Syndromes of severe insulin resistance (IR) include mutations of or autoantibodies to the insulin receptor and lipoatrophy (1). Diabetic ketoacidosis (DKA), although rare, can occur in these patients, even in the context of hyperinsulinemia, due to impaired insulin signaling. DKA can be extremely challenging to treat, and few clinicians are experienced or comfortable in using the high doses of insulin required. We describe aggressive management of DKA in three patients with syndromic severe IR.

CASE 1
An 18-year-old man with compound heterozygous mutation of the insulin receptor presented with DKA. He had poorly controlled diabetes (A1C 14% [130 mmol/mol]) treated with U-500 insulin (1,500 units/day), metreleptin (recombinant human methionyl leptin as an experimental drug), and metformin (2 g/day).

Two weeks prior, he underwent a root canal for an abscessed tooth but did not take the prescribed antibiotics. Antibiotics were subsequently initiated. One day after discharge, he developed abdominal pain, nausea, vomiting, and worsening jaw pain and swelling. Two days later, he developed fatigue, malaise, and Kussmaul respirations.

He presented to an outside hospital with DKA with a pH of 7.08, partial pressure CO$_2$ of 27 mmHg, and bicarbonate of 8 mmol/L. He received fluid resuscitation for an estimated 10% dehydration. In collaboration with National Institutes of Health (NIH) physicians, an insulin drip was started at 100 units/h that was gradually increased to 1,000 units/h on the first day and 2,000 units/h on the second day, without improvement of acidosis (Fig. 1A). Because of the lack of improvement despite massive doses of insulin (>50,000 units/day) and intravenous antibiotics, bicarbonate was given and dental extraction performed. He improved thereafter on 2,000 units/h of insulin, which was gradually weaned to 500 units/h. Acidosis resolved and he was transitioned back to subcutaneous insulin, 500 units t.i.d.

CASE 2
A 20-year-old woman with an autoantibody to the insulin receptor (type B IR) presented to an outside hospital with DKA (2). Six months prior, she presented with a 35-lb weight loss and severe hyperglycemia (>500 mg/dL). She was treated with metformin, pioglitazone, and escalating doses of insulin without improvement (A1C 12% [108 mmol/mol]).

Six months after diagnosis, she presented to an outside hospital with anorexia, fever, tachycardia, and tachypnea. Exam showed uveitis, severe diffuse acanthosis nigricans, and multiple granulating perineal and gluteal abscesses.

She was in DKA with a venous pH of 6.95, partial pressure CO$_2$ of 17 mmHg, and bicarbonate of 4 mmol/L. Her serum glucose was 359 mg/dL. Because of severe dehydration, she received 14 L of fluid in the first 72 h. In collaboration with NIH physicians, she was treated with an insulin drip plus subcutaneous U-500 insulin, which was slowly increased from 2 mL (1,000 units) to 9 mL (4,500 units) every 6 h (maximum insulin >18,000 units/day). The workup revealed a group B Streptococcus agalactiae urinary tract infection and multiple methicillin-resistant Staphylococcus aureus (MRSA) abscesses, the likely triggers of her DKA. She was treated with intravenous antibiotics. She improved dramatically following aggressive fluid resuscitation and bicarbonate administration. Insulin drip was discontinued and she continued subcutaneous insulin, 4,500 units every 6 h.
CASE 3
A 63-year-old man with history of type 2 diabetes, managed with metformin for 8 years, presented to an outside hospital with weakness, fatigue, polyuria, anorexia, and 20-lb weight loss. A recent A1C was 13.4% (123 mmol/mol). He was acidic with a pH of 7.1, bicarbonate of 9 mmol/L, and serum glucose >600 mg/dL. He was managed with intravenous insulin, 40 units/h, but attempts to transition him to subcutaneous insulin resulted in recurrent DKA. The workup revealed type B IR, and he was transferred to NIH.

The patient was maintained on an insulin drip at 40 units/h while subcutaneous insulin (U-500), 1,000 units t.i.d., was initiated. Insulin drip was successfully weaned on day 3, and he was maintained on U-500 insulin, 1,000 units q.i.d., with glucose levels of 130–180 mg/dL. A precipitating factor for DKA was not identified.

CONCLUSIONS
We describe three cases demonstrating the complexity of managing DKA in patients with severe IR. High doses of insulin, elimination of the inciting triggers, and aggressive fluid resuscitation are keys to management.

Insulin treatment in DKA has evolved from the use of high-dose insulin, up to 100 units/h, to lower doses of 5–10 units/h (0.1 units/kg/h) (3,4). However, low doses of insulin used in standard DKA protocols are not sufficient for patients with severe IR. The unusually high doses of insulin required for DKA in severe IR raise safety concerns for providers not experienced with severe IR.

At very high doses, the dose-response curve for insulin is extremely shallow (Fig. 1B) (5), requiring aggressive dose increases. The first case clearly demonstrates that despite a 10-fold increase in the hourly rate of insulin infusion, from 100 units/h to 1,000 units/h over less than 24 h, the patient’s acidosis did not resolve. The primary safety concern with high-dose insulin is hypoglycemia; however, patients with severe IR are at very low risk for this during DKA. If hypoglycemia occurs, it can be managed with intravenous dextrose. Because of the rarity of DKA in severe IR, there is no information regarding other potential toxicities of very high-dose insulin use.

Two patients required bicarbonate therapy during their DKA management as insulin alone failed to correct the acidosis. Bicarbonate therapy is not indicated in mild to moderate forms of DKA as metabolic acidosis will correct with insulin (3). Proponents of bicarbonate therapy point to the potential deleterious effects of acidosis on cardiac hemodynamics (4).

Infection is a common precipitating factor for DKA and was present in two of these patients. Despite massive insulin doses, acidosis did not resolve without treatment of the underlying cause of DKA. In patients with severe IR, prompt evaluation and treatment of infections are important to reduce the risk of DKA, as once DKA occurs, management is extremely challenging. Relapsing DKA may occur if patients are transitioned to subcutaneous insulin at inadequate doses.

These cases highlight the importance of aggressive management of DKA in severe IR, including high-dose insulin, fluids, bicarbonate, and treatment of underlying infection. Cooperation between critical care physicians and endocrinologists is essential for safe and effective management.

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