



Finding Ways Around High Dose Insulin Requirements: U-500 Insulin, Weight Loss, and Future Therapies



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Outline of Talk

- High Dose Insulin Requirements- History of Treatment
 - Examples of severe insulin resistance
 - Identifying patients with "other" forms of diabetes
 - Impact of energy intake on insulin sensitivity
 - "High-Dose Insulin Requirements"—Mechanical issues
- Principles of treating to target glycemia
 - DCCT, DPP, UKPDS
- Use of Insulin therapy
 - U-500 insulin
 - Pharmacology and Availability
 - Manufactured by Lilly USA, LLC
 - Pharmacologic profile
 - Cost



Outline (cont)

- Deciding when to begin U-500 insulin
 - Principles that guide practice
 - Determining patient's U-500 requirements
- Dosing of U-500 Insulin
 - >100-299, 300-599, >600 units/day
 - Dose adjustments
- Specifics with Insulin Pumps
- Practical Issues in Administration
 - Inpatient Setting
 - Outpatient Setting
- Impact of Diet
 - Examples of diet therapy on insulin requirements



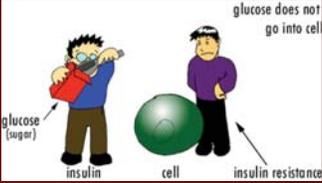
Outline (cont)

- Teaching Points
 - Encourage decrease caloric intake
 - Examples of Regimen Handouts
 - Teaching patients how to express their regimen to others
- Conclusions
 - Weight loss and decreased caloric intake, and increasing activity are essential to controlling insulin doses
 - U-500 insulin is effective and cost efficient in high dose insulin requiring patient
 - Diabetes educator plays key role in teaching patient to use and administer U-500 insulin



Patients with "High-Dose Insulin Requirements"

- Typically defined as "severe insulin resistance"
- Patients requiring more than 200 units of insulin/day, for > 2 days
- Pediatric (and in general in terms of weight) patients requiring more than 2-3 units/kg/day





Insulin Requirements

- Influenced by type of diabetes
- Influenced by energy intake
 - Insulin requirements when fasting
 - Insulin requirements after bariatric surgery
- Influenced by device/mechanical issues:
 - Pumps with bolus rate limits of 1 unit per 40 seconds, maximum bolus of 25-30 units, and cartridge that holds 180-300 units
 - Pens with maximum amount of 60 unit or 80 unit bolus

ADA Classification of Diabetes

- Type 1 Diabetes
- Type 2 Diabetes
- Gestational Diabetes
- Other specific types of diabetes

*All can be associated with high dose insulin requirements

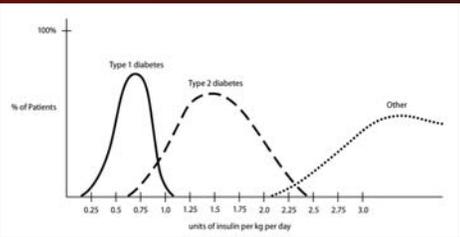


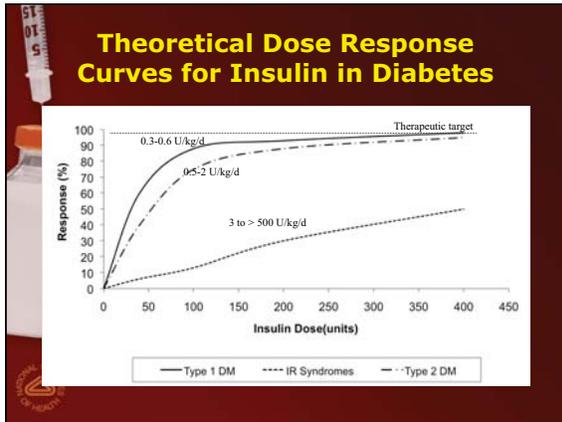
Review of "Other" Diabetes

- Genetic defects of β cell function
- Genetic defects of Insulin Action
 - Studies at NIH of patients with Type A, Leprechaunism, Lipodystrophy. Typically most commonly associated with use of U-500 insulin
- Type B (also associated with U-500)
- Endocrinopathies (Acromegaly, Cushing's)
- Drug induced (steroids, etc)

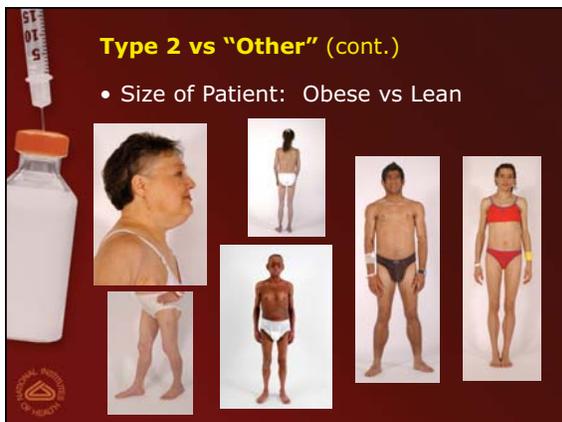


Typical Insulin Requirements for Various Forms of Diabetes Mellitus





- ### Type 2 vs "Other"—Simple Screening
- Laboratory findings
 - Fasting TG's level
 - Severity of insulin resistance (i.e. insulin or c-peptide levels)
 - Insulin requirements on weight maintenance/weight loss diet
 - Physical symptoms of hyperinsulinemia
 - Age of Patient: Young vs "Older"



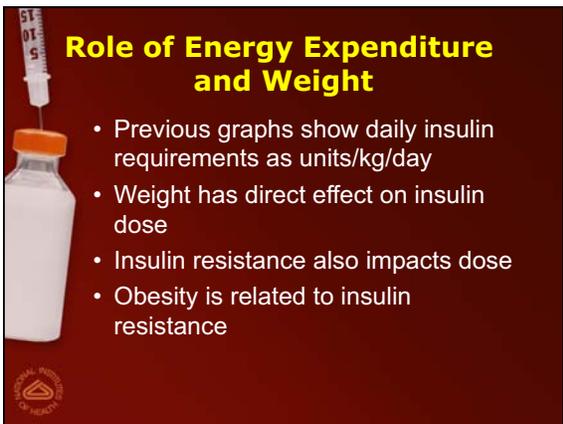
Type 2 vs. Other (cont.)

- Physical Findings: *acanthosis nigricans* and *polycystic ovarian syndrome*



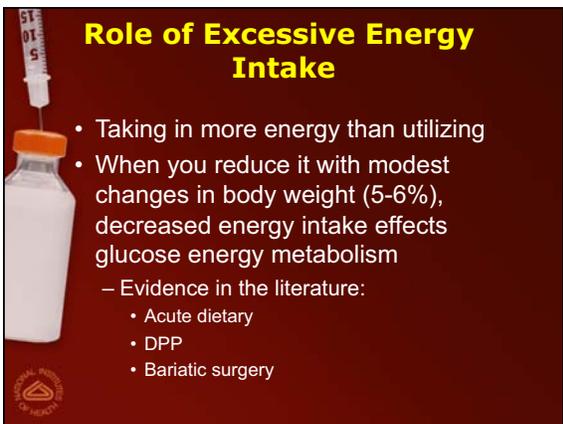
Role of Energy Expenditure and Weight

- Previous graphs show daily insulin requirements as units/kg/day
- Weight has direct effect on insulin dose
- Insulin resistance also impacts dose
- Obesity is related to insulin resistance



Role of Excessive Energy Intake

- Taking in more energy than utilizing
- When you reduce it with modest changes in body weight (5-6%), decreased energy intake effects glucose energy metabolism
 - Evidence in the literature:
 - Acute dietary
 - DPP
 - Bariatric surgery





Excess energy intake... (cont.)

Fluctuations in the Affinity and Concentration of Insulin Receptors on Circulating Monocytes of Obese Patients

EFFECTS OF STARVATION, REFEEDING, AND DIETING

ROBERT S. BAIG, PHILLIP GORDEN, JESSE BOTH, C. ROSALE KAHN, and PIERRE DE MEYTS

From the Diabetes Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20814

One of the first articles, describing a study done at our Institute, looking at the acute physiologic effects of decreased energy intake on insulin sensitivity.



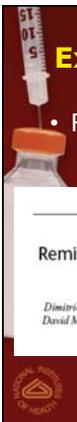


Excess energy intake...(cont.)

Findings of the Diabetes Prevention Program:

This is another example, and well known, of how weight loss, even modest (5%), results in improvement in insulin sensitivity.





Excess energy intake...(cont.)

- Recent example:

ORIGINAL STUDY

Remission of Type 2 Diabetes After Gastric Bypass and Banding Mechanisms and 2 Year Outcomes

Dimitrios J. Pournaras, MRCSP, Alan Osborne, MRCSP, Simon C. Hawkins, MRCSP, Royce P. Vincent, MSc, David Mahon, MD, FRCS, Paul Ewings, PhD, Mohammad A. Ghatei, PhD, Stephen R. Bloom, FRCP, DSc, Richard Welbourn, MD, FRCS, and Carel W le Roux, MRCP, PhD





Putting it all together: Example from Pima Indians

- Median dose of insulin for a group of Pima Indians: 70 units/day.
- Average weight: 100 kg.
- Average HgbA1c: 9.4%
- High incidence of microvascular disease





Why?

- Principles behind insulin therapy
- Hyperglycemia over time will lead to microvascular/cardiovascular complications
- Insulin leads to weight gain and obesity, which also has co-morbidities
- Complications of weight gain (excess energy intake) vs. hyperglycemia



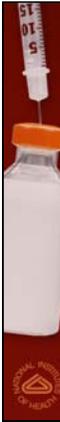


Answer

- Evidenced based medicine--treat diabetes
 - DCCT, EDIC, UKPDS, ADVANCE and other trials
- Evidence shows clear rationale for maintaining glucose levels as close to "target" as possible
- Yes, obesity is bad, but hyperglycemia can lead to microvascular disease, cardiovascular disease.
- Looking back to "model patient populations": microvascular disease is rampant amongst the Pima Indian populations.



Insulin Developments 1924-1997



- 1924 U-80 introduced
- 1946 Isophane insulin (NPH--Toronto-Hagedorn Labs)
- 1952 **Beef U-500 Regular** (Lilly); insulin zinc suspensions developed (Hallas-Moller; Copenhagen-Novo)
- 1973 U-100 introduced
- 1980 **Pork U-500 Regular** (Lilly)
- 1982 human insulin (pork modification [Novo]; recombinant technology [Humulin@Genentech/Lilly])
- 1996 Lispro (Humalog@--Lilly)
- 1997 **Human U-500** (Humulin@ U-500 Regular--Lilly)



Use of U-500 Insulin in the Literature—First Reports



- 1976 Kahn et al. wrote about syndromes of insulin resistance
- 1989 Fain's case report using U-500 with educator perspective
- 2000 First recorded use of U-500 during pregnancy
- 2003 Detailed use in pump in T2DM
- 2005 Cochran et al., U-500 algorithm
- 2008 Cochran et al., U-500 use in children



NIH Patients on U-500




As of 9/2010

Syndrome	No. of Patients	Dose Range, units/kg per day	Age Range, years	Weight, Mean (SD), kg	Weight Range, kg
Type A IR	6	6-566	10-57	58.2	44-80
Rabson-Mendenhall	5	7.6-80	9-27	34	22-48
Type B IR	31	3-416	10-64	56.7	32-68
Lipodystrophy	24	3-28	12-57	60.1	28-92
Type 2 DM	15	1.4-5.6	34-65	117.5	78-149
Totals:	81	1.5-566	9-64	66	22-146





Efficacy of U-100 Insulin Delivery in High-Dose Requiring Patients

Practically (mechanical influences):

- Syringes highest volume is 100 units.
- Pens highest volume is 60-80 units, with the total insulin pen cartridge only holding up to 300 units.
- Pump cartridges hold 180-300 units.
- Pump bolus rates and limits (25-30 units)
- Batteries for pumps need to be changed more frequently (every week as opposed to month)
- Insurance for supplies often at set levels/amounts (often based on Type 1 diabetes model)



Manufacturer	Model	Reservoir Volume	Basal Increment	Bolus Increments and Maximum	Bolus Duration for 1 Unit	Battery Life	Battery Type
Animas (U.S.)	OneTouch Ping™ Glucose Management System	200 uL	0.025 unit	0.05 unit or 0.5, 1.0 or 1.0 units	1 or 2 seconds	4-6 weeks with lithium 2-4 weeks with alkaline	1 AA lithium or 1 AA alkaline
Insulet Corporation	OneStep Insulin Management System	200 uL	0.05 unit	0.05, 0.1, 0.5, 1, up to 30 units	40 seconds	1000 3 weeks	Two AAA alkaline
Medtronic	MiniMed Paradigm 722	1.8 mL	0.05 unit	0.1 unit, range of 0.1 to 25 units	40 seconds	2 to 4 weeks	One AAA alkaline; readily available
	MiniMed Paradigm 722	300 uL	0.05 unit	0.05 to 30 units, in 0.05 unit steps	3 seconds	2 to 3 weeks	One Duracell CR2
Nipro Diabetes Systems (U.S.)	Amigo	300 uL	0.05 unit	0.05 to 30 units, in 0.05 unit steps	3 seconds	2 to 3 weeks	One Duracell CR2

Chart from: Diabetes Health Professional, Dec-Jan, 2010, pp.22-23.



Efficacy of U-100 (cont.)

Patient comfort

- Multiple large volume injections-difficult/painful
- Complicated/painful regimen minimizes compliance
- Risk of abscesses in single injection site i.e. pumps

Absorption and Action of Insulin

- Large injection volume impedes absorption
- Dose response curves are flattened and shifted to the right, thus potency of larger volume of insulin is actually reduced

What is U-500 Insulin?

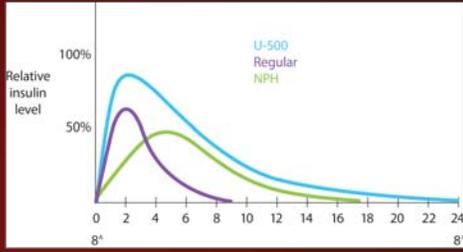
- Human Regular Insulin
- 5 times more concentrated than U-100
- Dose Response
 - Onset: within 30 minutes
 - Peak: 1.75 to 4 hours
 - Duration of action: 6 to 10 hours, up to 24 hours
- Often compared to "NPH drug profile"



U-500 Human Regular



Theoretical Time Action Profile



Time (hours)	U-500 Regular (Relative Insulin Level)	NPH (Relative Insulin Level)
0	0	0
2	~80%	~40%
4	~60%	~50%
6	~40%	~60%
8	~20%	~50%
10	~10%	~40%
12	~5%	~30%
14	~2%	~20%
16	~1%	~15%
18	~0.5%	~10%
20	~0.2%	~5%
22	~0.1%	~2%
24	~0.05%	~1%



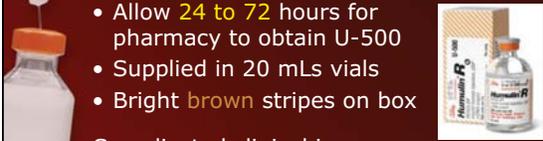
Cost Comparisons

COST ANALYSIS OF INSULIN			
Insulin/ Strength	Unit of issue	Price per vial in U.S. dollars	Price per unit in U.S. dollars
Insulin Regular 100U/mL	10 mL vial	\$57.96	\$0.06
Insulin Lispro 100U/mL	10 mL vial	\$119.58	\$0.12
Insulin NPH 100U/mL	10 mL vial	\$57.96	\$0.06
Insulin Glargine 100U/mL	10 mL vial	\$111.14	\$0.11
Insulin Aspart 100U/mL	10 mL vial	\$119.58	\$0.12
U-500 Insulin Regular 500U/mL	20 mL vial	\$337.44	\$0.03

**Average Wholesale Prices as of August 4, 2010

Availability

- Allow **24 to 72** hours for pharmacy to obtain U-500
- Supplied in 20 mLs vials
- Bright **brown** stripes on box



Complicated clinical issues
 – contact Jeffrey Alan
 Jackson, MD *Lead physician for U-500R at Lilly. USA*
(317) 277-5742

Safety/Handling Considerations

- Hypoglycemia (similar incidence to U-100)
- No syringe **currently** available to measure “actual units” of U-500
- Hospitals must delineate as **CONCENTRATED** in formulary
- Pharmacies cannot stock unless have existing patient on U-500
- Stability comparable to other forms
 - Storage and shelf life
- Pre-draw syringes should be stored with needle upright.



Starting U-500

- *Verify* if and how patient is taking current U-100 regimen
 - Is delivery device optimal?
 - Can patient describe regimen well (since they supposedly do it every day)
- *Determine* daily insulin requirements

Useful method:
 U-100 Regular four times daily (30%, 25%, 25%, 20%; weight based)



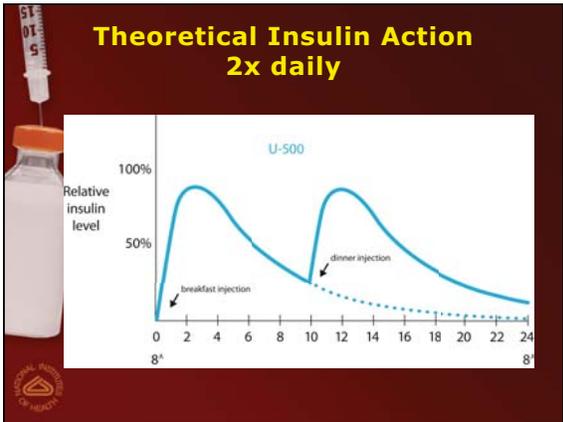
Dosing of U-500

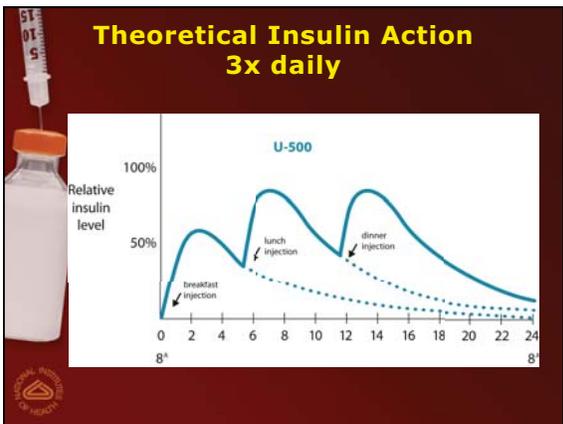
- 1) *Stop* all forms of insulin U-100
- 2) HgbA1c <8%, reduce 10-20%
 HgbA1c >10%, increase 10-20%
- 3) U-500 "Basal/Bolus Therapy"
 - A. twice daily
 - B. three times daily
 - C. four times daily, for over 600U/day
- 4) Determine best delivery method



Algorithm for the Administration and Dosing of U-500 Insulin

INSULIN DAILY DOSE	INJECTION FREQUENCY/SCHEDULE/DELIVERY	GUIDE FOR HOW DOSES ARE DIVIDED DAILY VIA PERCENTAGE (%) OF THE TOTAL DAILY DOSE
100-300 units/day	Twice daily (i.e. 8A, 6PM) -- Basal Insulin	60/40
	Three times daily (i.e. 8A, 12noon, 6PM) -- Basal Insulin	40/30/30
	Via insulin pump (unit = 0.01 mLs, 0.01 mLs of U-500 insulin = 5 units)	Three mealtime boluses (30/25/25) In addition a set basal rate of 20% of the total daily dose (minimum basal rate changes per day) Or basal at 50% of total daily dose, and divide up boluses (20/20/10). Nighttime basal may need to be hormonally adjusted.
300-600 units/day	Three times daily	40/30/30
	Four times daily (i.e. 8A, 12noon, 5PM, 10PM)	30/30/30/10
	Via insulin pump (unit = 0.01 mLs, 0.01 mLs of U-500 insulin = 5 units)	Three-four mealtime boluses For basal rate 20% of daily dose, boluses are (30/30/20 or 30/25/20%). For basal at 50% of total daily dose, and divide up boluses (20/20/10 or 20/15/10-5). Bedtime snack bolus should be 10% or less of total daily dose.
> 600 units/day	Four times daily ** do not inject more than 2 mLs in any one injection site	30/30/30/10





Appropriate Prescription Example

- *TB syringe*
 - Insulin Human Regular U-500, inject 150 units, 0.3 mLs subcutaneously, 3 times daily before meals. Dispense 2 vials.
- *Insulin syringe*
 - Insulin Human Regular U-500, inject 150 units, 30 unit markings subcutaneously, 3 times daily before meals. Dispense 2 vials.

Dosage Conversion Chart

Volume - Tuberculin Syringe (mLs)	U-100 Syringe (unit markings)	U-500 Insulin Dose (actual units)
0.1	10	50
0.2	20	100
0.3	30	150
0.4	40	200
0.5	50	250
0.6	60	300
0.7	70	350
0.8	80	400
0.9	90	450
1.0	100	500

Insulin Pump Use

- Technically "off-label" use through pump
- Doses 100-600 units/day
- Not recommended for >600U/day
- Not in volume, use "pump units"
 - 1 "pump unit" = 0.01mLs
 - 0.01mLs = 5U of U500
 - 1 "pump unit" = 5 actual units of U-500




Insulin Pump Use (cont.)...

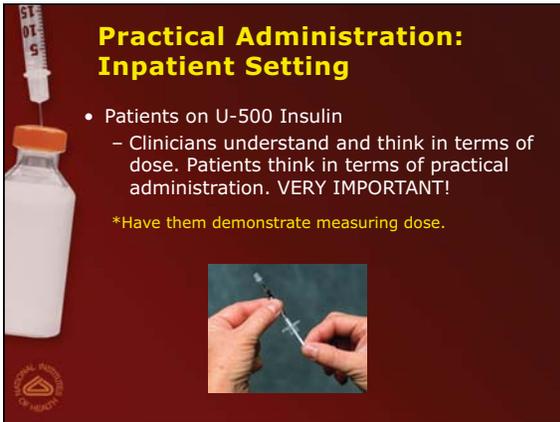
- Patients on U-500 MDI, 50% of TDD ÷ 24, single basal hourly rate. Remaining 50% distributed as pre-meal boluses
- Patients on U-100, 50% of TDD ÷ 5 then ÷ 24 to determine basal.
- Insulin on board: Set at 6 hours
- Important info: 1) fasting basal, 2) endogenous insulin production



Practical Administration: Inpatient Setting

- Patients on U-500 Insulin
 - Clinicians understand and think in terms of dose. Patients think in terms of practical administration. VERY IMPORTANT!

*Have them demonstrate measuring dose.



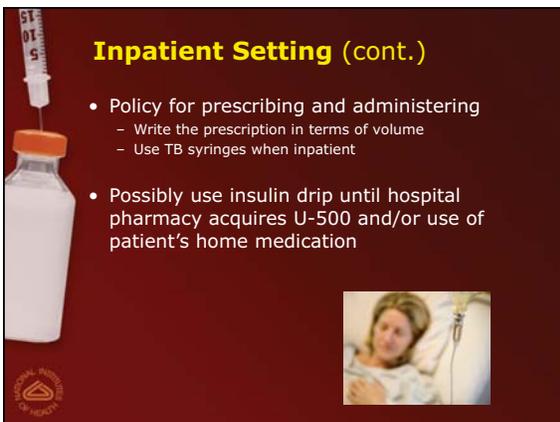
Dose Verification Tool

⊗⊗⊗ THIS IS NOT AN ORDER ⊗⊗⊗ **INSULIN HOME DOSE VERIFICATION:**
DOSE & SYRINGE MUST BE VERIFIED PRIOR TO DISPENSING MEDICATION.

Patient or care provider verbalized and demonstrated measuring to the marks described for each dose below:	
Patient uses INSULIN SYRINGE at home - dose is reported as Unit markings measured on an INSULIN syringe	Patient uses a TUBERCULIN SYRINGE at home - dose is reported in volume (mL)
<input type="checkbox"/> Breakfast Dose: \$ X _____ unit markings on an INSULIN SYRINGE = _____ units U-500 insulin administered.	<input type="checkbox"/> Breakfast Dose: 500 X _____ mL = _____ units U-500 insulin administered.
<input type="checkbox"/> Lunch Dose: \$ X _____ unit markings on an INSULIN SYRINGE = _____ units U-500 insulin administered.	<input type="checkbox"/> Lunch Dose: 500 X _____ mL = _____ units U-500 insulin administered.
<input type="checkbox"/> Dinner Dose: \$ X _____ unit markings on an INSULIN SYRINGE = _____ units U-500 insulin administered.	<input type="checkbox"/> Dinner Dose: 500 X _____ mL = _____ units U-500 insulin administered.
<input type="checkbox"/> Bedtime Dose: \$ X _____ unit markings on an INSULIN SYRINGE = _____ units U-500 insulin administered.	<input type="checkbox"/> Bedtime Dose: 500 X _____ mL = _____ units U-500 insulin administered.

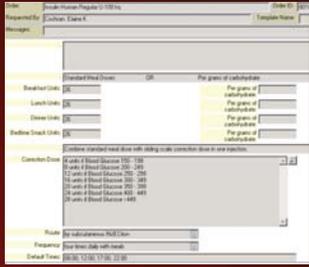
Inpatient Setting (cont.)

- Policy for prescribing and administering
 - Write the prescription in terms of volume
 - Use TB syringes when inpatient
- Possibly use insulin drip until hospital pharmacy acquires U-500 and/or use of patient's home medication



Inpatient Setting (cont.)

- Four times daily Insulin Regular U-100, is also effective up to 300U/day, until U-500 can be obtained in the hospital.



The screenshot shows a software window for 'Insulin Regular U-100'. It includes fields for 'Standard New Order', 'Per gram of carbohydrate', and 'Per gram of alcohol'. There are also sections for 'Caution Code' and 'Default Time'.

Inpatient Setting: Syringe Selection

TB Syringe
 -Recommended for volume measurement
 - 0.5 mLs, 1.0 mLs
 - Available in safety needle form

Insulin syringe
 -"unit markings"

*Prescription must match syringe



The image shows two insulin syringes. The one on the left is blue and the one on the right is orange. Both have markings for units and milliliters.

Inpatient Setting:

- Resources such as the American Journal of Health-System Pharmacy
- Standing order insulin vs. Corrective Regimens
- Pharmacy prepare dose vs. Nurses drawing up dose
- IMPACT OF DIET
 - Patient may only require U-100 insulin in the hospital, as they are eating less
 - Examples of diet (energy intake) on insulin doses

Inpatient Setting (cont.)

Volume - Tuberculin Syringe (mLs)	U-100 Syringe (unit markings)	U-500 Insulin Dose (actual units)
0.1	10	50
0.2	20	100
0.3	30	150
0.4	40	200
0.5	50	250
0.6	60	300
0.7	70	350
0.8	80	400
0.9	90	450
1.0	100	500

Outpatient Setting

- Health insurance coverage issues of insulin and supplies
- Specialized teaching:
 - Transcribing dose such that patient understands
 - Reinforcing proper regimen communication



Outpatient Setting (cont.)

Before Breakfast (Between 7A-10A) and Lunch (11A-1P):

Blood sugar	Insulin U-500 to inject	Actual units of insulin
80-124	0.15 mLs (15 unit markings)	=75 units
125-249	0.2 mLs (20 unit markings)	=100 units
250-299	0.3 mLs (30 unit markings)	=150 units
300-349	0.5 mLs (50 unit markings)	=250 units
350-449	0.6 mLs (60 unit markings)	=300 units
>449	0.8 mLs (80 unit markings) and Call MD for >449	=400 units

Before Dinner (Between 5P-8P):

Blood sugar	Insulin U-500 to give	Actual units of insulin
80-124	0.08 mLs (8 unit markings)	=40 units
125-199	0.12 mLs (12 unit markings)	=60 units
200-299	0.2 mLs (20 unit markings)	=100 units
300-349	0.3 mLs (30 unit markings)	=150 units
350-449	0.4 mLs (40 unit markings)	=200 units
>449	0.5 mLs (50 unit markings) and Call MD for >449	=250 units

Contact 1-800 Lilly Rx for U-500 Leave Behind

Future Therapies-NIDDK Research

- Research looking at regulating the “human thermostat”, and energy excess issues
- Our research with leptin therapy
 - Hormone secreted in adipose tissue
 - Hormone controls appetite

Conclusions

- Insulin requirements are based on type of diabetes, degree of insulin resistance, weight, and energy intake
- Epidemic of obesity is increasing the incidence of type 2 diabetes, and high dose insulin requirements
- Evidence from diabetes complications trials provides principles to treat hyperglycemia
- U-500 insulin has been used since 1952
- U-500 has onset and peak of action similar to regular insulin, but duration of action more like NPH
- Dosing algorithm based on anecdotal experience of hundreds of patients
 - U-500 needs to be weighted more towards morning and mid-day, lesser amounts evening and bedtime.



Conclusions (cont.)

- Hospital use of U-500
 - TB syringe recommended
 - Hospital policy of use needed
 - Impact of diet on insulin requirements
 - Existing U-500 patients should demonstrate their dose on the syringe they use to prescriber
- Inpatient and Outpatient Use
 - Specialized diabetes instruction
 - Reinforce caloric reduction, increase exercise
 - Unique written materials
 - When verifying the dose—have patient show their dose on the syringe





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- Phillip Gorden, MD
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 - Irl Hirsch, MD
 - Wendy Lane, MD
 - Jay Skyler, MD
- U-500 "colleagues"
 - Virginia Valentine, CNS

...and my courageous patients





Questions?

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- Office phone: (301) 496-2718
- Lilly USA, LLC
 - 1-800 LILLY RX