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

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Bethesda, Maryland
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

![Graph showing typical insulin requirements for Type 1 diabetes, Type 2 diabetes, and other forms of diabetes.](image)
Theoretical Dose Response Curves for Insulin in Diabetes

- 0.3-0.6 U/kg/d
- 0.5-2 U/kg/d
- 3 to > 500 U/kg/d

Therapeutic target
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.)

- Size of Patient: Obese vs Lean
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.)

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, MRCS*, †, Alan Osborne, MRCS*, Simon C. Hawkins, MRCS, Royce P. Vincent, MSc†, David Mahon, MD, FRCS*, Paul Ewings, PhD*, Mohammad A. Ghatari, 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
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

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>No. of Patients</th>
<th>Dose Range, units/kg per day</th>
<th>Age Range, years</th>
<th>Weight, Mean (SD), kg</th>
<th>Weight Range, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A IR</td>
<td>6</td>
<td>6–566</td>
<td>16–57</td>
<td>56.2</td>
<td>44–60</td>
</tr>
<tr>
<td>Rabson-Mendenhall</td>
<td>5</td>
<td>7.6–80</td>
<td>9–27</td>
<td>34</td>
<td>22–48</td>
</tr>
<tr>
<td>Type B IR</td>
<td>31</td>
<td>3–416</td>
<td>10–64</td>
<td>56.7</td>
<td>32–68</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>24</td>
<td>3–28</td>
<td>12–57</td>
<td>60.1</td>
<td>28–92</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>15</td>
<td>1.4–5.6</td>
<td>34–65</td>
<td>117.5</td>
<td>78–149</td>
</tr>
<tr>
<td><strong>Totals:</strong></td>
<td><strong>81</strong></td>
<td><strong>1.5–566</strong></td>
<td><strong>9–64</strong></td>
<td><strong>66</strong></td>
<td><strong>22–146</strong></td>
</tr>
</tbody>
</table>
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)
<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Model</th>
<th>Reservoir Volume</th>
<th>Basal Increment</th>
<th>Bolus Increments and Maximum</th>
<th>Bolus Duration for 1 Unit</th>
<th>Battery Life</th>
<th>Battery Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animas (U.S.)</td>
<td>OneTouch® Ping™ Glucose Management System</td>
<td>2mLs</td>
<td>0.025 unit</td>
<td>0.05 visual or 0.1, 1.0 or 5.0 audio</td>
<td>1 or 3 seconds</td>
<td>4-6 weeks with lithium 2-4 weeks with alkaline</td>
<td>1 AA lithium or 1 AA alkaline</td>
</tr>
<tr>
<td>Insulet Corporation</td>
<td>OmniPod Insulin Management System</td>
<td>2mLs</td>
<td>0.05 unit</td>
<td>0.05, 0.1, 0.5, 1, up to 30 units</td>
<td>40 seconds</td>
<td>PDM: 3 weeks</td>
<td>Two AAA alkaline</td>
</tr>
<tr>
<td>Medtronic</td>
<td>MiniMed Paradigm™ 522</td>
<td>1.8 mLs</td>
<td>0.05 unit</td>
<td>0.1 unit, range of 0.1 to 25 units</td>
<td>40 seconds</td>
<td>2 to 4 weeks</td>
<td>One AAA alkaline; readily available</td>
</tr>
<tr>
<td></td>
<td>MiniMed Paradigm™ 722</td>
<td>3mLs</td>
<td>0.05 unit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nipro Diabetes Systems (U.S.)</td>
<td>Amigo</td>
<td>3mLs</td>
<td>0.05 unit</td>
<td>0.05 to 30 units, in 0.05 unit steps</td>
<td>5 seconds</td>
<td>2 to 3 weeks</td>
<td>One. Duracell, CR2</td>
</tr>
</tbody>
</table>

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

Relative insulin level

U-500
Regular
NPH

0 2 4 6 8 10 12 14 16 18 20 22 24
8^A

100%
50%
### Cost Analysis of Insulin

<table>
<thead>
<tr>
<th>Insulin/ Strength</th>
<th>Unit of issue</th>
<th>Price per vial in U.S. dollars</th>
<th>Price per unit in U.S. dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Regular 100U/mL</td>
<td>10 mL vial</td>
<td>$57.96</td>
<td>$0.06</td>
</tr>
<tr>
<td>Insulin Lispro 100U/mL</td>
<td>10 mL vial</td>
<td>$119.58</td>
<td>$0.12</td>
</tr>
<tr>
<td>Insulin NPH 100U/mL</td>
<td>10 mL vial</td>
<td>$57.96</td>
<td>$0.06</td>
</tr>
<tr>
<td>Insulin Glargine 100U/mL</td>
<td>10 mL vial</td>
<td>$111.14</td>
<td>$0.11</td>
</tr>
<tr>
<td>Insulin Aspart 100U/mL</td>
<td>10 mL vial</td>
<td>$119.58</td>
<td>$0.12</td>
</tr>
<tr>
<td>U-500 Insulin Regular 500U/mL</td>
<td>20 mL vial</td>
<td>$337.44</td>
<td>$0.03</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>INSULIN DAILY DOSE</th>
<th>INJECTION FREQUENCY/SCHEDULE/DELIVERY</th>
<th>GUIDE FOR HOW DOSES ARE DIVIDED DAILY VIA PERCENTAGE (%) OF THE TOTAL DAILY DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-300 units/day</td>
<td>Twice daily (i.e. 8A, 6PM) +/- Basal Insulin</td>
<td>60/40</td>
</tr>
<tr>
<td></td>
<td>Three times daily (i.e. 8A, 12noon, 6PM) +/- Basal Insulin</td>
<td>40/30/30</td>
</tr>
<tr>
<td></td>
<td>Via insulin pump (1 unit = 0.01 mLs. 0.01 mLs of U-500 insulin = 5 units)</td>
<td>Three mealtime boluses (30/25/25) In addition a set basal rate of 20% of the total daily dose (minimize 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 dramatically reduced</td>
</tr>
<tr>
<td>300-600 units/day</td>
<td>Three times daily</td>
<td>40/30/30</td>
</tr>
<tr>
<td></td>
<td>Four times daily (i.e. 8A, 12noon, 5PM, 10PM)</td>
<td>30/30/30/10</td>
</tr>
<tr>
<td></td>
<td>Via insulin pump (1 unit = 0.01 mLs. 0.01 mLs of U-500 insulin = 5 units)</td>
<td>Three-four mealtime boluses For basal rate 20% of daily dose, boluses are (30/30/20 or 30/25/20/5). 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.</td>
</tr>
<tr>
<td>&gt; 600 units/day</td>
<td>Four times daily ** do not inject more than 2 mLs in any one injection site</td>
<td>30/30/30/10</td>
</tr>
</tbody>
</table>
Theoretical Insulin Action
2x daily
Theoretical Insulin Action
3x daily
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

<table>
<thead>
<tr>
<th>Volume – Tuberculin Syringe (mLs)</th>
<th>U-100 Syringe (unit markings)</th>
<th>U-500 Insulin Dose (actual units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>0.2</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>0.3</td>
<td>30</td>
<td>150</td>
</tr>
<tr>
<td>0.4</td>
<td>40</td>
<td>200</td>
</tr>
<tr>
<td>0.5</td>
<td>50</td>
<td>250</td>
</tr>
<tr>
<td>0.6</td>
<td>60</td>
<td>300</td>
</tr>
<tr>
<td>0.7</td>
<td>70</td>
<td>350</td>
</tr>
<tr>
<td>0.8</td>
<td>80</td>
<td>400</td>
</tr>
<tr>
<td>0.9</td>
<td>90</td>
<td>450</td>
</tr>
<tr>
<td>1.0</td>
<td>100</td>
<td>500</td>
</tr>
</tbody>
</table>
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.
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.
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
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.)

<table>
<thead>
<tr>
<th>Volume – Tuberculin Syringe (mLs)</th>
<th>U-100 Syringe (unit markings)</th>
<th>U-500 Insulin Dose (actual units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>0.2</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>0.3</td>
<td>30</td>
<td>150</td>
</tr>
<tr>
<td>0.4</td>
<td>40</td>
<td>200</td>
</tr>
<tr>
<td>0.5</td>
<td>50</td>
<td>250</td>
</tr>
<tr>
<td>0.6</td>
<td>60</td>
<td>300</td>
</tr>
<tr>
<td>0.7</td>
<td>70</td>
<td>350</td>
</tr>
<tr>
<td>0.8</td>
<td>80</td>
<td>400</td>
</tr>
<tr>
<td>0.9</td>
<td>90</td>
<td>450</td>
</tr>
<tr>
<td>1.0</td>
<td>100</td>
<td>500</td>
</tr>
</tbody>
</table>
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):

<table>
<thead>
<tr>
<th>Blood sugar</th>
<th>Insulin U-500 to inject</th>
<th>Actual units of insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>80-124</td>
<td>0.15 mls (15 unit markings)</td>
<td>= 75 units</td>
</tr>
<tr>
<td>125-249</td>
<td>0.2 mls (20 unit markings)</td>
<td>= 100 units</td>
</tr>
<tr>
<td>250-299</td>
<td>0.3 mls (30 unit markings)</td>
<td>= 150 units</td>
</tr>
<tr>
<td>300-349</td>
<td>0.5 mls (50 unit markings)</td>
<td>= 250 units</td>
</tr>
<tr>
<td>350-449</td>
<td>0.6 mls (60 unit markings)</td>
<td>= 300 units</td>
</tr>
<tr>
<td>&gt;449</td>
<td>0.8 mls (80 unit markings) and Call MD for &gt;449</td>
<td>= 400 units</td>
</tr>
</tbody>
</table>

#### Before Dinner (Between 5P-8P):

<table>
<thead>
<tr>
<th>Blood sugar</th>
<th>Insulin U-500 to give</th>
<th>Actual units of insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>80-124</td>
<td>0.08 mls (8 unit markings)</td>
<td>= 40 units</td>
</tr>
<tr>
<td>125-199</td>
<td>0.12 mls (12 unit markings)</td>
<td>= 60 units</td>
</tr>
<tr>
<td>200-299</td>
<td>0.2 mls (20 unit markings)</td>
<td>= 100 units</td>
</tr>
<tr>
<td>300-349</td>
<td>0.3 mls (30 unit markings)</td>
<td>= 150 units</td>
</tr>
<tr>
<td>350-449</td>
<td>0.4 mls (40 unit markings)</td>
<td>= 200 units</td>
</tr>
<tr>
<td>&gt;449</td>
<td>0.5 mls (50 unit markings) and Call MD for &gt;449</td>
<td>= 250 units</td>
</tr>
</tbody>
</table>
Contact 1-800 Lilly Rx for U-500 Leave Behind

Choose Humulin® U-500 (Concentrated) insulin for treatment of diabetes patients with a high daily insulin requirement

Indications and Usage
- Humulin® R (U-500) is especially useful for the treatment of insulin-resistant patients with diabetes requiring daily doses of more than 200 units, since a single dose may be administered subcutaneously in a reasonable volume.
- Patients with diabetes can develop severe insulin resistance or become so unresponsive to the effect of insulin that daily doses of several hundred or even more units are required.
- Humulin® R (U-500) takes effect rapidly within 30 minutes but has a relatively long duration of activity allowing a single dose (up to 24 hours) as compared with other regular insulins. This effect has been credited to the high concentration of the preparation.
- Most patients will require 2 or 3 injections of Humulin® R (U-500) per day.

Important Dosing Considerations
- An insulin syringe or tuberculin syringe recommended for measuring the dose. When prescribing Humulin® R (U-500), the type of syringe (U-100 insulin syringe or tuberculin syringe) should be specified, and the amount of insulin to be taken should be explained in both actual dose and unit markings (insulin syringe or ml, tuberculin syringe).
- The actual unit dose of Humulin® R (U-500) does not equal the unit markings of a U-100 insulin syringe, nor a tuberculin syringe has volume terms instead of unit markings. It is important to follow the dosing table and formulas below for accurate dosing.

<table>
<thead>
<tr>
<th>Humulin® R (U-500)</th>
<th>U-100 syringe</th>
<th>Tuberculin syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>5</td>
<td>0.60</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>1.20</td>
</tr>
<tr>
<td>75</td>
<td>15</td>
<td>1.80</td>
</tr>
<tr>
<td>100</td>
<td>20</td>
<td>2.40</td>
</tr>
<tr>
<td>125</td>
<td>25</td>
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<tr>
<td>250</td>
<td>50</td>
<td>6.00</td>
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Dosage Formulas:
- Dose (actual units) x 0.2 = unit markings in a U-100 insulin syringe
- Dose (actual units) x 0.6 = volume (ml) in a tuberculin syringe

Select Safety Information
- Extreme caution must be used in measuring the dose of Humulin® R (U-500) accurately.
- Humulin® R (U-500) (500 units/mL) is 3 times the concentration of Humulin® R (U-100).
- Utilizing a syringe and an insulin syringe will allow the patient to inject U-500 insulin accurately.
- Hypoglycemia is one of the most frequent adverse effects associated with insulin therapy. Hypoglycemia with Humulin® R (U-500) may be prolonged life-threatening. Overdosage may result in irreversible hypoglycemia.

Important Safety Information
Humulin® R (U-500), concentrated regular insulin human injection, USP (U-500) is especially useful for the treatment of patients with diabetes who have shown marked insulin resistance (daily requirement of more than 200 units). Because of the larger dose, it may be administered subcutaneously in a reasonable volume.

Hypoglycemia is one of the most frequent adverse effects associated with insulin therapy. Hypoglycemia can occur suddenly, and symptoms may vary among individuals. Individuals allergic to horseradish or papain should not administer or administer Humulin® R (U-500)

Hypoglycemia is a common and potentially serious side effect of insulin therapy. Hypoglycemia in children may be more difficult to recognize after the original injection of Humulin® R (U-500).

Other Side Effects
Abdominal pain or indigestion may occur with the administration of insulin subcutaneously. Pain may subside or disappear after the initial injection of insulin.

Dosage and Administration
Humulin® R (U-500) should be administered subcutaneously. It is recommended that a U-500 insulin syringe and tuberculin syringe be used for measuring the dose.

For additional safety profiles and other important prescribing considerations, see the accompanying full prescribing information.
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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  – Jay Skyler, MD

• U-500 “colleagues”
  – Virginia Valentine, CNS

...and my courageous patients
Questions?

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