Glycemic Control in the Hospital
140-180 ***or*** ≤110 mg/dL

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The Transformation of ICU Care Using Intensive Insulin Therapy

Early on, the work of Umpierrez et al., Furnary et al. and Van den Berghe et al. transformed the approach to hyperglycemia and led to the widespread adoption of IIT in critically ill patients:

American Association Clinical Endocrinologists
ICU: 80-110 mg/dL[1]

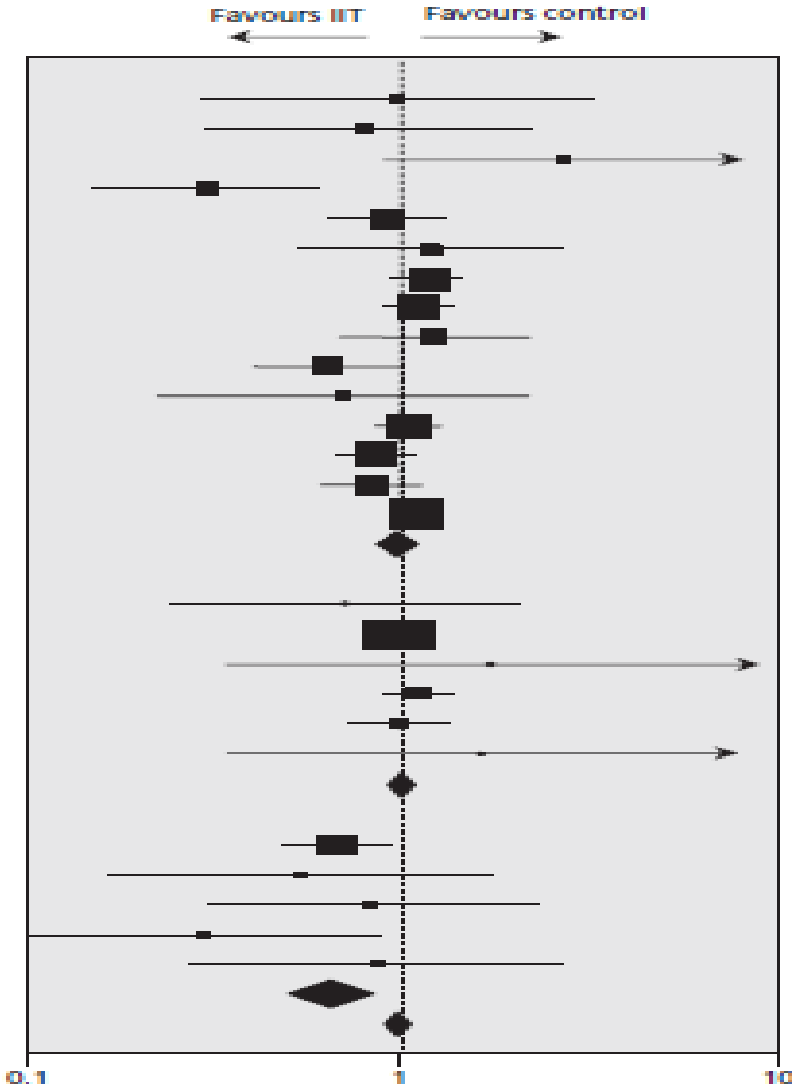
American Diabetes Association
ICU: Goal ~110 (and <140 mg/dL)[2]

[1]Rodbard HW, et al. Endocr Pract 2007;13(Suppl 1) p60

[2]American Diabetes Association. Diabetes Care 2008;31(Suppl 1):pS37

Problem…The Benefits of Intensive Insulin Therapy Could Not be Corroborated in Recent Randomized Trials

Study	No. deaths / total no. patients: IIT	Control	Risk ratio (95% CI)
Mixed ICU			
Yu et al.[35]	4/28	4/27	0.96 (0.27–3.47)
Henderson et al.[21]	5/32	7/35	0.78 (0.28–2.22)
Mitchell et al.[15]	9/35	3/35	3.00 (0.89–10.16)
Wang et al.[38]	7/58	26/58	0.27 (0.13–0.57)
Azevedo et al.[22]	38/168	42/169	0.91 (0.62–1.34)
McMullin et al.[24]	6/11	4/9	1.23 (0.49–3.04)
Devos et al.[13]	107/550	89/551	1.20 (0.93–1.55)
Brunkhorst et al.[11]	98/247	102/288	1.12 (0.90–1.39)
Iapichino et al.[32]	15/45	12/45	1.25 (0.66–2.36)
He et al.[30]	16/58	29/64	0.61 (0.37–1.00)
Zhang et al.[40]	4/168	6/170	0.67 (0.19–2.35)
De La Rosa Gdel et al.[12]	102/254	96/250	1.05 (0.84–1.30)
Arabi et al.[10]	72/266	83/257	0.84 (0.64–1.09)
Mackenzie et al.[33]	39/121	47/119	0.82 (0.58–1.15)
NICE-SUGAR[18]	829/3010	751/3012	1.10 (1.01–1.20)
All mixed ICU patients	1351/5051	1301/5089	0.99 (0.87–1.12)
Medical ICU			
Bland et al.[25]	1/5	2/5	0.50 (0.06–3.91)
Van den Berghe et al.[3]	214/595	228/605	0.95 (0.82–1.11)
Walters et al.[37]	1/13	0/12	2.79 (0.12–62.48)
Farah et al.[27]	22/41	22/48	1.17 (0.77–1.78)
Oksanen et al.[36]	13/39	18/51	0.94 (0.53–1.68)
Bruno et al.[26]	2/31	0/15	2.50 (0.13–49.05)
All medical ICU patients	253/724	270/736	1.00 (0.78–1.28)
Surgical ICU			
Van den Berghe et al.[8]	55/765	85/783	0.66 (0.48–0.92)
Grey et al.[28]	4/34	6/27	0.53 (0.17–1.69)
Bilotta et al.[34]	6/40	7/38	0.81 (0.30–2.20)
He et al.[29]	7/150	6/38	0.30 (0.11–0.83)
Bilotta et al.[23]	5/48	6/49	0.85 (0.28–2.60)
All surgical ICU patients	77/1037	110/935	0.63 (0.44–0.91)
All ICU patients	1681/6812	1681/6760	0.93 (0.83–1.04)



Griesdale DEG, et al. CMAJ. 2009;180:821-827

The Major Concern of IIT is Hypoglycemia

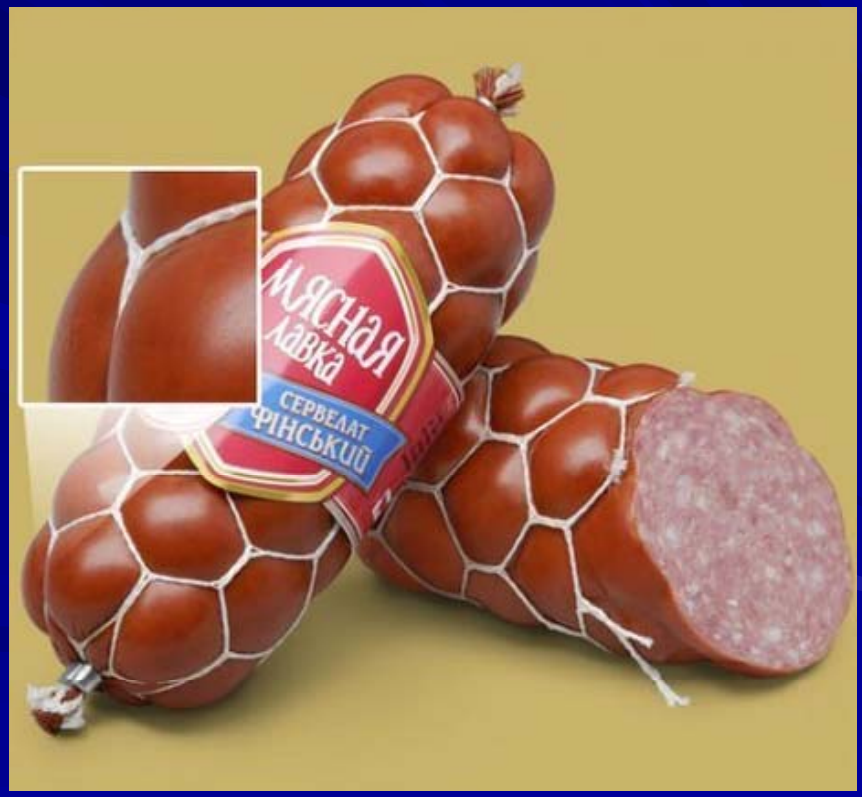
Severe hypoglycemia is often defined as <40 mg/dL
- Incidence up to 29%[1,2] (average 16%)

NICE-SUGAR trial has fueled the debate on IIT[3]
- No benefit lowering glucose below approximately 140-180 mg/dL[4]

Recent consensus statement by AACE and the ADA
- "*Reasonable, achievable and safe glycemic targets*"
- "Goal: 140-180 mg/dL"

[1]Arabi YM. Crit Care Med 2008;36:3190-3197
[2]Griesdale DEG, et al. CMAJ. 2009;180:821-827
[3]NICE-SUGAR Study Investigators. NEJM 2009;360:1280-1297
[4]Inzucchi SE, Siegel MD. NEJM 2009:360:1346-1349

Sometimes You Really Need to See the Whole Picture…



Factors to be Considered with the Inability of Recent Trials to Show Benefit of Intensive Insulin Therapy

Fundamental aspects of the application of IIT

1. Bedside glucose measurements
2. Insulin delivery
3. Post ICU glycemic control
4. Insulin dose-guiding methodology

Careful examination of the data reveals that the details are absent from contemporary discourses on IIT

Oud L, Spellman CW. Insulin 2010;5(2)94-99

Bedside Glucose Measurement

Glucose meters are the de facto standard for glucose monitoring in IIT trials. Are there point-of-care errors?

1. Methodology inconsistently reported in multicenter trials

   Example: NICE-SUGAR used various glucometers, central lab and blood gas analyzers interchangeably

2. College American Pathologists[1]

   CV of 17 glucose methods reported was 12-14%

   Bias between any 2 methods was up to 41%

3. To deliver a planned dose of insulin 95% of the time requires imprecision <2%[2]

[1]Scott MG et al. Clin Chem 2009;55:18-20

[2]Body JC, Burns DE. Clin Chem 2001;47:209-214

Insulin Delivery Systems

IV insulin infusions are administered with volumetric pumps.

How accurate are these pumps?

Progressive inaccuracy occurs at low flow rates

4 different pump mechanisms were analyzed[1]

Flow rate CV varied 35% ± 44% @ 10 ml/h

Flow rate CV varied 138% ±196% @ 1 ml/h

Pump-related flow/dose errors were #1 category of incidents in 2004 Canadian hospital alert[2]

Pump inaccuracy led to 2009 recall of specific pumps[3]

[1] Klem et al. Crit Care Med 1993;21:1213-1217

[2] http://www.hc-sc.gc.ca/dhp mps/medeff/advisories-avis/prof/_2004/infusion_pumps_nth-ah-eng.php

[3] http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsfor HumanMedicalProducts/ucm174797.htm.

Insulin Delivery Systems

Information on the various infusion pumps used in IIT trials is inconsistently reported[1-3]

No data on the pumps used in the NICE-SUGAR trial was reported[4]

[1]Van den Berghe et al. NEJM 2001;345:1359-1367

[2]Van den Berghe et al. NEJM 2006;354:449-461

[3]Brunkhorst et al. NEJM 2008;358:125-139

[4]NICE-SUGAE Study Investigators. NEJM 2009;360:1283-1297

Post-ICU Glycemic Control

Persistent hyperglycemia is common in non-ICU patients[1]

Severe persistent hyperglycemia is common in patients who received IIT within the 1st 48 hours s/p discharge from the ICU[2]

Numerous studies have documented increased mortality in hyperglycemic non-ICU patients[3,4]

[1]Cook et al. J Hosp Med 2007;2:204-211

[2]Shaw SA, Macala K. Crit Care Med 2007;34:A164

[3]Umpierrez GE et al. J Clin Endocrinol Metab 2002;87:978-982

[4]Capes et al. Stroke 2001;32:2426-2432

Post-ICU Glycemic Control

None of the reported IIT trials have examined glycemic control or glycemic targets following ICU discharge.

There are no corresponding studies of tight control in non-ICU populations

We suggest that it is naïve to assume that post-ICU glycemic control would not affect patient outcomes and that imbalances in post-ICU care may contribute to the apparent lack of benefit and possible harm of IIT in recent trials

Insulin Dose-Guiding Methodology

How good are the algorithms for IIT?

- The methods for IV insulin infusion in all large-scale IIT trials reported to date *are paper-based protocols*
- Recent evaluation of 12 paper-based protocols showed recommendations for insulin dosing varied from 27-115 units[1]
- Only ~20% of glucose measurements are within the glycemic target range using paper-base protocols[2]

[1]Wilson M et al. Diabetes Care 2007;30:1005-1011
[2]Morris JS et al. Crit Care Med 2008;36:1787-1795

Insulin Dose-Guiding Methodology

Randomized IIT trials used mean blood glucose levels as the primary end-point for efficacy of glucose control

Most of the large studies,[1-3] including NICE-SUGAR,[4] *failed to achieve the targeted blood glucose levels*

The only large randomized study that showed decreased mortality of IIT achieved glucose targets[1]

[1]Van den Berghe G, et al. NEJM 2006;354:449-461
[2]Brunkhorst FM et al. NEJM 2008;358:125-139
[3]Preiser JC et al. Intensive Care Med 2009;DOI:10.1007/s00134-009-1585-2
[4]NICE-SUGAR Study Investigators NEJM 2009;360:1283-1297

What's the Upshot?

Problems with IIT trials are:

1. Little information on glucose monitoring and imprecision of glucometers (least important?)
2. Insulin infusion pump errors at low flow rates
3. Poor glycemic control on the general wards that confounds the outcomes of IIT trials
4. Paper-based protocols that cannot be implemented
5. No data on whether there is benefit of IIT because hypoglycemia cannot be eliminated

Oud L, Spellman CW. Insulin 2010;5(2)94-99

Where Do We Go?

Consider computerized bedside protocols (CBP) as an alternative to paper-based methods

There are FDA-approved CBPs,[1-3] and several have achieved rates of with-in target glucose >60%[4-8]

[1]http://www.hospira.com/Products/endotool.aspx

[2]http://www.glucotec.com/index.asp

[3]http://www.glucostabilizer.net

[4]hvorka R, et al. J Clin Endocrinol Metab 2007;92:2960-2964

[5]Juneja R et al. Diabetes Technol Ther 2007;9:232-240

[6]Hermayer KL et al. Diabetes Technol Ther 2007;9:523-534

[7]Saager L et al. J Cardiothorac Vasc Anesth 2008;22:377-382

[8]Plank J et al. Diabetes Care 2006;29:271-276

Computerized Bedside Protocols

Vogelzang et al were able to maintain patients' blood glucose in the range of 72-135 for 89% of the ICU stay[1]

Prevention of hypoglycemia has been one of the key outcomes of CBPs

Severe hypoglycemia was completely eliminated[2-5] in several studies or reduced to less than 1%[1,6]

CBPs significantly reduce glucose variability[1]

[1]Vogelzang M et al. Intensive Care Medicine 2008;34:1421-1427
[2]Plank J et al. Intensive Care Med 2008;34(Suppl 1):S222
[3]Hvorka R, et al. J Clin Endocrinol Metab 2007;92:2960-2964
[4]Davidson PC et al. J Diabetes Sci Technol 2008;2:369-375
[5]Plank J et al. Diabetes Care 2006;29:271-276
[6]Saager L et al. J Cardiothorac Vasc Anesth 2008;22:377-382

Computerized Bedside Protocols

Only limited data are available on the impact of CBPs

- Dortch et al reported reduced hospital mortality in trauma patients managed with CBP[1]
- Toschlog et al reported decreased infectious complications and length of stay comparing CBP with paper-based protocols[2]

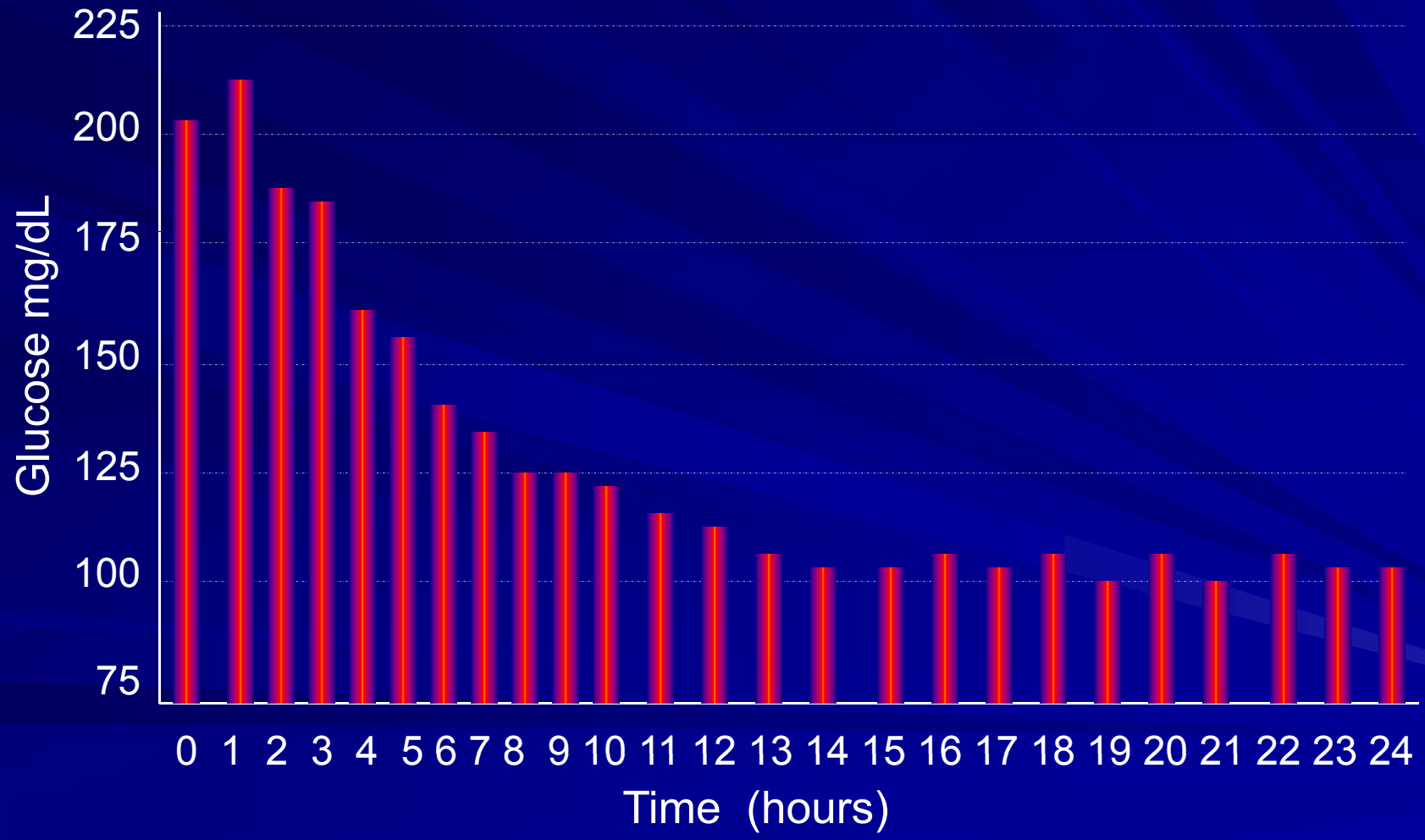
[1]Dortch MJ et al. J parenter Enteral Nutr 2008;32:18-27

[2]Toschlog EA et al. J Trauma 2007;62:1370-1376

TTUHSC-Medical Center Hospital Experience with Computerized Bedside Protocols[1]

1 http://www.glucostabilizer.net

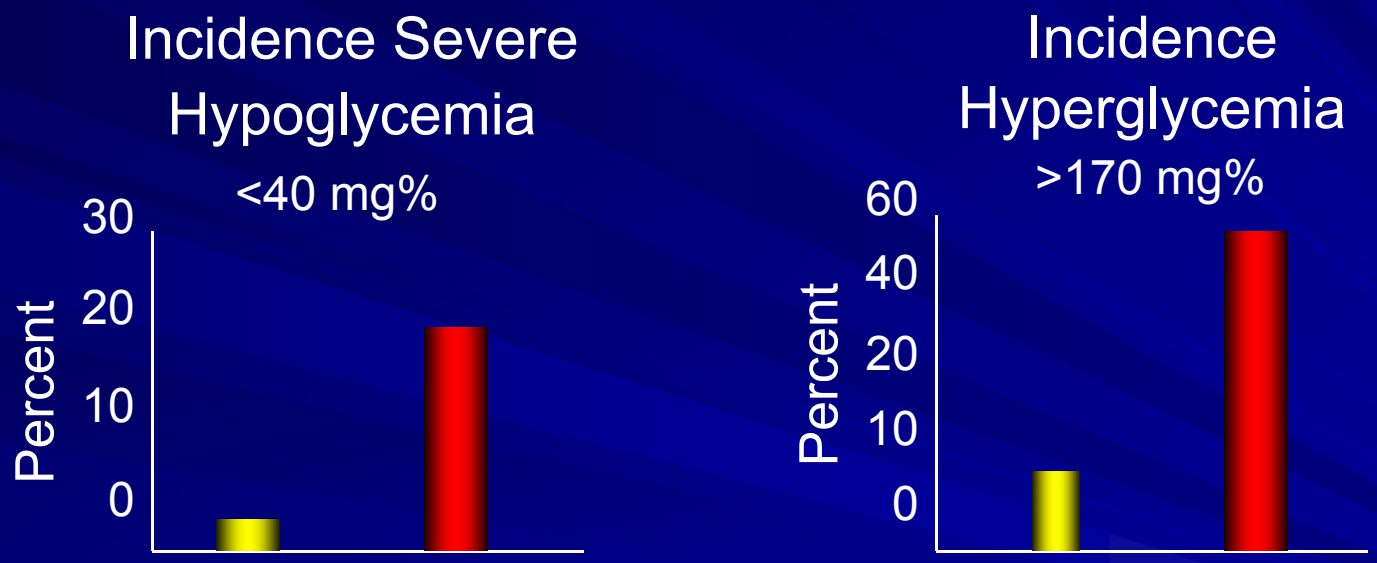
Glycemic Control: Average All Glucose Values During The First 24 Hours



Oud L, Spellman CW. Unpublished data 2010

CBP vs Paper-Based Management: Percent Patients with ≥1 Glycemic Excursions[1]

Glucose Target 90-130 mg/dL



CBP n = 673

Paper-Based n= 887

Oud L, Spellman CW. Unpublished data 2010

Transition From IV to SQ Insulin

- Assumption: Glycemic control on telemetry or the general medical floor is thought to be beneficial, but good data is lacking
- Arguments for ongoing glycemic control include the idea that care for the hospitalized patient should be at least equal to that recommended for out patients
- No widely used protocol exists for switching from IV to SQ insulin
- Sliding scale insulin use must be eliminated

Transition from I.V. to S.Q. Insulin for Patients with Diabetes or Hyperglycemia

GOALS: NPO or PO

FPG 100-130 mg/dL
2h pp <180 mg/dL
Avoid hypoglycemia

GOALS: TPN or Enteral

<180 mg/dL
Avoid hypoglycemia

Transition From I.V. to S.Q. Insulin[1-4]

1. **Patient's Total Daily Dose** (TDD) S.Q. Insulin = I.V. units of Insulin per hour x 20 hours
   Note: *If patient was nondiabetic and using <1 unit per hour, insulin can be discontinued*
2. **Give *one-time* injection of** Basal Insulin[5-7] + Bridging Dose[8] of aspart, lispro or glulisine
   Basal dose = TDD
   Bridge dose = 10% of TDD
3. **Stop IV insulin infusion**
4. **Start patient on pathway** 1, 2, 3 or 4[1-3] depending on route or number of meals per day

1: Patient will not start eating

Prandial Insulin = None
Basal Insulin = TDD q AM

2: Patient eats <3 meals/day

Each prandial dose = 10% TDD
Basal Insulin: 90%TDD if 1 meal
Basal Insulin: 80%TDD if 2 meals

3: Patient will eat 3x per/day

Prandial Insulin[8] = ½TDD÷ t.i.d. AC
Basal Insulin = ½TDD q AM

4: TPN or Enteral Nutrition

TPN: Use R insulin, Dose = 80% TDD
May add part or all to TPN bag
Tube: (Insulin SQ)
Constant rate
Basal insulin =TDD
Intermittent use[8]
Basal insulin = ½ TDD
Prandial insulin = ½ TDD÷ t.i.d. AC

Changing Basal Insulin

Adjust Each Morning

FPG	Insulin Change
<60 mg/dL	- 4 units
60-80	- 2
81-99	- 1
100-130	No Change
121-140	+ 2
141-160	+ 4
161-180	+ 6
>180	+ 8

Changing Prandial Insulin

- Add to prandial dose if glucose is high before meal
- Use alone to correct any random high glucose

Glucose mg/dL	TDD <40 units/d	TDD ~40-80 units/d	TDD >80 units/d
140-199	+ 1 unit	+ 1 unit	+ 2 units
200-249	+ 2	+ 3	+ 4
250-299	+ 3	+ 5	+ 7
300-349	+ 4	+ 7	+10
>349	+ 5	+ 8	+12

Changing Prandial[8] or Basal Insulin

Any glucose <80	↓ insulin 20%
All glucose 80-179	No Change
Any glucose ≥180	↑ insulin 10%

Correcting Hyperglycemia

- Use prandial insulin[8] q4-6 h
- Dose = "Changing Prandial Insulin"

Reevaluate Total Daily Dose of Insulin

1. Recalculate the TDD every 1-2 days as the doses of insulin are adjusted.
2. The ratio of basal to prandial insulin should be approximately 50:50

[1] www.diabetes.org/for-health-professionals-and-scientists/insulin-administration.jsp,
[2] Donaldson S, et al. Diabetes Educator. 2006;32:954
[3] Hirsch IB. Insulin. 2006;1(Suppl A):S18-24
[4] Kitabchi AE, Freire AX, Umpierrez GE. Metabolism Clin Exper. 2008;57:116-120
[5] If patient is transferred out of the unit in the later evening and will begin eating in the A.M. give *half* the basal dose and *all* of the bridging dose. Begin full basal dose the next morning.
[6] No evidence-based inpatient data is available for the transition from IV to SQ dosing of detemir
[7] If NPH is used, then give 2/3 of the TDD and distribute as 2/3 in the morning and 1/3 at bedtime.
[8] Aspart, lispro or glulisine is recommended because the action profiles better approximate normal physiology. Regular insulin may be substituted.

Texas Diabetes Council

Texas Department of State Health Services

The Transition from I.V. to SQ insulin: *The 1st SQ Dose of Insulin*

"Bridging Method"

1. Total Daily Dose (TDD) insulin = IV rate X 20
2. Give *one-time injection* of:
   Basal insulin + "Bridge" aspart, glulisine or lispro

   Basal = TDD
   Bridge = 10% TDD
3. Stop IV insulin infusion
4. Patient enters pathway 1, 2, 3 or 4 for subsequent insulin management

www.texasdiabetescouncil.org

www.diabetes.org/for-health-professionals-and-scientists/insulin-administration.jsp

Donaldson S, et al. *Diabetes Educator*. 2006;32:954

Pathway 1
The Patient Will Be NPO

- Prandial insulin = None
- Basal insulin = TDD given each morning

Titrate Basal Insulin q A.M.

FPG	Insulin Change
<60 mg/dL	- 4 units
60-80	- 2
81-99	- 1
100-130	No Change
121-140	+ 2
141-160	+ 4
161-180	+ 6
>180	+ 8

Titrate Prandial Insulin

Glucose mg/dL	TDD <40 U/d	TDD 40-80 U/d	TDD >80 U/d
140-199	+ 1 U	+ 1 U	+ 2 U
200-249	+ 2	+ 3	+ 4
250-299	+ 3	+ 5	+ 7
300-349	+ 4	+ 7	+10
>349	+ 5	+ 8	+12

Pathway 2
The Patient Will Eat <3 Meals per Day

- Prandial insulin = Each dose will be 10% of TDD
- Basal insulin = TDD *and* reduce dose by 10% for each planned prandial injection

Titrate Basal Insulin q A.M.

FPG	Insulin Change
<60 mg/dL	- 4 units
60-80	- 2
81-99	- 1
100-130	No Change
121-140	+ 2
141-160	+ 4
161-180	+ 6
>180	+ 8

Titrate Prandial Insulin

Glucose mg/dL	TDD <40 U/d	TDD 40-80 U/d	TDD >80 U/d
140-199	+ 1 U	+ 1 U	+ 2 U
200-249	+ 2	+ 3	+ 4
250-299	+ 3	+ 5	+ 7
300-349	+ 4	+ 7	+10
>349	+ 5	+ 8	+12

www.texasdiabetescouncil.org

Pathway 3
The Patient Will Eat 3 Meals per Day

- Prandial insulin = ½ TDD divided between meals
- Basal insulin = ½ TDD given each morning

Titrate Basal Insulin q A.M.

FPG	Insulin Change
<60 mg/dL	- 4 units
60-80	- 2
81-99	- 1
100-130	No Change
121-140	+ 2
141-160	+ 4
161-180	+ 6
>180	+ 8

Titrate Prandial Insulin

Glucose mg/dL	TDD <40 U/d	TDD 40-80 U/d	TDD >80 U/d
140-199	+ 1 U	+ 1 U	+ 2 U
200-249	+ 2	+ 3	+ 4
250-299	+ 3	+ 5	+ 7
300-349	+ 4	+ 7	+10
>349	+ 5	+ 8	+12

Pathway 4
The Patient Will Receive TPN or Enteral Nutrition

- TPN Use R insulin, dose = 80% TDD
- Tube Basal insulin = TDD

Changing R or Basal Insulin	
Any glucose <80	↓ insulin 20%
All glucose 80-179	No Change
Any glucose ≥180	↑ insulin 10%

Correcting Hyperglycemia With R Insulin			
Glucose mg/dL	TDD <40 U/d	TDD 40-80 U/d	TDD >80 U/d
140-199	+ 1 U	+ 1 U	+ 2 U
200-249	+ 2	+ 3	+ 4
250-299	+ 3	+ 5	+ 7
300-349	+ 4	+ 7	+10
>349	+ 5	+ 8	+12

So, What Do I Use If "Sliding Scale" Insulin Orders are not Accepted?

- Calculate "Correction Doses" of insulin
  - Use the "Rule of 1800" for the fast analogs
  - Use the "Rule of 1500" for Regular insulin
- Why are the "rules" of 1800 or 1500 used?

Ans Everyone is different and the "rules" are actually calculations of *insulin sensitivity!*

Hirsch IB. JAMA 2009;301:213

Calculating the Insulin "Correction Dose"

Example: A patient uses 100 units of insulin per day:

Basal dose = 50 units

Prandial dose = ~16 units

Correction dose = ~1 unit per 20 mg glucose >140

Rule 1800: 1800/100 = ~20. This means that 1 extra unit of insulin will decrease blood glucose 20 mg/dL

If the glucose was 220 mg/dL before a meal, then 16 units will be needed to cover the meal *AND* extra insulin is needed to correct the hyperglycemia.

So, the prandial dose will be 16 + 4 or 20 units

Hirsch IB. JAMA 2009;301:213

Starting Insulin for the Non-ICU Patient

- No oral agents
- No pre-mixed insulin
- Obtain A1C on admission
- Monitor glucose: AC, HS, 02:00
- Use basal-prandial insulin regimens
- Elective surgery: Consider postponing if A1c is ≥9%
- Patient will be NPO
  - Give basal insulin; Hold bolus insulin
  - Give supplemental insulin if glucose >140 mg/dL
- No *"Sliding Scale"* insulin regimens are permitted

Hirsch IB, Braithwaite SS. Res. Staff Physician. 2007;53(2):1
Baldwin D, et. al. Diabetes Care. 2005;28:1008-1011
www.diabetes.org/for-health-professionals-and-scientists/insulin-administration.jsp

Starting Basal-Prandial Insulin For The Non-ICU Patient

- If patient has been using SQ insulin

  Glargine: Continue same dose
  Detemir: Continue same dose

  NPH: Give 80% of total dose as glargine or
  Give unit-for-unit as detemir

  Reg: Give unit-for-unit as aspart, glulisine or lispro

  Premix: Give 50% of total dose as glargine or detemir

  Give “unit-for-unit” of fast component as aspart, glulisine or lispro

  Pump: Continue or Δ to basal-prandial, unit-for unit

Package inserts, Texas Diabetes Council, Donaldson S, et al. *Diabetes Educator*. 2006;32:954

Starting Basal-Prandial Insulin For The Non-ICU Patient

- If insulin requirements are unknown, begin insulin based on *current weight*

T1DM	0.3 – 0.5 units/Kg
New T2DM	0.2 – 0.3 units/Kg
Known T2DM	0.3 – 0.5 units/Kg
Renal insufficiency	Reduce dose 20-40%

- Distribute as half basal and half as prandial
  - Basal: Give glargine or detemir q a.m.
  - Prandial: Divided t.i.d. with meals

Package inserts, Texas Diabetes Council & Donaldson S, et al. *Diabetes Educator*. 2006;32:954

Discharging The Patient

- Discharge plans are based on the *A1c at admission*

  Known diabetes:

  Discharge on insulin if A1c was >7%
  Resume previous care if A1c was at goal

  Hyperglycemia discovered:

  Discharge if A1c was less than ~5.5%
  Discharge on oral agents if A1c was >6.5%

www.diabetes.org/for-health-professionals-and-scientists/insulin-administration.jsp


Thank you
Questions???