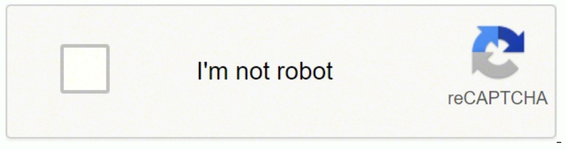

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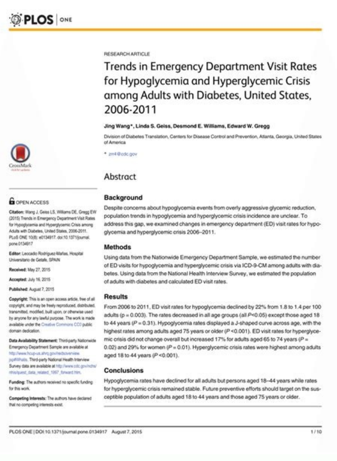

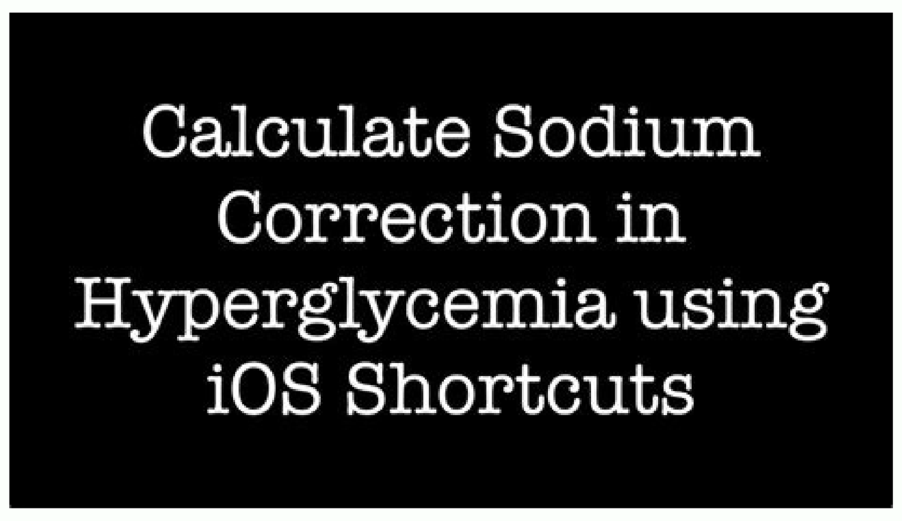

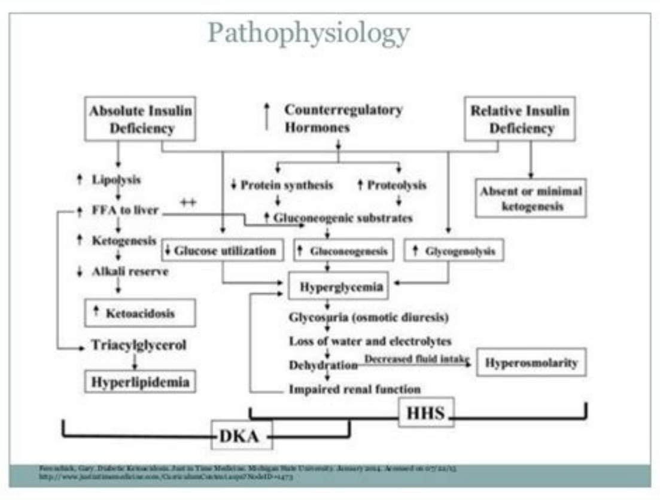

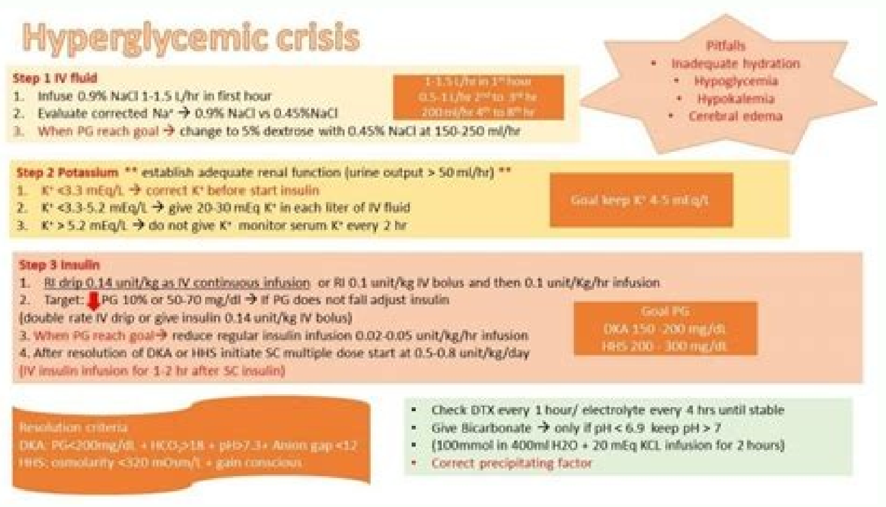

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Phosphate administration may result in hypocalcemia when used in high dose (139,142).A similar therapeutic approach can be also recommended for treatment of HHS, but no bicarbonate therapy is needed for HHS, and changing to glucose-containing fluid is done when blood glucose reaches 300 mg/dL.Protocol for the management of adult patients with HHS.Severe hyperosmolarity and dehydration associated with insulin resistance and presence of detectable plasma insulin level are the hallmarks of HHS pathophysiology. Our study showed that glucose, bicarbonate, BUN and osmolality, and not pH were significantly different between non-comatose and comatose patients. Umpierrez GE, Kelly JP, Navarrete JE, Casals MM, Kitabchi AE. 1998;158(16):1799–1802. Nephrol Dial Transplant. 1933;12(2):297–326. For example, DKA patients with concomitant fever or sepsis may have additional respiratory alkalosis manifesting by lower-than-expected PCO_2. In 2010, among adults aged 20 years or older, hyperglycemic crisis caused 2,361 deaths (15). Am Fam Physician. 2004;53(8):2079–2086. Increased lipolysis and its consequences on gluconeogenesis in non-insulin-dependent diabetes mellitus. Suggested approaches for the management of patients with DKA and HHS are illustrated in Figures 9 and 10.DKA and HHS are volume-depleted states with total body water deficit of approximately 6 L in DKA and 9 L in HHS (16,118,119). Patients must be advised to continue insulin and to seek professional advice early in the course of the illness. 1986;12(5-6):383–389. [PubMed: 6430087]147.Kamel KS, Halperin ML. 1995;12(2):76–8. DKA and HHS remain important causes of morbidity and mortality among diabetic patients despite well-developed diagnostic criteria and treatment protocols (1). 2004;117(5):291–296. 1979;90(1):36–42. Plasma acid-base patterns in diabetic ketoacidosis. 1971;50(8):1702–1711. 2015;38(9):1687–1693. Effects of acute insulin deficiency on glucose and ketone body turnover in man: evidence for the primacy of overproduction of glucose and ketone bodies in the genesis of diabetic ketoacidosis. 1994;32(1):85–87. 1997;86(11):1172–1176. 1989;5(3):271–284. A dose-defining insulin algorithm for attainment and maintenance of glycemic targets during therapy of hyperglycemic crises. Despite the excessive water loss, the admission serum sodium tends to be low. Hyperchloremic acidosis is caused by the loss of large amounts of ketoanions, which are usually metabolized to bicarbonate during the evolution of DKA, and excess infusion of chloride containing fluids during treatment (150).Cerebral edema, a frequently fatal complication of DKA, occurs in 0.7–1.0% of children, particularly those with newly diagnosed diabetes (120). [PubMed: 237799]86.Edge JA, Roy Y, Bergomi A, Murphy NP, Ford-Adams ME, Ong KK, Dunger DB. BMJ. 1979;67(5):897–900. The pathogenesis of pulmonary edema may be similar to that of cerebral edema suggesting that the sequestration of fluid in the tissues may be more widespread than is thought. Nonspecific hyperamylasemia and hyperlipasemia in diabetic ketoacidosis: incidence and correlation with biochemical abnormalities. Acetoacetate and beta-hydroxybutyrate differentially regulate endothelin-1 and vascular endothelial growth factor in mouse brain microvascular endothelial cells. 1975;233(2):166–168. Arch Intern Med. SGLT2 inhibitors and diabetic ketoacidosis: data from the FDA Adverse Event Reporting System. [PMC free article: PMC5505435] [PubMed: 28745091]173.Cardona-Hernandez R, Schwandt A, Alkandari H, Bratke H, Chobot A, Coles N, Corathers S, Goksen D, Goss P, Imane Z, Nagl K, O'Riordan SMP, Jefferies C, Group SS. [PubMed: 2105195]121.Pasquel FJ, Umpierrez GE. DIABETIC ACIDOSIS: A Detailed Study of Electrolyte Balances Following the Withdrawal and Reestablishment of Insulin Therapy. 2011;34(9):1891–1896. Pathogenesis of cerebral edema after treatment of diabetic ketoacidosis. Active use of cocaine: an independent risk factor for recurrent diabetic ketoacidosis in a city hospital. HbA1c may be useful in differentiating chronic hyperglycemia of uncontrolled diabetes from acute metabolic decompensation in a previously well-controlled diabetic patient (17). The common clinical presentation of DKA and HHS is due to hyperglycemia and include polyuria, polyphagia, polydipsia, weight loss, weakness, and physical signs of intravascular volume depletion, such as dry buccal mucosa, sunken eye balls, poor skin turgor, tachycardia, hypotension and shock in severe cases. Diabetic ketoacidosis and infection: leukocyte count and differential as early predictors of serious infection. Hypothermia in diabetic acidosis. (1).The two most common precipitating factors in the development of DKA or HHS are inadequate insulin therapy (whether omitted or insufficient insulin regimen) or the presence of infection (46,47). 1988;113(1 Pt 1):10–14. 2000;95(11):3123–3128. Recent advances in the monitoring and management of diabetic ketoacidosis. Hyperamylasemia, which correlates with pH and serum osmolality and elevated level of lipase, may occur in 16 - 25% of patients with DKA (106). Drugs such as corticosteroids, thiazide diuretics, sympathomimetic agents (e.g., dobutamine and terbutaline), and second generation antipsychotic agents may precipitate DKA or HHS (17). In this condition the plasma becomes milky and lipemia retinalis may be visible in physical examination (100). [PubMed: 11194218]9.Matz R. Additionally, since β-OHB is converted to acetoacetate during treatment (109), the serum ketone test may remain positive for a prolonged period suggesting erroneously that ketonemia is deteriorating; therefore, the follow up measurement of ketones during the treatment by nitroprusside method is not recommended (16). Influence of endogenous insulin secretion on splanchnic glucose and amino acid metabolism in man. Diagnosis of mixed acid-base disorders in diabetic ketoacidosis. However, patients with severe DKA (low bicarbonate 3.3 mmol/L (8). 1980;3(1):53–56. Close observation, early detection of symptoms and appropriate medical care would be helpful in preventing HHS in the elderly.A study in adolescents with T1D suggests that some of the risk factors for DKA include higher HbA1c, uninsured children, and psychological problems (168). Role of glucagon and other hormones in development of diabetic ketoacidosis. A) Incidence of DKA 1980-2009 B) Crude and Age-Adjusted Death Rates for Hyperglycemic Crises as Underlying Cause per 100,000 Diabetic Population, United States, 1980–2009 C) Age-Adjusted DKA hospitalization rate per 1,000 persons with diabetes and in-hospital case-fatality rate, United States, 2000–2014 (5).DKA consists of the biochemical triad of hyperglycemia, ketonemia, and high anion gap metabolic acidosis (19) (Figure 2). In young patients with T1D, insulin omission due to fear of hypoglycemia or weight gain, the stress of chronic disease, and eating disorders, may contribute in 20% of recurrent DKA (57). [PubMed: 28183452]123.Fisher JN, Shahshahani MN, Kitabchi AE. [PMC free article: PMC4542270] [PubMed: 26078479]79.Umpierrez G, Freire AX. [PubMed: 805337]92.Harden CL, Rosenbaum DH, Daras M. The goal is to replace half of the estimated water and sodium deficit over a period of 12-24 hours [161]. It is important to start HHS therapy with the infusion of normal saline and monitor corrected serum sodium in order to determine appropriate timing of the change to hypotonic fluids. [PubMed: 9536592]64.Vidal Cortada J, Conget Donlo JI, Navarro Tellez MP, Halperin Rabinovic I, Vilardell Latorre E. Diabetes Metab Res Rev. The latter may take twice as long as to achieve blood glucose control. 2020;43(2):349–357. Furthermore, muscle glycogen is catabolized to lactic acid via glycogenolysis. [PubMed: 3543638]91.Guisado R, Arieff AI. [PubMed: 805854]81.Matz R. These ketosis-prone type 2 diabetic patients develop sudden-onset impairment in insulin secretion and action, resulting in profound insulinopenia (66). Abdominal pain, which correlates with the severity of acidosis (79), may be severe enough to be confused with acute abdomen in 50-75% of cases (80). [PubMed: 24569496]100.Kaminska ES, Pourmotabbed G. Diabet Med. The levels of these factors return to normal after insulin therapy and correction of hyperglycemia (42). [PubMed: 8238083]117.Freidenberg GR, Kosnik EJ, Sotos JF. Prevention of hypophosphatemia by phosphate infusion during treatment of diabetic ketoacidosis and hyperosmolar coma. [PubMed: 2656155]38.McGarry JD, Woeltje KF, Kuwajima M, Foster DW. Data are % of all cases except Nyenwe et al where new onset disease was not included in the percentage and complete data on these items were not given; therefore, the total is less than 100%. 1976;84(6):633–638. [PubMed: 29342264]172.Parkin CG, Graham C, Smolskis J. Hyperglycemic, high anion-gap metabolic acidosis in patients receiving SGLT-2 inhibitors for diabetes management. [PMC free article: PMC6973545] [PubMed: 30728224]77.Ahmed M, McKenna MJ, Crowley RK. 1980;3:15-20. Characteristics of and Mortality Associated With Diabetic Ketoacidosis Among US Patients Hospitalized With or Without COVID-19. Abdominal pain in diabetic metabolic decompensation. High prevalence of glucose-6-phosphate dehydrogenase deficiency without gene mutation suggests a novel genetic mechanism predisposing to ketosis-prone diabetes. Diabetic ketoacidosis is also characterized by increased gluconeogenesis, lipolysis, ketogenesis, and decreased glycolysis (16).In DKA, there is a severe alteration of carbohydrate, protein, and lipid metabolism (8). Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. It also occurs in T2D under conditions of extreme stress, such as serious infection, trauma, cardiovascular or other emergencies, and, less often, as a presenting manifestation of T2D, a disorder called ketosis-prone T2D (16). Management of the hyperosmolar hyperglycemic syndrome. 2006;49:2002-2009. Intravascular volume expansion reduces serum blood glucose, BUN, and potassium levels without significant changes in pH or HCO_3.The mechanism for lowering glucose is believed to be due to osmotic diuresis and modulation of counter-regulatory hormone release (23,120). Ann Intern Med. There was a decline in mortality from 2000 to 2014 across all age groups and both sexes with largest absolute decrease among persons aged ≥75 years (5). 2021 [PubMed: 33653821]174.Fleming N, Hamblin PS, Story D, Ekinci EI. 1987;3(1):111–126. An electrocardiogram, blood, urine or sputum cultures and chest X-ray should also be performed, if indicated. Clinically, they differ by the severity of dehydration, ketosis, and metabolic acidosis (17).DKA most often occurs in patients with T1D. Clin Chem. 2014;37(11):3124–3131. Decreased glucose utilization is further exaggerated by increased levels of circulating catecholamines and FFA (34).Excess catecholamines coupled with insulinopenia promote triglyceride breakdown (lipolysis) to free fatty acids (FFA) and glycerol in adipose tissue. This inflammatory and procoagulant state may explain the well-known association between hyperglycemic crisis and thrombotic state (43,44).While DKA is a state of near absolute insulinopenia, there is sufficient amount of insulin present in HHS to prevent lipolysis and ketogenesis but not adequate to cause glucose utilization (as it takes 1/10 as much insulin to suppress lipolysis as it does to stimulate glucose utilization) (33,34). 2018;41(8):1631–1638. 1986;105(6):836–840. [PubMed: 109338]29.Foster DW, McGarry JD. 2004;27:1541-1546. [PubMed: 10628611]133.Glaser NS, Wootton-Gorges SL, Marcin JP, Buonocore MH, Dicarlo J, Neely EK, Barnes P, Bottomly J, Kuppermann N. 1997;157:669-675. [PubMed: 402311]142.Winter RJ, Harris CJ, Phillips LS, Green OC. [PubMed: 20103820]154.Hoorn EJ, Carlotti AP, Costa LA, MacMahon B, Bohn G, Zietse R, Halperin ML, Bohn D. 1987;147(3):499–501. There are also case reports of patients with DKA as the primary manifestation of acromegaly (62-64).Increasing numbers of DKA cases have been reported in patients with Type 2 DM. 1996;311(5):225–233. Quantitative displacement of acid-base equilibrium in metabolic acidosis. 1990;13(1):22–33. An 8-year study in schools and private practices. [PubMed: 4915800]42.Stentz FB, Umpierrez GE, Cuervo R, Kitabchi AE. Nivolumab, an Anti-Programmed Cell Death-1 Antibody, Induces Fulminant Type 1 Diabetes. The case for venous rather than arterial blood gases in diabetic ketoacidosis. Understanding and prompt awareness of potential special situations such as DKA or HHS presentation in the comatose state, possibility of mixed acid-base disorders obscuring the diagnosis of DKA, and risk of brain edema during therapy are important to reduce the risks of complications without affecting recovery from hyperglycemic crisis. Evolving Evidence of Diabetic Ketoacidosis in Patients Taking Sodium-Glucose Cotransporter 2 Inhibitors. 2020;43(12):e196–e197. [PMC free article: PMC442833] [PubMed: 1729269]37.Balasse EO, Fery F. New perspectives in the regulation of ketogenesis. Effectiveness of a prevention program for diabetic ketoacidosis in children. Gluconeogenesis and its regulation. The relationship of depressed consciousness and severity of hyperosmolality or DKA causes has been controversial (82,83). Fluid resuscitation in diabetic emergencies--a reappraisal. To prevent hypokalemia, potassium replacement is initiated after serum levels fall below 5.3 mmol/L in patients with adequate urine output (50 ml/h). [PubMed: 26278296]45.Gerich JE, Martin MM, Recant L. Kussmaul respiration, acetone breath, nausea, vomiting, and abdominal pain may also occur primarily in DKA and are due to ketosis and acidosis. Nevertheless, in a recent retrospective study, both severe hypokalemia defined as K ≤ 2.5 mEq/L and severe hypoglycemia < 40 mg/dL were significantly and independently associated with increased risk of mortality in patients admitted to the tertiary care center for treatment of hypoglycemic crisis (18). Prophylactic use of heparin, if there is no gastrointestinal hemorrhage, should be considered.About one in five patients with T1D admitted for DKA will be readmitted for DKA within 30 days (162). [PubMed: 17360297]59.Warner EA, Greene GS, Buchsbaum MS, Cooper DS, Robinson BE. In people with T2D, low-carbohydrate diet, excessive ETOH intake, presence of autoimmunity, and/or exposure to stress situations such as infection, surgery, trauma, dehydration are now identified as DKA risk factors in those treated with SGLT-2 inhibitors (50,76).Common precipitating factors in DKA. The UK case-control study of cerebral oedema complicating diabetic ketoacidosis in children. Timely diagnosis, comprehensive clinical and biochemical evaluation, and effective management is key to the successful resolution of DKA and HHS. Regulation of ketogenesis and the renaissance of carnitine palmitoyltransferase. Chiasson JL, Aris-Jilwan N, Bélanger R, et al. The levels of β-hydroxybutyrate (β-OHB) of ≥3.8mmol/L measured by a specific assay were shown to be highly sensitive and specific for DKA diagnosis (93). Clinical practice guideline on diagnosis and treatment of hyponatraemia. 1983;57(1):177–180. Over 30% of patients have features of both DKA and HHS (16) with most recent evidence confirming that about 1 out of 4 patients will have both conditions at the time of presentation with hyperglycemic crisis (18). Ketosis-prone diabetes--a new subgroup of patients with atypical type 1 and type 2 diabetes? 1999;42(2):128–138. [PubMed: 31548241]74.75.Pasquel FJ, Messler J, Booth R, Kubacka B, Mumpower A, Umpierrez G, Aloi J. 1981;18(2):123–128. Emerg Med Australas. [PubMed: 16043723]129.Atchley DW, Loeb RF, Richards DW, Benedict EM, Driscoll ME. Therefore, inappropriately high or low levels of PCO_2, determined by ABG will suggest the presence of a mixed acid-based disorder. Association of socioeconomic status and DKA readmission in adults with type 1 diabetes: analysis of the US National Readmission Database. In contrast, a higher than calculated PCO_2 level signifies additional respiratory acidosis and can be seen in patients with underlying chronic lung disease. Neurologic manifestations of diabetic comas: correlation with biochemical alterations in the brain. 2018;41(12):e150–e151. [PubMed: 3101715]104.Razavi Nematollahi L, Kitabchi AE, Stentz FB, Wan JY, Larijani BA, Tehrani MM, Gozashti MH, Omidfar K, Taheri E. This is observed due to several reasons. Phosphate depletion in DKA is universal but on admission, like the potassium, it may be low, normal or high (102).The differences and similarities in the admission biochemical data in patients with DKA or HHS are shown in Figure 7.Biochemical data in patients with HHS and DKA (1).Leukocytosis is a common finding in patients with DKA or HHS, but leukocytosis greater than 25,000 /μL suggests ongoing infection requiring further work up (103). It should be emphasized that urinary losses of water and electrolytes are also need to be considered.The cornerstone of DKA and HHS therapy is insulin in physiologic doses. Phosphorus deficiency and hypophosphatemia. Osmotic diuresis and ketonuria also promote a total body sodium deficit via urinary losses, although concurrent conditions, such as diarrhea and vomiting, can further contribute to sodium losses. Hyperamylasemia in diabetic ketoacidosis: sources and significance. Serum beta-hydroxybutyrate measurement in patients with uncontrolled diabetes mellitus. Proinflammatory cytokines in response to insulin-induced hypoglycemic stress in healthy subjects. I. 2003;88(11):5090–5098. 1976;136:987-990. [PubMed: 6766521]3.Ramphul K, Joynauth J. In that study, a combination of acidosis and hyperosmolarity at presentation may identify a subset of patients with severe DKA (7% in this study) who may benefit from more aggressive treatment and monitoring. In cases when the serum glucose concentration improves to a greater extent than the serum sodium concentration rises, serum effective osmolality will decrease and may precipitate brain edema (153,154). Diabetes care. [PubMed: 7389550]171.Charleer S, Mathieu C, Nobels F, De Block C, Radermecker RP, Hermans MP, Taes Y, Vercammen C. In HHS, the reduction in insulin infusion rate and/or use of D5 ½ NS should be started when blood glucose reaches 300 mg/dL, because overzealous use of hypotonic fluids has been associated with the development of cerebral edema (121). 2004;53(3):645–653. [PubMed: 9083292]153.Haringhuizen A, Tjan DH, Grool A, van Vugt R, van Zante AR. Metabolism: clinical and experimental. Acid-base aspects of ketoacidosis. Acetone metabolism in humans during diabetic ketoacidosis. Am J Med Sci. Annals of internal medicine. Recent analyses suggested that patients who are black, female, and/or having Medicaid insurance had the highest risk of being admitted with DKA (3).Hyperglycemic Crises. 2006;18(1):64–67. More frequently, the initial serum potassium level is normal or low which is a danger sign. The latter provides a carbon skeleton for gluconeogenesis, while the former serves as a substrate for the formation of ketone bodies (35,36). Mechanical problems with continuous subcutaneous insulin infusion (CSII) devices can precipitate DKA (60); however, with an improvement in technology and better education of patients, the incidence of DKA have been declining in insulin pump users (61). High Growth-Hormone Levels in Diabetic Ketoacidosis: A Possible Cause of Insulin Resistance. [PMC free article: PMC435909] [PubMed: 16694129]130.Beigelman PM. [PubMed: 10030312]111.Porter WH, Yao HH, Karounos DG. Clinical Outcomes in Patients With Isolated or Combined Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State: A Retrospective, Hospital-Based Cohort Study. Education of the patient about sick day management is very vital to prevent DKA, and should include information on when to contact the health care provider, blood glucose goals, use of insulin, and initiation of appropriate nutrition during illness and should be reviewed with patients periodically. Predictors of intensive care unit and hospital length of stay in diabetic ketoacidosis. The influence of blood hydrogen ion concentration on the level of consciousness in diabetic ketoacidosis. [PubMed: 6828000]115.Bjellerup P, Kallner A, Kollind M. 2012;23(3):238–240. The initial fluid of choice is isotonic saline at the rate of 15–20 ml /kg body weight per hour or 1–1.5 L during the first hour. 1983;309(3):159–169. Extracellular and intracellular buffers neutralize hydrogen ions produced during hydrolysis of ketoacids. Hyperglycemic Emergencies in Adults. Lancet. In other studies, education of primary care providers and school personnel in identifying the signs and symptoms of DKA has been shown to be effective in decreasing the incidence of DKA at the onset of diabetes (169). Diabetes Manage. [PubMed: 12663577]62.63.Szeto CC, Li KY, Ko GT, Chow CC, Yeung VT, Chan JC, Cockram CS. In DKA, we recommend using intravenous (IV) bolus of regular insulin (0.1 u/kg body weight) followed by a continuous infusion of regular insulin at the dose of 0.1u/kg/hr. Neurological status in patients with DKA may vary from full alertness to a profound lethargy and coma, However, mental status changes in DKA are less frequent than HHS. The DEEARAILS pneumonic can help recalling these clinical situations.Precipitating factors for DKA in patients taking SGLT2 inhibitors. Occasionally, patients with HHS may present with focal neurological deficits and seizures (91,92). The change in HCO_3^- concentration (Δ HCO_3^-/normal serum HCO_3^- – observed serum HCO_3^-) usually corresponds to equal changes in serum anion gap (Δ AG/observed AG – normal AG, both corrected for decreases and increases in plasma albumin concentration). QJM. An equivalent arterial pH value is calculated by adding 0.03 to the venous pH value (144). The mortality rate for DKA and hyperglycemic crises has been falling over the years (Figure 1b) (4) with estimates of fatality remaining under 1% for DKA (3); mortality can reach up to 20% in HHS (14). Initiation of insulin therapy, which leads to the transfer of potassium into cells, may cause fatal hypokalemia if potassium is not replaced early. Plasma norepinephrine and epinephrine in untreated diabetics, during fasting and after insulin administration. [PubMed: 1765864]48.Fadini GP, Bonora BM, Avogaro A. Marliss EB, Ohman JL Jr, Aoki TT, Kozak GP. 1999;60(5):1468–1476. 1982;307(26):1603–1610. 2018;103(3):1224–1232. [PubMed: 10064091]35.McGarry JD. Hyperosmolar nature of diabetic coma. Figure 6 summarizes the biochemical criteria for DKA and HHS and electrolyte deficits in these two conditions. It also provides a simple method for calculating anion gap and serum osmolality.Diagnostic Criteria and Typical Total Body Deficits of Water and Electrolytes in Diabetic Ketoacidosis (DKA) and Hyperglycemic Hyperosmolar Syndrome (HHS)DKA can be classified as mild, moderate, or severe based on the severity of metabolic acidosis and the presence of altered mental status (17). viii. Am J Gastroenterol. Collateral Damage: Insulin-Dependent Diabetes Induced With Checkpoint Inhibitors. 1968;69(5):891–901. Hyperchloremic acidosis during the recovery phase of diabetic ketosis. [PubMed: 10333896]170.Runyan JW Jr, Zwaag RV, Joyner MB, Miller ST. [PubMed: 5698485]22.Kitabchi AE, Ayyagari V, Guerra SM. 1983;32(3):308–315. However, our study in children demonstrated the effectiveness of intravenous injection of insulin without a bolus dose (125). Flatbush diabetes. Hyperosmolarity and acidosis in diabetes mellitus: a three-year experience in Rhode Island. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. [PubMed: 12663608]164.Musey VC, Lee JK, Crawford R, Klatka MA, McAdams D, Phillips LS. Counterproductive effects of sodium bicarbonate in diabetic ketoacidosis. [PubMed: 3920521]135.Okuda Y, Adrogue HJ, Field JB, Nohara H, Yamashita K. GLC determination of serum-ethylene glycol, interferences in ketotic patients. Ultimately, the amount of excreted ketoanions depends on degree of kidney function preservation with the largest amount of ketoanion loss in patients with relatively preserved glomerular filtration rate (145). Therefore, elevated pancreatic enzymes may not be reliable for the diagnosis of pancreatitis in the DKA setting. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, and empagliflozin) that are used for diabetes treatment have been implicated in the development of DKA in patients with both T1D and T2D (48). [PMC free article: PMC7301161] [PubMed: 30305348]57.Polonsky WH, Anderson BJ, Lohrer PA, Aponte JE, Jacobson AM, Cole CF. 1987;19(1):23–25. The administration of continuous IV infusion of regular insulin is the preferred route because of its short half-life and easy titration and the delayed onset of action and prolonged half-life of subcutaneous regular insulin. 2010;68(1):35–37. Subclinical brain swelling in children during treatment of diabetic ketoacidosis. 2011;1:397-412. 2004;145(2):164–171. Hyperglycemic crises in diabetes mellitus: diabetic ketoacidosis and hyperglycemic hyperosmolar state. In patients with new onset diabetes, a multi-dose insulin regimen should be started at a dose of 0.5-0.8 U/kg per day, including regular or rapid-acting and basal insulin until an optimal dose is established (17).The most common complications of DKA and HHS include hypoglycemia and hypokalemia due to overzealous treatment with insulin and bicarbonate (hypokalemia), but these complications occur infrequently with current low dose insulin regimens. [PubMed: 12020331]169.Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacalone T, Chiarelli F. More recently, it has been proposed that consciousness level in adolescents with DKA was related to the severity of acidosis (pH) and not to a blood glucose levels (86). Patients who received intravenous insulin attained an immediate pharmacologic level of insulin concentration. Immediate discontinuation of intravenous insulin may lead to hyperglycemia or recurrence of ketoacidosis. Diabetic ketoacidosis in a community-based population. 2003;168:859-866. [PubMed: 6309004]139.Fisher JN, Kitabchi AE. In addition, Δ-Δ ratio will be over 2 suggesting that there is less than expected reduction in bicarbonate as compared with increase in AG and confirm the presence of a mixed acid-base disorder (combination of metabolic acidosis and metabolic alkalosis). J Clin Endocrinol Metab. The Long-Term Incidence of Hospitalization for Ketoacidosis in Adults with Established T1D-A Prospective Cohort Study. Therefore, in the presence of acidosis, DKA as an etiology of abdominal pain should be considered. 1980;50(1):131–136. 1975;24(5):665–679. 1999;22(9):1517–1523. 1992;89(1):169–175. Ketosis-prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of beta-cell dysfunction and insulin resistance. Neth J Med. Severe dehydration, older age, and the presence of comorbid conditions in patients with HHS account for the higher mortality in these patients (17). [PubMed: 5952215]132.Viallon A, Zeni F, Lafond P, Venet C, Tardy B, Page Y, Bertrand JC. 2014.16.Kitabchi AE, Nyenwe EA. 2006;7(1):11–15. The syndrome of alcoholic ketoacidosis. Intracerebral crises during treatment of diabetic ketoacidosis. [PubMed: 17452217]155.Smedman L, Escobar R, Hesser U, Persson B. Predisposing factors for the diabetic hyperosmolar state. 1996;81(1):314–320. 1998;31(1):41–48. As glucose concentration improves following insulin infusion and administration of the intravenous fluids, serum osmotic gradient previously contributed by hyperglycemia reduces which limits water shifts from the intracellular compartment. Avoidance or temporary discontinuation of SGLT-2 inhibitors in clinical situations that independently increase risk of intravascular volume depletion and/or development of ketosis-prone conditions listed in the Figure 11 can mitigate the DKA risk. [PubMed: 111594]107.Yadav D, Nair S, Norkus EP, Pitchumoni CS. Laboratory and clinical evaluation of assays for beta-hydroxybutyrate. Therefore, it would appear that if intravenous insulin is used, priming or bolus dose insulin might not be necessary.Several clinical studies have shown the potency and cost effectiveness of subcutaneous rapid-acting insulin analogs (lispro or aspart) in the management of patients with uncomplicated mild to moderate DKA (126,127). 2017;60(8):1385–1389. In addition, numerous underlying medical illness and medications that cause the release of counter regulatory hormones and/or compromise the access to water can result in severe volume depletion and HHS (46). Adapted from (94).The use of bicarbonate in treatment of DKA remains controversial. 2009;32:1335-1343. 1975;24(6):594–599. Given the increased DKA risks associated with HbA1c ≥ 9% in patients with T1D, all efforts should be applied to understand and potentially address reasons for poor chronic glycemic control as this may prevent DKA admission. [PubMed: 2004625]93.Sheikh-Ali M, Karon BS, Basu A, Kudva YC, Muller LA, Xu J, Schwenk WF, Miles JM. Economic impact of diabetic ketoacidosis in a multiethnic indigent population: analysis of costs based on the precipitating cause. Diabetic ketoacidosis associated with cocaine use. 1980;29(11):926–930. 2021;4(3):e211091. Altered redox state obscuring ketoacidosis in diabetic patients with lactic acidosis. [PubMed: 406561]124.Sacks HS, Shahshahani M, Kitabchi AE, Fisher JN, Young RT. [PubMed: 122259]24.Muller WA, Faloona GR, Unger RH. Can J Diabetes. The patients received subcutaneous rapid-acting insulin doses of 0.2 U/kg initially, followed by 0.1 U/kg every 1 hour or an initial dose of 0.3 U/kg followed by 0.2 U/kg every 2 hours until blood glucose was < 250 mg/dL. The hospitalization rates for DKA and amputation were decreased by 69% due to continuing care and education (170). Crit Care Med. 1997;51(4):1237–1244. 2006;29(12):2739–2748. CfDCa. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Critical components of the hyperglycemic crises' management include coordinating fluid resuscitation, insulin therapy, and electrolyte replacement along with the continuous patient monitoring using available laboratory tools to predict the resolution of the hyperglycemic crisis. There is early evidence that use of continuous glucose monitoring (CGM) can decrease DKA incidence (171,172). Acromegaly in a woman presenting with diabetic ketoacidosis and insulin resistance. If deteriorating clinical symptoms occur, the mortality rate may become higher than 70%, with only 7–14% of patients recovering without permanent neurological deficit. As mentioned earlier, when plasma glucose reaches 200-250 mg/dL in DKA or 300 in HHS, insulin rate should be decreased to 0.05 U/kg/hr, followed, as indicated, by the change in hydration fluid to D5 ½ NS. [PubMed: 28500396]49.Bonora BM, Avogaro A, Fadini GP. 2018;35(1):12–32. Therapeutic implications. 1970;282(12):668–675. Its prevalence and significance. 2000;16(5):316–324. 1979;25(3):496–497. Clinical and metabolic features of these patients include high rates of obesity, a strong family history of diabetes, a measurable pancreatic insulin reserve, and a low prevalence of autoimmune markers of β-cell destruction (67-69). [PubMed: 6802095]103.Slovis CM, Mork VG, Slovis RJ, Bain RP. [PubMed: 22356837]44.Wakabayashi S, Tsujimoto T, Kishimoto M, Ikeda N, Inoue K, Ihana N, Hamasaki H, Noto H, Yamamoto-Honda R, Kajio H, Noda M. 2016;22(6):753-762. [PMC free article: PMC442070] [PubMed: 5097575]32.Hue L. [PubMed: 102229]151.Duck SC, Wyatt DT. An Update on the Incidence and Burden of Diabetic Ketoacidosis in the U.S. Diabetes care. However, some of them may have ketonemia. Diabetic ketoacidosis charges relative to medical charges of adult patients with type I diabetes. However, patients who received intravenous insulin showed a more rapid decline in blood glucose and ketone bodies in the first 2 hours of treatment. However, in our recent retrospective study, it was shown that acidosis was independently associated with altered sensorium, but hyperosmolarity and serum "ketone" levels were not (88) (Figure 5). In general, the body is shifted into a major catabolic state with breakdown of glycogen stores, hydrolysis of triglycerides from adipose tissues, and mobilization of amino acids from muscle (16). 2018;67(12):362–365. 1970;283:978-980. Insulin therapy, correction of acidosis, and volume expansion decrease serum potassium concentrations. Each ketoanion can be converted back to HCO_3^- during resolution of DKA and, therefore, ketoanion loss results in the loss of HCO_3^-. LADA= latent autoimmune diabetes in adults1.2.Johnson DD, Palumbo PJ, Chu CP. 1998;6(4):53–62. [PubMed: 7821139]58.Nyenwe EA, Loganathan RS, Blum S, Ezuteh DO, Erani DM, Wan JY, Palace MR, Kitabchi AE. First, hyperglycemia-induced osmotic diuresis leads to excretion of large amounts of sodium and potassium ions that is accompanied by the excretion of ketoanions. About 2/3 of adults presenting to the emergency department or admitted with DKA have a past history of type 1 diabetes (T1D), while almost 90% of the HHS patients have a known diagnosis of type 2 diabetes (T2D) (5). Presentations with overlapping DKA and HHS accounted for 27% of admissions for hyperglycemic crises based on one report (18).The underlying defects in DKA and HHS are 1) reduced net effective action of circulating insulin as a result of decreased insulin secretion (DKA) or ineffective action of insulin in HHS (20-22), 2) elevated levels of counter regulatory hormones: glucagon (23,24), catecholamines (23,25), cortisol (23), and growth hormone (26,27), resulting in increased hepatic glucose production and impaired glucose utilization in peripheral tissues, and 3) dehydration and electrolyte abnormalities, mainly due to osmotic diuresis caused by glycosuria (28) (Figure 3). Therefore, the initial fluid therapy is directed toward expansion of intravascular volume and securing adequate urine flow. [PubMed: 10480519]72.Sobngwi E, Gautier JF, Kevorkian JP, Villette JM, Riveline JP, Zhang S, Vexiau P, Leal SM, Vaisse C, Mauvais-Jarvis F. [PubMed: 3084904]102.Wilson HK, Keuer SP, Lea AS, Boyd AE 3rd, Eknoyan G. 2019;7(1):e000621. [PubMed: 6434787]146.Oster JR, Epstein M. Thrombotic conditions and disseminated intravascular coagulation may contribute to the morbidity and mortality of hyperglycemic emergencies (159-161). Mudaliar S, Mohideen P, Deutsch R, et al. Adapted from Kitabchi et al. Diabetes Metab Rev. Abdominal pain in patients with hyperglycemic crises. 1972;3(1):36–41. 2016;239(2):155–158. [PubMed: 27082665]96.Kum-Nji JS, Gosmanov AR, Steinberg H, Dagogo-Jack S. A follow up study demonstrated that a priming or loading dose given as one half by IV route and another half by intramuscular route was as effective as one dose given intravenously in lowering the level of ketone bodies in the first hour (124). A bolus or priming dose of insulin has been used in a number of studies. 1977;12(3):121–128. However, total body potassium deficit is usually present from urinary potassium losses due to osmotic diuresis and ketone excretion. For example, in alcoholic ketoacidosis (AKA), total ketone bodies are much greater than in DKA with a higher β-OHB to acetoacetate ratio of 7:1 versus a ratio of 3:1 in DKA (8). [PubMed: 28945942]167.Laffel LM, Brackett J, Ho J, Anderson BJ. Newer glucose meters have the capability to measure β-OHB, which overcomes this problem (110,111). Wrenn KD, Slovis CM, Minion GE, Rutkowski R. Therefore, the treatment goal of DKA is to improve hyperglycemia and to stop ketosis with subsequent resolution of acidosis. However, hyperglycemia treatment is associated with "recovery" in serum sodium that restores water transfer between extracellular and intracellular compartments and prevents water accumulation in cells (99). Atlanta, GA: U.S. Department of Health and Human Services; 2014. Total body sodium loss can result in contraction of extracellular fluid volume and signs of intravascular volume depletion. 2005;90(8):4446–4451. [PubMed: 3104431]119.Diabetes Canada Clinical Practice Guidelines Expert C. Diabetic ketoacidosis complicated by generalized venous thrombosis: a case report and review. An anion gap of >20 mEq/L usually supports the diagnosis of DKA in these patients (94). [PubMed: 10432173]157.Edge JA. Diabetic ketoacidosis: reappraisal of therapeutic approach. Mechanism of cerebral edema in children with diabetic ketoacidosis. Diabetic Ketoacidosis in Patients with Type 2 Diabetes Recently Commenced on Sglt-2 Inhibitors: An Ongoing Concern. The cost of inpatient DKA care in the US has increased to 5.1 billion USD in 2014, corresponding to approximate charges related to DKA care varying between 20-26 thousand USD per admission (12,13) and continued to increase in 2017 when DKA admissions costed healthcare about 6.76 billion USD, corresponding to about 31 thousand USD per each admission (3). Factors associated with brain herniation in the treatment of diabetic ketoacidosis. If the corrected sodium level remains low, hypertriglyceridemia (secondary to uncontrolled diabetes) should be also suspected. Pembrolizumab versus Ipilimumab in Advanced Melanoma. The 2014 DKA hospitalization rates were the highest in persons aged 3.3 mmol/L in order to prevent arrhythmias and respiratory muscle weakness (131).Protocol for the management of adult patients with DKA. A EK. Therefore, intravenous administration of sodium and chloride-containing fluids leads to further HCO_3^- reduction and hyperchloremic metabolic acidosis (143,145). The metabolic derangements and treatment of diabetic ketoacidosis. The terms "hyperglycemic hyperosmolar nonketotic state" and "hyperglycemic hyperosmolar nonketotic coma" have been replaced with the term "hyperglycemic hyperosmolar state" (HHS) to highlight that 1) the hyperglycemic hyperosmolar state may consist of moderate to variable degrees of clinical ketosis detected by nitroprusside method, and 2) alterations in consciousness may often be present without coma.The triad of DKA (hyperglycemia, acidemia, and ketonemia) and other conditions with which the individual components are associated. [PMC free article: PMC5877353] [PubMed: 29596400]6.Zhong VW, Juhaeri J, Mayer-Davis EJ. Although the osmotically mediated mechanism seems most plausible, one study using magnetic resonance imaging (MRI) showed that cerebral edema was due to increased cerebral perfusion (135). Acta Diabetol Lat. Ketoacid production in DKA results in reduction in plasma bicarbonate (HCO_3^-) levels due to neutralization of hydrogen ion produced during dissociation of ketoacids in the extravascular fluid space. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. Endocrinol Metab Clin North Am. 2006;35(4):725–751. On the other hand, an SGLT-2 inhibitor can be also associated with hyperglycemic DKA in individuals who have sufficient glycogen storage to maintain hyperglycemia even in the setting of enhanced glucosuria (49,96).The major cause of water deficit in DKA and HHS is glucose-mediated osmotic diuresis, which leads to loss of water in excess of electrolytes (97). Intravenous glargine and regular insulin have similar effects on endogenous glucose output and peripheral activation/deactivation kinetic profiles. [PubMed: 14260239]28.Waldhausl W, Kleinberger G, Korn A, Dudczak R, Bratusch-Marrain P, Nowotny P. Qual Manag Health Care. 2015;54(16):2025–2028. Changing the process of diabetes care improves metabolic outcomes and reduces hospitalizations. A prospective randomized study in patients with pH between 6.9 and 7.1 showed that bicarbonate therapy had no risk or benefit in DKA (136). Fatty acids, lipotoxicity and insulin secretion. We recommend measurement of β-OHB in instances when a mixed acid-base disorder is present in patients with hyperglycemic crisis and DKA is suspected.Patients may present with metabolic conditions resembling DKA or HHS. During the recovery phase of DKA, patients commonly develop a short-lived hyperchloremic non-anion gap acidosis, which usually has few clinical consequences (149). [PubMed: 14602730]68.Maldonado M, Hampe CS, Gaur LK, D'Amico S, Iyer D, Hammerle LP, Bolgiano D, Rodriguez L, Rajan A, Lernmark A, Balasubramanyam A. Inequalities in glycaemic control, hypoglycaemia and diabetic ketoacidosis according to socio-economic status and area-level deprivation in Type 1 diabetes mellitus: a systematic review. It is, however, accepted now that true or corrected serum sodium concentration in patients experiencing hyperglycemic crisis should be calculated by adding 2.4 mmol/L to the measured serum sodium concentration for every 100 mg/dL incremental rise in serum glucose concentration above serum glucose concentration of 100 mg/dL (99). The cause of cerebral edema is not known with certainty. Controversies in the management of hyperglycaemic emergencies in adults with diabetes. 1980;29(2):87–95. The high H^+ level allows more influx of Na^+ thus increasing more influx of water to the cell with consequent edema (155). There were no differences in length of hospital stay, total amount of insulin needed for resolution of hyperglycemia or ketoacidosis, or in the incidence of hypoglycemia among treatment groups. Available evidence shows that almost 50% of newly diagnosed adult African American and Hispanic patients with DKA have T2D (65). [PubMed: 29773640]13.Fernando SM, Bagshaw SM, Rochwerg B, McIsaac DI, Thavorn K, Forster AJ, Tran A, Reardon PM, Rosenberg E, Tanuseputro P, Kyeremanteng K. [PubMed: 6769772]84.Rosival V. 1971;20(7):485–489. JAMA Netw Open. Cerebral intravascular coagulation in diabetic ketoacidosis. [PMC free article: PMC6501850] [PubMed: 31114699]163.Maldonado MR, Chong ER, Oehl MA, Balasubramanyam A. We recommend avoiding too rapid correction of hyperglycemia (which may be associated with cerebral edema especially in children) and also inhibiting hypoglycemia (23,120). The use of insulin analogs allowed treatment of DKA in general wards or the emergency department and so reduced cost of hospitalization by 30% without any significant changes in hypoglycemic events (126). J Pediatr. Patients with DKA and vomiting may have relatively normal plasma bicarbonate levels and close to normal pH. Several studies on serum osmolarity and mental alteration have established a positive linear relationship between osmolarity, pH, and mental obtundation (87). [PubMed: 12040551]80.Campbell IW, Duncan LJ, Innes JA, MacCuish AC, Munro JF. 1980;303(15):863–865. 2018;41(9):1870–1877. The exact etiology of this non-specific leukocytosis is not known. Bicarbonate therapy has been associated with some adverse effects, such as hypokalemia (132), decreased tissue oxygen uptake and cerebral edema (133,134) and delay in the resolution of ketosis (135). 2020;8(1) [PMC free article: PMC7050364] [PubMed: 32111715]159.Buyukasik Y, Ileri NS, Haznedaroglu IC, Karaahmetoglu S, Muftuoglu O, Kirazli S, Dundar S. Acid-base problems in diabetic ketoacidosis. Effect of Continuous Glucose Monitoring on Glycemic Control, Acute Admissions, and Quality of Life: A Real-World Study. 1980;3(1):15–20. 2017;23(4):506-508. 1994;17(10):1178–1185. [PubMed: 6773727]88.89.Freire AX, Umpierrez GE, Afessa B, Latif KA, Bridges L, Kitabchi AE. Severe hyperglycemia: effects of rehydration on endocrine derangements and blood glucose concentration. Hypoxemia may be related to the reduction in colloid osmotic pressure that leads to accumulation of water in lungs and decreased lung compliance. Continuous Glucose Monitoring Use in Type 1 Diabetes: Longitudinal Analysis Demonstrates Meaningful Improvements in HbA1c and Reductions in Health Care Utilization. 1987;5(1):1–5. 1999;159(4):381–384. [PMC free article: PMC4207202] [PubMed: 25342831]122.Cardoso L, Vicente N, Rodrigues D, Gomes L, Carrilho F. [PubMed: 6815530]144.Kelly AM. 2006;144(5):350–357. Patients with HHS typically have pH >7.30, bicarbonate level >20 mEq/L, and negative ketone bodies in plasma and urine. In patients with hypotension, aggressive fluid therapy with isotonic saline should continue until blood pressure is stabilized. Insulinopenia and elevated cortisol levels also lead to a shift from protein synthesis to proteolysis with resultant increase in production of amino acids (alanine and glutamine), which further serve as substrates for gluconeogenesis (8,31). [PubMed: 16454777]145.Adrogue HJ, Eknoyan G, Suki WK. The efficacy of low-dose versus conventional therapy of insulin for treatment of diabetic ketoacidosis. Umpierrez GE, Smiley D, Kitabchi AE. Medicine (Baltimore). Management involves Attention to precipitating cause Fluid and electrolyte management Insulin therapy Patient monitoring Prevention of metabolic complications during recovery Transition to long-term therapy Patient education and discharge planning should aim at prevention of recurrence. [PubMed: 4994561]46.Wachtel TJ, Silliman RA, Lamberton P. [PubMed: 29386248]7.Thomas M, Harjutsalo V, Feodoroff M, Forsblom C, Gordin D, Groop PH. Hyponatraemia Guideline Development G. 2008;31(4):643–647. International Consensus on Risk Management of Diabetic Ketoacidosis in Patients With Type 1 Diabetes Treated With Sodium-Glucose Cotransporter (SGLT) Inhibitors. Some studies suggested that pH is the cause of mental status changes (84); while, others concluded that osmolality (85) is responsible for the comatose state. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. [PubMed: 15336577]128.Della Manna T, Steinmetz L, Campos PR, Farhat SC, Schvartsman C, Kuperman H, Setian N, Damiani D. [PubMed:

25651248]148.Wallace TM, Matthews DR. [PubMed: 820228]23.Kitabchi AE, Young R, Sacks H, Morris L. [PubMed: 9589259]160.McLaren EH, Cullen DR, Brown MJ. Miner Electrolyte Metab. Patients with known diabetes may be given insulin at the dose they were receiving before the onset of hyperglycemic crises. Horm Metab Res Suppl. With frequent additional bicarbonate losses in urine in the form of ketoanions during DKA, the initiation of intravenous volume resuscitation with chloride-containing solutions can further lower plasma bicarbonate and unmask non-anion gap metabolic acidosis when Δ-Δ becomes less than 1 due to changes in plasma bicarbonate that exceed the expected changes in AG. Adding 20–30 mmol potassium to each liter of infused fluid is sufficient to maintain a serum potassium concentration within the normal range of 4–5 mmol/L (8). [PubMed: 8194658]71.Umpierrez GE, Woo W, Hagopian WA, Isaacs SD, Palmer JP, Gaur LK, Nepom GT, Clark WS, Mixon PS, Kitabchi AE. From Kitabchi and Wall (19).Both DKA and HHS are characterized by hyperglycemia and absolute or relative insulinopenia. Close follow up is very important, as it has been shown that three-monthly visits to the endocrine clinic will reduce the number of ER admission for DKA (167). Med Clin North Am. 1995;79(1):9–37. [PubMed: 404553]41.Cahill GF Jr. Starvation in man. Also, anti-cancer medications that belong to classes of immune checkpoint inhibitors such as Ipilimumab, Nivolumab, Pembrolizumab, can cause new-onset diabetes mellitus in up to 1% of the patients receiving immune checkpoint inhibitors with about half of these patients presenting with DKA as the initial presentation of diabetes, particularly in those individuals who may have underlying beta-cell autoimmunity (51,52) (53-56). 1971;20(4):228–238. 1989;5(3):247–270. Clinical significance. Failure of adjunctive bicarbonate to improve outcome in severe pediatric diabetic ketoacidosis. [PubMed: 8325282]150.Oh MS, Carroll HJ, Goldstein DA, Fein IA. 1979;28(6):577–584. Identifying this group of patients, who are at a higher risk for poorer prognosis, may be helpful in triaging them, thus further improving the outcome (88). Phosphate therapy in diabetic ketoacidosis. After the initial arterial pH is drawn, venous pH can be used to assess the acid/base status. Insulin pump therapy: a meta-analysis. Increased production of ketone bodies (β-hydroxybutyrate and acetoacetate) leads to ketonemia (39). [PMC free article: PMC7948057] [PubMed: 33688962]76.Danne T, Garg S, Peters AL, Buse JB, Mathieu C, Pettus JH, Alexander CM, Battelino T, Ampudia-Blasco FJ, Bode BW, Cariou B, Close KL, Dandona P, Dutta S, Ferrannini E, Fourlanos S, Grunberger G, Heller SR, Henry RR, Kurian MJ, Kushner JA, Oron T, Parkin CG, Pieber TR, Rodbard HW, Schatz D, Skyler JS, Tamborlane WV, Yokote K, Phillip M. Intern Med. The temporal relationship between endogenously secreted stress hormones and metabolic decompensation in diabetic man. Edge JA, Jakes RW, Roy Y, et al. On the other hand, development of HHS is insidious and may occur over days to weeks (16). Therefore, for the diagnosis of DKA, clinical judgment and consideration of other biochemical data are required to interpret the value of positive nitroprusside reactions in patients on captopril. The resolution of DKA is reached when the blood glucose is < 200 mg/dl, serum bicarbonate is ≥15 mEq/L, pH is >7.30 and anion gap is ≤12 mEq/L (17). [PubMed: 29955867]54.Liu J, Zhou H, Zhang Y, Fang W, Yang Y, Huang Y, Zhang L. 2018;42 Suppl 1:S109–S114. Potassium in severe diabetic ketoacidosis. 1999;27(12):2690–2693. Efficacy of low-dose insulin therapy for severely obtunded patients in diabetic ketoacidosis. 2001;344:264-269. J Gen Intern Med. American Association of Clinical Endocrinologists and American College of Endocrinology Position Statement on the Association of Sglt-2 Inhibitors and Diabetic Ketoacidosis. Hyperglucagonemia in diabetic ketoacidosis. 2020;43(7):e79–e80. [PubMed: 27297738]52.Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J, Lorigan P, Neyns B, Blank CU, Hamid O, Mateus C, Shapira-Frommer R, Kosh M, Zhou H, Ibrahim N, Ebbinghaus S, Ribas A. In addition, in HHS there is a smaller increase in counter regulatory hormones (20,45).Pathogenesis of DKA and HHS: stress, infection, or insufficient insulin. [PubMed: 4631908]82.Alberti KG, Nattrass M. Finally, with recent accumulation of knowledge of health hazards related to the COVID-19 pandemic, there is early evidence that COVID-19 infection can trigger DKA in patients with diabetes who otherwise may not have risk factors to develop ketoacidosis (74). Insulin substitution approach should be very conservative as it is expected that insulin resistance will improve with rehydration. Predictors of acute complications in children with type 1 diabetes. COVID-19-positive patients with diabetes outside of the hospital environment should be particularly vigilant in point-of-care monitoring of home blood glucose and/or β-OHB until the resolution of infection. Relationship of blood acetoacetate and 3-hydroxybutyrate in diabetes. Conscious level in children with diabetic ketoacidosis is related to severity of acidosis and not to blood glucose concentration. Management of hyperglycemic crises in patients with diabetes. 2004;27(8):1873–1878. Epilepsia. 1993;11(1):77–80. Ann Emerg Med. 1983;75(2):263–268. Hyperglycemia presenting with occipital seizures. HHS is resolved when serum osmolality is < 320 mOsm/kg with a gradual recovery to mental alertness. There are no randomized controlled studies that evaluated safe and effective strategies in the treatment of HHS (121). 1997;20(3):349–354. 1999;13(2):91–97. It is important to point out that the IV use of fast-acting insulin analogs is not recommended for patients with severe DKA or HHS, as there are no studies to support their use. 1979;28(5):517–523. Coagulation abnormalities in diabetic coma before and 24 hours after treatment. Since approval in 2013 of SGLT-2 inhibitors for therapy of T2D, multiple reports emerged demonstrating that the use of these medications can result in “euglycemic” DKA (48,78,95). Mayo Clin Proc. 1973;79:213-219. Cessation of insulin therapy is the major precipitating cause of diabetic ketoacidosis. [PubMed: 29650082]120.Rosenbloom AL. Trends in Diabetic Ketoacidosis Hospitalizations and In-Hospital Mortality - United States, 2000-2014. 2019;42(6):1147–1154. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. For complete coverage of all related areas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG.Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) represent two extremes in the spectrum of decompensated diabetes. Diabetic ketoacidosis: role of the kidney in the acid-base homeostasis re-evaluated. [PubMed: 9437340]138.Lever E, Jaspan JB. The Journal of clinical investigation. The optimal rate of glucose reduction is between 50-70 mg/hr. Isopropyl alcohol, which is commonly available as rubbing alcohol, can cause considerable ketosis and high serum osmolar gap without metabolic acidosis. Further, in US adults with T1D, HbA1c ≥ 9% was associated with 12-fold higher incidence of DKA (73). The released triglycerides and amino acids from the peripheral tissues become substrates for the production of glucose and ketone bodies by the liver (29). Most of the patients with HHS and an effective serum osmolality of >320 mOsm/kg are obtunded or comatose; on the other hand, the altered mental status rarely exists in patients with serum osmolality of