The Treatment of Pediatric Diabetes in the New Millennium

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Pediatric Diabetes Statistics (2007 US data)

- **Prevalence under 20 years:**
  - 2nd most prevalent chronic disease of childhood
  - 186,300 or 0.22% of all people in this age group have diabetes
  - 1 in every 400-600 children and adolescents has type 1 diabetes
  - 2 million adolescents (or 1 in 6 overweight adolescents) aged 12-19 have pre-diabetes
  - Resistance of adolescents to transition to adult endocrinology providers due to multiple barriers prolongs care by pediatric diabetes specialists
Diabetes diagnosis

Fasting blood Sugar > 126 mg/dl (on 2 separate Occasions)

Symptoms and Signs of diabetes (polys) with random Blood sugar > 200 Mg/dl

2hr oral glucose tolerance Test (75 mg carb) Blood sugar > 200 mg/dl

Hb A1c >= 6.5% 3 month estimated Mean blood sugar Of 139.85 mg/dl
Multiple variations of pediatric diabetes—no longer “juvenile diabetes”

- Autoimmune Type 1 Diabetes
- Idiopathic Type 1 Diabetes
- Type 2 Diabetes
- Type 1.5 Diabetes
- Cystic Fibrosis Related Diabetes
- Medication (steroid/chemotherapy etc.) Induced Diabetes
- MODY Diabetes (autosomal dominant)
- Diabetes secondary to pancreatectomy
- Permanent Neonatal Diabetes
Permanent Neonatal Diabetes

1. Occurs primarily in patients under 6 mos (a fraction under 1 year)
2. Very rare: 1 in 100,000-300,00 patients
3. Absence of autoimmune markers in PND
4. Mutations in the kir6.2 subunit (encoded by KCNJ11) of the $K_{atp}$ channel of the pancreatic islet cell and other subunits encoded by the ABCC8 gene

Pathophysiology and Treatment of PND

- The KCNJ11 mutation does not allow the release of insulin produced by the pancreatic islet cells due to the blocking of different ion channels in the cell membrane.

- Transition from Insulin regimen to High doses of sulfonylureas (0.8-1.8 mg/kg/day) that modify the ion channels are successful in eliminating the insulin requirement in most patients with PNDM caused by KCNJ11 and ABCC8 mutations.
Proposed Model of the Action of Sulfonylurea on Beta Cells Expressing Mutations in the Kir6.2 Subunit of the KATP Channel

Hattersley et al., NEJM 355:5 August 3, 2006
<table>
<thead>
<tr>
<th>Is it type 1 (or 2)? Or 1.5?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical Type 1 characteristics</strong></td>
</tr>
<tr>
<td>- Sudden onset</td>
</tr>
<tr>
<td>- Thin phenotype</td>
</tr>
<tr>
<td>- Insulin dependant</td>
</tr>
<tr>
<td>- DKA presentation</td>
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<tr>
<td>- Pancreatic antibodies</td>
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<tr>
<td>- Associated autoimmune diseases</td>
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</tbody>
</table>

| **Typical Type 2 characteristics** |
| - Insidious onset |
| - Family history |
| - Obese phenotype |
| - Acanthosis nigricans |
| - Insulin resistance |
| - May present with DKA |
| - Rx with oral agents (metformin) |
| - C-peptide present |
| - Negative GAD-65 antibodies |
1.5 Diabetes???

- Combination of both phenotypic and laboratory characteristics of both type 1 and 2
- Presentation of diabetes with DKA with physical characteristics of acanthosis nigricans, obesity, and POSITIVE GAD-65 antibodies
- May require insulin/and or oral agents at different times of life cycle
Treatment of T2DM - Classical Hierarchy

1. Behavioral modification with diet and exercise.
2. Dietician consultation
3. Psychosocial support - individual therapy
4. Support Groups
5. Oral Medications
6. Basal Insulin (initially)
7. Basal and Bolus insulin
8. Bariatric surgery?

WHY NOT USE INSULIN INITIALLY to DECREASE GLUCOSE TOXICITY and THEN BEGIN ORAL MEDICATION?

(Reverse paradigm in pediatrics)
Insulin sensitizers-
- Metformin (Glucophage)- Primarily Type 2, Type 1 if insulin resistance
- Pioglitazone (Actos)

DPP4 inhibitors (Type 2)-
(inhibits dipeptidyl peptidase-4, slowing incretin metabolism, increasing insulin synthesis/release, decreasing glucagon levels)-
- Sitagliptin (Januvia)

Oral Hypoglycemics- Sulfonylureas (type 2)
- Glyburide, Glipizide
Act Like a Pancreas

- **Basal and Bolus insulins**
  - Basal: insulin required during fasting in order to cover blood sugar release by liver for energy
  - Bolus: insulin required to cover ingested carbohydrates
  - The pancreas secretes human insulin to cover fasting and post-prandial blood sugars
  - **GOAL**: mimic the function of the pancreas with basal and bolus insulins
# Insulins in current usage

## Basal Insulins
- NPH (intermediate-acting) - bid
- Lantus (24 hour and relatively peakless) qd
- Levemir (12 hour and relatively peakless) bid

## Bolus Insulins
- Regular insulin
- Analogues
  - Lispro (Humalog)
  - Aspart (Novolog)
  - Actrapid (Apidra)

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## Insulin Overview

<table>
<thead>
<tr>
<th>Insulin Action</th>
<th>Regular (Bolus)</th>
<th>Humalog Novolog Apidra (Bolus)</th>
<th>NPH (Basal)</th>
<th>Lantus (Basal)</th>
<th>Levemir (Basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>30 minutes</td>
<td>5-30 minutes</td>
<td>1-2 hours</td>
<td>1-2 hours</td>
<td>1-2 hours</td>
</tr>
<tr>
<td>Peak</td>
<td>2-3 hours</td>
<td>1-2 hours</td>
<td>6-8 hours</td>
<td>None</td>
<td>None, but slight in larger doses</td>
</tr>
<tr>
<td>Duration</td>
<td>4-6 hours</td>
<td>3-4 hours</td>
<td>10-12 hours</td>
<td>20-24 hours</td>
<td>12-18 hours</td>
</tr>
<tr>
<td>Other</td>
<td>Clear</td>
<td>Clear</td>
<td>Cloudy</td>
<td>Clear Keep for one month only! Do not mix with other insulins in same syringe. Give once a day within 1-2 hour window.</td>
<td>Clear Keep for one month only! Do not mix with other insulins in same syringe. May need once or twice a day</td>
</tr>
</tbody>
</table>
Insulin Regimens in current use—split mixed (T1DM)

- **Conventional Split mixed insulin (2 or 3 shots/day)**

  - Breakfast: basal insulin (NPH) + bolus insulin (regular or analog [humalog, novolog, or apidra])
  
  - Dinner: bolus insulin (regular or analog) (3 shots/day) OR bolus insulin + basal (NPH) (2 shots/day)
  
  - Bedtime: basal insulin (NPH) (3 shots/day)
Two Shot Regimen

- Regular or Rapid Insulin
- NPH Insulin

Insulin Effect

B L D Bed

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Three Shot Regimen

Insulin Effect

- Regular or Rapid Insulin
- NPH Insulin

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Modified Basal Bolus therapy

fixed dosage of rapid acting insulin for meals

- breakfast: 6 units
- lunch: 6 units
- dinner: 6 units

basal insulin once (or twice daily) in am or pm

- (Glargine) Lantus (bedtime or am) once daily
- (Detemir) Levemir (am and pm) twice daily
**Insulin Regimens in current use—basal/bolus (T1DM)**

**Classic Basal Bolus therapy:**

Bolus insulin determined by:

1. Insulin/carbohydrate ratio
2. Correction factor (insulin sensitivity factor)
3. Target blood sugar

(bolus insulin = insulin for carbohydrates + insulin for correction of bs)

**Basal insulin:** Glargine once daily or Levemir twice daily
Optimized Insulin Replacement Regimen: Mimicking Physiology With Basal and Prandial Insulin Needs

Requirements to begin insulin pump therapy

1. 3-6 months of classic basal/bolus therapy
2. Testing blood sugars \( \geq 4 \) times/day
3. Ability to Problem solve (parent/older child/teen)
4. Psychology pre-pump evaluation
5. “Pump” night— to check out all available pumps
6. Saline trial with personalized instruction by certified pump trainer (CPT)
7. CPT Instruction “go live” with insulin pump
8. Daily follow-up with Certified pump trainer with blood sugars, carbohydrate counts, insulin doses etc.
Barriers/Facilitators with Pump Therapy

- Support system
  - Family
  - School
  - Caregivers
- Independence level of patient
- Language
- Math skills
- Current diabetes management behavior

Courtesy of C L Henderson RN, CDE, CPT
Insulin Regimens in current use—basal/bolus therapy—insulin pump

- **Basal features**
  - Multiple basal rates
  - By time of day
- **Bolus features**
  - Carbohydrate ratios
  - Correction factors
  - By time of day
- **History functions**
  - Bolus history
- **Start/stop**
  - All delivery
  - Bolus
- **Alarms/alerts**
  - Low cartridge
  - Low battery
  - Occlusion
- **Blood sugar meters**
  - Attached
  - Communicate

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Insulin Pump Basics

• **Available Pumps**
  - Animas Ping
  - Deltec Cozmo
    (no further upgrades)
  - MiniMed Rev (revolution)
  - Insulet OmniPod
  - Roche (upgrade soon)
  - Nipro Amigo

• **Model number on back of pump**

• **Contacting Technical Support**

• **Back up pump settings on computer**

(courtesy C L Henderson RN, CDE, CPT)
Infusion Sets

- Infusion set placement
  - Abdomen
  - Back hip
  - Leg
  - Arm

- Types of infusion sets
  - 90 degree
  - Angled
  - Metal

- Issues
  - Site
  - Bent cannula
  - Occlusion

(courtesy C L Henderson RN, CDE, CPT)
Continuous Glucose Monitoring

- New Technology
- Three systems
  - DexCom
  - MiniMed Guardian
  - FreeStyle Navigator

(courtesy C L Henderson RN, CDE, CPT)
Continuous Glucose Monitoring

- Measures interstitial fluid in tissue
- Sensors last three to seven days
- Results every five minutes
- Identify trends of diabetes management
  - Food
  - Insulin
  - Activity

(courtesy C L Henderson RN, CDE, CPT)
Continuous Glucose Monitoring

- Alarms for rapid trends of blood sugars

- Alarms for crossing low or high blood sugar thresholds

(courtesy C L Henderson RN, CDE, CPT)
Continuous Glucose Monitoring

Glucose Modal Day Report
11/12/2008 - 11/21/2008

Time Period
Pre-Bidst Post-Bidst Pre-Lunch Post-Lunch Pre-Dinner Post-Dinner Bed Sleep

Glucose (mg/dL)

6:00 AM 12:00 PM 6:00 PM 12:00 AM

550 500 450 400 350 300 250 200 150 100 50 0
Continuous Glucose Monitoring

Sensor Modal Day
Patient: One Sample 1
ID: 1111111

Time of Day
3:00 AM  6:00 AM  9:00 AM  12:00 PM  3:00 PM  6:00 PM  9:00 PM

Glucose - mg/dL
0  100  200  300  400

Click sensor plot line to read data value

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Disadvantages of CGM

- Does not replace usual home blood sugar monitoring (finger sticking)
  - Interstitial monitoring
  - 20-30 minute delay from blood testing
- Inconvenient - not able to disconnect during testing
- Increased patient education
Future of Technology

- Improved technology and sophistication with management
- Increased reliance on technology
- Better trend management
- Increased patient education
- More costly
- Cure by artificial pancreas (marriage of continuous glucose sensor with insulin pump OR ....)
Current Research: 3 Major Directions

1. Monoclonal antibody studies (ongoing) that prevent destruction of the pancreatic islets by killer T Cells (Protégé Study and Defend) in different trial phases

2. Diamyd vaccine (GAD-65 antibody) phase III clinical trials (2008) to delay destruction of pancreatic islets

3. Diabecell therapy: islet cells are derived from piglets and are encapsulated and can be administered by an injection into the abdominal cavity (peritoneum) by laparoscopy under local anesthesia (2007)

4. Combination “chemotherapy” depending on stage
Questions?
## Resources at Children's

- **Office Main Line**: (202) 476-2121
- **Office Fax Line**: (202) 476-4095

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
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<tbody>
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<td>Dr. Paul Kaplowitz, Endocrinology Dept Chairman</td>
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<tr>
<td>Celia Henderson, BSN, CDE</td>
<td>Dr. Fran Cogen, CDE, Diabetes Pgm Director</td>
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<td>Helen Jenkins, RN, BSN, CDE</td>
<td>Dr. Audrey Austin</td>
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<td>Dr. Elizabeth Parker</td>
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<td>Kelly Sinclair, RD, LD, CDE</td>
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<tr>
<td>Randi Streisand, PhD, CDE</td>
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Resources

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Resources

http://www.ndep.nih.gov/resources/school.htm

.pdf file available for download

Or order a copy
Resources


Glucagon Emergency Administration Training Tool

A Resource for School Nurses and School Personnel
Diabetes Website Resources

- www.Lillydiabetes.com
- www.DiabetesEnEspanol.com
- www.LillyDiabetesToday.com
- www.WebMD.com
- www.niddk.nih.gov
- www.childrenwithdiabetes.com
- www.aace.com
- www.medscape.com
- www.aadenet.org
- www.jdrf.org
- www.cdc.gov/diabetes
- www.mydiabetescentral.com (Dr. Cogen’s blog)