INSULIN THERAPY IN TYPE 1 DIABETES
Goals of management

- Manage symptoms
- Prevent acute and late complications
- Improve quality of life
- Avoid premature diabetes-associated death
- An individualised approach

Glycaemic control

BP

Lipids

Patient education

Eye care

Management

Lifestyle (e.g. diet & exercise)

Foot care

Microalbuminuria & kidneys
Diabetes Management Principles

- An effective insulin regimen
- Monitoring of glucose
- As flexible with food and activity as possible
- Must remember
  - Young children need routine and rules
  - Young children need to develop autonomy
  - Young children need to explore and experience
  - Young children need to begin to make decisions
Question

What are the glycemic targets for young children?
### Glycemic Targets

Glucose values are plasma (mg/mL)

<table>
<thead>
<tr>
<th>Age</th>
<th>Pre-Meal BG</th>
<th>HS/Night BG</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toddler (0-5 yrs)</td>
<td>100-180</td>
<td>110-200</td>
<td>≥7.5 &amp; ≤8.5%</td>
</tr>
<tr>
<td>School-age (6-11 yrs)</td>
<td>90-180</td>
<td>100-180</td>
<td>&lt;8%</td>
</tr>
<tr>
<td>Adolescent (12-19 yrs)</td>
<td>90-130</td>
<td>90-150</td>
<td>&lt;7.5%</td>
</tr>
</tbody>
</table>

*Diabetes Care* 28:186-212, 2005
## ISPAD guidelines: Target indicators of glycaemic control for children & adolescents

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ideal (non-diabetic)</th>
<th>Optimal</th>
<th>Suboptimal</th>
<th>High risk (action required)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>&lt;6.0</td>
<td>&lt;7.5</td>
<td>7.5–9.0</td>
<td>&gt;9.0</td>
</tr>
<tr>
<td><strong>(DCCT stand.)</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>SMBG values, mmol/L†</strong></td>
<td>3.6–5.6</td>
<td>5.0–8.0</td>
<td>&gt;8.0</td>
<td>&gt;9.0</td>
</tr>
<tr>
<td><strong>BG, mmol/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PPBG</strong></td>
<td>4.5–7.0</td>
<td>5–10</td>
<td>10–14</td>
<td>&gt;14</td>
</tr>
<tr>
<td><strong>Bedtime BG</strong></td>
<td>4.0–5.6</td>
<td>6.7–10.0</td>
<td>&lt;6.7 or 10–11</td>
<td>&lt;4.4 or &gt;11.0</td>
</tr>
<tr>
<td><strong>Nocturnal BG</strong></td>
<td>3.6–5.6</td>
<td>4.5–9.0</td>
<td>&lt;4.2 or &gt;9.0</td>
<td>&lt;4.0 or &gt;11.0</td>
</tr>
</tbody>
</table>

*Levels recommended for adults shown in square brackets;  
†AM fasting or pre-prandial; DCCT=Diabetes Control and Complications Trial  
SMBG=self-monitored blood glucose; BG=blood glucose; PPBG=post-prandial blood glucose

Can Intensive Management Be Done Safely in Young Children?
The ideal insulin therapy should mimic endogenous insulin secretion
Insulin management

- **Fixed dose regimens:**
  - requires scheduled meals and snacks and is not flexible enough for most young children

- **Basal: bolus regimens:**
  - **MDI**
    - useful only if child is willing to take frequent injections
  - **Insulin pumps**
    - child must be willing to wear the pump
Insulin Terminology

- **Basal insulin**
  - Long-acting, all Type 1 and most Type 2 DM patients should have basal insulin whether they are eating or not (insulin glargine, insulin detemir, or NPH)

- **Nutritional or pre-meal / prandial insulin**
  - Short-acting insulin given with meals in anticipation of carbohydrate load glycemic spike (scheduled insulin aspart, insulin lispro, insulin glulisine, regular insulin)

- **Correction or supplemental insulin**
  - Short-acting insulin given to cover high glucose; if substantial use, it should drive adjustment of basal and nutritional insulins
Approximate pharmacokinetic profiles of human insulin and insulin analogues

N.B. Duration of action will vary widely between and within people
NPH = neutral protamine hagedorn/isophane insulin
Rationale for basal-bolus therapy

• Basal-bolus should be the regimen of choice for maintaining overall glycaemic control\(^1\)

• An ideal basal insulin
  • Peakless profile, prolonged duration of action
  • Flexible dosing
  • Suppresses hepatic glucose production between meals and overnight\(^1\)

• An ideal bolus insulin (a bolus with every meal)
  • Rapid onset and short duration of action
  • Limits postmeal hyperglycaemia\(^1\)
  • Prevents post-prandial hypoglycaemia\(^2\)

Commonly used insulin regimens

- **Basal-bolus insulin regimens**
  - 1 long-acting basal + mealtime insulin injections
  - or
  - 2 intermediate-acting basal + mealtime insulin injections\(^1,2\)

- **Pre-mixed insulin regimens**
  - 2 or more pre-mixed insulin injections\(^2\)

- **Continuous subcutaneous insulin infusion (CSII)**
  - Continuous (rapid-acting) insulin infusion to meet basal insulin needs + 3 or more mealtime doses\(^2\)

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Action profile of different basal insulins

Rates of glucose infusion needed to maintain plasma glucose at 130 mg/dL (7.2 mmol/L) after s.c. injection in patients with T1DM (n=20) for 24 hours.

Activity profiles of glargine and detemir diverge after 12 hours in T1DM patients

Activity profile of insulin glargine allows once-daily dosing, whereas most patients require twice-daily dosing with detemir – particularly T1DM patients

GIR = glucose infusion rate

Type 1 Diabetes: Serum Insulin Concentrations Following Subcutaneous Injection of Insulin Lispro or Human Regular

Rapid-acting insulin analogues reduce risk of PP hyperglycaemia and late hypoglycaemia

Regular human insulin (RHI) vs. Insulin lispro, insulin aspart, or insulin glulisine

Better PPBG control

Lower risk of late post-prandial hypoglycaemia

Plasma-free insulin (µU/mL) vs. Time after insulin injection or meal ingestion (hours)

PPBG = post-prandial blood glucose

Bolli GB. *Av Diabetol* 2007;23:326–32.
Basal/Bolus Treatment Program with Rapid-acting and Long-acting Analogs

Plasma insulin

Breakfast  Lunch  Dinner

Aspart  Aspart  Aspart
Lispro    Lispro    Lispro
Glulisene Glulisine Glulisine

Glargine or Detemir
The ideal insulin therapy should mimic endogenous insulin secretion.
Effectiveness of Postprandial Humalog in Toddlers

Rutledge, Chase, Klingensmith et al Pediatrics 100:968,97

- Determine if postprandial rapid-acting insulin effective
- Subjects < 5 years old
- Results: 2-hour glucose excursions lower with postprandial Humalog compared to preprandial regular
- Similar to preprandial Humalog
Outcomes of Pump Therapy

Kaufman, et al, Diabetes Metabolism and Reviews, 2000

6 month data 130 subjects

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<tr>
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<th>PRE</th>
<th>POST</th>
<th>P value</th>
</tr>
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<tr>
<td>HbA1c %</td>
<td>8.4 ± 1.8</td>
<td>7.8 ± 1.2</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>22.8 ± 4</td>
<td>23.2 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Hypoglycemia events/pt/y</td>
<td>0.06</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>DKA events/pt/y</td>
<td>0.15</td>
<td>0.09</td>
<td>0.05</td>
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### Results of Insulin Pump Therapy In Young Children

*Kaufman, et al, Diabetes Spectrum, 2001*

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<tr>
<td>HbA1c</td>
<td>8.5±1.8</td>
<td>7.4±1.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean BG</td>
<td>157±64</td>
<td>92±31</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypo-glycemia</td>
<td>0.18</td>
<td>0.09</td>
<td>ND</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>82±6</td>
<td>90±5</td>
<td>0.009</td>
</tr>
<tr>
<td>Family Cohesion</td>
<td></td>
<td></td>
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Why About the Risk of Hypoglycemia From Intensive Regimens?
Adverse Events in Intensively Treated Children and Adolescents with Type 1

- 139 Subjects, ages 1-18 yrs on MDI
- Mean HbA1c 6.9%
- Severe Hypoglycemia - 0.17 events/pt/yr
  - Decreased from 1-2 injections
  - Correlated with previous severe hypoglycemia $r=.38, p<0.0001$
- DKA rate 0.015 events/pt/yr
- MDI effective and safe
Conclusion
Ultimate Goals Of Diabetes Treatment

- Sustained Normal Blood Glucose Control
  =
- Lowest Possible Incidence of Hypoglycemia
  =
- No Long-Term Diabetes Complications
- No Acute Diabetes Complications

Best Quality of Life with Diabetes
For the child and your family
Summary

Basal-bolus therapy is the treatment of choice

- Separate FBG and PPBG control
- Flexible dosing and timing of injections

Insulin glargine and insulin glulisine are an effective combination for basal-bolus therapy

- Glargine: peakless 24 hour coverage
- Glulisine: fast onset of action and effective PPBG control
- As effective in children and adolescents as adults
- Adding glulisine to basal insulin provided more effective glycaemic control than adding lispro in children and adolescents T1DM patients
  - Particularly in adolescents aged 13–17 years

The particularities of adolescents need to be considered when treating T1DM