

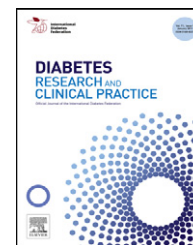


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**International
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Review

Evidence-based management of hyperglycemic emergencies in diabetes mellitus

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ABSTRACT

The hyperglycemic emergencies, diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are potentially fatal complications of uncontrolled diabetes mellitus. The incidence of DKA and the economic burden of its treatment continue to rise, but its associated mortality rate which was uniformly high has diminished remarkably over the years. This improvement in outcome is largely due to better understanding of the pathogenesis of hyperglycemic emergencies and the application of evidence-based guidelines in the treatment of patients. In this article, we present a critical review of the evidence behind the recommendations that have resulted in the improved prognosis of patients with hyperglycemic crises. A succinct discussion of the pathophysiology and important etiological factors in DKA and HHS are provided as a prerequisite for understanding the rationale for the effective therapeutic maneuvers employed in these acute severe metabolic conditions. The evidence for the role of preventive measures in DKA and HHS is also discussed. The unanswered questions and future research needs are also highlighted.

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Contents

1. Background	341
2. Etiology	341
3. Literature search strategy	341
4. Clinical questions	342
5. Pathogenesis	343
6. What is optimal fluid therapy in patients with DKA?	343
6.1. Recommendations	344
7. What is the most efficacious route and dose of insulin in the treatment of patients with DKA?	344
7.1. Recommendations	345
8. After recovery from DKA, can some patients with type 2 diabetes be managed with oral drugs?	345
8.1. Recommendation	345
9. What is the role of electrolyte repletion therapy in DKA?	345
9.1. Potassium	345
9.2. Recommendation	345

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9.3. Bicarbonate	346
9.4. Recommendations	346
9.5. Phosphate	346
9.6. Recommendations	346
10. Is there any role for anti-coagulation in DKA?	346
10.1. Recommendation	346
11. Treatment of HHS	346
12. Is there any role for preventive measures in hyperglycemic emergencies?	347
12.1. Recommendations	347
13. Euglycemic ketoacidosis	347
14. Other important considerations	347
15. Future research needs	348
References	349

1. Background

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are acute severe metabolic complications of uncontrolled diabetes mellitus. The estimated annual incidence rate of DKA is 13.6 and 14.9 per 1000 type 1 diabetic patients in the UK [1] and Sweden [2] respectively. In the USA, the incidence varies with age from 4 to 8 in all age groups to 13.4 per 1000 patients in subjects younger than 30 years [3,4]. Hospital admission for DKA has increased by 30% over the last decade in the USA [5]. The incidence of HHS is difficult to determine owing to paucity of population-based studies and the concomitant presence of co-morbid conditions. Nevertheless, the incidence of HHS is estimated to be about 1% of all primary diabetic admissions [6]. Amongst adults in the UK and USA, the overall mortality rate of DKA is less than 1% [1,5], but may be higher than 5% in the elderly and patients with severe co-morbid conditions [7,8]. DKA remains a leading cause of mortality in children and young adults with type 1 diabetes [9,10].

Hospital admission and mortality due to DKA remains high in developing countries, with reported incidence of about 80 per 1000 diabetic admissions and mortality rate of 30% in one African nation [11]. The estimated mortality rate in patients with HHS remains alarmingly high world wide at 5–20% in developed countries [12]. Hyperglycemic crises are also economically burdensome with DKA accounting for estimated annual direct and indirect cost of 2 billion dollars in the USA [13]. DKA, which occurs primarily in type 1 diabetes is becoming increasingly recognized in patients with type 2 diabetes, with about a third of DKA hospitalizations in the USA and Sweden occurring in people with type 2 diabetes [2,5]. Similarly, hyperosmolarity which is the hallmark of HHS occurs most commonly in type 2 diabetes, but can be seen in type 1 diabetic patients with DKA. Table 1 compares the laboratory characteristics in the two conditions.

The first detailed clinical description of diabetes by Aretaeus of Cappadocia in the 2nd century AD suggested that the disease was invariably fatal from hyperglycemic crisis [14]. The outlook remained uniformly poor until the discovery of insulin and its subsequent therapeutic application in 1922. Mortality associated with hyperglycemic emergencies has reduced significantly over the years with the widespread use of current guidelines which incorporates low-dose insulin and

appropriate fluid and electrolyte repletion therapy. This review presents the scientific evidence for the current recommendations, which have improved the outcome in patients with hyperglycemic emergencies, especially DKA.

2. Etiology

Mortality in patients with DKA is frequently related to the underlying etiological precipitant rather than the metabolic sequelae of hyperglycemia or ketoacidosis [15]. Therefore, a diligent search for a precipitating illness should be undertaken in every hyperglycemic emergency. Omission or inadequate dosing of insulin and infection are the most common precipitants of DKA or HHS [12,16]. Other causes include pancreatitis, silent myocardial infarction and cerebrovascular accident. Drugs which interfere with carbohydrate metabolism, such as corticosteroids, thiazide diuretics, and sympathomimetic agents like dobutamine and terbutaline [12] and second-generation antipsychotics agents [17] may precipitate HHS or DKA. Cocaine has also been associated with recurrent DKA [18]. Restricted water intake due to ill health or immobilization, compounded by altered thirst response of the elderly contributes to severe dehydration and HHS. In patients with type 1 diabetes, psychological problems and eating disorders may contribute to 20% of recurrent DKA [19]. Insulin delivery by continuous subcutaneous infusion devices was associated with increased incidence of DKA [20]; but improvement in technology and better patient education appear to have corrected this anomaly. Prospective studies would be required to confirm this observation [12,21]. Also, DKA has been reported as the primary manifestation of acromegaly [22] and adrenal disorders such as pheochromocytoma and Cushing's syndrome [23–25]. The etiological agents in DKA and HHS are shown in Table 2.

3. Literature search strategy

We conducted a literature search through PubMed using “hyperglycemic crises” and “diabetic ketoacidosis” as search terms. Original articles, consensus statements or guidelines and reviews published in English were selected for review. The grading of evidence is based on the system used by the International Diabetes Federation (Appendix A).

Table 1 – Diagnostic criteria and typical total body deficits of water and electrolytes in diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS).

	DKA			HHS
	Mild	Moderate	Severe	
Diagnostic criteria and classification				
Plasma glucose (mg/dl) ^a	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00–<7.24	<7.00	>7.30
Serum bicarbonate (mequiv./l)	15–18	10–<15	<10	>15
Urine ketone ^b	Positive	Positive	Positive	Small
Serum ketone ^b	Positive	Positive	Positive	Small
Effective serum osmolality ^c	Variable	Variable	Variable	>320
Anion gap ^d	>10	>12	>12	Variable
Mental status	Alert	Alert/Drowsy	Stupor/Coma	Variable
Typical deficits				
Total water (l)	6			9
Water (ml/kg) ^e	100			100–200
Na ⁺ (mequiv./kg)	7–10			5–13
Cl ⁻ (mequiv./kg)	3–5			5–15
K ⁺ (mequiv./kg)	3–5			4–6
PO ₄ (mmol/kg)	5–7			3–7
Mg ²⁺ (mequiv./kg)	1–2			1–2
Ca ²⁺ (mequiv./kg)	1–2			1–2

Data adapted from [12].

^a Euglycemic DKA has been reported.

^b Nitroprusside reaction method.

^c Calculation: effective serum osmolality: 2 [measured Na⁺ (mequiv./l) + glucose (mg/dl)/18 (mOsm/kg)].

^d Calculation: anion gap: (Na⁺)–(Cl⁻ + HCO₃⁻) (mequiv./l) [normal = 12 ± 2].

^e Per kg of body weight.

4. Clinical questions

1. What is optimal fluid therapy in patients with hyperglycemic crises?
2. What is the most efficacious route and dose of insulin in the treatment of patients with DKA and HHS?
3. After recovery from DKA, can some patients with type 2 diabetes be managed with oral drugs?
4. What is the role of electrolyte repletion in DKA and HHS?
5. Is there any role for anti-coagulation in hyperglycemic emergencies?
6. Is there any role for preventive measures in hyperglycemic emergencies?

Table 2 – Precipitating factors for DKA.

Study location/dates	Number of cases	Infection	Cardiovascular	of cases	Noncompliance	New onset	Other conditions	Unknown
Frankfurt, Germany Petzold et al., 1971	472	19	6	38	+	+	+	
Birmingham, UK Soler et al., 1968–72	258	28	3	23	+	+	+	
Erfurt, Germany Panzram 1970–71	133	35	4	21	+	+	+	
Basel, Switzerland Berger et al., 1968–78	163	56	5	31	+	+	+	
Rhode Island, USA Faich et al., 1975–79	152	43	–	26	+	+	+	
Memphis, USA Kitabchi et al., 1974–85	202	38	–	28	22	10	4	
Atlanta, USA Umpierrez et al., 1993–94	144	28	–	41	17	10	4	
New York, USA Nyenwe et al., 2001–04	219	25	3	44	25	12	15	
Nairobi, Kenya Mbugua et al., 2005	48	23	–	34	–	–	–	

Adapted with modification from ref. [15].

Data are % of all cases except in Nyenwe et al., where new onset disease was not included in the percentage + complete data on these items were not given, therefore, the total is less than 100%.

A basic knowledge of the pathogenesis of DKA and HHS is a prerequisite for understanding the rationale for the therapeutic approach adopted in patients with hyperglycemic emergencies. Therefore a succinct review of the pathophysiology of DKA and HHS is considered a worthwhile prelude to addressing the questions raised above.

5. Pathogenesis

DKA is characterized by (1) reduced net effective action of circulating insulin due to decreased insulin secretion and/or insulin resistance, (2) elevation in level of counter-regulatory hormones such as glucagon, growth hormone, cortisol, and catecholamines, which give rise to (3) hyperglycemia from accelerated gluconeogenesis, glycogenolysis, impaired peripheral glucose utilization [12,15,16] and exaggerated lipolysis with consequent elevation in free fatty acid concentration. Increased hepatic supply of free fatty acids coupled with diminished insulin:glucagon ratio results in unrestrained fatty acid oxidation to ketone bodies (β -hydroxybutyrate and acetoacetate) [26], with resulting ketonemia and metabolic acidosis. In HHS, endogenous insulin secretion is greater than occurs in DKA. Hence, there is enough effective insulin action to extinguish excessive lipolysis and subsequent ketogenesis but inadequate to facilitate glucose utilization by other insulin-sensitive tissues such as muscle and liver [15]. Although increased ketosis is rare in HHS, severe hyperglycemia does ensue, thus giving rise to severe osmotic diuresis and dehydration [15,16]. Dehydration results in hypovolemia, depressed glomerular filtration rate, and reduced glucose excretion in urine which also contributes to hyperglycemia in DKA and HHS [27].

Available evidence suggests that hyperglycemic emergencies are associated with an inflammatory state which is marked by elevation in proinflammatory cytokines such as tumor necrosis factor- α , interleukins and C-reactive protein. Also, reactive oxygen species, lipid peroxidation, as well as cardiovascular risk factors such as plasminogen activator inhibitor-1 are elevated [28]. All of these parameters return to normal with correction of the metabolic perturbations in DKA and HHS. This inflammatory and procoagulant state may explain the relatively high incidence of thrombotic events in hyperglycemic emergencies.

Glycosuria induced osmotic diuresis produces significant deficit in water and electrolyte homeostasis via loss of multiple minerals and electrolytes including, sodium, potassium, calcium, magnesium, chloride, and phosphate [29,30]. Ketoanion excretion, which is associated with obligatory urinary cation loss also contributes to electrolyte derangement. Intracellular dehydration ensues as hyperglycemia induced water loss leads to plasma hypertonicity and its associated efflux of water from the cells. There is also efflux of potassium to the extracellular compartment, a phenomenon that is aggravated by acidosis, breakdown of intracellular protein and lack of effective insulin action [31]. Additional contributing factors to excessive volume depletion include diuretic use, fever, diarrhoea, nausea and vomiting. Severe dehydration, older age, and the presence of co-morbid conditions in patients with HHS account for the higher mortality in these patients.

6. What is optimal fluid therapy in patients with DKA?

Rehydration corrects the volume deficit in DKA and HHS, the reversal of which is essential for adequate tissue perfusion and ultimate resolution of the associated metabolic abnormalities. Prospective studies in patients with severe DKA have demonstrated that fluid repletion alone, results in significant improvement in hyperglycemia, reduction in the level of counter-regulatory hormones and amelioration of peripheral insulin resistance [27,32]. Thus adequate rehydration produces optimal response to subsequent low dose insulin therapy. Serum sodium concentration in subjects with hyperglycemic crises may be falsely low due to the osmotic flux of water from the intracellular to the extracellular space in the presence of hyperglycemia. Thus, severe hypernatraemia may develop as hyperglycemia is treated. Such patients would require sufficient free water to prevent complications of hypertonicity such as prolonged neurological dysfunction. Thus the effective serum sodium should be calculated to correct for the level of hyperglycemia by adding 1.6 mmol/l (1.6 mequiv./l) of sodium for every 5.6 mmol/l (100 mg/dl) of glucose above 5.6 mmol/l (100 mg/dl).

Although the benefits of proper rehydration remains unequivocal, the choice of fluid for resuscitation in the critically ill patient has been a subject of controversy, which has been addressed by several studies. Martin et al. in a prospective study which compared the effects of hypotonic, isotonic and hypertonic fluids in patients with severe diabetic ketoacidosis observed that there was little difference in the volume of fluid retained when repair solutions of varying tonicity were employed. However, in comparison with hypotonic and isotonic fluids, hypertonic fluids resulted in worsening of hyperosmolarity, hypernatraemia and hyperchloraemia, indicating that hypertonic fluids may be detrimental [29]. Furthermore, it was noted that some patients treated with hypotonic fluids developed diuresis, hence, this study concluded that in patients with severe dehydration, rapid repletion of the plasma and extracellular volume with isotonic fluids is indicated.

Again for many years, it remained uncertain whether colloids such as dextran, and hetastarch were superior to crystalloids such as normal saline and Ringer's lactate in the treatment of critically ill patients including those with DKA. Crystalloids were thought to require larger volumes of fluid which predisposed to edema in different organs including the brain and lung [33]. However, current evidence indicates that colloids did not confer any mortality benefits over crystalloids in the critically ill [34,35]. A recent meta-analysis of prospective randomized controlled studies which compared crystalloids and colloids in critically ill patients concluded that there was no evidence that resuscitation with colloids reduced the risk of death, compared to resuscitation with crystalloids [34]. In the light of available evidence and low cost effectiveness of colloids, their continued use may be hard to rationalize [34].

In a prospective randomized controlled study, Caputo et al. investigated the optimal rate of hydration in 27 patients with DKA. Subjects were randomized to receive either 1000 ml/h or 500 ml/h of 0.9% saline solution. Both groups who were

biochemically similar at baseline responded in a comparable fashion to treatment with no difference in the rate of resolution of their biochemical defects, suggesting that 500 ml/h may be a cost effective rate of rehydration in DKA [36]. Another prospective randomized study which investigated the choice of fluid for maintenance of adequate glycemic level for the resolution of DKA (5% versus 10% dextrose along with continued insulin infusion), found that 10% dextrose resulted in significantly lower level of ketonemia and higher level of hyperglycemia, but did not confer any advantage in the improvement in capillary blood pH or bicarbonate [37].

6.1. Recommendations

Given the body of evidence reviewed above, it would be prudent to recommend that initial fluid therapy in DKA should consist of isotonic saline (0.9% NaCl) infused at the rate of 15–20 ml/kg/h or 1–1.5 l during the first hour. The rate of hydration thereafter should be guided by hemodynamic status, the state of hydration, serum electrolyte levels, and urinary output, generally, 0.45% saline at 250–500 ml/h is appropriate in patients who are eunatraemic or hypernatraemic, while 0.9% NaCl at a similar rate is appropriate in hyponatraemic subjects [12] [Level 1+]. It is noteworthy that excessive use of isotonic saline contributes to transient hyperchloremic metabolic acidosis after resolution of ketoacidosis. This condition, which is self-limiting is also contributed to by effective urinary loss of bicarbonate as sodium salt resulting in slower recovery of serum bicarbonate level.

1. Estimated fluid deficits should be corrected in the first 24 h. Adequate fluid repletion is assessed by clinical evaluation, hemodynamic monitoring, fluid input/output chart and serum biochemistry. Patients with renal or cardiac compromise may be monitored by serum osmolality and frequent assessment of cardiac, renal, and mental status during fluid resuscitation to avoid circulatory overload [12,16] [Level 1–].
2. When plasma glucose is ≤ 200 mg/dl, 5% dextrose should be added to repletion fluids to prevent hypoglycemia while continuing insulin administration until ketonemia is resolved [12,16,37] [Level 1+].

7. What is the most efficacious route and dose of insulin in the treatment of patients with DKA?

Important studies about three decades ago established low or physiologic dose regular insulin therapy as the cornerstone for the management of hyperglycemic emergencies [38,39]. In a prospective randomized controlled trial, Kitabchi and colleagues investigated the effect of low-dose vs high-dose insulin therapy in 48 patients with DKA [39,40]. In this study, the biochemical profiles were similar in the two arms before randomization; both groups showed no significant difference in the rate of resolution of the biochemical aberrations of DKA. Additionally, the counter-regulatory hormones glucagon and cortisol declined at the same rate in the two groups. However, 25% and 30% of the patients who received high-dose insulin developed hypoglycemia and hypokalemia

respectively compared to 0% and 4% respectively in the low-dose group. Thus, this study showed unequivocally that physiologic dose insulin therapy was superior to pharmacologic dose regimen in patients with DKA. However, a small retrospective analysis of patients seen at the Mayo Clinic between 1950 and 1992 found significantly higher incidence of hypoglycemia amongst subjects treated with insulin bolus regimen (27%) compared to 3% in those treated with continuous insulin infusion; but there was no difference in the incidence of hypokalemia between the two groups [41].

Also, there was controversy regarding the best route of administration of insulin in DKA. This was resolved by another prospective study in which 45 patients were randomized to receive low-dose insulin therapy by intravenous, intramuscular or subcutaneous route. It was observed that in comparison with intramuscular and subcutaneous insulin, intravenous insulin produced a more significant decline in hyperglycemia and ketonemia in the first 2 h of treatment, but the three groups showed similar response after 8 h of treatment [40,42]. A follow up randomized study of 30 patients [43], demonstrated that a priming dose given half by intravenous route and half by intramuscular route was as effective as one dose given intravenously in resolving hyperketonemia and that the addition of albumin to the infusate, which was the practice in the past to prevent adsorption of insulin to the tubing and containers was not necessary.

Previous treatment protocols have recommended the administration of an initial intravenous bolus of regular insulin (0.1 unit/kg) followed by the infusion of 0.1 unit/kg/h [15,16], but a recent prospective randomized study showed that a bolus dose is not required if patients are given hourly insulin infusion at 0.14 unit/kg body wt [44]. Low-dose insulin infusion protocols decrease plasma glucose concentration at a rate of 50–75 mg/dl/h. If plasma glucose does not decrease by that amount in the first hour, a bolus of 0.14 unit/kg body wt should be administered intravenously followed by continuation of the prior insulin infusion rate [12,16]. When the plasma glucose reaches 200 mg/dl, the insulin infusion rate should be reduced to 0.02–0.05 unit/kg/h. Also, dextrose should be added to the intravenous fluids at this point. The rate of insulin administration or the concentration of dextrose may need to be adjusted to maintain glucose values between 150 and 200 mg/dl in DKA resolution of the hyperglycemic crisis.

Several prospective randomized open label trials have demonstrated the efficacy and cost effectiveness of subcutaneous rapid-acting insulin analogs (lispro, aspart and glulisine) in the treatment of uncomplicated mild to moderate DKA [45–49]. In two of these studies, the patients received subcutaneous insulin lispro or aspart at a dose of 0.2 unit/kg initially, followed by 0.1 unit/kg every 1 h or an initial dose of 0.3 units/kg followed by 0.2 unit/kg every 2 h until blood glucose was < 250 mg/dl, when insulin dose was decreased to 0.05 or 0.1 unit/kg respectively and given every 1 or 2 h until resolution of DKA [45,46]. There were no differences in length of hospital stay, total amount of insulin needed for resolution of hyperglycemia or ketoacidosis. Patients treated with insulin analogs were managed in the open medical wards which reduced cost of hospitalization by 30% [45–47]. Considering that these findings have not been substantiated in practice, it

would be prudent to treat patients with severe DKA, hypotension, anasarca, or associated severe critical illness with intravenous regular insulin in the ICU [12]. In the rare case of a patient with allergy to human insulin presenting with hyperglycemic crisis, desensitization to human insulin may be performed before treatment with human insulin. A recent case report documented the successful treatment of a woman with allergy to human insulin and its analogs with continuous subcutaneous infusion of human insulin [50].

Patients with hyperglycemic emergency should be treated with insulin infusion until resolution of the hyperglycemic episode. Criteria for resolution of ketoacidosis include a blood glucose <200 mg/dl and two of the following criteria: a serum bicarbonate level ≥ 15 mequiv./l, a venous pH >7.3, and a calculated anion gap in normal range. Direct measurement of plasma β -hydroxybutyrate may also be useful in determining resolution of ketoacidosis in some cases. Resolution of HHS is marked by normal osmolality and restoration of normal mentation. Subcutaneous insulin therapy can be started when resolution has occurred. Patients previously treated with insulin may be recommenced on their home dose if they had been well controlled. Insulin-naïve patients should receive a multi-dose insulin regimen beginning at the dose of 0.5–0.8 unit/kg/day [12].

7.1. Recommendations

1. IV regular insulin 0.14 unit/kg/h as continuous infusion, or a bolus of 0.1 unit/kg followed by 0.1 unit/kg/h. If blood glucose does not fall by 10% in the first hour, give 0.14 unit/kg as a bolus, then continue infusion at the previous rate [12,43,45] [Level 1++].
2. When the plasma glucose reaches 200 mg/dl, the insulin infusion rate should be reduced to 0.02–0.05 unit/kg/h. Also, dextrose should be added to the intravenous fluids at this point. The rate of insulin administration or the concentration of dextrose may need to be adjusted to maintain glucose values between 150 and 200 mg/dl until resolution of DKA [12,16] [Level 1+].
3. Subcutaneously administered insulin analogs may be used in the medical ward or emergency room in mild–moderate DKA [48,49][Level 1+].
4. Once DKA has resolved, patients who are able to eat can be started on a multiple dose insulin regimen with a long acting insulin to cover basal insulin requirements and short/rapid acting insulin given before meals as needed to control plasma glucose. Intravenous insulin infusion should be continued for 1–2 h after the subcutaneous insulin is given to ensure adequate plasma insulin levels. Patients who are unable to eat should continue to receive intravenous insulin infusion and fluid replacement [12,16] [Level 1++].

8. After recovery from DKA, can some patients with type 2 diabetes be managed with oral drugs?

The occurrence of DKA in patients with type 2 diabetes is becoming increasingly well recognized in different ethnic groups, especially in people of African and Hispanic descent

[2,5]. These patients with ketosis-prone type 2 diabetes develop acute impairment in insulin secretion resulting in profound insulinopenia. Recovery of β -cell function occurs with resolution of DKA [51–53], and discontinuation of insulin therapy has been reported in 76% of such patients with 40% of them maintaining good glycemic control without insulin a decade after onset of diabetes [40,52]. The etiology of acute but transient β -cell failure is not known with certainty; putative factors include glucotoxicity, lipotoxicity and genetic predisposition.

8.1. Recommendation

1. Some patients with type 2 diabetes who present with DKA may be treated with oral anti-diabetic agents and lifestyle modification after they have recovered β -cell function [52] [Level 1–].

9. What is the role of electrolyte repletion therapy in DKA?

Hyperglycemic emergencies are associated with considerable loss of electrolytes (see Table 1), while some of these electrolytes (sodium, potassium and chloride) can be corrected quickly, others may take several days or weeks to normalize [9,30,54].

9.1. Potassium

Generally, total-body potassium is depleted in hyperglycemic emergencies, but mild to moderate hyperkalemia is commonly encountered in patients with DKA and HHS, due to acidosis, proteolysis and insulinopenia [12,15,16]. Hypokalemia may supervene as these biochemical abnormalities are corrected. A prospective study of 29 consecutive cases of DKA found that 82% of the patients were either normokalemic or hyperkalemic. However, in course of therapy 63% of them developed hypokalemia. Correction of hypokalemia required 59–239 mequiv. of potassium with an average requirement of 145 mequiv. [29]. Occasionally patients with DKA may present with significant hypokalemia, in which case insulin therapy should be delayed until potassium concentration is corrected to >3.5 mequiv./l to avoid arrhythmias and respiratory muscle weakness [55,56].

9.2. Recommendation

1. Potassium repletion should be initiated at serum potassium levels below 5.3 mequiv./l, in patients without renal impairment. Addition of 20–30 mequiv. potassium to each liter of infused fluid should maintain normokalemia in most patients [12,15,16] [Level 1++]. Considering that total body potassium deficit may be profound in some patients, some subjects with severe hypokalemia may require more than 30 mequiv. of potassium in the first hour after commencement of insulin therapy [Level 4]
2. In hypokalemic patients, insulin therapy should be delayed until potassium concentration is corrected to >3.5 mequiv./l [12,15,16] [Level 1++].

3. Patients with hypokalemia should be monitored for arrhythmias [12,15,16] [Level 1+].
4. The rare patient with severe hyperkalemia (>6.0 mequiv./l) on admission with concomitant electrocardiographic changes may benefit from bicarbonate therapy [Level 4].

9.3. Bicarbonate

The use of bicarbonate in DKA remains a controversial subject. Some workers believe that insulin therapy which inhibits lipolysis would correct ketoacidosis without administration of bicarbonate. Others argue that severe metabolic acidosis is associated with serious complications such as impaired myocardial contractility, cerebral vasodilatation, coma, and gastrointestinal sequelae. Prospective randomized controlled studies have not demonstrated any benefits of bicarbonate therapy in DKA patients with pH ≥ 6.9 [57–59]. In a detailed randomized study of 21 adults, administration of bicarbonate did not confer any advantages in the rate of decline of glucose or ketonemia or in the rate of increase in pH or serum bicarbonate level in the blood or cerebrospinal fluid. There were also no significant differences in the rate of resolution of DKA between the two groups. It was also observed that the brain was relatively protected from severe acidosis as the pH levels were higher in the CSF compared to the blood [57]. In another randomized study of 32 patients, bicarbonate therapy was associated with delay in the fall of total ketone bodies, blood lactate and lactate: pyruvate ratio [59]. The delay in the resolution of ketosis observed in this study was confirmed in both human and animal experiments in another small prospective randomized controlled study [60]. No prospective randomized studies concerning the use of bicarbonate in DKA with pH values < 6.9 have been reported [12], therefore the decision to use bicarbonate or not should be made based on the clinical state of the patient. Subjects who are clinically well compensated (no clinical features of severe metabolic acidosis) may not require administration of bicarbonate while it would be prudent to use bicarbonate in individuals with severe acidosis who may deteriorate without bicarbonate therapy.

9.4. Recommendations

1. Since severe acidosis may be associated with adverse effects, it is recommended that adults with pH < 6.9 who may deteriorate without bicarbonate therapy be given 100 mmol sodium bicarbonate (two ampules) in 400 ml sterile water with 20 mequiv. KCl administered at a rate of 200 ml/h for 2 h until the venous pH is > 7.0 . If the pH is still < 7.0 after infusion, we recommend repeating infusion every 2 h until pH reaches > 7.0 [12,16] [Level 4]. Given the fact that bicarbonate therapy can cause hypokalemia, subjects treated with bicarbonate should receive potassium as stated above and would require more close monitoring.
2. Similarly, Patients who have stretched their compensatory mechanism to its limits (low bicarbonate < 10 , or $P_{CO_2} < 12$) may experience deterioration of their pH and may be treated with bicarbonate as above [Level 4].
3. Patients with pH ≥ 6.9 do not require bicarbonate therapy [12,51–54] [Level 1++].

9.5. Phosphate

The average deficit of phosphate in patients with DKA and HHS, is about 1 mmol/kg body weight. However, as with potassium, serum phosphate levels at presentation are usually normal or high but rapidly decrease with insulin therapy. Randomized studies in patients with DKA showed that phosphate repletion did not confer any additional benefit on clinical outcome, but overenthusiastic phosphate repletion could precipitate hypocalcemia [61,62]. A prospective study which randomized 30 patients with DKA to receive 12.5 mequiv./h of a buffered potassium phosphate salt at a rate of 12.5 mequiv./h or potassium chloride 12.5 mequiv./h alone found that both groups had comparable levels of 2, 3-diphosphoglyceric acid at the end of 48 h. Phosphate therapy, which was not associated with any demonstrable effect on tissue oxygenation or clinical response, was noted to cause hypocalcaemia in some patients [62].

9.6. Recommendations

1. There is no indication for phosphate therapy in most patients with DKA. However, in patients with potential complications of hypophosphatemia such as cardiac and skeletal muscle weaknesses or rhabdomyolysis, the use of phosphate may be justified. When needed, 20–30 mequiv./l potassium phosphate can be added to replacement fluids [12,15,16] [Level 2++].
2. Considering the fact that potassium chloride overload may cause hyperchloremic acidosis, it may be prudent to recommend that potassium be given 1/3 as potassium phosphate and 2/3 as potassium chloride [16] [Level 2++].
3. Serum calcium level should be monitored in patients receiving phosphate infusion [15] [Level 2+].

10. Is there any role for anti-coagulation in DKA?

It has been shown that hyperglycemic emergencies predispose to inflammatory and procoagulant states; this may account for the increased incidence of thrombotic events in DKA and HHS [28]. Thrombotic conditions such as disseminated intravascular coagulation contribute to the morbidity and mortality in hyperglycemic crises [63].

10.1. Recommendation

1. Prophylactic use of heparin may be beneficial in DKA if there is no associated bleeding disorder [Level 4].

11. Treatment of HHS

Subjects with HHS may also exhibit some degree of ketosis, and may have other conditions that lead to acidosis such as respiratory and renal failure and lactic acidosis. Altered mentation and focal neurological deficit are more frequent in HHS than DKA due to severe hypertonicity (Table 1). Dehydration is usually more profound in HHS as a result of longer period of metabolic decompensation, intercurrent

illness, poor fluid intake and in some patients concomitant diuretic therapy [64]. The combination of severe dehydration, co-morbidities and advanced age contribute to the poor prognosis in HHS [64]. Patients with HHS may have extreme hyperglycemia with falsely low serum sodium due to osmotic dilution of plasma by efflux of intracellular water. In such patients, severe hyponatremia could develop as hyperglycemia is corrected. These patients would require sufficient free water repletion in order to prevent complications of hypertonicity as noted above. Additionally, reduced glucose excretion due to low glomerular filtration rate in patients with HHS contributes to extreme hyperglycemia.

The treatment of HHS is similar to that of DKA consisting of controlled rehydration, electrolyte repletion, and low-dose insulin therapy. Initial fluid therapy in HHS should consist of isotonic saline infused at the rate of 15–20ml/kg/h or 1–1.5 l during the first hour [Level 1+]. Thereafter slower rehydration would be prudent as rapid reduction in plasma tonicity has been linked to cerebral and pulmonary edema [65,66]. Generally, 0.45% saline at 250–500 ml/h is adequate in patients with normal or high plasma sodium levels, while isotonic saline at a similar rate is appropriate in hyponatraemic subjects [12]. When plasma glucose is ≤ 300 mg/dl, 5% dextrose should be added to repletion fluids to prevent hypoglycemia while continuing insulin administration until the hyperosmolar state has resolved [12,16,37] [Level 1+]. Hemodynamic status should be monitored closely as some of the patients with HHS may have cardiac or renal decompensation. Monitoring of central venous pressure and urinary output may be required to guide appropriate fluid therapy.

Low-dose insulin infusion protocols should be administered as described for patients with DKA; initial intravenous bolus of regular insulin (0.1 unit/kg) followed by the infusion of 0.1 units/kg hourly or continuous hourly insulin infusion at 0.14 unit/kg body wt [44]. When the plasma glucose reaches ≤ 300 mg/dl, the insulin infusion rate should be reduced to 0.02–0.05 unit/kg/h and dextrose should be added to the intravenous fluids. The rate of insulin administration or the concentration of dextrose may need to be adjusted to maintain glucose values between 250 and 300 mg/dl in until resolution of HHS.

Potassium repletion is provided as for DKA with the requisite monitoring as discussed. Subjects with lactic acidosis will require aggressive bicarbonate therapy [Level 4]. Considering that thrombotic phenomena confer significant morbidity and mortality in HHS, anticoagulation may be indicated where there are no contraindications [Level 4].

12. Is there any role for preventive measures in hyperglycemic emergencies?

Prospective clinical studies have identified omission or poor adherence to insulin therapy as the major precipitant of DKA in some populations. In a review of 56 consecutive cases of DKA in a large urban hospital, cessation of insulin therapy was reported as the etiological factor in two-thirds of the patients [67]. In another study of 167 episodes of DKA in an indigent population, noncompliance was identified as the major trigger of DKA in about 60% of the cases [68]. A prospective

interventional study in ambulatory teen age patients with type 1 diabetes, which incorporated frequent outpatient clinics, observed that diabetes related hospitalization was significantly less in the intervention group and glycemic control was also better in the same group [69]. Illicit drug use, which has been associated with recurrent episodes of DKA may also be a target for the prevention of DKA [18,70]. Again, an intensive home-based psychotherapy program was shown to reduce hospital admission for DKA over 24 months in a prospective randomized study of 127 youths [71]. A significant proportion of HHS cases in the elderly occur in nursing home residents with or without prior history of diabetes. In these elderly patients inadequate attention to fluid therapy contributes to poor outcome [72]. From the foregoing, it is evident that the majority of hyperglycemic emergencies are preventable through better access to medical care, proper patient and care giver education, and effective communication with health care providers regarding intercurrent illness.

12.1. Recommendations

1. Education of the diabetic patient and their care givers on the process of care in diabetes and sick day management is vital to preventing hyperglycemic emergencies [Level 1–].
2. Patients who use illicit drugs may benefit from drug rehabilitation [Level 2–].
3. Table 3 shows the recommendations for the management of hyperglycemic emergencies and the evidence supporting them.

13. Euglycemic ketoacidosis

The term euglycemic diabetic ketoacidosis was used by Munro et al. to describe 37 of 211 episodes of DKA in which the patients had blood glucose of 300 mg/dl or less with plasma bicarbonate level of 10 mequiv./l or less. Nearly all the subjects were young type 1 diabetic patients who had anorexia and vomiting but continued to take insulin [73]. Important etiologic factors in euglycemic DKA include starvation or low caloric intake, vomiting, pregnancy and depression [74]. In patients with euglycemic DKA, it is important that ketonemia or ketonuria, blood pH and bicarbonate levels are checked in order to make the diagnosis of this critical condition, since hyperglycemia may not be impressive. Treatment of euglycemic DKA consists of fluid and electrolyte repletion as clinical condition dictates. Insulin therapy along with administration of glucose to prevent hypoglycemia should be given until resolution of the DKA episode [75].

14. Other important considerations

The three ketone bodies produced in DKA are β -hydroxybutyric acid, acetoacetic acid and acetone; of these, β -hydroxybutyric acid is the more abundant ketoacid especially in severe DKA. Ketone bodies are usually measured in most laboratories with the nitroprusside method, which reacts with acetoacetate and acetone, the less predominant ketones in DKA. Therefore, some subjects with severe DKA may test

Table 3 – Recommendations and the evidence supporting them.

Observed derangement	Recommendations	Level of evidence	Reference
Dehydration	1. Initial treatment-0.9% NaCl at the rate of 15–20 ml/kg/h or 1–1.5 l during the first hour.	1+	[12]
	2. Maintenance-guided by clinical state. 0.45% saline at 250–500 ml/h is appropriate in patients who are eunatraemic or hypernatraemic, while 0.9% NaCl at a similar rate is appropriate in hyponatraemic subjects.		
	3. When plasma glucose is ≤ 200 mg/dl in DKA or ≤ 300 mg/dl in HONK, 5% dextrose should be added to repletion continue insulin until ketonemia resolves.	1+	[12,15,33]
Hyperglycemia/ ketonemia	1. IV regular insulin 0.14 units/kg/h as continuous infusion, or a bolus of 0.1 units/kg followed by 0.1 units/kg/h.	1++	[12,36,37]
	2. If blood glucose does not fall by 10% in the first hour, give 0.14 units/kg as a bolus, then continue infusion at the previous rate.		
	3. When the plasma glucose reaches 200 mg/dl in DKA or 300 mg/dl in HONK, insulin infusion rate should be reduced to 0.02–0.05 units/kg/h. Also, dextrose should be added to the intravenous fluids	1+	[12,15]
	4. Subcutaneously administered insulin analogs may be used in the medical ward or emergency room in mild–moderate DKA.	1+	[41,42]
	5. Once DKA has resolved, patients can be started on a multiple dose insulin regimen. Patients who are unable to eat should continue to receive intravenous insulin infusion and fluid replacement	1++	[12,15]
	6. Some patients with type 2 diabetes may be treated with oral anti-diabetic agents and lifestyle modification after recovery	1–	[47]
Acidosis	1. Adults with pH < 6.9 may be given 100 mmol sodium bicarbonate in 400 ml sterile water with 20 mequiv. KCl administered at a rate of 200 ml/h for 2 h until the venous pH is > 7.0 .	4	[12,15]
	2. Patients with pH ≥ 6.9 do not require bicarbonate therapy.	1++	[12,52–55]
Abnormal phosphate level	1. There is no indication for phosphate therapy in most patients with DKA. In patients with potential complications of hypophosphatemia the use of phosphate may be justified. 20–30 mequiv./l potassium phosphate can be added to replacement fluids.	2++	[12,14,15]
	2. Potassium replacement may be given 1/3 as potassium phosphate and 2/3 as potassium chloride.	2++	[15]
	Serum calcium level should be monitored in patients receiving phosphate infusion.	2++	[14]
Hypercoagulable state	Prophylactic use of heparin may be beneficial in DKA and full anticoagulation may be indicated where there are no contraindications in HONK.	4	[15,58]
Prevention	1. Education of the diabetic patient and care givers on the process of care and sick day management.	1–	[61,63]
	2. Patients who use illicit drugs may benefit from drug rehabilitation.	2–	[18,62]

falsely negative for ketone bodies by the nitroprusside method. Furthermore, β -hydroxybutyrate is converted to acetoacetate during treatment of DKA; hence, the nitroprusside reaction could become strongly positive in a patient who in fact is recovering from DKA. Direct measurement of β -hydroxybutyrate in the blood, which is now available in some centers, is useful in the diagnosis and determination of resolution of DKA in this regard [76].

Hyperglycemic crises remain potentially fatal diseases; mortality is usually related to the precipitating intercurrent illness rather than the biochemical perturbations of the disease [15]. Therefore, a diligent search should be made for the precipitant in all cases of DKA or HHS. Omission of insulin therapy and infection are frequent etiological factors in DKA [12,77]. Hence it would be prudent to provide adequate broad spectrum antibiotic coverage in subjects who have fever and/or leucocytosis without an identifiable focus while reports of microbiological investigations are awaited. Leucocytosis is a common in patients with hyperglycemic emergencies, but white blood cell count greater than 25,000 μ L may suggest active infection which would require further work-up and empiric antibiotic therapy [78].

Cerebral edema occurs in about 0.3–1% of all episodes of DKA in children and has mortality rate of up to 25% [79–81], while about 25% of survivors have permanent neurologic sequelae [81]. The etiopathogenesis and best treatment modality for DKA associated cerebral edema remain poorly understood, but case reports indicate that treatment with mannitol (0.25–1.0 g/kg) over 20 min or hypertonic saline (3%), 5–10 ml/kg over 30 min may be beneficial. Intubation may be indicated for airway protection and adequate ventilation, but hyperventilation has been associated with poor prognosis [82]. Although glucocorticoids are useful in cerebral edema due to trauma and mass lesions, there are no data indicating that steroids are beneficial in cerebral edema in patients with DKA [79].

15. Future research needs

Remarkable progress has been made in the management of subjects with hyperglycemic emergencies, especially DKA, however, there are still areas that require further investigation. The use of bicarbonate in patients with pH < 6.9 is yet to be investigated. Prospective randomized studies would be

required to demonstrate the effect of bicarbonate in this category of patients. The explanation for the absence of severe ketosis in HHS is still lacking; understanding this mechanism may give further insight into ameliorating the morbidity and mortality in the high risk patients with DKA. Again, the mechanism for the induction of proinflammatory cytokines and cardiac risk factors in patients with hyperglycemic emergencies and no prior history of cardiovascular disease, infection, or injury remains unclear. Elucidating the pathophysiology of this pathway may prove invaluable in the prevention of excess cardiovascular and thrombotic morbidity associated with hyperglycemic crises, especially HHS.

Fast-acting insulin analogs have been shown to be as effective as intravenously administered regular insulin in mild to moderate DKA, but it is not known if regular insulin would be equally efficacious in such patients. Using regular insulin by subcutaneous route, which would be much more economical than insulin analogs should be investigated. The rising prevalence of DKA is attributable to its increasing occurrence in patients with ketosis-prone type 2 diabetes. The mechanism for acute severe decompensation in β -cell function leading to ketoacidosis is not clearly understood requires further investigation. The etiology of altered mentation in DKA remains to be conclusively elucidated. A retrospective study has demonstrated that acidosis is the predominant determinant of level of consciousness [83], but a prospective randomized study would be needed to validate this observation.

Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Levels of evidence¹

1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1–	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias.
2++	High-quality systematic reviews of case-control or cohort studies. High-quality case control or cohort studies with very low risk of confounding bias and a high probability that the relationship is causal.
2+	Well-conducted case-control or cohort studies with low risk of confounding bias or chance and a moderate probability that the relationship is causal. Well-conducted basic science with low risk of bias.
2–	Case-control or cohort studies with a high risk of confounding bias or chance and significant risk that the relationship is not causal.
3	Non-analytic studies (for example case reports, case series).
4	Expert opinion.

¹ From International Diabetes Federation (2006). Guideline for management of post meal glucose accessed online at http://www.idf.org/webdata/docs/Guideline_PMG_final.pdf on December 20, 2010.

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