DEMYSTIFYING INSULIN THERAPY

ASHLYN SMITH, PA-C
ENDOCRINOLOGY ASSOCIATES
SCOTTSDALE, AZ
SECRETARY, AMERICAN SOCIETY OF ENDOCRINE PHYSICIAN ASSISTANTS
ARIZONA STATE ASSOCIATION OF PHYSICIAN ASSISTANTS SPRING CME CONFERENCE MARCH 7, 2018

OBJECTIVES

• Review the variety of insulin therapies available for the treatment of Type 1 and Type 2 Diabetes Mellitus (DM)
• Examine the current guidelines for initiating/augmenting insulin therapy
• Recognize the available and upcoming insulin pumps
• Discuss troubleshooting techniques for insulin therapy

PATHOPHYSIOLOGY OF DM2: THE OMINOUS OCTET
INSULIN: A HOT TOPIC

CLINICAL INERTIA

• Failure to initiate or intensify therapy when necessary
• Average length of time for a clinician to add new DM agent when A1c is uncontrolled?
• Every 1% decrease in A1c results in 37% decrease in microvascular complications and 21% decrease in macrovascular complications (DCCT)

CLINICAL INERTIA

• Most pronounced clinical inertia is initiating insulin therapy
• Each new add on non-insulin therapy can decrease A1c by only 0.7-1.0%
• Progressive nature of DM: insulin is a matter of when, not if
• Hypoglycemia is the rate-limiting step to achieving glycemic control
• Multiple barriers to augmenting therapy
BARRIERS TO INSULIN THERAPY

PATIENT BARRIERS
- Anxiety
  - Fear of hypoglycemia/insulin reactions
  - "My uncle started insulin and then he lost his leg"
  - Sense of failure/disappointment/disease progression
- Lifestyle
  - Variable eating schedule
  - Exercise considerations
  - Travel: appropriate insulin transport, eating on the road
- Support
  - Family/community support system
  - Eyesight/dexterity considerations
  - Financial limitations
- Education
  - Dosing schedule and titration
  - Language barriers
  - Learning disabilities

PRACTICE/INDUSTRY BARRIERS
- Time
  - Education insulin vial/syringe or pen use, self-monitoring of blood glucose ( SMBG), insulin titration, hypoglycemia identification/treatment
  - Follow up calls/appointments
  - EMR
- Cost
  - Insulin analogs
  - Test strips
  - Copays/deductibles
- Resources
  - Patient education materials
  - Glucometer demos
  - Insulin demo kits
  - Support staff education
### CLINICIAN BARRIERS

<table>
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<th>Support</th>
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<td>• Support staff</td>
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### TREATMENT GOALS

- **HEMOGLOBIN A1C (HbA1C) GOALS**
  - **AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS (AACE)**
    - HbA1c ≤ 6.5%
    - Less stringent target >6.5% if seriously ill or at risk for hypoglycemia
  - **AMERICAN COLLEGE OF ENDOCRINOLOGY (ACE)**
    - HbA1c < 7%
    - More intensive target <6.5% for appropriate patients
    - Low risk of hypoglycemia
    - Short duration of DM
    - Long life expectancy
    - No cardiovascular disease
  - **AMERICAN DIABETES ASSOCIATION (ADA)**
    - Less stringent target <8% in higher risk patients
    - Severe hypoglycemia
    - Shorter life expectancy
    - DM complications
    - Serious illness
    - Long duration of DM

- **Individualize HbA1c Goals**
Individualize HbA1c goals based on each patient's DM history, comorbidities, risk factors, and psychosocial aspects.

ADA 2018 GUIDELINES
Start with monotherapy unless:
• HbA1c is greater than or equal to 9%, consider dual therapy
• HbA1c is greater than or equal to 10%, blood glucose is greater than or equal to 300mg/dL or patient is markedly symptomatic, consider combination injectable therapy
WHEN TO START INSULIN THERAPY

**ADA**
- Consider when A1c > 9%
- Start combination injectable therapy when
  - A1c > 10%
  - OR BG > 300mg/dL
  - OR pt is symptomatic
  - OR BG/A1c goals are not met after 3 months on triple therapy

**AACE/ACE**
- Consider as part of dual or triple therapy if A1c < 7.5%
- Start insulin therapy when
  - A1c > 9% and pt is symptomatic
  - OR BG A1c remains above goal after 3 months on triple therapy

STARTING INSULIN THERAPY

- Start the conversation early
- Natural progression of DM2
- Avoid using insulin as a threat or a sign of treatment failure
- Discuss blood sugar goals
- Discuss expectations for insulin therapy
  - Titration, if applicable
  - Potential for adding mealtime coverage
  - Hypoglycemia identification and treatment
- Demonstrate glucometer use and insulin pen or vial/syringe use
- Close follow up
CONSIDERATIONS FOR SELECTING AN INITIAL INSULIN REGIMEN

- **Basal** therapy preferred
  - Physiologic
  - Option to add mealtime insulin or alternative prandial agent
- Alternative: Premixed insulin
  - Poor adherence to basal-bolus regimen
  - High risk of hypoglycemia
- Alternative: NPH
  - Cost (available OTC at some retailers)
  - Used with or without mealtime insulin
  - High risk of hypoglycemia
INSULIN DOSING

• “Physiologic regimen” is most commonly used:
  - **Basal insulin**
    - Intermediate-, Long-, or Ultra-Long-acting to suppress endogenous hepatic glucose production
    - Insulin glargine (U-100 and U-300), detemir, or degludec decrease nighttime hypoglycemia over NPH
  - **Bolus insulin**
    - Ultra-rapid, rapid- or short-acting to cover carb intake
    - Total Daily Dose (TDD) = 0.5 to 1.0 units X kg

INSULIN THERAPY OPTIONS

• **Basal ("Background"):** glargine (U-100 and U-300), detemir, degludec

INSULIN THERAPY OPTIONS

• **Intermediate:** insulin NPH
**INSULIN DOSING: BASAL THERAPY**

**ADA**
- 10 units/day

**ADA and AACE/ACE (A1c <8%)**
- 0.1-0.2 units/kg/day

**AACE/ACE (A1c >8%)**
- 0.2-0.3 units/kg/day

**INSULIN DOSING: BASAL TITRATION**

**ADA: Once or twice/week**
- Increase basal dose by 2-4 units
- Increase basal dose by 10-15%

**AACE/ACE: Every 2-3 days**
- Increase TDD by 2 units
- OR

<table>
<thead>
<tr>
<th>Fasting BG</th>
<th>Dose Increase</th>
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<tr>
<td>&gt;180mg/dL</td>
<td>30% of TDD</td>
</tr>
<tr>
<td>140-180mg/dL</td>
<td>10% of TDD</td>
</tr>
<tr>
<td>110-139mg/dL</td>
<td>1 unit</td>
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OVERBASALIZATION

- A1c or postprandial blood glucose remain elevated despite normal fasting blood sugar?
  - Do NOT increase basal therapy
  - Typical basal therapy does not exceed 0.5u/kg/day
  - Overbasalization: increasing basal therapy inappropriately which raises the risk of nocturnal hypoglycemia
    - Hypoglycemic unawareness is higher overnight
    - Increases risk of hypoglycemia adverse effects (ie seizure, cardiac arrhythmia, and death)
  - As A1c approaches goal, postprandial BG is more influential

ADA Standards of Medical Care in Diabetes—2018. Diabetes Care Volume 41, Supplement 1, January 2018

2018 AACE/ACE T2D Management, Endocr Pract. 2018;24(No. 1)
OVERBASALIZATION: ALTERNATIVES

Add prandial/bolus insulin with one or more meals
- ADA and AACE/ACE
- Option to start with largest meal only
- Decrease risk of hypoglycemia/weight gain
- Decrease burden of multiple injections
- Option to add on more meals

Add GLP-1 agonist or SGLT2i or DPP4i
- ADA: non-inferior efficacy of basal insulin + GLP-1
  - Less weight gain/hypoglycemia
  - Convenience and potential for GLS-augment
- AACE/ACE: basal insulin + either GLP-1/SGLT2i/DPP4i
  - GLP-1 may be more effective
  - Then SGLT2i

Change to premixed insulin
- ADA only
- Not preferred
- Rigid meal/snack schedule
- Increased hypoglycemia risk
- May improve adherence

INSULIN THERAPY OPTIONS

- **Bolus** ("Mealtime" or "Correction"):
  - Ultra-rapid aspart: FDA approval 9/2017
  - Lispro, aspart, or glulisine
  - Insulin regular
INSULIN THERAPY OPTIONS

- Premixed:
  - Insulin NPH/insulin regular
  - Insulin lispro protamine/insulin lispro, insulin aspart protamine/insulin aspart

**INSULIN DOSING: SINGLE MEAL BOLUS THERAPY**

**ADA**
- 4 units
- OR
- 10% of basal dose
- OR
- 0.1 u/kg/day

**AACE/ACE**
- 5 units
- OR
- 10% of basal dose
**INSULIN DOSING: BOLUS TITRATION**

**ADA: ONCE OR TWICE/WEEK**
- Increase bolus dose by 1-2 units
- OR
- Increase bolus dose by 10-15%

**AACE/AACE EVERY 2-3 DAYS**
- Increase bolus dose by 1-2 units
- OR
- Increase bolus dose by 10%

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**INSULIN DOSING: FULL BASAL-BOLUS REGIMEN**

- **Establishing a fixed mealtime starting dose:**
  - **Recall:**
    - 0.5 to 1.0 units X kg = Total Daily Dose (TDD)
    - 50:50 Basal:bolus
    - TDD/2 = total bolus units
    - 3 meals/day
    - (Total Bolus Units)/3 = X units

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**How patients will use a Fixed Mealtime Dose (X)**

- For each meal, take X units of insulin
- Making adjustments to fixed mealtime dose:
  - Check two hour postprandial blood glucose levels to assess efficacy of mealtime dose
  - Pattern of postprandial highs? Increase mealtime dose (and vice versa)
INSULIN PUMPS

- Continuous infusion of insulin lispro, aspart, or glulisine via subcutaneous cannula
- Lower HbA1c with fewer hypoglycemic events and fewer office visits
- Pump candidates
  - Check BG 4 times daily
  - Due not achieve HbA1c goal
  - More frequent hypoglycemia or DKA
  - Variable lifestyle
  - Family and patient interest
- Suggested pump TDD by Yale Diabetes Center
  - Pump TDD = 0.75 x Pre-pump TDD

INSULIN PUMP THERAPY

MITIGATING DIFFICULTIES
COMMON PITFALLS OF INSULIN THERAPY

- Hypoglycemia
  - AM and overnight
  - Daytime
  - Exercise-induced
- Missed insulin doses
- Weight gain
- High insulin doses
- Variable insulin action

PATTERNS OF HYPOGLYCEMIA

- Overnight
  - Somogyi Effect: rebound fasting hypoglycemia after nocturnal hypoglycemia
  - Differentiate from Dawn Phenomenon: fasting hyperglycemia due to elevated AM HGH levels and waning insulin action without preceding hypoglycemia
- Fasting
- Postprandial
- Exercise- or activity-induced

TROUBLE-SHOOTING: AM AND OVERNIGHT HYPOGLYCEMIA

- Check bedtime (HS) BG
- Decrease basal dose
  - Overbasalization?
  - Educate pt on titration
- Alternatively, pt to take HS snack
- Considerations for effect of exercise
CONTINUOUS GLUCOSE MONITORING (CGM)

- Can be used with or without insulin pump
- Best for patients with:
  - High risk of hypoglycemia
  - Hypoglycemic unawareness
  - Frequent hypoglycemia
  - Fear of hypoglycemia

TROUBLE-SHOOTING:

DAYTIME HYPOGLYCEMIA

- Postprandial hypoglycemia
  - I:C ratio
    - “High carb” and “low carb” dosing (not preferred)
- Protein and fiber intake to minimize glycemic excursions
- Association with exercise?
- Consistent pre-meal timing of insulin dosing
- Always consider CGM

TROUBLE-SHOOTING:

EXERCISE-INDUCED HYPOGLYCEMIA

- Give half insulin dose prior to planned exercise/increased physical activity
  - For unexpected exercise, ensure BG >150mg/dL prior to starting exercise
- SMBG Qhr throughout exercise and for at least 2 hrs post-exercise
- Consider adjusting basal insulin dose
TROUBLE-SHOOTING:
MISSING INSULIN DOSES

- Set timers
- Set insulin on counter
  - Room temperature for 30 days
- V-Go insulin delivery device
- Consider pump
- Premixed insulin

TROUBLE-SHOOTING:
WEIGHT GAIN

- Lowest effective insulin dose
- Alternative/additional medications with weight loss effects
  - Consider GLP-1 agonist for prandial coverage
  - Alternatively SGLT2i or DPP4i
- Consider weight loss medications
- Consider DM ed/nutritionist

TROUBLE-SHOOTING:
HIGH INSULIN DOSAGES

- Lifestyle interventions to minimize insulin dose
- Continuous infusion of insulin=lower TDD
  - V-Go
  - Insulin pump
- Insulin degludec
  - U-200 pen dial up to 160u
- Humulin U-500
  - TDD >200 units
  - Limited availability
  - Educate pt about 5X concentration
TROUBLE-SHOOTING: VARIABLE INSULIN ACTION

• Consider initiating I:C ratio
• Educate pt on identifying lipohypertrophy
• Consider heat-exposed or expired insulin
• Refer to DM ed/nutrionist

INSULIN THERAPY: SUMMARY

• Consider: A1c >9% or as part of dual/triple therapy if A1c <7.5%
• Start if:
  • A1c > 9% or 10%
  • OR BG >300mg/dL
  • OR pt is symptomatic
  • OR BG/A1c goals are not met after 3 months on triple therapy
• Basal therapy: insulin detemir, U-100 or U-300 glargine, or degludec
  • Alternatively premixed insulin or NPH
• 10 units/day
• 0.1-0.2u/kg/day THEN TITRATE
• 0.2-0.3u/kg/day if A1c >8%
• Avoid clinical inertia
• Lower A1c/BG
• Decrease rates of microvascular/macrovascular complications
• Improve patients' health, longevity, and overall quality of life
AUGMENTING TX/ADDING PRANDIAL THERAPY

**When?**
- If A1c goals are not met after 3 months
- Fasting blood glucose at goal with elevated A1c/postprandial BG
- Basal therapy is at 0.5 u/kg/day

**What?**
- Bolus insulin therapy: Lispro, aspart, or glulisine
- GLP-1 agonist
- Alternatively:
  - SGLT2i/DPP4i
  - Premixed insulin
- 4-5 units
- 10% of basal dose
- 0.1 u/kg/day

**How?**
- THEN TITRATE
- Avoid clinical inertia
- Avoid overbasalization
- Limit hypoglycemia
- As A1c approaches goal, postprandial BG is more influential

**Why?**

QUESTIONS!