The Art & Science of Effective Insulin Injections

Giving It Your Best Shot: Improving Insulin Injection Comfort, Safety & Efficacy
August 14th, 2016
San Diego, CA

Disclosure to Participants

2016 Conflict of Interest (COI) Disclosures:
Jane Jeffrie Seley
Consulting: Johnson & Johnson Diabetes Institute
Advisory Board Meeting:
Bayer Diabetes Care
Alliance (Boehringer-Ingelheim/Lilly)
Sanofi

Giving It Your Best Shot TOPICS

• Skin Thickness
• Avoiding intramuscular (IM) injections
• Needle length
• Proper use of insulin pens and syringes
• Addressing Injection Pain, Fear & Anxiety

4th International Forum for Injection Technique & Therapy Expert Recommendations (FITTER)

• 183 clinicians from 54 countries plus 15,000 attended virtually
• Focused on injection technique, insulin infusion & safety
• Reviewed >750 papers & data from large insulin injection technique survey (ITQ) to draft evidence-based recommendations

http://www.fitter4diabetes.com/
**4th Injection Technique Questionnaire**

**ITQ Survey Details**
- Inclusion Criteria – Injecting insulin for at least 6 months
- 13,289 participants from 42 countries
- Feb 2014–June 2015
- 5826 observed by RN

**Participating Countries**

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**Global ITQ Survey Results**

**Global ITQ Survey Results**

- Which device did patients use?
  - **DEVICE**
    - Syringe: 1238 (9.6%)
    - Pen: 11,070 (85.6%)
    - Pen + Pump: 184 (1.4%)
    - Pen + Syringe: 337 (2.6%)

  *85.6% pen use is a global total. Pen use in U.S. is lower than Europe.*

**Where did patients inject insulin?**

<table>
<thead>
<tr>
<th>Injection Site</th>
<th>%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdomen</td>
<td>90.9%</td>
</tr>
<tr>
<td>Thigh</td>
<td>43.0%</td>
</tr>
<tr>
<td>Buttocks</td>
<td>13.8%</td>
</tr>
<tr>
<td>Arm</td>
<td>31.9%</td>
</tr>
</tbody>
</table>

*Adds up to >100% since some patients used more than one site.

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**Giving It Your Best Shot**

**Skin Thickness & Avoiding IM Injections**
- Skin thickness varies from ~1.25–3.25 mm
- Mean thickness ~2-2.5 mm, slightly less in children
- 4mm pen needle safe & effective for all pts, even obese
- Children up to 6 yrs old & very thin adults should lift skin fold, inject at 90° angle

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**How many injections a day do pts take?**

<table>
<thead>
<tr>
<th>INJECTIONS/DAY</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1523</td>
<td>16.0</td>
</tr>
<tr>
<td>2</td>
<td>2480</td>
<td>26.0</td>
</tr>
<tr>
<td>3</td>
<td>1340</td>
<td>13.8</td>
</tr>
<tr>
<td>4</td>
<td>3213</td>
<td>33.7</td>
</tr>
<tr>
<td>5</td>
<td>735</td>
<td>7.7</td>
</tr>
<tr>
<td>6</td>
<td>197</td>
<td>2.1</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>0.7</td>
</tr>
<tr>
<td>&gt;7</td>
<td>71</td>
<td>0.7</td>
</tr>
<tr>
<td>Total</td>
<td>9929</td>
<td>100.0</td>
</tr>
</tbody>
</table>

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**Needle Length: Patient Vs. Nurse Report**

<table>
<thead>
<tr>
<th>NEEDLE LENGTH</th>
<th>% (PT Report)</th>
<th>NEEDLE LENGTH</th>
<th>% (RN Report)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.7 mm</td>
<td>1.0</td>
<td>12.7 mm</td>
<td>0.9</td>
</tr>
<tr>
<td>8 mm</td>
<td>16.0</td>
<td>8 mm</td>
<td>27.1</td>
</tr>
<tr>
<td>6 mm</td>
<td>15.1</td>
<td>6 mm</td>
<td>20.1</td>
</tr>
<tr>
<td>5 mm</td>
<td>28.6</td>
<td>5 mm</td>
<td>20.3</td>
</tr>
<tr>
<td>4mm (launched 2010)</td>
<td>20.9</td>
<td>4mm</td>
<td>28.1</td>
</tr>
<tr>
<td>Don’t know</td>
<td>13.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Giving It Your Best Shot

Care of the Injection Site
• Patients: Disinfect if site is not clean, do not inject through clothing
• Hospitals: (where infections can spread) should use ETOH & allow to fully dry
• Patients should never inject into sites of lipohypertrophy, inflammation, edema, ulceration or infection

Giving It Your Best Shot Summary: Adult
• Avoid injecting into intradermal & intramuscular spaces, scars and lipohypertrophy
• 4mm pen needles at 90 degree angle for all adults
• When using needle lengths >5mm or a syringe: lift skinfold to avoid IM injections.
• Recommended Sites: abdomen, thigh, buttocks, upper arms
• Site Rotation: Space injections ~1 finger's breadth apart, Do Not reuse same site for 4 weeks

Giving It Your Best Shot

Proper use of insulin pens and syringes
• Prime pens to check flow & remove dead space
• Never share pens due to risk of biological material contamination
• Use pen needle once & remove immediately to prevent air entering cartridge & insulin leaking out
• Count to 10 (Universal Count) when injecting to get full dose & prevent leakage

Giving It Your Best Shot Summary: Children
• Avoid injecting into intradermal & IM spaces, scars and lipohypertrophy
• Rotate sites: to prevent lipohypertrophy
• Preferred sites: Abdomen, thighs, upper buttocks & flanks, upper arm
• Use 4mm pen needles for all children & young adults
• Use two finger lifted skinfold to prevent IM injection

Watch for FITTER Publication
FITTER Strategic Advisory Board (in press). Forum for Injection Technique and Therapy Expert Recommendations (FITTER); Injection Technique Questionnaire (ITQ) Survey Results (2 papers) and New Recommendations for Insulin Injection and Infusion. Mayo Clinic Proceedings, September 2016. Open access online
Definition of Lipodystrophy

• “Disorder of the fat tissue”

• Two types:
  - Lipodystrophy (LA): indenting and cratering of fat tissue
  - Lipohypertrophy (LH): enlargement of adipocytes and swelling and/or induration of fat

Prevalence of Lipohypertrophy

• Blanco, 2013, 430 pts in 19 Spanish centers
  - 64.4% prevalence: T1 72.3%; T2 53.4%

• Grassi, 2014, 388 pts in 18 Italian centers
  - 48.7% prevalence

• Ji, 2014, 401 pts in 4 Chinese centers
  - 53.1% prevalence


Lipohypertrophy by Body Site

• LH was found in 52.4% of abdomens examined, 15.5% of thighs and 9.4% of arms

• LH is frequent reported in CSII patients

• A survey of 91 adult CSII patients revealed that the most common infusion site problem was LH (26.1%)
  - More often with long duration of CSII (4.8 yrs. [2.38–9.45] vs. 3.0 yrs. [1.50–4.25]; P=0.01)
Infusion Site Issues Another Understudied Factor

Lipo, lipo and more lipo

Risk Factors for Lipohypertrophy

- Duration of insulin use
  - longer use associated with more LH (p=0.001)
- Site rotation
  - failure to rotate associated with higher LH risk (p=0.004)
- Changing needles
  - needle reuse also associated with LH (p=0.004)

LH leads to decreased insulin absorption

- Type 1 diabetes for +30yrs
- None dominant arm
- Secondary to daily injections
- Needle re-use common

METHODOLOGY:
- Randomized, single-center, repeated single dose, 2-period trial with a 24 hr clamp
- Type 1 DM for at least 3 years, presence of LH Tissue and NA Tissue
- 13 pts received four s.c. single-dose injections of 0.15 U/kg insulin lispro (Humalog) during one 24-hour euglycemic clamp with doses being administered approx Q6 hr, x2 into LHT and x2 into NAT, in random order.
  - After an overnight fast, pts connected to ClampArt®. A variable IV infusion of human insulin was started to reach a target blood glucose level of 100 mg/dL.
  - After lispro dosing, an I.V. glucose infusion rate (GIR) was automatically adjusted by ClampArt® to maintain a BG level close to target for 5 hr post-dosing, during each of the four clamp intervals.

Diabetes Landmark Studies:
- First glucose clamp study of LH
- Powered to detect ≥ 20% changes in PK/PD

Euglycemic Clamp Study

Insulin absorption is reduced by 34% when injected into LHT
LH leads to decreased insulin absorption

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- First glucose clamp study of LH
- Powered to detect ≥ 20% changes in PK/PD

Euglycemic Clamp Study
- Insulin absorption is reduced by 34% when injected into LH
- PD effect in the first 4 hrs is 27% lower when injecting insulin into LH

Do you have swelling/lumps @ injection sites?

<table>
<thead>
<tr>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>3855</td>
</tr>
<tr>
<td>No</td>
<td>9334</td>
</tr>
<tr>
<td>Total</td>
<td>99.2%</td>
</tr>
</tbody>
</table>

Insulin Technique Questionnaire

- Global study: N= 13,264 patients worldwide; 304 US patients
- Type 1 33.8%; Type 2 65.2%; GDM 1%
- Patient reported %s of LH
- RN identified %s of LH by site & visual inspection vs. palpation
- Frequency of HCP examining injection sites

Frequency of examining injection sites

- Routinely every visit: 28%
- Once a year: 19%
- Only if it causes a problem at site: 20%
- Can’t remember any site ever being checked: 33%

LH found on RN injection site exams

<table>
<thead>
<tr>
<th></th>
<th>Visual inspection</th>
<th>Palpation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdomen</td>
<td>17.3%</td>
<td>21.1%</td>
</tr>
<tr>
<td>Thigh</td>
<td>9.8%</td>
<td>11.2%</td>
</tr>
<tr>
<td>Buttocks</td>
<td>2.1%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Arms</td>
<td>11.2%</td>
<td>13.4%</td>
</tr>
</tbody>
</table>

Overall RNs found LH in 30.8% of patients

Conclusions from Questionnaire

- 1/3 of injecting patients worldwide have LH
- 40% of patients inject into the LH regularly
- LH is most frequent in T1, ≥ 8 injections/day, long term insulin use, needle re-users and those who don’t rotate correctly or inject into broad zones
- Injecting into LH leads to 20% higher TDD of insulin and 0.5% higher HbA1c
- All currently available insulins are associated with LH
- LH is associated with many sub-optimal practices & potentially harmful outcomes (hypoglycemia, variability, DKA)
- LH continues at epidemic rates but still commonly goes undetected or untreated
Recommendations to Providers

Teach site rotation to ALL patients
  - inject in broader areas
  - distinct pattern: W or X
  - do NOT inject in LH

Examine injection/infusion sites on every visit
Teach that injections into LH decrease insulin absorption by 34%, i.e., 6.5 units instead of 10

Next Up

- Donna Tomky, MSN, RN, ANP-BC, CDE, CDTC, FAADE
- New Developments in Insulin Infusion

Disclosure to Participants

Conflict of Interest (COI) and Financial Relationship Disclosures
  - Advisory Board for Voluntis
  - Advisory Board for Becton Dickinson

Times They Are A-Changing:
Strategies That Reduce Insulin Infusion Set Problems

- Importance of Insulin (Pump) Infusion sets
- Detection, Treatment and Prevention of IIS Problems
  - Unexplained hyperglycemia/hypoglycemia
  - Insulin precipitation
  - Flow reliability
  - Integument issues
  - Cannula length
- Current and future IIS guidelines
IMPORTANCE OF INSULIN INFUSION SETS (IIS)

- CSII has been Rx modality for DM > 30 years
- IIS required to deliver insulin into SC tissue
  - Role is often underappreciated by HCP
  - Over-shadowed by innovative advances of CSII Pumps
  - Common complications → infusion site, technical & metabolic
- IIS are the “Achilles heel” of CSII

What are Users Doing in USA?

- Infusion Set Composition—Teflon (75%) vs Steel (25%)
- Insulin Type—Rapid Acting (71%) vs Short-acting (29%)
- Frequency of IIS Change—Teflon (3.4) vs Steel (4.9) days
  (*47.4% Steel IIS users report changing 1 x/week)
- 1 in 10 IIS users report changing their infusion set early at least once a month due to hyperglycemia
- Frequency of painful insertion—Frequently (5.3%); Sometimes (26.4%); Infrequently (68.3%)

Infusion Sets Are The Biggest Problem With Pumps

“...the worst part about wearing a pump is the infusion site. It hurts to insert. It gets inflamed. You get kinking of the cannula. And using a CGM. I’m just shocked by how frequently this happens... what probably is happening to some degree is we’re not getting the insulin dosing that we think we are...”

Infusion Site Complications in CSII

- Cross section study of T1DM 50 pts evaluated rate of dermatological complications
  - Scars <3mm diameter (94%)
  - Scars >3mm diameter (12%)
  - Erythema (66% → 86.4% of those being mild severity)
  - Erythematous nodules (42%)
  - Lipohypertrophy (44%)
  - Bruising (4%)
  - Cellulitis not evident
  - Less severity in 90° infusion sets

Causes of Unexplained Hyperglycemia (Hypoglycemia)?

- Insulin infusion set (kinking, occlusion, air, dislodgement)
- Insulin (instability, precipitation)
- Skin irritations
- Infections, inflammation at infusion site
- Lipohypertrophy (fibrosis, scarring)
- Pump Failure
- User Error

How Often Should Infusion Sets Be Changed?

- Adapted with permission from I-Hirsch presentation FITTER 2015.
Infusion Set Failure

• “I eat the same thing day-to-day, activity is the same, routine is the same... why are my blood sugars so different? What’s going on??”
  - Anonymous Pump Wearer

• Problems I notice are high blood sugars after an infusion set change. It’s not anything new, but in fact it has been going on for a very long time. I’ve tried many things to offset the high numbers without resolution... I’ve fasted for 8 hrs after set change... still my numbers went to the low 200s and stayed there for 8 hrs!”
  - Frustrated Pump Wearer

Commonest Infusion Set Failure

• Kinking (64.1%)
• Blockage (54.3%)
• Blockage was associated with >3 days of IIS use

Insulin Occlusions with CSII

Insulin Occlusions: Laboratory Study

- Eight pumps assigned for all 3 rapid-acting analogues provided a basal dose of 0.1 u/h with boluses of 2 units three times daily
- No difference between the 3 insulins in occlusion rate during first 72 hours
- After 72 hours, dramatic increase in occlusions: insulin glulisine 41%, insulin aspart 9%, insulin lispro 6%
- Conclusion: no difference in occlusion rates up to 72 hours, after that time interval, occlusion rates for all insulin increase with glulisine having the greatest frequency. Author suggest all infusion sets should be changed before 72 hours after insertion

Infusion Set Occlusions: Outside of the Laboratory

- Are common!
- In one study, 30% of subjects had at least one occlusion alarm leading to hyperglycemia during a 13 week period while 60% had “unexplained hyperglycemia” that may or may not respond to a correction bolus.
- Another report noted 15% failure rate of initial insertions with a polymer set
- Anecdotal observation: these unexplained hyperglycemias increase in frequency with longer pump wear, especially after 20 years of CSII use

Evaluating Flow Reliability in Preclinical and Clinical Studies

“Silent Occlusion” is a continuous rise in inline pressure which occurs for ≥ 30 minutes that does not trigger an occlusion alarm.

ADA/EASD Statement

- Notes label for changing insulin cartridge varies between insulins: from 2 days for glulisine to 5 days for aspart
- Unable to find guidelines on use of infusion sets specifically with CSII or on assessing difficulties associated with the long-term use of pump sites over long periods of time. No specific recommendation for frequency of site change
- ADA/EASD call for more transparency for pump manufacturers on compatibility of specific insulin formulation and infusion sets.

Novel Catheter May Reduce Silent Occlusions...FlowSmart™ Technology

- Incorporates side-ported technology to improve flow reliability* with minimal size to enhance patient experience
- US, EU, Canadian Regulatory clearance obtained in 2015
- Set Features:
  - 30G inserter needle and 28G catheter
  - Paradigm and Luer Lock compatible
  - Quick-Sertor insertion device compatible
  - Multi-trak with 8 different points of tubing attachment
  - Flexible base
  - Auto-deploying needle shield
- Developed with support from JDRF and Leona M. & Harry B. Helmsley Charitable Trust

Other Insulin Set Problems...

- Leakage at the infusion set-pump connection (16.3%)
- Lipohypertrophy (26.1%)
- Site infection (17.4%)
- Bleeding or bruising (14.1%)
- Some type of Pump malfunction (50%)

Diabetes Care 2015;38:716–722

Diabetes Care 2015;38:716–722

Silent Occlusions Reduced in Side-ported Infusion Catheter Studies

- Silent occlusions occurred frequently (>35%)
- Use of a side-ported infusion set reduced occurrence of silent occlusions >75% compared to conventional Teflon infusion set

Lipohypertrophy with CSII...

- Everybody knows it, but we have only minimal data
- Prevalence in CSII ~ 50%
- Most lesions are invisible
- Palpation is essential by HCP
  - Reduces insulin absorption → hyperglycemia
  - Variable insulin uptake → glucose variability
  - Risk of hypoglycemia

Adapted with permission from Dorothee Deiss FITTER Presentation 2015
What about Optimal IIS Cannula Length?

- Choosing needle length for pen needles applies to IIS cannula length
- IIS cannula > 9mm may increase risk of IM insertion in body areas with reduced adipose tissue, e.g. muscle
- Recommendation → 6 mm penetrates SC and stable with body movement related to CSII

In Summary…

- Current recommendations for CSII infusion set use has been based on anecdotal experience and tradition but not science
- Real-life use of infusion sets are the “Achilles heel” of CSII use due to skin challenges and occlusions of insulin; this has been our greatest gap in this technology
- Innovative technologies suggest an improvement of the unexplained hyperglycemia our patients note on a regular basis
- The implications of the BD Flowsmart™ has broad implications for both CSII users today and those using closed loop technologies in the future.
- Evidenced-based recommendations can provide foundations for concise guidelines for all involved with insulin delivery

Importance of FITTER and Call to Action

- Educate HCP and Users about
  - Insulin Infusion Set Options
  - Importance of site rotation
  - Troubleshooting
  - Significance of Unexplained Hyperglycemia
  - Problems related to lipohypertrophy and dermatological disorders

What’s Coming Next and Available Now?

- FITTER Evidence-based recommendations (in press) will provide a concise set of guidelines for patients and HCPs worldwide.
  - Increase the consistent delivery of insulin and other diabetes medications in subcutaneous space.
- Evert et al have published “Improving Patient Experience with Insulin Infusion Sets: Practical Guidelines and Future Directions (TDE, April 2016)
- MyAADE Network – Diabetes Technology COI discussions

Bolick N et al. Performance Qualification of a Novel Subcutaneous IIS using Medical Imaging. Diabetes. 2015:64 (Suppl 1)