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Targets*
 $A1_c \leq 6.5\%$
 $FPG/SMBG \leq 110 \text{ mg/dL}$
 $2\text{-hr PPG/SMBG} \leq 140\text{--}180 \text{ mg/dL}$
 *Individualization is recommended for those with chronic diseases or other comorbidities associated with high risk for hypoglycemic events, especially younger children[†] and elderly.
[†]American Diabetes Association. Clinical Practice Recommendations 2005.
Diabetes Care. 2005;28(suppl 1): S22.

Treatment Naïve¹;
 Symptomatic;
 $FPG \geq 260 \text{ mg/dL}$ in adults or
 $A1_c \geq 10\%$, ketoacidosis or
 recent rapid wt loss in children

OPTIONS^{2,3}
 (in order of preference)
 1. Once-daily Insulin
 2. Multi-dose Insulin (pediatric)
 3. Intensive Insulin Management

Oral Agent Failure;
 $A1_c$ above target but
 $< 8.5\%$

OPTIONS³
 (in order of preference)
 1. Once-daily Insulin⁴
 2. Multi-dose Insulin⁵
 3. Intensive Insulin Management⁵

Oral Agent Failure;
 $A1_c \geq 8.5\%$

OPTIONS^{3,6}
 (in order of preference)
 1. Multi-dose Insulin⁵
 2. Intensive Insulin Management⁵
 3. Once-daily Insulin⁴

ACB: Before breakfast
 ACS: Before supper
 FPG: Fasting plasma glucose
 HS: Bedtime
 LAI: Long-acting insulin = **Glargine**
 PCP: Primary care provider
 PPG: Postprandial plasma glucose
 SAI: Short-acting insulin = Regular (peak action 3-4 hrs); **Lispro** or **Aspart** (peak action 1 1/2 hr)
 SMBG: Self-monitored blood glucose
 SQ: Subcutaneous
 TDI: Total daily insulin in units

Once-daily Insulin Therapy (QDI)
At bedtime (HS): NPH (pen/vial) or q daily Long-acting insulin (LAI) (pen/vial) or
Before supper (ACS): NPH mix with Short-acting insulin (SAI) (2:1 ratio or sliding scale⁷) (vial) or premix 70/30 or 75/25 (pen/vial)
Starting dose⁸: 0.1–0.25 units/kg; or 6–10 units for elderly/thin/complicated patients
 Escalate dose every 2–3 days to attain SMBG/FPG target values; consider HS SMBG in adjusting dose of ACS mix/premix (SAI component)
Suggested titration schedule⁹
 If fasting SMBG
 >180 mg/dL + 6 units
 141–180 mg/dL + 4 units
 121–140 mg/dL + 2 units
 100–120 mg/dL + 1 unit
 <80 mg/dL - 2 units

Glycemic Targets Not Met After 6–12 Weeks

Multi-dose Insulin Therapy (MDI)¹⁰
-2 shots
 Split mix NPH + Short-acting insulin (SAI) (vial) (2:1 ratio AM, 1:1 ratio PM; or SAI sliding scale⁷)
or premix 70/30; 75/25 or 50/50 (pen/vial)
-3 shots (especially if nocturnal hypoglycemia)
 SAI: ACB and ACS sliding scale⁷ (pen/vial) +
 NPH: ACB and HS (pen/vial) or LAI: q daily (pen/vial)
Starting dose⁸: 0.3–0.5 units/kg/day (or if current dose >0.5 units/kg/day, take 80% of QDI dosage) divided 2/3 as NPH/LAI; 1/3 as SAI; titrate to achieve glycemic targets

Glycemic Targets Not Met After 3–6 Months

Intensive Diabetes Management— Physiologic Insulin Delivery¹⁰
1:1 basal:bolus ratio SQ
Basal: NPH at ACB, ACS or HS (or QID) (pen/vial); or Long-acting insulin (LAI) q daily (pen/vial)
Bolus: Short-acting insulin (SAI) at each meal (especially Lispro/Aspart) (pen/vial)
Premeal insulin dose includes:
 1. Insulin to cover carbohydrate ingested¹¹
 2. Additional insulin to correct for high SMBG (1 unit SAI lowers PG [mg/dL] by approximately 1500/TDI for Regular; 1800/TDI for Lispro/Aspart)
Starting dose⁸: 0.3–0.5 units/kg/day (or if current dose >0.5 units/kg/day, take 80% of total NPH dosage as glargine [basal]; bolus dose=80% of glargine dose divided tid)

Pramlintide^{10,12}
 Consider as adjunct therapy to insulin in patients unable to stabilize post-prandial glucose.

Follow $A1_c$ every 3–6 months and Adjust Regimen to Maintain Glycemic Targets (Insulin Requirement May Decrease as $A1_c$ improves)

Footnotes
¹See Glycemic Control Algorithm for Type 2 Diabetes Mellitus in Children and Adults
²Consider simultaneous combination oral agent therapy

³Combining metformin with insulin therapy has been shown to result in less weight gain and better glycemic control with lower insulin requirements
⁴Continue combination oral agent therapy ± sulfonylurea
⁵Continue metformin (± 3rd oral agent); probably discontinue sulfonylurea
⁶PCP may decide to “ease” patient with poor beta-cell reserve into insulin therapy initially with QDI

⁷~1-2 units for every 50 mg/dL above target SMBG; Regular insulin to be given 30-60 minutes AC meal
⁸Dosages may differ in children and adolescents; **consider referral to pediatric endocrinologist/comprehensive diabetes specialty team**
⁹Go lower and slower for thin/elderly/complicated patients
¹⁰**Consider referral to pediatric/adult endocrinologist/diabetes specialty team (option—insulin pump, Pramlintide)**
¹¹Typical “carb” bolus = 1 unit SAI covers 500/TDI x g carbohydrates from meal (~ 10-15 g); **strongly recommend referral to Registered/Licensed Dietitian or Certified Diabetes Educator with experience in diabetes nutrition counseling (see Worksheet D.)**
¹²IMPORTANT: See package insert for dosing.

INITIATION OF INSULIN THERAPY FOR TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADULTS¹: A SIMPLIFIED APPROACH



Targets

A_{1c} ≤6.5%

FPG/SMBG ≤110 mg/dL

2-hr PPG/SMBG ≤140–180 mg/dL

*Individualization is recommended for those with chronic disease states or other comorbidities associated with high risk of hypoglycemic events.

Abbreviations

FPG: Fasting plasma glucose

HS: Bedtime

PPG: Post-prandial plasma glucose

SMBG: Self-monitored blood glucose

TDI: Total daily insulin in units

Treatment Naive:

FPG ≥260mg/dL;

Symptomatic

Begin Combination Oral Agent Therapy ²

Oral Agent Failure;

A_{1c} above target

Strongly Consider Initiation of Insulin Therapy with Glargine (pen/vial) daily³ or NPH (pen/vial) HS⁴

Beginning Dosage: 10 units or 0.1–0.25 units/Kg

Suggested Titration Schedule--Adjust Every 2–3 Days

If Fasting SMBG⁵:

>180 mg/dL Add 6 units

If 141–180 mg/dL Add 4 units OR increase by 2 units every 2–3 days to FPG ~100 mg/dL

If 121–140 mg/dL Add 2 units

If 100–120 mg/dL Add 1 unit

If <80mg/dL Subtract 2 units

If A_{1c} Remains >6.5% over 3 months, Consider Discontinuing Oral Secretagogue and Initiating Multi-dose Insulin or Intensive Insulin Therapy¹ or Consult an Endocrinologist.

Footnotes

1. See Insulin Algorithm for Type 2 Diabetes Mellitus in Children and Adults.
2. Usually with an insulin secretagogue (sulfonylurea, repaglinide or nateglinide) and sensitizer (metformin or thiazolidinedione). See Glycemic Control Algorithm.
3. FDA-approved in 2003 for q daily dosing.
4. The pharmacokinetic profile of NPH compared to that of glargine is less predictable, therefore can result in blood sugar variations and increased nocturnal hypoglycemia. Cost of glargine is 1.5–2 times that of NPH. Lispro 75/25 or Aspart 70/30 can be considered at pre-supper adjusting dosage according to HS and fasting SMBG.
5. If daytime hypoglycemia develops, contact healthcare professional.
See web site (<http://www.texasdiabetescouncil.org>) for latest version and disclaimer.

WORKSHEET

Revised 10-20-05



TEXAS DIABETES
COUNCIL

Advancing to Intensive/Physiologic Basal: Bolus Insulin Therapy

Note: “Analog” = Rapid Acting (Bolus) Analog insulin throughout this document.

A. Conversion from once-daily insulin to intensive/physiologic insulin replacement:

Oral therapy failure: Once-daily glargine was added to the oral regimen and titrated to 30 units per day. How do you add analog insulin if the patient reports the following SMBG values?

	FPG	2-hr pp Brkft	2-hr pp Lunch	2-hr pp Dinner
Case 1	105	140	140	240
Case 2	105	140	190	240
Case 3	105	190	240	240

Case 1

- a. Continue the oral agents (\pm sulfonylurea) and 30 units glargine (or NPH)
- b. There are 2 approaches for adding analog 10 minutes before a meal:

#1 Arbitrary start: 5 units
 Titrate: Add 2 units every 2 days to reach 2-hr pp goal

#2 Carb-counting 1 unit/50 mg/dL over 2-hr pp goal

PLUS

 1 unit/15 grams carbohydrate
 Titrate: Add 1 unit/50 mg/dL $>$ 2-hr pp goal every 2 days

Cases 2 and 3

As above, but add and titrate analog before each meal where the postprandial glucose is above goal. Also, [see part D, below](#), for more information on how to optimize the use of analog insulin. Re-evaluate each week to be certain that about half of the total daily dose is basal and half is bolus insulin.

B. Conversion from once-daily premix to intensive/physiologic insulin replacement:

Oral therapy failure: Once-daily 70/30 premixed insulin was added and titrated to 30 units per day. The fasting glucose is at goal, but daytime control is poor. How do you convert to physiologic insulin therapy?

- a. **Basal insulin dose:** The first step in the conversion is based on the total dose of intermediate-acting insulin. In this case, the person is taking 21 units of NPH or aspart-protamine insulin ($70\% \times 30 \text{ units} = 21 \text{ units}$). So, give 21 units basal glargine (use “unit-for-unit” conversion for once-daily intermediate regimens.) *Remember; do not stop oral agents (\pm sulfonylurea) at this time.*
- b. **Bolus insulin dose:** There are several ways to start the analog.
 - i. *See Case 1, page 2 (Arbitrary start or Carb-counting)*
 - ii. Begin with the previous dose of fast-acting insulin, divide it before meals and titrate every 2 days. In this case, the person was using 30 units of 70/30 or about 9 units of fast-acting insulin ($30\% \times 30 \text{ units} = 9 \text{ units}$). So give 3 units of analog before each meal and titrate every 2 days as per Case 1.



C. Conversion from twice-daily premix to intensive/physiologic insulin replacement:

Oral therapy failure in an 80 kg person: 70/30 premixed insulin was started and advanced to 60 units per day: 40 units before breakfast and 20 units before dinner. The fasting glucose was at goal, but wide glycemic excursions occurred at other times during the day and night. How do you convert this person to physiologic insulin therapy? There are several approaches. Use which ever method you want.

- a. Start over and begin insulin at 0.5 units/kg. Give half as basal insulin and half as analog, divided before meals. In this case, the starting dose would be 40 units per day. Start giving 20 units glargine each morning and about 7 units analog before each meal. Titrate the basal and bolus insulins every 2 days to fasting and 2-hr postprandial goals.
- b. Conversion based on current insulin usage:

Basal dose: The first step in the conversion is based on the 80% of the total dose of intermediate-acting insulin. In this case, the person is taking 42 units of NPH or aspart-protamine insulin ($70\% \times 60 \text{ units} = 42 \text{ units}$). When a person is taking multiple doses of intermediate-acting insulin, we give only 80% as glargine. So, give 34 units basal glargine ($80\% \times 42 = 34$). Remember, *do not stop oral agents (+ sulfonyleurea) at this time.*

Bolus insulin dose: There are several ways to start the analog.

- i. *See Case 1, page 3 (Arbitrary start or Carb-counting)*
 - ii. Begin with the previous dose of fast-acting insulin, divide it before meals and titrate every 2 days. In this case, the person was using 60 units of 70/30 or 18 units of fast-acting insulin ($30\% \times 60 \text{ units} = 18 \text{ units}$). So, give 6 units of analog before each meal and titrate every 2 days as per Case 1.
- c. The “80%-80%” rule: Similar to the above method, but yields an ideal ratio of basal:bolus insulin in one step. The dose of basal glargine will be 80% of the total intermediate insulin, and the analog will be 80% of the glargine dose, divided before meals.

Basal dose: = 80% of total intermediate insulin
= $80\% \times 42 \text{ units}$ ($70\% \times 60 = 42$)
= 34 units glargine

Analog dose: = 80% of the glargine dose, divided tid
= $80\% \times 34 \text{ units}$, divided tid
= 27 units, divided tid
= 9 units aspart or lispro before meals

Note: Total dose of insulin is conserved and an ideal ratio between basal and bolus will always result with the “80%-80%” method.



D. Optimizing analog insulin use

Tight control of blood glucose requires that the patient participates in the management of their diabetes. This includes monitoring their blood glucose and learning to count carbohydrates or “carb count.” The following material explains how to calculate the dose of analog required to cover a meal and how to add extra analog to correct a hyperglycemic event.

a. Determining the dose of analog insulin to use before a meal

The “Rule of 500” is used to determine how many grams of carbohydrate 1 unit of analog insulin will cover. When this number is known, then the person can easily give the correct dose of analog by simply counting the grams of carbohydrate they intend to eat at the meal.

Specifically, 500 divided by the total daily insulin dose (500/TDI) yields the number of grams of carbohydrate that 1 unit of analog will cover. For example, if a person has established that they require about 50 units of insulin per day, then it follows that 1 unit of analog will cover 10 grams of carbohydrate ($500/50 = 10$). If the person carb counts 140 grams in the dinner meal, then the dose of analog will be 14 units given 10 minutes before eating.

b. Correcting for hyperglycemia

The “Rule of 1800” is used to determine how much insulin to use to bring a high glucose reading back to goal. Even with tight control, hyperglycemia occurs and people need to be able to correct this situation.

Specifically, 1800 divided by the total daily insulin dose yields a value indicating how much 1 unit of analog insulin will lower the blood glucose. Thus, if a person uses 90 units of insulin per day, then 1 unit of analog will reduce the blood glucose by 20 mg/dL ($1800/90 = 20$). *This augment dose of insulin can be used by itself to correct hyperglycemia, or added to the bolus dose if glucose is high before a meal.*

1. Riddle MC, Rosenstock J, Gerich, J. *Diabetes Care*, 2003; 26:3080-3086.
2. Spellman CW, Renda SM, Davis SN. *Realizing the Potential of Insulin Therapy in Type 2 Diabetes: A Case Presentation-Based Monograph*, presented at the American College of Osteopathic Internists 64th Annual Convention; Chicago, IL (September 30, 2004).
3. www.texasdiabetescouncil.org



Reviews/Important Articles:

- Abraira C, Colwell J, Nuttall F, et al. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes. *Arch Intern Med.* 1997;157(2):181-8.
- Anonymous. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352(9131):837-53.
- DeWitt DE, Dugdale DC. Using new insulin strategies in the outpatient treatment of diabetes: clinical applications. *JAMA.* 2003;289(17):2265-9.
- DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA.* 2003;289(17):2254-64.
- Implementation Conference for ACE Outpatient Diabetes Mellitus Consensus Conference Recommendations: Position Statement, February 2, 2005. Available online at <http://www.aace.com/pub/odimplementation/PositionStatement.pdf>. Accessed on May 2, 2005.
- Hirsch IB. Insulin analogues. *N Engl J Med.* 2005;352(2):174-83.

ONCE DAILY INSULIN

Morning vs. Bedtime NPH

Groop LC, Widen E, Ekstrand A, et al. Morning or bedtime NPH insulin combined with sulfonylurea in treatment of NIDDM. *Diabetes Care.* 1992;15(7):831-4.

Morning vs. Bedtime Glargine

Fritsche A, Schweitzer MA, Haring HU. Glimpiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. *Ann Intern Med.* 2003;138(12):952-9.

NPH vs. Glargine

Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care.* 2003;26(11):3080-6.

ONCE DAILY vs. TWICE DAILY REGIMEN

Raskin P, Allen E, Hollander P, et al. Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care.* 2005;28(2):260-5.

MULTIPLE DOSE INSULIN REGIMENS

2-shot regimens

NPH/Regular vs. NPH/ short acting analogue therapy

Vignati L, Anderson JH Jr, Iversen PW. Efficacy of insulin lispro in combination with NPH human insulin twice per day in patients with insulin-dependent or non-insulin-dependent diabetes mellitus. Multicenter Insulin LisproStudy Group. *Clin Ther.* 1997;19(6):1408-21.

2-shot regimens (continued)

70% NPH/ 30% Regular vs. Humalog Mix 75/25™ or Novolog Mix 70/30™

Roach P, Yue L, Arora V. Improved postprandial glycemic control during treatment with Humalog Mix25, a novel protamine-based insulin lispro formulation. Humalog Mix25 Study Group. *Diabetes Care.* 1999;22(8):1258-61.

Boehm BO, Home PD, Behrend C, et al. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in Type 1 and Type 2 diabetic patients. *Diabet Med.* 2002;19(5):393-9.

3-shot Regimens

Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract.* 1995;28(2):103-17.

Intensive Insulin Therapy

Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract.* 1995;28(2):103-17.

Saudek CD, Duckworth WC, Giobbie-Hurder A, et al. Implantable insulin pump vs multiple-dose insulin for non-insulin-dependent diabetes mellitus: a randomized clinical trial. Department of Veterans Affairs Implantable Insulin Pump Study Group. *JAMA.* 1996;276(16):1322-7.

Raskin P, Bode BW, Marks JB, et al. Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: a randomized, parallel-group, 24-week study. *Diabetes Care.* 2003;26(9):2598-603.

Bretzel RG, Arnolds S, Medding J, et al. A direct efficacy and safety comparison of insulin aspart, human soluble insulin, and human premix insulin (70/30) in patients with type 2 diabetes. *Diabetes Care.* 2004;27(5):1023-7.