diabetic ketoacidosis treated at a major pediatric center in the Mekong Delta between 2017 and 2021.

### Results

Diabetic ketoacidosis was more common in older children aged 11 – 16 years (66.7%), and females (70%). The majority of cases had not been diagnosed with previous diabetes (60%) and no history of diabetic ketoacidosis (90%). In univariate analysis, female gender (OR, 13.0; 95% CI, 1.4 – 124.3; p=0.026), previous diabetes diagnosis (OR, 7.8; 95% CI, 1.5 – 41.2; p=0.016), precipitating factors (OR, 10.1; 95% CI, 1.1 – 97.0; p=0.045), tachypnea (OR, 5.5; 95% CI, 1.1 – 26.4; p=0.033), Kussmaul breathing (OR, 5.4; 95% CI, 1.1 – 26.0; p=0.036), serum potassium level (OR, 3.5; 95% CI, 1.2 – 10.4; p=0.027), and anion gap (OR, 1.6; 95% CI, 1.8 – 2.3; p=0.003) were associated factors with severe DKA. All cases in our study had a 100% survival rate. Anion gap was an independent factor associated with severe diabetic ketoacidosis after adjustment multivariate analysis. ***Conclusion:*** Female, younger age, precipitating factors, tachypnea, Kussmaul's breathing, and relevant laboratory findings, including increased anion gap, should be considered to ensure successful management in pediatric diabetic ketoacidosis.

## Keywords

Diabetes mellitus; diabetic ketoacidosis; severe acidosis; pediatrics; precipitating factors.

## INTRODUCTION

Diabetes mellitus, especially Type 1 diabetes (T1D), stands as a predominant metabolic disorder afflicting children and adolescents, marking itself as a significant concern in pediatric healthcare globally.[1,2] The incidence of this disease has seen a concerning surge, with a notable 39.37% increase from 1990 to 2019.[3] This rise in cases is especially pronounced in regions such as North Africa and the Middle East, showcasing the highest regional growth

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rates (estimated annual percentage changes: 2.06; 95% CI: 1.94 – 2.17). Among the 204 countries surveyed, the United Republic of Tanzania reports the highest impact in terms of disability-adjusted life years (100.16 per 100,000 population). Meanwhile, Bangladesh experiences the highest death rate associated with diabetes, at 1.16 per 100,000 individuals.[3] Furthermore, studies emphasize a troubling rate of diabetes incidence in Vietnamese children between the ages of 11 and 14, with 6.1% being diagnosed via fasting blood glucose screenings.[4]

Diabetes is acknowledged as a complex condition, with its development and progression being shaped by a complex interaction of genetic, metabolic, and environmental elements.[3,5] Among the dire consequences of diabetes in youth is the heightened risk of cardiovascular diseases, which notably contributes to mortality rates. This risk is intricately linked with diabetes incidence, mediated through shared risk factors including dyslipidemia, hypertension, and obesity.[3,6,7] Despite advancements in therapeutic strategies for diabetes, challenges in treatment adherence remain pivotal, often leading to suboptimal disease management and severe complications.[8–11] Insulin therapy, a cornerstone in T1D management, exemplifies these challenges, particularly among pediatric patients, where non-adherence and poor glycemic control present significant hurdles.[12,13] Diabetic ketoacidosis (DKA), characterized by hyperglycemia, metabolic acidosis, and ketosis, stands as a critical and acute complication.[14] It is a leading cause of mortality in T1D individuals, particularly children, and accounts for up to 83% of diabetes-related deaths, underscoring its severity as a pediatric emergency and its potential to cause lasting disabilities.[15,16]

In Vietnam, the mortality rates due to DKA in children with T1D range significantly from 2.9% to 6.1%,[17,18] starkly higher than those observed in neighboring countries, which vary from 0.15% to 0.3%.[19–21] This disparity highlights the critical need for identifying and addressing DKA risk factors, which vary between patients with newly diagnosed T1D and those with pre-existing conditions, as outlined by the International Society of Childhood and Adolescent Diabetes (ISPAD) guidelines. Among newly identified patients, risk contributors include a younger age, a lower socio-economic standing, postponed diagnosis, and living in areas with a minimal prevalence of T1D. Conversely, in patients with existing T1D, factors such as insulin non-compliance, dietary mismanagement, and additional health or social challenges are prevalent.[22] The severity of DKA correlates with increased recovery times, longer hospital stays, and elevated mortality rates, emphasizing the importance of early detection and management of risk factors.[22]

The critical nature of DKA necessitates prompt emergency medical intervention, with severe cases requiring advanced and intensive care. Recognizing risk factors early and achieving timely diagnosis are imperative to improve patient outcomes and alleviate the healthcare system's burden. Consequently, this study aimed to elucidate the characteristics and treatment outcomes of DKA in children at Can Tho Children's Hospital, a leading pediatric specialty center, to better inform and enhance care strategies for this vulnerable population.

## MATERIALS AND METHODS

### *Study design and data collection*

This retrospective research was carried out on children ranging from 2 months to 16 years old, diagnosed with DKA, at a leading pediatric hospital in the Mekong Delta, Vietnam, between 2017 and 2021. DKA diagnosis followed the ISPAD criteria, which encompass (1) hyperglycemia (blood glucose levels >200 mg/dL or 11 mmol/L); (2) a venous pH of less than 7.3 or serum bicarbonate levels below 15 mmol/L; (3) the presence of ketones in the blood and urine.[22] Electrolyte levels were also assessed. Serum sodium level (<135 mmol/L, 135–155 mmol/L, >155 mmol/L), serum potassium level (<3.5 mmol/L, 3.5–5.5 mmol/L, >5.5 mmol/L), serum chloride level (increased at admission, increased during treatment), acute kidney injury with RIFLE classification (not recorded, risk, injury),[23] and HbA1c were recorded. The collected information comprised both demographic particulars and historical medical data such as age (2 months – 10 years old, 11 – 16 years old), gender, personal history of diabetes, history of diabetic acidosis, and precipitating factors (insulin omission, uncontrolled diet, infection, trauma). The collected symptoms include fever, consciousness, tachycardia, hypokinetic pulse, hypotension, prolonged capillary refill time (>2 seconds), tachypnea, Kussmaul breathing, dehydration level, and guarding sign. Children were excluded from the study when medical records data were insufficient. Diabetic ketoacidosis

(DKA) is described as a medical condition arising from a lack or insufficiency of insulin, leading to high blood glucose levels, dehydration, and the accumulation of ketones.[22,24] The severity of DKA is classified according to the level of acidosis in the blood, as follows[22] : Mild DKA is identified when the pH of venous blood is between 7.2 and 7.29, or when the bicarbonate level falls below 15 mmol/L. Moderate DKA is indicated by a venous blood pH ranging from 7.1 to 7.19, or when bicarbonate levels are below 10 mmol/L. Severe DKA occurs when the pH of venous blood is below 7.1, or bicarbonate levels are under 5 mmol/L.

### *Statistical analysis*

Data analysis was executed using SPSS software, version 18.0. For continuous variables exhibiting a normal distribution, mean and standard deviation (SD) were used for representation and comparisons were made via the t-test. Variables not following a normal distribution were depicted using median and interquartile range (IQR), with non-parametric tests employed for comparisons. Categorical data were displayed in terms of frequencies and percentages and examined through the chi-square test. The assessment of factors associated with severe diabetic ketoacidosis (DKA) in children was conducted through multivariable logistic regression models employing a backward elimination method, aimed at determining odds ratios (OR), 95% confidence intervals (CI), and identifying independent predictors. A p-value below 0.05 was considered to signify statistical significance.

## ETHICAL CLEARANCE

The Ethics Committee in Biomedical Research at Can Tho University of Medicine and Pharmacy, alongside the Director of Can Tho Children's Hospital, reviewed and granted approval for the ethical and scientific facets of this study (IRB approval No. 376/PCT – HĐĐĐ, dated June 24, 2021).

## RESULTS

During the period from 2017 to 2021, thirty children aged between 2 months and 16 years, who were diagnosed with diabetic ketoacidosis (DKA), were treated at a leading pediatric hospital in the Mekong Delta region of Vietnam. The majority age was 11 – 16 years (66.7%), with female predominating (70%). More than half of the sample (60%) had not been previously diagnosed with T1D, and only three out of thirty cases had a history of ketoacidosis. Infection (56.7%), particularly gastrointestinal infection, was the prevalent precipitating factor, followed by insulin omission (as detailed in Table 1).

**Table 1.** General characteristics of research participants

| Variable | Overall (n=30) |
|---|---|
| Age group, n (%)<br>2 months – 10 years old<br>11 – 16 years old | <br>10 (33.3)<br>20 (66.7) |
| Female gender, n (%) | 21 (70) |
| History of T1D, n (%) | 12 (40) |
| History of DKA, n (%) | 3 (10) |
| Precipitating factors, n (%)<br>Infection<br>Insulin omission<br>Absence | <br>17 (56.7)<br>5 (16.7)<br>8 (26.6) |

### **Clinical and laboratory profile of pediatric diabetic ketoacidosis*

Eleven cases out of thirty cases presented irritation at 36.7%. Tachypnea and Kussmaul breathing were the most common clinical symptoms noted at admission (43.3% and 50%, respectively). Approximately 43.3% of hospitalized cases showed signs of moderate to severe dehydration. In terms of laboratory findings, over two–thirds of the children had 2+ ketonuria (70%). Most admissions had a pH below 7.1 (43.3%), and the least common finding was an $HCO3^-$ level below 5 mmol/L (16.7%). Severe acidosis was recorded in 14 cases (46.7%), shown in Table 2.

**Table 2.** Clinical and laboratory features of children with diabetic ketoacidosis upon hospital admission

| Symptom | Overall (n=30) |
|---|---|
| **Clinical signs** | |
| Consciousness disturbance, n (%)<br>Consciousness<br>Irritation<br>Delirium | <br>10 (33.3)<br>11 (36.7)<br>9 (30) |
| Tachycardia, n (%) | 11 (36.7) |
| Hypokinetic pulse, n (%) | 3 (10) |
| CRT >2 seconds, n (%) | 3 (10) |
| Hypotension, n (%) | 3 (10) |

| Symptom | Overall (n=30) |
|---|---|
| Narrow pulse pressure, n (%) | 2 (6.7) |
| Tachypnea, n (%) | 15 (50) |
| Kussmaul breathing, n (%) | 13 (43.3) |
| Fever, n (%) | 11 (36.7) |
| Dehydration level, n (%)<br>Mild<br>Moderate<br>Severe | <br>17 (56.7)<br>9 (30)<br>4 (13.3) |
| Guarding sign, n (%) | 1 (3.3) |
| **Laboratory features** | |
| Ketonuria, n (%)<br>1+<br>2+<br>3+ | <br>4 (13.3)<br>21 (70)<br>5 (16.7) |
| pH, n (%)<br><7.10<br>7.10-7.19<br>7.20-7.29 | <br>13 (43.3)<br>7 (23.3)<br>10 (33.4) |
| $HCO_3^-$ at admission (mmol/L), n (%)<br>< 5.0<br>5.0-9.9<br>10.0-14.9 | <br>5 (16.7)<br>11 (36.6)<br>14 (46.7) |
| DKA severity, n (%)<br>Severe<br>Moderate<br>Mild | <br>14 (46.7)<br>6 (20)<br>10 (33.3) |
| Ketonuria, n (%)<br>1+<br>2+<br>3+ | <br>1 (3.3)<br>1 (3.3)<br>28 (93.4) |
| Serum sodium level (mmol/L), n (%)<br><135<br>135 – 155<br>> 155 | <br>16 (53.3)<br>12 (40)<br>2 (6.7) |
| Serum potassium level (mmol/L), n (%)<br><3.5<br>3.5 – 5.5<br>> 5.5 | <br>5 (16.7)<br>22 (73.3)<br>3 (10) |
| Serum chloride level, n (%)<br>Increased at ER<br>Increased during treatment | <br>1 (3.3)<br>17 (56.7) |
| AKI, n (%)<br>Not recorded<br>Risk<br>Injury | <br>21 (70)<br>8 (26.7)<br>1 (3.3) |
| Glycemia (mmol/L) (mean±SD) | 34.7±15.9 |
| HbA1c (mean±SD) | 13.3±3.1 |

### **Outcomes of treatment and determinants of severe acidosis in pediatric diabetic ketoacidosis*

Our investigation revealed a number of statistically significant factors linked to ketoacidosis severity in pediatric T1D patients. These factors encompassed female gender (p=0.017), a personal history of T1D (p=0.011), precipitating factors (p=0.039), tachypnea (p=0.028), Kussmaul respiration (p=0.030), serum potassium concentration (p=0.014), anion gap (p<0.001), and leukocyte (p=0.040), as shown in Table 3. Moreover, the anion gap (OR, 2.5; 95% CI, 1.1 – 5.9; p=0.032) remained significant after adjustment with gender in multivariate analysis of DKA severity, was risk factor associated with severe DKA in pediatric T1D patients, as shown in Table 4. In the current study, 100% of cases had successful management with a mean time of DKA of 27.6 ± 12.4 hours and an overall mean ICU length of stay of 47.1 ± 13.8 hours (Table 3-5).

**Table 3.** Comparison of several factors between severe acidosis and non–severe acidosis

| Factors | Severe acidosis (n=14) | Non-severe acidosis (n=16) | p |
|---|---|---|---|
| Age group, n (%)<br>2 months – 10 years old<br>11 – 16 years old | 3 (21.4)<br>11 (78.6) | 7 (43.8)<br>9 (56.2) | 0.260 |
| Female gender, n (%) | 13 (92.9) | 8 (50) | **0.017** |
| History of T1D, n (%) | 9 (64.3) | 3 (18.8) | **0.011** |
| History of DKA, n (%) | 11 (78.6) | 0 (0) | 0.072 |
| Precipitating factors, n (%) | 13 (92.9) | 9 (56.3) | **0.039** |
| Consciousness disturbance, n (%) | 12 (85.7) | 8 (50) | 0.058 |
| Tachypnea, n (%) | 10 (71.4) | 5 (31.3) | **0.028** |
| Kussmaul breathing, n (%) | 9 (64.3) | 4 (25) | **0.030** |
| Blood glucose level (mmol/L), mean±SD | 36.7±15.2 | 34.1±14.1 | 0.627 |

| Factors | Severe acidosis (n=14) | Non-severe acidosis (n=16) | p |
|---|---|---|---|
| Serum potassium level (mmol/L), mean±SD | 4.8±0.7 | 4.0±0.9 | **0.014** |
| Anion gap (mmol/L), mean±SD | 29.1±3.9 | 22.6±2.9 | **<0.001** |
| Leucocytes ($10^3$/mL), mean±SD | 22.5±7.5 | 16.9±6.8 | **0.040** |
| Blood osmotic pressure (mOsm/kg $H_2O$), mean±SD | 313.3±19.9 | 312.9±26.8 | 0.923 |

**Table 4.** Several factors related to severe acidosis in the logistic regression model

| Factors | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95% CI) | p | OR (95% CI) | p |
| Female gender | 13.0 (1.4 – 124.3) | **0.026** | 815.1 (0.9 – 708087) | **0.052** |
| History of T1D | 7.8 (1.5 – 41.2) | **0.016** | | |
| History of DKA | 8.3 (0.8 – 83.2) | 0.071 | | |
| Precipitating factors | 10.1 (1.1 – 97.0) | **0.045** | | |
| Consciousness disturbance | 6.0 (1.0 – 35.9) | 0.050 | | |
| Tachypnea | 5.5 (1.1 – 26.4) | **0.033** | | |
| Kussmaul breathing | 5.4 (1.1 – 26.0) | **0.036** | | |
| Serum potassium level (mmol/L) | 3.5 (1.2 – 10.4) | **0.027** | | |
| Anion gap (mmol/L) | 1.6 (1.8 – 2.3) | **0.003** | 2.5 (1.1 – 5.9) | **0.032** |
| Leukocytes ($10^3$/mL) | 1.1 (0.9 – 1.3) | 0.052 | | |

**Table 5.** Treatment outcome of diabetic ketoacidosis in children

| | Time (hours) |
|---|---|
| Mean time of DKA (n=30) | 27.6 ± 12.4 |
| Median time of shock (n=5) (IQR) | 1 (0.375 – 1.0) |
| ICU length of stay (n=30) | 47.1 ± 13.8 |

## DISCUSSION

In developing nations, DKA is considered a frequent complication in children with T1D. Globally, reports vary on the prevalence of ketoacidosis at T1D diagnosis (12.8% to 80%).[25] In our study, we observed differences between the two patient groups, those with severe and non-severe ketoacidosis, in terms of gender (p=0.017), a history of T1D (p=0.011), and precipitating factors (p=0.039). Additionally, differences were also noted in the presence of tachypnea (p=0.028), Kussmaul breathing (p=0.030), blood potassium levels (p=0.014), anion gap (p<0.001), and leukocyte counts (p=0.040).

According to the overall traits of the research population, the group from 11 to 16 years old had the highest proportion, similar to previously reported research results.[26,27] Furthermore, our analysis revealed no notable difference in acidosis severity across age groups (p=0.26), consistent with prior studies that found no association between age and the severity of DKA.[15,28,29] On the other hand, a systematic review indicated that children younger than 2 years were 3.51 times more likely to present with DKA than those aged 2 years or older (Odds Ratio [OR] 3.51; 95% Confidence Interval [CI] 2.85 – 4.32; p<0.001).[30] Thus, older age groups report higher rates in the total patients, but younger age groups have a significantly increased risk of DKA.

We recorded that female children were hospitalized for severe DKA with a rate of 92.9% and the difference between female children in the severe acidosis group and the non–severe acidosis group was statistically significant (p=0.017). In the univariate logistic regression analysis, the odds of severe acidosis were found to be 13 times greater in female children than in male children (OR=13; 95% CI: 1.4 – 124.3; p=0.026). The precise cause of this variation remains uncertain, yet it could relate to hormonal differences between genders (notably higher estrogen levels in females) and gender-specific differences in the secretion of stress-related cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1).[31] Nevertheless, another study generally found that gender was not significantly associated with the DKA severity.[30] Furthermore, children with a medical history of T1D were more likely to experience severe acidosis, showing an odds ratio (OR) of 7.8 (95% CI: 1.5–41.2,

p=0.016). However, a medical history of prior acidosis did not show a significant association with severe DKA, with an OR of 8.3 (95% CI: 0.8 – 83.2; p=0.071).

Moreover, infection was the most frequent precipitating factor, with 17 cases identified. Among these cases, gastrointestinal infections accounted for 6 out of 17 (35.3%), followed by urinary tract infections (23.5%). It was observed that children with precipitating factors were at an increased odds of developing to severe DKA (OR = 10.1; 95% CI: 1.1 – 97.0; p=0.045). Indeed, infection is the most prevalent precipitating factor in a lot of developing countries.[27,30] First–time experience of acidosis, infection, and insulin omission were linked to the severity of diabetic ketoacidosis (p<0.05).[32]

Disturbances of consciousness (irritation and delirium) are the most frequent physical symptoms, with 20 out of 30 cases (accounting for 66.7%). While other research has shown a significant correlation between the level of consciousness and a heightened risk of severe DKA, our study did not find a significant relationship with the severity of DKA (p=0.05).[33] Additionally, tachypnea and Kussmaul breathing were common symptoms, observed in 43.3% and 50% of cases, respectively, which are lower percentages than those found in another study in Vietnam (56.4% and 90.9%, respectively).[24] The body responds to acidosis by hyperventilation manifested in tachypnea, but it is also a sign of respiratory infections such as pneumonia, as a precipitating factor. However, we found that the rate of lower respiratory infections was only about 10%.

In terms of laboratory results, the group of children with severe acidosis had higher blood potassium than the group with non-severe acidosis (p=0.014). Study findings from Pulungan et al. revealed that blood potassium concentrations were elevated in individuals with severe acidosis when contrasted with those experiencing moderate and mild acidosis, yet the difference lacked statistical significance (p=0.504).[26] In the univariate logistic regression model, we found that children with a 1 mmol/L increase in blood potassium are 3.5-fold more likely to have severe acidosis (OR=3.5; 95% CI: 1.2 – 10.4; p=0.027). Razavi's study found that hypokalemia has a relation to the severity of diabetic ketoacidosis (p=0.02).[28] In other studies, hypoglycemia (20.8%), hypokalemia (24.5%), and hyperchloremic acidosis (18.9%) are among the common complications.[15] Several studies have illustrated the frequency of these complications.[34,35] Increased anion gap is common in diabetes, due to the increasing formation of ketone bodies. When ketones are increased, the body's alkaline buffer will neutralize the ketones and consequently reduce blood pH and $HCO_3^-$.

Contrary to previous theories, changes in the anion gap do not always correspond directly and equally to shifts in serum bicarbonate levels.[36,37] The observed phenomenon might stem from the presence of unaccounted-for cations (UC) and anions (UA). Thus, the accurate equation for the anion gap calculation becomes: $[Na^+] + [K^+] + UC = [Cl^-] + [HCO_3^-] + UA$. This equation can be simplified to $([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-]) = UA - UC$, delineating the anion gap. Hence, the anion gap is essentially the discrepancy between UA and UC.[25] Other plasma factors, particularly albumin, have the potential to alter the association among the acidosis severity, bicarbonate levels, and the anion gap measure.[36] In this study, we found a relationship between increased anion gap and the severity of diabetic ketoacidosis (p<0.001). In the multivariate logistic regression model, we recorded that children with a 1mmol/L increase in anion gap were 2.5-fold more likely to have severe acidosis (OR, 2.5; 95% CI, 1.1 – 5.9; p=0.032).

This current research contains a number of restrictions. The study's retrospective observational nature, which utilizes administrative data, prevents access to relevant interesting clinical information. Additionally, the limited sample size resulting from the study's design may not accurately reflect the broader population. In addition, the study's limited generalizability stems from its utilization of data sourced from a singular center. Further study requiring a larger number of cohort study participants is needed to yield higher-quality data on DKA in the Vietnamese pediatric population.

## CONCLUSIONS

In conclusion, when assessing severe diabetic ketoacidosis (DKA) in pediatric patients, clinicians, especially pediatric endocrinologists, should take into account factors such as female gender, younger age, a history of Type 1 Diabetes (T1D), precipitating factors,

and clinical symptoms like tachypnea and Kussmaul breathing, in addition to an increased anion gap. By utilizing a comprehensive approach to evaluate and manage severe DKA in children, clinicians can ensure swift and effective intervention, ultimately leading to improved patient outcomes.

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### Conflict of interest

The authors have no conflicts of interest to disclose.

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## AUTHORS' CONTRIBUTION

Idea owner of this study: PSN, LCT

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Data collection: PSN, LCT, HMN, TTKL, PHL

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Writing and submitting manuscript: HMN, VTN, LCT, DLT

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