

# Use of U-500 Insulin in the Treatment of Severe Insulin Resistance

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## ABSTRACT

**Background:** Glycemic control is essential in the management of diabetes. However, many patients with diabetes are not achieving therapeutic targets, partly because they are receiving insufficient doses of insulin. This is particularly problematic in patients with severe insulin resistance, defined as insulin requirement >200 units/kg per day (>3 units/kg per day for pediatric patients). It is difficult to use U-100 forms of insulin at doses >200 units/kg per day because of the volume of insulin being administered subcutaneously. U-500, a concentrated form of insulin, may be useful in the treatment of these patients.

**Objective:** Current practice regarding the use of U-500 insulin has been published elsewhere. This article presents an updated algorithm for the administration and dosing of U-500 insulin, based on clinical experience with severe forms of insulin resistance. Guidelines are provided for dose escalation of U-500 insulin.

**Methods:** We reviewed the results of treatment with U-500 insulin in patients with severe insulin resistance. We analyzed the results, updated a pre-existing algorithm, provided additional practical information on the administration and dosing of U-500 insulin, and compared the cost of U-500 with that of U-100 insulin.

**Results:** To date, we have treated 56 patients (age range, 9–54 years) with severe insulin resistance using U-500 insulin. Doses ranged from 1.5 to 566 units/kg per day. Based on the pharmacodynamic properties of U-500 insulin, this concentrated form must be administered and dosed differently than regular U-100 insulin. U-500 insulin cost more than U-100 insulin on a per-milliliter basis, but cost less in the end because of the lower volumes of insulin required and fewer syringes and pump cartridges needed to administer U-500 insulin.

**Conclusions:** In our experience, U-500 insulin is a useful tool in the management of patients with severe insulin resistance. U-500 insulin alleviates the volume-related problems associated with U-100 insulin, making treatment with higher doses of insulin ( $\geq 200$  units per day) more effective with U-500 insulin than with U-100 insulin. (*Insulin*. 2008;3:211–218) © 2008 Excerpta Medica Inc.

**Key words:** U-500 insulin, severe insulin resistance, obese, glycemia.

## INTRODUCTION

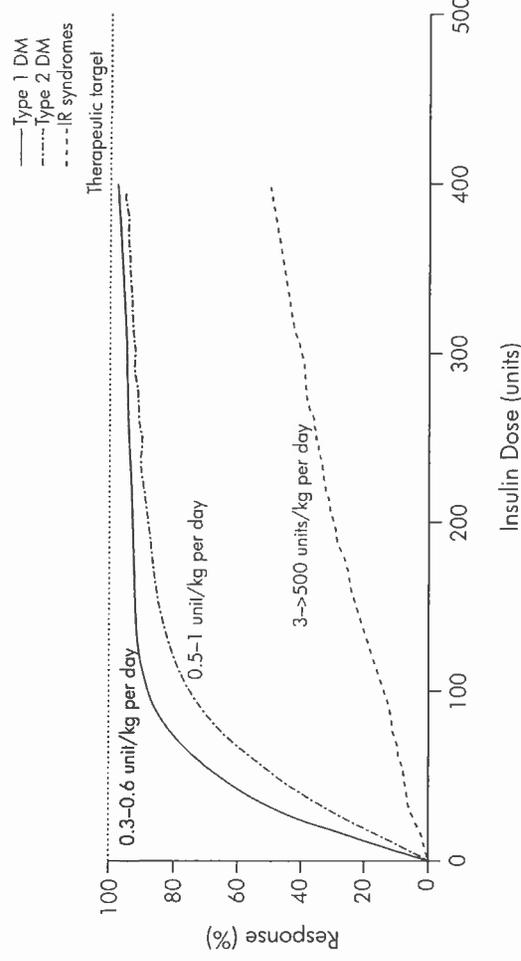
The American Diabetes Association classifies patients who have more severe insulin resistance than that found in type 2 diabetes mellitus (DM) as having “other specific types of diabetes.”<sup>1</sup> This greater severity of insulin resistance often precipitates various syndromes (Figure)<sup>2</sup> and typically requires treatment with insulin doses >200 units/day (>3 units/kg per day for pediatric patients).

Patients with type 2 DM and other specific types of diabetes are failing to reach their glycemic goals,<sup>3</sup> partly due to insufficient doses of insulin. Yet some physicians hesitate to prescribe higher doses of insulin because doses >200 units/day have yielded diminished responses (Figure).<sup>2,4,5</sup> Additional reluctance comes from the physical difficulty of administering higher doses of insulin due to the increased volume of the subcutaneous injection and/or the number of injections required. Weight gain and hypoglycemia—2 known side effects of insulin therapy<sup>6</sup>—add

to the skepticism surrounding augmentation of insulin doses.

Nonetheless, insulin doses should be increased as needed. Higher doses of insulin may still be effective despite a diminished response, and evidence-based medicine has shown that therapeutic goals are achievable through use of insulin therapy for  $\geq 40\%$  of patients with diabetes.<sup>4,5,7,8</sup> Treatment decisions should be guided by evidence-based medicine and the known benefits of treating patients to target levels of glycemia. Use of a more concentrated insulin preparation, such as U-500 insulin (Eli Lilly and Company, Indianapolis, Indiana),<sup>9</sup> usually addresses volume challenges.

Current practice regarding the use of U-500 insulin has been published elsewhere.<sup>10,11</sup> This article presents an updated algorithm for the administration and dosing of U-500 insulin, based on clinical experience with severe forms of insulin resistance, as well as guidelines for escalating doses of this concentrated preparation.



**Figure.** Theoretical total body insulin dose-response curve for insulin administration. Each curve is the composite of total body glucose uptake and hepatic output suppression. Representative dose ranges of daily insulin administration to achieve target goals are shown; ie, 0.3–0.6 unit/kg per day for type 1 diabetes mellitus (DM), 0.5–1 unit/kg per day for type 2 DM, and 3–>500 units/kg per day for syndromic insulin resistance (IR). Note that in type 2 DM and IR syndromes, the dose response at the target levels are markedly attenuated. Thus, much higher doses of insulin are required to achieve or approach target goals. The values of type 1 and type 2 DM are derived from the literature, and the values for the syndromic forms are taken from our own experience. Copyright © 2005 American Diabetes Association. From *Diabetes Care*, Vol. 28, 2005; 1240–1244.<sup>2</sup> Reprinted with permission from The American Diabetes Association.

### U-500 INSULIN THERAPY IN SEVERE INSULIN RESISTANCE

Our experience has focused primarily on the treatment of syndromic forms of insulin resistance, but we maintain that the principles of treating patients to target levels of glycemia with larger doses of insulin also apply to the growing subset of obese patients with type 2 DM. To date, we have treated 56 patients with U-500 insulin.<sup>12–18</sup> The syndromic forms of insulin resistance, including type A and type B insulin resistance syndrome, congenital and acquired generalized lipodystrophy, hyperandrogenism–insulin resistance–acanthosis nigricans, and Rabson-Mendenhall syndrome, afflict most of the patients (Table I).<sup>2,12–18</sup> We have treated 6 additional obese patients with type 2 DM (Table I) and continue to accrue patients with syndromic forms of insulin resistance.

Insulin doses for these patients have ranged from 1.5 units/kg per day to 566 units/kg per day, and both pediatric and adult patients have been treated (age range, 9–54 years) (Table I).<sup>2,12–18</sup> Treating these patients has enabled us to create a practical algorithm for administering U-500 insulin (Table II). This algorithm, an update of one we reported previously,<sup>2</sup> includes instructions (in percentage terms) on how to divide and weight doses, how to account for the dose-response properties of U-500 insulin, and how to use U-500 insulin with an insulin pump.

### PHARMACOLOGIC CONSIDERATIONS IN THE USE OF U-500 INSULIN

U-500 insulin is available only as a regular form of insulin. The duration of insulin activity is regulated by the rate of human insulin absorption after it is administered subcutaneously. Daily absorption rates of U-500 insulin seem to be consistent, and that same consistency in absorption exists in various regions of the body (see prescribing information).<sup>9,19</sup>

The most clinically significant distinguishing factors between the available forms of insulin include the onset, peak, and duration of action. Regular U-100 insulin demonstrates a peak effect within 2 to 4 hours of administration and a 5- to 7-hour duration of action compared with U-500, which has an onset and duration of action similar to that of regular insulin but a duration of action of up to 24 hours.<sup>19</sup> Duration of action is even more prolonged in patients with insulin-receptor abnormalities because of insulin degradation impairment.

Dose volume disrupts the pharmacodynamics of regular, neutral protamine Hagedorn (NPH), and other repository forms of insulin.<sup>19,20</sup> Higher doses have the potential to postpone peak action and prolong the duration of action. For example, an injection of 20 units of regular insulin has a significantly different time-action profile than an injection of 50 units.

**Table I.** Patients treated with U-500 insulin.

Syndrome	No. of Patients	Dose Range, units/kg per day	Age Range, y	Weight, Mean (SD), kg	Weight Range, kg	References
Type A IR	5	6-566	18-57	58.2	44-80	2,15,18
Rabson-Mendenhall	4	10-80	9-27	34.4	22-48	2,14,15
Type B IR	27	3-416	10-54	76.1	32-68	2,13
Lipodystrophy	12	3-28	12-36	58.5	28-82	2,12,16,17
HAIR-AN	2	1.6	33-54	135.0	124-146	2
Type 2 DM + Obesity	6	1.5-5.6	36-52	116.0	96-138	2

IR = insulin resistance; HAIR-AN = hyperandrogenism-insulin resistance-acanthosis nigricans; DM = diabetes mellitus.

**Table II.** Administration and dosing of U-500 insulin.

Total Daily Insulin Dose, units/day	Injection Frequency/Delivery Schedule	How Doses Are Weighted*	Dosing Adjustments
200-299	2 Injections per day (8 AM, 6 PM)	60/40 (ie, AM injection = 60% of TDD, PM injection = 40% of TDD)	BG level <50 mg/dL above or below target range: Increase or decrease U-500 in increments of 5 units (0.01 mL) per dose/bolus
	3 Injections per day (8 AM, 12 noon, 6 PM)	40/30/30, 45/35/20, or 40/40/20	BG level ≥50 mg/dL above or below target range: Increase or decrease U-500 in increments of 10 units (0.02 mL) per dose/bolus†
	Via insulin pump: 1 unit = 0.01 mL; 0.01 mL of U-500 insulin = 5 units	3 of 4 meditime boluses For basal rate 20% of TDD, boluses are 30/30/20 or 30/25/20/5 For basal rate 50% of TDD, boluses are 20/20/10 or 20/15/10/5 Bedtime snack bolus is ≤10% of TDD	BG level within 100 mg/dL above or below target range: Increase or decrease U-500 in increments of 25 units (0.05 mL) per dose/bolus
300-599	3 Injections per day (8 AM, 12 noon, 6 PM)	40/30/30, 45/35/20, or 40/40/20	BG level >100 mg/dL above or below target range: Increase or decrease U-500 at increments of 50 units (0.1 mL) per dose/bolus
	4 Injections daily (8 AM, 12 noon, 5 PM, 10 PM)	30/30/30/10	
	Via insulin pump: 1 unit = 0.01 mL; 0.01 mL of U-500 insulin = 5 units	3 of 4 meditime boluses For basal rate 20% of TDD, boluses are 30/30/20 or 30/25/20/5 For basal rate 50% of TDD, boluses are 20/20/10 or 20/15/10/5 Bedtime snack bolus is ≤10% of TDD	
≥600	4 Times daily Do NOT inject >2 mL in any injection site	30/30/30/10	

TDD = total daily dose; BG = blood glucose.

\*Based on percentage of TDD.

†Basal rates require finer adjustments because pumps can deliver fractions of units.

**A**n injection of 20 units of regular insulin has a significantly different time-action profile than an injection of 50 units.

The adverse reactions that have been reported for U-500 insulin are similar to those reported for U-100 insulin preparations. Hypoglycemia is one of the most frequent adverse events experienced by all insulin users. Of particular note for users of U-500 insulin is that deep, secondary hypoglycemic reactions may develop 18 to 24 hours after injection.<sup>9</sup> This risk posed by the secondary hypoglycemic reactions influences the methods used to administer, schedule, and dose U-500 insulin (see next section).

### DOSING OF U-500 INSULIN

The pharmacodynamic properties of U-500 insulin, which are similar to those of NPH insulin, require that U-500 be dosed and administered differently than regular insulin. This can best be summarized by looking at different daily dosages because this affects how it is administered. The following information is summarized for doses of 200 to 299 units/day, 300 to 599 units/day, and ≥600 units/day (Table II).

#### Doses 200 to 299 Units/Day

This dose range can be managed with multiple daily injections or use of an insulin pump. If it is decided to give twice-daily injections, we recommend 60% of the total daily dose (120–180 units) in the morning and 40% (80–120 units) in the evening. If 3 times daily is preferred, we recommend giving 40% to 45% of the total daily dose (80–135 units) in the morning, 30% to 40% (60–120 units) at lunch, and 20% to 30% (40–90 units) at dinner. If insulin is administered with an insulin pump, basal rates should be set higher during the day and lower at night. Frequent changes in basal rates should be avoided because the pharmacokinetics of U-500 insulin may cause a delayed effect in the blood. Changes to the basal rate should be initiated 1 to 2 hours before the desired effect, related to the onset of action of U-500 insulin, but also considering especially the end time of the basal rate. The basal rate period should end 1 to 2 hours before the desired time, related to the duration of action of U-500 insulin. Pump programs, including boluses and rate periods, are designed for short-acting forms of insulin and the onset and duration of action of U-500 insulin should be programmed into the pump. For example, if a rate is desired from 8 AM to 8 PM, the pump should be programmed for that rate from 7 AM to 7 PM, or at least modified somewhat.

Bolus doses should be programmed into the pump in the amounts recommended above for injection 3 times daily; corrective insulin factors and carbohydrate ratios should be entered manually, or a set basal regimen should be programmed. The patient should be instructed to not adminis-

ter a bolus dose more frequently than every 4 to 6 hours because this leads to overdosing and “stacking” of the U-500 insulin. Pumps refer to this as “insulin on board,” and such features are designed for the pharmacokinetics of rapid-acting insulin analogues. Boluses administered more frequently than every 4 to 6 hours will put the patient at risk for hypoglycemia when using U-500 insulin.

Lane<sup>21</sup> reported detailed instructions on the use of U-500 in an insulin pump and how parameters are to be entered into the pump when initiating therapy. Lane’s U-500 insulin guidelines and algorithms have been used for insulin pump regimens <200 units/day, but primarily for regimens >100 units/day (personal communication, May 2007).

#### Doses 300 to 599 Units/Day

We recommend bolus injections 3 times daily for this dose range. The doses can be divided as 40% to 45% (120–270 units) in the morning, 30% to 40% (90–240 units) for lunch, and 20% to 30% (60–180 units) for dinner (Table II). If blood glucose levels are consistently elevated in the morning, bolus injections 4 times daily should be considered. We recommend using higher doses during the daytime and a lower dose at bedtime—ie, 30% of the total daily dose (90–180 units) with each meal and 10% (30–60 units) at bedtime. Ballani et al<sup>10</sup> reported satisfaction with twice-daily injections, using total daily doses ≤650 units.

Insulin pumps may also be used, with the same cautions mentioned previously. Frequent changes in the basal rate should be avoided. Bolus amounts at dinner should be lower than those administered at breakfast and lunch. If a bedtime bolus dose is used, it should be <10% of the total daily dose.

#### Doses ≥600 Units/Day

We recommended injection 4 times daily exclusively for doses ≥600 units/day. The doses can be divided evenly, but if morning hypoglycemia is an issue, we recommend that the bedtime dose be reduced. Total daily doses of ≥2000 units may warrant use of syringes other than insulin syringes that will enable injecting >1 mL of insulin subcutaneously, but taking care not to inject >2 mL subcutaneously.<sup>22–24</sup>

It is worth mentioning that doses of insulin ≥600 units/day are used more frequently with “other” forms of insulin resistance. Even though the insulin dosing is significant, patients are not at any greater risk for hypoglycemia because of the magnitude of the dose. Some patients’ insulin resistance warrants such levels of insulin to prevent severe hyperglycemia and a catabolic state, but syndromic forms of insulin resistance do not spontaneously revert within hours. Remission of the insulin resistance and decreasing the patient’s insulin requirements can be achieved, even in those with antibody-mediated, insulin-receptor antibody syndromes. Fear of hypoglycemia should not deter one from administering these doses of insulin, if needed.

### Dose Adjustments

Typically, dose adjustments with U-100 forms of insulin are made from dose to dose based on principles of corrective insulin, insulin-to-carbohydrate ratios, and alterations in basal insulin. Because of the pharmacodynamics of U-500 insulin, dose changes are based on trends rather than on glucose levels at each dose. We often look at trends for the week and then increase or decrease the total daily dose by 15% to 20% for blood glucose levels outside of the target range. More specifically, in the dose range of 200 to 299 units/day, dose adjustments should be made in increments of 5 units (0.01 mL) per dose/bolus for blood glucose levels <50 mg/dL above or below the target range. For blood glucose levels  $\geq 50$  mg/dL above or below the target range, dose adjustments should be made in increments of 10 units (0.02 mL) per dose/bolus of insulin. This is based not only on practical measurements (markings on the insulin syringe), but also on sensitivity factor calculations (ie, the "1500 and 1800 rule") at this dose range (Table II). Because of the ability of insulin pumps to deliver fractions of units of insulin, basal rate adjustments can be made in smaller increments.

**B**ecause of the pharmacodynamics of U-500 insulin, dose changes are based on trends rather than on glucose levels at each dose.

When the total daily dose is 300 to 599 units/day and the blood glucose level is  $\leq 100$  mg/dL above or below the target range, adjustments should be made in increments of 25 units (0.05 mL) per dose/bolus. For blood glucose levels  $>100$  mg/dL above or below the target range, adjustments should be

made in increments of 50 units (0.1 mL) per dose/bolus (Table II).

When the total daily dose is  $\geq 600$  units/day, the adjustments are made in increments of 50 units (0.1 mL) per dose/bolus and evaluated weekly until target blood glucose levels are reached (Table II).

Patients often have significant variation in their blood glucose levels during the day, when their caloric and carbohydrate intake varies considerably at different mealtimes. We stress the need for consistency in caloric and carbohydrate content of their meals and often give patients ranges of carbohydrates to aim for based on nutritional recommendations. In these cases, we have found a modified "corrective insulin" regimen to be helpful. The principle of the regimen is not to specifically correct blood glucose levels with existing formulas typically used in type 1 DM, but rather to guide the patients to administer U-500 insulin when they have widely varying blood glucose levels. An example for one of our patients, a 13-year-old, 50-kg patient with congenital lipodystrophy, is provided in Table III.

### Practical Issues in the Administration of U-500 Insulin

It is important to remember that, unlike all other forms of insulin, the dose of U-500 insulin and the corresponding units on a regular insulin syringe are not comparable. For example, if a physician intends to prescribe 150 units of insulin 3 times daily and wants to use U-500 insulin, the proper prescription would be "Insulin U-500 Regular, 150 units, inject 0.3 mL subcutaneously, 3 times daily before meals." At our institution, before our prescribers wrote Insulin U-500 in this manner, at least one error would occur per patient admission specific to the dosing of U-500 insulin. Since August 2004, when we began expressing the prescription in terms of actual insulin units and actual volume to be injected subcutaneously, only one error in U-500 insulin dos-

**Table III.** Example of U-500 insulin regimen.\*

Before breakfast and dinner, when BG is...	Give...
$\geq 250$ mg/dL	0.3 mL (looks like 30 units) of U-500 (= 150 units of insulin)
150–249 mg/dL	0.2 mL (looks like 20 units) of U-500 (= 100 units of insulin)
125–149 mg/dL	0.15 mL (looks like 15 units) of U-500 (= 75 units of insulin)
70–124 mg/dL	0.1 mL (looks like 10 units) of U-500 (= 50 units of insulin)
$< 70$ mg/dL	Do not give anything
<b>Carbohydrate Targets</b>	
Breakfast:	45–60 g
Lunch:	50–75 g
Dinner:	60–85 g
Snacks (2):	30–40 g

BG = blood glucose; g = grams.

\*This regimen was designed for a 13-year-old, 50-kg patient with lipodystrophy syndrome. This regimen does not take the place of the basal regimens presented in Table IV, but demonstrates a variation from those templates.

ing has occurred. On average, we treat 15 patients a year with U-500 insulin, with patient visits of 3 to 5 days. We must always be vigilant when writing prescriptions for U-500 insulin, and we must visually monitor patients who use U-500 insulin to ensure that they are drawing up the correct amount of insulin in the syringe.

**U**nlike all other forms of insulin, the dose of U-500 insulin and the corresponding units on a regular insulin syringe are not comparable.

Patients typically use regular insulin syringes to draw up their U-500 insulin. In this example, 0.3 mL of U-500 insulin would measure 30 units on a regular insulin syringe. Confusion arises when patients are instructed to “draw up 30 units of insulin,” which leads the patient to think that the correct dose of insulin is 30 units rather than the 150 units that 0.3 mL of U-500 represents. Conversely, an overdosing error may occur if 150 units (1.5 mL) of U-500 is drawn up in a unit-based insulin syringe. Using a 0.5- or 1.0-mL tuberculin syringe that has only volume markings may help to avoid this confusion. However, because a patient cannot easily access tuberculin syringes, following this strategy may not be plausible outside of the hospital setting. Furthermore, because insulin syringes are considered to be elements of diabetic supplies, it is easier for a patient to obtain insurance reimbursement for insulin syringes than for tuberculin syringes. When it is known that the patient will be using an insulin syringe to draw up their U-500 insulin, it is essential to have a specialized health care provider or diabetes educator who is knowledgeable about U-500 insulin show the patient how to draw up the dose using the unit markings on the syringe.

Insulin pumps have been reported as effective delivery devices for U-500 insulin.<sup>21,22,25</sup> The best reported and communicated use of these devices is with total daily doses of insulin of 100 to 300 units/day (W. Lane, personal commu-

nication, May 2007); however, they may be effective for doses <600 units/day (pediatric doses of 3.0–4.5 units/kg per day). Doses larger than this are handled better with multiple daily injections because of the volume of insulin injected at the catheter injection site, which is usually indwelling for 2 to 3 days.

Another important concern with regard to insulin pumps is that these devices are created for rapid-acting forms of insulin. Bolus features of the pump are matched with the drug kinetics of rapid-acting insulin analogues. Using these features with U-500 insulin may increase the likelihood of hypoglycemia and “stacking” of the U-500 insulin.

Furthermore, insulin pumps indicate the dose in terms of units, which may lead to dosing errors. It is important to have the patient meet with a knowledgeable insulin pump management team and receive the necessary instructions, conversion tables, and guidance in explaining their insulin pump dosing to other health care providers they may encounter.

An often-posed question concerns the availability of U-500 insulin in insulin pens. These items are not currently available in the United States. In addition, the manufacturer of U-500 insulin (Eli Lilly and Company) currently does not recommend the use of U-500 via an insulin pen.

For the delivery of doses of U-500 insulin  $\geq 600$  units/day, the dosing may become such that the patient needs to inject >1 mL of U-500 insulin at an individual dosing time. Under such circumstances, to make the delivery of insulin more practical for the patient without increasing the number of injections, the patient could use 3-mL syringes with a 30-gauge, 1/2-inch needle (Becton, Dickinson and Company, Franklin Lakes, New Jersey). We would not encourage injection of >2 mL subcutaneously in any one site. Individual variations may occur, and it is important to assess the patient's response to the volumes of insulin being injected and to monitor the injection sites.

### COST AND AVAILABILITY OF U-500 INSULIN

Compared with other commonly used forms of insulin, U-500 insulin has been associated with cost savings (Table IV).<sup>2,22</sup> Although U-500 insulin is more expensive than other insu-

**Table IV.** Cost analysis of insulin.<sup>2,22</sup>

Insulin Type/Strength	Unit of Issue, mL	Mean Wholesale Price Per Vial,* US \$	Price Per Unit,* US \$
Insulin regular 500 units/mL	20	222.21	0.02
Insulin regular 100 units/mL	10	37.70	0.04
Insulin lispro 100 units/mL	10	87.89	0.09
Insulin aspart 100 units/mL	10	95.71	0.10
Insulin NPH 100 units/mL	10	37.70	0.04
Insulin glargine 100 units/mL	10	84.20	0.08
Insulin detemir 100 units/mL	10	90.31	0.09

NPH = neutral protamine Hagedorn.

\*As of September 1, 2007.

lins on a per-milliliter basis, the actual volume of insulin used is decreased, resulting in a lower cost per unit of insulin than for other insulins. Moreover, use of U-500 insulin requires fewer syringes to inject lower volumes of insulin and/or fewer pump cartridges (if using a pump), which also brings about cost savings, particularly with regard to pump-supply costs.<sup>22,26</sup>

In the United States, U-500 insulin is supplied in 20-mL vials. This concentrated form is differentiated from other forms of insulin by use of a larger vial and diagonal orange stripes on the box and on the printed U-500 insulin vial label.

## CONCLUSIONS

The algorithm presented in this article reflects our experience in treating syndromic forms of insulin resistance and several cases of severe insulin resistance, obesity, and type 2

DM. We have found U-500 insulin to be a useful tool in the management of our group of patients, and this concentrated form of insulin may help other patients with severe insulin resistance achieve their glycemic goals. U-500 insulin alleviates the volume-related problems associated with U-100 insulin, making treatment with higher doses of insulin ( $\geq 200$  units/day) more effective and more cost-efficient with U-500 insulin than with U-100 insulin.

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