Emerging Technologies
Bolus Calculators, Pumps And CGMs

Children With Diabetes
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John Walsh, PA, CDE
jwalsh@diabetesnet.com
(619) 497-0900
Advanced Metabolic Care + Research
700 West El Norte Pkwy
Escondido, CA 92126
(760) 743-1431

View slides at www.diabetesnet.com/presentations/
Disclosure

- Book sales – all pump companies
- Advisory Boards – Tandem Diabetes, Unomedical, Spring, Halozyme
- Consultant – Bayer, Roche, BD, Abbott, Tandem Diabetes, Medingo, Spring
- Speakers Bureau – Tandem Diabetes
- Sub-Investigator – Glaxo Smith Kline, Animus, Sanofi-Aventis, Bayer, Biodel, Dexcom, Novo Nordisk
- Pump Trainer – Accu-Chek, Animas, Medtronic, Omnipod
- Web Advertising – Sanofi-Aventis, Sooil, Medtronic, Animas, Accu-Chek, Abbott, etc.
What We’ll Cover

- Bolus Calculators
- New Pumps
- CGMs
- Pump/CGM Combos
- Closed Loop
- Future Pump Features
Terms

- **TDD** – total daily dose (all basals and boluses) of insulin
- **Basal** – background insulin released slowly through the day
- **Bolus** – a quick release of insulin
  - Carb bolus – covers carbs
  - Correction bolus – lowers high readings that arise from deficits in basal rates or carb boluses
- **Bolus Calculator (BC)** – calculates bolus recommendations
- **Bolus On Board (BOB)** – bolus insulin still active from recent boluses, active insulin, insulin on board
- **Duration of Insulin Action (DIA)** – how long a bolus will lower the BG – used to measure BOB
Bolus Calculator (BC)

Part of pump that gives bolus recommendation

Provides the “smarts” in smart pumps

First appeared in 2003 in Cosmo pump

Now appearing in meters, iPhones, apps, ????
Bolus Calculators

- Software recommends carb and correction boluses
- Settings: CarbF, CorrF, Corr target, DIA
- Tracking of BOB helps prevent insulin stacking
- Current BG is needed to measure BOB
- Accurate carb counts and BG values are needed
- Tracks and stores history

Unfortunately, no two BCs work the same way
Meter With Bolus Calculator – Abbott Freestyle InsuLinx

- Stores readings, bolus rec., meal markers, and carbs
- Touch screen
- Tracks BOB
  - Boluses can be entered retroactively
- Only 1 unit increments (injections)
- USB download, Windows or Mac
- FreeStyle Auto-Assist software

CE approved in Europe
In future, meter or pump controller may communicate with smart phone

No bolus calculator or pump control on phone itself

Wireless Bluetooth or cable interface

Not currently possible to use phone as medical device
BC or Meter in iPhone – Agamatrix

- Small meter attaches to iPhone
- Track blood glucose, carb intake and insulin dose
- Share BG data immediately with direct phone or internet access
- Agamatrix, Sanofi-Aventis, Apple
- Also: Wavesense Bolus Calc.

Submitted for CE approval
New Insulin Pumps
Remote Controls

- Meter sends BG to pump
- Bolusing from meter/PDA lets pump stay hidden
- Carb bolus, correction bolus, basal remotely controlled by meter/PDA
- Accurate, complete history
- Omnipod control must be present to bolus

Bolus and basal adjustments in Accu-Chek Combo (CE approved)
New Line Pumps

- Tandem t:slim
- Asante Pearl
- Dana Diabecare II-SG
- CellNOVO
- D-Medical Spring
Pumps – Asante Pearl

- Uses prefilled pen cartridges
- Modular design
- 3.88" x 1.72" x 0.75"
- Pay as you go pricing
- Uses luer lock infusion sets
- Alarms gradually get louder
- Built-in flashlight

FDA and CE approved
Pumps – Sooil Dana Diabecare IISG

- Small, light 300 u pump
- Color screen controller communicates via phone
- Meter/controller communicate with pump
- Reverse luer lock sets available only from Dana
- Accurate bolus recommendations

CE approved in Europe
Wax Motor Pump – CellNово

- Small wax cube is heated to pump 0.05 u volumes of insulin
- ? Slow boluses
- Controller sends data via phone lines to internet site/cell phone
- Connects to short infusion set
- 2 rechargeable pumps
- Unclear operation in heat/cold

CE approved in Europe
New Pressure Pumps

- Precise delivery – 1000ths of a unit
- No motor or gears
- Less weight
- No reservoir
- Some can detect leak or displacement of infusion set

Boyle’s Law: $pV = k$ or $\Delta V = k / \Delta p$
Pressure Pump – Tandem T-Slim

- Pressure generated small solenoid pump
- Lightweight, I-Phone style
- Hi-res color touch screen
- Informative and VERY easy to use
- Standard luer lock sets

Submitted for FDA and CE approval
Pressure Pump – Spring

- Components:
  - Hardware & screen – permanent
  - Reservoir and spring that creates pressure – one time use

- Spring is only “moving” part
- Pressure generated by spring in reservoir
- Simple, small, light, low cost
- 300 u reservoir

Submitted for FDA and CE approval
Early Closed Loop – Animas Vibe

- Insulin pump with high contrast color screen
- 1 week Dexcom G4 sensor with smallest needle
- Internet access via Diasend software

CE approved in Europe
Early Closed Loop – Medtronic Veo

- Low Glucose Suspend (LGS)
- Uses CGM to suspend basal for up to 2 hrs when low
- User can reactivate basal
- Reduce prolonged nighttime lows
- Ability to detect low BGs remains an issue

CE approved in 2009
Patch Pumps

Patch applied directly to body, separate external controller
<table>
<thead>
<tr>
<th>Patch Pump</th>
<th>Line Pump</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worn on body</td>
<td>More body site options</td>
</tr>
<tr>
<td>No external tubing in some</td>
<td>Variety of needle and tubing lengths</td>
</tr>
<tr>
<td>Some require controller be present to bolus</td>
<td>Easy pump removal for showering, sports</td>
</tr>
<tr>
<td>Can loosen, leak, be knocked off</td>
<td>Can loosen, leak, be knocked off</td>
</tr>
</tbody>
</table>
New Patch Pumps

Valeritas V-Go

Roche/Medingo Solo

Omnipod

Calibra

Debiotech Jewel

Also: Medtronic (2013), Medsolve, Altea
Pump – Roche Medingo Solo

- Precise dispensing screw
- Auto-inserter
- 200 units
- Weighs 1 oz
- Bolus button also on pump
- Controller has color screen, 5 ft range
- Accurate bolus calculations

Submitted for CE approval
Valeritas V-Go

- Simple design for Type 2 diabetes
- No controller
- Preselected basal rates
- Bolus button on pump
- No bolus calculator, BOB tracking, etc.

FDA approved
Patch Pump – Debiotech JewelPump

- Micro-Electro-Mechanical Systems tiny silicon motor
- Silicon wafer nanotechnology lets motor be mass produced
- Very light, 0.02 u delivery
- Separate infusion site
- Current 400 u insulin bladder makes it rather large
- ? Cost

Submitted for CE approval
Patch Pump – CeQur

- Designed for Type 2
- Bolus button on pump
- No controller
- Montreux, Switzerland
Infusion Set With Detach Detector

- Nice spring auto-inserter
- Luer lock set for most pumps
- Current pumps don’t alarm when infusion set detaches
- Set has another spring in base that occludes Teflon line if set detaches
- Faster detection of detached set when pump sounds occlusion alarm

Made by Spring/D-Medical – FDA & CE approved
Microneedles Speed Up Insulin

- Size of BD 1.5mm needle for injection

- Compared to
  
  - Current 0.5 to 3 mm microneedle rollers used to give facials
Color Screens
Progress In Monitoring

1300 BC

1971 AD

2011 AD
Continuous Glucose Monitors

Real-Time Readings

plus

Retrospective Data
CGM Ingredients

Sensor

Receiver

Transmitter

Dexcom sensor on left, Comfort infusion set on right
from insulinfactor.com
CGM Benefits

Real-Time

- The way most CGMs are used
- Tracking and trending – fewer extremes
- Avoid lows, especially night lows
- Avoid foods that spike glucose
- Immediate feedback – behavior mod made easy
- Shows direction you’re going
CGM Benefits

Retrospective View

- NOT used enough
- See patterns
- Test and tune basals, CarbF, CorrF
- Avoid night lows and hypo unawareness
- Peace of mind from fear of lows
Why Combine Pumps And CGMs?

Precise insulin delivery plus accurate glucose trends. Someone on a pump is more likely to handle 2nd device well.

CGM helps with:

dislodged infusion sets, missed meal boluses, detecting lows, lowering highs, basal and bolus testing, glucose stability, exercise, and stress, overriding bolus recommendations
Confidence For Performance
Clinical Indications For CGMs

- Frequent hypoglycemia (< 70 mg/dl, 2.9 mmol)
- Hypoglycemia unawareness
- Elevated A1c
- Glycemic variability
- Gastroparesis
- Lives alone
- Presence of complications
- Small children not yet able to recognize and vocalize they are low
Drawbacks To CGM

- Cost, availability of reimbursement
- False positive and false negative alarms
- Inaccurate readings, not totally reliable – focus on trends
- Calibration
- Sensor failure
- Need to do fingerstick to confirm CGM reading before treating
JDRF Study 2008:
CGM substantially improves glycemic control in adults with T1DM, *without* increasing hypoglycemia.

JDRF CGM Trial

322 people, 8 to 72 years of age at 10 diabetes centers over 26 weeks

<table>
<thead>
<tr>
<th>Age</th>
<th>6 days use per week</th>
<th>A1c</th>
<th>Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 - 14 yo</td>
<td>50%</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>15 - 24 yo</td>
<td>30%</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>25 - 72 yo</td>
<td>83%</td>
<td>- 0.53%</td>
<td>No change</td>
</tr>
</tbody>
</table>

A significant reduction in A1c was seen in those who used CGMS frequently in those over 25 and in those 8-14. More CGM users achieved A1c below 7% and lowered A1c by 0.5% or more.
Patients With A1c <7.0 With GCM

CGM Systems

DexCom™
SEVEN® PLUS

Medtronic MiniMed
Revel® REAL-Time*
Cgm Displays

Combines The OmniPod System with Dexcom continuous glucose monitoring system
Your one PDM now is your pump controller, CGM device and BGM device – eliminate the need for carrying 3 different meters / pumps
Upgrade path will be made available once product is approved
Expected filing date in Q1
# CGM And Pump Choices

<table>
<thead>
<tr>
<th>CGM:</th>
<th>Pump:</th>
<th>Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexcom 7+</td>
<td>Animas</td>
<td>2012?</td>
</tr>
<tr>
<td></td>
<td>Insulet</td>
<td>2011?</td>
</tr>
<tr>
<td></td>
<td>Tandem</td>
<td>2012?</td>
</tr>
<tr>
<td>Paradigm RT</td>
<td>Medtronic</td>
<td>now</td>
</tr>
<tr>
<td>AccuCk Combo</td>
<td>Combo*</td>
<td>2013?</td>
</tr>
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</table>
CareLink Online Reports

Sensor daily overlay

Sensor results by meal

<table>
<thead>
<tr>
<th>Range</th>
<th>Average</th>
<th>High</th>
<th>Low</th>
<th>Standard Dev.</th>
<th># of Readings</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM 100 - 150</td>
<td>146</td>
<td>245</td>
<td>50</td>
<td>50</td>
<td>150</td>
</tr>
<tr>
<td>AM 70 - 130</td>
<td>173</td>
<td>340</td>
<td>68</td>
<td>55</td>
<td>48</td>
</tr>
<tr>
<td>AM 50 - 90</td>
<td>227</td>
<td>318</td>
<td>138</td>
<td>51</td>
<td>119</td>
</tr>
<tr>
<td>AM 30 - 70</td>
<td>190</td>
<td>325</td>
<td>48</td>
<td>76</td>
<td>72</td>
</tr>
<tr>
<td>AM 10 - 30</td>
<td>234</td>
<td>352</td>
<td>100</td>
<td>58</td>
<td>144</td>
</tr>
<tr>
<td>AM 0 - 10</td>
<td>195</td>
<td>270</td>
<td>106</td>
<td>51</td>
<td>62</td>
</tr>
<tr>
<td>AM 5 - 9</td>
<td>195</td>
<td>302</td>
<td>134</td>
<td>42</td>
<td>120</td>
</tr>
<tr>
<td>AM 1 - 5</td>
<td>162</td>
<td>308</td>
<td>72</td>
<td>59</td>
<td>252</td>
</tr>
<tr>
<td>AM 0 - 1</td>
<td>185</td>
<td>340</td>
<td>48</td>
<td>85</td>
<td>955</td>
</tr>
</tbody>
</table>
CareLink Online Reports

Daily summaries & layered reports

Sensor tracing

Basals & boluses

Carbs, exercise, etc
DexCom™ 7 STS®

Dexcom DM2 Download Reports

Hourly Stats

Glucose Trend
DexCom™ 7 STS®

BG Distribution

Trend Analysis
Glucose Trends
Get Rid Of Excursions
Trends Show More Than Points

Insight

No clue what to do

Consistent Trend Data

Two Dexcom sensors worn by the same person

Trend line with +/- 30 mg/dl accuracy is OK for dosing!

Real Time Data – Off The Screen

- Glucose read every 5 min – 288 readings/day
- Trends
- Rate of change arrows
- Alarms – highs, lows, rate of change, predicted high or low
Types Of Alarms

High and low alarms are set by user – features such as predictive alarms and alarm vol./type vary by manufacturer.
Paradigm/Guardian® CGM Screens

On-Screen Reports

- 3 / 6 / 12 / 24-hr graphs
- Can scroll back for specific data points
- ↑↓ “direction” indicators
- Updates every 5 minutes
- Hi/Low Alerts
- Predictive Alerts (Guardian)
On-Screen Reports

- 1, 3, 6, 12, 24-hr graphs
- Updates every 5 minutes
- Hi/Low alerts
- Rate of Change alerts
- Immediate feedback from screen
Retrospective Data – From Download

- Data downloaded to computer or internet
- Trend graphs, tables, pie charts, modal day, % in and out of glucose goal range, averages, variability
- Feedback available only after data is downloaded
Retrospective
Some Glucose Trend Patterns


- High-to-lows
- Low-to-highs
Glucose Trends

- Excess low-to-highs
- Control improves by avoiding both
- Excess high-to-lows
What Hourly Stats Tell Us

Hourly Statistics from 12/11/2007 12:00 AM to 12/19/2007
Use CGM and get off the Rollercoaster!
Decision Time –
Look At BG, Trend, AND BOB!

CGM:
BG & Trend  110 ↑  110 ↓  110 →

Pump:
BOB  3 u  3 u  3 u
Time since bolus  2 hr  ½ hr  2 hr

THEN decide on action to take.
Experimental CGMs

Invasive and Non-Invasive
Implanted CGM Systems

Dexcom G1 2004

MicroCHIPS Illume

GlySens

GlucoWizzard™ Sensor
when compared to a US penny
Sensor Size (5 × 0.5 × 0.5) mm
CGM – Osmotic Pressure

- Future CGM implanted without surgery
- Measures osmotic pressure from glucose
- Currently testing immune system compatibility

LifeCare, Bergen, Norway
CGM – Implanted Fluorescent

Certain molecules fluoresce and change color as glucose rises and falls.

- Small size
- Low power
- Long life
- Very good accuracy
CGM – Near Infrared

Near infrared light scattering measures glucose levels

- Bulky
- Easy to use
- Less accurate than current CGMs
- Investigational
CGM – Eye Patch

Nanoparticles embedded in hydrogel lens

Lens color changes with glucose in tears

Device or glasses read glucose from color change

Greater lag time?

Accuracy?
Advances Underway
Advances In Pumps

- Smart phone communication
- Smaller, flatter patch pumps with bolus buttons
- Dual chamber pumps – glucagon, amylin, or GLP-1 agonists along with insulin
- Basal shutoff for lows
- More reliable infusion sets
- CGM integration into closed loop
Future Pump Features

- Show How Setting Changes Impact TDD & BG
- Temp Basal + Bolus Doses
- Super Bolus
- Meal Size Boluses
- Excess BOB Alert
- Exercise Compensator
- Infusion Set Monitor
- Automated Bolus and Basal Testing
Advances In Closed Loop

- Dual BG sensors reduces sensor error
- Manual plus automatic control
- Dual hormone delivery
  - insulin for highs
  - glucagon for lows
Faster Insulin Action

- Warm the infusion site
  - InsuPatch by InsuLine
- Faster insulins
  - Novo Nordisk
  - Biodel
- Speed up insulin absorption
  - Halozyme
- Intradermal 1.5 mm microneedles
  - BD
Halozyme Rapid Insulin

- Ultrafast, DIA ~ 3.75 to 4 hrs?
- Combines recombinant human hyaluronidase with rapid insulins
- Temporarily degrades local hyaluran, a structural protein in the interstitial space
- Might lower peaks and cause fewer lows
- In phase 2 clinical trials
Communication – Meter + Phone

- Several companies are developing meters for phones using Bluetooth
- Rapid alerts for care-givers of young, elderly, hypo-unaware
- Adds food databases, carb counters, apps, analysis
- Eventually management via cell phone
Diabetes Phone Apps

- Wavesense Diabetes Manager, Gluco Buddy, Diabetes Log, Bant, Glucose Mate, Diabetic Meal Planner Lite
- Many apps available for iPhone, Pre, Blackberry
- Help for dosing, logging, carb counting, bolus calcs
Super Bolus – Shift Basal To Bolus

Future: Super Bolus shifts part of the next 2 to 3.5 hrs of basal insulin into the bolus with less risk of a low later.¹,²

Helps when eating over 30 or 40 grams of carb

Max carbs/meal = Wt(lb) X 0.36 to stay in control ²

How Long To A Closed Loop?

- Needed:
  - Faster insulin
  - Better CGM accuracy
  - Less sensor lag time
  - Better handle on life’s variables
- Dual pumps with glucagon
- Glucose control algorithms and hardware that don’t fail
Reading – Still The Best Way To Learn

- Slides at www.diabetesnet.com/diabetes-resources/diabetes-presentations/
- Books at www.diabetesnet.com/dmall/ or 800-988-4772

- Pumping INSULIN
  Fourth Edition
  John Walsh, P.A., C.D.E.
  and Ruth Roberts, M.A.

- CGM Guide
  Continuous Glucose Monitoring
  Steven V. Edelman, M.D.
  Timothy S. Bailey, M.D.

- Using INSULIN
  Everything You Need For Success On A Smart Insulin Pump
  With "Kid and Tracy" by Sharon Brown, RN, BS, CDE