Insulin Update 2024

Kristy Klinger, PharmD, PhC, CDCES, BC-ADM
USPHS-IHS, CAPT Retired
Gallup Community Health
Gallup, NM

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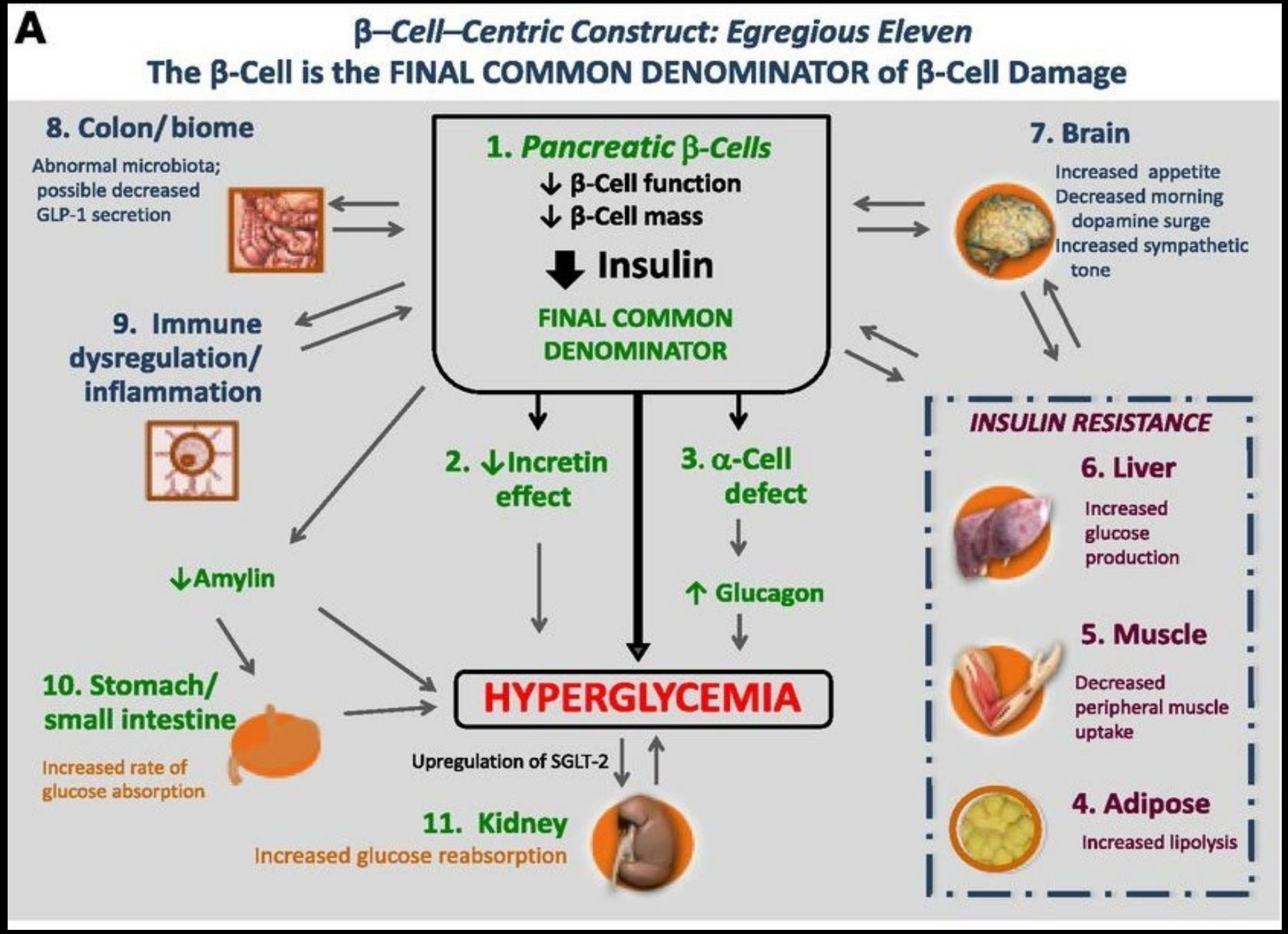
Learning Objectives

- Identify situations where insulin is the recommended treatment for diabetes management.
- Describe the protocol on how to dose insulin and convert patients to different types of insulin.
- Examine the variety of biosimilar insulins and compare and contrast differences.



Schwartz, S. S. (2016, January 23). Beta-Cell Construct: Egregious Eleven. Diabetes in Control. Retrieved October 19, 2021, from https://www.diabetesincontrol.com/beta-cell-construct-egregious-eleven/

Patient Barriers to Optimal Insulin Therapy

- Fear of taking insulin (i.e. needle phobia, side effects)
- Health beliefs regarding insulin
- Complexity of regimen
- Cost

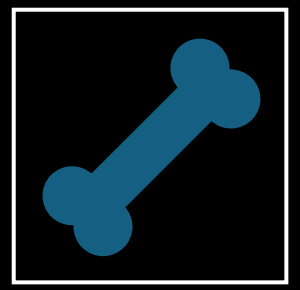
Provider Barriers to Optimal Insulin Therapy

- Not prepared for patient's response at the suggestion of insulin
- Provider beliefs
  - "Too complicated for my patient"
  - Use insulin as a threat
  - Last resort
- Learning to adjust insulin doses takes practice
- Inadequate follow-up and support
  - Dose titrations (i.e. doesn't work)
  - Side effects (i.e. hypoglycemia)
  - Not shown how to use
  - Don't have the supplies

Common Diabetes Terminology

- A1C
- Insulin resistance
- Glucose toxicity
- Catabolism

Common “Misterminology”



”Brittle Diabetic”

“Insulin dependent diabetes”

“A little too sweet”

Sample Patient Case

46 year old male. Previous history of heavy alcohol use, but no alcohol for 10 years. A1c 8 months ago was 5.9%.

Presents to ED feeling very ill. Unintentional weight loss of 12 pounds in past 2 months and appears underweight today. Sunken facial features and polydipsia/polyuria. A1c today is 12.8% and Blood sugar 500.

DKA or HHS???

Autoimmune vs. T2DM???

Diabetic Ketoacidosis – Vs- Hyperosmolar Hyperglycemic State

Test	Reference Range	DKA	HHS
Serum Glucose (mg/dL)	70-140	>250	>600
Serum osmolality (mOsm/kg)	275-295	>320	>320
Sodium bicarb (mEq/L)	22-26	<15	>15
Arterial pH	7.36-7.44	<7.2	>7.3
Ketones	absent	Moderate to high	Absent to small
Bun (mg/dL)	5-20	32	61
SCr (mg/dL)	0.7-1.2	WNL	Slight elevation
Serum K (mmol/L)	3.5-5.0	WNL	WNL
Serum Na (mmol/L)	135-145	Typically low	Typically elevated
Serum Phos (mg/dL)	2.3-4.3	varies	varies

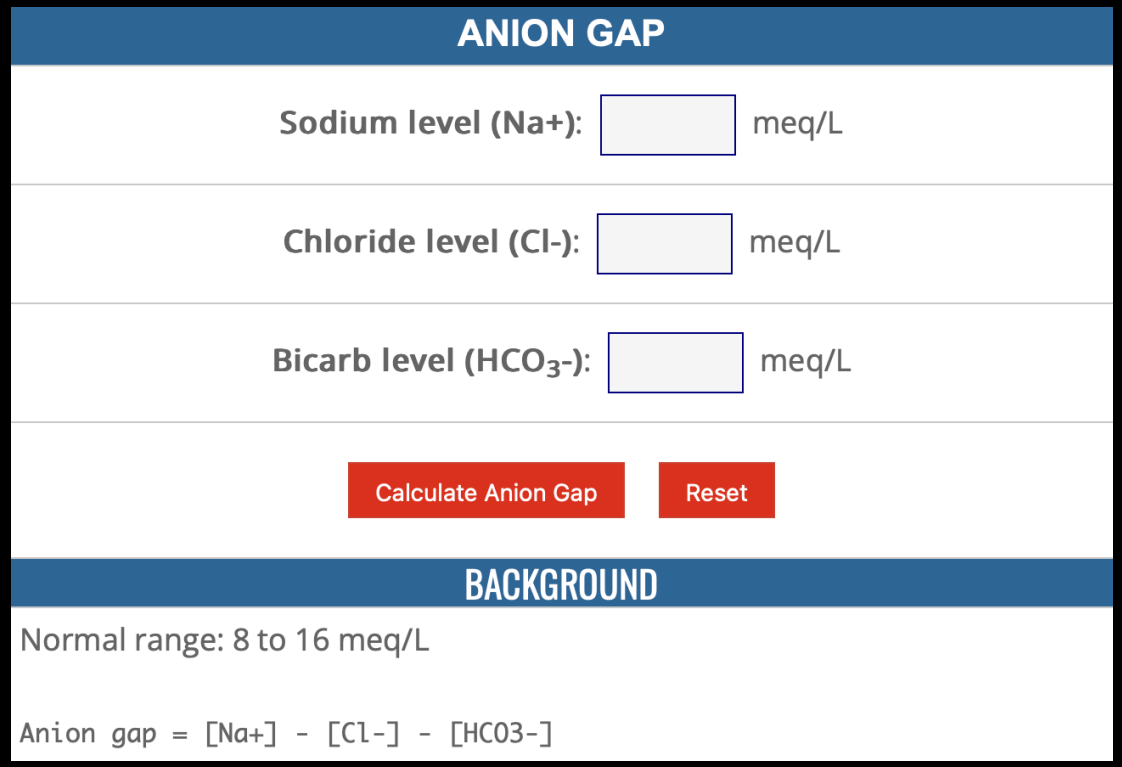
Increased due to dehydration

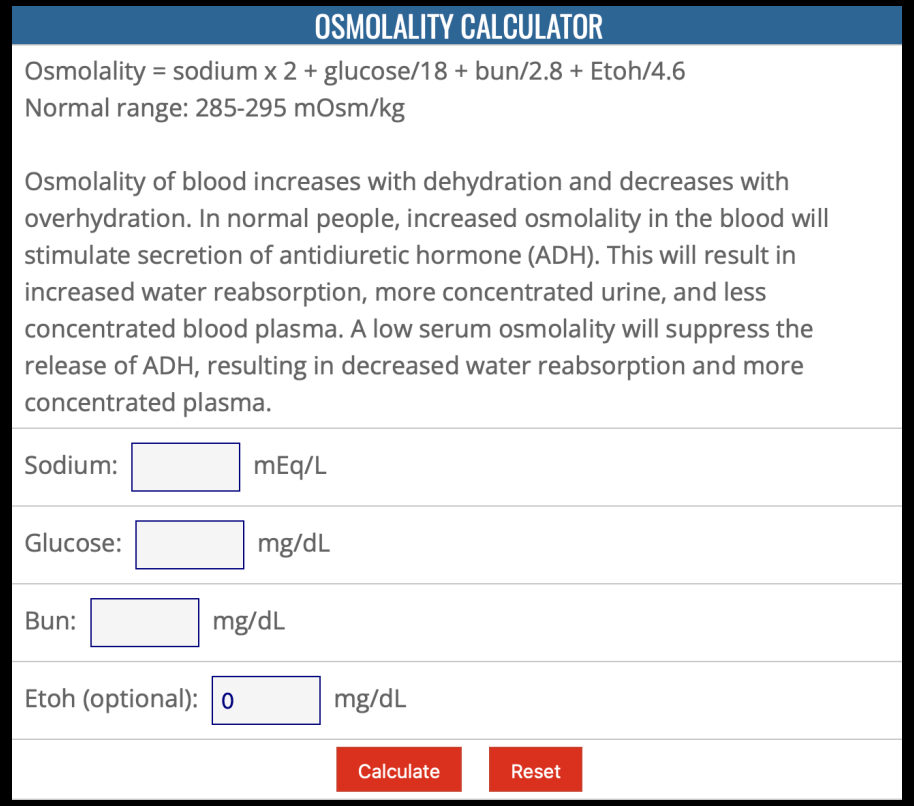
Losses often masked by dehydration

Nugent BW. Hypersomolar hyperglycemic state. Emerg Med Clin North Am. 2005;Aug 23(3):629-48.

DKA vs. HHS

- Use a free online calculator such as globalrph.com





Insulin as Primary Therapy

- Autoimmune Mediated Diabetes
  - Type 1 Diabetes Mellitus
  - Latent Autoimmune Diabetes of Adulthood (LADA)
- Diabetic Ketoacidosis
- Hyperosmolar Hyperglycemic Syndrome
- Diabetes in Pregnancy and Gestational Diabetes
- Type 2 Diabetes Mellitus
  - Catabolism
  - Pancreatic insufficiency
    - Due to chronic pancreatitis , surgery, cystic fibrosis
    - Long standing T2DM, less than desirable A1c despite optimal other medications
  - Diabetes from “seemingly out of nowhere”

Similarities between Autoimmune Diabetes (T1DM and LADA) –AND- Diabetes Due to Chronic Pancreatitis

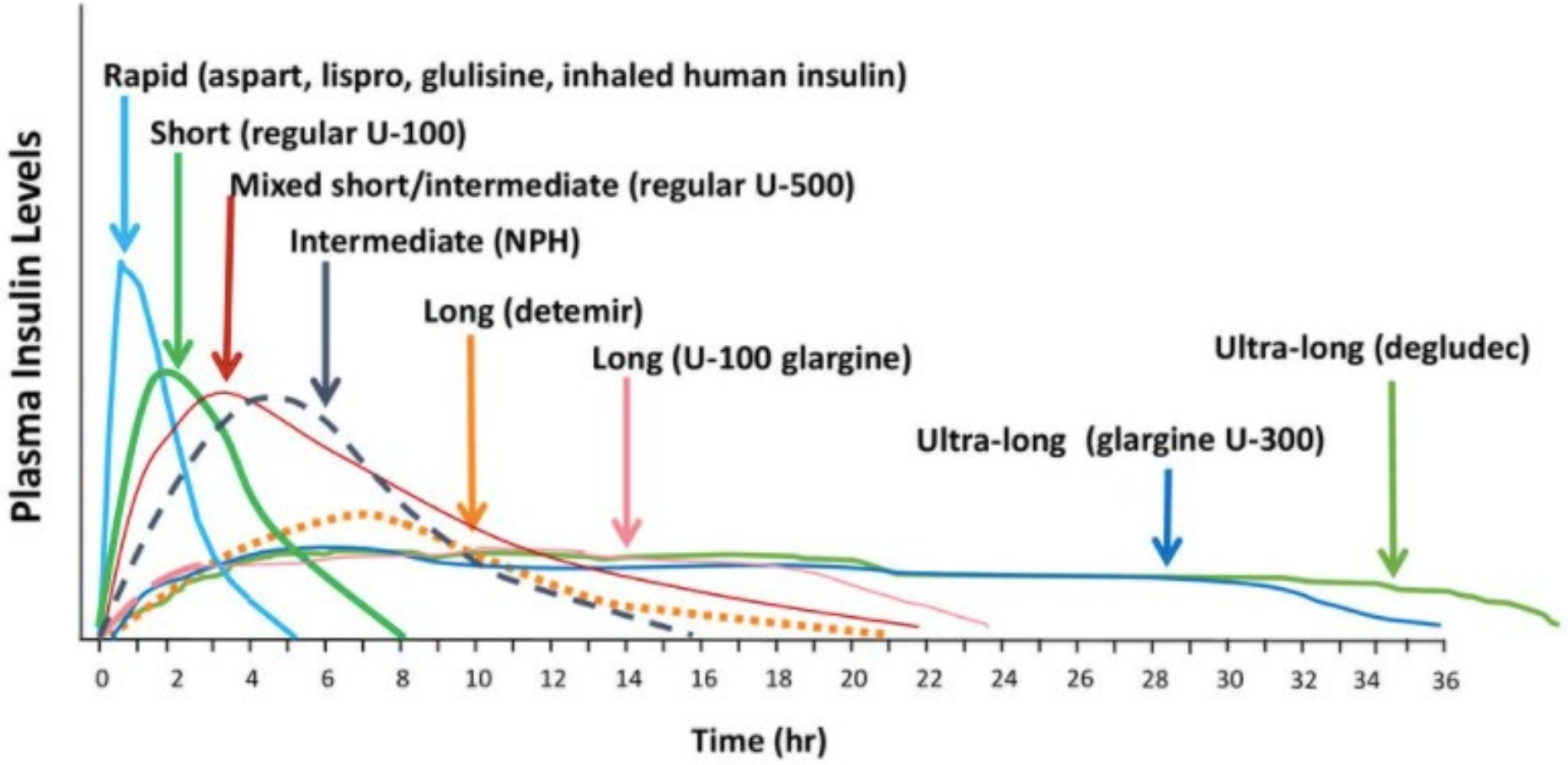
- Insulin deficiency is primary disease process
- Body weight is typically lean to underweight
- Lack of insulin resistance
- C-peptide levels will be low even at high glucose levels

Differences between Autoimmune Diabetes (T1DM and LADA) –AND- Diabetes Due to Chronic Pancreatitis

- Age of Onset - Type 1 usually very young age
- Presence of Autoimmune Antibodies (usually one is positive)
  - GAD-65
  - Islet cell Ab
  - Zinc Transporter
  - IA-2 (Insulinoma Associated Protein)
  - Others TBD???
- T1DM and LADA – use of oral meds is generally **not recommended** at this time

Diabetes is Like A Wildfire.....

Pharmacokinetic Profile of Currently Available Single Insulin Products



Hirsch IB. *N Engl J Med*. 2005; 352:174-83.
Flood TM. *J Fam Pract*. 2007; 56(suppl 1):S1-S12.
Becker RH et al. *Diabetes Care*. 2015; 38:637-43.

Initiation and Titration of Insulin

Pdf available at ihs.gov
Division of Diabetes Treatment and Prevention, Clinical Resources, Treatment Algorightms

Step 1: Start basal insulin therapy

- Start long-acting analog 10 units or 0.1-0.2 units/kg once a day (may advance to BID if necessary).
- Increase by 2-4 units or 10-15% every 3-4 days until fasting blood glucose (FBG) values fall within target range, generally 80-130 mg/dL, OR adjust dose following review of CGM profile.

↓ **If A1C* not at goal but FBG at target and/or basal insulin dose >0.5 unit/kg/day**

If not already on a GLP1-RA or tirzepatide, consider adding to basal insulin or starting long-acting insulin/GLP1-RA combination before adding mealtime insulin.

Step 2: Add mealtime insulin before largest meal

- Start rapid-acting analog 2-4 units or 10% of basal insulin dose before largest meal.
- Increase insulin by 1-2 units or 10-15% until blood glucose (BG) within target range, generally 80-130 mg/dL premeal or <180 mg/dL 1-2 hours after meals, OR utilize CGM profile to guide dose adjustments (individualize).

↓ **If A1C* not within target range**

Step 3: Add mealtime insulin before other meals

- Start additional rapid-acting analog 2-4 units or 10% of basal insulin dose before other meals (focus on one meal at a time).
- Increase insulin by 1-2 units or 10-15% every 3-7 days until BG falls within target range, generally 80-130 mg/dL premeal or <180 mg/dL 1-2 hours after meals, OR utilize CGM profile to guide dose adjustments (individualize).

KK’s Initiation of Basal and Initial Titration

- 10 units once daily – (6 units if normal or underweight)
- Focus on AM fasting sugars
- Initial AM fasting goal – get into the 100’s
- **weekly calls if able and increase by 10 units if >200, smaller increase if already in upper 100’s.

- Once AM fastings in the 100’s, then change focus and start checking 1 to 2 hours after dinner sugars
- Address post prandial sugars with additional meds if necessary

Patient Managed - Super Simple Insulin Titration

- Especially effective if weekly follow up not possible
- Engages patient in checking and dosing
- Check AM fasting sugar
- If AM fasting sugar >200, then increase basal insulin dose by 1 unit that day
- If most AM fasting sugars are <200, then stay at that basal dose until seen again by provider
- If AM fasting sugar <80, then decrease basal dose by 5 units daily

*can take patients VERY long to get to optimal dose if insulin resistant

Adequacy of Basal Insulin Dose

- Indications of “over basalization”
  - Basal dose > 0.5units/kg/day, and not yet on prandial insulin
  - HS to AM drop of more than 50 points
  - High variability
  - Large post-prandial to pre-prandial differentials
- Consider prandial insulin over other post prandial meds when:
    - Already on GLP-1 or not able to use
      - Examples of “not able to use” – T1DM, intolerance, gastroparesis, chronic pancreatitis, weight loss not desirable
    - Post prandial sugars VERY high
    - Pancreatic insufficiency patients

Moving from Over Basalized to Balanced

- Calculate a total daily dose
- Compare to physiologic insulin ratios
  - 50/50 – heavy carb eaters
  - 70/30 – more carb balanced eaters
  - Evaluate where to go……..
    - Simply add on bolus doses?
    - Keep daily dose the same, but adjust ratios
  - Discuss your rational with the patient

Insulin Detemir

- 2024 production scheduled to cease
- Considered a basal insulin
  - Lower doses < 20 hours duration of action
  - Higher doses >20 hours duration of action
- Dose conversions
  - Calculate total daily dose of detemir
  - If at A1c goal or hypoglycemia: convert at 80%
  - If above A1c goal and no hypoglycemia: convert one to one

**in general, patients required a slightly higher dose of detemir to reach the same lower effect of insulins such as glargine.

Test Your Knowledge

- Pt on detemir 25 units BID, but detemir no longer available
- Patient's insurance covers insulin glargine (and degludec)
  - Patient with A1c close to goal and felt one episode of low sugar (into the low 80's) overnight last week .
  - What would you recommend?
    - Glargine (or degludec) at 40 units once daily (new dose 80% of old)
  - Patient with A1c of 12%, lowest sugar in past 3 weeks was 212.
  - What would you recommend?
    - Glargine (or degludec) at 50 units daily (one to one conversion)

  **concentrated glargine or concentrated degludec might be preferable if patient is on higher doses of basal insulin

Combo Insulins to Separate Basal/Bolus

- Combo pens usually limited to 60 units per injection
- 70/30 - 70% long, 30% short
- 75/25- 75% long, 25% short
- 50/50 – 50% long, 50% short
- Conversion (example 70/30 to glargine/aspart)
  - Calculate total daily dose
  - 70% total daily dose to be given as once daily basal
  - 30% total daily dose DIVIDED and given with 2-3 largest meals
  - This is a starting place and can be adjusted individually to move toward needs of patient evidenced by blood glucose or symptoms.

Test Your Knowledge

- Pt on 50 units BID of Humulin 75/25
  - Patient with A1c close to goal and felt one episode of low sugar (into the low 80's) overnight last week .
  - What would you recommend?
    - Glargine (or degludec) at 60 units once daily (new dose 80% of old basal)
    - Aspart or lispro 20 units split between 2 or 3 meals. (80% of old bolus)
  - Patient with A1c of 12%, lowest sugar in past 3 weeks was 212.
  - What would you recommend?
    - Glargine (or degludec) at 75 units daily (75% long, one to one conversion)
    - Aspart or lispro 25 units split between 2 or 3 meals. (100% short, one to one)

Pdf available at ihs.gov
Division of Diabetes Treatment and Prevention,
Clinical Resources, Treatment Algorithms

Insulin Therapy in Diabetes Treatment

Insulin Therapy in Diabetes Treatment

The tables below provide estimates of insulin pharmacokinetic profiles of various preparations. Patients with type 2 diabetes may require high doses due to insulin resistance. Injection of large insulin boluses affects insulin absorption and activity.

	Administration/ Timing with Meals	Peak (hrs)	Duration (hrs)	Max Pen Dose (units)
Long Acting Insulin				
Detemir U-100 (*Levemir*)	Usually at bedtime	Slow or no pronounced peak	8-24	80
Glargine U-100 (*Lantus, Semglee* Basaglar*, Rezvoglar)**			Up to 24	80
Glargine U-300 (*Toujeo*)			24-36	80 *Toujeo*/ 160 *Toujeo Max*
Degludec U-100, U-200 (*Tresiba*)			Up to 42	80 (U-100)/ 160 (U-200)
Intermediate Acting Insulin				
NPH U-100 (***Novolin N***)	Usually at bedtime (onset 1-2 hrs)	2-8	14-24	60
Short Acting Insulin				
Regular U-100 (***Novolin R***, *Humulin R*)	30 min before	2-4	6-12	60
Rapid Acting Insulin				
Aspart U-100 (***Novolog***, *Kirsty+*)	Within 5-10 min before	~1-2	5-7	60
Aspart U-100 (*Fiasp*)	At the start or within 20 min after start	1	3-5	80
Lispro (*Humalog U-100, U-200; Admelog+ U-100*)	Within 15 min or immediately after	1-2	3-5	60 - *Humalog* 80 - *Admelog*
Lispro-aabc (*Lyumjev U-100, U-200*)	At the start or within 20 min after start	1	2-4	60 - *Lyumjev U-100,U-200*
Glulisine U-100 (*Apidra*)	Within 15 min before or 20 min after start	1-2	3-6	80

	Administration/ Timing with Meals	Peak (hrs)	Duration (hrs)	Max Pen Dose (units)
Premixed Insulin				
NPH/Regular U-100 (*Novolin 70/30*)	Use guidance for short- acting or rapid-acting insulin component	2-4	18-24	60
NPH/Aspart U-100(*Novolog Mix 70/30*)		1-2	12-24	60
NPH/Lispro U-100 (*Humalog Mix 75/25 and Mix 50/50*)		1-2	13-22	60
Concentrated Regular Insulin				
Regular U-500 (*Humulin R U-500 Kwikpen*)	30 min before	0.5-8	13-24	300
Patients with severe insulin resistance requiring >200 units per day of insulin are candidates for Regular U-500. Total daily dosing may be started BID split 50-50 with meals or TID split 40-30-30 with breakfast, lunch, and dinner meals respectively.				
Inhaled Insulin				
Inhaled Regular Insulin (*Affreza*)	At the start	0.5-0.9	1.5-3	12 unit cartridge
Long-Acting Insulin/Glucagon-like Peptide-1 Receptor Agonist Combinations				
Insulin degludec/ liraglutide (*Xultrophy 100/3.6*)	30 min before	No peak	24	50 units/ 1.8 mg
Insulin glargine/ lixisenatide (*Soliqua 100/33*)	Within 1 hour prior to first meal of the day	No peak	20-24	60 units/ 20 mcg

Biosimilar and Interchangeable Insulins

* ***Semglee*** (glargine-yfgn), ***Rezvoglar*** (glargine-aglr), and ***Basaglar*** are biosimilar and do not differ clinically from ***Lantus*** (insulin glargine).

\+ ***Admelog*** (lispro) is biosimilar to ***Humalog***, and ***Kirsty*** (aspart) is biosimilar to ***Novolog***.

Semglee and Rezvoglar are also interchangeable with ***Lantus***, meaning that the pharmacist can substitute without notifying the provider.

Medications on the IHS National Core Formulary are in **BOLD** above. Please consult a complete prescribing reference for more detailed information. No endorsement of specific products is implied.

Network meta-analysis estimates for change in HbA1c level (green) and incidence of nocturnal hypoglycemia (white) for each comparison of basal insulin analogues

Detemir	1.03 (0.88 to 1.21)	*1.39 (1.12 to 1.71)*	0.91 (0.70 to 1.20)	–	–	*0.64 (0.50 to 0.82)*
0.15 (0.04 to 0.25)	Glar-100	*1.34 (1.17 to 1.54)*	0.89 (0.71 to 1.11)	–	–	*0.62 (0.49 to 0.78)*
0.20 (0.05 to 0.35)	0.05 (–0.05 to 0.16)	Glar-300	*0.66 (0.51 to 0.86)*	–	–	*0.46 (0.35 to 0.61)*
0.15 (–0.02 to 0.33)	0.00 (–0.14 to 0.14)	–0.05 (–0.23 to 0.12)	Basaglar	–	–	*0.70 (0.51 to 0.97)*
0.13 (–0.15 to 0.41)	–0.02 (–0.28 to 0.24)	–0.07 (–0.35 to 0.20)	–0.02 (–0.32 to 0.27)	MK-1293	–	–
0.09 (–0.24 to 0.42)	–0.06 (–0.37 to 0.25)	–0.11 (–0.44 to 0.22)	–0.06 (–0.41 to 0.28)	–0.04 (–0.44 to 0.36)	Semglee	–
0.09 (–0.07 to 0.24)	–0.06 (–0.20 to 0.07)	–0.12 (–0.29 to 0.05)	–0.07 (–0.26 to 0.13)	–0.04 (–0.33 to 0.25)	0.00 (–0.34 to 0.34)	NPH

Favors glargine 100, glargine 300, A1C lowering

Favors glargine 300 for nocturnal hypoglycemia

Favors long-acting analogs over NPH for nocturnal hypoglycemia

Comparative Benefits and Harms of Basal Insulin Analogues for Type 2 Diabetes
2018. Anastasia-Vasiliki Madenidou, Paschalis Paschos, Thomas Karagiannis, Anastasia Katsoula, Eleni Athanasiadou, Konstantinos Kitsios, Eleni Bekiari, David R. Matthews, Apostolos Tsapas10.7326/m18-0443
Annals of Internal Medicine

REFERENCE PRODUCT

Original FDA-approved biological product.

Prescribed by a provider.

BIOSIMILAR

Highly similar and with no clinically meaningful differences when compared to the reference product.

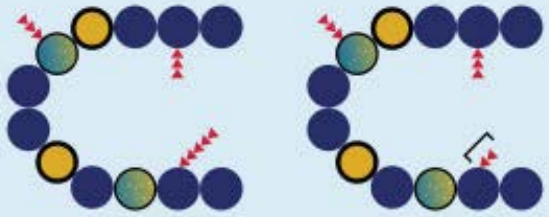
Prescribed by a provider.

INTERCHANGEABLE PRODUCT

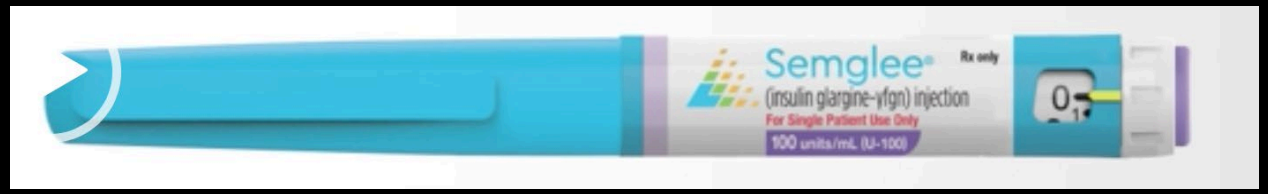
Highly similar and with no clinically meaningful differences when compared to the reference product.

The application includes additional data and information about the impact of switching or alternating between the product and the reference product.

May be substituted at the pharmacy without the intervention of the prescribing provider.



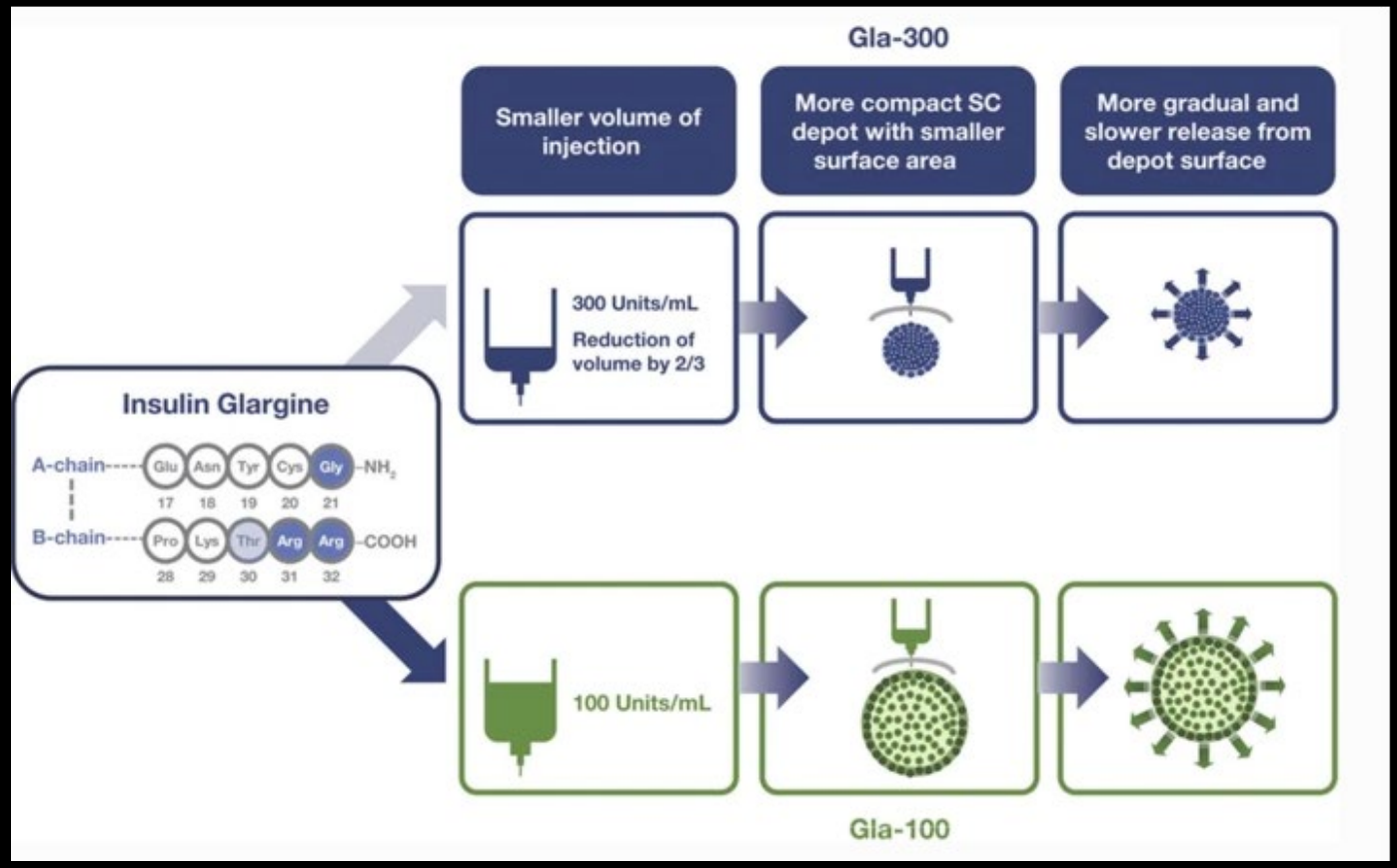
Glargine U100 Biosimilar AND Interchangeable



Glargine U100 Biosimilar NOT Interchangable

High Dose Basal Options

- Consider when requiring higher daily doses of basal insulin (esp >80 units/day)
- Up to 160 units per injection
- Insulin degludec 200units/ml (Tresiba®)
- Insulin glargine 300 units/ml (Toujeo Max SoloStar®)



Glargine U300

- >24 hour action
- MAX pen
  - doses up to 160 units per shot
  - 2 units increments, but only the 4 unit multiples shown on dial
- IHS National formulary

Nocturnal Hypo – Degludec vs. Glargine U100

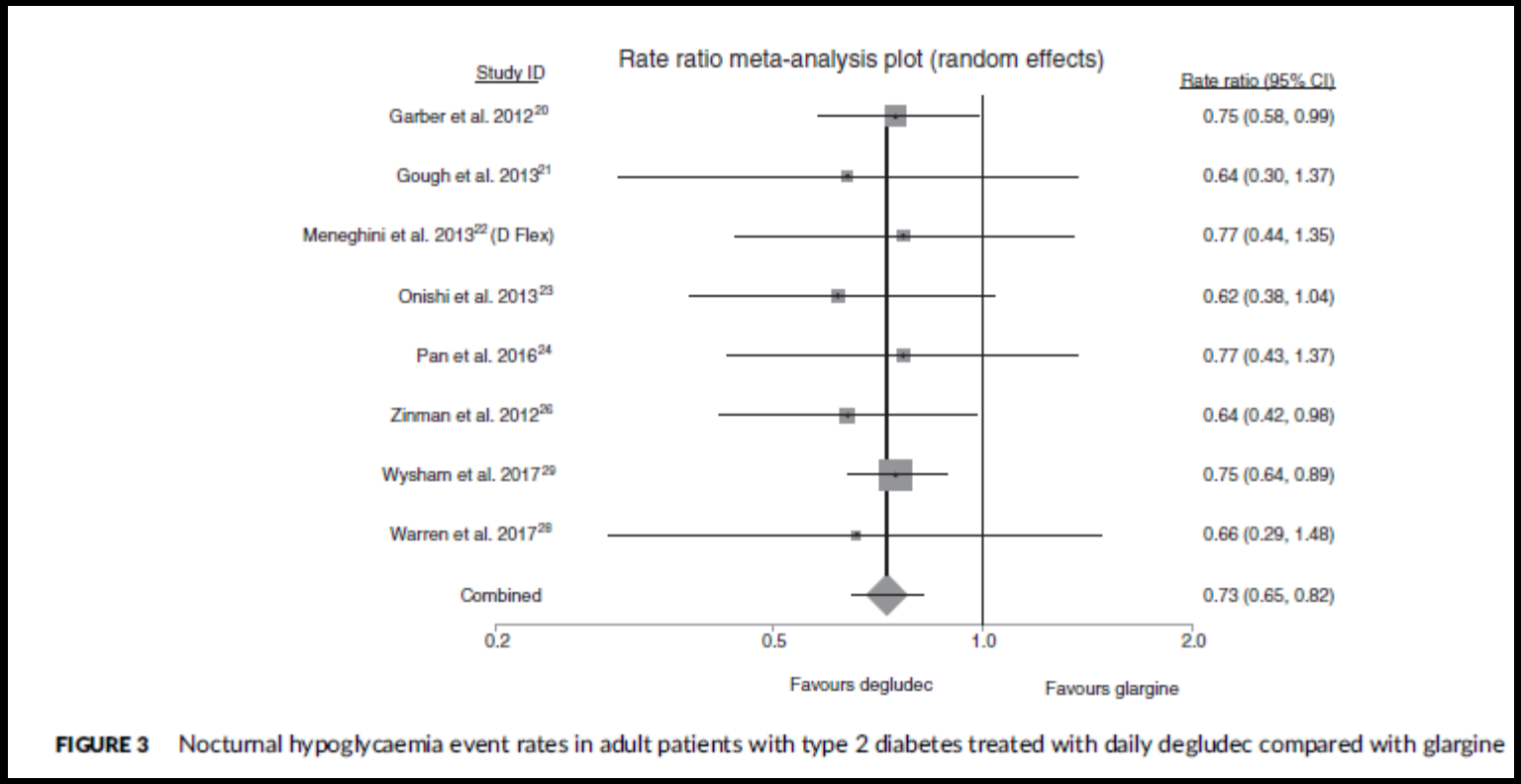


FIGURE 3 Nocturnal hypoglycaemia event rates in adult patients with type 2 diabetes treated with daily degludec compared with glargine

Holmes RS, Crabtree E, McDonagh MS. Comparative effectiveness and harms of long-acting insulins for type 1 and type 2 diabetes: A systematic review and meta-analysis. Diabetes Obes Metab. December 2018. doi:10.1111/dom.13614

Insulin Degludec U100 & U200

- FlexTouch device does not dial out, may be easier for arthritic hands
- >24 hour duration
- U100 pen
  - Max dose 80 units
  - Shows 2 unit increments
- U200 pen
  - Shows 4 unit increments
  - Max dose 160 units

Aspart U100


NovoLog®
FlexPen® Prefilled Syringe
Insulin aspart injection (rDNA origin)
Rx Only

Lispro U100 & U200

- Both only go to 60 units per dose

Lispro Biosimilars NOT Interchangeable

Lyumejev – aspart aabc, U100 and U200

Ultra-Rapid Insulins

Any clinically important advantages? – Likely not

Highly Concentrated Insulin (U500)

- Indicated if total daily dose of insulin is over 200 units per day
- This is a stand alone insulin – it provides both bolus AND basal insulin
- It is dosed twice or three times daily
- Pen dials to increments of 5 units
- MUST BE SURE that patient is actually taking insulin

Combo Pen Examples

IHS Food for Thought….

- OK to have more than one “version” on local formulary
- Make P&T Committee allowances for pharmacists to interchange biosimilars (with or with-interchangeable status) based on formulary & Point of Sale reimbursements
- When interchanging insulins – risk of patient taking BOTH. Therefore, patient education is of utmost importance. Pharmacists type in sig “replaces Detemir”
- MUST keep up to date on new forms available and occasionally check pricing as these are EVER changing.