Universitat de Girona
Facultat de Medicina

The application of an artificial intelligence tool to improve diabetic ketoacidosis treatment security in the Emergency Department

A quasi-experimental study

FINAL DEGREE PROJECT

Author: Jordi Mayol Traveria

Clinical tutor: Àngels Gispert Ametller

Methodological tutor: Rafael Marcos Gragera

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1. ABSTRACT

BACKGROUND

Diabetic ketoacidosis (DKA) is one of the most serious diabetes complications. It is characterized by hyperglycemia, anion gap metabolic acidosis and increased total body ketone concentration. DKA is the most common cause of death in youth type 1 diabetic patients and an important cause of morbimortality in type 2 diabetic patients. Its management is complex, however, if it is well performed DKA has a good prognosis. Lately, the need to standardize DKA treatment has become an important issue in our Department.

OBJECTIVE

Our main objective is to decrease hospital length of stay of DKA patients treated in Hospital Universitari Josep Trueta's Emergency Department (ED) with the application of a computer decision support and electronic order sets (CDS&EOS) to minimize security errors.

DESIGN

Quasi-experimental study designed as a before-and-after evaluation of the application of a CDS&EOS in ED's SILICON® to standardize DKA management.

PARTICIPANTS

A consecutive non-probabilistic model will be used to select DKA patients aged 18 years old or older treated in Hospital Universitari Josep Trueta's ED.

METHODS

The study will include 134 participants in total, 67 for each group (pre and post-intervention). Each sample will be selected in an 18-month period, with a washout period between them. Data will be collected prospectively between May 2021 and October 2024. The association between the independent and dependent variables will be adjusted to avoid possible confounding factors.

KEY WORDS

Diabetic ketoacidosis, treatment, security, diabetes mellitus, prescription error, administration error, standardize.

2. ABBREVIATIONS AND ACRONYMS

CCI	Charlson Comorbidity Index
CDS&EOS	Computer Decision Support and Electronic Order Sets
CEIC	Comitè d'Ètica d'Investigació Clínica
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
ED	Emergency Department
GCS	Glasgow Coma Scale
HHS	Hyperglycemic Hyperosmolar State
HUJT	Hospital Universitari Josep Trueta
IS	Isotonic Saline
IV	Intravenous
RT	Research Team
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SBP	Systolic Blood Pressure

3. INTRODUCTION

3.1. DIABETES MELLITUS

Diabetes mellitus (DM) is a heterogeneous metabolic disorder characterized by chronic hyperglycemia caused by the impairment of insulin secretion, defect of insulin action or both. The deficient action of insulin results in abnormalities on carbohydrate, fat, and protein metabolism (1–4).

DM classic symptomatology is thirst, polydipsia, polyuria, polyphagia, weight loss, asthenia, and less commonly growth impairment and susceptibility to certain infections.

Chronic hyperglycemia is associated with long term injury or impairment of some organs, especially eyes, kidneys, nerves, heart and blood vessels (5).

3.1.1. CLASSIFICATION

Most patients with diabetes can be classified into 2 categories: type 1 diabetes and type 2 diabetes. Sometimes it may be difficult to fit a patient in a single group as it will depend on the circumstances at the time of diagnosis and the evolution of the disease (1,3).

DM classification is summarized in *Table 1*.

3.1.1.1. PREDIABETES

Prediabetes is a risk state defined by above normal glycaemic levels in which the patient does not meet the criteria for diabetes but presents a high risk for developing diabetes. Prediabetes prevalence has risen in the last years and it is expected to continue increasing (6).

3.1.1.2. TYPE 1 DIABETES

Previously known as insulin-dependent diabetes or juvenile-onset diabetes, type 1 diabetes constitutes the 5-10% of the diabetic patients.

It is caused by the destruction of pancreatic β-cells which implies insulin deficiency, with little or no plasma C-peptide levels. The destruction is most frequently cellular-autoimmune mediated and not related with obesity. Type 1 diabetic patients usually need insulin treatment to survive.

In that case, one or more markers of the immune activity such as islet cell autoantibodies, insulin autoantibodies, GAD autoantibodies (GAD65), and autoantibodies to tyrosine phosphatases IA-2 and IA-2b are present in 85-90% of patients.

Autoimmune-mediated (type 1) diabetes has also strong HLA-association. These HLA-DR/DQ alleles can be protective or disease predisposing.

The onset of symptoms is variable depending on the rate of β-cells destruction. Usually, it is fast and occurs in childhood and adolescence and may appear as ketoacidosis as its first manifestation. Whereas others with residual β-cells function experiment the first symptoms in adulthood.

Autoimmune activity has various genetic predispositions, and it has been postulated susceptibility to some environmental factors such as toxics, virus, microbial superantigens, nitrates, nitrites, gluten, caffeine, or stress.

It is associated with other autoimmune diseases as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, autoimmune hepatitis, myasthenia gravis, celiac sprue, and pernicious anaemia.

Idiopathic type 1 DM is not related with autoimmunity and its ethology is unknown. Patients with type 1 diabetes may have severe insulinopenia and suffer from episodic ketoacidosis. It is more common in people of African or Asian descent, it is frequently inherited, and it is not related to HLA (3,5).

3.1.1.3. TYPE 2 DIABETES

Type 2 diabetes is the most frequent type and affects 90-95% of patients. Its cause is insulin resistance and relative insulin deficiency.

There are presumably many causes, but they are not well known. The risk of suffering this form of diabetes increases with age, obesity or abdominal distributed body fat, and lack of physical activity. Also, women with gestational DM and individuals with hypertension or dyslipidemia have higher susceptibility. It has more genetic predisposition than type 1 diabetes, but it is complex and not totally known.

This type of diabetes tends to develop more slowly, thus, symptoms appear in advanced stages of the disease and go undiagnosed for many years. However, even if patients are asymptomatic, they have an increased risk of vascular complications.

Glucose blood levels are high even with normal or elevated insulin levels as a result of the peripheral insulin resistance.

It is not common to have insulin deficiency. Therefore, insulin treatment is not needed to survive at least initially. Although weight loss and/or pharmacological treatment can improve insulin resistance, glycemia levels are rarely restored to normal.

Ketoacidosis can appear as a complication, but a stress factor such as infection is usually needed (3,5).

3.1.1.4. OTHER SPECIFIC TYPES OF DIABETES (3,5,7)

- Genetic defects of β-cell function.
- Genetic defects in insulin action.
- Diseases of the exocrine pancreas.
- Endocrinopathies.
- Drug- or Chemical-induced diabetes.
- Infections.
- Uncommon forms of immune-mediated diabetes.
- Genetic syndromes sometimes associated with diabetes.
- Gestational diabetes mellitus.

Table 1. Diabetes mellitus classification (3).

I. Type 1 DM	1-A. Immune mediated	
	1-B. Idiopathic	
II. Type 2 DM	May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance	
III. Other specific types	A. Genetic defects of β-cell function	1. MODY 3 (Chromosome 12, HNF-1α) 2. MODY 1 (Chromosome 20, HNF-4 α) 3. MODY 2 (Chromosome 7, glucokinase) 4. Other very rare forms of MODY (MODY 4, IPF-1; MODY 6, NeuroD1; MODY 7, CEL VNTR) 5. Transient neonatal diabetes (6q24) 6. Permanent neonatal diabetes (KCNJ11) 7. Mitochondrial DNA 8. Others
	B. Genetic defects in insulin action	1. Type A insulin resistance 2. Leprechaunism 3. Rabson-Mendenhall syndrome 4. Lipoatrophic diabetes 5. Others
	C. Diseases of the exocrine pancreas	1. Pancreatitis 2. Trauma/pancreatectomy 3. Neoplasia 4. Cystic fibrosis 5. Hemochromatosis 6. Fibrocalculous pancreatopathy 7. Others
	D. Endocrinopathies	1. Acromegaly 2. Cushing's syndrome 3. Glucagonoma 4. Pheochromocytoma 5. Hyperthyroidism 6. Somatostatinoma 7. Aldosteronoma 8. Others
	E. Drug or chemical induced	1. Vacor 2. Pentamidine 3. Nicotinic acid 4. Glucocorticoids 5. Thyroid hormone 6. Diazoxide 7. β-Adrenergic agonists 8. Thiazides 9. Dilantin 10. γ-Interferon 11. Others
	F. Infections	1. Congenital rubella 2. Cytomegalovirus 3. Others
	G. Uncommon forms of immune-mediated diabetes	1. Down syndrome 2. Klinefelter syndrome 3. Turner syndrome 4. Wolfram syndrome 5. Friedreich ataxia 6. Huntington chorea 7. Laurence-Moon-Biedl syndrome 8. Myotonic dystrophy 9. Porphyria 10. Prader-Willi syndrome 11. Others
IV. Gestational DM		

3.1.2. EPIDEMIOLOGY

DM is a high-prevalence worldwide disease. In 2019 an estimated 463 million people were diagnosed or undiagnosed with diabetes, and it is expected to increase to 578,4 million by 2030 and to 700,2 million by 2045 according to the International Diabetes Federation (8).

DM prevalence in Spain is 13,8% (9) and DM incidence is 20/100.000 person years (10).

Type 1 diabetes incidence is increasing, particularly in children under 15 years old. This is relevant to this workpaper as ketoacidosis is, as discussed before, a frequent complication of type 1 diabetes (8).

Diabetes-related hospitalization episodes have decreased significantly, as well as its duration. However, mortality and readmission rates remain stable.

It has been observed variability at hospital diabetes-related mortality rates, indicating possible improvement on its management (9).

3.1.3. DIAGNOSIS

To diagnose DM, 3 tests are mainly used: fasting plasma glucose (FPG), 2-hour plasma glucose (2-h PG) during a 75-g oral glucose tolerance test (OGTT) and AC1 test or HbA1c.

Two abnormal test results from the same sample are needed to diagnose the patient. If only one test is altered, the test must be repeated from another sample to confirm the diagnosis.

If the patient has classic symptoms of hyperglycemia or hyperglycemic crisis, it is only needed a random plasma glucose ≥200 mg/dL (11,1 mmol/L).

If test results are close to the diagnose threshold it is recommended to repeat the test in 3-6 months (1–3,5).

Taking that into account, the diagnosis is made if the patient meets the following criteria:

- FPG ≥126 mg/dL (7,0 mmol/L).
- 2-h PG ≥200 mg/dL (11,1 mmol/L) during an OGTT.
- HbA1c ≥6,5%.
- Random PG ≥200 mg/dL (11,1 mmol/L) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

3.1.4. COMPLICATIONS

Table 2. Diabetes mellitus complications. Adapted from (11,12).

Acute complications	Chronic complications		
	Non-vascular complications	Vascular complications	
		Microvascular	Macrovascular
- Diabetic ketoacidosis - Hyperglycaemic hyper-osmolar state - Lactic acidosis	- Gastroparesis - Sexual dysfunction - Skin changes - Infections	- Retinopathy - Neuropathy - Nephropathy	-Coronary artery disease - Peripheral vascular disease - Cerebrovascular disease

Diabetic ketoacidosis will be discussed below as it is the main topic of this paperwork.

3.2. DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA) is an acute life-threatening diabetic complication characterized by:

Table 3. Diabetic ketoacidosis diagnostic criteria. Adapted from (11,13–18) .

Hyperglycemia	Blood glucose >200mg/dL or >11 mmol/L – usually between 350 to 500 mg/dL or 19,4 to 27,8 mmol/L
Anion gap metabolic acidosis	Venous pH <7,3 or bicarbonate <15,0 mmol/L
Increased total body ketone concentration or significant ketonuria	Blood ß-hydroxybutyrate ≥3 mmol/L or more than 2+ on standard urine sticks

DKA and Hyperglycemic Hyperosmolar State (HHS) are important causes of morbidity and mortality in diabetic patients. The treatment of these patients costs a high amount of social care resources (13–15).

3.2.1. EPIDEMIOLOGY

DKA typically appears in type 1 diabetic patients (66%), but type 2 diabetic patients can also suffer from diabetic complication (34%) under conditions of extreme stress of acute illness such as trauma, surgery, or infections (13,16).

DKA is more frequent in adults than in children: 56% of DKA patients are between 18 and 44 years old, 24% between 45 and 65 years old, and 18% <18 years old (13).

Patients with Hb1Ac ≥7,5%, longer diabetes duration, adolescents and females have higher risk of DKA.

Studies have determined a DKA hospital admission rate of 25-48/1000 diabetic patient-years (17,18).

The most common cause of death in type 1 diabetic <24 year-old-patients is DKA, being the half of all deaths. Meanwhile, in adults, especially those with a concomitant life-threatening illness, DKA itself causes a low percentage of deaths. In that case, the cause of death usually is due to the condition that caused the metabolic decompensation (13).

Mortality, as well as incidence, varies across the world. Data from developed countries such as the US or UK indicates mortality rates around 1%, while in other countries like India in-hospital mortality rises to 30% (18).

The history of multiple DKA episodes increases the risk of long-term mortality, being 5,2% in patients with a single DKA episode and 23,4% in patients with recurrent DKA decompensations (17).

Prognosis is highly worsened in patients at extreme young or old age, coma patients, and those with hypotension or severe comorbidities (13).

3.2.2. PATHOGENESIS

Normal response to hyperglycemia

Insulin and glucagon are hormones that help regulate serum glucose concentration. When extracellular glucose concentration rises after a meal and pancreatic beta cells detect the increase, insulin is released into the blood flow (19).

Insulin reduces the hepatic glycogenolysis and gluconeogenesis and increases glucose uptake by skeletal muscle and adipose tissue, restoring the normal glucose concentration. Also, insulin inhibits glucagon secretion and decreases hepatic glucose production (20,21).

Spectrum of metabolic abnormalities

DKA is produced in uncontrolled diabetic patients because of:

- Insulin deficiency and/or resistance.
- Glucagon excess.

Glucagon excess may contribute to the development of DKA but it is not essential. Low insulin levels do not inhibit glucagon secretion.

In DKA, insulin counterregulatory hormones such as catecholamines, cortisol, and growth hormone are also raised, and they increase glucose and ketoacid production.

Absolute insulin deficit in a diabetic patient can induce DKA, but in those patients with relative insulin deficiency, DKA is induced in response to stress, which contributes to increase the counterregulatory hormones previously described (16).

Hyperglycemia

DKA patients usually have serum glucose concentration between 350 and 500 mg/dL (19,4 to 27,8 mmol/L). These levels are not as high as in HHS because DKA symptoms frequently appear earlier than HHS ones, and also DKA patients usually are younger so they have better renal function and a greater capacity to excrete glucose (22).

The hyperglycemia observed in DKA is produced by insulin deficiency and/or resistance as represented in *Figure 1* (18,23,24).

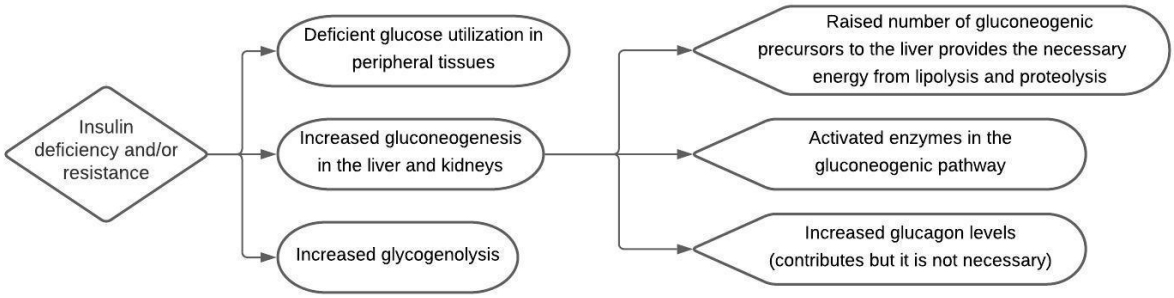

Figure 1. Effects of insulin deficiency and/or resistance.

Ketone production

Insulin deficit and resistance induce lipolysis from peripheral fat stores.

Fatty acids are produced and transported to the hepatocytes, where they are activated with the union of coenzyme-A (acyl-CoA). Finally, the acyl-CoA enters the hepatocyte's mitochondria.

Inside the mitochondria, fatty acids are divided into two-carbon units in the form of acetyl-CoA by beta-oxidation. The acetyl-CoA can:

- Create adenosine triphosphate (ATP) entering the Krebs cycle.
- Be exported to the cytoplasm and synthetize new fatty acids.
- Create acetoacetic acid by the ketogenic pathway.

Ketones are an alternative source of energy in situations when glucose is not available, as it happens in the insulin deficiency or resistance that leads to DKA.

Acetoacetic acid is the first ketone body to be formed and can enzymatically be converted to β-hydroxybutyric acid and to acetone (18,25–27).

Ketone production is schematized on *Figure 2*.

DKA appears more often in type 1 diabetes which has complete or almost complete insulin deficiency, but also can occur in type 2 diabetes under stress, as mentioned before.

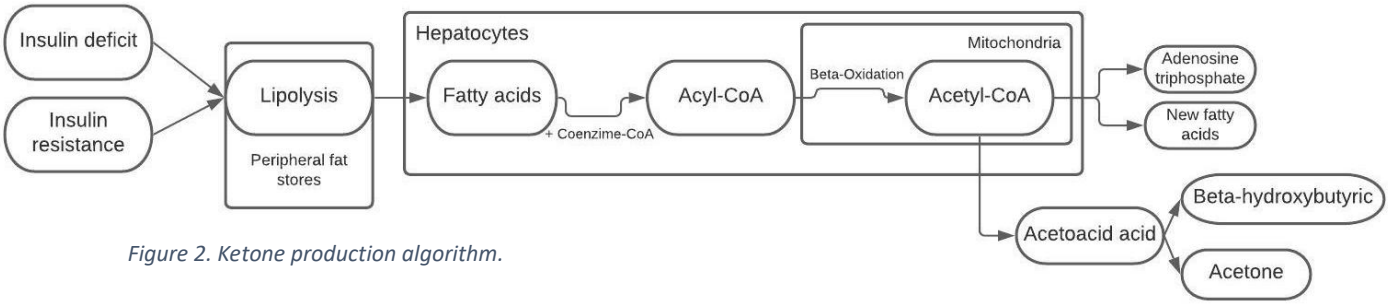

Figure 2. Ketone production algorithm.

Anion gap metabolic acidosis

The β-hydroxybutyric and acetoacetic acids excess are the cause of the typical elevated anion gap metabolic acidosis (28,29).

Anion Gap = Serum Sodium – (Serum Chloride + Bicarbonate)

The gravity and increase of anion gap metabolic acidosis depend on several factors (30):

- Duration and ratio of keto acid production.
- Ratio of keto acid metabolism.
- Acetoacetic acid to acetone conversion.
- Ketoacid anions volume of distribution.
- Ratio of ketoacid anions loss in the urine.
- Ratio of renal net acid excretion.

Keto acid anion excretion rate depends on patient's renal function and glomerular filtration rate, and patient's volume status.

The intravenous (IV) treatment with isotonic fluids increases the renal excretion of ketoacid anions reducing the anion gap, but it must be taken into account that anions are eliminated as sodium and potassium salts. The loss of these salts means losing potential bicarbonate. The urine loss of bicarbonate causes hyperchloremic anion gap acidosis. On the other hand, if keto acids are metabolized, bicarbonate is regenerated (27,31,32).

There is evidence that a small but clinically significant portion of the anion gap increase in DKA patients is produced by D-lactic acid. Keto acids, dihydroxyacetone and acetone can be converted to D-lactic acid (33).

Plasma osmolality and sodium

DKA patients have an increased plasma osmolality due to:

- Hyperglycemia.
- Osmosis diuresis induced by glycosuria that leads to a loss of electrolyte-free water.
- High plasma acetone levels.
- Variable ingestion of water, and vomitus or nasogastric suction water loss.

The increased plasma osmolality causes a release of water from the cells to the extracellular fluid. Thus, plasma sodium concentration is reduced. Studies have shown a 2mEq/L decrease in sodium for every 100 mg/100 mL glucose concentration increase (13,27,34).

Potassium

DKA patients have a potassium deficit around 300 to 600 mEq due to:

- Renal loss:
    - Glucose osmotic diuresis.
    - Excretion of potassium and sodium keto acid anion salts (sodium is reabsorbed in exchange for potassium in the distal renal tubule).
- Gastrointestinal loss.
- Cell loss because of glycogenolysis and proteolysis.

Serum potassium concentration is frequently normal or even elevated in DKA patients despite the loss of serum potassium mentioned. It is explained by the hyperosmolality and insulin deficiency.

As plasma osmolality rises, water leaves the cells to the extracellular fluid with potassium.

Normal levels of insulin induce the shift of potassium into the cells. Due to the lack of insulin, serum potassium levels increase.

Acidemia also contributes to the shift of potassium to the extracellular fluid by exchanging potassium for hydrogen ions (27,35).

Inflammation

Hyperglycemia leads to a proinflammatory state that:

- Generates oxidative stress and reactive oxygen species.
- Produces proinflammatory cytokines (α-TNF, IL-1B, IL-6 and IL-8).
- Rises lipid peroxidation markers, plasminogen activator inhibitor-1 and CRP (36).
- Activates T-lymphocytes (37).

These changes are involved in the pathogenesis of DKA and can cause organ dysfunction, such as pancreatic β-cells destruction. With adequate insulin therapy, the inflammation is controlled (16,38).

3.2.3. PRECIPITATING FACTORS

Infection is the most frequent precipitating factor in the development of DKA (30-50%), frequently caused by urinary tract infections or pneumonia.

Poor adherence to treatment is also an important precipitating cause, as well as non-compliance related to poor access to treatment (20-25%) (39).

Psychological and psychiatric factors also have been identified as precipitating factors, especially eating disorders (16,22).

Other acute conditions can cause DKA:

- Cerebrovascular accident.
- Alcohol or another drug abuse.
- Pancreatitis.
- Pulmonary embolism.
- Myocardial infarction.
- Trauma.

The use of some drugs can modify the carbohydrate metabolism and cause DKA, such as corticosteroids, thiazides, beta blockers, sympathomimetic agents or pentamidine.

The treatment of type 2 DM with sodium glucose co-transporter 2 (SGLT-2) has been identified as the cause of an atypical presentation of DKA, the “euglycemic DKA” (29).

As commented before, DKA can be the first manifestation of new-onset type 1 DM and less frequently type 2 diabetes (22).

3.2.4. DIAGNOSIS

3.2.4.1. CLINICAL PRESENTATION

DKA tends to develop over a 24-hour period. The first symptoms are related to marked hyperglycemia, such as polyuria polydipsia, weight loss, and can appear a few days before hospital admission (22).

As hyperglycemia progresses, patients usually present with vomiting and abdominal pain. Advanced cases can develop neurologic symptoms i.e. lethargy, obnubilation and focal signs as a consequence of high osmolality and severe acidosis.

Abdominal pain can be a DKA consequence or a sign of the precipitating cause, so it must be studied with caution. Abdominal pain can mimic an acute abdomen, but in most patients the pain spontaneously resolves after correcting the metabolic impairment. Abdominal pain has been associated with the severity of metabolic acidosis.

Signs of dehydration are evinced in the physical examination, e.g. loss of skin turgor, tachycardia, dry mucous membranes, and hypotension. Patients are usually normothermic or even hypothermic due to peripheral vasodilation at hospital admission, and present with fruity or acetone breath odor and Kussmaul respiration. Mental status varies a lot, from full alertness to severe lethargy (16,29,40).

3.2.4.2. LABORATORY FINDINGS

Table 4. Laboratory findings and DKA classification. Adapted from (14).

	Mild	Moderate	Severe
Plasma glucose (mg/dL)	>250	>250	>250
Plasma glucose (mmol/L)	>13,9	>13,9	>13,9
Arterial pH	7,25 to 18	7,00 to 7,24	<7,00
Serum bicarbonate (mEq/L)	15 to 18	10 to <15	<10
Urine ketones	Positive	Positive	Positive
Serum ketones – Nitroprusside reaction	Positive	Positive	Positive
Serum ketones – Enzymatic assay of β-hydroxybutyrate (normal range <0,6 mmol/L)	3 to 4 mmol/L	4 to 8 mmol/L	>8 mmol/L
Effective serum osmolality (mOsm/Kg)	Variable	Variable	Variable
Anion gap	>10	>12	>12
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma

3.2.5. TREATMENT (16,41–43)

At the initial assessment of a DKA patient in the Emergency Department (ED), the procedures mentioned in *Figure 3* must be performed. The chronogram of DKA management is represented in *Table 5*.

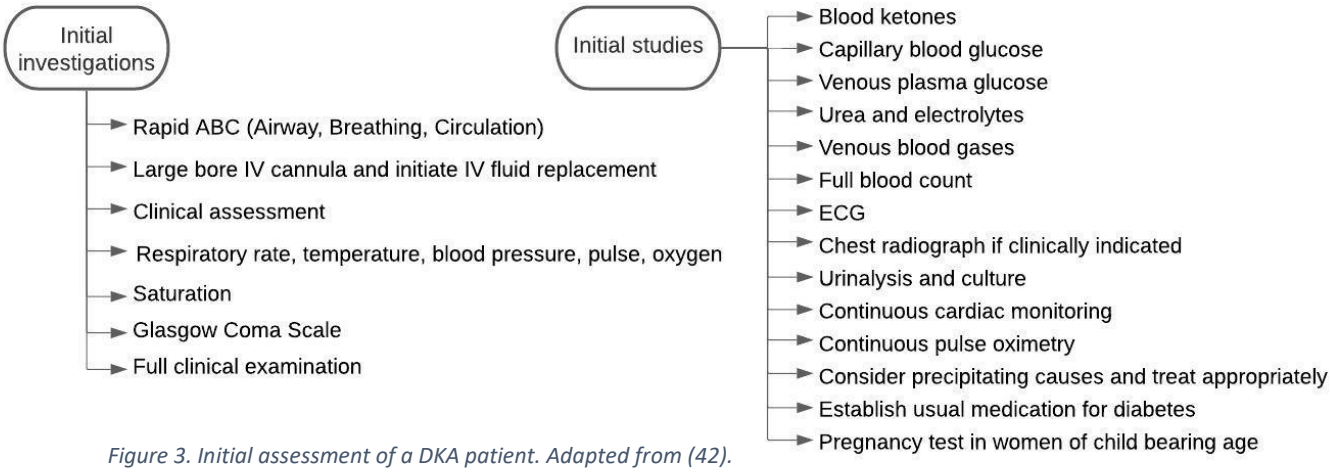

Figure 3. Initial assessment of a DKA patient. Adapted from (42).

Table 5. DKA management chronogram. Adapted from (42).

Hour 1	1 to 6 hours	6 to 12 hours	12 to 24 hours
- Initiate IV 0.9% NaCl solution - Initiate fixed IV insulin infusion after fluid therapy has been initiated - Set the patient monitoring regime, usually hourly blood glucose and ketone measurement, and 2 hourly serum potassium and bicarbonate for the first six hours - Biochemical and clinical assessment of the patient - Involve the diabetes specialist team	- Clear the blood of ketones and suppress ketogenesis - Achieve a rate of fall of ketones of at least 0.5mmol/L/h - In the absence of ketone measurement, bicarbonate should rise by 3 mmol/L/h and blood glucose should fall by 3 mmol/L/h - Maintain serum potassium in the normal range - Avoid hypoglycemia	- Ensure that clinical and biochemical parameters are improving - Continue IV fluid replacement - Continue insulin administration - Evaluate treatment complications e.g. fluid overload, cerebral edema - Continue treating precipitating factors if necessary - Avoid hypoglycemia	- Ensure that the clinical and biochemical parameters are improving or have normalised - Continue IV fluids if the patient is not eating and drinking - If the patient is not eating and drinking and there is no ketonemia move to a variable IV insulin infusion - Re-evaluate for treatment complications e.g. fluid overload, cerebral edema - Continue treating any precipitating factors if necessary

Fluid therapy

IV fluid and electrolyte replacement are used to correct hypovolemia and hyperosmolality. The effects of fluid therapy are summarized in *Figure 4*.

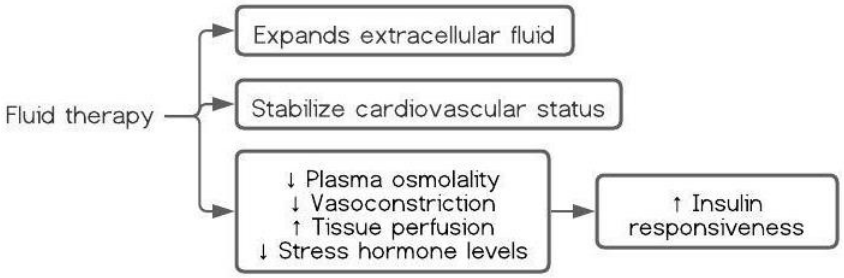

Figure 4. Fluid theraphy algorithm.

The initial isotonic saline (0,9% NaCl solution) infusion rate depends upon the severity of the patient's dehydration:

- Patients with hypovolemic shock or systolic blood pressure (SBP) <90 mmHg should be infused with 500 ml of isotonic saline (IS) for about 10-15 minutes. When SBP is >90 mmHg patients are treated according to the next group.
- Patients with hypovolemia without shock, IS should be infused at a rate of 15-20 mL/Kg/h during the first 2 hours (approximately 1L/h).
- Euvolemic patients need to be infused at a lower rate.

After 2-3 hours, fluid therapy varies according to the hydration state, levels of serum electrolytes, the urine output, and most importantly according to the sodium concentration corrected by hyperglycemia (for every 100 mg/100 mL increase above normal in glucose concentration 2 mEq/L in plasma Na concentration is added).

Typical fluid replacement regimen is schematized in *Table 6*.

According to corrected serum sodium concentration:

- <135 mEq/L: 250-500 mL/h of IS should be infused.
- ≥135 mEq/L: one-half IS (0,45% NaCl solution) is infused at a rate of 250-500 mL/h to provide electrolyte-free water.

  The one-half IS therapy is also indicated with concurrent potassium replacement as potassium is as osmotically active as sodium affecting the saline solution.

When plasma glucose levels are around 200-250 mg/dL, 5% dextrose should be added to the saline solution. Hyperglycemia is corrected faster than ketoacidosis, as a result, this addition is needed to avoid hypoglycemia while ketone levels decrease.

Frequent hemodynamic and laboratory monitoring (every 1-2 hours) should be done to assess the adequacy of fluid therapy.

Osmolality should not be reduced too quickly to prevent cerebral edema.

Patients with heart or kidney failure, young (18-25 years) or elderly, or others with serious comorbidities should be monitored more frequently to avoid iatrogenic fluid overload.

Table 6. Typical fluid replacement regimen for a previously well 70 kg adult. Illustrative guide. Adapted from (42).

Fluid	Volume
0,9% sodium cloride 1L	1000 mL over the 1st hour
0,9% sodium cloride 1L with postassium chloride	1000 mL over next 2 hours
0,9% sodium cloride 1L with postassium chloride	1000 mL over next 2 hours
0,9% sodium cloride 1L with postassium chloride	1000 mL over next 4 hours
0,9% sodium cloride 1L with postassium chloride	1000 mL over next 4 hours
0,9% sodium cloride 1L with postassium chloride	1000 mL over next 6 hours

Potassium replacement

If serum potassium is <5,3 mEq/L and there is adequate urine output (>50mL/h), potassium replacement should be initiated. *Table 7* summarizes the potassium replacement.

Table 7. Potassium replacement summary.

Initial serum potassium	Management
< 3,3 mEq/L	20 to 40 mEq/L KCl added to each L of saline
3,3-5,3 mEq/L	20 to 30 mEq/L KCl added to each L of saline
> 5,3 mEq/L	Potassium replacement should be delayed

The goal of the treatment is to maintain serum potassium levels around 4 to 5 mEq/L.

Severe hypokalemia must be treated intensely to prevent from suffering cardiac arrhythmias, respiratory muscle weakness and cardiac arrest.

The addition of potassium to IV fluids has an impact on the saline osmolality, so it must be considered. Potassium is added to IS or half IS depending on the hydration state, corrected sodium concentration, blood pressure, KCl dose, and clinical assessment.

The administration of insulin enhances the entrance of serum potassium into the cells causing a high decrease of serum potassium despite potassium replacement.

Frequent monitoring is essential to ensure the correct replacement of serum potassium.

Insulin administration

The use of IV regular insulin or rapid acting insulin analogues have shown to be effective for the treatment of DKA. However, the continuous IV infusion of regular insulin is preferred principally for its lower price and for its short half-life and easy titration. The effects of insulin therapy are shown in *Figure 5*.

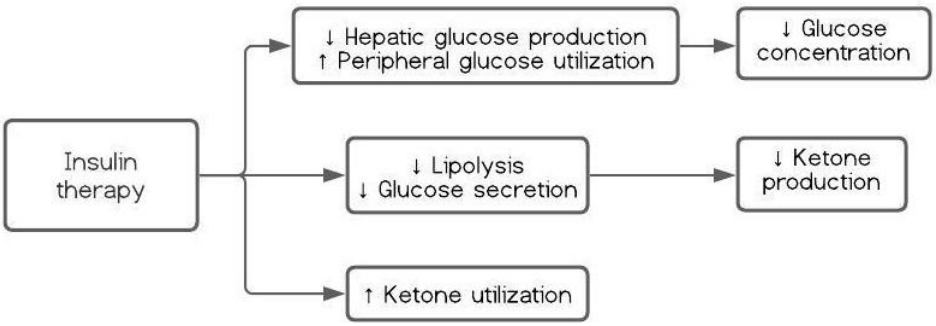

Figure 5. Insulin therapy effects algorithm.

It is recommended to start the treatment with low-dose IV insulin according to clinical and laboratory findings:

- Patients with a serum potassium of <3,3 mEq/L → treatment with aggressive fluid therapy and potassium replacement, insulin infusion should be delayed.
- Patients with moderate to severe DKA with a serum potassium of ≥3,3 mEq/L → start IV insulin therapy.

Recommended treatment algorithms for DKA consists of:

1. Initial dose of IV regular insulin of 0,1 units/kg.
2. Followed by the infusion of 0,1 units/Kg/h.

Recently, new studies have reported a new algorithm:

1. No use of initial insulin bolus.
2. Insulin infusion of 0,14 units/kg/h.

However, the absence of initial insulin bolus may not be sufficient to suppress hepatic ketone body production without adding insulin doses.

With IV insulin treatment the glucose plasma concentration should decrease at a rate of 50-75 mg/dL/h. If it decreases at a lower rate, after checking the IV access, the insulin infusion should be increased hourly until glucose levels decrease steadily.

When plasma glucose is around 200 mg/dL insulin infusion rate should be reduced to 0,02-0,05 units/kg/h and dextrose should be added to IV fluids, as mentioned earlier.

There is evidence that shows that rapid-acting insulin analogues every 1-2 hours is effective for the treatment of mild to moderate DKA.

Long-acting or intermediate-acting insulin analogues have no role in the DKA management. They are used after recovery before discontinuation of IV insulin to ensure adequate insulin levels.

The insulin dose needed to inhibit lipolysis is much lower than to reduce serum glucose. Thus, if a patient's glucose concentration decreases, the insulin dose administered is enough to stop ketone production.

Bicarbonate therapy and metabolic acidosis

There is some controversy over the use of bicarbonate in DKA treatment for its potential adverse effects, shown in *Figure 6*.

Accordingly, bicarbonate replacement is only indicated if:

- Arterial pH ≤6,9 in patients which cerebral vasodilatation and decreased myocardial contractility can impair tissue perfusion.
- Potential life-threatening hyperkalemia (serum potassium >6,4 mEq/L).

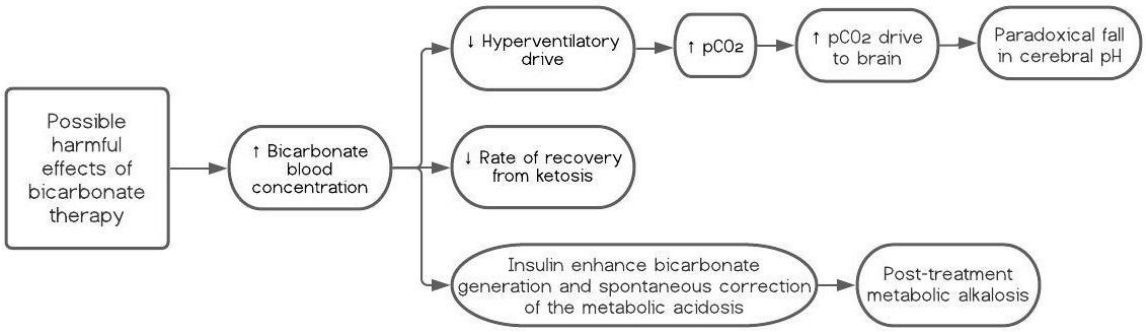

Figure 6. Possible adverse effects of bicarbonate therapy algorithm.

Phosphate replacement

Phosphate replacement is not recommended as routine for its potential adverse effects (hypocalcaemia or hypomagnesemia).

It must only be considered if serum phosphate is <1mg/dL or <0,32 mmol/L, especially in cardiac dysfunction, respiratory depression and/or haemolytic anaemia.

If needed, 20-30 mEq added to 1L of IV fluid.

3.2.6. COMPLICATIONS (13,16,29,41)

Hypoglycemia

Hypoglycaemia appears in 10-25% of patients with DKA, being the most common complication during treatment.

The most important risk factors associated with hypoglycemia are the lack of appropriate monitoring, and the failure to reduce the rate of insulin infusion and/or to add dextrose to saline solution when blood glucose concentration is around 200-250 mg/dL.

Patients may not experiment the typical adrenergic manifestations of nervousness, sweating, hunger, fatigue, and tachycardia. For this reason, frequent monitoring (every 1-2h) is mandatory.

Recurrent episodes of hypoglycaemia can be associated with a state of hypoglycemia unawareness, which can complicate the management of diabetes after the recovery from DKA.

Hypokalemia

Hypokalemia is the second most frequent complication during the treatment of DKA. Potassium levels decrease due to insulin treatment and correction of acidosis, which stimulate cellular potassium uptake in peripheral tissues. To prevent this, it is important frequent monitoring and potassium replacement.

Cerebral edema

Cerebral edema is present in almost 1% of children with DKA and less frequently in adults. The mortality rate is 20-40% of the cases and represents 57-87% of all DKA deaths in children.

Cerebral edema clinically results in a decreased level of consciousness and headache, abnormal verbal and motor response to pain, cranial nerve paralysis (particularly III, IV, and VI), pathologic respiratory pattern (tachypnea, grunting, Cheyne-Stokes respiration,

respiratory arrest), seizures, sphincter incontinence, elevated blood pressure, and papilledema.

Its pathogenesis is not clearly known. It is suspected to be caused by a rapid shift in the extracellular and intracellular fluids and changes in osmolality caused by rapid reduction in serum osmolality and osmolyte accumulation in brain cells in hyperosmolar conditions.

The treatment consists of IV mannitol 0,5-1 g/kg dose over 20 minutes and should be repeated after 30 minutes if there is no response. Reducing the rate of fluid administration and mechanical ventilation can contribute to reducing brain swelling.

Rhabdomyolysis

Renal monitoring every 2-3 hours is important for early detection and for preventing acute kidney failure.

Rhabdomyolysis is typically exhibited by a triad of symptoms which include myalgia, weakness, and dark urine.

Pulmonary edema

Patients with congestive heart failure or chronic kidney disease with excessive fluid replacement can suffer from pulmonary edema.

Prescription and administration related

Even if DKA treatment is well established, its management is complex and there are factors that can affect its effectiveness and safety.

Clinical variation has been reported, especially on fluid administration, electrolyte replacement, insulin therapy, and laboratory-investigation frequency (44–47).

Additionally, treating DKA patients in the ED, in which other patients with life-threatening illnesses are treated, can result in an increased risk for delays and errors in the management of patients presenting with DKA (44).

This clinical variation has been related with an increased rate of the treatment complications previously mentioned.

Prescription errors consist of mistakes made by the physician on the selection of the most appropriate medication, its dose, route or frequency of administration (48).

Medication administration, one of nurses' main responsibilities, can be another cause of errors. They are produced when there is a mistake in one of the "5 rights" (right patient, right drug, right dose, right time, and right route) (49).

Prescription errors, such as the lack of frequent monitoring or not monitoring all the necessary parameters, and administration errors, resulting from the need of frequent treatment modifications, can lead to overly weak or aggressive treatment (45).

The main points for a safer management of DKA are to avoid rote memory acting, and to standardize and simplify the process (47).

The Hospital Universitari Josep Trueta (HUJT)'s ED Security Commission has collected data about prescription and administration errors from 2020. The results are summarized in *Table 8*.

2.6.8. PREVENTION

Prevention is one of the most important aspects of DKA management.

Appropriate education, improved self-care and compliance, and self-monitoring of blood glucose are very relevant to prevent further DKA episodes (11). Around 50% of DKA admissions could be prevented with better adherence to self-care and improved outpatient treatment programs (13).

The rise of DKA episodes caused by stopping the insulin treatment for economic reasons emphasises the need for our health care systems to address this issue (13,16).

Table 8. Prescription and administration errors of HUJT's ED.

ERROR	TOTAL EPISODES RATE		COMPLICATIONS
FLUID			
	PRESCRIPTION	ADMINISTRATION	
Lower volume or at lower rate than needed	5%	10%	Hyperglycemia Ketonemia Metabolic acidosis Prerenal kidney failure
Higher volume or at higher rate than needed	3%	<1%	Fluid overload Cardiac failure Cerebral edema
Wrong saline	<1%	0%	Hyperglycemia if dextrose Hypernatremia or hyponatremia if wrong saline
INSULIN			
	PRESCRIPTION	ADMINISTRATION	
Wrong initial IV regular insulin bolus dose per weight	<1%	<1%	Hyperglycemia or hypoglycemia
Wrong insulin infusion rate	<1%	<1%	Hyperglycemia or hypoglycemia
Early stoppage of insulin infusion	2%	5%	Hypoglycemia, ketonemia
Wrong mobile insulin instructions	10%	10%	Hypoglycemia, hyperglycemia, ketonemia
POTASSIUM CHLORIDE			
	PRESCRIPTION	ADMINISTRATION	
Wrong dose	<1%	<1%	Hyperkalemia or hypokalemia
BICARBONATE			
	PRESCRIPTION	ADMINISTRATION	
Wrong dose	2%	<1%	Metabolic acidosis or alkalosis
DIET			
	PRESCRIPTION	ADMINISTRATION	
Not to respect the 3h schedule		<1%	Hypoglycemia, hyperglycemia, ketonemia
To start when not indicated	<1%		Vomiting, bronco-aspiration, hyperglycemia
Not to start when indicated	2%		Hypoglycemia, ketonemia

4. JUSTIFICATION

DM is a high prevalent metabolic disorder whose prevalence is expected to continue rising worldwide (8).

In the last years, the number and duration of complicated diabetes-related hospitalizations have decreased, however, mortality rates have not changed (9).

DKA is a life-threatening diabetic complication characterized by hyperglycemia, anion gap metabolic acidosis and increased total body ketone concentration (16). Studies show that DKA is the most common cause of death in youth type 1 diabetes, and an important cause of morbimortality in type 2 diabetic patients (13).

Furthermore, costs related to hospitalization for DM complications are estimated to be 3-5% of total healthcare cost. With the improvement of DKA management the amount of capital investment could be reduced (9).

The difference in mortality rates among different countries or hospitals highlights the importance of a well-structured DKA management (18).

There are published studies that evaluate the effectiveness of some specific interventions in the DKA treatment, but few of them have evaluated protocols for extended ED management (44).

There is evidence that having a structured and standardized treatment protocol has a positive impact on safety and resource utilization (46,50). However, most of these studies have been done on pediatric population or other settings.

According to data collected from 2019 DKA episodes treated in HUJT's ED, there were a total of 55 episodes with a mean stay in the ED of 14,36 hours (SD = 10,22). A total of 47,3% were female patients and 52,7% were male. We found that 21,82% were reconsulting patients with new DKA episodes.

22 out of 55 episodes (40%) ended up with the admission to the Endocrinology service after a mean time spent in the ED of 13,59 hours. Thus, the mean in-hospital stay of DKA patients may be much higher than the calculated in the ED.

One of the 55 episodes ended in death, being almost 2% of the total.

Taking all that into account, this study will provide evidence whether the use of a computer decision support and electronic order sets to standardize the DKA treatment protocol is effective to improve the security and, thus, to minimize the main time spent in ED by DKA patients treated in the HUJT.

5. HYPOTHESIS

The application of a computer decision support and electronic order sets to standardize DKA management in Hospital Universitari Josep Trueta's Emergency Department increases the safety of the treatment.

6. OBJECTIVES

Main objective

1. To decrease hospital length of stay of DKA patients treated in HUJT's ED with the application of a computer decision support and electronic order sets (CDS&EOS) to minimize security errors.

Secondary objectives

2. To decrease incidence of significant treatment complications in DKA patients treated in HUJT's ED with the application of a CDS&EOS to minimize security errors.
3. To decrease mortality in DKA patients treated in HUJT's ED with the application of a CDS&EOS to minimize security errors.
4. To reduce the need for hospitalization in DKA patients treated in HUJT's ED with the application of a CDS&EOS to minimize security errors.
5. To decrease prescription errors in DKA patients treated in HUJT's ED with the application of a CDS&EOS to minimize security errors.
6. To decrease administration errors in DKA patients treated in HUJT's ED with the application of a CDS&EOS to minimize security errors.

7. SUBJECTS AND METHODS

7.1. STUDY DESIGN

This study is a quasi-experimental study, designed as a before-and-after evaluation of an intervention to improve DKA treatment's safety. The intervention consists of the application of a SILICON® computer decision support and electronic order sets in HUJT's ED to standardize DKA management.

7.2. STUDY POPULATION

The study population will include all DKA patients treated in HUJT's ED with the following inclusion and exclusion criteria.

7.2.1. INCLUSION CRITERIA

- Patients with DKA suspicion.
- 18-year-old patients or older.
- Patients who agree to participate in the study, understand and sign the informed consent.

7.2.2. EXCLUSION CRITERIA

- Patients under 18 years old.
- Patients diagnosed with HHS.
- Patients who reject to participate in the study or do not sign the informed consent.
- Patients with missing information in the data collection sheet.

7.3. SAMPLING

7.3.1. SAMPLE SIZE

The main variable of the study is the length of stay of DKA patients treated in HUJT's ED. Calculations made from non-published data from 2019 DKA episodes treated in HUJT's ED show a mean time spent in the ED of 14,36 hours and a standard deviation of 10,22.

The sample size was calculated with the online free application *Calculadora de Grandària Mostral* (GRANMO).

Accepting an alpha risk of 0,05 and a beta risk of 0,2 in a two-sided test, 67 subjects are necessary in the first group and 67 in the second to recognize as statistically significant a difference greater than or equal to 5 units. The common standard deviation is assumed to be 10,22. It has been anticipated to have a drop-out rate of 1%.

7.3.2. SAMPLE SELECTION

Participants will be selected by a non-probabilistic consecutive model. All patients who attend the ED and meet the inclusion criteria will be asked to participate and will be given the information document and the informed consent (available in *Annex 1* and *Annex 2*). Physicians will highlight the confidentiality and voluntary aspects of patients' participation.

Considering an annual average of 55 DKA episodes in HUJT's ED, sample selection will take place over a period of 36 months, 18 months per period to reach the necessary sample size of 67 participants in each group, 134 participants in total.

7.4. VARIABLES

7.4.1. INDEPENDENT VARIABLE

The independent variable is the **application of a computer decision support and electronic order sets** to standardize DKA treatment. It is a dichotomous nominal qualitative variable and will be expressed as:

- Control group: **not application** of CDS&EOS.
- Experimental group: **application** of CDS&EOS.

The computer decision support and electronic order sets will consist of an algorithm introduced in ED's SILICON®. SILICON® is the software for e-prescription and hospital pharmacy management used in HUJT.

With this modification, when patient's anthropometric measures and laboratory measurements are introduced, the software will continuously notify the clinical team about which treatment needs to be prescribed and administered, which analytical control has to be carried out and when it needs to be done.

7.4.2. DEPENDENT VARIABLES

MAIN OBJECTIVE**:**

1. To decrease hospital length of stay of DKA patients.

Length of stay in hospital: a continuous quantitative variable expressed in **hours**.

SECONDARY OBJECTIVES**:**

2. To decrease incidence of significant treatment complications in DKA patients.

Significant treatment complications: a discrete quantitative variable. The result will be obtained from the sum of the following individual dichotomous nominal variables expressed by **yes** or **not.**

- **Hypoglycemia**, defined by plasma glucose <70 mg/dL or 3,9 mmol/L.
- **Hyperglycemia**, defined by plasma glucose >126 or 7 mmol/L.
- **Hypokalemia**, defined by serum potassium level <3,6 mmol/L.
- **Hyperkalemia**, defined by serum potassium level >5 mmol/L.

- **Hypernatremia**, defined by serum sodium level >145 mEq/L.
- **Cerebral edema**, diagnosed by physical examination and imaging tests.
- **Prerenal kidney failure**, defined by an increase of serum Cr level to 1,5-2 or >0,3 mg/dL and diuresis <0,5 mL/Kg/h in 6 hours.
- **Rhabdomyolysis**, diagnosed by serum CK levels >500 IU/L and AKI.
- **Pulmonary edema**, diagnosed by physical examination, plasma BNP >400 pg/ml and imaging tests.

3. To decrease mortality in DKA patients.

Overall mortality: a dichotomous nominal qualitative variable expressed as **yes** or **not**.

4. To reduce the need for hospitalization in DKA patients.

End of ED episode: a non-dichotomous nominal qualitative variable. It will be expressed by **ICU admission**, **endocrinological department admission**, or **direct discharge**.

5. To decrease prescription errors in DKA patients.

Prescription errors: a discrete quantitative variable. The result will be obtained from the sum of the following individual dichotomous nominal variables expressed by **yes** or **not.** These variables are defined in *Table 8***.**

- **Fluid prescription error**.
- **Insulin prescription error**.
- **Potassium chloride prescription error**.
- **Bicarbonate prescription error**.
- **Diet prescription error**.

6. To decrease administration errors in DKA patients.

Administration errors: a discrete quantitative variable. The result will be obtained from the sum of the following individual dichotomous nominal variables expressed by **yes** or **not.** These variables are defined in *Table 8***.**

- **Fluid administration error**.
- **Insulin administration error**.
- **Potassium chloride administration error**.
- **Bicarbonate administration error**.
- **Diet administration error**.

7.4.3. CO-VARIABLES

Table 9. Co-variables of the study.

Co-variable	Type of variable	Categories or values
Age	Continuous quantitative	Years
Sex	Dichotomous nominal qualitative	Male / Female
Weight	Continuous quantitative	Kg
Glasgow Coma Scale at admission	Discrete quantitative	3 to 15
Blood pH at admission	Dichotomous nominal qualitative	≤6,9 / >6,9
Precipitating factor	Non-dichotomous nominal qualitative	Infection / Poor treatment adherence / Cerebrovascular event / Pancreatitis / Trauma / Drug abuse / Dietary transgression / Other
Door to time attendance	Continuous quantitative	Minutes
Day of the week of admission	Non-dichotomous nominal qualitative	Monday / Tuesday / Wednesday / Thursday / Friday / Saturday / Sunday
Admission time	Ordinal qualitative	8:00h to 14:59h / 15:00h to 21:59h / 22:00h to 7:59h
Number of prior DKA episodes	Discrete quantitative	No.
Number of prior ICU admissions	Discrete quantitative	No.
Comorbidities	Ordinal qualitative	1 / 2 / 3 / 4 / 5 / ≥6
Level of studies	Non-dichotomous nominal qualitative	University degree / Secondary studies / Primary studies / No studies

Glasgow Coma Scale (GCS) is a clinical scale to assess the impairment of conscious level according to eye opening, verbal response and motor response (51). GCS is available in *Annex 4*.

Comorbidities will be determined by The Charlson Comorbidity Index (CCI). The CCI uses 17 selected clinical conditions that singly or in combination may alter the short-term mortality risk. It is used to predict 1-year mortality risk according to the weighted score to each of the 17 comorbidities (52). CCI is shown in *Annex 5*.

7.4.4. DATA COLLECTION METHODS

The information needed to perform the study will be collected prospectively using data collection sheets filled out by the physician and nurse in charge of the participants' treatment.

It will be done only if the patient reads and understands the protocol information sheet and agrees and signs the informed consent. If the patient is not able to give the consent before collecting the information because of lack of consciousness and/or the severity of the disease, it will be given to the participant afterwards or to first-degree relatives if they are present.

Protocol information sheet and Informed consent will be available in Catalan, Spanish and English. The Catalan version is available in *Annex 1* and *Annex 2*.

The same data collection sheet will be used during the 36-months period of data recruitment, applying the same methodology in both periods (pre and post-intervention).

Between both periods, ED physicians and nurses will receive full training in the use of the CDS&EOS. The first 6 months following the implementation will be excluded as a washout period. The collection of the sample of the post-intervention group will start the same month as the pre-intervention group, but in this case, it will be done 2 years later, to avoid differences between both groups.

Demographic patient items, and the variables and co-variables mentioned before will be registered in data collection sheets. Each participant will be identified with an identification number for personal data protection and confidentiality.

Data collection sheets will be archived, and the data manager will weekly introduce them to the database to standardize the process and finally analyse the data. Data will be introduced in the database at regular short time intervals to detect possible missing information. If the information cannot be completed, the participant will be excluded from the study.

The data manager will be a hired professional not involved in patient's treatment.

A copy of the data collection sheet is available in *Annex 3*.

8. STATISTICAL ANALYSIS

A statistical analyst will perform all the statistical analyses with an appropriate software.

8.1. DESCRIPTIVE ANALYSIS

All qualitative variables will be expressed as percentages with a 95% confidence interval.

For quantitative variables mean with standard deviation will be used assuming a normal distribution. If normal distribution cannot be assumed median and interquartile range will be used.

The results of both groups, before and after the intervention, will be stratified by the covariates.

8.2. BIVARIATE INFERENCE

Categorical variables will be compared using the Chi Square test or Fisher exact tests (when more than 20% of cells have expected frequencies <5).

For continuous variables, a two-sided Student's T-test will be used if normal distribution can be assumed. On the other hand, if normal distribution cannot be assumed, Mann–Whitney U test will be used.

8.3. MULTIVARIATE ANALYSIS

Finally, multivariate logistic regression analysis will be performed to add the covariates that could skew the main association we want to analyse.

To consider that there is a significant difference we will assume a confidence interval of 95% and a P value <0,05.

9. WORK PLAN

9.1. RESEARCH TEAM PERSONNEL

The participants of the study will be the research team or RT (Dra. Àngels Gispert and Jordi Mayol), HUJT's ED physicians and nurses, a data manager, a computer technician, a CDS&EOS trainer, and a statistical analyst.

9.2. STUDY STAGES

The study will be performed in 5 stages that will consist of:

STAGE 0: Study design (5 months)

- **Activity 1**. Bibliographic research (November 2020 – December 2020).

We have carried out bibliographic research to review the most important aspects of DKA management, specially those aspects concerning the improvement of ED's safety.

- **Activity 2.** Design of the study protocol (January 2021).
- **Activity 3.** Ethical evaluation of the protocol by the *Comitè d'Ètica d'Investigació Clínica* (CEIC) of HUJT (February 2021).
- **Activity 4.** Permission request HUJT and ED's management to start the study (March 2021).
- **Activity 5.** CDS&EOS set-up (March 2021).

A SILICON® intern will set up the informatic tool which will be used in HUJT's ED to standardize DKA management.

STAGE 1: Coordination and organization (1 month)

- **Activity 6.** Coordination meeting (1st week April 2021).

We will hold a meeting with all the professionals involved in the study, including physicians and nurses, to present the study design.

- **Activity 7**. Initial training session (2nd week April 2021).

Physicians, nurses, and nurse assistants will receive a DKA management seminar by an ED endocrinologist, and also training by the data manager to ensure a standardized data collection. Training sessions will be done in groups of 10, placed according to job, and will end with a practical workshop with mixed teams.

- **Activity 8**. Database creation (3-4th weeks April 2021).

The data manager will be in charge of creating the database, in which he/she will afterwards introduce the information collected from the data collection sheets. Each patient will be listed and encoded with a number to preserve their confidentiality.

STAGE 2: Pre-intervention recruitment (18 months)

- **Activity 9.** Pre-intervention patient recruitment (May 2021 – October 2022).

Patient recruitment of the pre-intervention group will take over an 18-month period.

Looking at the data taken from the episodes, the data manager will check if any prescription or administration errors were made during treatment. The data manager will also introduce the collected information in the database on a weekly basis.

STAGE 3: Intervention (6 months)

- **Activity 10.** Implementation of the computer decision support and electronic order sets (November 2022).
- **Activity 11.** Training on computer decision support and electronic order sets (November 2022 – April 2023).

All physicians and nurses working in the ED will receive a training session on how to use the new informatic tool. The trainer will provide a two-week follow-up to check if it is well-applied.

Afterwards we will exclude all data from the following 6 months as a washout.

STAGE 4: Post-intervention recruitment (18 months)

- **Activity 12.** Post-intervention patient recruitment (May 2023 – October 2024).

Patient recruitment of the post-intervention group will take 18 months.

Looking at the data taken from the episodes, the data manager will check if any prescription or administration errors were made during treatment. The data manager will also introduce the collected information in the database on a weekly basis.

STAGE 5: Statistical analysis, interpretation, and publication (9 month)

- **Activity 13**. Data analysis (November 2024).

A hired external statistical analyst will analyse the data collected from both periods and obtain the study results.

- **Activity 14**. Interpretation and discussion of the results (December 2024).

The RT will discuss the results obtained and finally debate and obtain the study conclusions.

- **Activity 15**. Paper redaction, revision, publication, and dissemination (January 2025 – July 2025).

We will write a journal article with an accurate explanation of the whole process, presenting the interpretation of results and conclusions obtained in the RT meeting. Afterwards the paper will be submitted for publication.

The RT will attend a national and an international congress to present the study.

9.3. CHRONOGRAM

Table 10. Study chronogram.

ACTIVITIES	2020		2021					2022			2023		2024			2025	PERSONNEL
	N	D	J	F	M	A	M-D	J-O	N	D	J-A	M-D	J-O	N	D	J-J	
STAGE 0: Study design																	
1. Bibliographic research																	RT
2. Protocol design																	RT
3. Ethical evaluation of the protocol																	CEIC
4. ED and hospital management authorization																	ED head, hospital manager, IT
5. CDS&EOS set-up																	SILICON® intern
STAGE 1: Coordination and organization																	
6. Coordination meeting																	IT, ED clinical team
7. Initial training session																	IT, ED clinical team, data manager
8. Database creation																	Data manager
STAGE 2: Pre-intervention recruitment																	
9. Pre-intervention patient recruitment																	ED clinical team
STAGE 3: Intervention																	
10. Informatic tool application																	Computer technician
11. Informatic tool training																	Trainer
STAGE 4: Post-intervention recruitment																	
12. Post-intervention patient recruitment																	ED clinical team
STAGE 5: Statistical analysis, interpretation, and publication																	
13. Data analysis																	Statistician
14. Results interpretation and discussion																	RT
15. Results publication and dissemination																	RT

RT: Resarch team (Dra. Àngels Gispert and Jordi Mayol)

10. BUDGET

PERSONNEL EXPENSES

The ED professionals will collaborate in the study as part of their usual clinical assistance. The physician who will teach the DKA seminar will receive a reduction of attendance hours as a compensation for the time invested in training.

The data manager will be an external professional hired as a part-time worker. It is estimated that a period of 10 hours will be invested in order to create the database, and 3 hours a week will be needed to introduce the information in the database during the participants recruitment period. Taking into account that participants recruitment will last 36 months, and considering an hourly rate of 40€/h, the final cost will be 4.720€.

Furthermore, the CDS&EOS trainer will work part-time for a period of two weeks teaching small groups and will provide follow-up to check if it is well-applied. Given an estimated hourly rate of 45€/h, working 5 hours a day for 2 weeks (5 days per week) the final cost would be 2.250€.

For the statistical analysis, a statistician will be hired for 35 hours with a salary of 40€/h. The final cost will be 1.400€.

A SILICON® intern will programme the informatic tool as a part of their job, so it will not represent any additional expenses.

EXECUTION EXPENSES

The material needed for routine clinical practice for DKA management is available in our hospital so it will not involve any additional cost for the study.

The cost of printing the information sheets, informed consents, and data collection sheets, a total of 6 pages per participant, will be 32,16€.

The materials consulted for the bibliography research have not represented any additional expenses.

STUDY PUBLICATION EXPENSES

The publishing, revision, edition, English correction, layout and formatting of the study as a journal article will have an estimated cost of 2.000€.

STUDY DISSEMINATION EXPENSES

The study will be presented in a national and an international Emergency congress. Considering the price of registrations, transport, accommodation and diets, the final cost will be 2.000€.

Table 11. Study budget summary.

TYPE OF COST	UNIT COST	HOURS/UNITS	TOTAL
PERSONNEL EXPENSES			
Data manager	40€/h	10 hours (create database) 3 hours x 1 week x 36 months (fill database)	4.720 €
Trainer	45€/h	5 hours/day x 5 days/week x 2 weeks	2.250€
Statistician	40€/h	35 hours	1.400€
Subtotal			8.370€
EXECUTION EXPENSES			
Printing (protocol information sheet, informed consent document, data collection sheet)	0,05€	6 pages/participant 0,04€/page 134 participants	32,16€
STUDY PUBLICATION EXPENSES			
Paper edition and revision			2.000€
STUDY DISSEMINATION EXPENSES			
Congress attendance	1.000€	2	2.000€
		TOTAL	**12.402,16€**

11. ETHICAL AND LEGAL CONSIDERATIONS

The protocol will be presented to the CEIC of HUJT for its evaluation and approval before starting the project.

This study will be conducted in compliance with the ethical principles and guidelines established by The World Medical Association in the *Declaration of Helsinki in June 1964* and last revised in October 2013, and the principles of *The Principles of Biomedical Ethics by Beauchamp and Childress of 1979*.

All patients participating in the study will be informed by ED physicians and will receive the protocol information sheet (*Annex 1*). If they understand and sign voluntarily the informed consent document (*Annex 2*), they will be included in the study. It is important to explain to every individual that they can accept or decline to participate in the study without modifying the quality of its medical care. If patients cannot give their approval because of being unconscious or dead, first-degree relatives would receive the informed consent. Besides, participants will have the right of revoking the informed consent if they reconsider their participation in the study. In that case they would have to sign the revocation of the informed consent document (*Annex 6*).

Additionally, considering the *Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos personales y Garantía de los derechos digitales,* and the *Real Decreto 1720/2007, de 21 de diciembre por el que se aprueba el Reglamento de desarrollo de la Ley Orgánica 15/1999,* the *2016/679 (EU) Regulation of the European Parliament and of 27 April 2016 Council on the protection of natural persons with regard to the processing of personal data and on the free movement of such data*, the study will provide anonymity to patients by identifying them with numbers in the database, and will respect and protect personal data cession, data processing and confidentiality. All data collected will only be used for the intended purpose of this study.

Ley 14/2007, de 3 de Julio, de Investigación Biomédica, will be considered since biological samples will be collected and analysed during the investigation.

The authors of this research declare to have no conflicts of interest related to this study.

12. STUDY LIMITATIONS

There are some limitations that should be considered as they may interfere with the study results.

One of the most important limitations of the study is related to its design. As a before-and-after evaluation, we want to assess the consequences of our intervention, but we cannot assure that changes observed are caused by the intervention itself or other external factors have contributed to the obtained results. The differences between both participant groups could affect the study results. Therefore, we will adjust the possible confounding variables by doing a multivariate analysis. Additionally, as SARS-CoV-2 pandemic may have affected medical attention in the ED, we will not collect data from previous years to avoid the bias.

This is a single-centre study, so it may be difficult to generalize the conclusions to other settings. As there exists evidence in other settings, our objective is to prove if it works in our Department.

The use of a non-probabilistic consecutive model to collect our sample may cause differences between both study groups. However, to reduce the bias we will select a proper sample size and, as mentioned above, adjust the possible confounding variables with a multivariate analysis.

We do not expect a significant number of dropouts as the study does not have a following-up process. Voluntary discharge before the resolution of the disease can be the only source.

Due to the high flow of patients attending the ED, there may be changes between the two groups. However, this cannot be controlled, and it is one of the objectives we want to assess if, with a more standardized protocol, the high attendance pressure does not affect treatment security.

According to ED clinical experience, the ED tends to be more overloaded during winter, and receive more critical traumatic patients during summer, in comparison with other months of the year. Considering that, to reduce the difference between both groups the sample collection will be performed in the same months of the year.

There are several physicians and nurses working in HUJT's ED and they may collect the study data in different ways. For this reason, we have created a data collection sheet and will carry out some training before the study starts, to standardize the process and reduce the bias. Also, only the data manager will be in charge to introduce the registered data into the database to standardize the process.

Another limitation may be related with the documentation of tasks. Often, the documentation lags behind task performance, thus, the evaluation of outcomes of interest precision may be limited. Therefore, the initial training will focus on this aspect to reduce the bias.

Training sessions will be taught only by a professional with clinical and training experience to avoid an interobserver bias.

Additionally, as there are a lot of physicians working in the ED with different levels of experience, their different approach to the patient could cause a bias. However, the ED has been working to homogenize different physicians' treatment to avoid significant differences.

Furthermore, Hawthorne Effect must be considered, as physicians could modify their usual clinical approach if they feel evaluated.

Finally, DKA management relies significantly on laboratory findings. To avoid measurement bias, all samples will be studied in the same laboratory and conducted by well-trained professionals.

13. FEASIBILITY

Firstly, this study will be performed in HUJT's ED, where approximately 55 DKA patients are treated annually, according to administration data provided by the HUJT's technical secretary. Therefore, it is estimated that approximately 3 years will be needed to achieve an appropriate sample size.

On the other hand, we do not expect a significant number of dropouts, as our study focus is on DKA treatment, not on its follow-up.

Secondly, we will hire an external statistician, a data manager, and a CDS&EOS trainer. The physicians and nurses who work at HUJT's ED will collaborate with the study as a part of their clinical assistance and will not suppose any additional expenses, nor all diagnostic and therapeutic resources. For this reason, we believe our study is economically feasible.

Finally, we believe that our study design will be appropriate as long as all the co-variables can be controlled as expected.

Consequently, we consider that it is viable to perform our study in HUJT's ED regarding the professionals involved, the sample availability, and the estimated budget.

14. CLINICAL AND HEALTH IMPACT

DKA is a life-threatening condition which has a good prognose with appropriate treatment. However, its management in the ED can sometimes have not the ideal conditions, leading to some avoidable complications.

Some research teams have done studies to standardize DKA management, reduce treatment variability, and consequently, improve treatment security.

With our study, we want to provide evidence that the use of a computer decision support and electronic order sets will improve the security of DKA treatment in HUJT's ED.

If our study shows a decrease in DKA patients' average time spent in the ED, other hospitals from our region could apply similar strategies to improve the safety of their ED.

Moreover, if our study shows a reduction of treatment complications and prescription and administration errors, patients would receive an improved and safer clinical service.

Besides, diabetes complications treatment supposes a high percentage of the public healthcare budget. So, by reducing the treatment time of these patients, we could reduce the high amount of money spent.

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16. ANNEXES

16.1. PROTOCOL INFORMATION SHEET

FULL D'INFORMACIÓ PER A PARTICIPANTS

Agraïm el seu interès i participació en aquest estudi, "The application of an artificial intelligence tool to improve diabetic ketoacidosis treatment security in the Emergency Department". La seva participació serà de gran ajuda per a poder dur a terme aquest projecte i així intentar millorar el maneig de la cetoacidosi diabètica a urgències.

Si us plau, llegeixi atentament tota la informació i pregunti qualsevol dubte que li sorgeixi a la persona que li entrega el present document.

Col·laboració sol·licitada

Si vostè accepta participar a l'estudi, les seves dades corresponents a l'entrevista clínica i proves complementàries de l'estada a urgències quedaran registrades per a la posterior anàlisi. Totes les dades recollides s'introduiran en un formulari, que posteriorment s'emmagatzemarà a una base de dades de forma totalment anònima.

Volem informar-lo/la que la decisió de participar o no a l'estudi, en cap cas modificarà l'atenció mèdica que rebrà.

Generalitats del projecte

L'estudi es realitzarà amb les dades obtingudes de pacients amb cetoacidosi diabètica tractats al servei d'Urgències de l'Hospital Universitari Josep Trueta amb una durada total aproximada de 3 anys.

El projecte ha estat avaluat i aprovat pel Comitè Ètic d'Investigació Clínica de l'Hospital Universitari Josep Trueta de Girona.

El principal objectiu de l'estudi és millorar la seguretat del tractament de la cetoacidosi diabètica, i així reduir el temps d'estada del pacient a Urgències com les complicacions que se'n poden derivar.

Confidencialitat

Totes les dades obtingudes, mèdiques i personals, seran tractades amb total confidencialitat, d'acord amb la Llei Orgànica 3/2018, del 5 de desembre, de protecció de dades personals i garantia dels drets digitals i el Reglament del Parlament Europeu i del Consell 2016/679 del 27 d'Abril.

Tota la informació recollida, en cas que amb la publicació dels resultats de l'estudi es faci pública, s'exposarà de forma anònima i global, mai de forma individualitzada.

Les dades obtingudes només s'utilitzaran pel present estudi.

Compensació econòmica

La participació a l'estudi és de forma totalment voluntària, en cap cas es rebrà cap compensació econòmica.

Revocació del consentiment

En qualsevol moment, sense necessitat de justificar-se, vostè té el dret a demanar la revocació del seu consentiment i així eliminar les seves dades recollides per a la realització de l'estudi. Aquesta decisió en cap cas influirà en l'atenció mèdica que rebrà.

Contacte

Per qualsevol dubte que pugui sorgir en relació amb l'estudi al qual accepta participar, no dubti posar-se en contacte amb l'equip d'investigació a través de:

Telèfon de contacte: .....

Correu electrònic: .....

16.2. INFORMED CONSENT DOCUMENT

CONSENTIMENT INFORMAT PER A LA REALITZACIÓ DE L'ESTUDI

The application of an artificial intelligence tool to improve diabetic ketoacidosis treatment security in the Emergency Department

Jo (Nom i Cognoms) _____, amb DNI/NIE_____.

- He llegit el document d'informació sobre l'estudi.
- He pogut fer totes les preguntes i resoldre els meus dubtes sobre l'estudi.
- He entès tota la informació que apareix en el document d'informació.
- Entenc que la meva participació és voluntària i no remunerada, i soc lliure de no participar a l'estudi.
- Se m'han explicat i entenc els possibles riscs i beneficis de la meva participació en l'estudi.
- Se m'ha informat que les meves dades i resultats de proves obtingudes son confidencials.
- Se m'ha informat que la informació obtinguda només s'utilitzarà pels objectius específics d'aquest estudi.

Accepto que l'equip d'investigació pugui contactar amb mi en un futur si es considera oportú.

Comprenc que tot i haver firmat el consentiment informat, puc revocar-lo en qualsevol moment, sense donar explicacions, ni que afecti la meva assistència sanitària.

Signatura participant:	Signatura professional sanitari:
	Número de col·legiat:

Data: _____ , _____ de _____ de l'any _____

16.3. DATA COLLECTION SHEET

FORMULARI DE RECOL·LECCIÓ DE DADES

CODI DEL PARTICIPANT: __ __ __ __

Data: __ / __ / __ **Hora d'arribada**: _____ **Dia de la setmana**: _____

GRUP: ☐ PRE-INTERVENCIÓ ☐ POST-INTERVENCIÓ

DADES PERSONALS

Sexe: ☐ Femení ☐ Masculí

Data de naixement (DD/MM/AAAA): __ / __ / ____

Pes: _____ Kg

Nivell d'estudis:

☐ Estudis Universitaris ☐ Estudis Secundaris

☐ Estudis Primaris ☐ Sense estudis reglats

Nº d'episodis anteriors de cetoacidosi diabètica: _____

Nº d'ingressos anteriors a UCI en episodi de cetoacidosi diabètica: _____

Comorbiditats (nº): ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ ≥6

☐ Cardiopatia isquèmica (1)
☐ Insuficiència cardíaca congestiva (1)
☐ Malaltia vascular perifèrica (1)
☐ Accident cervell-vascular (1)
☐ Demència (1)
☐ Malaltia pulmonar (1)
☐ Malaltia del teixit connectiu (1)
☐ Úlcera pèptica (1)
☐ Malaltia hepàtica (1)
☐ Diabetis mellitus (1)
☐ Complicacions de diabetis (2)
☐ Paraplegia (2)
☐ Malaltia renal (2)
☐ Càncer (2)
☐ Càncer metastàtic (3)
☐ Malaltia hepàtica greu (3)
☐ VIH (6)

DADES DE L'EPISODI

Temps d'arribada fins a rebre atenció mèdica: _____ (h)

Nivell de Glasgow a l'arribada: _____

Obertura ulls	Resposta verbal	Resposta motora
1 Sense resposta	1 Sense resposta	1 Sense resposta
2 Al dolor	2 Sorolls incomprensibles	2 Descerebració
3 A ordres verbals	3 Paraules inapropiades	3 Decorticació
4 Espontània	4 Conversa confusa	4 Retira al dolor
	5 Orientat	5 Localitza el dolor
		6 Obeeix ordres

Factor precipitant:

☐ Infecció
☐ Pobre adherència al tractament
☐ Accident cervell-vascular
☐ Pancreatitis
☐ Traumatisme
☐ Abús de drogues
☐ Transgressió dietètica
☐ Altre

pH sanguini a l'arribada:

☐ ≤ 6,9 ☐ > 6,9

Temps d'estada a l'hospital: _____ (h)

Èxitus: ☐ Sí ☐ No

Fi d'episodi a Urgències:

☐ Ingrés UCI ☐ Ingrés Endocrinologia

☐ Alta a domicili

Complicacions del tractament: _____ (nº)

Hipoglicèmia	☐ Sí	☐ No
Hiperglucèmia	☐ Sí	☐ No
Hipopotassèmia	☐ Sí	☐ No
Hiperpotassèmia	☐ Sí	☐ No
Hipernatrèmia	☐ Sí	☐ No
Insuficiència renal pre-renal	☐ Sí	☐ No
Edema cerebral	☐ Sí	☐ No
Rabdomiòlisi	☐ Sí	☐ No
Edema pulmonar	☐ Sí	☐ No

Errors de prescripció : _____ (nº)

Error en la prescripció de fluids:	☐ Sí	☐ No
Error en la prescripció d'insulina:	☐ Sí	☐ No
Error en la prescripció de clorur potàssic:	☐ Sí	☐ No
Error en la prescripció de bicarbonat:	☐ Sí	☐ No
Error en la prescripció de dieta:	☐ Sí	☐ No

Errors d'administració: _____ (nº)

Error d'administració de fluids:	☐ Sí	☐ No
Error d'administració d'insulina:	☐ Sí	☐ No
Error d'administració de clorur potàssic:	☐ Sí	☐ No
Error d'administració de bicarbonat:	☐ Sí	☐ No
Error d'administració de dieta:	☐ Sí	☐ No

16.4. GLASGOW COMA SCALE

Table 12. Glascow Coma Scale. Adapted from (51).

Glasgow Coma Scale
Eye opening (E)
1 None
2 To pressure
3 To speech
4 Spontaneous
Verbal response (V)
1 None
2 Sounds
3 Words
4 Confused
5 Orientated
Best motor response (M)
1 None
2 Extension
3 Abnormal flexion
4 Normal flexion (withdrawal)
5 Localising
6 Obeying commands
Each component is assessed by a standardised approach that permits objective evaluation and documentation of information about the level of consciousness. Changes in terminology from the original 1974 version are incorporated.

16.5. CHARLSON COMORBIDITY INDEX

Table 13. Diagnostic categories, original ICD-9-CM codes, and corresponding ICD-10-AM codes (52).

Diagnostic categories, original ICD-9-CM codes, and corresponding ICD-10-AM codes

		Codes	
Condition	Weights	ICD-9-CM	ICD-10-AM
Acute myocardial infarction	1	410, 412	I21, I22, I252
Congestive heart failure	1	428	I50
Peripheral vascular disease	1	441, 4439, 7854, V434	I71, I790, I739, R02, Z958, Z959
Cerebral vascular accident	1	430–438	I60, I61, I62, I63, I65, I66,G450, G451, G452, G458, G459, G46, I64, G454, I670, I671, I672, I674, I675, I676, I677 I678, I679, I681, I682, I688, I69
Dementia	1	290	F00, F01, F02, F051
Pulmonary disease	1	490, 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505	J40, J41, J42, J44, J43, J45, J46, J47, J67, J44, J60, J61, J62, J63, J66, J64, J65
Connective tissue disorder	1	7100, 7101, 7104, 7140, 7141, 7142, 71481(now 5171), 725	M32, M34, M332, M053, M058, M059, M060, M063, M069, M050, M052, M051, M353
Peptic ulcer	1	531, 532, 533, 534	K25, K26, K27, K28
Liver disease	1	5712, 5714, 5715, 5716	K702, K703, K73, K717, K740, K742, K746, K743, K744, K745
Diabetes	1	25002501, 2502, 2503, 2507	E109, E119, E139, E149, E101, E111, E131, E141, E105, E115, E135, E145
Diabetes complications	2	2504, 2505, 2506	E102, E112, E132, E142 E103, E113, E133, E143 E104, E114, E134, E144
Paraplegia	2	342, 3441	G81 G041, G820, G821, G822
Renal disease	2	582, 5830, 5831, 5832, 5833, 5835, 5836, 5837, 5834, 585586588	N03, N052, N053, N054, N055, N056, N072, N073, N074, N01, N18, N19, N25
Cancer	2	14, 15, 16, 18, 170, 171, 172, 174, 175, 176, 179, 190, 191, 192, 193, 194, 1950, 1951, 1952, 1953, 1954, 1955, 1958, 200, 201, 202, 203, 204, 205, 206, 207, 208	C0, C1, C2, C3, C40, C41, C43, C45, C46, C47, C48, C49, C5, C6, C70, C71, C72, C73, C74, C75, C76, C80, C81, C82, C83, C84, C85, C883, C887, C889, C900, C901, C91, C92, C93, C940, C941, C942, C943, C9451, C947, C95, C96
Metastatic cancer	3	196, 197, 198, 1990, 1991	C77, C78, C79, C80
Severe liver disease	3	5722, 5723, 5724, 5728	K729, K766, K767, K721
HIV	6	042, 043, 044	B20, B21, B22, B23, B24

Table 14. Frequency of in-hospital death in relation to Charlon Index level (52).

Frequency of in-hospital death in relation to Charlson Index level

	In-hospital death during admission being evaluated, %					
	ICD-9-CM		ICD-10-AM			
Charlson score	1996–97	1997–98	1998–99	1999–00	2000–01	2001–02
0	0.3	**0.3**	**0.4**	0.3	0.4	0.4
1	3.1	**2.7**	**2.7**	2.5	3.4	3.2
2	6.3	**5.4**	**5.8**	5.0	6.6	5.6
3	11.5	**9.7**	**9.6**	9.0	11.6	10.7
4	16.1	**14.4**	**13.3**	12.8	14.9	13.6
5	17.3	**16.9**	**16.2**	14.9	16.3	14.7
≥6	25.1	**24.7**	**24.9**	21.1	24.8	23.6
Test for trend, *P*-value	<.0001	**.0001**	**.0001**	.0001	.0001	.0001

Bold text indicates the transition years, when ICD-9 changed to ICD-10.

16.6. REVOCATION OF THE INFORMED CONSENT DOCUMENT

REVOCACIÓ DEL CONSENTIMENT INFORMAT

Jo (Nom i Cognoms) _____, amb DNI/NIE_____.

Revoco el consentiment prèviament firmat per a la participació en l'estudi: "The application of an artificial intelligence tool to improve diabetic ketoacidosis treatment security in the Emergency Department".

Signatura participant:	Signatura professional sanitari:
	Número de col·legiat:

Data: _____ , _____ de _____ de l'any _____