CLINICAL DECISIONS
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Choice of Intravenous Fluid for Resuscitation in Diabetic Ketoacidosis

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options as assigned. Readers can participate in forming community opinion by choosing one of the options.

CASE VIGNETTE

A Woman with Diabetic Ketoacidosis

Suellen Li, M.D.[1]

A 34-year-old woman with a history of type 1 diabetes mellitus presents to the emergency department with a 1-day history of nausea, vomiting, and abdominal pain. She reports that she lost her job recently and has been rationing her insulin to save money. Her prescribed medication regimen is 28 units of insulin glargine nightly and 8 units of insulin lispro with meals.

On presentation, her temperature is 36.5°C, blood pressure 98/51 mm Hg, heart rate 107 beats per minute and regular, respiratory rate 20 breaths per minute, and oxygen saturation 98% while she is breathing ambient air. Her physical examination is notable for dry mucous membranes and decreased skin turgor. There is no notable tenderness on palpation of the abdomen. Laboratory studies show a creatinine level of 1.6 mg per deciliter (141 μmol per liter; reference range, 0.6 to 1.1 mg per deciliter [53 to 97 μmol per liter]), sodium level of 131 mmol per liter (reference range, 135 to 145), potassium level of 5.7 mmol per liter (reference range, 3.5 to 5.0), and bicarbonate level of 10 mmol per liter (reference range, 23 to 32) and an anion gap of 28 mmol per liter (reference range, 3 to 17). Her glucose level is 372 mg per deciliter (20.6 mmol per liter; reference range, 70 to 110 mg per deciliter [3.9 to 6.1 mmol per liter]), the pH is 7.26 (reference range, 7.35 to 7.45), and the serum beta-hydroxybutyrate level is 5.1 mmol per liter (reference range, <0.4). Her glycated hemoglobin level is 8.7%. A diagnosis of diabetic ketoacidosis is made, an insulin infusion is initiated, and the patient is admitted to the medicine floor for further management of the condition.

You are the on-call provider taking care of this patient and are ordering intravenous fluids for volume resuscitation. You know that most guidelines recommend the use of isotonic saline (0.9% normal saline) for fluid resuscitation in patients with diabetic ketoacidosis but that some recent studies have suggested that the use of balanced crystalloid fluids such as lactated Ringer's solution is associated with faster resolution of diabetic ketoacidosis. You must decide which intravenous fluid to recommend for volume resuscitation in this patient.

TREATMENT OPTIONS

Which one of the following approaches would you recommend for this patient? Base your choice on the published literature, your own experience, guidelines, and other sources of information, as appropriate.

1. **Recommend fluid resuscitation with balanced crystalloid fluids.**
2. **Recommend fluid resuscitation with isotonic saline.**

To aid in your decision making, we asked two experts in the field to summarize the evidence in favor of approaches assigned by the editors. Given your knowledge of the issue and the points made by the experts, which approach would you choose?

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OPTION 1

Recommend Fluid Resuscitation with Balanced Crystalloid Fluids

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The clinical presentation in this case is that of a young patient with hemodynamic and physical examination signs of hypovolemia, coupled with renal impairment, hyperkalemia, and metabolic acidosis on a background of diabetic ketoacidosis. The key management imperative is to rapidly expand the intravascular compartment for hemodynamic resuscitation, while concomitantly managing these observed disturbances in metabolic indexes, which I will consider in turn.

The presence of renal impairment with hyperkalemia typically warrants strong consideration for the use of normal saline. Because urinary potassium excretion is directly related to distal tubular sodium delivery, isotonic normal saline will optimize distal sodium delivery and augment urinary potassium excretion as compared with the relatively hypotonic lactated Ringer's solution.[1] However, in the case of diabetic ketoacidosis, elevation in the plasma potassium concentration is transient and secondary to the effects of hyperosmolarity-induced transcellular shift. The administration of insulin will rapidly reverse transcellular shift, which often results in hypokalemia. Indeed, many patients presenting with diabetic ketoacidosis have underlying total body potassium depletion due to prolonged periods of osmotic diuresis and kaliuresis. As such, the physiologic objective of augmenting kaliuresis with normal saline to manage hyperkalemia can be deprioritized in this context. However, as hyperosmolarity is corrected, serial potassium monitoring with early and aggressive addition of potassium to crystalloid therapy is required, since the low potassium concentration of 4 mmol per liter in lactated Ringer's solution is insufficient to protect against hypokalemia-induced cardiac dysrhythmias.[1]

Second, the patient's presenting acid–base disturbance is that of an anion gap metabolic acidosis due to diabetic ketoacidosis. Volume resuscitation and improvement in renal function increase urinary excretion of ketoacids, which would otherwise have been metabolized to bicarbonate after administration of insulin. Loss of ketoacids in the urine will tend to reduce the anion gap and shift the acidosis to a hyperchloremic acidosis. The hypovolemia in this case is hemodynamically significant, and so the expected volume deficit is large; administration of large volumes of normal saline has been shown to lead to the generation of hyperchloremic metabolic acidosis.[2] In the initial treatment phase of diabetic ketoacidosis, in which the expected loss of ketoacids in the urine will tend toward development of hyperchloremic acidosis, the use of lactated Ringer's solution is preferred because it reduces the risk of generating additional hyperchloremic metabolic acidosis and exacerbating acidemia. However, it is important to note that the lactate content of lactated Ringer's solution will be converted to bicarbonate, and infusion of large volumes of potential bicarbonate in lactated Ringer's solution carries the risk of paradoxical central nervous system acidosis in diabetic ketoacidosis.[3] Therefore, lactated Ringer's solution is preferred in the initial treatment phase, but frequent reassessment of this patient's acid–base balance is important to guide a subsequent transition to normal saline given this consideration.

No large randomized trials have conclusively provided data on the question of optimal crystalloid therapy in diabetic ketoacidosis. A small meta-analysis that included a subgroup analysis of two randomized trials of normal saline and balanced solutions suggested that the time to resolution of diabetic ketoacidosis was shorter among patients who received balanced solutions.[4] Several dedicated randomized trials on this question are ongoing, the results of which will help inform clinical management.

In the absence of robust data to guide clinical management, nuanced clinical reasoning based on underlying physiology is key. In this case of diabetic ketoacidosis with hypovolemia, initial fluid resuscitation with lactated Ringer's solution, followed by careful reassessment and subsequent adjustment to normal saline, most aptly meets the pathophysiological demand of rapid volume expansion while concomitantly managing the electrolyte and acid–base derangements observed in this patient's presenting clinical syndrome.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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OPTION 2

Recommend Fluid Resuscitation with Isotonic Saline

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The management of diabetic ketoacidosis involves two critical transitions. The first entails crossing over from dextrose-free crystalloid fluids — typically 0.9% normal saline according to most guidelines — to fluids containing dextrose. The second encompasses the cessation of intravenous insulin and the transition to subcutaneous insulin on resolution of diabetic ketoacidosis. Preceding the first transition, the primary goal of treatment is to address hypovolemia and electrolyte deficiencies. Among these electrolyte deficiencies — which stem primarily from osmotic diuresis and transcellular shifts — sodium, chloride, and potassium are paramount.[5] The second goal is to mitigate acidosis by halting production of ketones and promoting their metabolism through the administration of intravenous insulin.

In the clinical scenario presented, the patient has mild hyponatremia, initial hyperkalemia due to acidosis-induced transcellular shifts, a high anion gap, and an elevated beta-hydroxybutyrate level. Most guidelines advocate the use of 0.9% normal saline in the initial phase of management of diabetic ketoacidosis to replenish the sodium and chloride deficiencies because the sodium concentration in 0.9% normal saline (154 mmol per liter) is higher than that in lactated Ringer's solution (130 mmol per liter).[6] Typically, this necessitates administering 2 to 4 liters of fluid for volume resuscitation, after which most patients would have achieved the blood glucose threshold that marks the onset of the first transition. The focus then shifts toward reducing ketones and mitigating acidosis, a process that requires concurrent insulin administration with dextrose solution to prevent hypoglycemia.

Two systematic reviews have assessed the outcomes of management of diabetic ketoacidosis with the use of either saline or a balanced solution such as lactated Ringer's solution.[4,7] However, the challenge of the meta-analyses is the heterogeneity among the included studies, which differed in insulin infusion rates, concentrations of administered dextrose after the transition, and intervals of monitoring and of testing for resolution.

The principal argument for replacing saline with balanced solutions is based on Stewart's physicochemical approach to acid–base chemistry.[8] According to this approach, electrical neutrality must always be maintained, and if an excess of chloride is administered, a reduction in other anions, such as bicarbonate, will result. This explains the development of hyperchloremic metabolic acidosis with prolonged and excessive resuscitation with saline. Proponents of using lactated Ringer's solution argue that prolonged use of normal saline results in considerable harm, such as an increased risk of renal failure. However, in a large randomized, controlled trial comparing the use of balanced solutions with saline in critically ill adults, outcomes, including renal failure, did not differ significantly between the two groups, despite a clearly detected difference in chloride concentration and pH.[9]

The available evidence does not justify deviating from current clinical guidelines advocating the use of 0.9% normal saline in the fluid resuscitation phase of the management of diabetic ketoacidosis. For the patient described in the vignette, the duration of resuscitation with normal saline and insulin therapy is anticipated not to exceed 4 to 6 hours, followed by a transition to dextrose-containing fluids for continued insulin infusion. This approach minimizes the risk of eventual hyperchloremic metabolic acidosis and facilitates the timely resolution of diabetic ketoacidosis.

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