




Review of U-500 Insulin

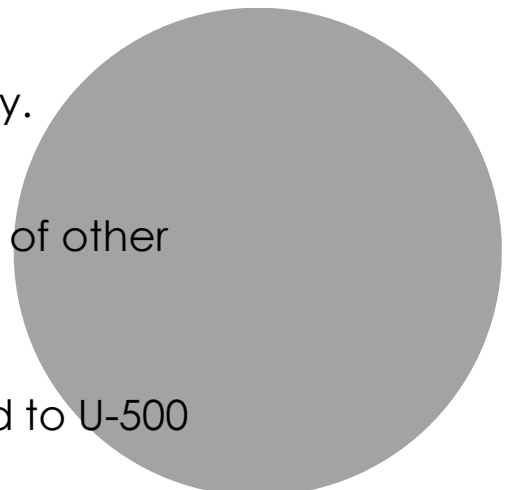
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CHI MEMORIAL

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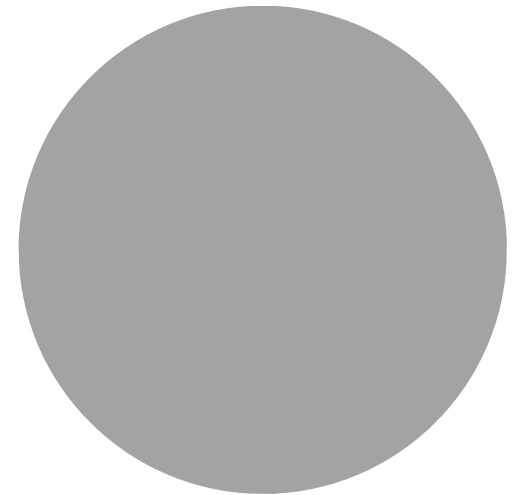
Learning Objectives



- ▶ Identify patients who could benefit from U-500 insulin therapy.
 - ▶ Differentiate the pharmacokinetics of U-500 insulin from that of other standard insulin therapies.
 - ▶ Formulate a dose regimen for individuals who are converted to U-500 insulin.
 - ▶ List safety concerns regarding use of U-500 insulin and propose solutions.
 - ▶ Explain how to effectively counsel patients prescribed U-500 insulin.
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Scope of the Problem

- ▶ Incidence of diabetes increased 16.5% from 2004-2007
- ▶ National obesity epidemic closely related
- ▶ Insulin requirements have likewise increased



Severe Insulin Resistance



- ▶ Requiring >200 units of insulin or > 2 units/kg daily
- ▶ Major therapeutic challenge in terms of achieving glycemic control

Causes of Severe Insulin Resistance



- ▶ Obesity
- ▶ Stressful Conditions
 - ▶ Pregnancy
 - ▶ Infection
 - ▶ Steroid Use
- ▶ Genetic Defects
- ▶ Insulin receptor antibodies
- ▶ Endocrine disorders
 - ▶ Polycystic ovarian syndrome
 - ▶ Hemochromatosis
 - ▶ Cushing syndrome
 - ▶ Werner syndrome
 - ▶ Acanthosis nigricans
 - ▶ HAIR-AN syndrome
 - ▶ Lipodystrophy

Glycemic Targets

	ADA	ACE
Hemoglobin A1C	< 7%	≤ 6.5%
Pre-prandial BG	70-130 mg/dL	< 110 mg/dL
Post-prandial BG	<180 mg/dL	< 140 mg/dL

Benefits of Glycemic Control



- ▶ Prevent microvascular complications
 - ▶ Retinopathy
 - ▶ Nephropathy
 - ▶ Neuropathy
- ▶ Prevent macrovascular complications
 - ▶ Coronary heart disease
 - ▶ Stroke
 - ▶ Peripheral vascular disease

The Problem

- ▶ Unable to achieve glycemic control despite high doses of standard insulin therapy
- ▶ Volume of insulin is difficult and uncomfortable to administer
- ▶ Exhibits variable absorption

Standard Insulin Products

Insulin Type	Description	Onset	Peak	Duration
Lispro	Rapid-acting	15-30 min	0.5-2.5 hrs	3-6.5 hrs
Aspart	Rapid-acting	10-20 min	1-3 hrs	3-5 hrs
Glulisine	Rapid-acting	10-15 min	1-1.5 hrs	3-5 hrs
Regular	Short-acting	30-60 min	1-5 hrs	6-10 hrs
NPH	Intermediate-acting	60-120 min	6-14 hrs	16-24 hrs
Glargine	Long-acting	1.1 hrs	4-6 hrs	8-20 hrs
Detemir	Long-acting	0.8-2 hrs	---	12-24 hrs

U-500

- ▶ U-500 was first introduced in 1952 by Eli Lilly
- ▶ Concentrated insulin
- ▶ Formulation is regular human insulin
- ▶ Clear solution contains 500 units/mL (20 ml vial)



U-500

- ▶ Prescribing of U-500 increased 137% from 2007 to 2009
- ▶ No universal guidelines exist regarding clinical use
- ▶ Product unfamiliarity → Inappropriate prescribing & serious medication errors

Potential Candidates for U-500



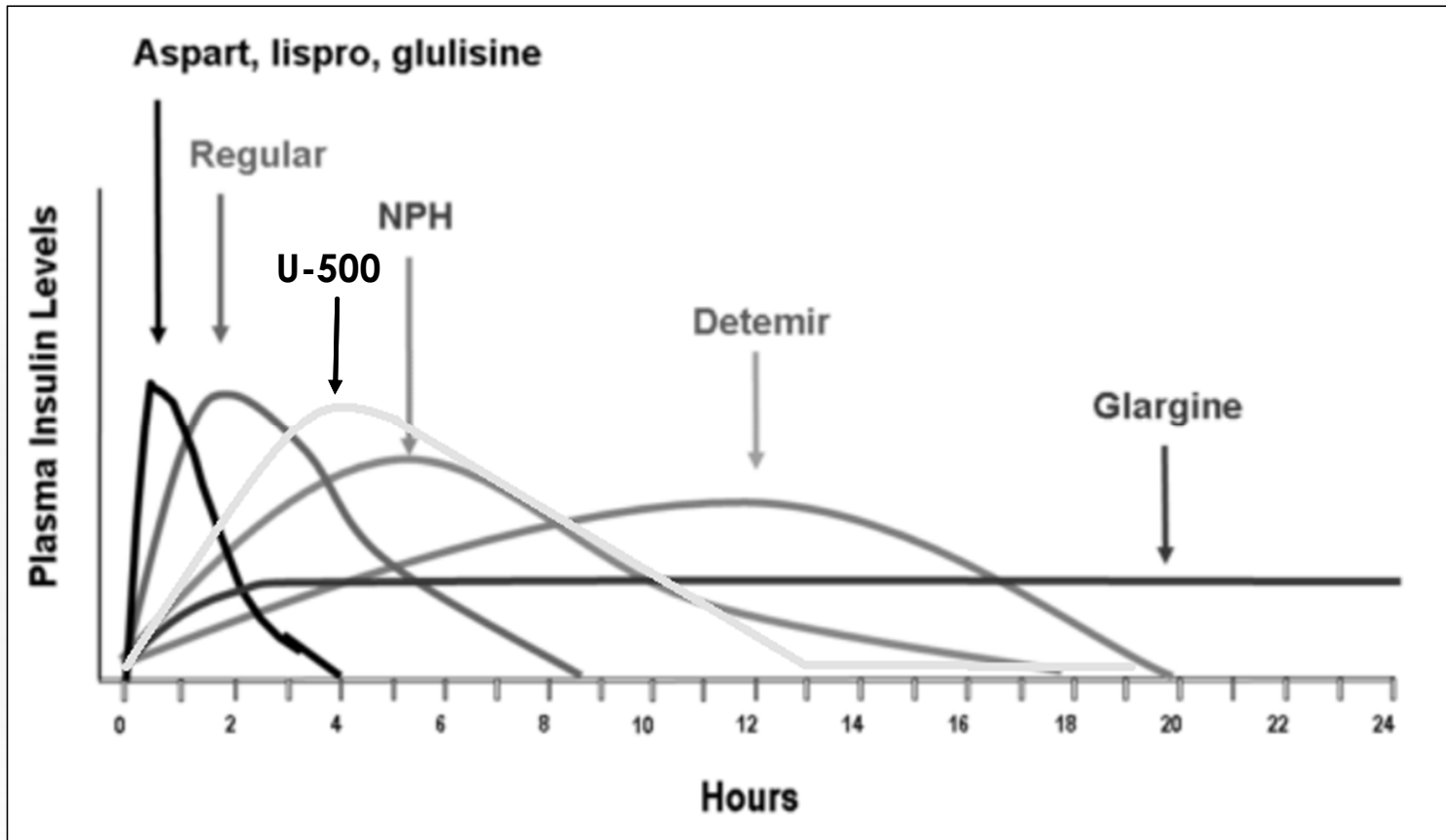
- ▶ Insulin requirements > 200 units or 2 units/kg/day
- ▶ Poor glycemic control (A1C $> 8.5\%$)
- ▶ Compliance with insulin regimen and blood glucose monitoring
- ▶ Willing to follow-up frequently during dose titration
- ▶ Able to clearly see markings on syringe
- ▶ No hypoglycemia or hypoglycemic unawareness at current insulin dose

Pharmacokinetics of U-500 Insulin

	Non-obese subjects	Obese subjects
Onset of action	0.5 hours	0.75 hrs
Peak effect	3.5-4.5 hours	7-8.5 hours
Duration of action	6 to > 10 hours	11.5 hrs

- ▶ Onset of action similar to regular insulin with delayed peak effect
- ▶ Duration of action similar to NPH insulin

Pharmacokinetics of U-500 Insulin



Pharmacokinetics of U-500 Insulin



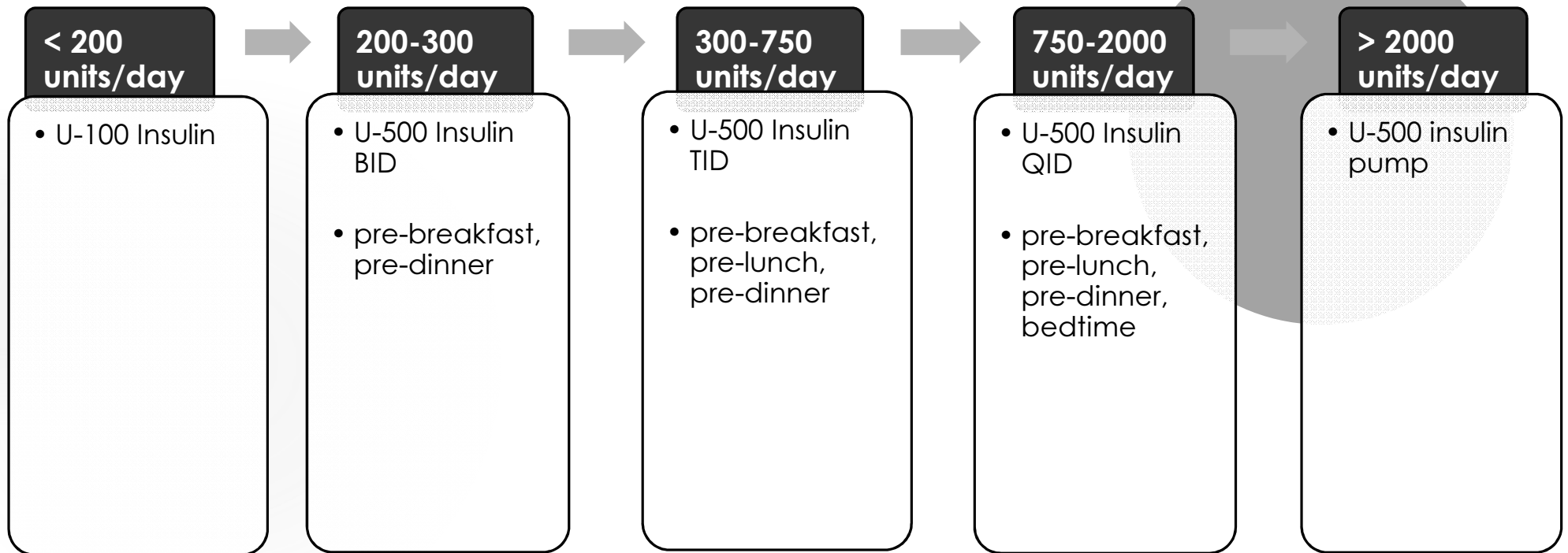
- ▶ U-500 insulin has a unique pharmacokinetic profile
- ▶ Onset of action: 30-60 mins
- ▶ Duration of action variable: 6-12 hours
- ▶ Administer 30 mins before meals
- ▶ Dose at least BID
- ▶ Correction doses not recommended

Dose Conversion to U-500 Insulin



- ▶ No guidelines or randomized trials
- ▶ Clinicians must devise dosing strategies
- ▶ Different methods proposed in primary literature based on experience

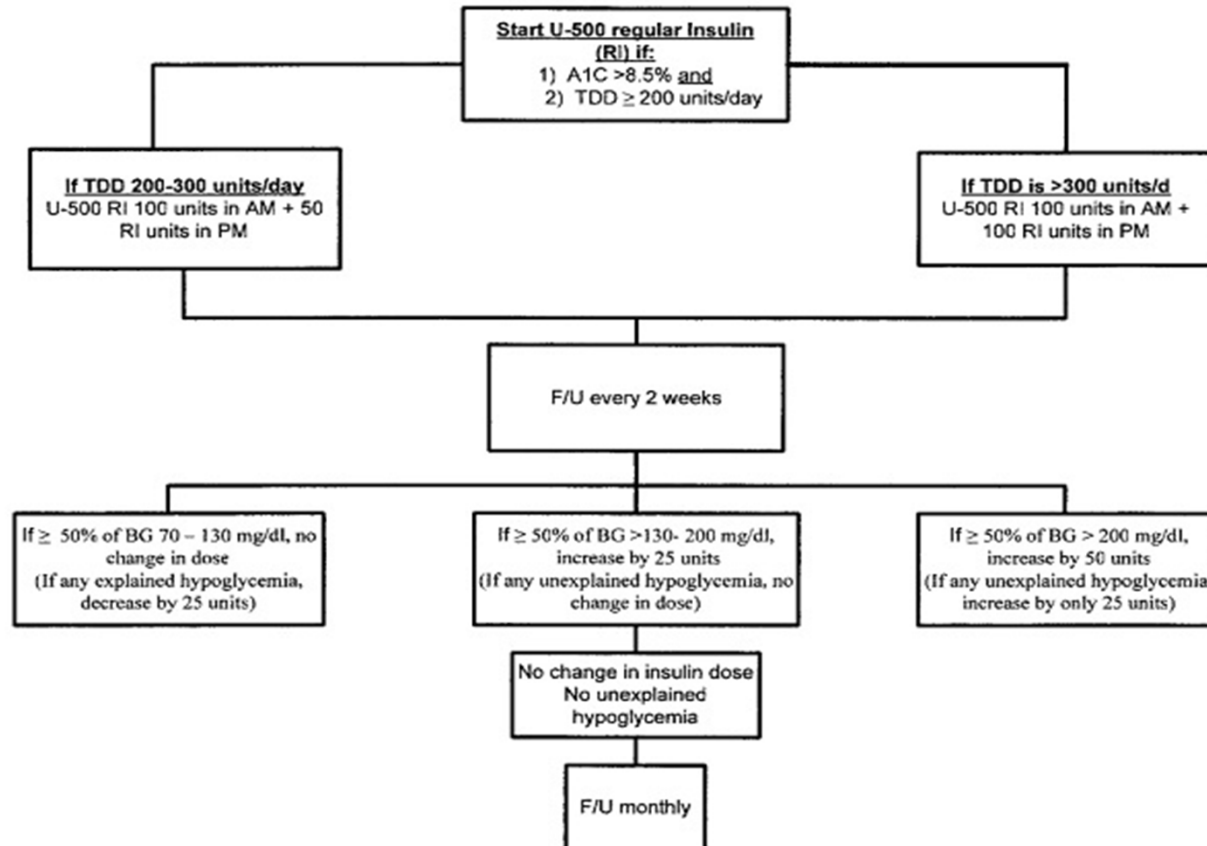
Dosing U-500 Insulin



Dosing Strategy 1

- ▶ 1. Add up total daily dose (TDD) of U-100 insulin from all insulin sources
- ▶ 2. Subtract 10-20% from total daily insulin dose = new total daily dose U-500 in units
- ▶ 3. Divide by 500 to get number of mL U-500 required for daily dose
- ▶ 4. Dived totally daily volume in 2-4 doses

Dosing Strategy 2



Dosing Strategy 3

- ▶ Empirically ↓ dose 10-20% for HbA1C ≤ 8%
- ▶ Empirically ↑ dose 10-20% for HbA1C ≥ 10%

Required TDD (units)	Frequency	U-500 Insulin Dosage (%)
150-300	BID	50/50 or 60/40
	TID	33/33/33
	CSII*	50/50 = 3 mealtime (50%) + 24 hr basal insulin infusion (50%)
300-600	TID	33/33/33
	QID	30/30/30/10
	CSII*	50/50 = 3 mealtime (50%) + 24 hr basal insulin infusion (50%)
>600	QID	30/30/30/10

Dose Titration

- ▶ Similar concept to dose titration of U-100 insulin
 - ▶ Pre-lunch and pre-dinner blood glucose determines morning dose
 - ▶ Bedtime blood glucose determines dinner time dose
- ▶ Increase dose titration increments as total daily dose increased
 - ▶ TDD 200-299 – Adjust by 5-10 units per dose
 - ▶ TDD 300-599 – Adjust by 25-50 units per dose
 - ▶ TDD \geq 600 – Adjust by 50 units per dose

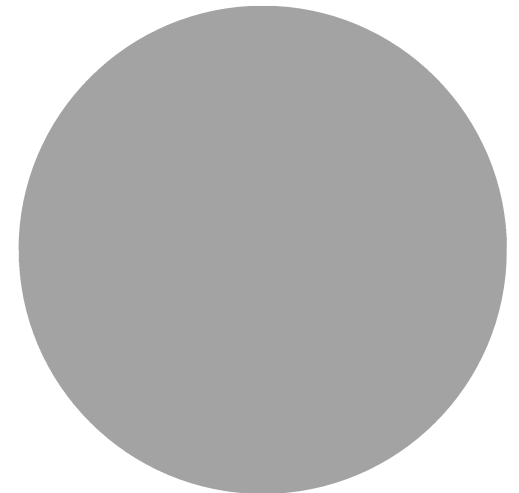
Example Dose Calculation

**55 y/o M with Type 2 DM is currently on 125 units of NPH three times a day.
HbA_{1C} = 8.7%**

- ▶ Step 1: Calculate TDD
 - ▶ **125 + 125 + 125 = 375 units of insulin daily**
- ▶ Step 2: Apply 20% dose reduction
 - ▶ **375 – (0.2 x 375) = 300 units**
- ▶ Step 3: Calculated total daily volume
 - ▶ **300 units x 1ml/500 units = 0.6 mL daily**
- ▶ Step 4: Determine dosing frequency
 - ▶ **100 units (0.2 mL) TID before meals**

Clinical Safety

- ▶ Two main safety concerns
 - ▶ Weight gain
 - ▶ Hypoglycemia
- ▶ Preventative measures
 - ▶ Glucose tabs, glucagon kit
 - ▶ Comprehensive patient education
 - ▶ Systems to reduce medication errors



Medication Errors Reported

- ▶ U-100 used instead of U-500
 - ▶ Stock them separately
- ▶ U-100 syringe used
 - ▶ Use tuberculin syringes only
- ▶ Prescriptions/orders unclear
 - ▶ Indicate dose by volume and units
 - ▶ Take time to clarify dose on prescriptions/orders

TB Syringe

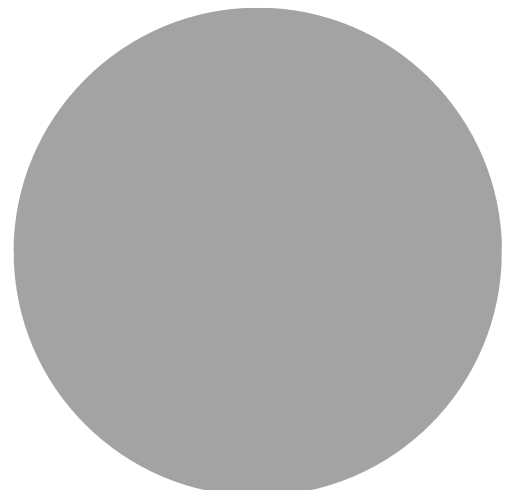


U-100 Syringe



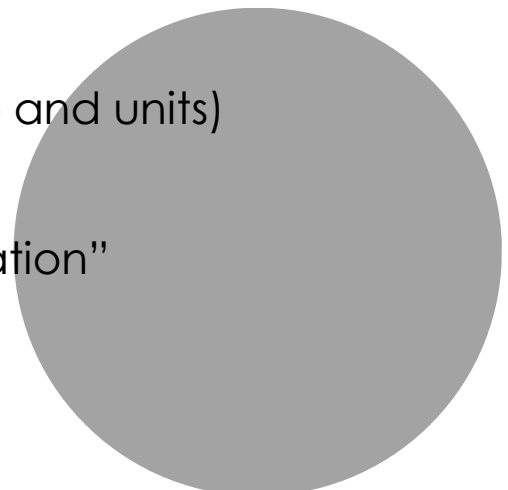
Patient Counseling Points



- ▶ 5x concentrated insulin requires lower volumes
 - ▶ Small changes in dose = bigger shifts in blood glucose
 - ▶ Clear, colorless
 - ▶ Storage requirements
 - ▶ Correct syringe and dose measurement
 - ▶ Administration location and technique
 - ▶ Onset, peak, and duration of action
 - ▶ Signs, symptoms of hypoglycemia
 - ▶ Sick day therapy
 - ▶ Syringe disposal
 - ▶ No adjustments without clinical recommendations
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Pharmacy's Final Checklist



- ✓ Verify U-500 insulin and appropriateness of dose (volume and units)
 - ✓ Discontinue other basal and bolus insulin
 - ✓ Label dose with volume, units, and as "high alert medication"
 - ✓ Double check
 - ✓ Do not load
 - ✓ Hand deliver
 - ✓ Dispense in tuberculin syringe
 - ✓ Comprehensive patient education for new starts
 - ✓ Ensure follow-up scheduled
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Assessment Question 1

- ▶ What minimum daily dose of insulin qualifies a patient as a potential candidate for U-500 Insulin?
 - A. 20 units daily
 - B. 200 units daily
 - C. 400 units daily
 - D. 1000 units daily

Assessment Question 2

- ▶ Which best describes the pharmacokinetics of U-500 insulin?
 - A. Long-acting basal insulin
 - B. Short-acting bolus insulin
 - C. Rapid-acting bolus insulin
 - D. Exhibits both basal and bolus pharmacokinetics

Assessment Question 3

- ▶ Based on pharmacokinetics, how often should U-500 insulin be dosed?
 - A. Once daily
 - B. 2-4 times daily
 - C. At least 4 times daily
 - D. Every 4 hours around the clock

References

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