Severe Hyperglycemia, Diabetic Ketoacidosis, and Hyperglycemic Hyperosmolar State -
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Abstract

Emergency admissions due to hyperglycemia remain some of the most common and challenging metabolic conditions to deal with. Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are biochemically different conditions that require different approaches to treatment. They often occur in different age groups, and there is a need for co-ordinated care from the multidisciplinary team to ensure the timely delivery of the correct treatments. Over the last few years, the management of these conditions has changed. With DKA, the use of bedside monitoring of plasma ketone levels now drives treatment. With HHS, the treatment now focusses on the use of fluid rehydration rather than insulin treatment as the means by which glucose lowering should be achieved, with insulin only being introduced when the rate of glucose lowering levels off.

This chapter, which is based largely on published guidelines from the US and UK on the management of these conditions highlights the recent changes in management, the differences between the guidelines, and the rationale for these changes.

Introduction

The hyperglycemic urgency, severe hyperglycemia, and emergencies, DKA and HHS are acute severe metabolic complications of uncontrolled diabetes mellitus [1]. Severe hyperglycemia can escalate into the potentially fatal complications of DKA and HHS. Subsequently, these conditions demand immediate recognition and treatment.

Severe hypergycemia is characterized by significant hyperglycemia (i.e. glycosylated hemoglobin [HbA_{1c}] ≥10%); or fasting plasma glucose [FPG] >250 mg/dl [~14 mmol/L]; or random plasma glucose >300 mg/dl [16.7mmol/L]); or when symptomatic (e.g. sudden persistent weight-loss, polyuria, and polydipsia) [2].

DKA is a complex disordered metabolic state characterized by severe hyperglycemia (i.e. plasma glucose levels >250 mg/dl [~14 mmol/L]), ketonemia (ketosis), and metabolic acidosis (pH ≤7.3, serum bicarbonate <18 mEq/L [18 mmol/L]). The 2009 American Diabetes Association (ADA) Hyperglycemic Crises consensus guidelines further subdivides DKA into mild DKA (serum bicarbonate of 15 to 18 mEq/L [15 to 18 mmol/L], pH 7.25 to 7.30); moderate DKA (serum bicarbonate 10 to <15 mEq/L [10 to <15 mmol/L], pH 7.00 to 7.24): and severe DKA (serum bicarbonate <10 mEq/L [10 mmol/L], pH <7.00). More recently, the UK 2013 Joint British Diabetes Societies Inpatient (JBDS IP) group DKA guidelines have incorporated serum ketone levels (3-beta-hydroxybutyrate [βHBA]) in the definition of DKA [3]. The measurement of βHBA for diagnosis and monitoring of DKA was also recommended in the 2011 ADA Diabetes Laboratory guidelines [4]. The 2013 JBDS IP group DKA definition requires the combined presence of 3 biochemical abnormalities: ketonemia ≥3 mmol/L or significant ketonuria (≥2+ urine ketones on standard urine sticks); blood glucose >200 mg/dl (11.1 mmol/L) or known diabetes; and venous (or arterial) blood bicarbonate <15 mEq/L (15 mmol/L) and/or pH <7.3. DKA primarily affects persons with type 1 diabetes and may be an initial manifestation of previously undiagnosed type 1 diabetes (~25%) or may result from increased insulin requirements in existing patients during situations that increase the release of counterregulatory hormones (i.e. glucagon, cortisol, epinephrine, and growth hormone). When hyperglycemia initially presents in the presence of ketones or other signs of metabolic decompensation, the diagnosis of type 1 diabetes is generally straightforward (especially in children and adolescents). However, ketonemia can also be found in individuals with type 2 diabetes (i.e. ketosis-prone hyperglycemia, especially in persons of African descent), with 5 to 25% having DKA [5].

HHS is characterized by marked hyperglycemia (blood glucose levels >600 mg/dl [33.3 mmol/L]); hyperosmolarity (plasma osmolarity >320 mOsm/kg [320 mmol/kg]) and dehydration; the absence of ketoacidosis; and depression of the sensorium. The 2012 JBDS IP group HHS definition includes: marked hyperglycemia (>540 mg/dl [30 mmol/L]); no significant ketonemia (<3 mmol/L);

no acidosis (pH>7.3, bicarbonate >15 mEq/L (15 mmol/L); hypovolemia; and osmolality usually >320 mosmol/kg [320 mmol/kg]. These guidelines also highlight that a mixed picture of HHS and DKA may occur. HHS is seen most frequently in persons with type 2 diabetes, however, approximately 20% of cases have no history of this diagnosis.

In the US, the prevalence of DKA has risen whilst mortality has decreased. This is related to an improved understanding of the pathophysiology of DKA together with close monitoring and correction of electrolytes. More than one-third of DKA hospitalizations are due to re-admissions. Mortality rates have fallen significantly in the last 20 years from 7.96% to 0.67% [6;7]. The mortality rate is still high in low-income countries and among non-hospitalized patients [8]. This high mortality rate illustrates the necessity of early diagnosis and the implementation of effective prevention programmes. The ready availability of insulin to all parts of the world should remain a priority. Cerebral edema remains the most common cause of mortality, particularly in young children and adolescents. The main causes of mortality in the adult population include severe hypokalemia (and related cardiac dysrhythmias), adult respiratory distress syndrome (ARDS), and comorbid states such as pneumonia, ACS and sepsis [9]. In comparison, HHS is rare but mortality attributed to HHS is considerably higher than that attributed to DKA, with recent mortality rates of 5–20%. The prognosis of both conditions is substantially worsened at the extremes of age in the presence of coma, hypotension, and severe comorbidities.

Pathophysiology

DKA usually occurs as a consequence of absolute or relative insulin deficiency that is accompanied by an increase in counterregulatory hormones [10]. This type of hormonal imbalance enhances hepatic gluconeogenesis and glycogenolysis resulting in severe hyperglycemia. Enhanced lipolysis increases serum free fatty acids that are then metabolised as an alternative energy source in the process of ketogenesis [11]. This results in accumulation of large quantities of ketone bodies and subsequent metabolic acidosis. Ketones include acetone, βHBA, and acetoacetate. The predominant ketone in DKA is βHBA.

There are several mechanisms responsible for fluid depletion in DKA. These include osmotic diuresis due to hyperglycemia, vomiting (commonly associated with DKA) and eventually, inability to take in fluid due to a diminished level of consciousness. Electrolyte shifts and depletion are in part related to the osmotic diuresis. Hyperkalemia and hypokalemia need particular attention. Unlike DKA, which is a condition most frequently associated with absolute insulin deficiency, in HHS there is sufficient insulin to prevent ketogenesis, but insufficient insulin to either prevent hepatic gluconeogenesis and cellular glucose uptake [12]. If counterregulatory hormone excess is also present (e.g. concomitant illness), then this leads to a rise in blood glucose, and a subsequent osmotic diuresis. If sufficient water is not available, this leads to dehydration and resultant impaired renal function. The high plasma glucose causes a raised serum osmolality. The impaired renal function then leads to a further inability to excrete glucose thus perpetuating the hyperglycaemia, osmotic diuresis, volume depletion, and dehydration [11]. Alterations in mental status are common with serum osmolalities over 330 mosmol/kg (330 mmol/kg).

Etiology

DKA and HHS can be precipitated by various conditions (which can be easily remembered by the letter **I**), including **I**nsulin deficiency (i.e. diabetes presentation or failure to take enough insulin); **I**atrogenic (e.g. glucocorticoids, thiazides, and atypical antipsychotic drugs); **I**nfection (the most common precipitating factor for both DKA and HHS); **I**nflammation (e.g. acute pancreatitis, cholecystitis); **I**schemia or **I**nfarction (e.g. acute coronary syndromes [ACS], stroke, bowel); and **I**ntoxication (e.g. alcohol, cocaine).

Few studies have assessed factors associated with DKA in adults with type 1 diabetes. However, the T1D Exchange clinic registry at 70 US endocrinology centers recently performed a cross-sectional analysis including 7012 participants with type 1 diabetes [13]. Higher frequencies of DKA were associated with lower socioeconomic status ($P < 0.001$); and higher HbA1c levels ($P < 0.001$), with 21.0% of those with HbA1c ≥10.0% having an event in the past 12 months.

Notably, the frequency was no higher in insulin pump users than injection users, an important finding because DKA is a potential risk with pump infusion site failure.

Diagnostic considerations

The diagnostic criteria of severe hyperglycemia, DKA, and HHS are outlined in the introduction.

The initial laboratory evaluation of patients includes determination of plasma glucose, blood urea nitrogen (BUN, or urea), creatinine, electrolytes (with calculated anion gap), serum osmolality, serum and urinary ketones, urinalysis, baseline venous (or arterial) blood gases, complete (full) blood count with differential, and ESR or CRP (if indicated). An electrocardiogram (ECG), chest X-ray, and urine, sputum, and blood cultures should also be obtained. Other investigations are performed as warranted by the clinical situation (e.g. cardiac troponins, serum lactate, appropriate imaging, toxicology, and drug screen).

Point of care ketone testing should be used to measure the plasma ketone concentrations (in particular, βHBA), because this is the direct marker of disease severity. The anion gap is calculated by subtracting the sum of chloride (Cl) and bicarbonate (HCO3) concentration from the uncorrected (see below) sodium (Na) concentration: [Na - (Cl + HCO3)]. A normal anion gap is between 7 and 9 mEq/L (7-9 mmol/L) and an anion gap >10-12 mEq/L (10-12 mmol/L) indicates the presence of increased anion gap metabolic acidosis. Whilst arterial blood gas (ABG) is the most accurate method of assessing ventilation and acid-base status, venous blood gas (VBG) is preferred to ABG for bicarbonate and pH measurements because the differences in arterial and venous pH (e.g. venous pH only 0.03 lower than arterial), bicarbonate and potassium measurements are not great enough (in either direction) to alter management.

The admission serum sodium is usually low or normal despite water loss (renal and gut) because of an intracellular–extracellular fluid shift. To assess the severity of sodium and water deficit, serum sodium may be corrected by adding 1.6 mg/L (1.6 mmol/L) to the measured serum sodium for each 100 mg/dl (5.6 mmol/L) of glucose above 100 mg/dl (5.6 mmol/L) up to 440 mg/dl (~24

mmol/L) [14]. For glucose levels >440 mg/dl (~24 mmol/L), serum sodium may be corrected by adding 4 mg/L (4 mmol/L) to the measured serum sodium for each 100 mg/dl glucose above this threshold. Serum potassium levels may also be low, normal, or elevated, despite total body potassium depletion resulting from protracted polyuria and vomiting.

On admission, leukocytosis with cell counts in the 10,000 –15,000 mm^3 range is the rule in DKA and is generally attributed to stress and may not be indicative of an infection. However, leukocytosis with cell counts >25,000 mm^3 may designate infection and appropriate evaluation is indicated.

Hyperamylasemia has been reported in 21–79% of patients with DKA; however, there is little correlation between the presence, degree, or isoenzyme type of hyperamylasemia (e.g. salivary amylase can also be increased in DKA) and the presence of gastrointestinal symptoms (nausea, vomiting, and abdominal pain) or pancreatic imaging studies. A serum lipase determination may be beneficial in the differential diagnosis of pancreatitis; however, lipase can also be elevated in DKA in the absence of pancreatitis.

Not all patients with ketoacidosis have DKA. Starvation ketosis and alcoholic ketoacidosis are distinguished by clinical history and by plasma glucose concentrations that range from mildly elevated (rarely >200 mg/dl [11.1 mmol/L]) to hypoglycemia. A clinical history of previous drug abuse and intoxication should be sought.

Clinical signs and features

The process of HHS usually evolves over several days to weeks, whereas the evolution of the acute DKA episode tends to be much shorter (typically <24 h). For both DKA and HHS, the classical clinical picture includes a history of polyuria, polydipsia, weight loss, vomiting, dehydration, weakness, and mental status change. Physical findings may include increased rate and depth of respiration in DKA (i.e. Kussmaul’s breathing) with odor of acetone, tachycardia, and hypotension. Assessment of fluid status encompasses subjective observations (skin turgor, mucous membranes, and cerebral dysfunction), objective measurements (blood pressure, pulse,

postural measurements, body weight) and laboratory measurements (serum sodium, serum osmolality, BUN, hematocrit, and urine osmolality). Severe hypovolemia may manifest as tachycardia (pulse >100 bpm) and/or hypotension (systolic blood pressure <100 mmHg). Each has its limitations particularly on initial assessment where previous comparator data may not be available.

Mental status can vary from full alertness to profound lethargy or coma, with the latter more frequent in HHS. Acute impairment in cognitive function may be associated with dehydration but is not specific to the condition and is not necessarily present. Alterations in mental status are common with serum osmolalities over 330 mosmol/kg (330 mmol/kg). Focal neurologic signs (hemianopia and hemiparesis), positive Babinski reflexes, aphasia, visual hallucinations, seizures (focal or generalized), and coma may also be features of HHS. As HHS more frequently occurs in older people, the neurological findings may be mistaken for a stroke.

Although infection is a common precipitating factor for both DKA and HHS, patients can be normothermic or even hypothermic primarily because of peripheral vasodilation. Nausea, vomiting, diffuse abdominal pain are frequent in patients with DKA (>50%) but are uncommon in HHS. Further evaluation is necessary if this complaint does not resolve with resolution of dehydration and metabolic acidosis.

Management of Severe Hyperglycemia, DKA, and HHS

Successful treatment of severe hyperglycemia, DKA and HHS requires correction of hyperglycemia, dehydration, and electrolyte imbalances; identification of comorbid precipitating events; and above all, frequent patient monitoring.

Acute intervention

Once severe hyperglycemia, DKA, or HHS is recognized the patient should be managed in an appropriate location. This could be in the outpatient setting (e.g. rapid access clinic) for selected cases of severe hyperglycemia and mild DKA. However, the majority of patients will be hospitalized and managed in an emergency assessment unit (EAU), acute medical unit (AMU),

high dependency unit (HDU), or intensive care unit (ICU). As with all acute medical patients, prompt assessment and management of the ABCs should occur (i.e. Airway; Breathing; Circulation). Other markers of DKA and HHS severity should be assessed and recorded (Table 1).

General Supportive Care

Supportive care includes inserting large bore IV cannula and starting appropriate IV fluid resuscitation, electrolyte replacement, nutritional support, continuous cardiac monitoring, and pulse oximetry.

- Hyperglycemia Bundle: Due to the increased risk of arterial and venous thromboembolism (VTE), all patients with DKA or HHS should receive low molecular weight heparin (LMWH) for the full duration of admission unless contraindicated. HHS (and some DKA) patients are also at high risk of pressure ulceration. An initial foot assessment should be undertaken and heel protectors applied in those with neuropathy, peripheral arterial disease (PAD) or lower limb deformity. The feet should be re-examined daily. Consider NG tube with airway protection to prevent aspiration if Glasgow Coma Scale (GCS) is <12 or excessive vomiting. Consider urinary catheterization if the patient is incontinent, difficulty monitoring urine output (minimum urine output should be no less than 0.5ml/kg/hr), or anuric (i.e. not passed urine by 60 minutes).

Hyperglycemia Specific Therapy

Severe Hyperglycemia

Healthcare providers are concerned by the risk of severe hyperglycemia during acute illness in persons with diabetes, especially those treated with insulin therapy. Prevention of hyperglycemia, and their management with a step-by-step procedure (generally referred to as “sick-day” rules) when they eventually occur, are integral to diabetes management. Blood glucose levels normally increase during illness because of the release of stress hormones. Thus, sick-day rules should be initiated. The instructions include maintaining usual food plan, non-insulin therapies, and/or

insulin regimen whenever possible. Low-caloric fluid intake should be increased as appropriate. Persons with diabetes, who experience nausea or vomiting, should initiate the sick-day food plan. In patients treated with insulin, blood glucose and ketone (if available) monitoring should be carried out as recommended (e.g. every 2 to 4 hours). If blood glucose is >250 mg/dl (~14 mmol/L) on two consecutive tests, persons with diabetes are recommended to contact their clinician due to the possible need to supplement their current insulin regimen with short- or rapid-acting insulin as necessary. The individual must be instructed to contact their healthcare provider when the blood glucose is persistently raised (e.g. >300 mg/dl [16.6 mmol/L]) and/or they develop moderate to high ketonuria (i.e. ≥2+ urine ketones) and/or increased serum ketones if available. DKA or HHS can occur in this setting, thus frequent contact is necessary between clinician and the individual to prevent the situation from deteriorating further.

The most important consideration in the initial assessment of acute illness in persons with diabetes is whether the individual needs inpatient admission or can be safely managed in the community or outpatient setting (including review in a rapid-access clinic). The majority of these situations will be managed in the community or outpatient setting. However, this decision has to take into account various factors including medical (e.g. severity of metabolic decompensation, associated comorbidities, presence of confusion or impaired consciousness) and social issues (e.g. whether the patient lives alone or has adequate family support, whether there are reliable communication channels between healthcare provider and person with diabetes and/or caregivers). Inpatient admission can be considered when (1) severe and prolonged hyperglycemia, (2) presence of high ketones for more than 6 hours, (3) vomiting, diarrhea, and/or abdominal pain (4) inadequate phone contact between healthcare provider and person with diabetes and/or caregiver, or (5) at the discretion of the clinician and/or according to local practice guidelines.

DKA and HHS

The 2009 ADA Hyperglycemic Crises consensus guidelines protocols for the management of patients with DKA and HHS are summarized in Fig. 1. The overall goals in treating DKA are to improve circulatory volume and tissue perfusion, decrease blood glucose, and correct the acidosis and electrolyte imbalances. These objectives usually are accomplished through the administration of low-dose insulin and IV fluid and electrolyte replacement solutions. An initial loading dose of short-acting or rapid-acting insulin is often given IV, followed by IV continuous insulin infusion (CII). Frequent laboratory tests are used to monitor blood glucose, venous pH, creatinine, and serum electrolyte levels and to guide fluid and electrolyte replacement. It is important to replace fluid and electrolytes and correct pH while bringing the blood glucose concentration to a normal level. Too rapid a drop in blood glucose may cause hypoglycemia. A sudden change in the osmolality of extracellular fluid can also occur when blood glucose levels are lowered too rapidly, and this can cause cerebral edema. Serum potassium levels often fall as acidosis is corrected and potassium moves from the extracellular into the intracellular compartment. Thus, it may be necessary to add potassium to the IV infusion. Identification and treatment of the underlying cause, such as infection, also are important.

During treatment of DKA, hyperglycemia is corrected faster than ketoacidosis. The mean duration of treatment until blood glucose is <250 mg/dl (~14 mmol/L) and ketoacidosis (pH >7.30; bicarbonate >18 mEq/L [18 mmol/L) is corrected is 6 and 12 h, respectively. Once the plasma glucose is <200 mg/dl (11.1 mmol/L), 5% dextrose should be added to replacement fluids to allow continued insulin administration until ketonemia is controlled while at the same time avoiding hypoglycemia. For DKA occurring in individuals with type 2 diabetes (i.e. ketosis-prone hyperglycemia), the initial management is similar to standard DKA [5].

In comparison, 2013 JBDS IP group DKA guidelines reflect two major recent developments a) a change in the way patients with DKA present clinically and b) there has been development of rapid near-patient testing technology. Until recently there was no easily available assay for ketone bodies, hence capillary glucose, venous pH and bicarbonate were used to diagnose and monitor response to treatment in DKA. Near patient testing for βHBA is now readily available for

the monitoring of the abnormal metabolite allowing for a shift away from using glucose levels to drive treatment decisions in the management of DKA.

Some of the major recommendations of the 2013 JBDS IP group DKA guidelines includes:

a) Aim to treat the cause of the acidosis (i.e. ketonemia). Subsequently, bedside ketone monitors should be used to measure βHBA, because this is the direct marker of disease severity. The resolution of DKA depends upon the suppression of ketonemia, and measurement of blood ketones now represents best practice in monitoring the response to treatment [15-18].

b) Insulin is given as a standard dose per kg until the ketones are cleared. A weight-based, fixed rate IV insulin infusion (FRIII) via an infusion pump should be used. 50 units short-acting insulin or rapid-acting insulin made up to 50ml with 0.9% sodium chloride solution (resulting concentration of insulin is 1 unit per ml). The initial starting dose of a fixed dose per kg body weight (0.1 units per kg per hour [i.e. 7 units per hour for a 70 Kg individual]) enables rapid blood ketone clearance. The fixed rate may be adjusted if the metabolic targets are not met (i.e. reduction of the blood ketone concentration by at least 0.5 mmol/L/hour; increase in venous bicarbonate concentrations by at least 3 mEq/L/hour [3 mmol/L/hour]); or reduction capillary blood glucose by at least 50 mg/dl/hour [3 mmol/L/hour]). The insulin infusion rate is increased by 1.0 unit/hr increments hourly until the ketones are falling at target rates (also check infusion set for leaks and connection problems).There is no need to give a bolus dose of insulin as long as the CII is set up promptly. Only use a variable-rate IV insulin infusion (VRIII) with 10% dextrose when the blood glucose is <250 mg/dl (~14 mmol/L).

c) Subcutaneous injections of long-acting insulin should be continued if the patient is already using these agents. They provide background insulin when the CII is discontinued, and should avoid excess length of stay. This does not obviate the need for giving short-acting or rapid-acting insulin before discontinuing the CII. Most units

experienced in managing DKA now also continue intermediate-acting insulin (NPH) if that is what the patient normally uses. The CII is thus a “top up” on the (inadequate) background insulin already circulating. Patients presenting with newly diagnosed type 1 diabetes should be given long-acting insulin (or NPH insulin, depending on local policy) at a dose of 0.25 units/Kg subcutaneously once daily to mitigate against rebound ketosis when they are taken off the FRIII [19].

d) Use 0.9% sodium chloride solution for resuscitation, not colloid. If the systolic blood pressure (BP) is <90mmHg, consider causes other than fluid depletion, such as heart failure, sepsis, etc. Give 500 ml of 0.9% sodium chloride solution over 10-15 minutes and repeat if necessary (i.e. fluid challenge). If there has been no improvement in BP, call for urgent senior help. If the systolic BP is >90 mmHg use the typical recommendations outlined in Table 2. More cautious fluid replacement should be considered in young people aged 18-25 years, elderly, pregnant, heart or renal failure (also consider HDU and/or central line). Reduce the rate of fluid replacement in the elderly/cardiac disease/mild-moderate DKA (e.g. bicarbonate >10 mEq/L [10 mmol/l]). More rapid infusion increases risk of ARDS and cerebral edema.

e) Measure venous blood gas for pH, bicarbonate and potassium at 60 minutes, 2 hours and 2 hourly thereafter.

f) Keep potassium between 4.5 and 5.5 mEq/L (4.5-5.5 mmol/L) (Table 3). Hypokalemia and hyperkalemia are life threatening conditions and are common in DKA.

g) Avoid hypoglycemia. If the glucose falls below 250 mg/dl (~14.0 mmol/L), commence 10% dextrose given at 125mls/hour alongside the 0.9% sodium chloride solution. This is to avoid hypoglycemia if the FRIII is still required to drive down the ketones and acidosis.

h) Bicarbonate should not generally be given because it may worsen intracellular acidosis, and it may precipitate cerebral edema, particularly in children and adolescents [20;21].

i) Hypophosphatemia and hypomagnesemia are common in DKA and HHS, however routine replacement is not recommended, unless associated with significant malnutrition.

j) It is expected that by 24 hours the ketonemia (<0.6 mmol/L) and acidosis (venous bicarbonate >15 mEq/L [15 mmol/L]; venous pH >7.3) should have resolved. 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 VRIII. Transfer to subcutaneous insulin if the patient is eating and drinking normally. Ensure that the subcutaneous insulin is started before the IV insulin is discontinued. Ideally give the subcutaneous short-acting or rapid-acting insulin at a meal and discontinue IV insulin one hour later.

k) Where available, the diabetes inpatient team should ideally be involved as early as is practical after admission.

Unlike DKA, guidelines on the management of the HHS in adults are uncommon and often there is little to differentiate them from the management of DKA. However, HHS is different from DKA and treatment requires a different approach. The person with HHS is often elderly, frequently with multiple comorbidities but always very sick. Even when specific hospital guidelines are available, adherence to and use of these is variable amongst inpatient teams. The major goals of treatment of HHS are to gradually and safely normalize the osmolality; replace fluid and electrolyte losses; and normalize blood glucose. Other goals includes identifying and treating the underlying cause; prevent arterial or venous thrombosis; prevent other potential complications (e.g. cerebral edema); and prevent foot ulceration.

Some of the major recommendations of the 2012 JBDS IP group HHS guidelines includes:

(a) Measure or calculate osmolality (2x Na [mEq/L] + glucose [mg/dl)]/18 + BUN [mg/dl]/2.8; or (2x Na [mmol/L] + glucose [mmol/L] + urea [mmol/L]) frequently to monitor the response to treatment.

(b) The goal of the initial therapy is expansion of the intra and extravascular volume and to restore peripheral perfusion. The fluid replacement of choice is 0.9%

sodium chloride. Measurement or calculation of osmolality should be undertaken every hour initially and the rate of fluid replacement adjusted to ensure a positive fluid balance sufficient to promote a gradual decline in osmolality. Urinary fluid losses may be considerable due to osmotic diuresis which may persist for hours as glucose concentrations slowly decrease. The fall in osmolality with lowering of blood glucose and shift of water into the intracellular space inevitably results in a rise in serum sodium. This is not necessarily an indication to give hypotonic solutions (so-called 'isotonic' 0.9% sodium chloride is relatively hypotonic compared to the serum) especially if the person remains clinically hypovolemic. A rise in serum sodium concentration must be interpreted in the context of what is happening to tonicity (effective osmolality). Provided plasma glucose is declining at a safe rate – for example, no-more than 90 mg/dl/hr (5 mmol/L/hr) this will be accompanied by a rise in serum sodium, but a fall in osmolality. Serum sodium concentrations should be frequently monitored, and the concentration of sodium in fluids adjusted to promote a gradual decline in corrected serum sodium. An optimal rate of decline in serum sodium is 0.5 mEq/L (0.5 mmol/L) per hour has been recommended for hypernatremic dehydration. The rate of fall of plasma sodium should not exceed 10-12 mEq/L (10-12 mmol/L) per day. The aim of treatment should be to replace approximately 50% of estimated fluid loss within the first 12 hr and the remainder in the following 12 hours although this will, in part, be determined by the initial severity, degree of renal impairment and associated comorbidities, which may limit the speed of correction.

(c) If significant ketonemia is present (βHBA >1 mmol/L) this indicates relative hypoinsulinemia and insulin should be started at time zero. If significant ketonemia is not present (βHBA <1 mmol/L) insulin should not be started. Fluid replacement alone with 0.9% sodium chloride will result in a drop in blood

glucose and because most patients with HHS are insulin sensitive, there is a risk of lowering the osmolality precipitously. Insulin treatment prior to adequate fluid replacement may result in cardiovascular collapse as water moves out of the intravascular space, with a resulting decline in intravascular volume. Lack of appropriate decline in serum glucose with rehydration should prompt reassessment and evaluation of renal function. Insulin may be started at this point, or if already in place the infusion rate increased (increased by 1 unit/hr). The recommended insulin dose is an FRIII given at 0.05 units per kg per hour (e.g. 4 units/hour in an 80 kg person) is used. A fall of glucose at a rate of up to 90 mg/dl/hr (5 mmol/L/hr) is ideal.

(d) Avoid hypoglycemia. A blood glucose target of between 180 and ~270 mg/dl (10 and 15mmol/L) is a reasonable goal in the first 24 hours. If the blood glucose falls below 180 mg/dl (14 mmol/L), commence 5% or 10% dextrose at 125 ml/h and continue the 0.9% sodium chloride solution.

(e) Potassium replacement. This is the same as DKA and the same principles can be applied using Table 3.

(f) Complete normalization of electrolytes and osmolality may take up to 72 hours.

(g) Assess for any complications of treatment (e.g. fluid overload, cerebral edema, osmotic demyelination syndrome [e.g. a deteriorating conscious level])

(h) Because of the increased risk of arterial and venous thromboembolism, all patients should receive prophylactic LMWH for the full duration of admission unless contraindicated. Consideration should be given to extending prophylaxis beyond the duration of admission in HHS patients deemed to be at high risk.

(i) Discharge planning: because many of these patients have multiple comorbidities, recovery will largely be determined by their previous functional level and the underlying precipitant of HHS. IV insulin can usually be discontinued once they are eating and drinking but their fluids may be required

for longer if intake remains inadequate. Many patients may require conversion to subcutaneous insulin treatment. For patients with previously undiagnosed diabetes or who were well controlled on oral agents, switching from insulin to the appropriate non-insulin therapy should be considered after a period of stability.

(j) Where available, the diabetes inpatient team should ideally be involved as early as is practical after admission.

Treatment of Precipitating Illness

For both DKA and HHS, consider any precipitating causes (especially sepsis) and treat appropriately.

Conclusions

Severe hyperglycemia, DKA, and HHS demand immediate recognition and treatment. However, prevention is of these states is always preferred and this requires appropriate education of patients, carers, and healthcare practitioners on an ongoing basis.

Legends

Figure 1

Protocol for management of adult patients with DKA or HHS. DKA diagnostic criteria: blood glucose 250 mg/dl (13.8 mmol/L), arterial pH 7.3, bicarbonate <15 mEq/l (15 mmol/L), and moderate ketonuria or ketonemia. HHS diagnostic criteria: serum glucose >600 mg/dl, arterial pH >7.3, serum bicarbonate >15 mEq/l, and minimal ketonuria and ketonemia. †15–20 ml/kg/h; ‡serum Na should be corrected for hyperglycemia (for each 100 mg/dl [5.6 mmol/L) > glucose 100 mg/dl (5.6 mmol/L), add 1.6 mEq/l (1.6 mmol/L) to sodium value for corrected serum value). Bwt,body weight; IV, intravenous; SC, subcutaneous.

Table 1

Markers of severity in DKA (taken from Reference 3) and HHS (Taken from Reference 22).

After a diagnosis of DKA or HHS has been made, the presence of any of the following during the admission should prompt a swift senior review and/or indicate admission to a High Dependence Unit (HDU) environment.

GCS, Glasgow Coma Scale; AVPU (Alert, Voice, Pain, Unresponsive) scale

Table 2

Recommended rate of fluid replacement in DKA assuming the individual has normal baseline cardiovascular reserve. (Taken from Reference 3)

Table 3

Recommended rate of potassium replacement in DKA and HHS assuming the individual has normal baseline renal function. (Taken from Reference 3)

Reference List

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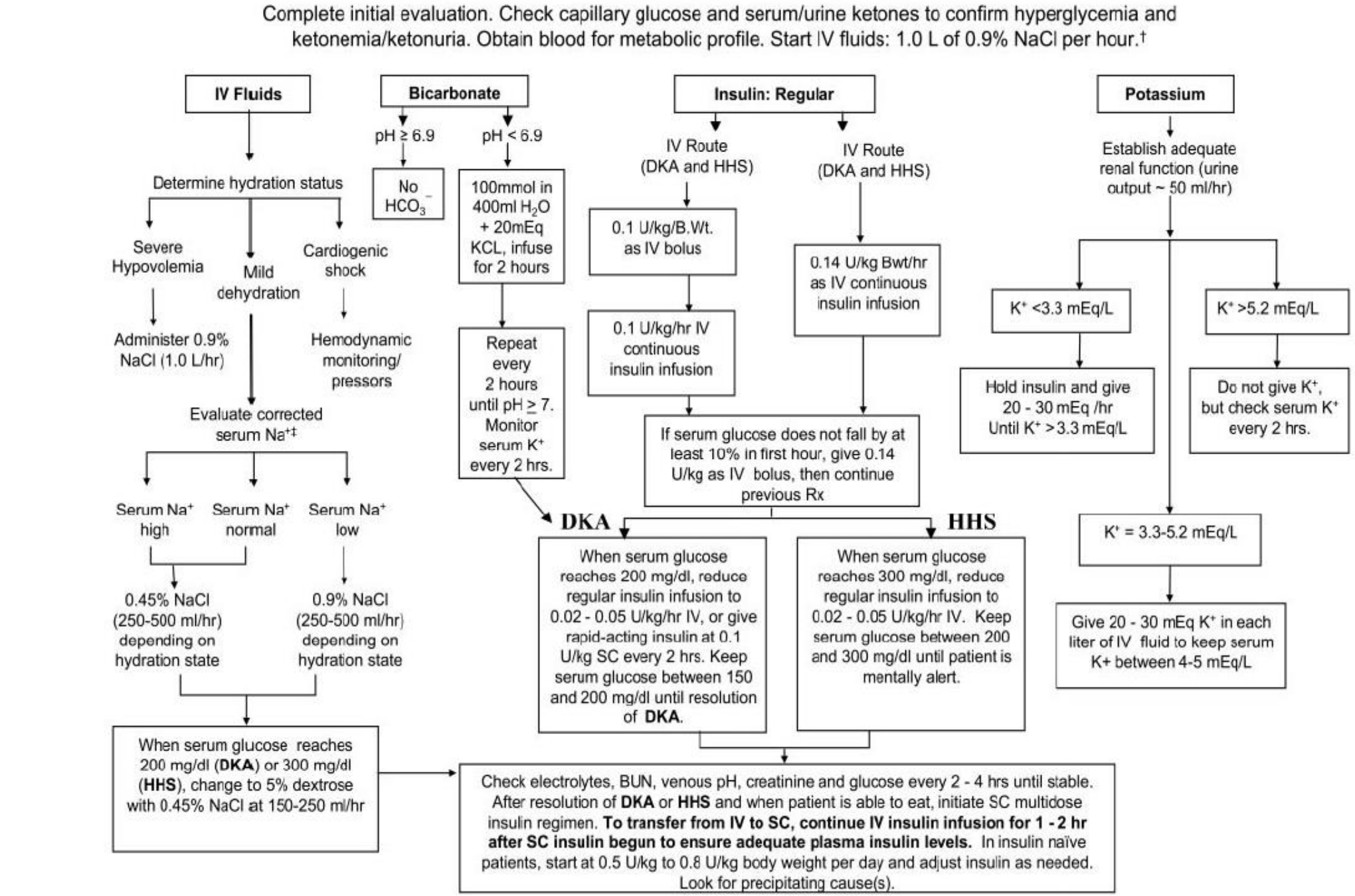
Complete initial evaluation. Check capillary glucose and serum/urine ketones to confirm hyperglycemia and ketonemia/ketonuria. Obtain blood for metabolic profile. Start IV fluids: 1.0 L of 0.9% NaCl per hour.†
IV Fluids
Determine hydration status
Severe Hypovolemia
Mild dehydration
Cardiogenic shock
Administer 0.9% NaCl (1.0 L/hr)
Hemodynamic monitoring/ pressors
Evaluate corrected serum Na+‡
Serum Na+ high
Serum Na+ normal
Serum Na+ low
0.45% NaCl (250-500 ml/hr) depending on hydration state
0.9% NaCl (250-500 ml/hr) depending on hydration state
When serum glucose reaches 200 mg/dl (DKA) or 300 mg/dl (HHS), change to 5% dextrose with 0.45% NaCl at 150-250 ml/hr
Bicarbonate
pH ≥ 6.9
No HCO3−
pH < 6.9
100mmol in 400ml H2O + 20mEq KCL, infuse for 2 hours
Repeat every 2 hours until pH ≥ 7. Monitor serum K+ every 2 hrs.
Insulin: Regular
IV Route (DKA and HHS)
0.1 U/kg/B.Wt. as IV bolus
0.1 U/kg/hr IV continuous insulin infusion
IV Route (DKA and HHS)
0.14 U/kg Bwt/hr as IV continuous insulin infusion
If serum glucose does not fall by at least 10% in first hour, give 0.14 U/kg as IV bolus, then continue previous Rx
DKA
When serum glucose reaches 200 mg/dl, reduce regular insulin infusion to 0.02 - 0.05 U/kg/hr IV, or give rapid-acting insulin at 0.1 U/kg SC every 2 hrs. Keep serum glucose between 150 and 200 mg/dl until resolution of DKA.
HHS
When serum glucose reaches 300 mg/dl, reduce regular insulin infusion to 0.02 - 0.05 U/kg/hr IV. Keep serum glucose between 200 and 300 mg/dl until patient is mentally alert.
Potassium
Establish adequate renal function (urine output ~ 50 ml/hr)
K+ <3.3 mEq/L
Hold insulin and give 20 - 30 mEq /hr Until K+ >3.3 mEq/L
K+ >5.2 mEq/L
Do not give K+, but check serum K+ every 2 hrs.
K+ = 3.3-5.2 mEq/L
Give 20 - 30 mEq K+ in each liter of IV fluid to keep serum K+ between 4-5 mEq/L
Check electrolytes, BUN, venous pH, creatinine and glucose every 2 - 4 hrs until stable. After resolution of DKA or HHS and when patient is able to eat, initiate SC multidose insulin regimen. To transfer from IV to SC, continue IV insulin infusion for 1 - 2 hr after SC insulin begun to ensure adequate plasma insulin levels. In insulin naïve patients, start at 0.5 U/kg to 0.8 U/kg body weight per day and adjust insulin as needed. Look for precipitating cause(s).

Figure 1

Table 1

Marker of Severity	DKA (JBDS IP Group 2013)	HHS (JBDS IP Group 2012)
Mental Status	GCS <12 or abnormal AVPU	GCS <12 or abnormal AVPU
Oxygen saturation	<92% on air (assuming normal baseline respiratory function)	<92% on air (assuming normal baseline respiratory function)
Venous/arterial pH	pH <7.1	pH <7.1
Potassium	Hypokalemia (< 3.5 mEq/L [3.5 mmol/L]) or Hyperkalemia (> 6 mEq/L [6 mmol/L)	Hypokalemia (< 3.5 mEq/L [3.5 mmol/L]) or Hyperkalemia (> 6 mEq/L [6 mmol/L)
Systolic blood pressure	<90 mmHg	<90 mmHg
Pulse	>100 or <60 bpm	>100 or <60 bpm
Urine output	<0.5 mls/Kg/hr or other evidence of acute kidney injury (AKI)	<0.5 mls/Kg/hr or other evidence of acute kidney injury (AKI)
Blood ketones	>6 mmol/L	>1 mmol/L
Bicarbonate level	<5 mEq/L (5 mmol/L)	
Anion gap	>16 mEq/L (16 mmol/L)	
Sodium		>160 mEq/L (160 mmol/L)

Osmolality		>350 mosm/kg
Miscellaneous		Hypothermia Acute or serious comorbidity (e.g. ACS, heart failure, or Stroke)

Table 2

Fluid	Volume
0.9% sodium chloride 1L	1000 ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000 ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000 ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000 ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000 ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000 ml over next 4 hours
Re-assessment of cardiovascular status at 12 hours is mandatory, further fluid may be required	

Table 3

Potassium level in first 24 hours (mEq/L [mmol/L])	Potassium replacement in mEq/L (mmol/L) of infusion solution
Over 5.5	Nil
3.5-5.5	40 mEq/L (40 mmol/L)
Below 3.5	Senior review because additional potassium needs to be given