

A review of the efficacy of the Milwaukee Protocol in the treatment of ketoacidosis in pediatric intensive care unit patients at Rebro Hospital between 2009-2014

Malik, Mohammad Imran Khan

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UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

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GRADUATE THESIS



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This graduation paper has been completed at the Department of Paediatrics at the University Hospital Centre Zagreb (Rebro hospital) under the supervision of Dr. sc. Mario Ćuk and was submitted for evaluation during the academic year 2013 /2014.

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LIST OF ABBREVIATIONS

DKADiabetic Ketoacidosis

CE.....Cerebral oedema

DMIDiabetes Mellitus type I

DMIIDiabetes Mellitus type II

IR.....Insulin receptor

AA.....Acetoacetate

BHB.....Beta-hydroxybutyrate

U..... Unit

ICU.....Intensive Care Unit

IV.....Intravenous

MP.....Milwaukee protocol

SC.....Subcutaneous

O.....Oxygen

H⁺..... Proton

K⁺.....Potassium

Na⁺.....Sodium

HCO₃.....Bicarbonate

CO₂..... Carbon dioxide

PO₄²⁻ Phosphate

kg Kilogram

mmol..... Millimole

mEq..... Milliequivalent

[].....Concentration

L..... Litre

↑..... Increase

↓..... Decrease

LR.....Lactated ringer

pCO₂.....Partial pressure of Carbon dioxide

NaCl.....Sodium chloride

hr.....Hour

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1.0 SUMMARY

Title: A review of the efficacy of the Milwaukee protocol in the treatment of ketoacidosis in paediatric intensive care unit patients at Rebro hospital between 2009-2014.

Name: Imran Malik

Ketoacidosis is a condition of increased pathologic levels of ketone bodies in the body that results in the acidification of blood. The major types are alcoholic and diabetic ketoacidosis. DKA is defined as an arterial pH < 7.25, serum bicarbonate < 15mEq/L and elevated ketones in serum or urine (Marcdante et al. 2010). Other sources define DKA with the above criteria but also additionally a glucose concentration >11mmol/L (>200mg/dL) together with glucosuria and ketouria (Rosenbloom 2010) (Wolfsdorf et al. 2009).

Paediatric patients reviewed at Rebro Hospital (University Hospital Centre Zagreb) were all treated for the latter condition. This thesis surmises the treatment methodology as devised by the Milwaukee Protocol and attempts to evaluate the efficacy of this treatment over the period of 01.01.2009 – 30.06.2014.

Patient records were obtained from the Rebro Hospital archives and details on ICU treatment of diabetic ketoacidosis were evaluated. Personal identifying data was removed. During the period analysed patient archive records indicate that 21 patients were admitted into the paediatric ICU at University Hospital Centre Zagreb for treatment of DKA. 20 patient records were obtained, of which 19 patients were confirmed to have been treated according to the Milwaukee protocol. It was assumed that the other 2 cases were as well as it is the hospital policy to follow this protocol. Successful treatment was observed in 100% of cases. Success is defined here as the sufficient control of the metabolic derangement as indicated by meeting the following Milwaukee Protocol exit criteria: $\text{HCO}_3^- > 15 \text{ mmol/l}$, pH

> 7.30, Na: 135-145 mmol/l with no emesis (Kliegman et al. 2011) and resulting in discharge of patient from ICU.

Conclusions drawn include the need for a coordinated response based on a hospital wide policy with clear pro forma. Management of DKA condition should be under the supervision of centres that have experience dealing with the issue; at University hospital Zagreb (Rebro hospital) this should be the paediatric ICU centre. Vital signs, neurologic status and laboratory indices for DKA biomarkers should be monitored at timely intervals as to prevent further adverse effects. It is suggested that data be recorded electronically and on ICU forms designed to record DKA. In cases of cerebral oedema, Rebro hospital should develop protocols to be able to identify CE development early on and treat rapidly with mannitol or hypertonic IV saline. With respect to treatment fluid resuscitation should begin before intravenous insulin administration (0.1. U/Kg/hr), beginning with a bolus of 10-20mL/kg 0.9% saline, followed by a maintenance supply of 0.45% saline that should address 5-10% of fluid loss from dehydration (Rosenbloom 2010) (Kliegman et al. 2011).

Keywords: Diabetic Ketoacidosis (DKA), Milwaukee Protocol, cerebral oedema, children, prevention, treatment

2.0 LITERATURE REVIEW

2.1 Defining DKA

DKA can be defined as a state of aberrant catabolism triggered by hyperglycaemia, in itself induced by absolute or relative deficiency of insulin (Kliegman et al. 2011). A result of which, leads to a ketosis, a rise in ketoacids in the blood causing metabolic acidosis with an elevated anion gap (Marcdante et al. 2010).

Table 1. DKA biochemical diagnosis criteria

HYPERGLYCEMIA	Blood glucose: > 200mg/dL (>11mmol/L)
KETOSIS	Elevated serum or urine ketones Serum ketones > 5mEq/L
ACIDOSIS	Arterial pH < 7.25 Serum HCO ₃ ⁻ < 15mEq/L (15mmol/l)

DKA is a characterising feature of undiagnosed new-onset DM I. It is also observed in DM I patients who fail to meet their bodies requirement of insulin in a state of increased counter- regulatory hormones (glucagon, GH, catecholamines and cortisol). Examples of a failure to meet the body's need for insulin in a DM I patient include inadequate insulin dosing or unaccounted states of increased insulin demand such as suffering from an concomitant illness. Patients with DM II have also been noted to develop DKA. DKA is an acute medical emergency that warrants urgent attention and treatment with insulin and rehydration therapy.

An anabolic hormone, the role of insulin is to regulate glucose and lipid metabolism along with its stress-responsive catabolic counterparts: glucagon, growth hormone, catecholamines and cortisol. DKA development is intrinsically tied in with dysregulation of these systems: the relative deficiency of insulin coupled with a relative excess of catabolic hormones. DKA that ensues is an example of a super-fasted state.

2.1.1 Glucose

A breakdown product of food as well as formed endogenously, increased levels of serum glucose stimulates insulin production. Once glucose has entered insulin activated cells, it can be metabolised to pyruvate via glycolysis or stored as glycogen in muscle and liver cells in the process of glycogenesis. Pyruvate is a key metabolite utilised in the Krebs cycle in mitochondria for the formation of ATP, the energy currency of cells (Hall 2006). The hyperglycaemia of DKA results in osmotic diuresis, and often subsequent volume depletion and significant loss of electrolytes: potassium, sodium and phosphate (Kliegman et al. 2011).

2.1.2 Insulin

Secreted by the pancreas in response to breakdown products of digested food, insulin binds to IR on cells. These tyrosine kinase receptors in turns trigger many protein activation cascades that result in the following: 1) the translocation of GLUT-4 (glucose transporter) to the plasma membrane of insulin sensitive cells allowing for glucose to cross an otherwise impermeable membrane, 2) glycogen synthesis, 3) glycolysis, 4) free fatty acid synthesis and inhibition of lipolysis. Insulin also stimulates protein formation and stimulates transcellular shifts of potassium and phosphate.

Insulin treatment corrects the metabolic acidosis and allows for conversion of AA and BHB into bicarbonate, helping to rectify the acidic pH of metabolic acidosis. In patients with low concentrations of these ketoacids, due to urinary excretion of them, complete rectification of metabolic acidosis is slower as it is dependent on renal production of bicarbonate (Kliegman et al. 2011).

2.2 Pathophysiology of DKA

In summary the anabolic hormone insulin is paramount for the energy needs of cells and promotes the storage of both fats and glucose as triglycerides and glycogen respectively. In contrast counter-regulatory hormones are involved in the catabolic processes of glycogenolysis, proteolysis (gluconeogenesis) and lipolysis (formation of free fatty acids and ketone bodies). Thus, without insulin, the body is reliant on the catabolism of glycogen, protein and fat to meet energy demands (Hall 2006) (Kliegman et al. 2011).

In states of insulin deficiency compensatory mechanisms are stimulated by secretion of the aforementioned stress and counter-regulatory hormones: hepatic gluconeogenesis, glycogenolysis and lipolysis (Figure 1). Glucagon is metabolised and excessive hepatic glucose production occurs. However in the absence of insulin, the glucose remains locked out of cells and hyperglycaemia ensues.

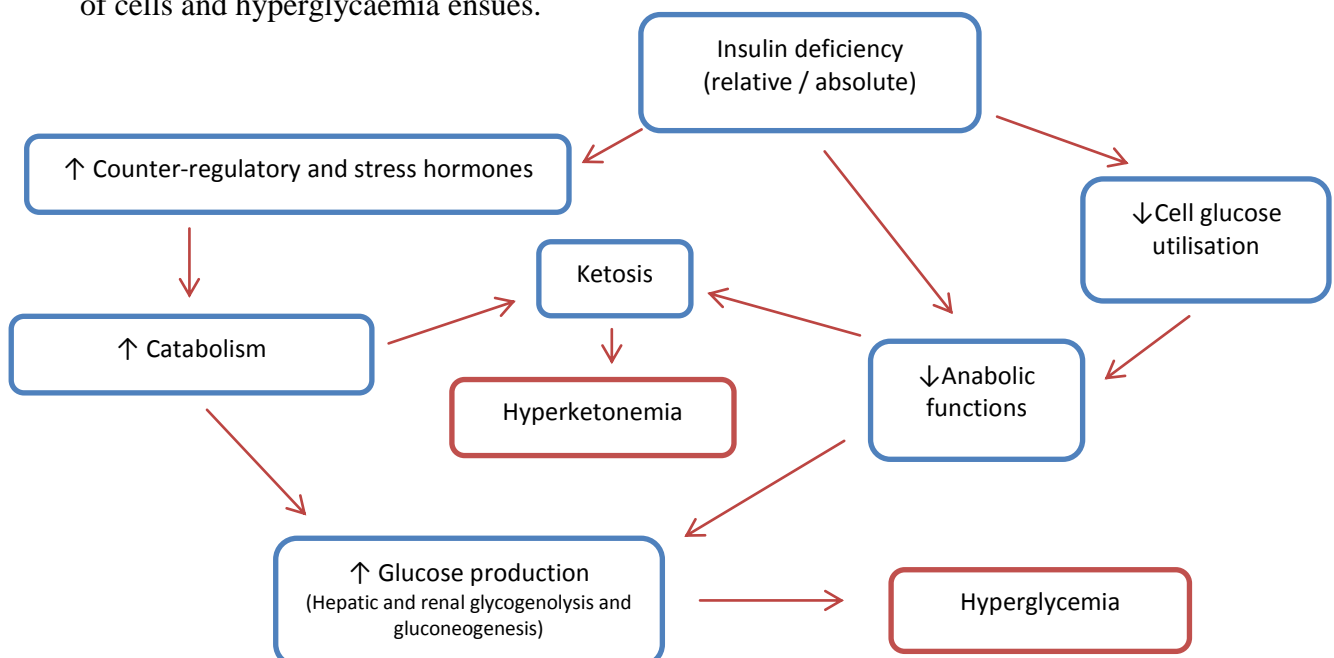


Figure 1. DKA pathogenesis.

The metabolism of fats to free fatty acids thus becomes a key source of substrate for the liver, along with proteins, for glucose formation. Palmitoyl-CoA, a fatty acid formed from beta-oxidation of fats is harnessed by the Krebs cycle to create ATP. A by-product of this FFA metabolism are the ketones: acetone, acetoacetate and beta-hydroxybutyrate, of which the latter two are ketoacids (Figure 2). Thus, along with hyperglycaemia there is an increase in serum FFA and acidic metabolites.

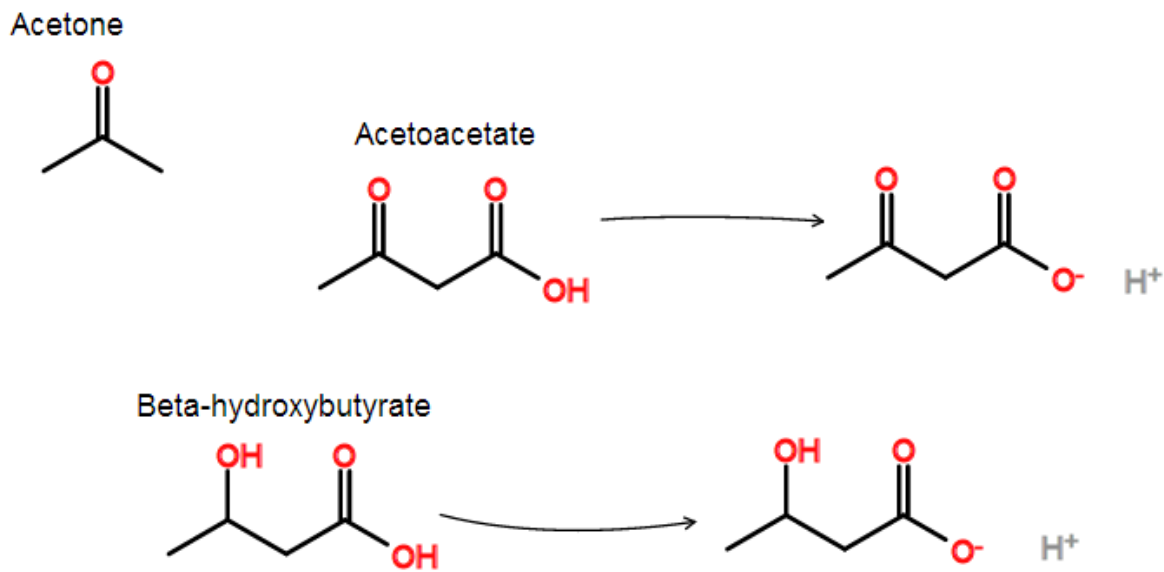


Figure 2. Ketone bodies: showing formation of negatively charged conjugate bases of the ketoacids. The conjugate bases cause the increased anion gap in DKA metabolic acidosis.

The increased serum glucose eventually exceeds renal threshold for reabsorption of glucose (160-180mg/dl) and glucose escapes into the urine causing an osmotic diuresis to develop and subsequent dehydration of the patient. This dehydration contributes to a shift of electrolytes from within cells to their extracellular surroundings (Figure 3).

The presence of ketoacids shifts the pH of blood into the acidic range and raises the anion gap. Lactic acidosis can also contribute to evolving metabolic acidosis in conditions of decreased tissue perfusion due to dehydration. Cells with H^+/K^+ pumps attempt to rectify the acidic conditions by exchanging intracellular K^+ for extracellular H^+ (Hall 2006). This increases serum K^+ , shifting K^+ from the intracellular space to plasma but eventually leading to total body K^+ depletion as the electrolyte is expelled by the kidneys. Measurements of plasma K^+ (pseudo-eukalemia or pseudohyperkalemia) can thus mask the actual total body K^+ depletion. And it should be noted then that clinically serum potassium concentration may be recorded as within the normal range, above or below in a DKA patient at diagnosis (Kliegman et al. 2011). Correspondingly EKG readings may indicate hyperkalaemia (peaked T wave) or hypokalaemia (U wave or low T wave) (Raghavan 2014).

Total body phosphate levels are also decreased as a result of PO_4^{2-} renal excretion; the elimination of the electrolyte is a by-product of renal concerted efforts to remove excess hydrogen ions.

Vomiting and tachypnea induced by acidotic state can exacerbate dehydration by providing an avenue for further fluid and insensible water loss respectively. Developing DKA state can be masked or compensated by increasing fluid intake though eventually patients are unable to maintain the large fluid intake requirement required to offset it. The dehydrated state of the individual can lead to shock when volume depletion is large enough. Until that point is crossed, the degree of dehydration can be concealed by normal blood pressure readings and polyuria (Wolfsdorf et al. 2009).

Hyponatremia state is also common in DKA as sodium is lost as a result of osmotic diuresis and in patients who are vomiting. Bicarbonate (or total CO_2) is also decreased.

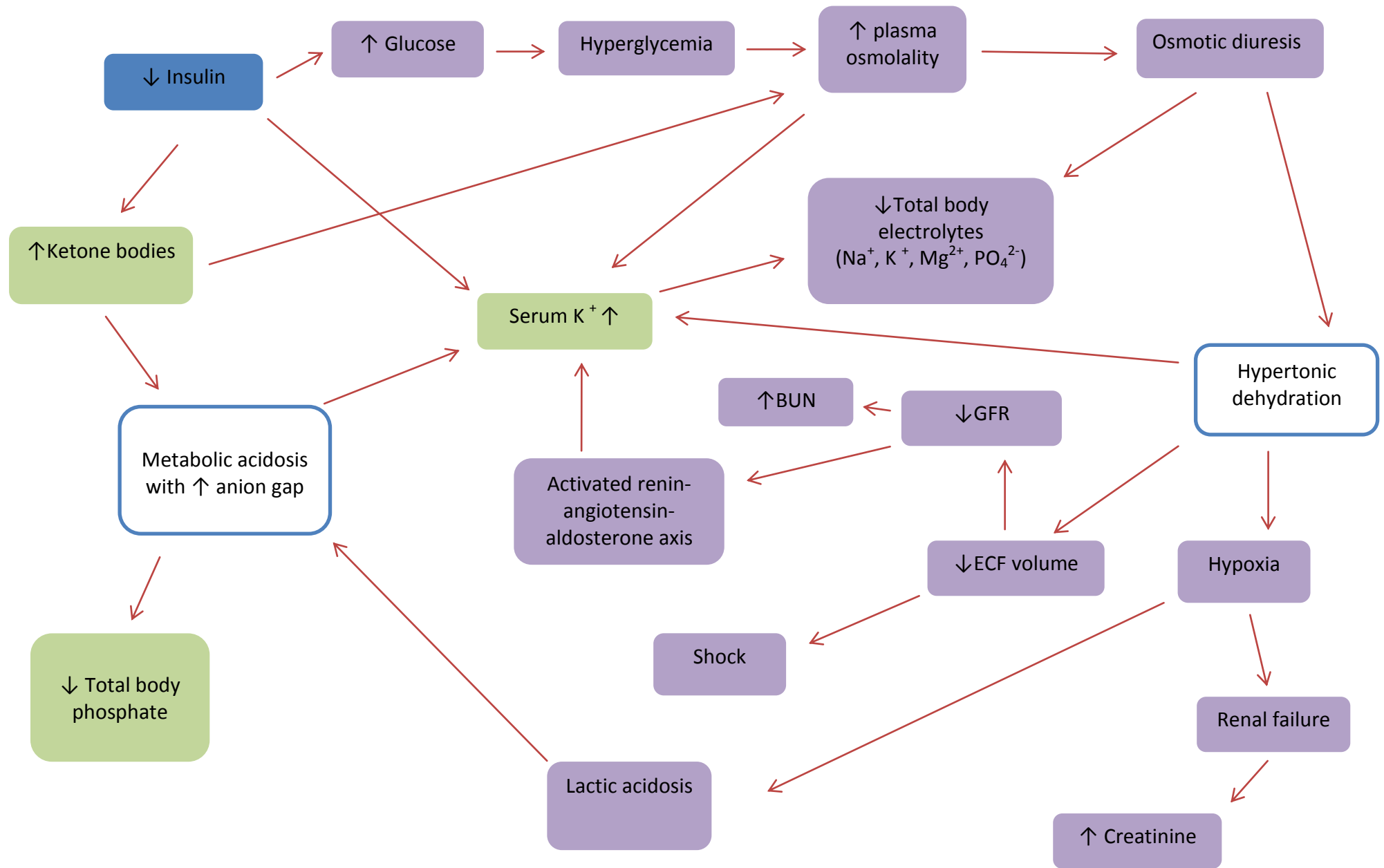


Figure 3. Algorithm of key steps in DKA pathophysiology. Colour coded to highlight the areas that treatment should target: dehydration, metabolic acidosis and hyperglycaemia. Key: ↑ increased ↓ decreased.

2.3 Epidemiology of DKA

At risk groups include new-onset and insulin dose omitting diabetics as well as those with poorly controlled concurrent illnesses. In this risk category 20-40% of diabetic children will experience DKA (Kliegman et al. 2011). Between 1995-2003 incidence for type 1 diabetes mellitus in Croatia, for children aged 14 and under, was 8.87/100000 person-years, with an average increasing annual incidence of 9% (Stipancic et al. 2008). Incidence of paediatric diabetic ketoacidosis in Croatia between 1995 - 2003 involved 607 cases with the greatest number occurring in central Croatia (247 cases) followed by southern Croatia (243). In this study ketoacidosis was defined as either pH < 7.3 or pH <7.3 and/or bicarbonate <15 mmol/L (Stipančić et al. 2012). In the US DKA has a mortality rate of 2-5% (Young 2014).

2.4 Clinical picture of DKA

Initial presentation of patients with DKA includes the following features: polyuria, polydipsia, nausea and vomiting. Polyuria observed in this dehydrated state is due to osmotic diuresis and can be used to differentiate from patients with GI disorders such as gastroenteritis (though it should be noted infections such as gastroenteritis can instigate DKA). Other clinical features may include altered mental state and presenting with an acute abdomen-like symptomology. Abdominal pain, tenderness and distention are frequent symptoms, with the latter two symptoms being secondary to vomiting and paralytic ileus respectively. Fruity smelling breath (due to acetone) and Küssmaul breathing (deep, rapid respiration) is observed in DKA patients as they attempt to blow off CO₂ and compensate for the acidosis (Kliegman et al. 2011). Glucosuria and ketouria are often present as DKA develops (Rosenbloom 2010). Cerebral oedema is one of the most dangerous complications of DKA and occurs more commonly in the paediatric population than the adult population

(Kitabchi and Wall 1999). Clinical signs include altered mental status which either demonstrates gradual deterioration of consciousness or gradual improvement followed by abrupt deterioration of neurological status. Other clinical signs include incontinence, recurrent vomiting, severe headache with sudden onset, papilledema, seizures, ophthalmoplegia and agitation (Kliegman et al. 2011).

2.4.1 Laboratory values

Refer to Table 1 for major criteria. Serum glucose values in hyperglycaemic DKA patients range from 200mg/dL to >1000 mg/dL. Serum bicarbonate levels tend to be <15mEq/L.

Resembling potassium serum levels, sodium serum levels may be high, low or normal. In the case of sodium this is due to imbalance of sodium, insensible water losses, vomiting or urinary losses. But it should be noted that the measure sodium value will be depressed due hyperlipidaemia and hyperglycaemia. Hyperlipidaemia displaces sodium in most commonly used laboratory assays. In hyperglycaemia glucose exerts osmotic pressure in the extracellular space resulting in dilution of sodium as fluid follows from the intracellular space to the extracellular space (Frieda, Davidson, and Hall 2004). So the true sodium level (Figure 4) can be calculated as follows for glucose levels above 100mg/dL (5.6mmol/L):

$$A \quad \frac{[Na^+] + \text{glucose} - 100 \times 1.6}{100} \qquad B \quad \frac{[Na^+] + \text{glucose} - 5.6 \times 1.6}{5.6}$$

Figure 4. True sodium level calculations for glucose levels above 100mg/dL (5.6mmol/L).

Key: A: glucose measure in mg/dL and B: glucose measured in mmol/L

Thus in the case of A, sodium should increase by about 1.6mmol/L for each 100mg/dL decline in glucose.

Total body stores of chloride and magnesium are also depleted (Kliegman et al. 2011). Blood urea nitrogen (BUN) can be elevated in dehydrated patients with pre-renal azotaemia. Increased BUN and creatinine levels are signs of intravascular volume depletion. Note serum creatinine may be falsely increased where data has been recorded using autoanalyser methodology as ketones present interfere with the results. Leucocytosis can be present and left-shifted without an underlying infection. DKA can be classified (see Table 2) as mild, moderate or severe. With regards to treatment of DKA, in practice, these terms are arbitrary. Hyperamylasemia is observed in DKA patients and could be due to pancreatitis, though in instances where the serum lipase is not elevated it is less likely to be so (Raghavan 2014).

Within Croatia different criteria have been used in different hospitals to define DKA (Stipančić et al. 2012) and thus with University Hospital Zagreb it cannot be excluded, over the time frame studied, that different DKA diagnostic criteria has been employed.

Table 2. Classification of DKA. Modified from Kliegman et al. Nelson Textbook of Paediatrics, 2011 p.1976.

	Normal	Mild	Moderate	Severe**
Venous CO₂ (mEq/L)*	20-28	16-20	10-15	<10
Venous pH*	7.35-7.45	7.25-7.35	7.15-7.25	<7.15
Clinical Presentation	-	Orientated, alert but fatigued	Küssmaul breathing, orientated but somnolence; arousable	Küssmaul or depressed breathing; somnolence to depressed sensorium to coma

* Measurements for CO₂ and pH are method dependent; normal range may vary.

**Severe hypernatremia (corrected Na>150mEq/L) would be classified as severe diabetic ketoacidosis.

2.6 Treatment

Management of DKA within an ICU during the first 24-48 hours or until corrected is advisable. Management goals are listed below in Figure 5.

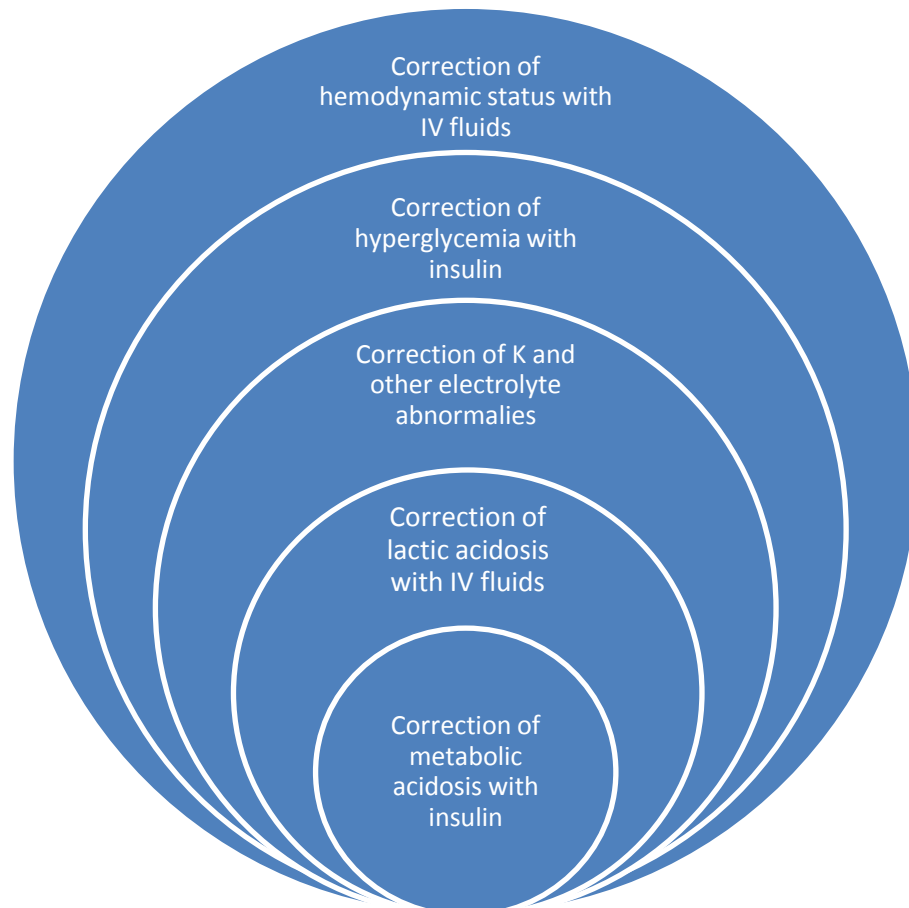


Figure 5. Goals of DKA management

Chest x rays to rule out pulmonary infection. CSF studies an option. Low threshold for CT scanning in paediatric patients with altered mental status possibly due to CE. Note many changes caused by CE are seen late in the course and thus treatment measures (hypertonic saline or mannitol) should not be delayed in suspected CE cases.

2.6.1 Milwaukee protocol

Having been developed over 20 years ago, the MP has an impeccable safety record in large clinic settings with no mortality or known neurologic sequelae in any child treated initially along its guidelines. Regardless of age of the child or the degree of DKA, MP has been designed to treat all such cases (Figure 6). The aim of MP is to correct most electrolyte abnormalities, pH and to rehydrate a moderately ill patient within 24 hours (Kliegman et al. 2011).

An assumption is made that there is standard water deficit of 85 mL/Kg (8.5% dehydration). The MP corrects this deficit in the first 24 hours. When this figure is added to maintenance the sum is about 4L/m² for children regardless of size. Milder DKA states take about 10-20 hours to be corrected and more severe cases around 30-36 hours (see Table 3) (Kliegman et al. 2011). Close monitoring is required in the implementation of MP due to the inherent risks correction of DKA is associated with.

Milwaukee Protocol exit criteria: HCO₃ > 15 mmol/l, pH > 7.30, Na: 135-145 mmol/l with no emesis. Upon which patients can be transitioned to oral intake and SC insulin. IV is capped and SC insulin given with the first meal initially (Kliegman et al. 2011).

Table 3. Fluid required for maintenance in normal children with DKA. Modified from Wolfsdorf et al. 2009 page 119.

Electrolyte	Average losses/kg	Body weight	Maintenance/24 hours
H ₂ O	70ml	≤10kg	100ml/kg/24hr
		11-20kg	1000ml + 50ml/kg/24hr for every kg in this range.
Na ⁺	6mmol	>20kg	1500ml + 20ml/kg/24hr of every kg above 20kg
			2-4mmol/100ml maintenance IV fluid
K ⁺	5mmol		2-3mmol/100ml maintenance IV fluid
Cl ⁻	4mmol		
PO ₄ ²⁻	0.5-2.5mmol*		1-2mmol/100ml maintenance IV fluid

* Phosphate losses given as a range.

Points of note include the immediate administration of insulin at the beginning of treatment, and that this is not delivered as a bolus but as an infusion. An insulin bolus may incur a state of hypoglycaemia and/or hypokalaemia. The insulin infusion is given at rate of 0.1U/Kg/hr (Figure 6). Sodium levels should be calculated to obtain true values (Figure 4). Insulin is given at the beginning to catalyse the movement of glucose intracellularly as well as dampen down hepatic glucose production and impede movement of fatty acids to the liver from its surroundings (Kliegman et al. 2011). Rehydration in itself lowers glucose levels by increasing GFR and enhancing renal excretion of excess glucose. Osmotic diuresis ends once glucose goes below 180mmol/L and rehydration occurs at a quicker rate without additional increase in fluid infusion rate (Kliegman et al. 2011). In the first hour up to 20ml/Kg IV saline bolus is given to neonates of normal birth weight 1 month and older. For neonates approximately 10ml/kg saline is used and for underweight neonates approximately 5ml/kg is given.

It should be noted that the initial bolus given is an isotonic solution without any added sugar. This is because the patient is in a hypertonic state and thus retains most of the initial infusion in the blood vessels. This way quick volume expansion is achieved (Figure 6). Subsequent infusions use hypotonic fluid to address the free water deficit. This ensures intracellular rehydration and accounts for any loss of hypotonic fluid via the urinary system.

Because the metabolic acidosis takes longer to correct than hyperglycaemia, insulin infusion is dependent on the former condition rather than the latter. Once the hyperglycaemic state has been corrected, glucose is added to prevent hypoglycaemia developing.

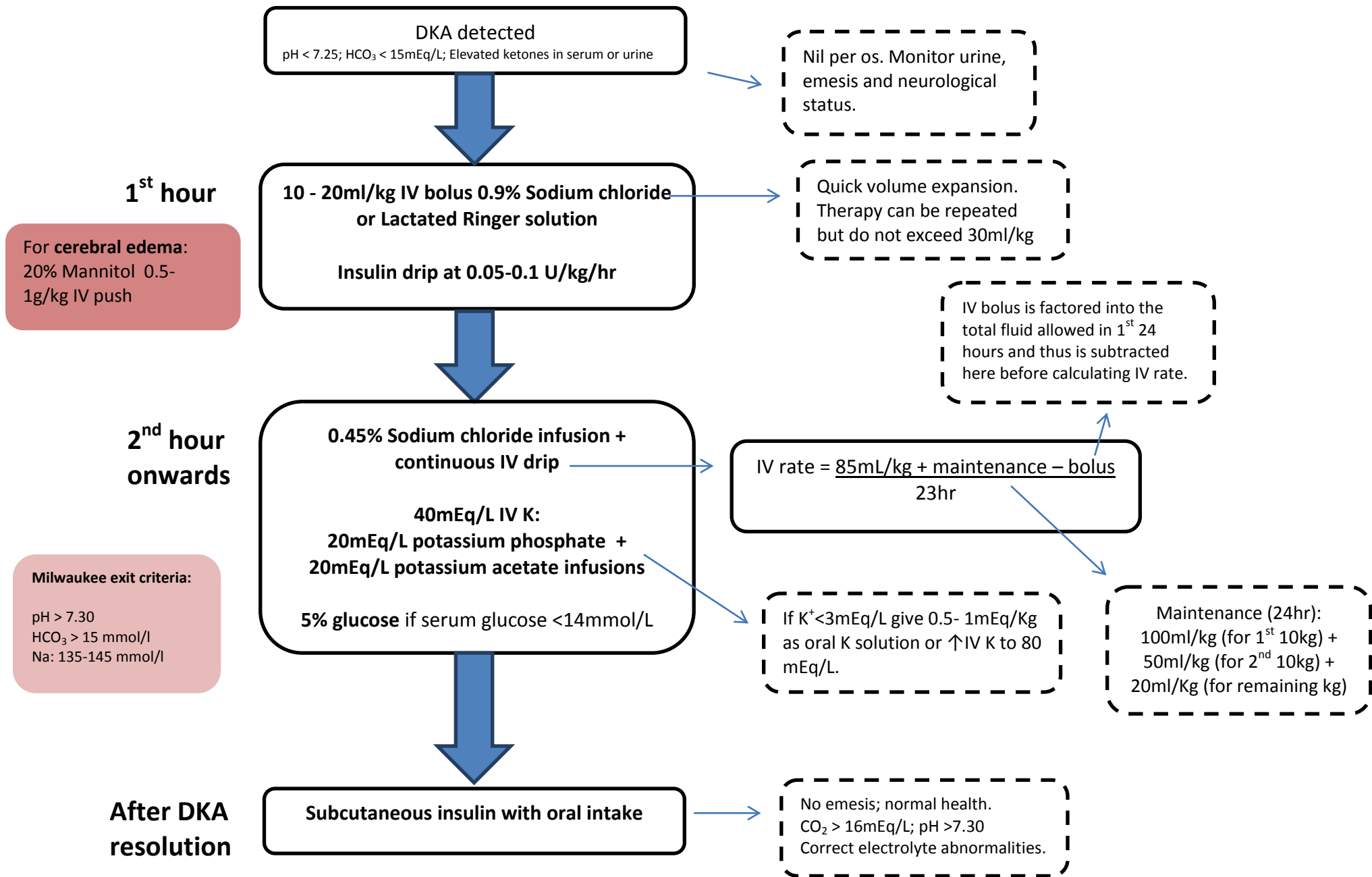


Figure 6. Diabetic ketoacidosis treatment: Milwaukee protocol. Modified from Kliegman et al. Nelson Textbook of Paediatrics. 2011 p.1979

Complications of DKA and its treatment are numerous, but can be grouped as:

- 1) Vascular: hypotension, shock, myocardial infarction, stroke, CE, acute tubular necrosis and renal failure
- 2) Electrolyte and glucose based: hyper/hypokalaemia, hypoglycaemia
- 3) Infectious: sepsis, infections
- 4) Other: aspiration pneumonia

2.6.2 Cerebral oedema

Reversal of DKA is associated with several risks such as hypokalaemia, hypoglycaemia and CE. CE is an important cause of morbidity and mortality in children with DKA. It can arise as the condition progresses as well as from as a complication of treatment. Risk factors are thought to be early insulin and high volume of fluid administration. However the international adoption of gradual rehydration protocols has not altered the incidence of CE in the last 15-20 years. Radiographic data upon presentation of patient's symptoms is often found not be of use. Close monitoring of DKA patients' neurological status along with immediate availability of mannitol for use in suspected CE patients. Effective serum osmolality = $2 \times [\text{Uncorrected Na}] + [\text{Glucose}]$. Severely hypernatremic patients (corrected serum $>15\text{mEq/L}$) may have more success being treated with isotonic fluids for a longer time period and at a more measured rate of rehydration. Note sodium should steadily increase with therapy and decreasing sodium levels may point toward an excessive build-up of free water and an augmented risk of CE.

Treatment protocol involves mannitol (fig. 5), decreasing maintenance IV fluid rate to 70%, elevation of head and considering intubation and controlled hyperventilation- the latter causing vasoconstriction due to induced hypocarbia state (Rosenbloom 2010).

2.6.3 Bicarbonate therapy

Current guidelines restrict the use of bicarbonate in DKA to severe cases. In general base therapy in DKA is a controversial topic that warrants further study. Evidence provides little support to idea that base therapy improves patient outcome, but does show that there are a host of risks associated with its implementation. These include causing hypernatremia, volume overload and alkalemia. A rapid change in pH to alkalemia from acidemia can lead to potassium and phosphate depleted states. Patients with underlying respiratory pathologies are at risk from accumulating CO₂ generated by bicarbonate therapy including compromised cellular function- CO₂ can diffuse into cells and lower the intracellular pH (Kliegman et al. 2011). It should be noted that metabolic alkalosis in DKA patients, treated with bicarbonate therapy and pre-treated with insulin, is not common in those with normal renal function. While insulin does allow ketoacids to form bicarbonate, often there is significant enough loss of ketoacids in urine to prevent a pathological amount of bicarbonate generation to occur. Patients with impaired renal function or volume depletion, factors that impede kidney function, are the major risk factors for metabolic alkalosis (Kliegman et al. 2011).

3.0 PATIENT DATA REVIEW

In Croatia paediatric patients are defined as those under the age of 18. At Rebro hospital a total of 21 cases of diabetic ketoacidosis were recorded between 1st January 2009 – 30th June 2014. All paediatric patients diagnosed with DKA were treated in the paediatric ICU wing. Research results were conducted via database search and data was obtained from the Rebro hospital archives. It was assumed that all paediatric DKA cases were recorded correctly into the archive database. Of the 21 positive results for medical cases of DKA, 20 patient files were retrieved. One patient file was missing and another lacked ICU data on treatment (9 and 20). Only a log of their entry into the hospital and names were recorded here (Table 3). Figure 7 shows that the greatest number of cases occurred in 2009, however it should be noted that in 2014 the frequency thus far is 0.5 cases per month, higher than for 2009 (0.42 cases per month).

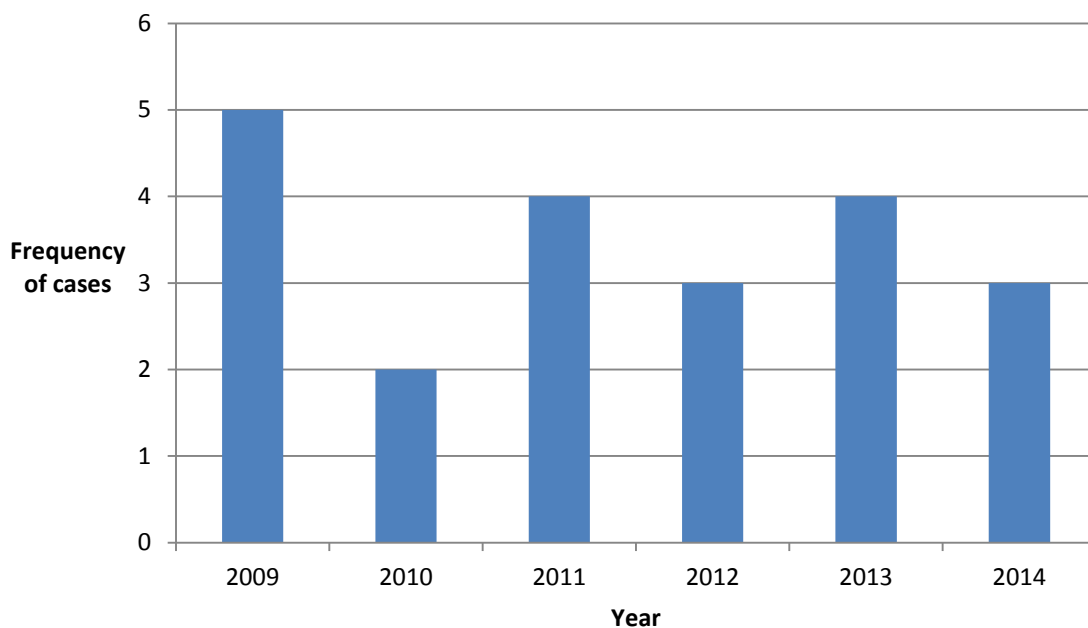


Figure 7. DKA incidence between 1st January 2009 – 30th June 2014.

Table 4: Summary of key data of patients admitted to pediatric ICU at Rebro hospital.

Year	Case	Pt Age	Pt Wt (kg)	Length of MP treatment (hours)	Lowest pH	pCO ₂ (kPa) @ time of lowest pH	BE (mmol/l) @ time of lowest pH	Lowest serum bicarbonate (mmol/l)	Peak hyperglycemia (mmol/l)	Lowest/Highest kalaemia outside of normal range (mmol/l)	Lowest/Highest natremia outside of normal range (mmol/l)	NaCl or LR	Comorbidities and notes
2009	1	9.9	53	45	7.06//24	2.3	-23.6	4.8//26	>27.8 ↓// -	NA/6.5	NA	NaCl	DMI
	2	17.7	87	31	7.15//21	2.5	-22.3	6.6//21	>27.8 ↓// -	NA/5.9	NA	NaCl	DMI
	3	0.18	13	15	7.11//9	2.3	-24.1	4.9//12	>27.8 ↓↑// -	2.9/NA	126/NA	NaCl	DMI
	4	12.3	35	9	7.13/8	1.7	-24.9	4.3//8	22.8↓// -	NA	134/NA	NaCl	DMI; Autoimmune thyroiditis
	5	7.3	27	16	6.99/-	2.5	-26.8	3.1//-	26.3↓// -	NA	127/NA	NaCl	DMI
2010	6	9.1	30	14	7.08//8	2.9	-23.5	6.5//8	>27.8 ↓// -	NA/6.3	133/NA	NaCl	DMI
	7	3.7	13	14	7.15↑//-	0.85	-23.4	7.0↑//-	17.1 ↓// -	NA	NA	NaCl	DMI ; Herpes labialis
2011	8	1.9	10	17	7.04//14	2.1	-24.5	4.1//16	>27.8 ↓// -	NA/6.9	NA	NaCl	DMI
	9	1.0											DMI – missing ICU data
	10	17.7	72.4	45	6.89//43	1.9	-	3.0 //43	>27.8 ↓// -	NA/5.9	NA	NaCl	DMI; Autoimmune thyroiditis; Hyperlipidemia
	11	14.5	59	12	7.12//10	2.3	-21.8	5.5//11	17.7 ↓// -	NA/5.8	NA	NaCl	DMI; Graves disease; Primary hypothyroidism; Hyperlipidaemia
2012	12	9.5	60	65	6.98//61	1.6	-	<3.0↑//65	17.8 ↓// -	2.5/5.3	127/146	NaCl	DMI ; Pancreatitis; Cushing syndrome; Secondary aplastic anemia; Osteoporosis; Hypertension; Juvenile idiopathic arthritis (systemic form)
	13	8.11	17	16	6.91↑//-	1.5	-	<3.0↑//-	20.3 ↓// -	NA/6.4	NA	NaCl	DMI; Celiac disease; Turner syndrome; Autoimmune thyroiditis
	14	8.2	35	41	6.92↑//-	1.7	-	<3.0↑//-	>27.8 ↓// -	NA	133/NA	NaCl	DMI; possible celiac disease;
2013	15	10.2	40	12	7.08↑//-	1.7	-24.0	3.9↑//-	29.1 ↓// -	NA/5.1	NA	NaCl	DMI ; Suspected seizure
	16	14.7	87	28	7.06//19	3.2	-22.0	5.7//19	17.5 ↓// -	NA/5.8	129/NA	NaCl	DMI; Autoimmune thyroiditis; Hyperlipidaemia
	17	7.2	18	18	7.18//3	2.9	-18.3	8.2	>27.8 ↓// -	NA/5.4	NA/147.2	NaCl	DMI
	18	7.11	40	37	6.99//13	1.7	-26.5	3.0//17	16.7↓↑// -	3.2/5.1	NA/168.5	NaCl	DMI ; CE (mannitol 20%); General weakness; Nosebleeds; Sore throat.
2014	19	12.2	65	8	6.99//21	2.5	-26.8	4.1//23	19.8 ↓// -	NA	NA	NaCl	DMI; Autoimmune thyroiditis; Primary hyperthyroidism
	20	4.3											Patient file missing
	21	15.2	47	22	7.02//18	2.5	-26.1	4.5//8	17.0↓↑// -	NA	NA	NaCl	DMI

Key: // = the number of hours of treatment required to bring variable back into a normal range * = Missing patient file Age = years.months - = unknown
 NA = non applicable as within normal range Pt = Patient Wt = weight ↑ = increased over time of treatment ↓ = decreased over time of treatment
 DMI = Diabetes Mellitus type I **DMI** = newly diagnosed DMI MP: Milwaukee Protocol

Table 4 provides a summary of the patient data obtained from the Central archives at Rebro Hospital. High glycaemic serum levels, low pH coupled with low bicarbonates and normal (or compensating) pCO₂ levels with elevated ketones indicate DKA. Most of the laboratory work up was conducted using blood sourced from capillaries, though for case 18 data was largely sourced from venous blood.

It is beyond the scope of this review to analyse every case in detail but what is shown in Table 3 validates Milwaukee protocol as an effective protocol for treating diabetic ketoacidosis, regardless of the range of circumstances presented. With regards to insulin and fluids, a fast acting insulin Actrapid and NaCl were the medicaments of choice in all cases. Lactated ringer was not used at all. Comorbidities were treated accordingly and CE was present in one case (18). 20% Mannitol (100ml) was given over the course of 30 minutes to correct the CE. Cases 1 and 16 involved the same individual, 7 years apart. Case 7 lacked ICU data, and it is assumed to have been lost.

DKA was treated successfully in all patients with patient records showing 13 of the 19 cases met the exit criteria for MP while in the ICU. Of the remaining 6 cases, discharge letters within their patient files also confirm successful treatment. As it is the practice of the Paediatric department at Rebro Hospital to treat all patients within the Paediatric ICU for DKA, it is assumed that their full treatment occurred there. The exception to this is case 19, where the patient was moved to the Endocrinology ward- the reason why is unknown. In the cases (5, 7, 13-15) that contain ICU notes that do not meet the exit criteria set forth by the MP several suggestions have been listed as to why they end in such a manner. The first is that they did meet the exit criteria and the data was omitted accidentally, intentionally or lost. Alternatively, physicians may have been working towards a different exit protocol criterion, or felt the remaining acidic pH was not of ketonic nature, but for example, due to lactic acidosis (those this was not supported by the last lactate readings noted). Ticks next to

laboratory readings, drawn in by presumably the attending physician, would suggest satisfaction with presented results, but what this indicates other than that is a matter of conjecture.

Ketonemia, ketouria and glucosuria was observed in all patients at the beginning of therapy. As therapy progressed these biochemical variables diminished, and in all cases ketouria and ketoemia were abolished. This occurred within 6-12 hours of therapy. With regards to lactates and ketones, they were not recorded in Table 4 as the former had little impact on these cases and the latter followed a pattern of peaking at the beginning before being extinguished over the course of the treatment. In patient notes ketones in serum and urine were checked with much less frequency than other DKA variables. This is perhaps due to the specialist tests required or the dependency on urine production. Table 4 shows that in general bicarbonate levels took longer to control than pH.

100% of the medical cases involved patients with DMI, of which over a third of cases (36.8%) occurred in individuals with previously undiagnosed type 1 diabetes mellitus. These are classic examples of absolute insulin deficiency induced DKA (Wolfsdorf et al. 2009). MP treatment was found to quickly positively impact blood glucose levels in all cases, lowering blood glucose within a day or two to below 10mmol/l. But it should be noted that within the ICU time frame none of the cases were controlled to within the normal range. How long it took to control blood glucose within the normal range is therefore listed as unknown. The highest blood glucose reading tended to be reading on presentation and while the general declining trend in blood glucose levels, both case 3, 18 and 21 demonstrated periods where glucose levels spiked. While in case 3 and 21 it is unclear as to why this occurred, in case 18 it can be attributed to the mannitol infusion to treat CE, given at a time just preceding the spike.

Episodes of hyperkalemia, hyponatremia and hypernatremia (corrected within two hours on average) were observed as were increased lactate and creatinine levels in some patients. Hyperkalaemia was generally observed towards the end of therapy, though in case 13 it was observed for much of the individual's stay in the ICU. In this instance it was most likely due to the IV potassium infusion. In these cases there were no situations of hyponatremia or hypernatremia.

5 out of 19 medical cases involved patients with DMI and a thyroid disease. This perhaps warrants further investigation.

In general the initial readings were the most extreme, though there were several instances where readings worsened after the first hour due to underestimation of quantities of medicine required. This in turn highlights the paramount nature of close monitoring of all relevant biochemical variables on a frequent basis. Hourly monitoring was the most common observed frequency interval, though in some patient files there were time gaps larger than an hour. In these instances, it is assumed that this is due to poor logging of data than inattentive physicians as later logged data would indicate improving health status of patient.

Readings were logged on either one of two possible ICU A4 sized forms. The first was a generic ICU form where DKA readings were written into hand drawn tables- drawn in areas of the form where one could find space. This is because this type of form was not designed to record DKA readings in their entirety. The second form was an update of the first ICU form and contained a small table that could be used for four intervals of DKA recordings. Because the forms used to record DKA data were not designed for this, problems arise in locating where or whether if all of the necessary data was written on the form/s, the legibility of the handwriting and the physical state that these forms are in (stained paper, faded ink etc.)

In most instances to account for the disparity and these issues slips of printed out paper (250mm x 80mm) containing laboratory readings for the biochemical markers of DKA were added to the patient file. Some were stapled to the ICU sheet, others stapled together in an orderly fashion, and finally some were just placed in the patient file. This is important as in instances where the DKA tables were not filled out as these small paper slips were the only source of information.

4.0 CONCLUSION

In terms of treatment of diabetic ketoacidosis, Milwaukee protocol has been shown to be a successful and safe treatment strategy (when performed correctly) at Rebro hospital, over the period of 01.01.2009 – 30.06.2014. There was a 100% success rate in the treatment of DKA using the Milwaukee protocol. Execution of MP at the hospital is generally very effective but there are areas where further improvements can be made.

All DKA paediatric patients admitted to Rebro hospital should be treated only in the paediatric ICU. Policy with clear pro forma should be developed with a hospital wide MP algorithm and standardised exit criterion. Additionally, it is the author's recommendation that templates be designed to create quick and simple DKA forms which can be readily filled out and followed. An integrated computer system that automatically logs DKA data to this form would save time and decrease human error in the process.

Limitations of the study included absent data from medical files and inadequate follow up, illegible handwriting, different formatting of patient files and the author's knowledge of Croatian.

Efficacy is defined as "the ability to produce a desired or intended result" (Oxford dictionaries 2014) and in that respect the efficacy of DKA treatment at Rebro hospital has been of excellent standards over the course of this review period. Further funding or modernisation of the ICU department can only bring greater success and cost savings.

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7.0 BIOGRAPHY

The author was born in London, the United Kingdom of Great Britain, in 1983. It was in London where he completed his primary and secondary (high school) education before moving to study Biomedical Chemistry at the University of Warwick. Obtaining a Second Class honours Bachelor of Science degree in 2006, the author travelled around Europe before embarking on medical studies in Croatia at the University of Zagreb. The author is currently in his 6th academic year and on course to graduate in the fall of 2014.

Interests of the author include photography, writing, nutrition and travelling. Within the field of medicine interests include paediatrics, family medicine, radiology and surgery. His intention is the practice in English speaking country. He has found the experience of researching the topic of DKA intriguing and looks forward to pursuing a career in medicine and research.