Open Journal of
Clinical & Medical
Case Reports

Volume 3 (2017)
Issue 9

ISSN 2379-1039

Aggressive fluid resuscitation in a series of pediatric patients with diabetic ketoacidosis and shock

Markita L Suttle, MD*; W Joshua Frazier, MD; Jennifer Muszynski, MD

***Markita L Suttle, MD**
Department of Critical Care Medicine, Nationwide Children's Hospital, 700 Children's Drive, Columbus, Ohio 43205, USA
E-mail: markita.suttle@nationwidechildrens.org

Abstract

Cerebral edema remains the major life-threatening complication of children with diabetic ketoacidosis (DKA). Though the mechanism for cerebral edema remains unclear, one theory is grounded in rapid osmotic shifts and supports the use of judicious fluid administration. In circumstances of both DKA and persistent shock, conservative fluid resuscitation may be inadequate to maintain perfusion. Recent guidelines for the management of DKA recommend more aggressive fluid resuscitation for coexisting shock, but practitioners may remain hesitant given the ongoing uncertainty about fluid volume and cerebral edema. This series describes seven patients with DKA and shock who received large resuscitative fluid volumes, yet had normal neurologic outcomes.

Keywords

pediatrics; pediatric intensive care; shock; resuscitation; diabetic ketoacidosis

Abbreviations

DKA: diabetic ketoacidosis; CPAP/PS: continuous positive airway pressure with pressure support; Bipap: bilevel positive airway pressure; ED: emergency department; EMS: emergency medical services; VA-ECMO: venoarterial extracorporeal membrane oxygenation

Introduction

Diabetic ketoacidosis (DKA) results from a deficiency of circulating insulin and increased levels of counter-regulatory hormones such as catecholamines, glucagon, cortisol, and growth hormone [1, 2]. This combination results in an accelerated catabolic state with increased glucose production by the liver and kidney, as well as impaired peripheral glucose utilization [3]. These factors result in hyperglycemia, increased ketone production and hyperosmolality, ultimately leading to osmotic diuresis, dehydration, metabolic acidosis and loss of electrolytes such as sodium, potassium, and phosphate [3].

With mortality estimates between 21-24%, cerebral edema remains the major life-threatening complication amongst children with diabetic ketoacidosis (DKA) [4, 5]. Some studies suggest that large fluid volumes given as initial treatment for DKA increase a patient's risk for cerebral edema [6], while others suggest no relationship at all [7, 8-10]. In circumstances of both DKA and shock, conservative fluid resuscitation may be inadequate to maintain systemic perfusion, risking cytotoxic brain swelling. The combination of these two diagnoses creates a therapeutic conflict. More recent DKA guidelines have

started to address the importance of prioritizing shock treatment in these patients [8], though practitioners may still be cautious given their fear of cerebral edema. We present seven patients with both DKA and shock who received large resuscitative fluid volumes, yet had normal neurologic outcomes.

Methods

Following IRB approval, we performed a retrospective medical records review of all pediatric patients diagnosed with both DKA and shock at our institution from January 2011 to December 2014. Collected data included clinical history, laboratory results, imaging results, and treatment and management strategies. All pediatric patients in this series demonstrated evidence of uncompensated, cold shock. Clinical exams were significant for tachycardia, delayed capillary refill, and hypotension (systolic blood pressure <5th percentile of normal for age).

Patient A: A 15 year-old male with history of essential hypertension presented to the emergency department after three days of vomiting and "flu-like" symptoms. He became progressively more confused upon arrival and was subsequently intubated for inability to protect his airway. Laboratory values consistent with DKA, are listed in Table 1. He developed signs of shock for which he received 2L of resuscitative fluid, in addition to an insulin drip and isotonic fluids at two times maintenance. A head CT was obtained the evening of admission and was read as normal, no signs of cerebral edema. He was transferred to the pediatric intensive care unit (PICU) where he required ongoing fluid resuscitation throughout the first 24 hrs of admission (Table 2). Utilizing mechanical ventilation titration, the patient's PaCO2 was corrected slowly over five hours, with the patient being placed on continuous positive airway pressure with pressure support (CPAP/PS) after twelve hours of PICU admission. His peak lactate was 1.0 mmol/L. A repeat head CT on day three of admission was again negative. All signs of shock, as well as DKA, resolved by thirty-six hours of admission. He was extubated to room air on day three. The patient's mental status gradually improved and he was ultimately transferred to the Endocrinology service on day six. He was found to have a buttocks abscess and underwent surgical drainage during his hospitalization. He was discharged to home after twenty-three days of admission with no noted neurologic deficits.

Patient B: A 3 year-old female presented to our ED after being found unresponsive at home. Family reported that they could not wake her after a four hour nap. The day prior to admission she was treated with intramuscular penicillin for *Streptococcal* pharyngitis. In the ED the patient was intubated for lack of respiratory effort, leading to bradycardic arrest resulting in two minutes of CPR and two doses of epinephrine. She showed evidence of persistent shock, requiring 60 ml/kg of resuscitative fluid and a dopamine drip. Initial laboratory values, consistent with DKA, are listed in Table 1. She was started on an insulin drip and isotonic fluid at two times maintenance. A head CT obtained was normal. In the PICU the patient required further fluid resuscitation and the addition of an epinephrine drip (see table 2). Stress-dose hydrocortisone was added for catecholamine-refractory shock. She received a traditional ventilator weaning strategy (normal pH goal) and her PaCO2 corrected over three hours. During the first twenty-four hours of admission the patient demonstrated dramatic urine output and glycosuria, prompting urine replacements in order to maintain her intravascular volume. Her peak lactate was 1.7 mmol/L. A head CT was repeated on day two of admission and was again negative. By forty-eight hours of admission the patient's shock, acidosis, and hyperglycemia resolved. She weaned off vasopressors, hydrocortisone was discontinued, and urine replacements were stopped. She was extubated on day five. Neurologically

the patient could follow commands, but was noted to have mildly increased tone in her upper and lower extremities. She was transferred to the Endocrinology service on day eight and at six months post-discharge she was reported to be back to her neurologic baseline with normal tone.

Patient C: A 16 year-old female presented to an outside hospital after being found unresponsive at home. Family reported that she had taken a nap for three hours and afterward was difficult to wake. The day prior to presentation the patient was treated for tonsillitis with ceftriaxone. Because of depressed mental status, she was intubated and a head CT was obtained and read as normal. Her initial laboratory values are presented in Table 1. These values, combined with an HgbA1C of 13.1%, supported a diagnosis of DKA. During transport to our ED, the patient developed shock resulting in a total of 5L fluid resuscitation. In the ED, dopamine and norepinephrine were initiated for fluid-refractory shock. A repeat head CT was again normal. She was started on an insulin drip and isotonic fluid at two times maintenance. In the PICU, the patient required ongoing fluid resuscitation and titration of vasopressors (see Table 2). Her peak lactate was 2.1 mmol/L. Within twenty-four hours of admission the patient's acidosis and hyperglycemia resolved. Shock resolved within thirty-four hours and she weaned from all vasopressor support. She was extubated to room air and had no neurologic deficits on examination. She was transitioned to intermittent insulin and transferred to the Endocrinology service on day three.

Patient D: A 20 year-old known type I diabetic male presented to an outside adult emergency department following a week of fever, abdominal pain, loose stools, and headache. Laboratory values consistent with DKA are listed in Table 1. He was given 3L of fluid resuscitation for severe dehydration and shock, as well as a bolus of insulin. He was started on both bicarbonate and insulin drips, intubated and subsequently transferred to our institution on isotonic fluids at two times maintenance. Upon arrival to our ED, the bicarbonate infusion was stopped and the patient's glucose was found to have dropped to 250 mg/dL. He received an additional 4L of resuscitative fluid, was started on a norepinephrine infusion, and placed on stress-dose hydrocortisone for fluid and catecholamine refractory shock prior to transfer to the PICU. A head CT was obtained and read as normal. In the PICU the patient's lactate peaked at 5.1 mmol/L. He was immediately placed upon CPAP/PS on the ventilator and was extubated to room air after three hours of admission. This patient's shock resolved rather quickly, with normalization of vitals and perfusion. His norepinephrine was weaned off within 4 hours and he required no further fluid boluses. Stress-dose hydrocortisone was discontinued on day two. The patient was discharged to home after two additional days on the Endocrinology floor with no focal neurologic deficits.

Patient E: A 13 year-old male with known type I diabetes presented to the emergency department following twenty-four hours of abdominal pain, vomiting and diarrhea. He appeared severely dehydrated on examination and was having frequent and substantial stool output requiring stool replacements in the ED. Initial laboratory values consistent with DKA are listed in Table 1. He was started on an insulin infusion as well as 1.5 times maintenance isotonic fluids. He underwent an abdominal CT secondary to pain and abdominal distension on examination and was found to have a small bowel obstruction that was treated with bowel rest and serial examinations. In the PICU the patient required ongoing fluid resuscitation and stool replacement (see Table 2). His lactate peaked at 3.9 mmol/L. He was started on an epinephrine infusion for fluid refractory shock (max rate 0.3 mcg/kg/min) and was placed on bilevel positive airway pressure (Bipap) as a means of lessening metabolic demand. Though sleepy at times, the

patient overall remained awake and communicative throughout the entirety of his acute shock phase. By thirty-six hours the patient's epinephrine infusion was weaned to off and he was removed from bipap. He was monitored in the PICU for one additional day, but was transferred to the Endocrinology service on day four. His bowel obstruction gradually resolved without surgical intervention and he was discharged to home after nine days with no neurologic deficits on examination. A head CT was never obtained.

Patient F: A 10 year-old female presented to an outside hospital ED via EMS after parents were unable to wake her from bed in the morning. The last time parents reported seeing her alert and awake was estimated at ten hours prior to that morning. Upon arrival to the outside ED she was noted to by hypothermic to 92°F and would only withdrawal to pain in her extremities. Laboratory values consistent with DKA, are listed in Table 1. Her vital signs were reported as normal except for mild tachycardia. She was given a dose of mannitol, a 1L fluid bolus, and started on an insulin infusion with maintenance fluids prior to direct admission to our PICU. Upon arrival to the PICU (1.5 hours later) her pH was 6.86, glucose 401 mg/dL, and bicarbonate <5 mmol/L. She was immediately started on dopamine for shock. She would initially respond to verbal command with confused speech, but her mental status rapidly declined to the point of inconsistently responding to painful stimulation. She was given an additional dose of mannitol prior to going for a stat head CT, which revealed mild diffuse cerebral swelling with visible cisterns (Figure 1). The patient was ultimately intubated for worsening mental status. Mechanical ventilation strategies were aimed at slowly correcting the patient's PaCO2 over eight hours and then transitioning to CPAP/PS. Shock management was escalated including the addition of norepinephrine (max 0.2 mcg/kg/min) and stress-dose hydrocortisone (2 mg/kg). Her peak lactate was 2.1 mmol/L and hemodynamic support was ongoing for close to seventy-two hours. Despite intubation, the patient was noted to be following commands as early as day two. She was eventually extubated to nasal cannula on day five and noted to be neurologically intact without focal deficits. She was transferred to the Endocrinology service on day six and discharged to home after eight total days of hospitalization.

Patient G: An 11 year-old female with poorly controlled type 1 diabetes mellitus was found unresponsive at home after lying down for a nap four hours prior. After attempts to wake her up at home, family eventually presented to an outside hospital (2 hours later). On initial evaluation in the outside ED, she was found to be hypothermic (87°F) and hypotensive. Initial laboratory values, consistent with DKA, are listed in Table 1. The patient was intubated, received 2L of resuscitative fluid, and was started on an insulin infusion prior to transport to our ED. Upon arrival to our ED the patient's hypothermia had resolved, but she demonstrated shock, resulting in 1.8L of fluid resuscitation, in addition to isotonic fluid at two times maintenance. A brain CT was obtained and read as normal with no apparent edema. Upon admission to the PICU, the patient required ongoing fluid resuscitation and the initiation of an epinephrine drip (see Table 2). She remained hypotensive despite increases in her vasoactive infusion, so stress-dose hydrocortisone was added. Her profound acidosis and shock persisted despite the continued escalation and titration in her support. A transthoracic echocardiogram (ECHO) was obtained, demonstrating severely depressed biventricular function, thus the decision was made to place the child on VA-ECMO. A repeat head CT was obtained prior to cannulation and again noted to be normal. The patient was cannulated via the right internal jugular vein and right carotid artery, with the following initial ECMO settings: blood flow rate 4.6L/min, cardiac index 2.0 L/min/m^2, sweep gas 1.9 L/min, FiO_2 60%. Her $PaCO_2$ just prior to initiating ECMO was 34 mmHg and it was gradually corrected over 3 hours in

prevent an excess of cerebral blood flow. An ECHO on day three showed persistence of cardiac dysfunction, prompting the addition of a milrinone infusion. This patient's peak lactate was 9 mmol/L. By day four the patient's acidosis and shock had resolved and a repeat ECHO demonstrated improved biventricular function on milrinone, even when challenged with decreased ECMO circuit flows. VA-ECMO was subsequently discontinued on day five and milrinone was transitioned to oral enalapril. She was successfully extubated on day eight and a repeat ECHO showed normal biventricular function. She was ultimately transferred to the Endocrinology service on day ten. She was discharged to home after twenty-two total days of hospitalization with no appreciable neurologic or cardiac sequelae.

Discussion

Cerebral edema remains the most life-threatening complication of DKA, though the causes of this entity remain unclear. One long-standing theory supports the idea of rapid fluid shifts into brain cells with the initiation of fluid and insulin therapy as a cause [11]. Work perfomed by *Edge et al* suggested that large fluid volume administration during the first four hours of DKA treatment increases a patient's odds of developing cerebral edema [12], and work by *Glaser* and colleagues suggested that a patient's relative risk for developing cerebral edema increased with increasing rate of intravenous fluid infusion [7]. Given this evidence, early DKA practice guidelines supported slow (over 48 hours) rehydration, utilizing fluid boluses only when resuscitation is felt to be warranted and again recommending slow infusion of said boluses, not to exceed 30 ml/kg [13]. In constrast to this approach, guidelines for severe sepsis and septic shock urge the rapid administration of an unlimited number of rapid isotonic fluid boluses, with the goal of quickly normalizing perfusion, blood pressure, and heart rate [14]. Though shock as a presentation in DKA is considered rare [8], it is reported in the literature from developing countries such as India and Pakistan with some frequency, and these studies have suggested incidence estimates ranging from 12-48% in their patient populations and intensive care units [15-18].

More recent guidelines for the management of DKA now recognize the importance of prioritizing shock management in these patients [8]. The 2014 International Society for Pediatric and Adolescent Diabetes Consensus guidelines for the management of DKA specifically state that for the rare patient with DKA in shock, providers should rapidly restore circulatory volume with isotonic saline in 20 ml/kg boluses infused as quickly as possible and that boluses may need to be repeated until tissue perfusion is adequate [8]. Despite these new recommendations, practitioners may still be hestitent to give these patients large volumes of fluid given the role that fluid resuscitation may serve in the development of cerebral edema, noting that greater fluid volumes given within the first 4 hours of treatment of DKA remain a potential risk factor for this severe complication [8].

By pediatric definition, all seven patients in our series had both DKA and shock that warranted fluid resuscitation. Additionally, all patients received greater than 30 ml/kg of fluid in acute fashion (less than 1 hour), yet had normal neurologic outcomes. Only one of our patients (Patient F) was found to have radiographic evidence of cerebral edema, the signs and symptoms of which were present upon presentation and prior to initiating fluid resuscitation. In comparison to the rest of the cohort, the only clinical factor that was significantly different about this patient is that she presented after a far greater unwitnessed period of time by family (estimated 10 hours). Current guidelines list severity of acidosis at presentation as a potential risk factor for cerebral edema in DKA [8], though duration of acidosis and/or

shock may in fact contribute. Refractory shock at admission may alone increase a patient's odds for the development of cerebral edema, as proposed by *Piva* and colleagues [19]; however, far greater study is necessary to determine the validity of these possibilities.

At this current time, the question of cerebral edema with fluid resuscitation in patients with both DKA and shock remains unanswered, including information about the best monitoring strategies (i.e. central venous pressure monitoring, corrected sodium trend, plasma osmolality*).* Recent guidelines highlight the importance of treating shock when present in patients with DKA, though ongoing attention to glucose management, reversal of ketosis, and electrolyte replacement remain of paramount importance as well. Further study is warranted into the likely complex effects of both fluid resuscitation and shock on the development of cerebral edema in pediatric patients with DKA.

Tables

Table 1: Patient Characteristics & Laboratory Values

	Age (yrs)	Gender	Diabetes Status	Acute co-morbidities	Initial glucose (mg/dL)	Initial pH	Initial Bicarbonate (mmol/L)	Initial BUN/Creatinine (mg/dL)
Patient A	15	male	new onset	Soft tissue abscess	1229	7.07	7	45/2.94
Patient B	3	female	new onset	*Streptococcal* pharyngitis	1450	6.84	6	70/2.36
Patient C	16	female	new onset	Tonsillitis	482	6.7	5	13/1.1
Patient D	20	male	known T1DM*	None identified	>600	6.95	6	17/1.0
Patient E	13	male	known T1DM*	Small bowel obstruction	565	6.99	6	17/0.94
Patient F	10	female	new onset	None identified	629	6.86	<5	39/2.75
Patient G	11	female	known T1DM*	None identified	1290	6.8	4	58/2.75

** T1DM = type 1 diabetes mellitus*

Table 2: Patient Treatments & Outcomes

	Total fluid 1st 24 hrs (ml/kg)	Δ glucose in 1st 24 hrs (mg/dL)	Δ Plasma osmolarity in 1st 24 hrs (mosmol/kg)	Vasoactive Medication Requirement	Mechanical ventilation	ECMO	PICU length of stay (days)	Hospital length of stay (days)	Neurologic outcome
Patient A	116	1009	-11	no	Yes	No	6	23	no deficits
Patient B	280	1076	-5	yes	Yes	No	8	23	increased tone upon discharge, no deficits at 6 months post-discharge
Patient C	145	379	-6	yes	Yes	No	3	4	no deficits
Patient D	100	>/= 472	-38	yes	Yes	No	2	4	no deficits
Patient E	190	282	-18	yes	No	No	4	9	no deficits
Patient F	175	281	-14	yes	Yes	No	6	8	mild edema on CT, no deficits upon discharge
Patient G	230	1119	-12	yes	Yes	Yes	10	22	no deficits

Figure

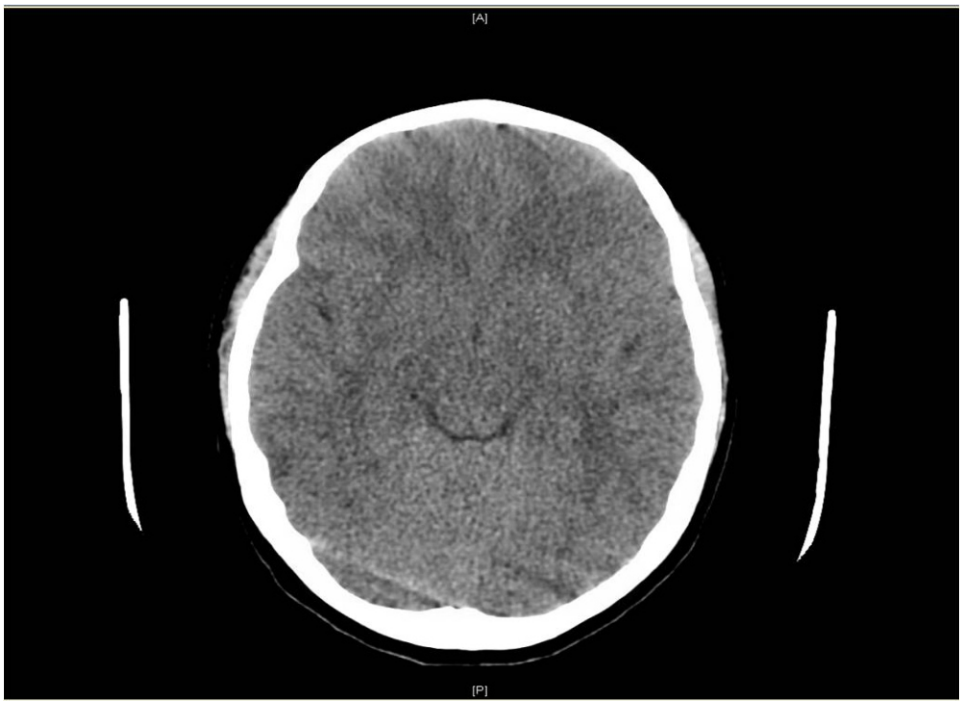

Figure 1: Brain CT of Patient F demonstrating mild cerebral edema.

References

1. Foster DW, McGarry JD. The metabolic derangements and treatment of diabetic ketoacidosis. N Engl J Med 1983: 309: 159–169.

2. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. Diabetes Care 2006: 29: 2739–2748.

3. Wolfsdorf J, Allgrove J, Craig ME, Edge J, Glaser N, Vandana J et al. ISPAD Clinical Practice Consensus Guidelines 2006-2007: Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Pediatric Diabetes 2014; 15 (Suppl 20): 154-179.

4. Wolfsdorf J, Craig ME, Daneman D, Dunger D, Edge J, Lee W, et al. Diabetic ketoacidosis in children and adolescents with diabetes. Pediatric Diabetes. 2009; 10 (Suppl 12): 118-33.

5. Levin DL. Cerebral edema in diabetic ketoacidosis (Review). Pediatr Crit Care Med 2008; 9(3): 320-329.

6. Hale P, Rezvani I, Braunstein A, Lipman T, Martinez N, Garibaldi L. Factors predicting cerebral edema in young children with diabetic ketoacidosis and new onset type I diabetes. Acta Paediatr 1997; 86: 626-31.

7. Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, et al. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. N Engl J Med 2001; 344: 264-269.

8. Mel J, Werther G. Incidence and outcome of diabetic cerebral edema in childhood: are there predictors? J Paediatr Child Health 1995; 31: 17-20.

9. Rosenbloom A. Intracerebral crises during treatment of diabetic ketoacidosis. Diabetes Care 1990; 13: 22-33.

10. Tiwari LK, Muralindharan J, Singhi S. Risk factors for cerebral edema in diabetic ketoacidosis in a developing country: Role of fluid refractory shock. Pediatr Crit Care Med 2012; 13(2): e91-96.

11. Clements RS Jr, Prockop LD, Winegard AL. A mechanism to explain acute cerebral edema during the treatment of diabetic acidosis. Diabetes 1968; 17: 299.

12. Edge JA, Jakes RW, Roy Y, Hawkins M, Winter D, Ford-Adams ME, et al. The UK case-control study of cerebral edema complicating diabetic ketoacidosis. Diabetologia 2006; 49: 2002-2009.

13. Wolfsdorf J, Craig ME, Daneman D, Dunger D, Edge J, Lee WRW, et al. ISPAD Clinical Practice Consensus Guidelines 2006-2007: Diabetic Ketoacidosis. Pediatric Diabetes 2007; 8: 28-42.

14. Brierly J, Carcillo JA, Choong K, Cornell T, DeCaen A, Deyman A, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med 2009; 37(2): 666-688.

15. Ganesh R, Arvindkumar R, Vasanthi T. Clinical profile and outcome of diabetic ketoacidosis in children. Natl Med J India 2009; 22: 18-19.

16. Syed M, Khawaja FB, Saleem T, Khalid U, Rashid A, Huma- yun KN. Clinical profile and outcomes of paediatric patients with diabetic ketoacidosis at a tertiary care hospital in Pakistan. J Pak Med Assoc 2011; 61: 1082-1087.

17. Tiwari LK, Jayashree M, Singhi S. Risk factors for cerebral edema in diabetic ketoacidosis in a developing country: Role of Fluid refractory shock. Pediatr Crit Care Med 2012; 13: e91-e96.

18. Kanwal SK, Bando A, Kumar V. Clinical profile of diabetic ketoacidosis in Indian children. Indian J Pediatr 2012; 79: 901-904.

19. Piva JP, Czepielwski M, Garcia PCR, Machado D. Current perspectives for treating children with diabetic ketoacidosis. Jornal de Pediatria (Rio J) 2007; 83(5 Suppl): S119-127.

Manuscript Information: Received: February 24, 2017; Accepted: May 11, 2017; Published: May 15, 2017

Authors Information: Markita L Suttle, Md[1]*; W Joshua Frazier, MD[1]; Jennifer Muszynski, MD[1,2]

[1]Department of Critical Care Medicine, Nationwide Children's Hospital, USA
[2]Center for Clinical & Translational Research, The Research Institute at Nationwide Children's Hospital, USA

Citation: Suttle ML, Frazier JW, Muszynski J. Aggressive fluid resuscitation in a series of pediatric patients with diabetic ketoacidosis and shock. Open J Clin Med Case Rep. 2017; 1257

Journal: Open Journal of Clinical and Medical Case Reports is an international, open access, peer reviewed Journal focusing exclusively on case reports covering all areas of clinical & medical sciences.

Visit the journal website at **www.jclinmedcasereports.com**

For reprints and other information, contact editorial office at **info@jclinmedcasereports.com**