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The Effects of Prehospital Care on Outcome in Pediatric Diabetic Ketoacidosis

Turan et al. Prehospital Care of Diabetic Ketoacidosis

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What is already known on this topic?
Despite the guidelines on initial management of pediatric diabetic ketoacidosis significant variations (intravenous fluids and insulin therapy) can be observed in the prehospital setting or peripheral health care facilities.

What this study adds?
This is the first study exploring the low utilization rate of prehospital emergency medical services for children with DKA. Inappropriate fluid type/dose and insulin were especially administered in the primary/secondary care hospitals. Patients who received inappropriate initial management were more likely to developed complications.

Abstract
Objective: Despite the guidelines, significant variations can be encountered on initial therapy for pediatric diabetic ketoacidosis (DKA) in the prehospital setting. These variations mostly on fluid administration, insulin dosing, route of administration, and other aspects of the initial resuscitation and stabilization. We aimed to identify the effect of transport care on outcomes in children with DKA admitted to the ED.
Methods: Patients admitted to the tertiary-care-pediatric-ED between 2015-2019 with a diagnosis of DKA were retrospectively identified. The pre–pediatric ED care including transport modality, patient demographics, clinical features, laboratory evaluation, fluid therapy, insulin dosing, and the short-term outcome recorded.
Results: The study cohort included 147 episodes of DKA in 136 patients (9 months-21 years). Emergency Medical Service (EMS) transported only one-third episodes (37.4%). EMS utilization rate was significantly higher in severe cases and most of them were >10 years (p=0.003, p=0.04). Eighty-five percent received intravenous fluid bolus during the transport. Fluids other than normal saline use was significantly higher when the transport time lasted >30 minutes (p=0.001). Acute kidney injury and cerebral edema developed in 21.7% and 7.4 % of episodes, respectively. These complications more likely developed in EMS transported group. Pediatric intensive care unit admission rate was also higher in EMS when compared to non-EMS group (p=0.01)
Conclusion: Parents were not likely to call the ambulance for most cases, the higher complication rate occurred in EMS patients. EMS providers and referral facilities should improve their knowledge of pediatric DKA.
Keywords: Diabetic ketoacidosis, prehospital care, diabetes mellitus, insulin, pediatric transport

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Introduction
Diabetic ketoacidosis (DKA) is one of the serious acute complications of type 1 diabetes mellitus (T1DM). It occurs at the onset of diabetes in half of the patients(1, 2). The annual rate of DKA in pediatric T1DM is 6-8%, with a case fatality rate ranging from 0.15 percent to 0.31**%** in developed countries. However, recent data from developing countries has shown that the mortality rate in children with DKA was 6-24% (3, 4, 5).
The principles of management DKA in the pediatric population include optimization of 1) volume status; 2) hyperglycemia and ketoacidosis; 3) electrolyte abnormalities, and; 4) potential precipitating factors. Although, the management of these patients should be organized in comprehensive/tertiary hospitals, the initial interventions performed before/during transport influence the final outcome. Still, some concerns remain on pre-hospital care of DKA in children (6). Despite the guidelines and recommendations on the optimal type and amount of intravenous fluid in the initial resuscitation of DKA, significant variations still have been performed in clinical practice. Similar inappropriate interventions such as insulin dosing, route of administration, and other aspects of the initial resuscitation and stabilization which are provided before transfer have been reported (7).
This is, to the best of our knowledge, the first study exploring the utilization rate of prehospital emergency medical services (EMS) for children with DKA, and the effect of transport modality provided care and their association on prognosis. Interventions performed before referral, on the route, administered fluid type/dose, insulin dosing and route of administration were also investigated.

2. MATERIAL AND METHODS
2.1. Study design

This is a retrospective cohort study conducted in the Emergency Department of Ege University Children's Hospital between 01 January 2015 – 31 May 2019. The local ethical committee (18-7/8) approved this study.

2.2. Definition and treatment protocol

DKA was defined based on the International Society for Pediatric and Adolescent Diabetes (ISPAD) clinical practice consensus guidelines (8). According to this guideline, DKA is defined by the presence of all of the following; hyperglycemia (blood glucose >200 mg/dL), metabolic acidosis (venous pH<7.3 or serum bicarbonate <15 mEq/L) and ketosis (blood beta-hydroxybutyrate >3 mmol/L or moderate-large urine ketones). Our institutional management protocol for DKA was consistent with ISPAD approach. The severity of DKA was structured into three groups: mild (pH=7.2–7.29), moderate (pH=7.1–7.19), and severe (pH<7.1).

For children with moderate and severe acidosis, initial resuscitation of 20 mL/kg of isotonic sodium chloride solution (0.9%), for mild cases, 10 ml/kg fluid was administered over 60 minutes. Following the initial fluid resuscitation continuous, low-dose intravenous (iv) insulin infusion rate 0.05U/kg/hr administered for children who are younger than 5 years old, and 0.1 U/kg/h rate used for children older than 5. Except for this approach all administered fluid (type/dosing) or insulin during transport in EMS were defined as an inappropriate fluid or insulin therapy.

2.3. Study Population and Data Collection

All patients admitted to our ED with DKA were included in the study. The data collection form was including information on; transport modality (ambulance or not), patient demographics, clinical features, laboratory evaluation, administered resuscitation therapy (fluid type and volume, insulin type and dose) on route and stabilization treatment in the ED. We also reviewed the medical records of all hospitalized patients to elucidate the developed complications (such as acute kidney injury, cerebral edema) and to find their association of outcome during their hospital stay.

2.4. Statistical analysis

Statistics Package for the Social Sciences 22.0 software (SPSS Inc.; Chicago, IL, ABD) was used for statistical analysis. Continuous data represented by the mean and standard deviation. Categorical variables expressed by frequency and cross tables. The chi-square test (or Fisher's exact probability test) used to compare demographics. Mann-Whitney U or t-test was performed for two independent groups. p values lower than 0.05 were regarded as statistically significant.

3. RESULTS

During the study period medical care given to 192 endocrine emergencies in our ED. Most of them were DKA (163/192) and developed in 150 patients (Figure 1). We excluded 16 episodes of 14 patients due to missing data. The final analyze was performed for 147 episodes of DKA in 136 patients. Sixty-one percentage was female and the mean age was 11.1 (±4.7) years (9 months to 21 years). Table 1 summarizes the demographic characteristics of patients in the study.

For most episodes caregivers or parents did not prefer transferring their kids by ambulance to the ED (62.6%). EMS transported only one-third of this cohort (37.4%) (Table 1). The most common EMS transfers (43/55) performed patients referral from the secondary care hospital. EMS brought 7 episodes from the field, and the remaining referral centers were 2 from tertiary care ED and 3 from the primary care physician office. Patients who arrived to the ED without using EMS were more likely sent from the primary care physician office (37.5%) (Table 1).

Tachycardia, dehydration, vomiting and altered mental status (Glasgow coma scale ≤14) were more common in the EMS brought group when compared with the non-ambulance group. Comparisons of the clinical features in patients brought with or without EMS shown in Table 1.

More than half of episodes (55.7%) were mild and only 13.6% were severe DKA (Figure 1). The comparison of patients' laboratory findings between the severity groups of DKA shown in table 2. The mean pH was 6.90 (range was 6.70-7.07) in the severe group. EMS utilization rate was significantly higher in severe cases and most of the severe cases were adolescents (older than 10 years) (p=0.000, p=0.04 respectively) (Table 3).

Nearly half of the patients (42.8%) present with DKA at the time of diagnosis. The other most common causes of DKA presentation were; insulin omission (34.1%), insulin pump dysfunction (14.9%) and precipitating factors such as infections (8.2%). The proportion of children with new-onset T1DM and severe DKA was higher in the adolescent group. Although inappropriate fluid uses were higher in patients under 5 years of age; complications were more common in patients older than 5 years (Table 4).

The most patients who brought by EMS (45/55) received intravenous fluid bolus and the most common administered fluid was (84.4%) normal saline (0.9% NaCl) during the transport. Only a minority of episodes received inappropriate fluid type (15.6%). Inappropriate fluid dosing was the most common mistake which is encountered in most (66.7%) (Figure 2). Inappropriate initial fluid doses and insulin treatments were associated with EMS transport (p=0.000 and p=0.009, respectively) (Table 3).

EMS transfer group (39/55) arrived within one hour to the ED, only 16 patients' transport duration lasted more than 1 hour. The rate of using inappropriate fluid was significantly higher when the transport time lasted more than 30 minutes (p=0.001). Totally 19 episodes received insulin therapy following fluid resuscitation. Although appropriate continuous, low-dose (begin with 0.05 (<5 years) to 0.1 U/kg/h), intravenous (IV) insulin infusion was performed for only 6 episodes, 13 episodes received inappropriate insulin therapy (11 subcutaneous; 2 subcutaneous and intravenous).

The median length of stay in the ED was 2.1 (IQR 1.0-4.0) hours. Acute kidney injury (AKI) and cerebral edema (CE) developed in 21.7% and 7.4% of patients, respectively. These complications more likely developed in moderate and severe DKA groups (Table 5). In addition, PICU admission rate was significantly higher in severe DKA who admitted by EMS, although there was no significant difference between EMS utilization and complications in severe DKA (p=0.000 and p=0.317, respectively) (Table 6). Hundred-seventeen episodes (80.2%) were admitted to the ward, and 14 to PICU. The rate of PICU admission was also higher in EMS when compared to non-EMS group (p=0.000) (Figure 1). We could not find a significant association between the patients who received inappropriate interventions when compared with patients who received appropriate interventions in EMS with PICU admission rate and complications.

DISCUSSION

The present study demonstrates several issues of concern regarding the prehospital management of pediatric DKA before referral and transfers to a tertiary care ED. Calling an ambulance (from the field to hospital) and using it (inter-hospital transport) is the recommended response for patients with DKA in Turkey. There are several reasons for this. It is the most common emergency of T1DM in children and is still leading the major cause of hospitalization, morbidity, and mortality (1, 2, 9). Most morbidities and deaths due to DKA take place out of the hospital, presumably from severe dehydration and acidosis, which can be treated by IV fluids and insulin. If the primary goals on the management of DKA performed appropriately earlier in the clinical course, that has been clearly shown to reduce morbidity and mortality (5). Unfortunately, this study shows that most children (62.6%) who have DKA do not access ambulances as their first medical contact. The reason for low rate of EMS utilization is not clear and that it needs further investigating.

This is the first Turkish study to examine in detail the nature of the request for EMS in children with DKA. Since no previous study has published ambulance transport rates to hospital, patients preferred to use primary care physicians or secondary care hospitals we believe that this may explain the higher rates of non-ambulance transport observed in this study.

The incidence of DKA as the first presentation of new-onset T1DM has a large variability from country to country. Although, the DKA incidence of new-onset T1DM has been decreasing in European countries, such as Austria (34%), Germany (21.1%), Finland (22.4%), Denmark (17.9%), Italy (41.9%) and France (43.9%); this range was between 80-88% in African countries (1, 10, 11). In our country, this incidence was shown as previously shown with a study as 33-55% (12, 13). In the current cohort of patients, there was a similar rate with this national data as well as France and Italy studies. As precipitating factors such as infections, alcohol abuse, and insulin dose omission were the remaining main causes of DKA in T1DM (14). Unlike developed countries where the infection is the most common precipitating factor for DKA, insulin disruption/omission was the major precipitating factor for DKA in the studied patients (34.8%) (14).

The severity of the episodes in the previous studies was reported mild/severe as 33% and 9%, respectively (13, 15). In the current cohort, severe DKA rate was 14.6 % which is similar to the data from Germany (16%), France (14.8%) and Italy (11.2%), less than Poland (22.5%), and Saudi Arabia (26.1%). This difference can be explained by lower parental educational achievement.

In previous studies, a young age, especially less than 2 years and low accessibility to medical care were identified as risk factors for DKA at T1DM diagnosis (11, 15, 16, 17, 18). This may be explained by more decreased b-cell dysfunction, aggressive diabetes and delayed detection of diabetes symptoms to be more frequent in young children. It has been shown that children less than 5 years of age are at higher risk of metabolic decompensation at the initial presentation (19). However, some studies indicated that informing the parents on diabetes symptoms decreased the risk of DKA at T1DM diagnosis in young children (20). In contrast to these studies, we have seen more frequent and more serious episodes in children aged > 10 years old. Children and adolescents at this age have likely escaped parental control; thus, detection or reporting of symptoms may be delayed. Similar to our findings a recent study in New Zealand reported that an increased risk for DKA at age around 11 years (21). This may depend on better awareness in parents who have children < 5 years and adolescents do not recognize symptoms.

The management of DKA in any setting (for patients with newly or previously diagnosed DKA) can be divided into four physiologic principles which are including restoration of fluid volume, inhibition of lipolysis, correction of electrolyte abnormalities and acidosis. Delayed, insufficient or inappropriate treatment is a potential risk for developing complications of DKA (22). The timing of fluid therapy as an initial treatment should be given within the first hour and it has a considerable effect on the outcome of DKA (23). Since the majority of patients spend their first time period in the ambulance (if they use it) they should receive the initial therapy on the route. Despite all suggestions, there are several concerns about the prehospital management of DKA (6). Although, only one-third of these cohort patients brought by ambulance to the ED our study demonstrates that, inappropriate fluid dose and insulin used for DKA during the transport. The incidence of severe DKA and complications of kidney injury, CE and PICU admission rate were particularly higher in patients transported with EMS. The high rate of the complications and morbidity associated with DKA in EMS-transported patients is related to both transport facilities and the severity of DKA. We believe that the majority of referring physicians (from the secondary care hospitals) and prehospital healthcare providers attending to these children lacked the clinical experience for managing DKA. The uncorrected hypovolemia in our cohort may have resulted in complications. Since the proportion of severe patients was located in the EMS group it can be another factor to explain this difference in developing complications. Since our study conducted retrospectively and the sample size is small, further, well-designed studies with a large sample size needed to clarify the real situation.

There are many factors that have contributed to developing complications in no -EMS group. Since the most common referral place in this group was home, the warning should be made for parents to bring their children in DKA with an ambulance. Fort the second most common referral center in the no-EMS group, feedback should be made to primary care physicians for transferring these patients by EMS with appropriate management protocol.

Limitations

There are several limitations in the present study. The retrospective design of our study the most crucial limitation. Since the design of our study is retrospective selection bias may be occurred. Single-center experience with small sample size cohort other issues that should be highlighted. Larger prospective well-designed studies needed to explore and explain this causal relationship.

CONCLUSION

The severity, complications, PICU admission and morbidity associated with DKA in our study is higher than that reported from developed countries. The root causes for the above were parental ignorance, inappropriate transports/fluid /insulin, delayed management due to lack of clinical experience and facilities for managing DKA in the primary/secondary health-care facilities. This is compounded by transport problems associated with referral hospital and lack of follow-up and continuum of care among known diabetics.

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Author contribution

C.T. and E.U.S. designed the study; C.T., E.G.B., E.E., A.Y. and E.U.S. performed experiments; C.T., E.G.B., E.E., and A.Y. collected and analyzed data; C.T., E.E., and E.U.S. provided reagents and mice; C.T., D.G. and E.U.S. wrote the manuscript; D.G. and E.U.S gave technical support and conceptual advice. All authors read and approved the final manuscript.

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Table 1. The patient characteristics and clinical features of episodes

Patient characteristics	
Age (mean, ±SD)	11.1 (±4.7)
< 5 years of age, n (%)	22 *(14.9)*
Number of adolescent (>10 years), n (%)	51 *(34.6)*
Girls:Boys ratio	1.6:1
Referral center	
EMS, n (%)	55 *(37.4)*
Home	2
Field	5
Primary care hospital	3
Secondary care hospital	43
Tertiary care hospital	2
Other	0
No EMS, n (%)	92 *(62.6)*
Home	49
Field	0
Primary care physician	33
Secondary care hospital	6
Tertiary care hospital	0
Other	4
Transport time, h (mean, min-max)	1.1 (0.25-3.2)
Clinical features (EMS / not EMS) (n)	
Tachycardia	22 / 42
Dehydration	22 / 41
Polydipsia	10 / 30
Vomiting	14 / 25
Polyuria	10 / 28
Kussmaul breathing	13 / 15
Loss of weight	8 / 19
Abdominal pain	7 / 16
Altered Mental Status	9 / 4
DKA Causes, n (%)	
New onset T1DM	63 *(42.8)*
Insulin omission	50 *(34.1)*
Disfunction of insulin pump	22 *(14.9)*
Infections	12 *(8.2)*

Table 2. Comparison of patients' laboratory findings between the severity groups of DKA

	DKA Groups					
	Mild		**Moderate**		**Severe**	
Laboratory findings	**EMS (n=23)**	**No-EMS (n=59)**	**EMS (n=17)**	**No EMS (n=28)**	**EMS (n=15)**	**No EMS (n=5)**
Bedside glucose, mg/dL Mean (±SD)	398 (±75)	402 (±109)	373 (±125)	366 (±80)	341 (±107)	435 (±67)
Venous pH Mean (±SD)	7.26 (±0.38)	7.27 (±0.23)	7.14 (±0.02)	7.15 (±0.03)	6.9 (±0.1)	6.9 (±0.12)
Serum bicarbonate, mmol/L Mean (±SD)	14.4 (±3.9)	16.6 (±4.3)	9.7 (±2.5)	9.7 (±2.1)	5.6 (±2.1)	5.7 (±0.1)
Serum lactate, mmol/L Mean (±SD)	1.6 (±0.99)	1.7 (±0.7)	1.4 (±0.9)	2.3 (±1.1)	2.2 (±1.2)	2.0 (±0.4)
Serum sodium, mmol/L Mean (±SD)	133.9(±2.7)	132.3 (±3.1)	132.4 (±3.1)	133.0 (±3.4)	132.6 (±4.1)	136 (±5.6)
Serum corrected sodium, mmol/L, Mean (±SD)	136.9(±3.4)	141.9 (±5.9)	137.6 (±4.4)	137.9 (±3.2)	139.4 (±1.3)	138.1 (±2.7)
Serum potassium, mmol/L Mean (±SD)	4.6 (±0.6)	4.3 (±0.4)	4.3 (±0.7)	4.3 (±0.7)	4.5 (±0.7)	3.7 (±0.2)

DKA: Diabetic ketoacidosis, EMS: Emergency Medical Service, SD: Standard deviation, IQR: interquartile range

Table 3. The association between DKA severity, appropriate treatments (fluid and insulin), complications, PICU admission rates with EMS utilization.

	EMS (n=55)	**No EMS (n=92)**	**Total (n)**	***p***
DKA Severity				
Mild	23	59	82	
Moderate	17	28	45	***0.000***
Severe	15	5	20	
Appropriate initial fluids treatment (type/dose)§				
Yes	12	91	103	***0.000***
No	33	1	34	
Appropriate insulin treatment (type/dose)φ				
Yes	3	4	7	***0.009***
No	12	0	12	
Complications				***0.039***
CE	8	3	11	
AKI	13	19	32	
PICU admission rate *(%)*	21.8	2.2	9.5	***0.000***

DKA: Diabetic ketoacidosis, EMS: Emergency Medical Service, CE: Cerebral edema, AKI: Acute kidney injury, PICU: Pediatric Intesive Care Unit

§ Appropriate initial fluids treatment (type/dose): For children with moderate and severe acidosis, initial resuscitation of 20 mL/kg of isotonic sodium chloride solution (0.9%), for mild cases 10 ml/kg fluid was administered over 60 minutes

φAppropriate insulin treatment (type/dose): low-dose intravenous (iv) insulin infusion rate 0.05U/kg/hr administered for children who is younger than 5 years old, and 0.1 U/kg/h rate used for children older than 5.

Table 4. Comparison of clinical features, interventions and complications between the age groups.

	Age Groups			***p***
	0-5 years (n)	**5-10 years** (n)	**>10 years** (n)	
Severe DKA	2	7	11	*0.121*
New-onset T1DM	12	18	33	***0.000***
Use of Inappropriate Fluids	5	8	21	***0.000***
Mistaken insulin use	2	4	7	*0.903*
Complications	4	7	32	***0.000***

DKA: Diabetic ketoacidosis, T1DM: Type 1 diabetes mellitus

Table 5. The association of DKA severity and EMS utilization between the rate of complications.

	Complications			***p***
	No (n, %)	**AKI (n, %)**	**CE (n, %)**	
Severity				
Mild	73 *(89)*	8 *(9.7)*	1 *(1.7)*	*0.645*
Moderate	25 *(55.5)*	14 *(31.1)*	6 *(13.4)*	***0.000***
Severe	6 *(30)*	10 *(50)*	4 *(20)*	***0.000***
EMS Utilization				
Yes	34 *(61.8)*	13 *(23.6)*	8 *(14.6)*	*0.065*
No	70 *(76.1)*	19 *(20.6)*	3 *(3.3)*	

EMS: Emergency Medical Service, CE: Cerebral edema, AKI: Acute kidney injury

Table 6. The comparison between the rate of complications, PICU admission and transport modality in severe DKA group

	Complications			***p***	**PICU admission (n, %)**	***p***
	No (n, %)	**AKI (n, %)**	**CE (n, %)**			
EMS	5	8	3	*0.317*	11 (73.3)	***0.000***
No EMS	1	2	1		1 (20)	
Total	6	10	4		12 (60)	

EMS: Emergency Medical Service, CE: Cerebral edema, AKI: Acute kidney injury, PICU: Pediatric Intesive Care Unit

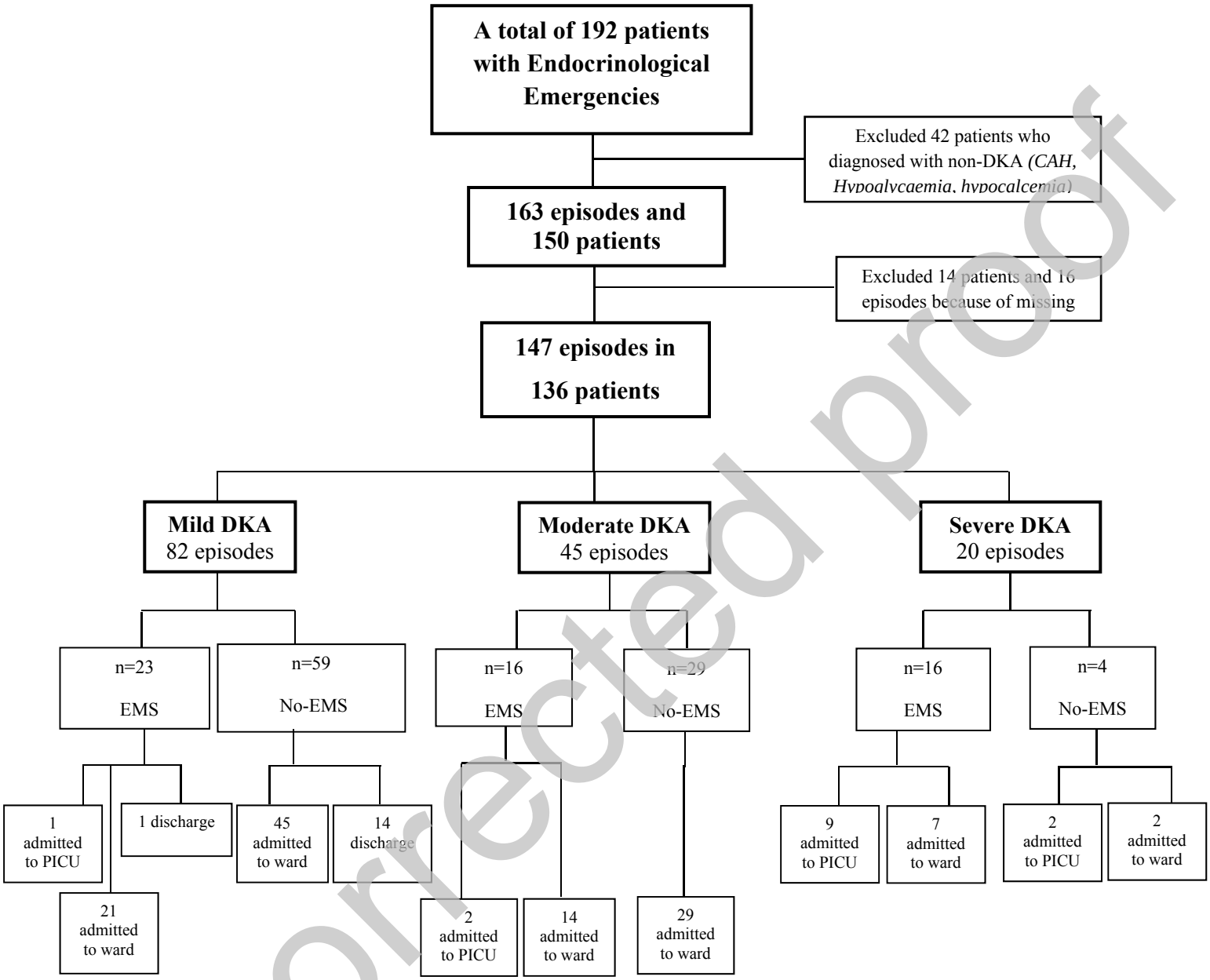

Figure 1: Distribution of episodes recruited in the study period.

DKA: Diabetic Ketoacidosis, CAH: Congenital Adrenal Hyperplasia, PICU: Pediatric Intensive Care Unit, EMS: Emergency Medical Services

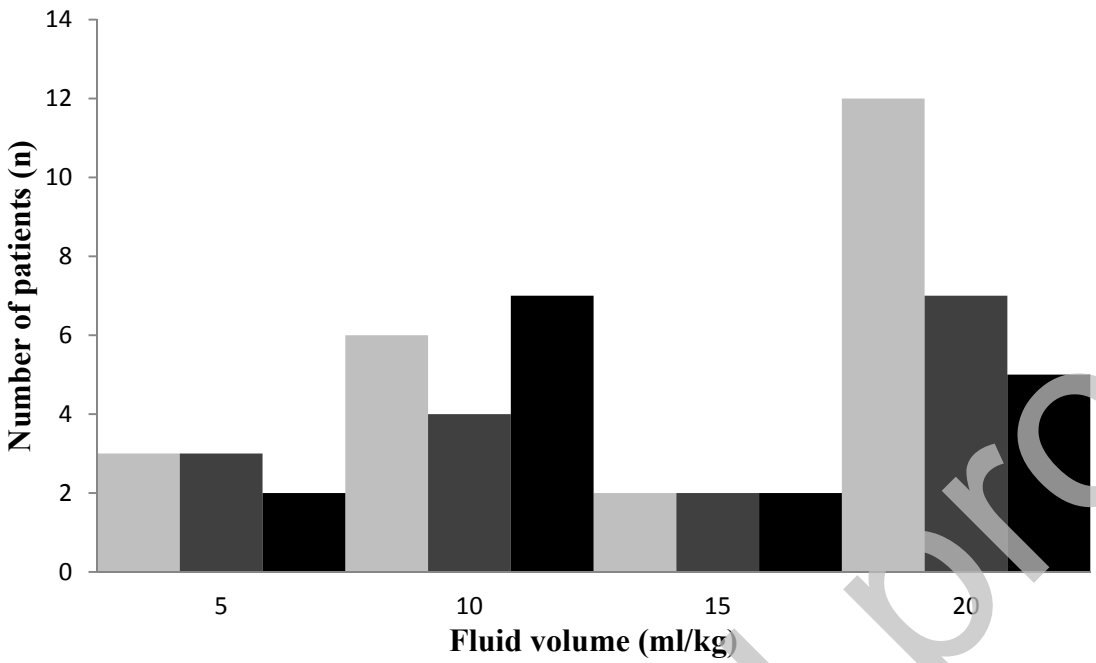

Figure 2. Administered **i**ntravenous fluid bolus volume (ml/kg) based on DKA severity