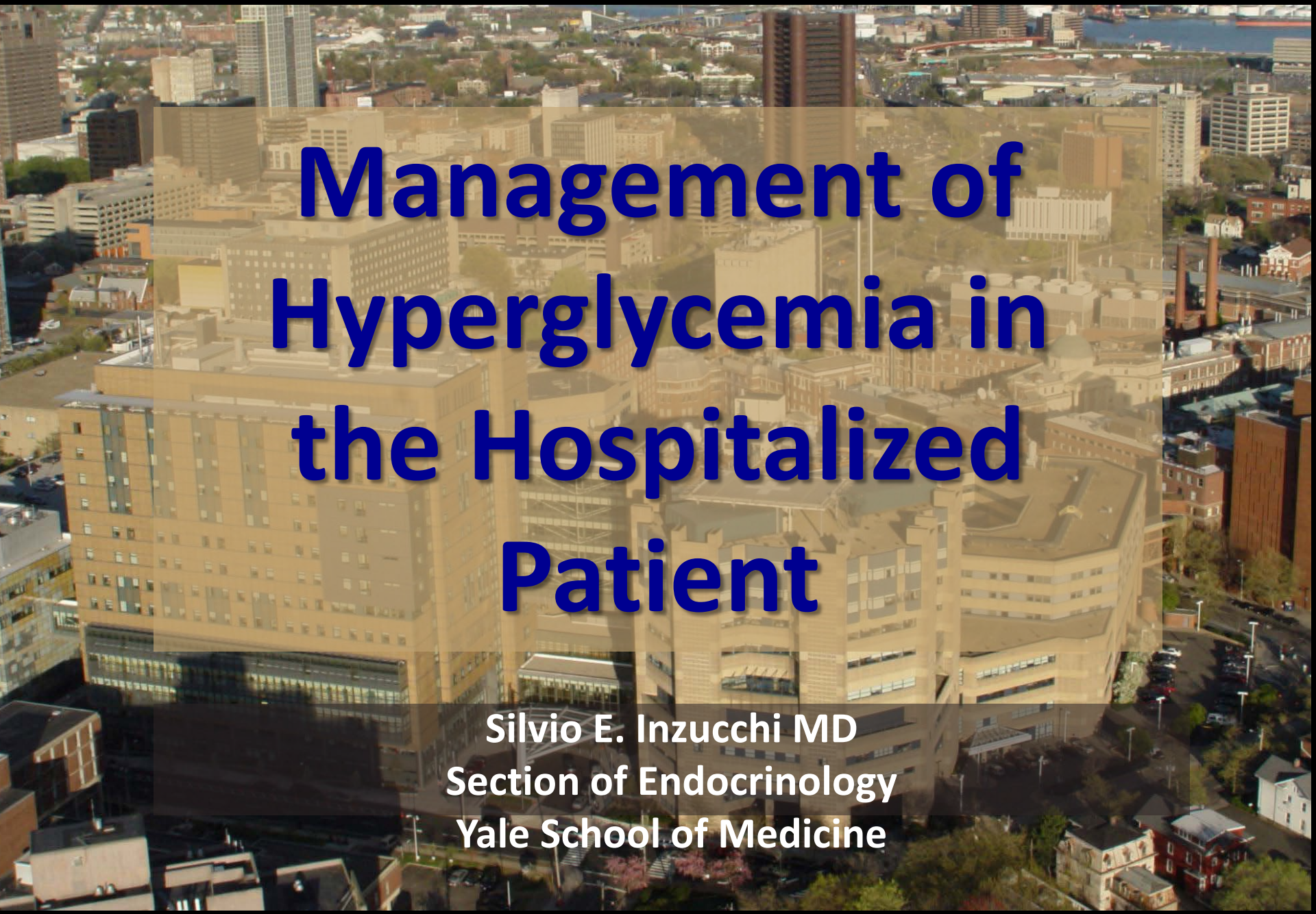
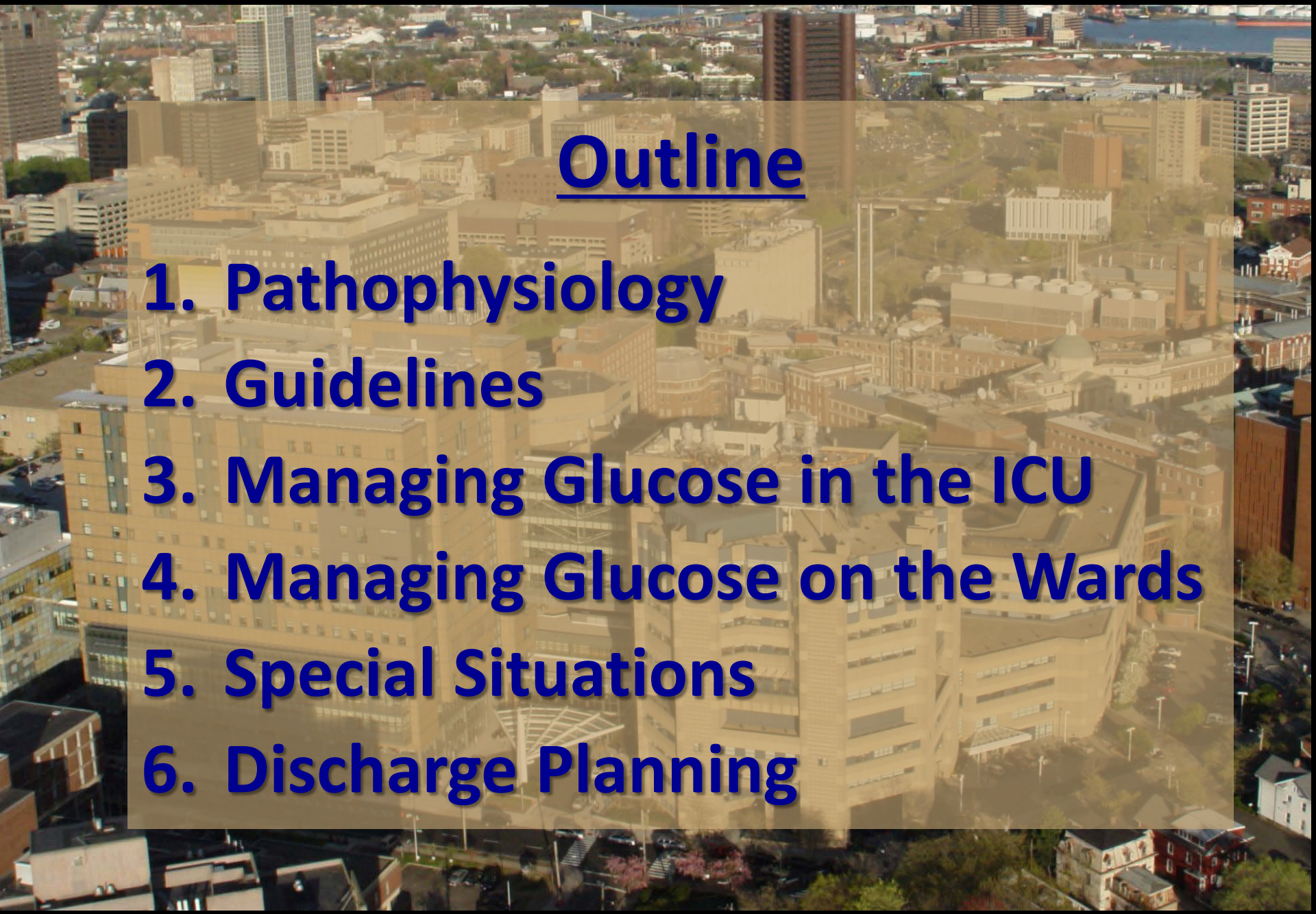


Management of Hyperglycemia in the Hospitalized Patient

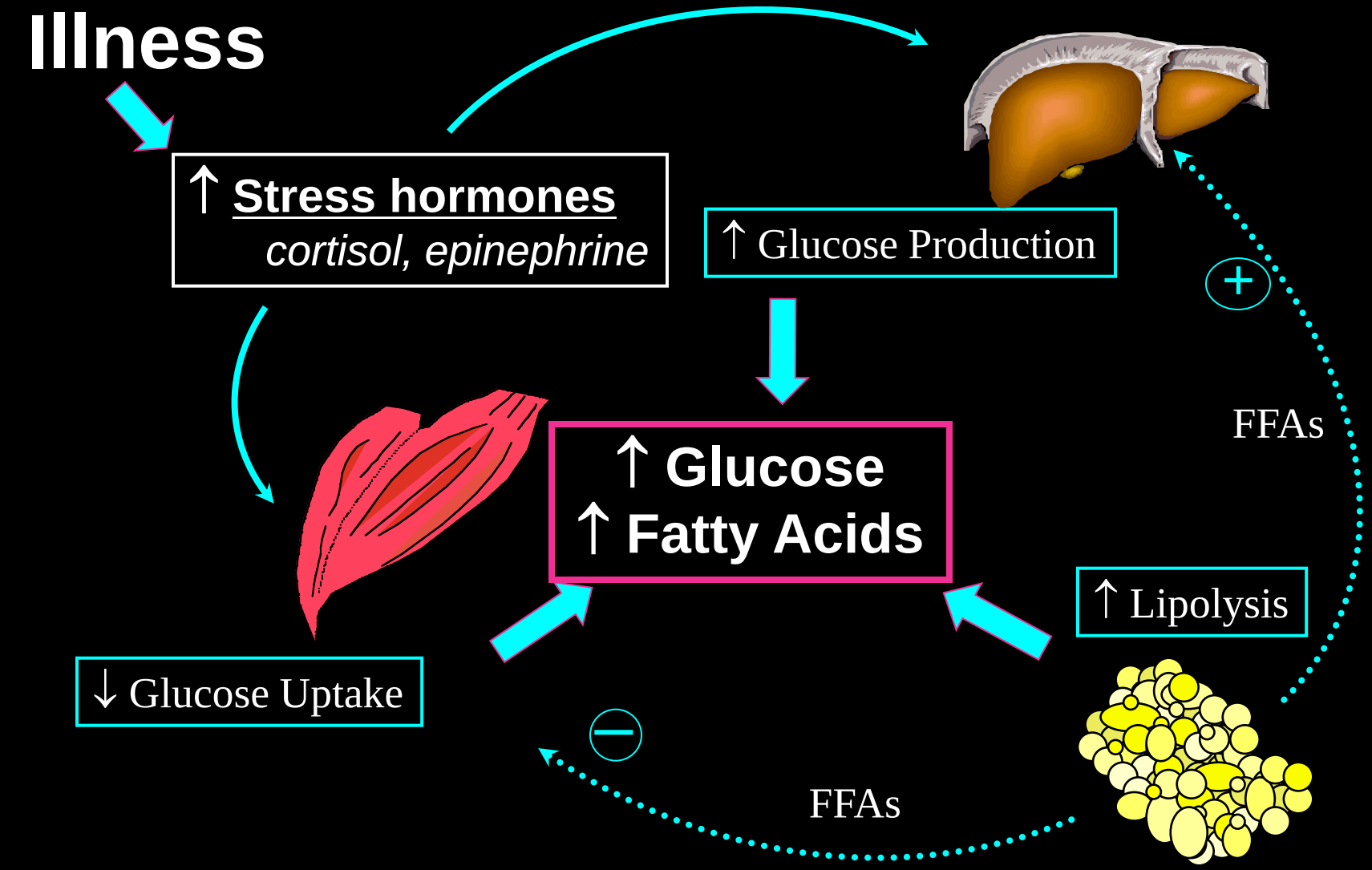
Silvio E. Inzucchi MD
Section of Endocrinology
Yale School of Medicine



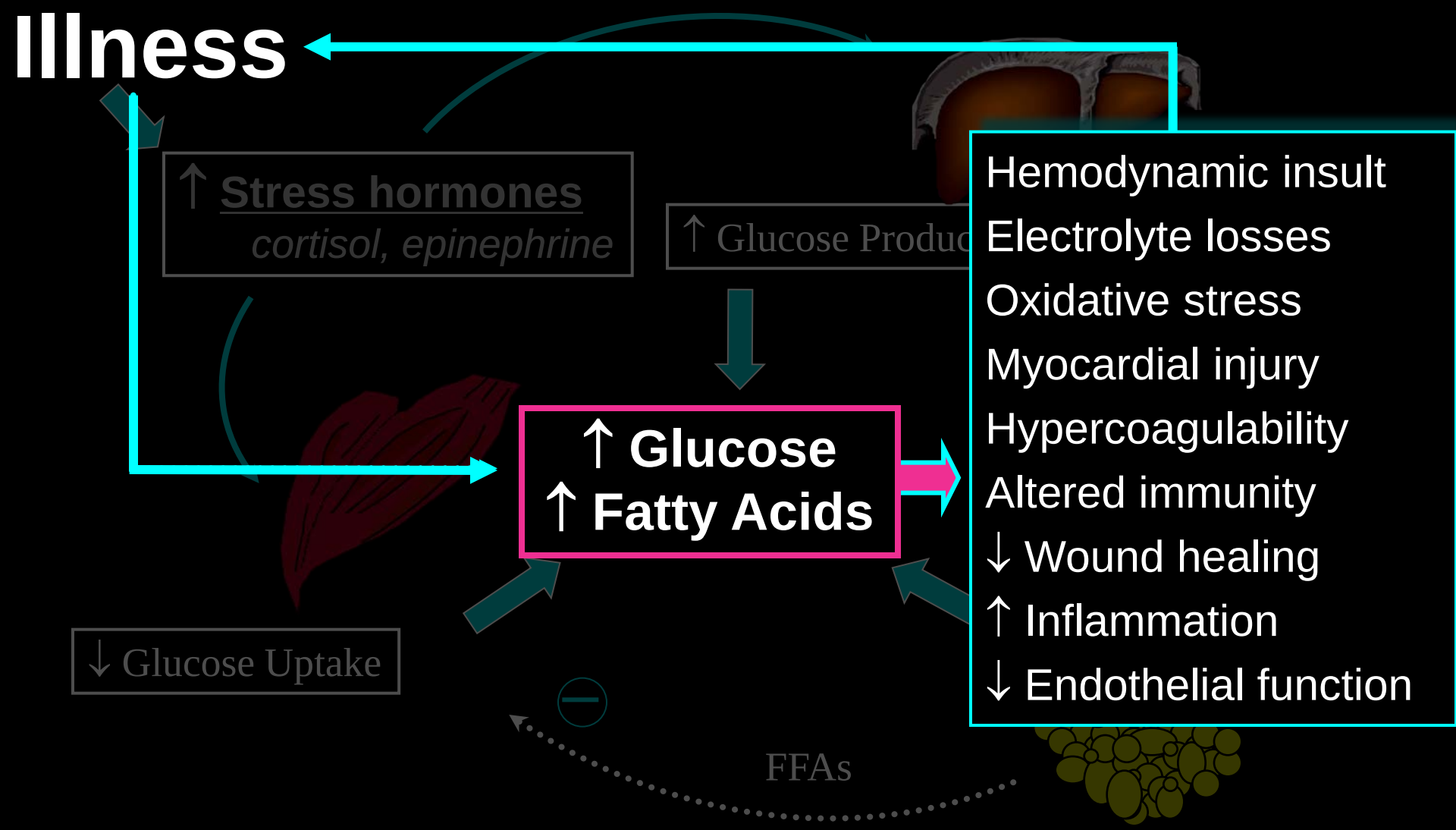
Outline

1. Pathophysiology
2. Guidelines
3. Managing Glucose in the ICU
4. Managing Glucose on the Wards
5. Special Situations
6. Discharge Planning

Illness leads to Stress Hyperglycemia



“Stress Hyperglycemia” Exacerbates Illness



New AACE-ADA Consensus Statement on Inpatient Glycemic Control

ICU Setting

- Insulin infusion preferred
- Starting threshold not higher than 180 mg/dl
- Maintain BG **140-1** (greater benefit likely *end of this range*)
- Lower targets (not evidence-based) may be appropriate in selected patients if already being successfully achieved
- <110 NOT recommended (not safe)

✓HbA1c

Non–ICU Setting

- Most patients:
  - **pre-meal BG <140 mg/dL**
  - **random BG <180 mg/dL**
- ...gent targets may be ... in stable patients
- ...gent targets may be appropriate in patients with severe comorbidities
- Scheduled SQ insulin with basal-nutritional-correction preferred; avoid prolonged therapy RISS alone

Moghissi E et al. *Diabetes Care 2009, Endocrine Practice 2009*

Rationale for Good Glycemic Control in the Hospital

1. Reduced mortality, complications, lower costs, & length of stay.
2. Evidence in ICU > evidence on general wards
3. Improved patient satisfaction
4. Emerging focus of QI organizations
5. Opportunity for patient (& family) education
6. Staff training on ‘best practice’
7. Model good behaviors for trainees


The ICU

Yale-New Haven Health System
Critical Care Insulin Infusion Protocol (IIP) for Adults

The following IIP is intended for use in hyperglycemic adult patients in the ICU or being transferred to the ICU from the PACU or ED. ***It should NOT be used in diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS), as these patients may require higher initial insulin doses, IV dextrose at some point, and important adjunctive therapies for their fluid/acid-base/electrolyte/divalent status.*** *In any patient with BG >500 mg/dL, the initial orders should also be carefully reviewed with the MD, since a higher initial insulin dose and additional monitoring/therapy may be required. If the patient's response to the insulin infusion is at any time unusual or unexpected, or if any situation arises that is not adequately addressed by this protocol, the MD must be contacted for assessment and further orders.*

Getting Started

1.) PATIENT SELECTION: Begin IIP in any critically ill patient with more than 2 BGs ≥180 mg/dl who is not expected to rapidly normalize their glycemic status. Patients who are eating (see #9 below); transferring out of ICU imminently (< 24 hrs); or pre-terminal or being considered for CMO status not appropriate candidates for this IIP. **In the CTICU only, IIP initiation threshold is a single BG ≥160 mg/dl.**

2.) **TARGET** BLOOD GLUCOSE (BG) RANGE: **120-160 mg/dL** 3.) ORDERS: MD order required for use in the ICU.

4.) INSULIN INFUSION SOLUTION: Obtain from pharmacy (1 unit Regular Human Insulin / 1 cc 0.9 % NaCl).

5.) PRIMING: Before connecting, flush 20 cc infusion through all tubing. 6.) ADMINISTRATION: Via infusion pump in 0.5 units/hr increments.

7.) BOLUS & INITIAL INFUSION RATE: Divide initial BG level by 100, then round to nearest 0.5 units for bolus AND initial infusion rate.

Examples: 1.) Initial BG = 325 mg/dL: 325 ÷ 100 = 3.25, round ↑ to 3.5: IV bolus 3.5 units + start infusion @ 3.5 units/hr.

2.) Initial BG = 274 mg/dL: 274 ÷ 100 = 2.74, round ↓ to 2.5: IV bolus 2.5 units + start infusion @ 2.5 units/hr.

8.) **CAUTION:** If enteral/parenteral (TPN, PPN, Tube feeds) nutrition abruptly stopped, reduce infusion rate by 50%.

9.) Patients requiring IV insulin are usually not eating. If eating, consider giving SQ Aspart PC to 'cover' the meal (1 unit/15 grams carbohydrates consumed (usual dose 3-6 units.) Dose may be adjusted proportionate to the percentage of the tray consumed (e.g., ½ dose if ½ tray eaten).

10.) Patients with T1DM, insulin-requiring T2DM, and those requiring >1 unit/hr should be transitioned to scheduled SQ insulin (i.e. NOT just regular insulin sliding scale) prior to discharge from ICU. Please contact Pharmacy or refer to the Pharmacy Intranet for the Transition Guidelines.

BG Monitoring

While on infusion, use glucose meter to check BG **hourly**. Once stable (3 consecutive values in target range), may reduce checks to **q 2 hr**. If stable for 12-24 hrs, may space checks to **q 4 hr**. *Resume hourly checks until stable again if:* any BG out of range; any change in insulin infusion rate; any significant change in clinical condition; initiation/discontinuation of steroids, pressors, TPN/PPN/tube feeds, dialysis, CVVH, or CAVH. In patients who are vasoconstricted/hypotensive, capillary BG (i.e., fingersticks) may be inaccurate; venous or arterial blood is preferred in this setting.

Adjusting Infusion Rate

If BG < 50 mg/dL:

HOLD INSULIN INFUSION & administer 1 amp (25 g) D50 IV; recheck BG q 15 minutes until ≥90 mg/dl.

➡ Then, recheck BG q 1 hr; when ≥140 mg/dL, wait 30 min, then restart infusion at 50% of most recent rate (rounded down to nearest 0.5 unit/hr.)

If BG 50-74 mg/dL:

HOLD INSULIN INFUSION & administer 1/2 Amp (12.5 g) D50 IV; recheck BG q 15 minutes until ≥90 mg/dl.

➡ Then, recheck BG q 1 hr; when ≥140 mg/dL, wait 30 min, then restart infusion at 50% of most recent rate (rounded down to nearest 0.5 unit/hr.)

If BG 75-99 mg/dL:

HOLD INSULIN INFUSION. Recheck BG q 15 minutes until BG reaches or remains ≥90 mg/dl.

➡ Then, recheck BG q 1 hr; when ≥140 mg/dL, wait 30 min, then restart infusion at 75% of most recent rate (rounded down to nearest 0.5 unit/hr.)

If BG ≥ 100 mg/dL:

Target BG: 120-160

Begin IV insulin:
BG ÷100 = ____ U/hr

STEP 1: Determine the CURRENT BG LEVEL - identifies a COLUMN in the table:

BG 100-119 mg/dL	BG 120-159 mg/dL	BG 160-199 mg/dL	BG ≥ 200 mg/dL

STEP 2: Determine the RATE OF CHANGE from the prior BG level - identifies a CELL in the table - Then move right for **INSTRUCTIONS:**

[Note: If the last BG was measured 2 or more hrs before the current BG, calculate the hourly rate of change. Example: If the BG at 2PM was 150 mg/dL and the BG at 4PM is 120 mg/dL, the total change over 2 hours is -30 mg/dL; however, the hourly change is –30 mg/dL ÷ 2 hours = -15 mg/dL/hr.]

BG 100-119 mg/dL	BG 120-159 mg/dL	BG 160-199 mg/dL	BG ≥ 200 mg/dL	INSTRUCTIONS*
		BG ↑ by > 60 mg/dL/hr	BG ↑	↑ INFUSION by "2Δ"
	BG ↑ by > 40 mg/dL/hr	BG ↑ by 1-60 mg/dL/hr *OR* BG UNCHANGED	BG UNCHANGED *OR* BG ↓ by 1-20 mg/dL/hr	↑ INFUSION by "Δ"
BG ↑	BG ↑ by 1-40 mg/dL/hr, BG UNCHANGED, *OR* BG ↓ by 1-20 mg/dL/hr	BG ↓ by 1-40 mg/dL/hr	BG ↓ by 21-60 mg/dL/hr	NO INFUSION CHANGE
BG UNCHANGED *OR* BG ↓ by 1-20 mg/dL/hr	BG ↓ by 21-40 mg/dL/hr	BG ↓ by 41-60 mg/dL/hr	BG ↓ by 61-80 mg/dL/hr	↓ INFUSION by "Δ"
BG ↓ by > 20 mg/dL/hr *see below*†	BG ↓ by > 40 mg/dL/hr	BG ↓ by > 60 mg/dL/hr	BG ↓ by > 80 mg/dL/hr	HOLD x 30 min, then ↓ INFUSION by "2Δ"

†**HOLD INSULIN INFUSION; √BG in 15 min to be sure ≥90 mg/dl. Then recheck BG q 1 hr; when ≥140 mg/dl, restart infusion @75% of most recent rate, rounded down to the nearest 0.5 unit/hr.**

STEP 3: CHANGES IN INFUSION RATE* ("Δ") are determined by the current rate:

Current Rate (Units/hr)	Δ = Rate Change (Units/hr)	2Δ = 2X Rate Change (Units/hr)
< 3.0	0.5	1
3.0 – 6.0	1	2
6.5 – 9.5	1.5	3
10.0 – 14.5	2	4
15 – 19.5	3*	6*
≥ 20*	4*	8*

* Depending on the clinical circumstances, infusion rates typically range between 2-12 units/hr. Doses >20 units/hr are unusual, and, if required, the responsible MD should be notified to explore other potential contributing factors (including technical problems, such as dilution errors, etc.)

A L E R T ! ! !
Except for hypoglycemia, NEVER terminate infusion unless transition orders to SQ insulin are in place! Any patient with type 1 diabetes, on insulin before admission, or requiring >1.0 units/hr should be transitioned to basal-bolus-correction (BBC) SQ insulin. Overlap with infusion by 2-3 hrs. (See 'YNHH Transition Guideline from IV Insulin Infusion.')

Comparison of Yale IIPs, 2004-2011

Year Published	2004	2004	2005	2005	2011
Clinical Setting	**MICU**	**CT-ICU**	**MICU**	**CT-ICU**	**MICU**
BG Target (mg/dl)	**100 - 140**	**100 - 140**	**90 - 120**	**90 - 120**	**120 - 160**
N (infusions)	**69**	**137**	**63**	**54**	**115**
Infusion hours (median [IQR])	**61** (27 – 128)	**16** (12 – 27)	**63** (28 – 133)	**15** (11 - 18)	**59** (25 - 127)
Baseline BG (±SD)	**299** ± 96	**218** ± 53	**238** ± 76	**189** ± 44	**306** ± 90
Time-to-target (hrs) (median [IQR])	**9** (7 – 13)	**5** (3 - 8)	**6** (4 - 9)	**7** (5 - 9)	**7** (5 - 12)
Mean BG (±SD)	**130**	**125**	**120** ± 29	**112** ± 23	**156** ± 23
Median BG (IQR)	-	-	**118** (101-134)	**110** (100-122	**150** (127-180)
% BG's < 60	**0.3%**	**0.2%**	**0.4%**	**0.3%**	**0.1%**
% BG's < 40	**0.05%**	**0%**	**0.02%**	**0%**	**0.02%**

Remember to *Transition* to SQ Insulin!

- **Any T1DM**
- **T2DM >1 u/hr**

Plan:

- Use recent hourly rate when stable
- Convert to total daily dose (TDD)
- TDD x 0.8
- 50% basal
- 50% nutritional
- Overlap 2-3 hrs

Yale-New Haven Hospital

Transition Guideline from IV Insulin Infusion

The following patients should ALWAYS be transitioned to scheduled subcutaneous (SQ) insulin when the intravenous (IV) insulin infusion is stopped:

- Type 1 diabetes (e.g., ketosis-prone; youth diagnosis; lean; labile control)
- Type 2 diabetes on insulin prior to admission.
- Anyone requiring >1 unit/hour of insulin infusion

For all others, use Sliding Scale: Lispro pre-meal if eating; Regular Q6hrs if NPO (start with 'mid-dose' scale.)

The 'B–B–C' insulin protocol (see Epic, under Order Sets) is the preferred regimen in most patients *(see below.)* If previously treated with insulin, resumption of the outpatient regimen can also be considered, depending on patient's status and the recent quality of blood glucose control as denoted by patient report and recent HbA1c.

STEP 1 : Average amount of IV insulin/hr required over last 4 hrs = _____ units/hr
(best calculated if IV rate stable and no meals consumed.)

STEP 2 : Multiply **this number by 24 hrs** = approximate total daily insulin needs = _____ units/day

STEP 3 : Take 80%* of this number ('safety factor') = _____ units/day

STEP 4 : Divide **this amount** into 50% Basal and 50% Bolus insulin:

50% = _____ units/day as **BASAL** insulin†

NOTE !
Maximum initial basal dose coming off drip is:
0.5 units/kg/day

50% = _____ units/day as mealtime **BOLUS** insulin‡

STEP 5 : ÷ **BOLUS‡ insulin** into 3 equal parts & give TID AC = _____ units/meal
(assuming roughly equal carbohydrate content at each meal.)

NOTE !
Maximum initial mealtime bolus dose coming off drip is:
0.1 units/kg/meal

STEP 6 : Add "**CORRECTION**" insulin§ to adjust for pre-meal hyperglycemia to mealtime **BOLUS** dose
(same type of insulin as the bolus!)

ALWAYS OVERLAP INSULIN INFUSION BY AT LEAST 1 HOUR AFTER ANY SQ RAPID-ACTING INSULIN OR 2-3 HOURS AFTER ANY SQ LONG-ACTING INSULIN ! ! !

* In patients who are tenuous, hypoglycemia-prone, or who were receiving at least 75 cc/hr of D5-containing IV fluids while on the insulin infusion, consider using a lower % (e.g., 60-70%) as the 'safety factor' in STEP 3

† Glargine (Lantus) is preferred basal insulin – may be injected at any time, Q24h. May use NPH, but dose BID, ideally QAM + QHS.

‡ Lispro (Humalog) is preferred mealtime bolus. This fixed mealtime dose will prevent post-prandial glucose spikes.

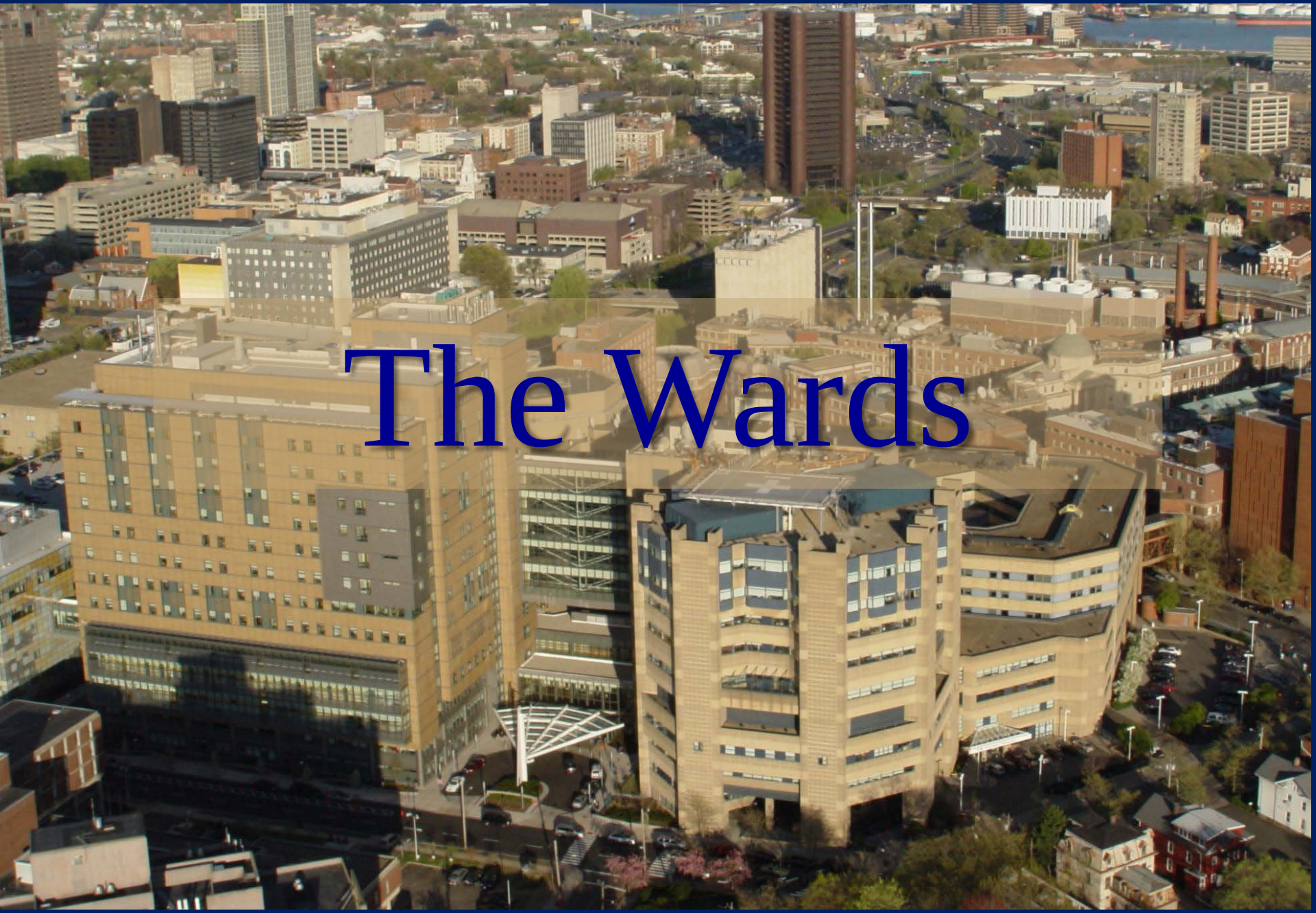
§ See Correction Insulin table for proper dosing, based on estimation of patient's insulin sensitivity.

SPECIAL CIRCUMSTANCES

1. **The Patients on Tube Feeds**: Give 50% of amount in STEP 3 as Basal and the balance as Regular Q 6 hrs (plus Regular Correction Scale.) This will allow more rapid adjustment of insulin dose if tube feeds stop.

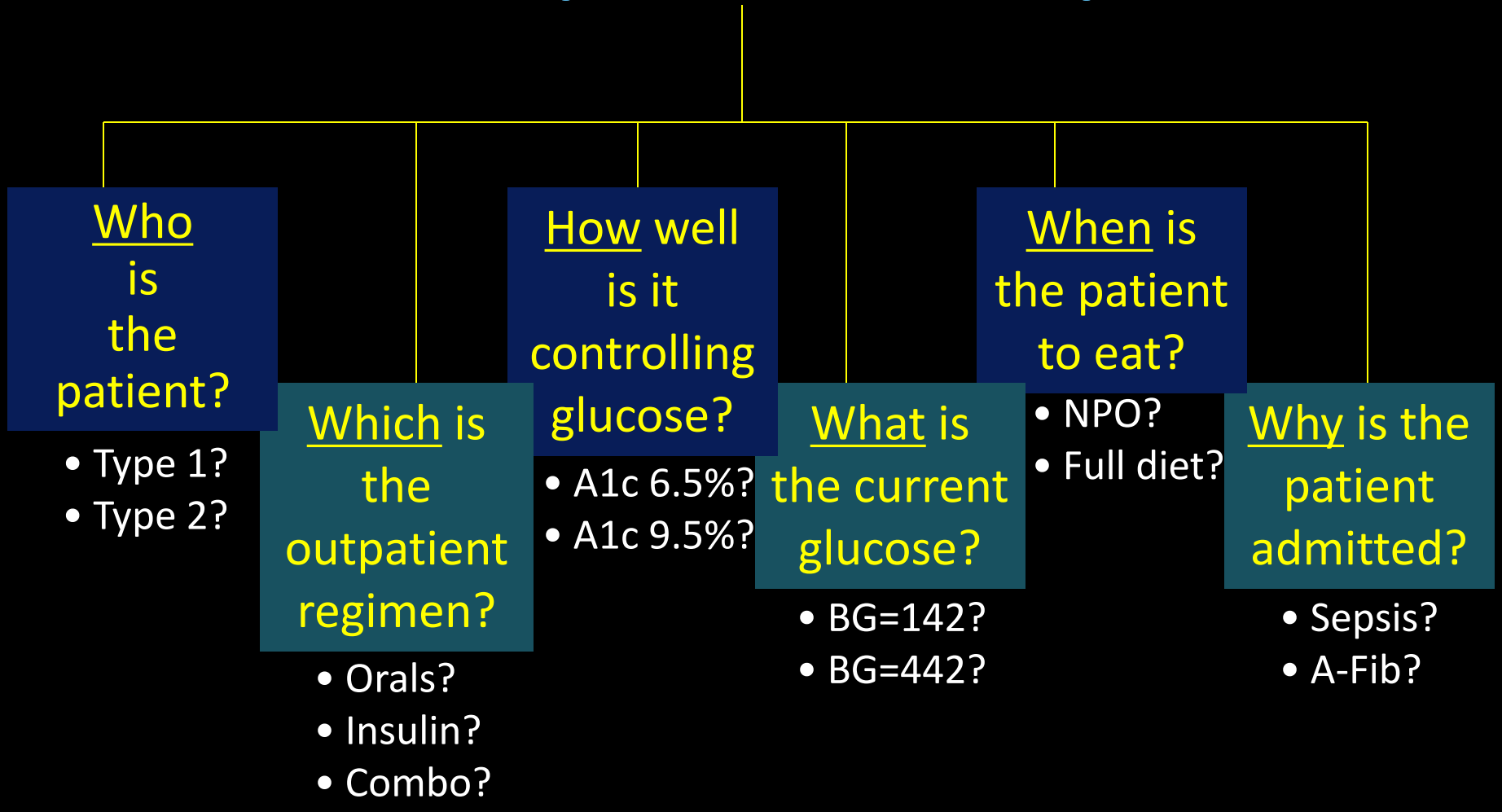
2. **The Patient on TPN/PPN**: Use protocol for Tube Feed Patients in #1 above. An alternative, in T2DM, is to provide the amount in STEP 3 within IV nutrition solution, to be distributed over 24 hrs (+ SQ Regular Insulin Sliding Scale.) In T1DM, can add 50% of STEP 3 amount within IV nutrition solution and the balance as SQ Basal insulin (+ SQ Regular Insulin Sliding Scale.) Confirm all calculations with Pharmacy.

QUESTIONS? CALL THE INPATIENT DIABETES TEAM
PAGER 412-4559 (WEEKENDS & NIGHTS: 412-7528)

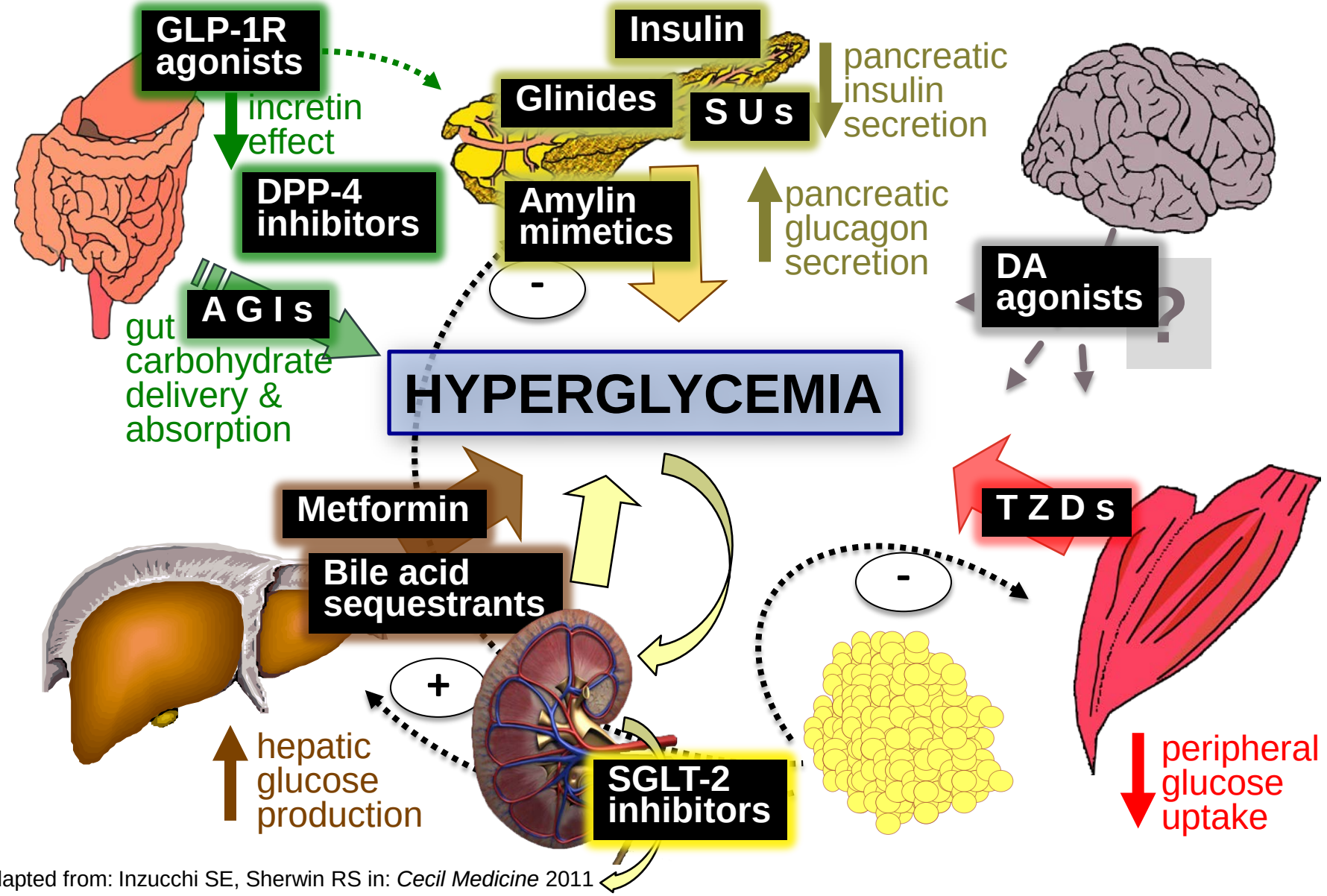

The Wards

Insulin Orders in the Hospital

What to do depends on several questions…

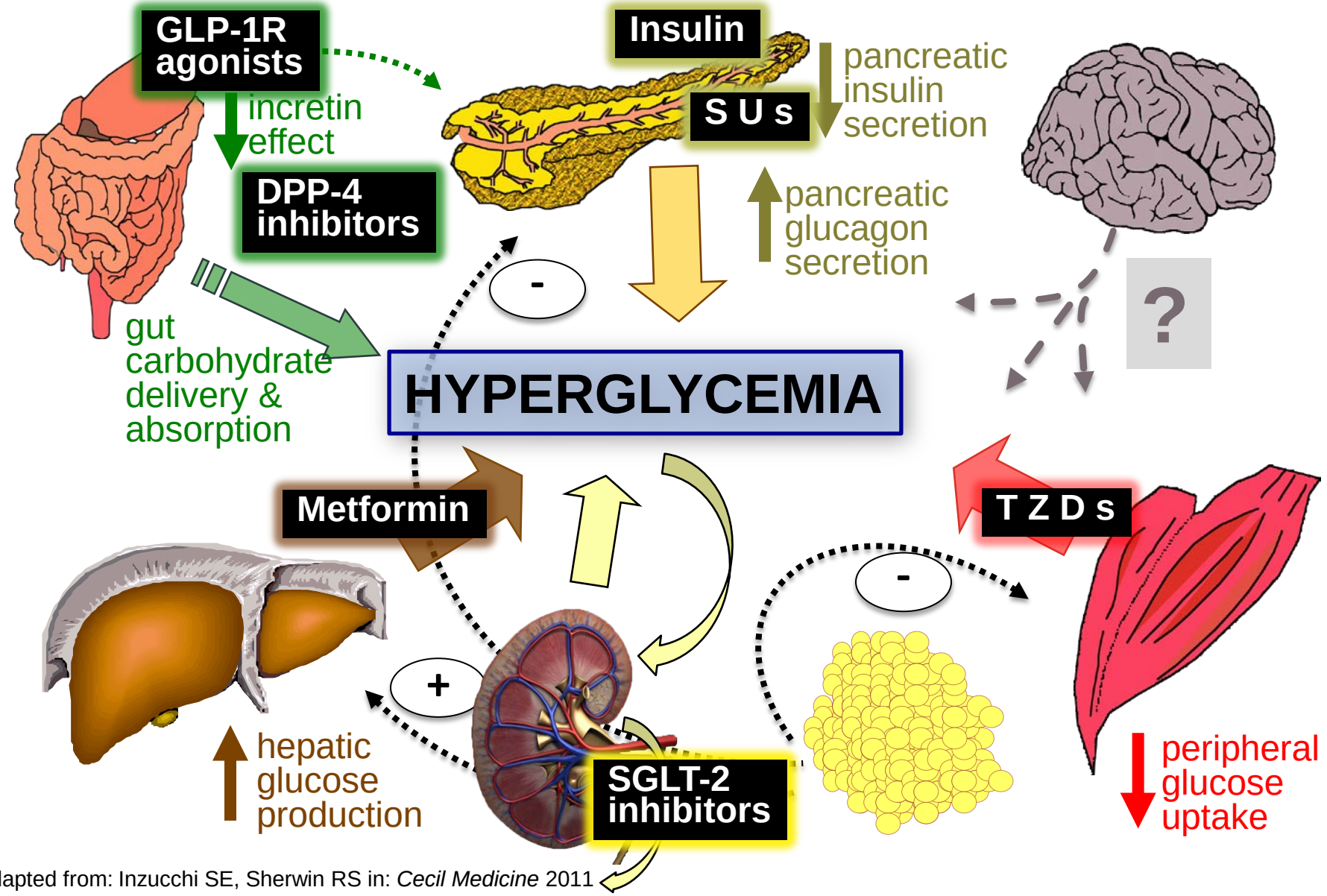


Multiple Pathophysiologically-Based Therapies for T2DM



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Major Pathophysiologically-Based Therapies for T2DM



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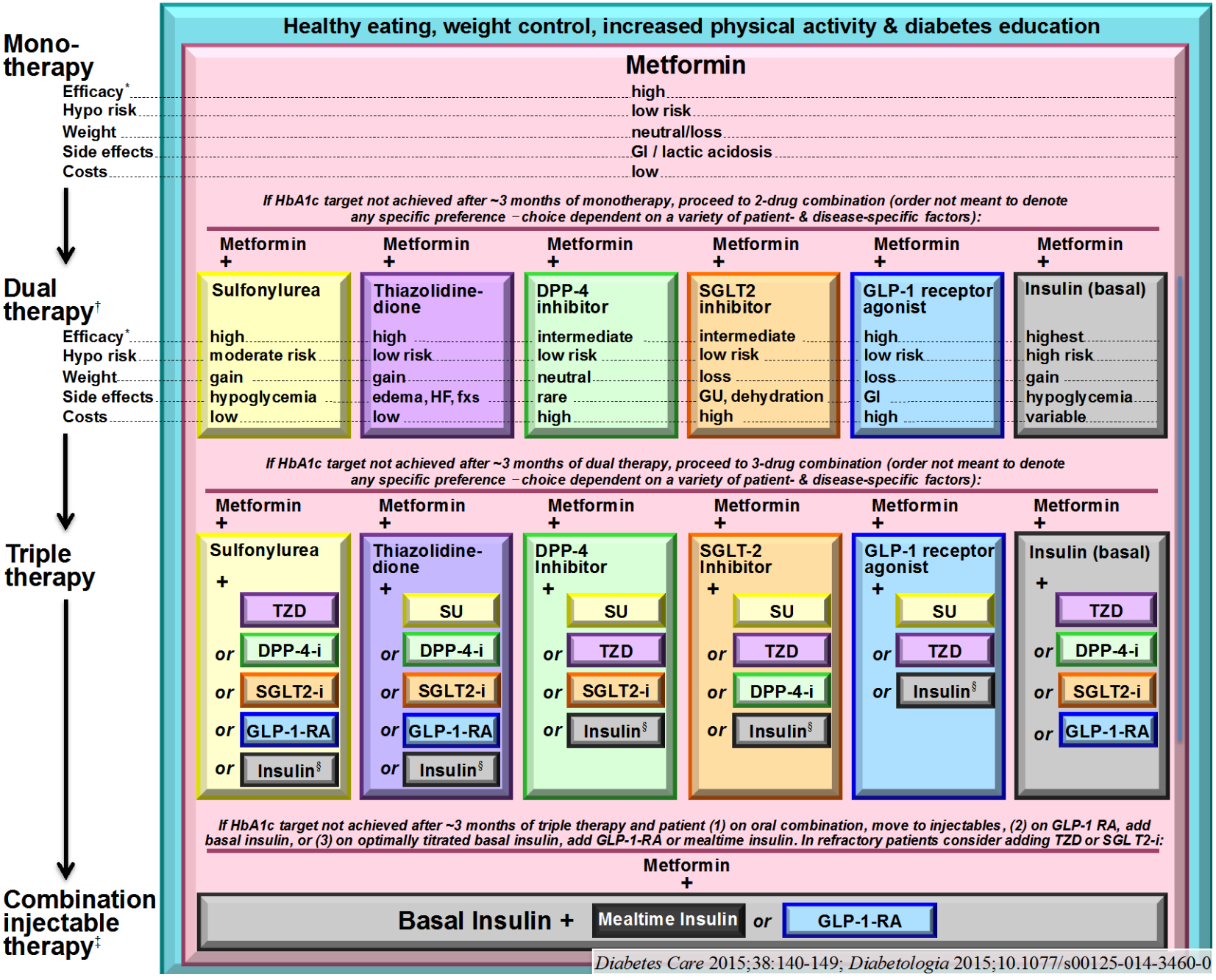
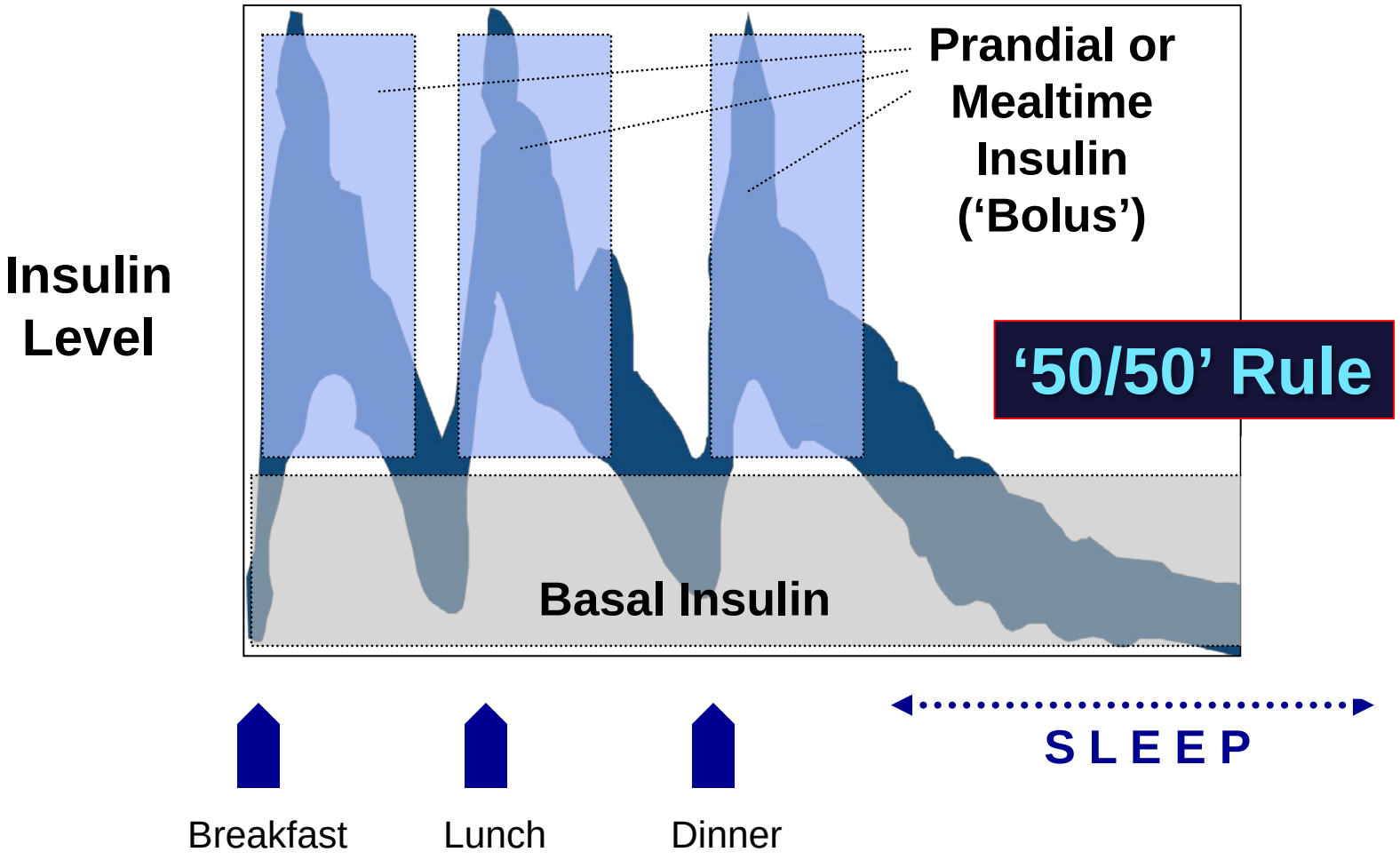
ADA-EASD Position Statement: Managing Hyperglycemia in T2DM (2015)



Diabetes Care 2015;38:140

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

Normal Secretory Pattern of Insulin



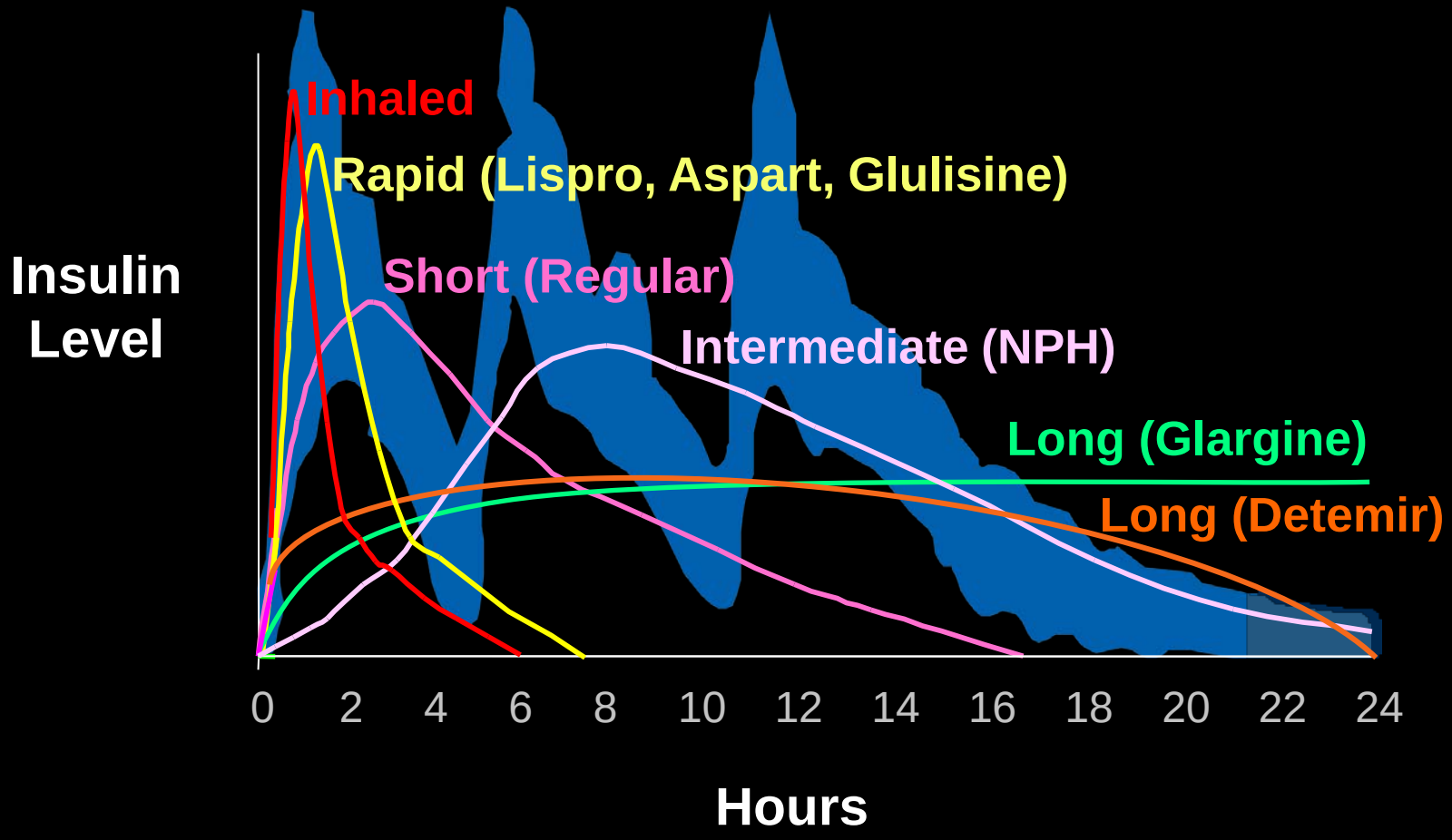
Comparison of Human Insulins & Insulin Analogues

	Insulin Type	Onset of Action	Peak Action	Duration of Action
RAPID SHORT	Lispro/Aspart*	5-15 min	1-2 hours	4-6 hours
	Human Regular	30-60 min	2-4 hours	6-10 hours
INTER	Human NPH	1-2 hours	4-8 hours	10-18 hours
BASAL	Glargine	3 hours	flat	~24 hours
	Detemir	2 hours	somewhat flat	12-24 hours

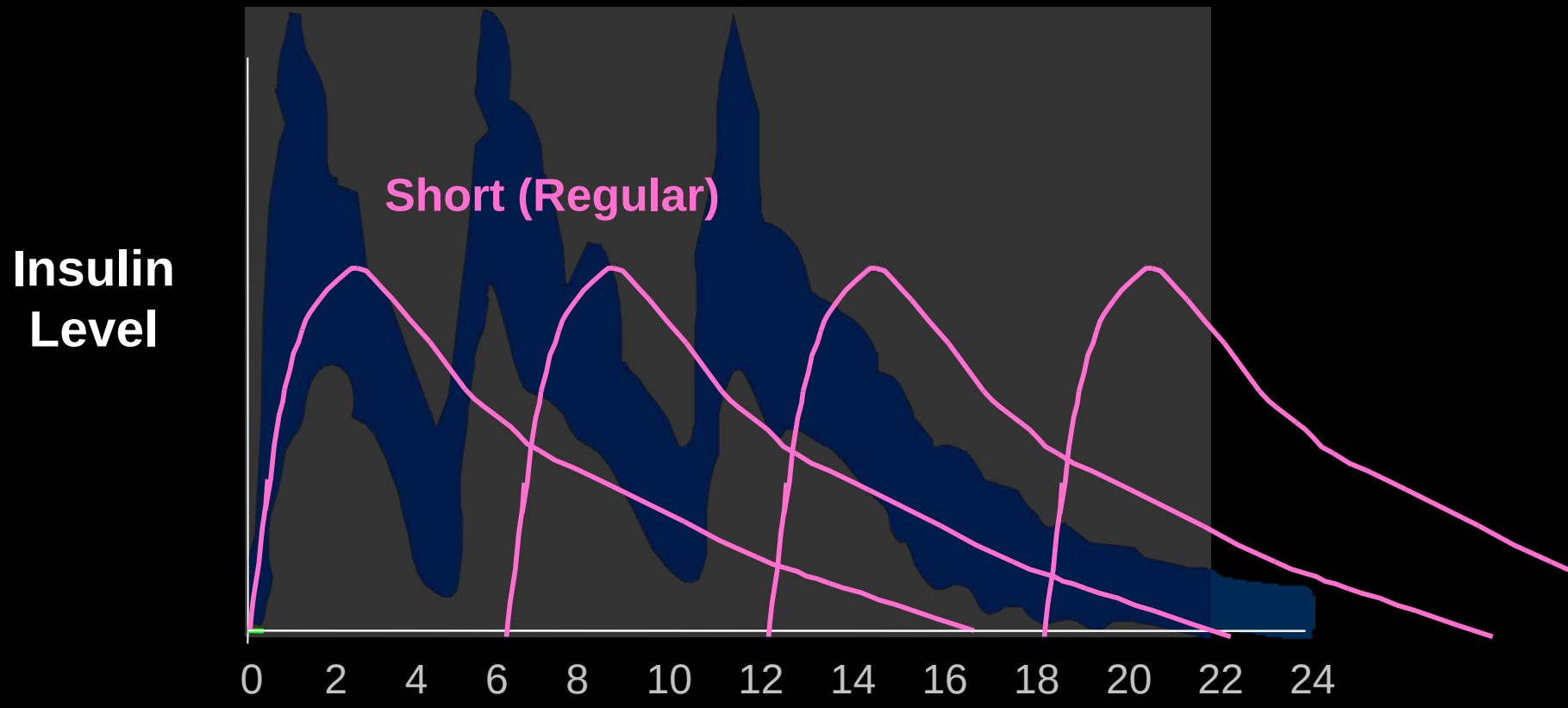
The time course of action of any insulin may vary in different individuals, or at different times or different injection locations in the same individual. Due to such variation, the time periods described above should be used as general guidelines only.

* Glulisine is a 3rd rapid analogue

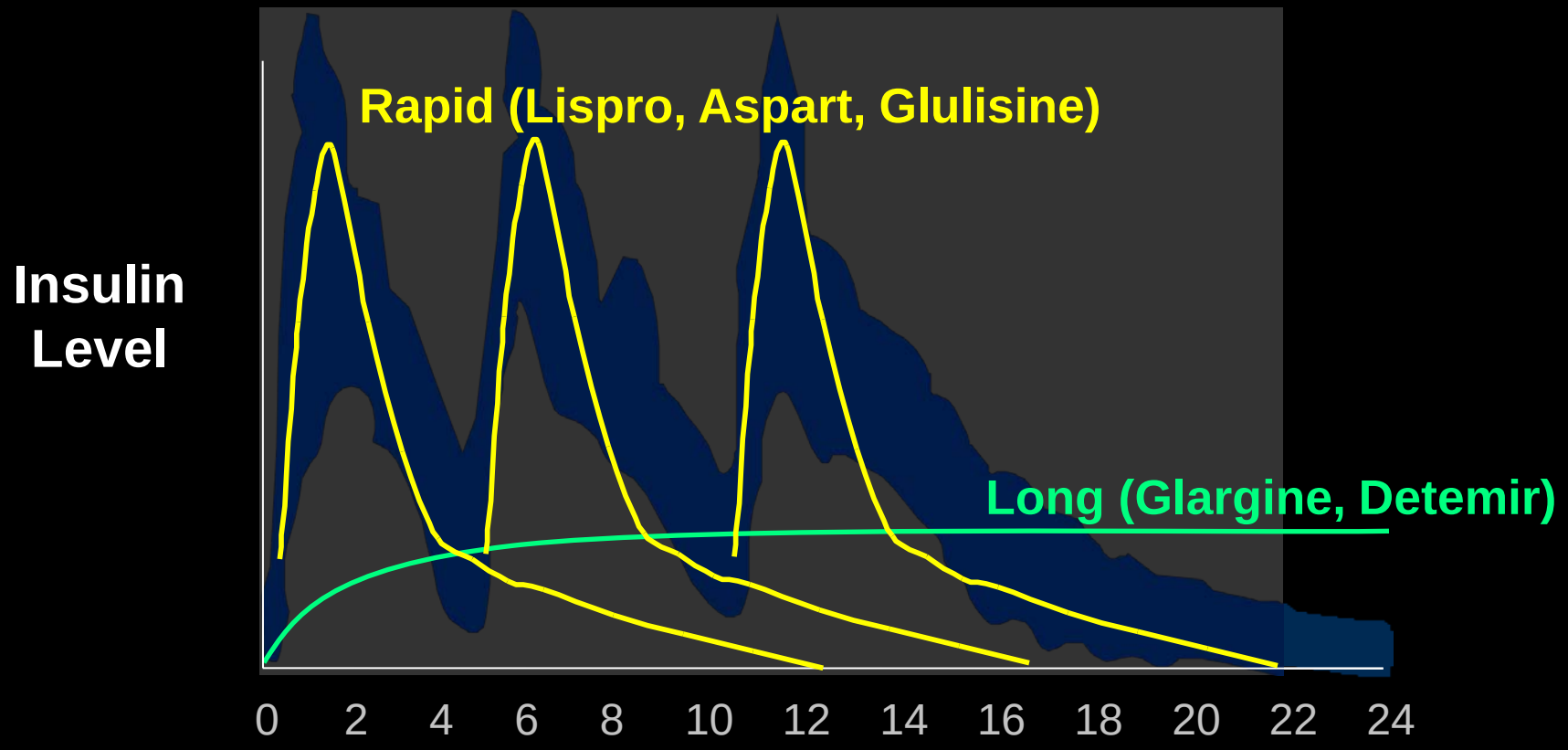
Pharmacokinetics of Insulins



Regular Insulin “Sliding Scale” (RISS)



“Basal - Bolus” Insulin Therapy



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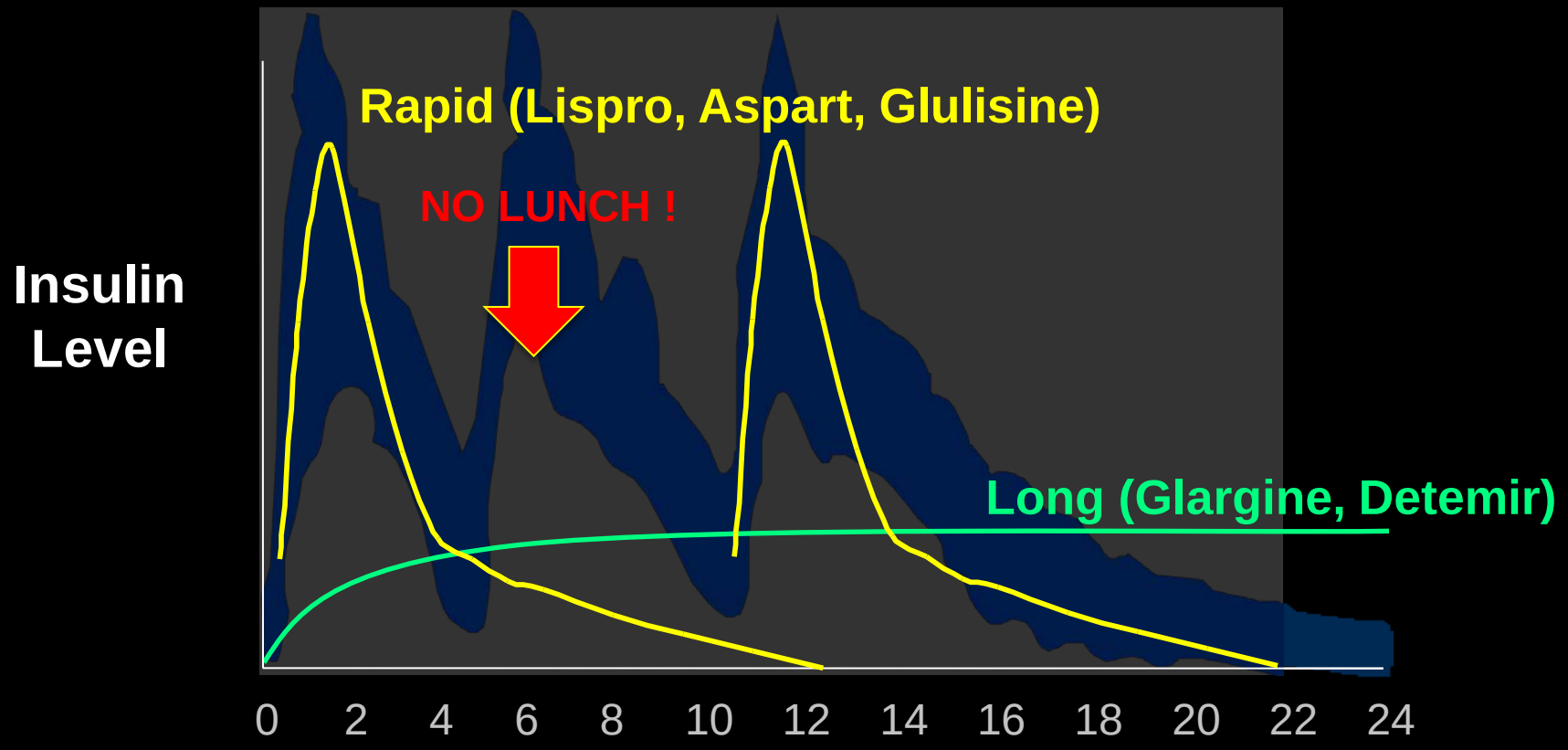
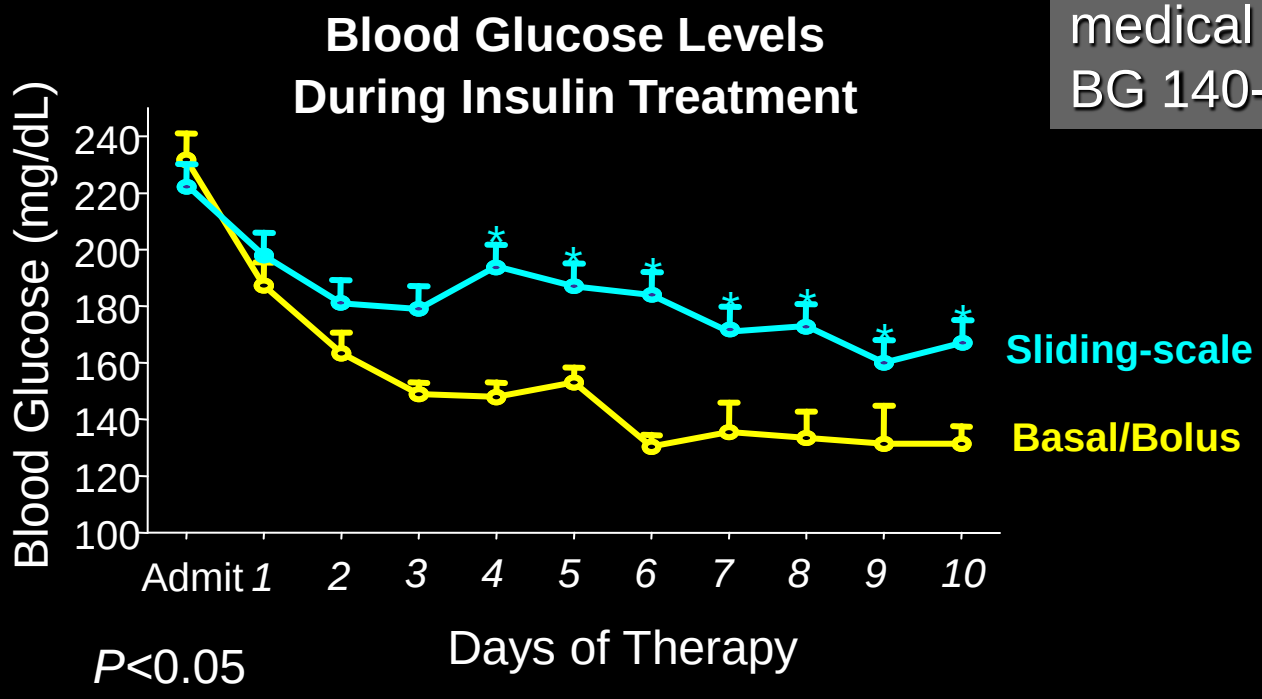


RABBIT-2 Study: Basal/Bolus vs. RISS in Non-ICU Patients

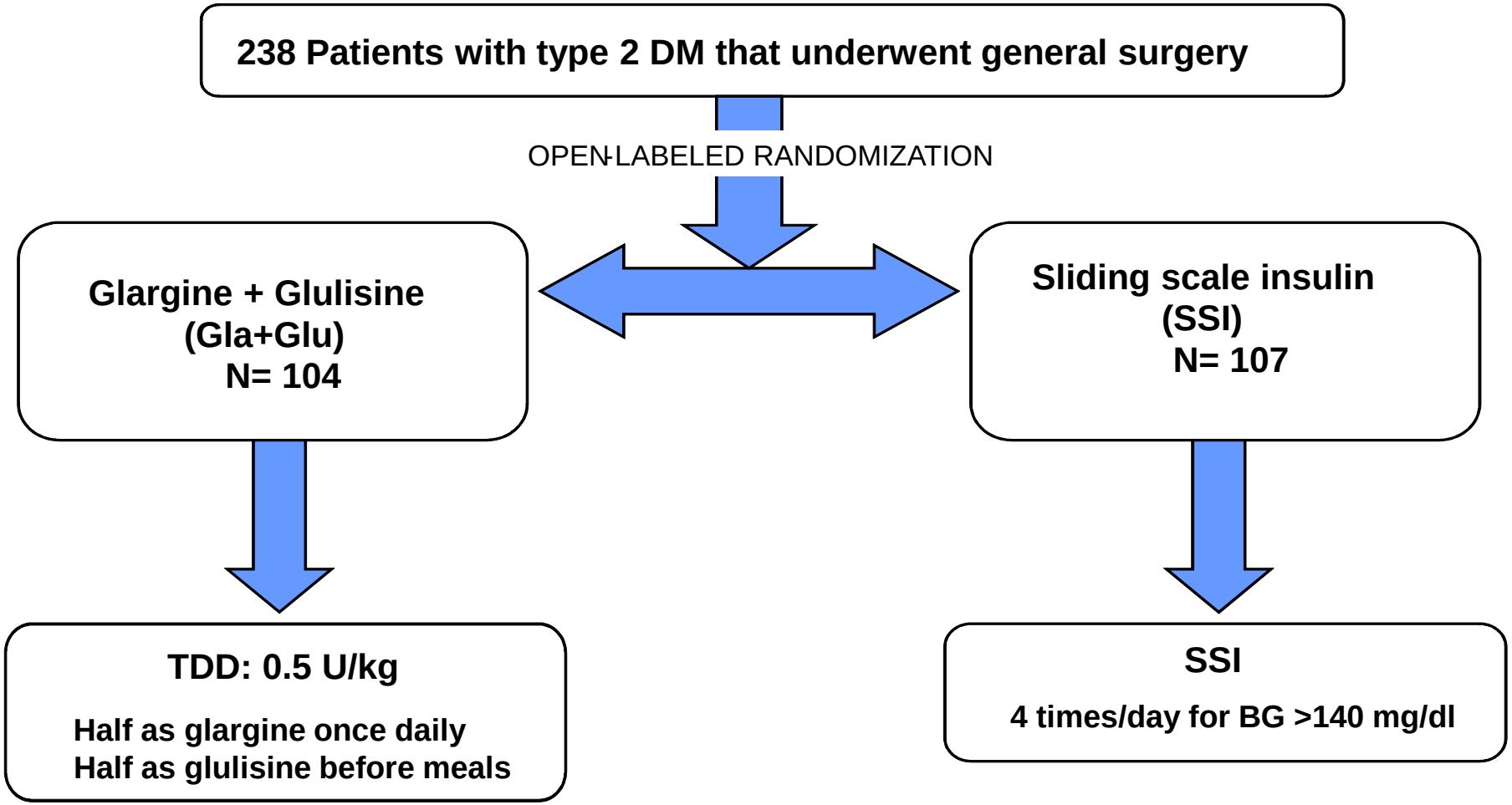
- Primary endpoint: differences in the mean daily BG
  - Mean overall BG difference between the groups during hospital stay was 27 mg/dL ($P<0.01$)

N=130 insulin-naïve medical service pts, BG 140-400 mg/dl

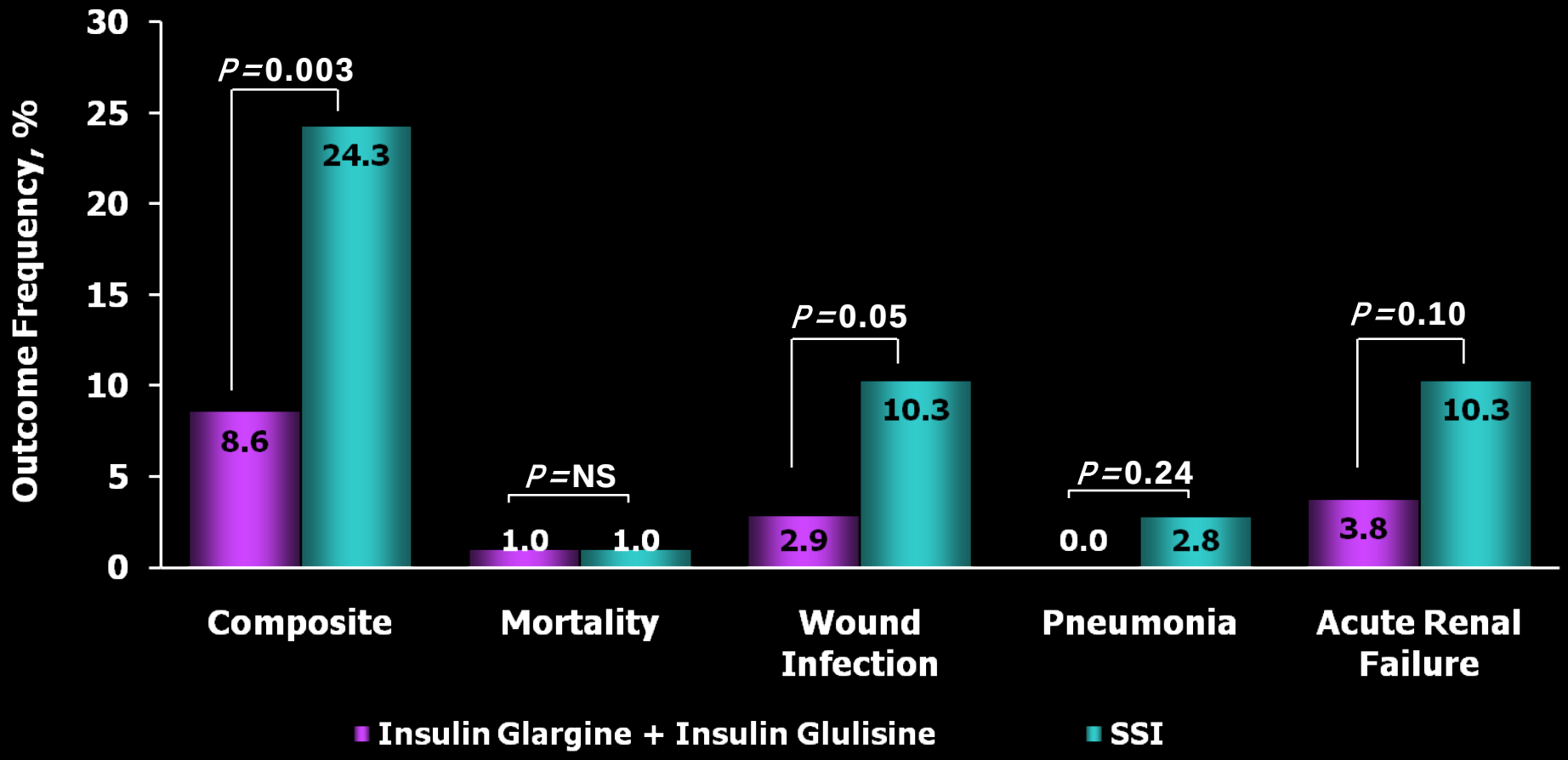


Adapted from Umpierrez GE et al. *Diabetes Care*. 2007;30:2181-2186.

RABBIT-Surgery Trial: Study Design



RABBIT Surgery Trial: Postoperative Complications



SSI = sliding scale insulin.

Hospital 'Basal-Bolus-Correction' Insulin Therapy

Basal

Typical dose: ~20-50 U/day

- ses hepatic glucose production
- BID dosing, based on weight, insulin sensitivity, prior dosing requirements
- start @ 0.2-0.3 units/kg/day (or convert from currently effective insulin dose.)

Bolus

Typical dose: ~2-10 U/meal

- al insulin" blunts postpran
- D AC dosing, based on (carb c
- weight, insulin sensitivity & prior do
- 0.05 units/kg/meal

Use same type of insulin ! (e.g., Lispro)

Correction

Typical scales (start @150 mg/dl):
1 - 2 - 3 - 4U
2 - 4 - 6 - 8U
3 - 6 - 9 - 12U

- premeal
- D) dosing, ba
- maller doses at be

'1700 Rule'

If on 68 U/day: 1700 / 68 = 25
1 U will drop BG by 25mg/dl

Admission Orders

Patients on Oral Agents

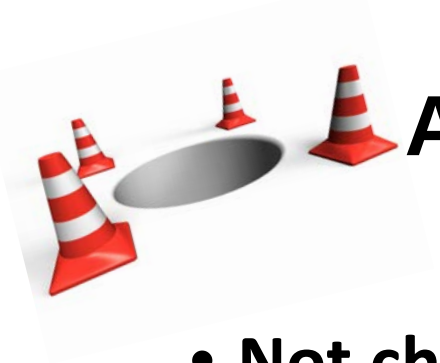
1. Generally, hold oral agents. (Usually a hospitalized patient will have developed at least a temporary contraindication.)
2. For *well controlled* patients:
   - Eating: RISS AC; + Basal soon if needed
   - NPO: RISS Q6 hrs; + Basal soon if needed
3. For *poorly controlled* patients:
   - Eating: Basal-Bolus-Correction
   - NPO: Basal-Correction

Admission Orders

Patients on Insulin

1. De
   co
2. Fo
   - I
   - I
3. Fo
   - I
   - I
   - (T1DM: ? IV insulin if very ill, pre-op, etc.)

- ✓ Adjust insulin doses every 1-2 days to achieve BG target.
- ✓ Note trajectory of BG pattern.
- ✓ Predict insulin needs if there is a nutritional change or if steroids started/stopped.
- ✓ Consult Endocrinology or Diabetes Service if control is elusive.
- ✓ Anticipate the ultimate discharge regimen.



Avoidable Pitfalls in Inpatient Diabetes Management

- Not checking an HbA1c
- Prolonged use of RISS
- Holding basal insulin in T1DM
- Not rapidly adjusting insulin for situations that are likely to lead to glucose excursions (NPO, steroids)
- Trying to control severe hyperglycemia with SQ insulin (switch to IV insulin infusion if BG >300-350 & SQ insulin unsuccessful after 4-6 hrs.)
- Not anticipating the discharge plan
- Discharging a patient on an overly complex regimen


Special Situations

Special Situations

Hypoglycemia

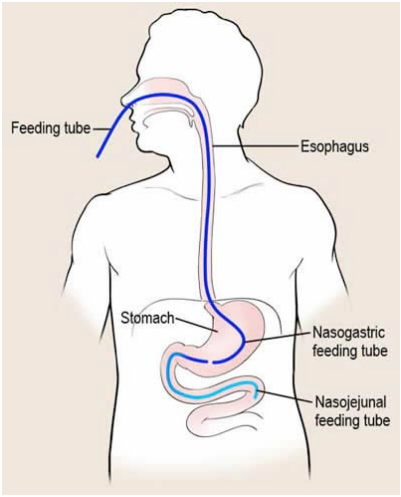
<70 mg/dl (<40 mg/dl = 'severe')

- Can take PO → 15 g carb (4 oz. orange juice)
- NPO → 12.5 g carb IV (1/2 amp D50)
- MS changes → 15 g carb IV (1 amp D50)

Rule of thumb: 15 g carb will ↑ BG 25-50 mg/dl

- ✔ Document in chart
- ✔ Assess reason for hypoglycemia (food, insulin dose, sepsis, renal failure, hepatic failure)
- ✔ Re-evaluated regimen; usually decrease insulin

Special Situations



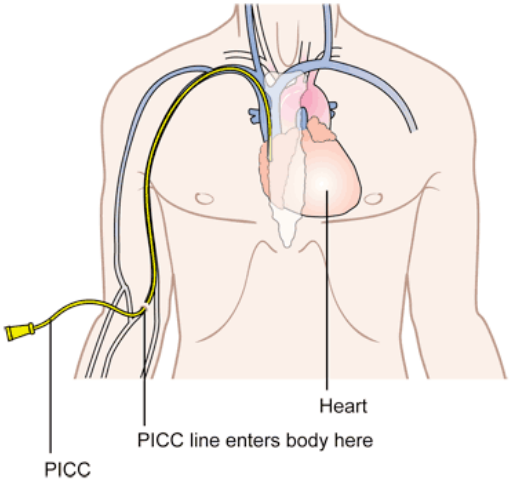
Tube Feeds

- Continuous.....50% Basal
  + 50% Reg Q6h + Correction
- Cycled (8-12h)....NPH @ start
- Boluses.....Regular @ start

⊙ If TFs stopped, if BG <100, replace carbohydrate amount with IV dextrose (D5, D10)

⊙ Example: If 50 cc/hr of a feed that contains 8 g/100cc, give back D5 @ 80 cc/hr (4 g/hr)

Special Situations



TPN

Treatment Options:

- **50% Basal**
  + 50% Reg Q6h (+ Correction)
- **IV insulin, 100% in TPN bag (T2DM, stress hyper)**
- **50% Basal + 50% in TPN bag (T1DM)**

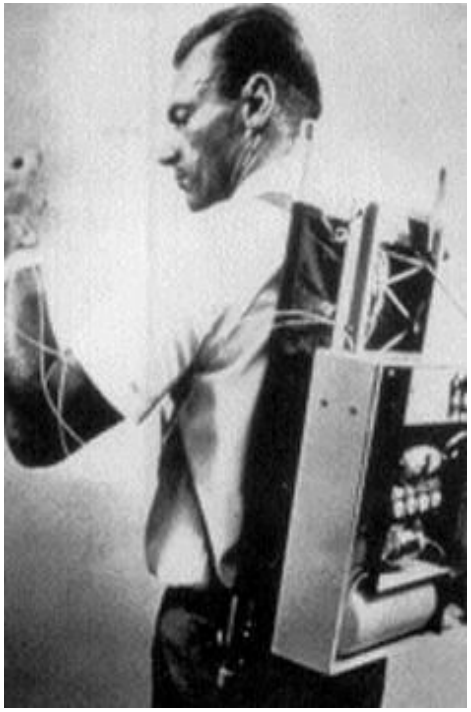
⊙ **If TPN stopped, if BG <100, replace carbohydrate amount with IV dextrose (D5, D10) through peripheral line.**

⊙ **Example: If TPN (D20) @50 cc/hr, need D10 at @100 cc/hr.**

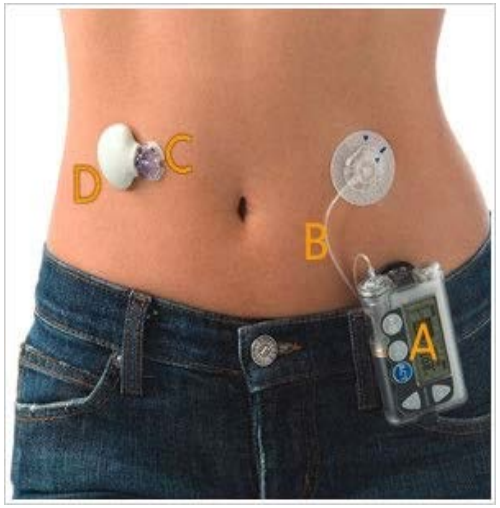
Special Situations

Insulin Pumps

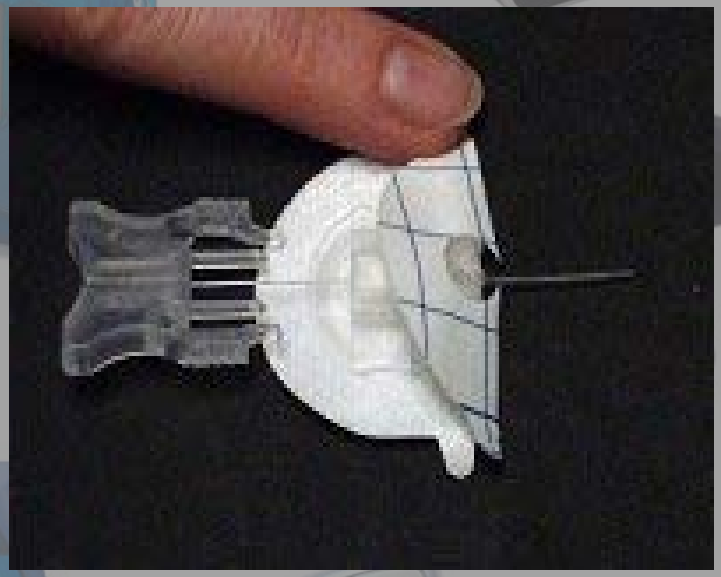
- **Electronic devices that deliver insulin through a SQ catheter – basal rate (variable) + boluses for meals.**

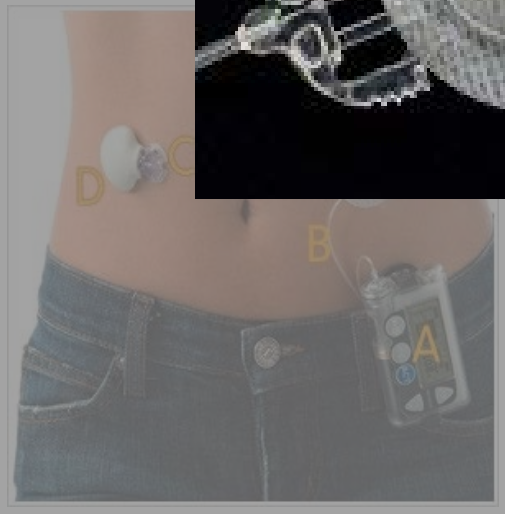


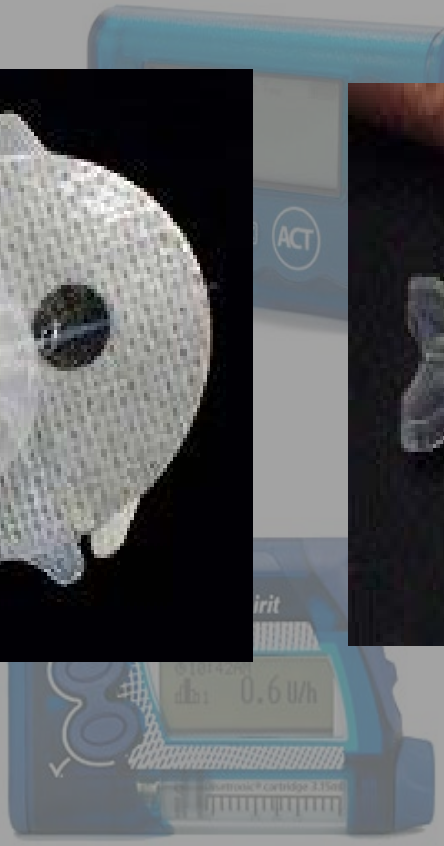
Insulin Pumps



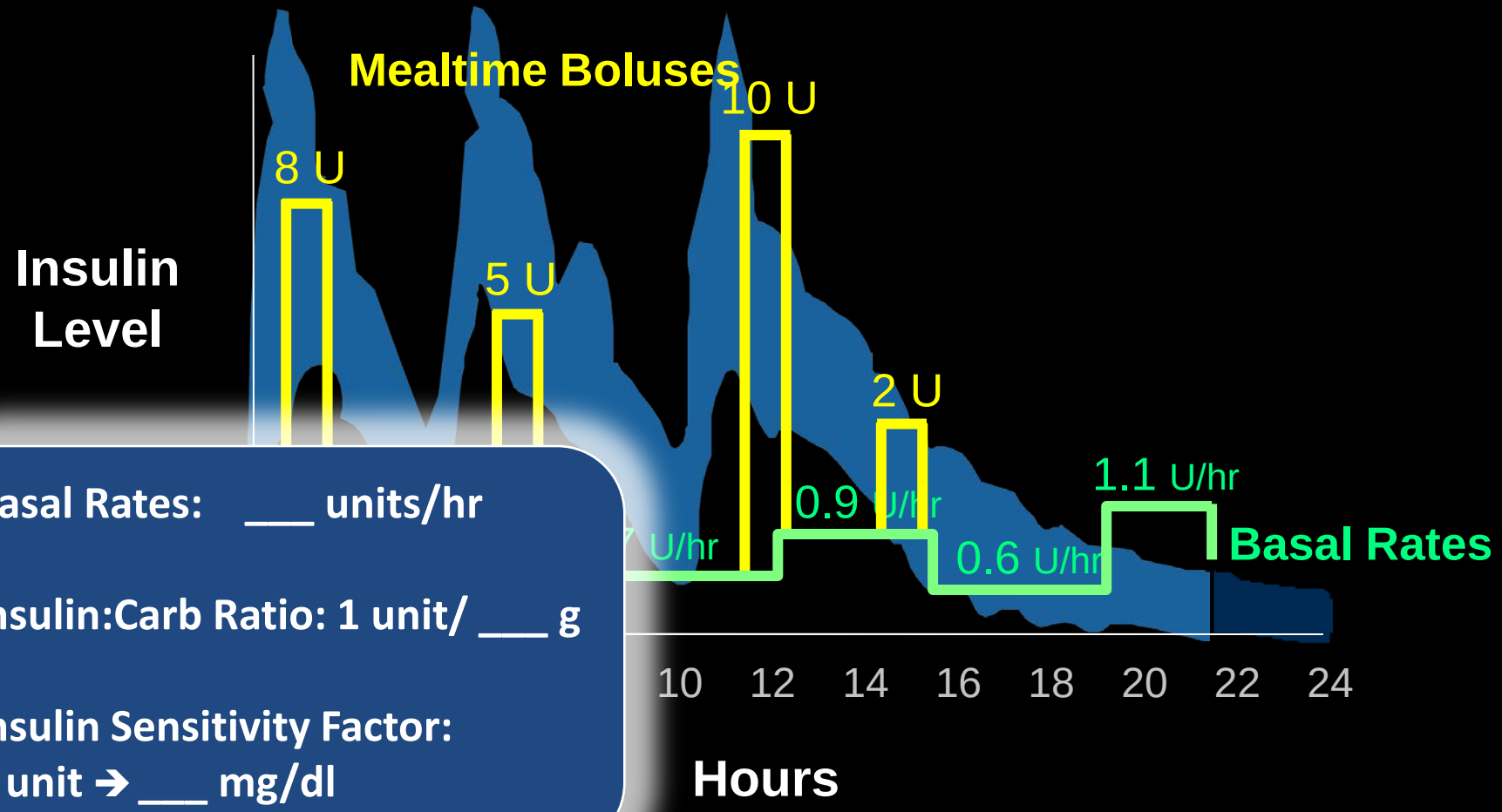
Insulin Pumps







Continuous Subcutaneous Insulin Infusion (CSII; Insulin Pump)



Basal Rates: ___ units/hr

Insulin:Carb Ratio: 1 unit/ ___ g

Insulin Sensitivity Factor:
1 unit ➔ ___ mg/dl

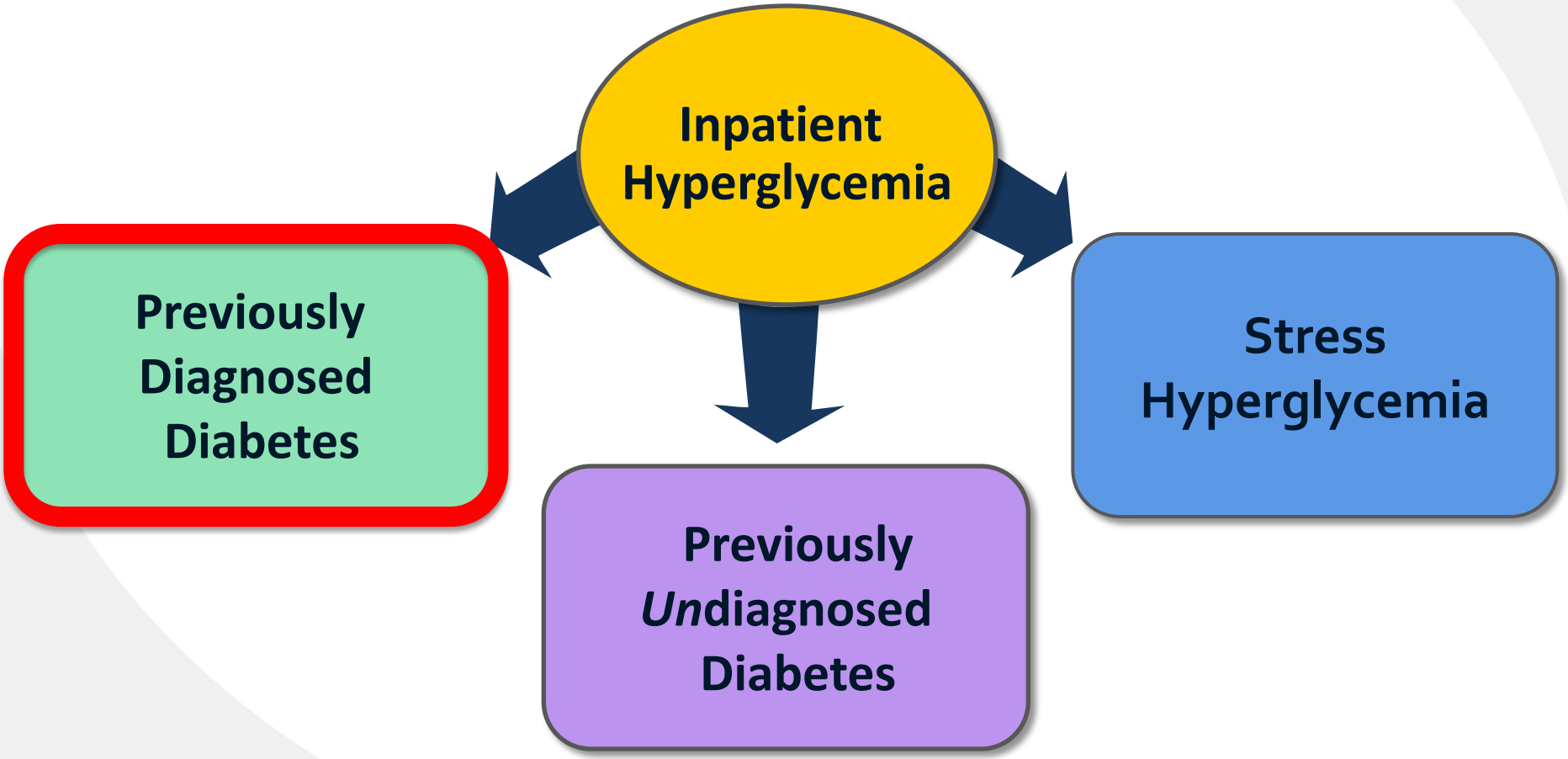
Special Situations

Insulin Pumps

- Electronic devices that deliver insulin through a SQ catheter – basal rate (variable) + boluses for meals.
- **Used predominately in T1DM. 'Pumpers' tend to be very fastidious about their BG control - reluctant to yield control to the inpatient medical team.**
- **Hospital personnel tend to be unfamiliar with pumps.**
- **Hospitals don't stock pump supplies.**
- **May allow pump patients to manage own diabetes during hospitalizations, but many logistical, ethical , & medicolegal issues!**

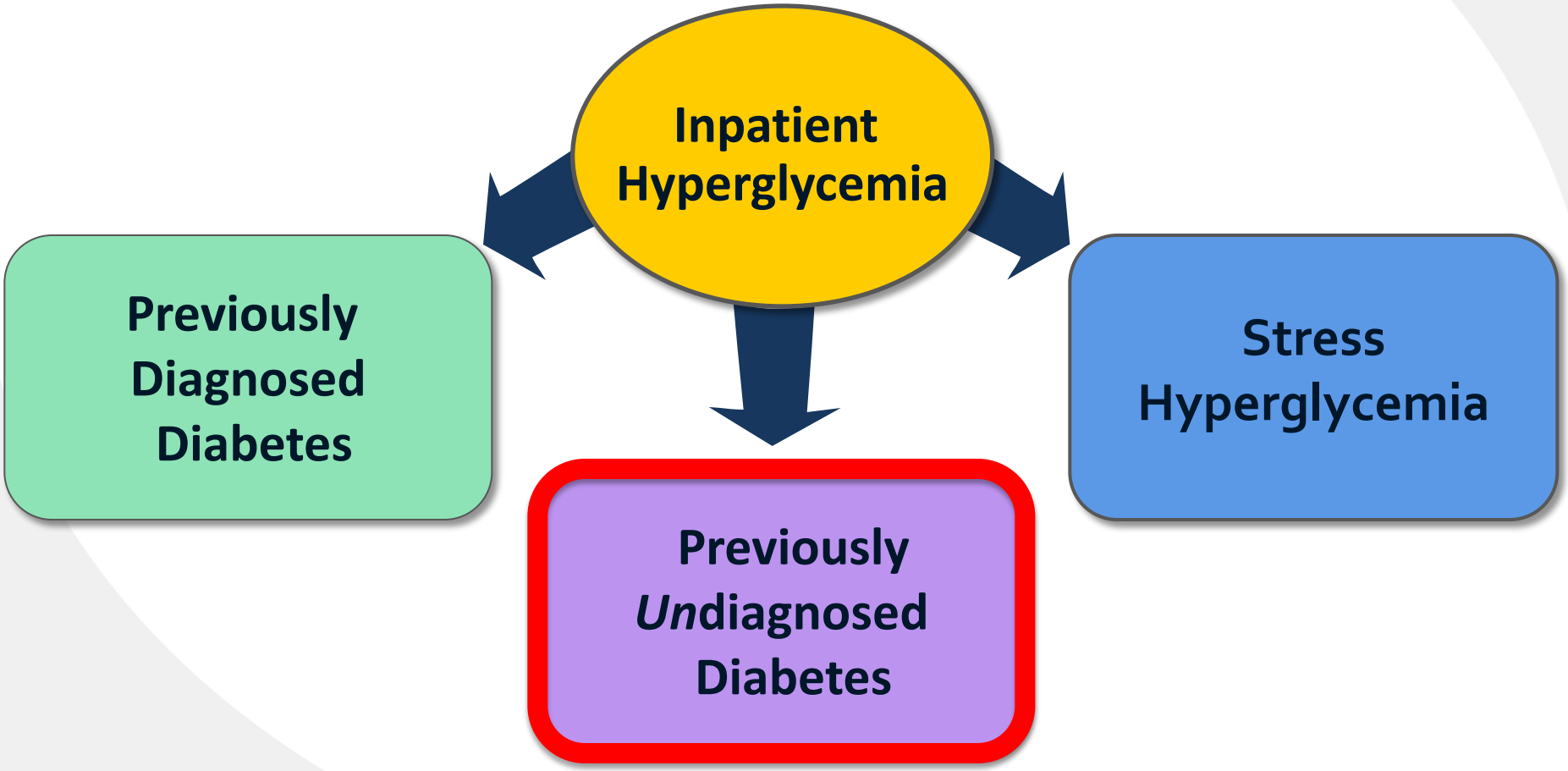
Discharge Planning

Etiologies of Inpatient Hyperglycemia



Umpierrez G, et al. *J Clin Endocrinol Metab. 2002;87:978*-982.

Etiologies of Inpatient Hyperglycemia



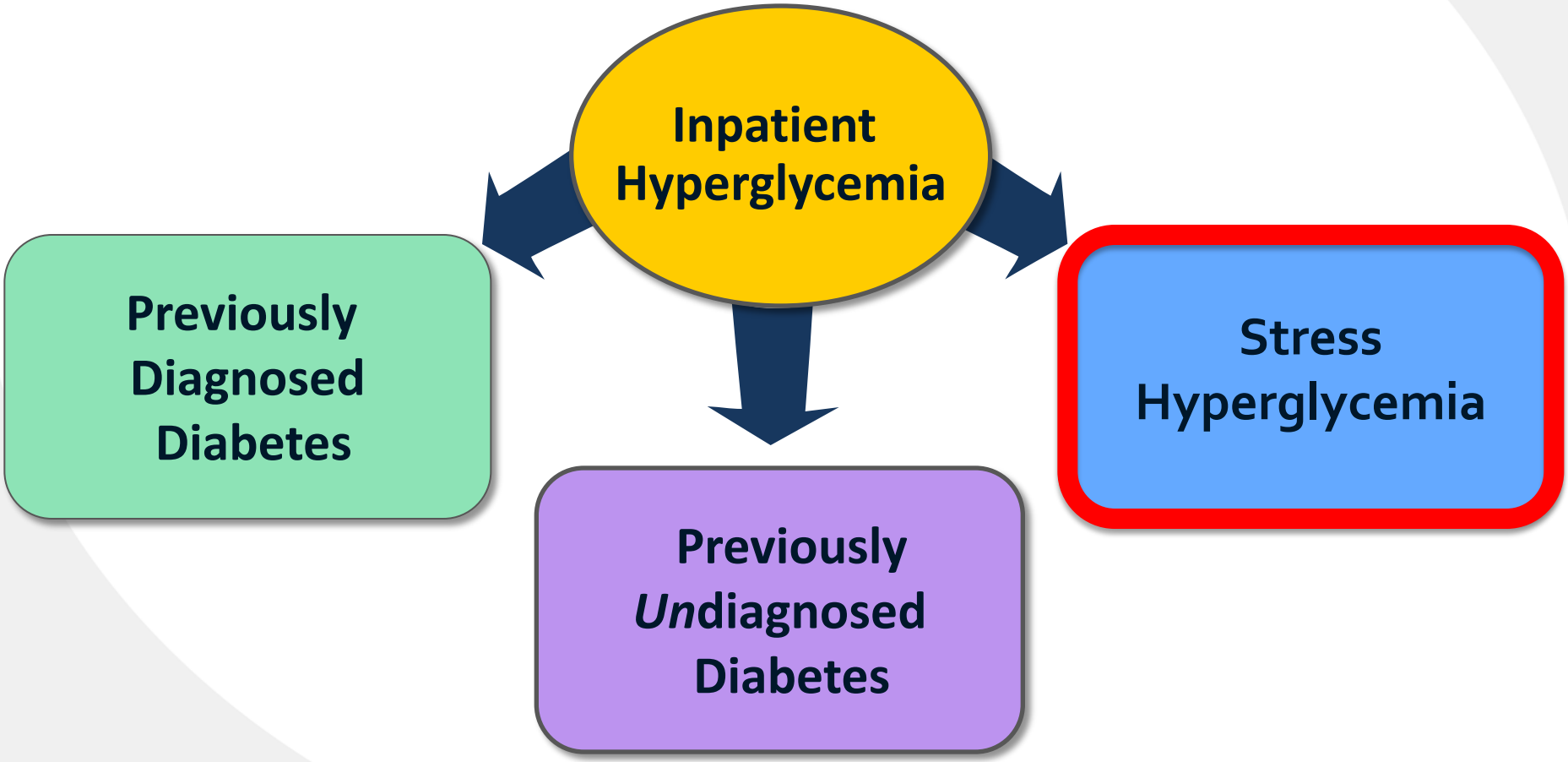
Umpierrez G, et al. *J Clin Endocrinol Metab. 2002;87:978*-982.

Diagnosis of Diabetes

	ADA 1997-2009	ADA 2010
FPG	≥ 126 mg/dl (7.0 mmol/l)	≥ 126 mg/dl (7.0 mmol/l)
2hPG (OGTT)	≥ 200 mg/dl (11.1 mmol/l)	≥ 200 mg/dl (11.1 mmol/l)
A1C	---	**≥ 6.5%**

Frank hyperglycemia (≥ 200 mg/dl [11.1 mmol/l]) also diagnostic if accompanied by classic symptoms.

Etiologies of Inpatient Hyperglycemia



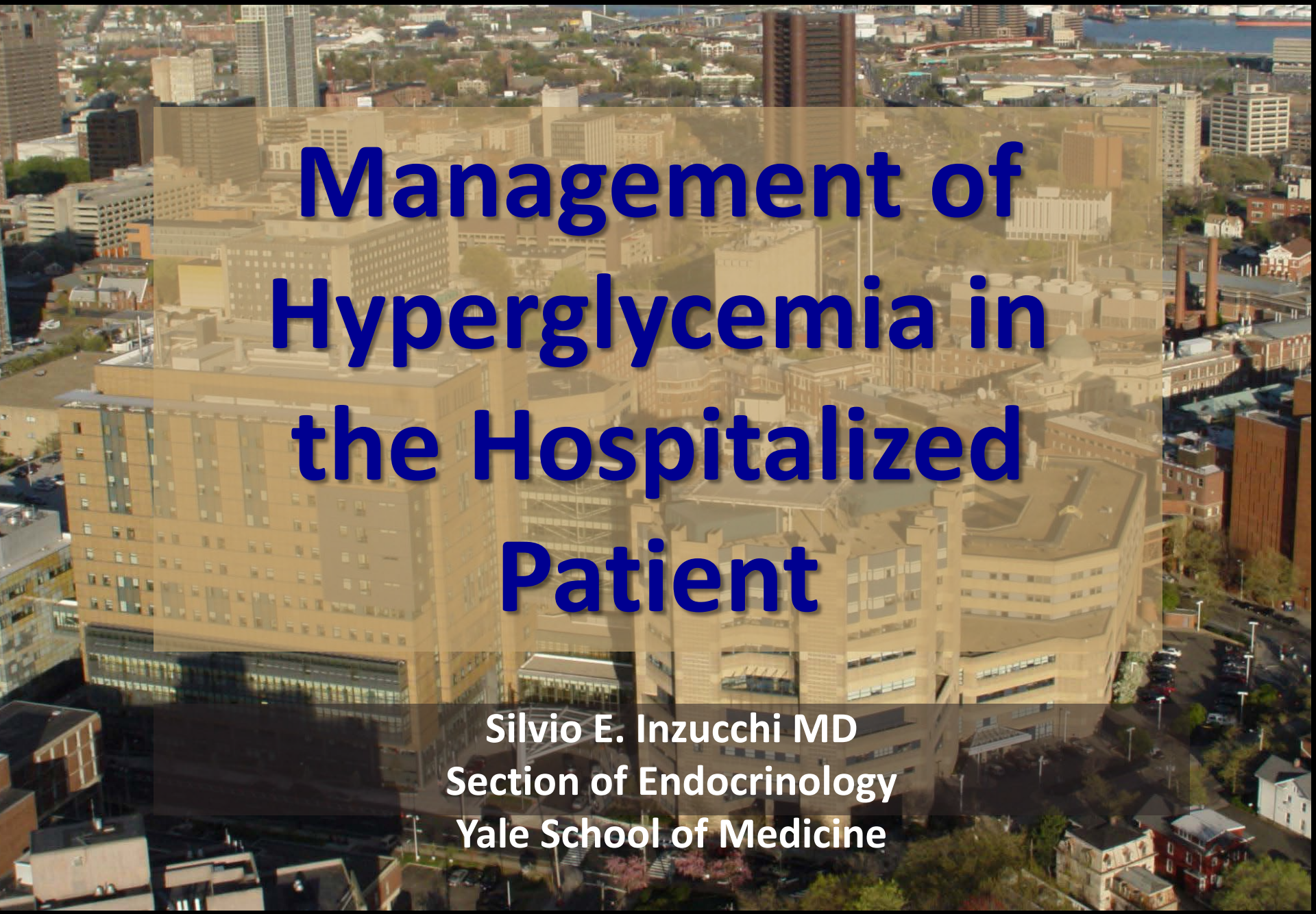
Umpierrez G, et al. *J Clin Endocrinol Metab. 2002;87:978*-982.

Discharge Planning

- **Be proactive – start early (1-2 days before.)**
- **What can this patient handle at home?**
- **Consider side effects, drug intolerances, comorbidities, insurance and costs.**
- **Rx's & supplies (med, insulins, syringes, pens, pen needles, meter, strips, lancets, etc.)**
- **Diabetes Education - *"Survival Skills"* training (newly diagnosed)**
- **Appointments: *Outpatient follow-up is key!***

Management of Hyperglycemia in the Hospitalized Patient: Summary

1. Glucose control is important in hospitalized patients.
2. In the ICU, use IV insulin (per protocol) when BG>180; target 140-180.
3. Outside of the ICU, generally don't use oral agents. Instead: SQ insulin, preferably with physiological regimens (basal + bolus + correction)
4. Be proactive in insulin adjustments; safety first!
5. Determine optimal discharge plan (w/ outpt follow-up)
6. Use your endocrinologists or diabetes nurses/CDEs to



Management of Hyperglycemia in the Hospitalized Patient

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