INPATIENT HYPERGLYCEMIA

Evidence-Based Approaches and Treatment

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Disclosures

No conflict of interest or significant financial relationships relevant to this presentation

55-year-old male with HTN, hyperlipidemia presenting with chest pain admitted for NSTEMI

He has no prior history of IFG/IGT

- **serum glucose on admission 225 mg/dL (12.5 mmol/L)**
- **fasting glucose next day 200 mg/dL (11.1 mmol/L)**

Is this important?
What is the role for monitoring? treating?

Objectives

- **Rationale for glycemic control in the hospital**
- **Evidence-based recommendations for glycemic targets**
- **Management strategies for common inpatient clinical scenarios**
- **Important aspects to consider with new therapies for diabetes including use of non-insulin agents and technology in the acute setting and implications for transition of care**
- **Approach to management of hyperglycemia in hospitalized patients with SARS-CoV-2**

Diabetes in the Acute Care Setting

- **Increased prevalence**
  - **> 30 million in US and predicted to almost triple by 2050 (~ 1 in 3 adults)**
  - **Worldwide: in 2017~425 million adults; projected rise to 629 million by 2045**
  - **14.2 million ED visits, 7.2 million hospital discharges**
- **Escalating cost of diabetes care**
  - **40% increase in last decade, $1 in 5 US dollars with ~43% of total costs due to inpatient care**

https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf
https://www.idf.org

Inpatient Hyperglycemia

Stress hyperglycemia

Previously undiagnosed diabetes

Established diabetes

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Stress Hyperglycemia and Evidence of Harm

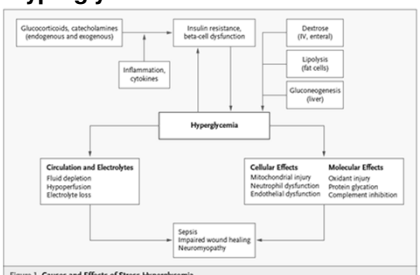

Figure 1. **Causes and Effects of Stress Hyperglycemia.**
Stress hyperglycemia can be caused by exogenous administration or endogenous production of glucose and by insulin resistance or reduced secretion of insulin owing to beta-cell dysfunction. The resulting hyperglycemia can potentiate insulin resistance. The consequences of elevated glucose levels may be manifested at the molecular or cellular level, combining to cause tissue abnormalities that include sepsis, impaired wound healing, and neuromyopathy. IV denotes intravenous.

Kavanagh BP and McCowen KC Clinical practice. Glycemic control in the ICU. N Engl J Med.2010 Dec 23;363(26):2540-6.

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Hyperglycemia in Hospitalized Patients

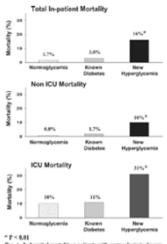
Medical/Surgical Patients (n=1886)
Fasting BG ≥ 126 mg/dL or random BG ≥ 200 mg/dL x 2

- **26% of admissions had known diabetes**
- **12% of admissions had previously undiagnosed or "new" diabetes**

In–Hospital Mortality Rate

"New Hyperglycemia"(16%)
Establish Diabetes (3%)
Normoglycemia (1.7%)
P < 0.01

Patients with "new hyperglycemia" have worse outcomes!



Umpierrez GE et al. Hyperglycemia: an independent marker of in-hospital mortality in patient s with undiagnosed diabetes J Clin Endocrinol Metab. 2002 Mar;87(3):978-82

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Why is this relevant?

- **Inpatient dysglycemia is common in patients with and without established diabetes**
- **Increased risk of hospital complications**
- **Increased health care utilization**
- **Higher-in hospital mortality**
- **"Stress Hyperglycemia" marker of severity of illness?**

Appropriate glycemic control can reduce these risks!

Kotagal M et al. Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. Ann Surg.2015 Jan;261(1):97-103.

Umpierrez GE et al. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes J Clin Endocrinol Metab. 2002 Mar;87(3):978-82

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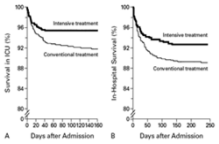
Intensive Insulin Therapy (IIT)

Van den Berghe 2001

Prospective RCT
SICU Leuven, Belgium (n=1548)
Conventional: IV infusion when BG > 215 mg/dL; target 180-200 mg/dL
Intensive (IIT): IV infusion when BG > 110 mg/dL; target 80-110 mg/dL



Relative Risk Reduction (%)
Antibiotic use > 10 d (-35%)*
Blood stream infections (-46%) *
Critical illness polyneuropathy (-44%)**
Mechanical ventilation > 14d (-37%)*
RRT (HD/CVVH) (-41%)*
ICU stay > 14d (-27%)*

* P≤ 0.01
** P≤ 0.001

Improved outcomes with "tight" glycemic control

Van den Berghe G et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001 Nov 8;345(19):1359-67.

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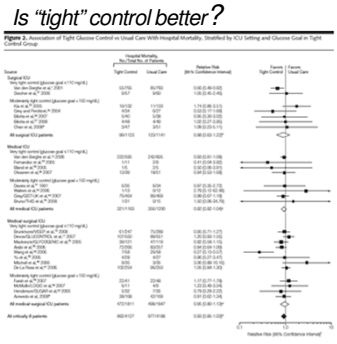
How low should we go?

Is "tight" control better?



Wiener RS et al. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA. 2008 Aug 27;300(8):933-44.

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Intensive Insulin Therapy (IIT)

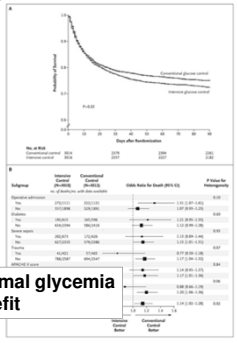
NICE-SUGAR

Multisite International RCT
MICU/SICU (n=6140)
Conventional: IV insulin with target <180 mg/dL
Intensive (IIT): IV infusion target 81-108 mg/dL

Increased mortality
Intensive therapy vs. Conventional therapy

Severe hypoglycemia in IIT
Intensive Therapy 6.8 %
Conventional Therapy 0.5%

pushing for near normal glycemia risk > benefit



Finfer S et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009 Mar 26;360(13):1283-97.

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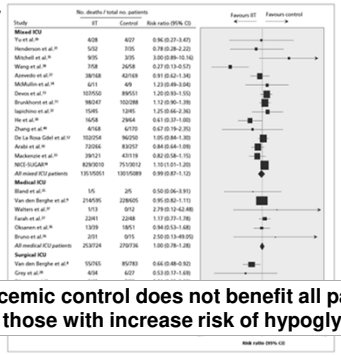
Mortality



"Tight" glycemic control does not benefit all patients
Especially those with increase risk of hypoglycemia

Griesdale DE et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009 Apr 14;180(8):821-7.

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Hypoglycemia

BG < 70 mg/dL (3.9 mmol/L)
Clinically significant hypoglycemia <54 mg/dL (3.0 mmol/L)
Severe hypoglycemia BG < 40 mg/dL (2.3 mmol/L)

Associated with poor outcomes
- **66% increased risk of death within 1 year**
- **longer LOS (~ 2.8 days)**
- **complications: ischemic changes, arrhythmias, prolonged QT, sudden death in type 1**

Risk factors in hospitalized patients:
older age
impairment in renal function
change in nutritional intake
interruption in glucose monitoring/failure to adjust therapy

Garg R, et al. Hypoglycemia, with or without insulin therapy, is associated with increased mortality among hospitalized patients. Diabetes Care. 2013 May;36(5):1107-10.

Turchin A et al. Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. Diabetes Care. 2009 Jul;32(7):1153-7.

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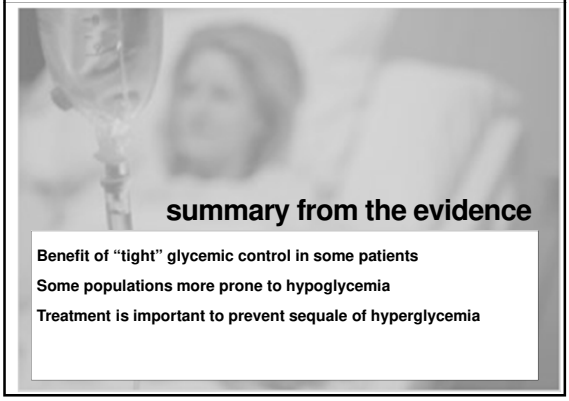

summary from the evidence

Benefit of "tight" glycemic control in some patients

Some populations more prone to hypoglycemia

Treatment is important to prevent sequale of hyperglycemia

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Assessment of Hyperglycemia in the Acute Care Setting

- **Glucose measurement in all patients admitted to hospital**
- **> 140 mg/dL (7.8 mmol/L) and history of DM, POCT AC and q HS**
- **Pre-meal testing done w/in 1 hour of meal**
- **NPO/enteral nutrition q4-6h**
- **If hyperglycemic, check HbA1c (if not checked within last 2-3 months)***

*** caveat don't forget about factors that will influence HbA1c (transfusions etc)**

Lansang MC and Umpierrez GE. Inpatient hyperglycemia management: A practical review for primary medical and surgical teams. Cleve Clin J Med. 2016 May;83(5 Suppl 1):S34-43.

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Target Glucose Levels: what is the sweet spot?

Organization	Critically Ill	Non-critically Ill Patient
ADA/AACE	< 140-180 mg/dL Initiate insulin >180 mg/dL	Pre-meal <140 mg/dL Random < 180 mg/dL*
ACP	140-200 mg/dL Recommends against IIT	
Critical Care Society	<150-180 mg/dL Initiate insulin >150 mg/dL	
Endocrine Society		Pre-meal < 140 mg/dL Random < 180 mg/dL* Adjust regimen < 100 mg/dL
Society of Thoracic Surgeons	Cardiac surgery: IV insulin <180 mg/dL peri-op ≤ 110 mg/dL fasting or premeal	
Joint British Diabetes Society		6-10 mmol/L (108-180 mg/dL) acceptable range 4-12 mm/L (72-216 mg/dL)

*Higher targets < 200 mg/dL acceptable in patients with terminal illness, limited life expectancy or increased risk of hypoglycemia

Modified from Lansang MC and Umpierrez GE. Inpatient hyperglycemia management: A practical review for primary medical and surgical teams. Cleve Clin J Med. 2016 May;83(5 Suppl 1):S34-43.

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Target Glucose Levels: what is the sweet spot?

Critically Ill Patient	Non-critically Ill Patient
< 180 mg/dL (< 10.0 mmol/L)	Pre-meal <140 mg/dL (< 7.8 mmol/L) Random < 180 mg/dL (< 10.0 mmol/L) •Higher glucose levels < 200 mg/dL (< 11.1 mmol/L) may be acceptable in some patients (terminally ill, multiple medical comorbidities)

Factors to consider for hospitalized patients

- **Different eating**
- **Different activity**
- **Medications (steroids, anti-rejection agents, dextrose-containing fluids)**
- **Illness related insulin resistance**
- **Patient factors: renal function**
- **Diabetes phenotype**

What about continuing outpatient medications?

Medication	Advantages	Disadvantages
Metformin	Low risk for hypoglycemia	MALA risk in patients with hypoperfusion (RI, cirrhosis, HF)
Sulfonylureas		Risk of hypoglycemia (RI, reduced po intake)
TZDs	Low risk of hypoglycemia	Slow onset, fluid retention C/I HF or hepatic dysfunction
DPP4-inhibitors	Low risk of hypoglycemia	
GLP-1 agonists	Low risk of hypoglycemia	GI effects
SGLT-2 inhibitors	Low risk of hypoglycemia	Limited data Increased risk GU infections Risk of dehydration, hypotension, euglycemic DKA

Insulin has been the mainstay for treatment of hyperglycemia in hospitalized patients

Stay tuned…data on oral agents is promising!

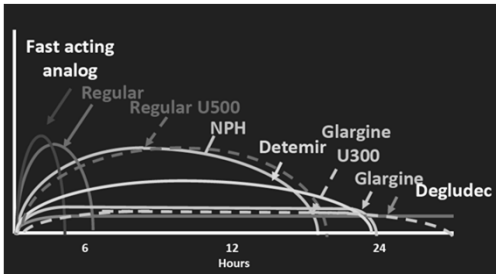
Modified from Lansang MC and Umpierrez GE. Inpatient hyperglycemia management: A practical review for primary medical and surgical teams. Cleve Clin J Med. 2016 May;83(5 Suppl 1):S34-43.

Armamentarium

It's all about the timing…

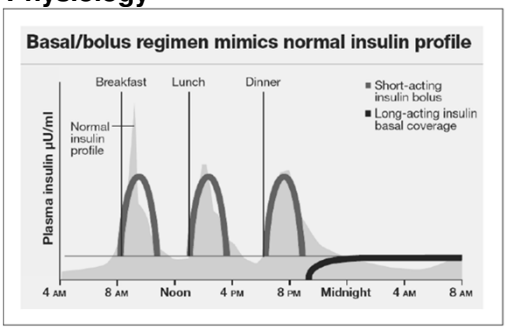
Type of Insulin	Name	Onset	Peak	Duration
Rapid Acting	Aspart (Novolog) Lispro (Humalog) Glulisine (Apidra)	5-15 min	1-2 h	4-6 h
Short Acting	Regular (Humulin R, Novolin R)	30-60 min	2-4 h	6-10 h
Intermediate Acting	NPH (Humulin N, Novolin N)	2-4 h	6-12 h	12-18 h
Long Acting	Glargine (Lantus, Basaglar) Determir (Levemir)	2-4 h	None	22-24 h 17-24 h
	Glargine (Toujeo) Degludec (Tresiba)	6 h 1h	none none	22-36 h 42 h
Pre-Mixed Insulin	NPH/regular (Humulin 70/30,Novolin 70/30)	30-60 min	2-12 h	12-18 h
	Lispro protamine/lispro (Humalog 75/25, Humalog 50/50)	5-15 min	1-2 h	12-18 h
	Aspart Protamine/Aspart (Novolog 70/30)	5-15 min	1-2 h	12-18 h

Timing is everything!



Reproduced with permission from McDonnell ME "Comparison of New Basal Versus Traditional Insulins" Endocrine Society 2016 Ancillary Symposia. April 1, 2016

Physiology



Magaji V and Johnson JM. Inpatient Management of Hyperglycemia and Diabetes. Clinical Diabetes 2011 (29): 3-9.

A Simple Approach

- Basal
- Prandial (Nutritional)
- Correctional

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Insulin is the recommended agent for glycemic control in hospitalized patient, but how?

- **IV insulin**
- **Sliding scale only**
- **Basal-bolus**
- **Basal only**

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When to use IV insulin…

- **Hyperglycemic crisis (DKA/HHS)**
- **Labor**
- **Critical illness**
- **Post transplantation**
- **Post cardiac surgery**

Flexibility with short half life (<15 min)

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What about SC insulin?

- **Basal-bolus**
- **Basal only**
- **Correctional only**

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Does Basal-Bolus work?

RABBIT-2: basal-bolus vs. sliding scale

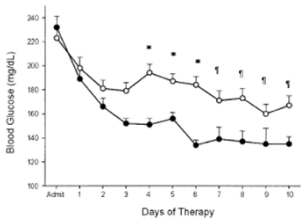

Figure 1—Changes in blood glucose concentrations in patients treated with glargine plus glulisine (●) and with SSI (○). *P < 0.01; ¶P < 0.05.

Multi-center, prospective RCT
Non-critically ill patients
Basal-bolus (n=104)
SS only (n=107)

Basal-bolus is a safe and effective means to achieve glycemic control

Umpierrez GE et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial) Diabetes Care. 2007 Sep;30(9):2181-6.

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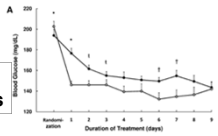
RABBIT-2 Surgery

Multicenter RCT surgical patients
Basal-bolus (n=104) vs. SS only (n=107)

Improved glycemic control
Improved perioperative outcomes



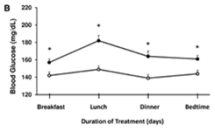


Table 2—Composite hospital complications and outcomes composite hospital complications

	All	SSI	Basal-bolus insulin	P value
Wound infections	14	11	3	0.050
Pneumonia	3	3	0	0.247
Acute respiratory failure	6	5	1	0.213
Acute renal failure	15	11	4	0.106
Bacteremia	3	2	1	0.999
Number of patients with complications	35	26	9	0.003
Mortality	2	1	1	NS
Postsurgery ICU admission (%)	16	19.6	12.5	NS
Length of stay (days)				
ICU	2.51 ± 1.90	3.19 ± 2.14	1.23 ± 0.60	0.003
Hospital	6.8 ± 8.9	6.3 ± 5.6	7.23 ± 11.39	NS

Umpierrez GE et al.. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diabetes Care. 2011 Feb;34(2):256-61.

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Estimating TDD

Home insulin regimen vs. weight-based approach

Weight-based~ 0.3-0.6 units/kg/day
Insulin-naïve: 0.3-0.5 units/kg/day
Elderly 0.3 units/kg/day

Maynard G et al. .Improved inpatient use of basal insulin, reduced hypoglycemia, and improved glycemic control: effect of structured subcutaneous insulin orders and an insulin management algorithm. J Hosp Med. 2009 Jan;4(1):3-15.

Schnipper JL et al.. Effects of a subcutaneous insulin protocol, clinical education, and computerized order set on the quality of inpatient management of hyperglycemia: results of a clinical trial. J Hosp Med. 2009 Jan;4(1):16-27.

Umpierrez GE et al.. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diabetes Care. 2011 Feb;34(2):256-61.

Factors to Consider when determining the TDD

- **For patients with known diabetes- what was control?**
- **Compliance**
  using long-acting to cover both basal and prandial needs is common
- **Risk factors for hypoglycemia**

  renal function
  elderly
  hepatic dysfunction
  pancreatic dysfunction

Maynard G et al. .Improved inpatient use of basal insulin, reduced hypoglycemia, and improved glycemic control: effect of structured subcutaneous insulin orders and an insulin management algorithm. J Hosp Med. 2009 Jan;4(1):3-15.

Schnipper JL et al. Effects of a subcutaneous insulin protocol, clinical education, and computerized order set on the quality of inpatient management of hyperglycemia: results of a clinical trial. J Hosp Med. 2009 Jan;4(1):16-27.

Estimating TDD

Remember this is a place to start…

Baseline weight-based TDD estimate	0.5 units/kg/day, adjust by factors listed below
Age > 70 years	**-0.1 units/kg/day**
Renal insufficiency (eGFR < 45)	**-0.1 units/kg/day**
Hepatic insufficiency (advanced cirrhosis)	**-0.1 units/kg/day**
Pancreatic deficiency (chronic pancreatitis, CF, s/p pancreatectomy)	**-0.1 units/kg/day**
HbA1c >10%	**+0.1 units/kg/day**
Currently on glucocorticoids with the equivalent of prednisone 40 mg/day or greater	**+0.1 units/kg/day**
FINAL TDD *estimate*	**=**

Breaking it up…

"The Split"

TDD
Basal (40-50 %)
Nutritional (50-60 %)

The "Sensitivity Factor" or "Correction Factor"

Correctional Insulin (sensitivity factor (SF)/correction factor (CF) used for sliding scale
Predicted effect 1 unit of insulin will have on glucose Calculated by "Rule of 1500 (1800)" based on predicted sensitivity 1500/TDD=CF Example TDD 50 units 1500/50=30; 1 unit of insulin will low BG by 30 mg/dL

Davidson PC et al. Analysis of guidelines for basal-bolus insulin dosing: basal insulin, correction factor, and carbohydrate-to-insulin ratio. Endocr Pract. 2008 Dec;14(9):1095-101

Correctional Insulin

"Low dose" (1:50 >151) for TDD < 40 units/day
"Moderate dose" (2:50 >151) for TDD 40-80 units/day
"High dose" (*custom*) for TDD > 81 units/day

Example Calculation

60 kg patient
Normal renal function

Step 1: Estimate TDD (0.5 units/kg x wt)
60 x 0.5= 30 units

Step 2: Determine "the split" (usually 50% basal, 50% prandial)
50% of 30 units= 15
15 units basal insulin
15 units total for prandial/3 (b/l/d)= 5 units AC

Step 3: Determine the "correction" (AKA sliding scale)
1500/TDD=CF
1500/30=50 (for every 1 unit of insulin, expect decrease by ~50 mg/dL)

Target Glucose Levels

Critically Ill Patient	Non-critically Ill Patient
< 180 mg/dL (< 10.0 mmol/L)	Pre-meal <140 mg/dL (< 7.8 mmol/L) Random < 180 mg/dL (< 10.0 mmol/L) •Higher glucose levels < 200 mg/dL (< 11.1 mmol/L) may be acceptable in some patients (terminally ill, multiple medical comorbidities)

Adjustments in Insulin Regimen

Assess glycemic control daily

- **If fasting above goal, adjust basal**
- **If pre-lunch above goal, adjust breakfast bolus**
- **If pre-dinner above goal, adjust lunch bolus**
- **If bedtime above goal, adjust dinner bolus**

- ***Strategy for adjustments***

Increase by 10% for glucose values 140-180 mg/dL (7.8-10.0 mmol/L)

Increase by 20% for glucose values over 180 mg/dL (> 10.0 mmol/L)

Decrease by 10% for glucose values 70-99 mg/dL (3.9-5.4 mmol/L)

Decrease by 20% for glucose values < 70 mg/dL (< 3.9 mmol/L)

Example
Fasting blood sugar is 250 mg/dL (13.9 mmol/L) so basal insulin should be increased by 20%

Umpierrez GE, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diabetes Care. 2011 Feb;34(2):256-61.

Tailor to Clinical Scenario

	Example insulin regimen
NPO	Basal insulin (long or intermediate acting insulin if basal requirement) Regular insulin correction scale q6h
Unreliable po intake	Basal insulin (long or intermediate acting insulin if basal requirement) RAI with dose reduction for decreased po intake and correction scale (or correction only)
Reliable po intake	Basal insulin (long or intermediate acting insulin if basal requirement) RAI with meals, correction scale with RAI to be given with nutritional dose
Parenteral nutrition	Basal insulin (long or intermediate acting insulin if basal requirement) Nutritional insulin given as regular insulin added to TPN bag
Enteral nutrition	Continuous EN: nutritional dose/4 given as regular insulin q6h ^ Cycled EN: NPH^ at onset (12h cycle), RAI or short acting insulin pending cycle length^. Bolus EN: RAI with bolus ^
Steroids	Basal insulin (long or intermediate acting insulin if basal requirement)-consider NPH RAI with "stacked doses" "NPH on top of" program

^ recommend using order set with safety " hold if TF/TPN held..."
"If TF/TPN interrupted patient will require frequent glucose monitoring and may require dextrose support for duration of pharmacologic activity of last SC insulin given"
If hypoglycemia, may give IV dextrose at rate of TF if needed to "ride out" insulin action

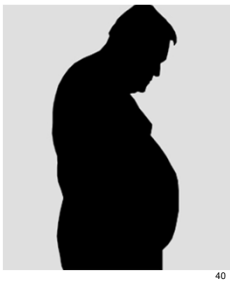
65-year-old male DM type 2 x 20 years admitted for GIB and is NPO

Outpatient Diabetes Regimen:

Glargine 80 units qHS
Lispro 20 units AC
Metformin 1000 mg BID
Sitagliptin 100 mg daily

Wt 120 kg
Cr 1.6 (baseline 1.0)
HbA1c 10.2%

Admits to compliance with oral agents but "sometimes forgets insulin"



Estimating TDD

Remember this is a place to start…

Wt 120 kg
Cr 1.6 (baseline 1.0)
HbA1c 10.2%

Baseline weight-based TDD estimate	0.5 units/kg/day, adjust by factors listed below
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Renal insufficiency (eGFR < 45)	**-0.1 units/kg/day**
Hepatic insufficiency (advanced cirrhosis)	**-0.1 units/kg/day**
Pancreatic deficiency (chronic pancreatitis, CF, s/p pancreatectomy)	**-0.1 units/kg/day**
HbA1c >10%	**+0.1 units/kg/day**
Currently on glucocorticoids with the equivalent of prednisone 40 mg/day or greater	**+0.1 units/kg/day**
FINAL TDD *estimate*	**= 0.5 units/kg/day**

Calculation

120 kg patient
Impaired renal function
HbA1c >10 %

Step 1: Estimate TDD (0.5 units/kg x wt)
120 x 0.5= 60 units

Step 2: Determine "the split" (usually 50% basal, 50% prandial)
50% of 60 units= 30
30 units basal insulin
NPO, no standing prandial insulin

Step 3: Determine the "correction" (AKA sliding scale)
1500/TDD=CF
1500/60=25 (for every 1 unit of insulin, expect decrease by ~25 mg/dL)

65-year-old male DM type 2 x 20 years admitted for GIB and is NPO

Wt 120 kg
Cr 1.4 (baseline 1.0)
HbA1c 10.2%

Started on Glargine 30 units qHS
Fasting next day is 225 mg/dL (12.5 mmol/L)
Remains NPO

What should you do next?

A. Increase basal by ~20% (36 units)

B. Continue current insulin

C. Decrease basal by ~10% (27 units)
as he will remain NPO

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65-year-old male DM type 2 x 20 years admitted for GIB and is NPO

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Cr 1.4 (baseline 1.0)
HbA1c 10.2%

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A. Increase basal by ~20% (36 units)

B. Continue current insulin

C. Decrease basal by ~10% (27 units)
as he will remain NPO

44

65-year-old male DM type 2 x 20 years admitted for GIB and is NPO

Wt 120 kg
Cr 1.4 (baseline 1.0)
HbA1c 10.2%

Glargine 44 units q HS
Fasting next day 120 mg/dL (6.7 mmol/L)
Diet ADAT, now ordered full carb consistent diet

What should you do next?

A. Continue current regimen

B. Increase basal insulin by 20%

A. Increase basal insulin by 10%

D. Continue current basal and correctional insulin
and begin prandial insulin

45

65 year old male DM type 2 x 20 years admitted for GIB and is NPO

Wt 120 kg
Cr 1.4 (baseline 1.0)
HbA1c 10.2%

Glargine 44 units q HS
Fasting next day 120 mg/dL (6.7 mmol/L)
Diet ADAT, now ordered full carb consistent diet

What should you do next?

A. Continue current regimen

B. Increase basal insulin by 20%

A. Increase basal insulin by 10%

D. Continue current basal and correctional insulin and begin prandial insulin

46

Calculation

Diet advanced, anticipate need for prandial insulin, may consider reduced dosed until eating reliably

- **120 kg patient**
- **impaired renal function**
- **HbA1c>10 %**

Step 1: Estimate TDD (0.5 units/kg x wt)
120 x 0.5= 60 units-~ 30 units basal -now titrated to 44 units

Step 2: Determine "the split" (usually 50% basal, 50% prandial)
50% of 60 units= 30
30 units basal insulin
NPO, no standing prandial insulin
10 units AC with weight-based, if using new basal 15 units AC
if worried about po intake may give 8-10 initially

Step 3: Determine the "correction" (AKA sliding scale)
1500/TDD=CF
1500/60=25 (for every 1 unit of insulin, expect decrease by ~25 mg/dL)

Helpful to have carb consistent diet for safety of insulin dosing

47

57-year-old female with DM type 2 and COPD presenting with SOB

Outpatient Diabetes Regimen:
Metformin 1000 mg BID
Sitagliptin 100 mg daily

Wt 66 kg
Cr 0.9
HbA1c 7.2%

Starting treatment for COPD exacerbation
BG >300 mg/dL (> 16.6 mmol/L)

What would you do next?

A . Continue home regimen

B. Start sliding scale insulin

C. Start basal-bolus insulin

BRIGHAM AND WOMEN'S HOSPITAL

57-year-old female with DM type 2 and COPD presenting with SOB

Outpatient Diabetes Regimen:
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What would you do next?

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BRIGHAM AND WOMEN'S HOSPITAL

Effect of Glucocorticoids on Glucose and Insulin

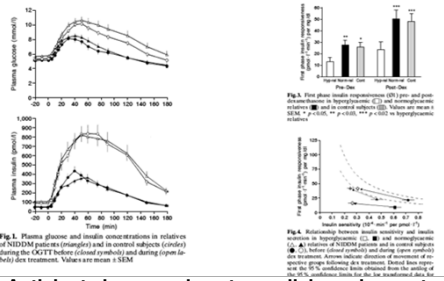


Fig. 1. Plasma glucose and insulin concentrations in relatives of NIDDM patients (*triangles*) and in control subjects (*circles*) during the OGTT before (*closed symbols*) and during (*open labels*) dex treatment. Values are mean ± SEM

Fig. 3. First phase insulin responsiveness (IR) pre- and post-dexamethasone in hyperglycaemic (□) and normoglycaemic relatives (■) and in control subjects (▨). Values are mean ± SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.02$ vs hyperglycaemic relatives

Fig. 4. Relationship between insulin sensitivity and insulin secretion in hyperglycaemic (○, ●) and normoglycaemic (△, ▲) relatives of NIDDM patients and in control subjects (□, ■) before (*open* and *closed symbols*) and during (*shaded symbols*) dex treatment. Arrows indicate direction of movement of respective groups following dex treatment. Dotted lines represent the 95 % confidence limits obtained from the ageing of the 95 % confidence limits for the log transformed data for

Anticipate increased post prandial requirements and glucose levels which worsen throughout the day

Henriksen JE etal. Risk and mechanism of dexamethasone-induced deterioration of glucose tolerance in non-diabetic first-degree relatives of NIDDM patients. Diabetologia. 1997 Dec;40(12):1439-48.

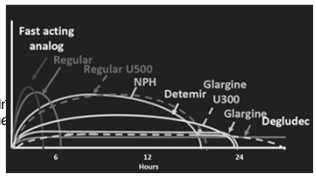
BRIGHAM AND WOMEN'S HOSPITAL

Steroid-induced Hyperglycemia

No consensus
Expert opinion using NPH to mimic anticipated rise

- NPH as basal
- NPH "on top of "regimen
- "stacked" prandial dosing

*Administered in AM at time of predr
Glargine preferred if dexamethasone



BRIGHAM AND WOMEN'S HOSPITAL

Steroid-induced Hyperglycemia

Table 3
Suggested Dosages of NPH Insulin for Tapering Dosages of Glucocorticoids

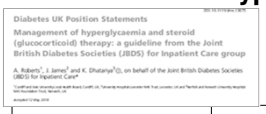
Prednisone dosage (mg/d)	Insulin dosage (U/kg)
≥40	0.4
30	0.3
20	0.2
10	0.1

*Administered in AM at time of prednisone administration
Glargine preferred if dexamethasone used or prednisone given twice a day

Clore JN and Thurby-Hay LGlucocorticoid-induced hyperglycemia. Endocr Pract. 2009 Jul-Aug;15(5):469-74.

BRIGHAM AND WOMEN'S HOSPITAL

Steroid-induced Hyperglycemia



Diabetes UK Position Statements
Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care group

Stress Hyperglycemia	Consider SU or basal insulin (in AM)
DM type 2 (not on insulin)	SU ± basal insulin (given in AM)
DM type 2 (on insulin)	Basal insulin: (consider switch to AM and increase dose) Premixed insulin: increase morning dose MDI: increase lunch and dinner RAI
DM type 1	Increase basal, increase lunch and dinner RAI

*Ad
Gla

Joint British Diabetes Societies (JBDS) for Inpatient Care. Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care group. Diabet Med. 2018 Aug;35(8):1011-1017.

BRIGHAM AND WOMEN'S HOSPITAL

Estimating TDD

Remember this is a place to start…

Wt 66 kg
Cr 0.9
HbA1c 7.2%

Baseline weight-based TDD estimate	0.5 units/kg/day, adjust by factors listed below
Age > 70 years	**-0.1 units/kg/day**
Renal insufficiency (eGFR < 45)	**-0.1 units/kg/day**
Hepatic insufficiency (advanced cirrhosis)	**-0.1 units/kg/day**
Pancreatic deficiency (chronic pancreatitis, CF, s/p pancreatectomy)	**-0.1 units/kg/day**
HbA1c >10%	**+0.1 units/kg/day**
Currently on glucocorticoids with the equivalent of prednisone 40 mg/day or greater	**+0.1 units/kg/day**
FINAL TDD *estimate*	**= 0.6 unit/kg/day**

Calculation

- **66 kg patient**
- **normal renal function**
- **HbA1c 7.2%**

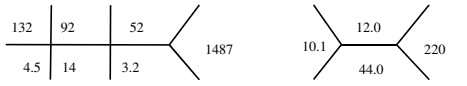
May use 50/50 or consider 40/60 split, using NPH and/or "stacked RAI" with steroids. Anticipate decreased requirements as steroids tapered

Step 1: Estimate TDD (0.6 units/kg x wt)
66 x 0.6= 40 units

Step 2: Determine "the split" (usually 50% basal, 50% prandial)
50% of 40 units= 20 units
20 units basal insulin (if using NPH can split 10/10 or 13/7)
20 units prandial insulin
20/3=6 units RAI AC (another strategy 4/5/6)

Step 3: Determine the "correction" (AKA sliding scale)
1500/TDD=CF
1500/40=38 (for every 1 unit of insulin, expect decrease by ~40 mg/dL)

32-year-old male no known past medical history presenting with fatigue and lethargy



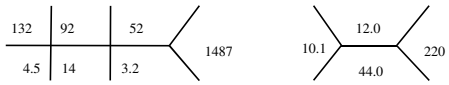
Mg 2.0 Phos 0.9
Arterial pH: 7.29
Urine ketones +2
Serum ketones: moderate
Anion gap: 26

What is most appropriate next step in management?

A. Start sliding scale insulin
B. Start basal bolus insulin regimen
C. Transfer to the unit for insulin infusion
D. Start SC insulin q2h

*

32-year-old male no known past medical history presenting with fatigue and lethargy



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A. Start sliding scale insulin
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D. Start SC insulin q2h

*

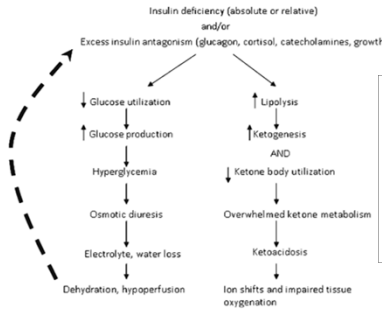
Criteria for Hyperglycemic Crisis

DKA
- **D: blood glucose >250 mg/dL (13.9 mmol/L)**
- **K: ketonemia (ketonuria)**
- **A: metabolic acidosis with pH < 7.3 OR Serum bicarbonate < 18 mEq/L**

HHS
- **Blood glucose > 600 mg/dL (> 33.0 mmol/L)**
- **Arterial pH > 7.30**
- **Bicarbonate > 18 mEq/L**
- **EFFECTIVE serum osm > 320 mOsm/kg**
- **Mild ketonuria or ketonemia may be present**

Effective osm= 2 [NA^+] + BG/18

Treatment



- **IVF**
- **Electrolyte Repletion**
- **Insulin**

Steenkamp DW et al. Adult hyperglycemic crisis: a review and perspective. Curr Diab Rep. 2013 Feb;13(1):130-7.

Management of DKA/HHS: *Fluids*

Hypovolemia: 0.5-1 L NS bolus with maintenance fluid rate dosed based on physiologic parameters and repletion of intravascular and extravascular volume

Maintenance and selection of fluids:
- **Hypernatremia (corrected Na^+ >135): consider change to D51/2 NS at 150-250 cc/hr**
- **Hypokalemia: replacement with IVF/ K^+**
- **Hyperchloremia and Hypobicarbonemia: consider changing to LR**
- **Hypoglycemia prevention: BG < 250 mg/dL, change IVF to D51/2 NS at 150-250 cc/hr**

BWH Hyperglycemic Crisis Guideline

Management of DKA/HHS: *Electrolytes*

If K^+ if < 3.3 mEq/L: hold insulin and replete K^+

If K^+ is 3.3- 5.3 mEq/L: give 20-30 mEq in each liter of IVF

If K^+ >5.3 mEq/L: do not give additional K^+, repeat K^+ 2 hours

Potassium Repletion: for initial KCL administration see table below. Monitor K+ q 4-6 h. For maintenance dosing See EPIC Order for K+ replacement scale.

Serum K+ (mEq/L)	Peripheral or Enteral	Central
>5 or/ urine output < 0.5 cc/kg/hr	None	None
4-5	10 mEq IV x 2 doses OR 20 mEq enterally	20 mEq IV
3-4	10 mEq IV x 4 doses OR 40 mEq enterally	20 mEq IV x 2 doses
<3	10 mEq IV x 6 doses OR 40 mEq enterally then 20 mEq 2hr after	20 mEq IV x 3 doses

Severe Hypophosphatemia < 1 mg/dL

Indications for bicarbonate is controversial, no prospective randomized trials, often not considered unless pH<6.9

Management of DKA/HHS: *Insulin*

K^+ > 3.3 mEq/L

IV regular insulin infusion bolus 0.1 units/kg followed by 0.1 units/kg/hr

	Intravenous Insulin * Please Note: All insulin regular continuous infusion orders must be entered in EPIC with the dose in units/hr for smart pump compatibility
Initial Dose	0.1 units/kg up to 10 units IV bolus
Initial Rate	0.1 unit/kg/hr Max 7 units/hr for patients with a new diagnosis of DM and no clinical suspicion of insulin resistance Max 10 units/hr for all other patients
If BG ↓ by < 50 mg/dl per hr	Repeat 0.1 units/kg bolus then resume infusion at 0.1 unit/kg/hr If BG fails to drop after 2nd bolus, check integrity of line and increase rate to 0.14 units/kg/hr
If BG ↓ by > 100 mg/dl per hr	Decrease rate to 0.05 unit/kg/hr
DKA: Blood glucose <250 mg/dl	0.05 units/kg/h until anion gap has closed (<12)
HHS: Blood glucose 250-300 mg/dl	0.05 units/kg/h until effective osmolality ≤ 315 mOsm/kg

*Subcutaneous long-acting insulin glargine can be simultaneously administered once hydration is adequate at a dose of 0.25 units/kg/day (normal renal function) or 0.15 units/kg/day (impaired renal function) to improve transition to subcutaneous regimen

Hyperglycemic Crisis: Classification of Patients

	Mild DKA	Moderate DKA	Severe DKA	HHS
Blood glucose (mg/dL)	>250	>250	>250	>600
pH	< 7.30	7.12-7.24	< 7.15	>7.30
HCO_3	15-18	10 to < 15	< 10	>18
Urine/Serum Ketones	+	+	+	+/-
Serum Osm (Osm_{eff})				>320
AG	elevated	elevated	elevated	variable
Mental Status	alert	alert/drowsy	stupor/coma	stupor/coma

Modified from Kitabchi et al. Diabetes Care 2009 32(7):1335-1343

Hyperglycemic Crisis Patient Triage

Classification	Mild DKA	Moderate DKA	Severe DKA	HHS	DKA/HHS Overlap Syndrome
Insulin	May consider SC	IV	IV	IV	IV
Level of Care	Intermediate Unit	Intermediate* /ICU	ICU	ICU	ICU

May consider SC insulin for mild/moderate uncomplicated DKA with treatment in intermediate unit with capability for q 2h FS q 4h labs

Subcutaneous Rapid Acting Insulin for DKA

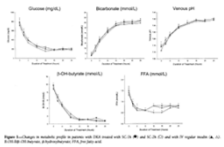
<u>SC- 1h</u>
Initial 0.3 units/kg
followed by 0.1 unit/kg q1h

<u>SC-2h</u>
Initial 0.3 units/kg
followed by 0.2 unit/kg q2h

Table 3—*Response to medical treatment*

	SC-1h	SC-2h	Regular IV insulin
n	15	15	15
Length of hospital stay (days)	3.4 ± 3	3.9 ± 5	4.5 ± 3
Duration of therapy until glucose <13.8 mmol/l (h)	6.9 ± 4	6.1 ± 4	7.1 ± 5
Duration of therapy until resolution of DKA (h)	10 ± 3	10.7 ± 3	11 ± 3
Amount of insulin until glucose <13.8 mmol/l (units)	67 ± 37	65 ± 26	62 ± 28
Amount of insulin until resolution of DKA (units)	85 ± 33	94 ± 32	82 ± 28
Episodes of hypoglycemia	1	1	1

re means ± SD.



Our practice:
SC-2h for mild uncomplicated DKA

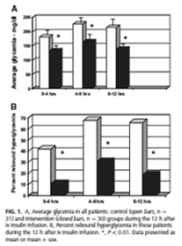
Umpierrez GE et al. Diabetes Care. 2004 Aug;27(8):1873-8.

Example Protocol for Use of Subcutaneous Insulin Protocol in Treatment of Mild Uncomplicated DKA

	Subcutaneous Insulin Aspart	Subcutaneous Insulin Glargine
Initial Dose	0.3 units/kg maximum 20 units	0.25 units/kg if GFR >40; 0.15 units/kg if GFR <40
Subsequent Dose	0.2 units/kg every 2 hours maximum 10 units	Redose in 24 hours based on response to initial dose
Blood glucose <250 mg/dl	0.05-0.1 units/kg every 2 hours	

Consideration for *Early Basal Therapy*

Initiation of long-acting insulin (0.25 units/kg) within 12h of insulin infusion decreased rate of rebound hyperglycemia (n=61, p<0.001)



Our practice

If eGFR >45: 0.25 unit/kg
If eGFR <45: 0.15 unit/kg

Hsia E et al. J Clin Endocrinol Metab. 2012 Sep;97(9):3132-7.

When to transition?... and how?

When AG closed and bicarbonate > 17-18 *(ish)*

At time of transition overlap and higher weight-based dose

Next day, need to redose

Transition from IV to SC
DON'T FORGET TO OVERLAP WITH BASAL
and remember timing is everything….

Rubin DJ et al. Weight-based, insulin dose-related hypoglycemia in hospitalized patients with diabetes. Diabetes Care. 2011 Aug;34(8):1723-8.
Steenkamp DW et al. Adult hyperglycemic crisis: a review and perspective. Curr Diab Rep. 2013 Feb;13(1):130-7.

Treatment

- **Hyperosmolality: how to correct safely?**

No RCT for rate of correction, but expert opinion is to avoid lowering effective osm by more than 3 mOsm/hr

Don't forget to correct the sodium for glucose

Correction yields a *very predictable* improvement in mental status. If you don't see this... look for another cause (?LP, toxic ingestion, etc.)

Pitfalls

- **Misdiagnosis**
- **Hyperglycemic crisis not yet adequately resolved**
- **Inadequate overlap of subcutaneous insulin with IV insulin**
- **Inadequate dosing of subcutaneous insulin**
- **Initial insulin program does not take into account expected nutritional plan**
- **Don't forget about etiology and co-existing illness**

What we know works …

- **Standardized Order sets (scheduled insulin and timing of FSBG) shown to improve glycemic control**
- **IV insulin protocols**

Maynard G, Lee J, Phillips G, Fink E, Renvall M.Improved inpatient use of basal insulin, reduced hypoglycemia, and improved glycemic control: effect of structured subcutaneous insulin orders and an insulin management algorithm. J Hosp Med. 2009 Jan;4(1):3-15.

Schnipper JL, Ndumele CD, Liang CL, Pendergrass ML. Effects of a subcutaneous insulin protocol, clinical education, and computerized order set on the quality of inpatient management of hyperglycemia: results of a clinical trial. J Hosp Med. 2009 Jan;4(1):16-27.

Transition of Care Planning

Discharge Treatment

A1c <8%*	**A1c 8%-10%***	**A1c >10%***
Re-start out-patient treatment regimen (OAD and/or insulin)	Re-start out-patient oral agents and D/C on once daily basal at 50% of hospital dose	D/C on basal-bolus at same hospital dose Alternative: re-start oral agents and D/C on once daily basal at 80% of hospital dose

***Use admission HbA1c to adjust therapy at discharge**

Umpierrez GE, discharge algorithm based on admission HbA1c for the management of patients with type 2 diabetes. Diabetes Care. 2014 Nov;37(11):2934-9.

Transition of Care Checklist

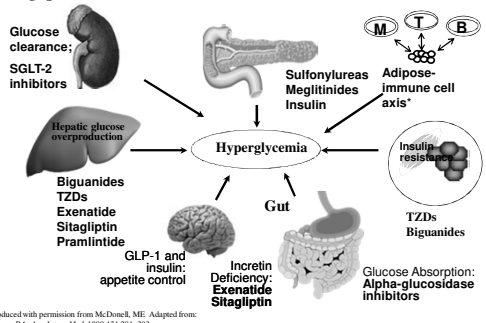
- ❑ **Diabetes Education ("survival skills")**
- ❑ **Insulin Teaching (*if applicable, should include pen and vial/syringe*)**
- ❑ **Glucometer Teaching**

Confirm patient has diabetes supplies:

- ❑ **Medications*** **(if using insulin vial-syringe; if insulin pen-pen needles)**
- ❑ **Test strips** **(must match glucometer)**
- ❑ **Lancets**
- ❑ **Clear communication with patient regarding discharge regimen***
- ❑ **Follow-up appointment scheduled**
- ❑ **PCP aware of any dose adjustments**

**Medications and supplies will vary depending of insurance coverage- often human insulin cheaper than analogs; helpful to know coverage for pen vs. vial/syringe prior to discharge*

Type 2 Diabetes in 2021



Reproduced with permission from McDonell, ME Adapted from:
DeFronzo RA. *Ann Intern Med*. 1999;131:281–303.
Buse JB, et al. In: *Williams Textbook of Endocrinology*. 10th ed. Philadelphia: Saunders; 2003:1427–1483.
Defuria, et al. Proc Natl Acad Sci. 2013

Advances In Diabetes Therapies: Implications in Hospital Medicine

- **Medications that may require dose adjustment following hospitalization**
- **SGLT-2 Inhibitors and risk of euglycemic DKA**
- **Newer and concentrated insulins**
- **Diabetes Technology (CSII and CGM)**

Metformin and Risk of Acidosis

Table 3.

Association of Time-Dependent Metformin Use With Acidosis Hospitalization by Time-Dependent Estimated Glomerular Filtration Rate (eGFR) Category in Geisinger Health System

Parameter	HR[a] (95% CI) for Acidosis Associated With Metformin Use by Time-Dependent eGFR Category, mL/min/1.73 m[2]				
	Overall[b]	≥90	60-89	45-59	30-44	<30
Person-time (on metformin/off metformin)	188 578/281 536	80 653/98 905	79 788/102 110	21 232/40 861	6358/29 834	548/9827
Acidosis events (on metformin/off metformin)	737/1598	206/323	288/446	157/286	64/314	22/229
Unadjusted (n = 75 413)	0.89 (0.81-0.97)	0.77 (0.65-0.92)	0.82 (0.71-0.95)	1.05 (0.87-1.26)	0.95 (0.73-1.25)	1.71 (1.10-2.64)
Demographic adjusted[c] (n = 75 413)	0.89 (0.81-0.97)	0.75 (0.63-0.90)	0.82 (0.71-0.96)	1.07 (0.88-1.30)	0.98 (0.75-1.28)	1.76 (1.14-2.73)
Fully adjusted[d] (n = 72 232)	0.98 (0.89-1.08)	0.88 (0.73-1.05)	0.87 (0.75-1.02)	1.16 (0.95-1.41)	1.09 (0.83-1.44)	2.07 (1.33-3.22)
Fully adjusted with time-dependent medication use[e] (n = 72 232)	0.94 (0.83-1.05)	0.80 (0.66-0.97)	0.81 (0.68-0.95)	1.14 (0.93-1.40)	1.13 (0.85-1.49)	2.21 (1.42-3.44)
Sensitivity analyses						
Fully adjusted[d] excluding baseline insulin users (n = 60 112)	1.02 (0.91-1.13)	0.88 (0.71-1.09)	0.89 (0.75-1.06)	1.21 (0.97-1.50)	1.16 (0.87-1.57)	2.22 (1.41-3.51)
Fully adjusted[d] including adjustment for baseline hemoglobin A_{1c} (n = 58 093)	1.01 (0.90-1.14)	0.84 (0.67-1.04)	0.93 (0.78-1.12)	1.23 (0.98-1.55)	1.07 (0.78-1.46)	2.22 (1.37-3.59)
Fully adjusted[d] in incident diabetes mellitus cohort (n = 49 839)	0.91 (0.79-1.04)	0.85 (0.68-1.06)	0.82 (0.66-1.01)	1.15 (0.86-1.53)	0.88 (0.55-1.39)	2.37 (1.20-4.71)
Fully adjusted[d] with early censoring of metformin (n = 72 232)	1.04 (0.95-1.15)	0.93 (0.78-1.12)	0.93 (0.80-1.09)	1.23 (1.01-1.50)	1.17 (0.89-1.54)	2.26 (1.45-3.51)

Increased risk at eGFR <30

Lazarus B1,2, Wu A1, Shin et al. Association of Metformin Use With Risk of Lactic Acidosis Across the Range of Kidney Function: A Community-Based Cohort Study. JAMA Intern Med. 2018 Jul 1;178(7):903-910.

Dose Adjustments Based on Renal Function:

Sitagliptin
Saxagliptin

GFR (ml/min)	≥ 50	30-49	<30
Sitagliptin	100 mg	50 mg	25 mg
Saxagliptin	5 mg	2.5 mg	2.5 mg
Linagliptin	5 mg	5 mg	5 mg

SGLT-2 Inhibitors and Risk of Euglycemic DKA

Table 1—Clinical characteristics of euDKA cases

Case patient	1	2	3	4	5	6	7	8	9
Age (years)	40	58	27	28	31	55	26	39	64
Sex	Female	Male	Female	Female	Female	Female	Female	Female	Female
T1/T2	T1	T2	T1	T1	T1	T1	T1	T1	T2
MDI/CSII	MDI	N/A	MDI	CSII	CSII	CSII	CSII	CSII	N/A
Duration (years)	17	2	25	6	15	18	13	26	6
BMI (kg/m²)	26.5	26.5	24.3	25.9	33.2	22.0	22.0	26.1	32.8
Prior A1C [% (mmol/mol)]	11.4 (101.3)	9.8 (83.6)	7.9 (63.7)	8.0 (63.9)	7.0 (53.0)	7.2 (55.2)	6.6 (48.6)	7.9 (63.0)	7.8 (62.0)
Canagliflozin dose (mg)	300	300	300	300	300	300	150	300	300
Potential contributors	U/R	Surgery 1 week prior	U/R, alcohol	Alcohol	Alcohol	Exercise, alcohol	Exercise	GI	None	U/R	Surgery 12 h prior
Insulin dose reduction just prior to euDKA	Yes	N/A	Yes	No	Yes	Yes	Yes	Unknown	No	N/A	No	Yes	N/A
Presenting plasma glucose (mg/dL [mmol/L])	220 (12.2)	150 (8.3)	150 (8.3)	96 (5.3)	224 (12.4)	158 (8.8)	~125 (~6.9)	209 (11.3)	190 (10.6)	150 (8.3)	233 (12.9)	169 (9.4)
									140			
									140			
P_{CO_2} (mmHg)	10								26			
Bicarbonate (mEq/L)	6	10	6	11	18		15	9		9	13 and then 5
Anion gap (mEq/L)	25	17	35	22	18		26	21		24	16 and then 19
Ketones*	Yes (serum and urine)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (serum and urine)
Where treated	ICU	ICU	ICU	Outpt.	ICU	Inpt.	Outpt.	ICU	ICU	Outpt.	Outpt.	ICU	ICU

CSII, continuous subcutaneous insulin infusion; GI, gastrointestinal; Inpt., inpatient; N/A, not available; Outpt., outpatient. *Urine ketones were strongly positive in all cases.

Cases noted in the perioperative period and acute illness/fluctuating volume status
Insulin deficient patients appear to be at greatest risk

Peters AL et al. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. Diabetes Care. 2015 Sep;38(9):1687-93.

Newer and Concentrated Insulins

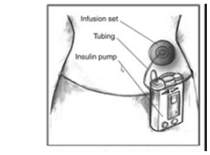
U-500 Transition of Care Planning is critical

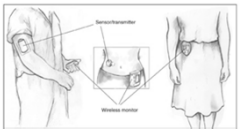
Table 1: Examples of prescribed doses of HUMULIN R U-500 converted to amount of HUMULIN R U-500 to draw up in a U-100 insulin syringe or a tuberculin syringe for delivery of HUMULIN R U-500 using these devices

HUMULIN R U-500 dose prescribed (units of insulin)	Delivery Using a U-100 insulin syringe Amount of HUMULIN R U-500 to draw up in the syringe in "unit marking"	Delivery Using a Tuberculin syringe Amount of HUMULIN R U-500 to draw up in the syringe in "volume marking"
	Conversion: Divide prescribed dose by 5	Conversion: Divide prescribed dose by 500
25 Units	Draw to the 5 unit mark on syringe	Draw to the 0.05 mL mark on syringe
50 Units	Draw to the 10 unit mark on syringe	Draw to the 0.1 mL mark on syringe
75 Units	Draw to the 15 unit mark on syringe	Draw to the 0.15 mL mark on syringe
100 Units	Draw to the 20 unit mark on syringe	Draw to the 0.2 mL mark on syringe
125 Units	Draw to the 25 unit mark on syringe	Draw to the 0.25 mL mark on syringe
150 Units	Draw to the 30 unit mark on syringe	Draw to the 0.3 mL mark on syringe
175 Units	Draw to the 35 unit mark on syringe	Draw to the 0.35 mL mark on syringe
200 Units	Draw to the 40 unit mark on syringe	Draw to the 0.4 mL mark on syringe
225 Units	Draw to the 45 unit mark on syringe	Draw to the 0.45 mL mark on syringe
250 Units	Draw to the 50 unit mark on syringe	Draw to the 0.5 mL mark on syringe
...	...	...
500 Units	Draw to the 100 unit mark on syringe	Draw to the 1.0 mL mark on syringe

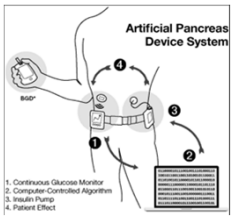
Package Insert
http://uspl.lilly.com/humulinru500/humulinru500.html

Diabetes Technology





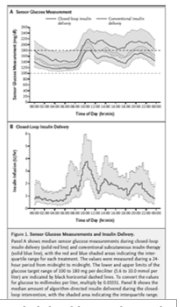
"Auto mode" vs. "manual mode" with hybrid closed loop insulin pump in acute care setting…



Closed Loop Insulin Delivery in the Acute Care Setting

Table 2. Primary and Secondary Outcomes.*

Outcome	Closed-Loop Group (N = 70)	Control Group (N = 66)	P Value
Time spent in sensor glucose measurement — %			
Within target range of 100 to 180 mg/dl: primary end point	65.8±16.8	41.5±16.9	<0.001
Mean <180 mg/dl	23.6±16.6	49.5±22.8	<0.001
Mean >360 mg/dl	1.2±4.8	2.6±7.0	0.18
Mean <100 mg/dl	10.6±6.7	9.0±13.2	0.37
Median <70 mg/dl (IQR)	0.5 (0.0–1.1)	0.0 (0.0–1.8)	0.13
Median <54 mg/dl (IQR)	0.0 (0.0–0.1)	0.0 (0.0–0.0)	0.80
Median <50 mg/dl (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.79
Glucose — mg/dl	154±29	188±43	<0.001
SD of glucose — mg/dl†	46±19	59±19	<0.001
Coefficient of variation in glucose level — %	29.4±6.4	31.5±8.3	0.13
Between-day coefficient of variation in glucose level — %	15.6±8.0	21.7±12.2	0.001
Median AUC per day for glucose level (IQR)‡			
<63 mg/dl	7.0 (0.0–298.7)	0.0 (0.0–305.7)	0.28
<54 mg/dl	0.0 (0.0–17.1)	0.0 (0.0–0.0)	0.63
Median total daily insulin dose (IQR) — U	44.4 (27.2–70.6)	40.2 (26.5–65.5)	0.50
Capillary glucose values — mg/dl§			
Before breakfast (5 to 8 a.m.)	134±32	156±58	0.009
Before lunch (11 a.m. to 1 p.m.)	171±49	227±63	<0.001
Before dinner (4 to 7 p.m.)	161±44	195±59	0.002
Before bedtime (9 p.m. to midnight)	170±54	218±81	<0.001
No. of events with capillary glucose <63 mg/dl¶	3	9	0.09



Improvement in glycemic control without increased risk of hypoglycemia

Bally L, et al. Closed-Loop Insulin Delivery for Glycemic Control in Noncritical Care NEJM 2018 Aug 9;379(6):547-556.

Hyperglycemia in the setting of COVID-19

What we've learned so far…

- **Hyperglycemia in patients with and without a history of diabetes is associated with increased mortality**
- **Glucose *on admission* is an independent predictor of severe prognosis**
- **Glycemic control matters!**
- ***Duration* of Hyperglycemia is important; window of opportunity to impact outcomes (days 2-3)**
- **Hyperglycemic Crisis in the setting of SARS-CoV-2 infection is common and is also associated with poor outcomes**

Bode B et al. J Diabetes Sci Technol. 2020 Jul;14(4):813-821
Coppelli A et al. Diabetes Care 2020;43:2545–2548
Klonoff DC et al. Diabetes Care. 2021 Feb;44(2):578-585

Pal R et al Diabetes Metab Syndr. Nov-Dec 2020;14(6):1563-1569.
Song S et al. Front Endocrinol. 2021 Mar 30;12:645529
Zhu L et al. Cell Metab. 2020 Jun 2;31(6):1068-1077

Challenges in Achieving Glycemic Control with COVID-19

- **Variability in insulin sensitivity over course of illness (*daily* and in some patients *hourly)***
- **Patients with pre-existing CKD or AKI in the setting of SARS-CoV-2 are at increased risk of hypoglycemia**
- **Significant variability in both SC and IV insulin requirements independent of therapy with glucocorticoids and vasopressors**

Stand of care for critically ill patients is IV insulin which requires frequent monitoring and adjustments (q1-2h)

As an alternative approach may consider SC insulin (q4h) to reduce time at bedside and preserve PPE

Korytkowski M et al. J Clin Endocrinol Metab. 2020 Jun 4

Example Subcutaneous Insulin Algorithm for Critically Ill Patients with COVID-19

Low dose strategy: Starts at total daily insulin dose between 0.4 – 0.6 units/kg/day

Patient characteristic	Glargine (Lantus) *	NPH	Aspart fixed dose	Aspart scale q 4h
Prior Diabetes	0.25 units/kg/dose q 24h OR	0.12 units/kg/dose q 12h		Low
No known Diabetes	0.2 units/kg/dose q 24h OR	0.1 units/kg/dose q 12h		Low
High dose steroids[¶] or continuous nutrition support		0.15 units/kg/dose q 12h	0.05 units/kg/dose scheduled q 4h	Low

Medium dose strategy: Starts at total daily insulin dose = 0.6 - 1.4 units/kg/day

Patient characteristic	Glargine (Lantus)	NPH	Aspart fixed dose	Aspart scale q 4h
Prior Diabetes	0.3 units/kg/dose q 24h OR	0.15 units/kg/dose q 12h	0.1 units/kg/dose scheduled q 4h	Moderate
No known diabetes	0.25 units/kg/dose q 24h OR	0.1 units/kg/dose q 12h	0.05 units/kg/dose schedules q 4h	Moderate
High dose steroids[¶] or Continuous nutrition support		0.25 units/kg/dose q 12h	0.15 units/kg/dose scheduled q 4h	Moderate

Recommend start at Low dose strategy for all patients EXCEPT patient on > 0.5 unit/kg/day TDD start Medium dose strategy

BWH COVID-19 Protocol 2020
https://covidprotocols.org/protocols/endocrine/

Example Subcutaneous Insulin Algorithm for Critically Ill Patients with COVID-19

High dose strategy A. Starts at total daily insulin dose = 1.5 to 1.95 units/kg/day. NOTE: Before moving to High Dose, INJECT INTO NEW subcutaneous injection site. Abdomen (anterior or side) and upper buttock are preferred for best subcutaneous absorption

Patient characteristic	Glargine (Lantus)	NPH	Aspart fixed dose	Aspart Scale q 4h
Prior Diabetes	0.5 units/kg/dose q 24h OR	0.25 units/kg/dose q 12h	0.15 units/kg/dose scheduled q 4h	**Custom
No known diabetes	0.3 units/kg/dose q 24h OR	0.15 units/kg/dose q 12h	0.1 units/kg/dose schedules q 4h	**Custom
High dose steroids[¶] or Continuous nutrition support		0.25 units/kg/dose q 8h	0.2 units/kg/dose scheduled q 4h	**Custom

High dose strategy B. Starts at total daily Insulin dose = 2.1-3 units/kg/day NOTE: This requires inpatient diabetes consultation. Please page Unit based Pharmacist, Endocrinology [11519] or DMS [34444] for starting IV hourly dose. If target glucose not achieved after 36 hours on step 2, consider continuous IV insulin protocol provider adjusted with modified targets and frequency of glucose monitoring.

Patient characteristic	Glargine (Lantus)	NPH	Aspart fixed dose	Aspart Scale q 4h
Prior Diabetes		0.3 units/kg/dose q 8h	0.2 units/kg/dose scheduled q 4h	**Custom
No known diabetes		0.3 units/kg/dose q 8h	0.2 units/kg/dose schedules q 4h	**Custom
High dose steroids[¶] or Continuous nutrition support		0.4 units/kg/dose q 8h	0.3 units/kg/dose scheduled q 4h	**Custom

*Glargine is preferred for patients at higher risk of hypoglycemia: GFR <30, Age >75, advanced cirrhosis

¶High dose steroids: equivalent of >40 mg prednisone, >100 mg hydrocortisone or >6 mg dexamethasone per day

BWH COVID-19 Protocol 2020
https://covidprotocols.org/protocols/endocrine/

COVID-19 Subcutaneous DKA Protocol

Insulin Therapy:
Administer both long acting insulin (glargine) dosed every 24 hours and rapid acting insulin (aspart), which should be dosed q4 hours

	Subcutaneous rapid acting insulin (aspart) q4 hours	Subcutaneous long acting insulin (glargine) q24 hours
Initial dose	0.3 units/kg/dose Maximum of 20 units	If eGFR >40: 0.25 units/kg/dose If eGFR <40: 0.15 units/kg/dose
Subsequent dose	0.2 units/kg every 4 h Maximum of 20 units	Re-dose glargine in 24 h based on response to initial dose
Blood glucose < 250 mg/dL	0.05-0.1 units/kg every 4 h and start IV Dextrose containing fluid	Re-dose glargine q 24h based on response to subsequent dose

DKA Monitoring and Transition Recommendations:
Patients will need q4-6h chemistry monitoring (BMP) and electrolyte repletion as above. When AG < 12 and bicarbonate > 18 mEq/L, transition to non-DKA subcutaneous regimen. Dextrose may be tapered to off. Please see NON-DKA HYPERGLYCEMIA guide above or pocket card reference guide. For patients who are not critically ill and/or eating meals: Please refer to the BWH Management of Diabetes and Hyperglycemia in non-ICU patients **guideline**.

BWH COVID-19 Protocol 2020
https://covidprotocols.org/protocols/endocrine/

Future of Inpatient Glucose Management

- **More OADs?**
- **Computer algorithms?**
- **CGM?**
- **Closed loop systems?**
- **Change in glycemic targets?**

Stay tuned for updated guidelines …

55-year-old male with HTN, hyperlipidemia presenting with chest pain admitted for NSTEMI

He has no prior history of IFG/IGT

- **serum glucose on admission 225 mg/dL (12.5 mmol/L)**
- **fasting glucose next day 200 mg/dL (11.1 mmol/L)**

Is this important?
What is the role for monitoring? treating?

Additional Slides for Reference
Hyperglycemia and COVID-19

PISA COVID Study

Retrospective study, Pisa, Italy (n=271)
Patients hospitalized with COVID-19
21% prior diagnosis of DM
Primary endpoints: in-hospital mortality, MV, ICU and ARDS

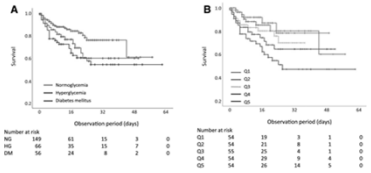


Figure 1—A: Kaplan-Meier analysis showing survival during hospitalization in COVID-19 patients. B: Kaplan-Meier analysis showing survival during hospitalization in COVID-19 patients stratified by quintiles of at-admission plasma glucose levels.

Glucose on admission is an independent predictor of severe prognosis

Coppelli A et al Diabetes Care 2020;43:2345–2348

Benefits of Glycemic Control in Hospitalized Patients with COVID-19

Retrospective Observational Study in patients with COVID-19 with and without DM (n=1122, 88 US hospitals)

Compared those with DM and/or uncontrolled hyperglycemia (n=451) to patients without DM or hyperglycemia (n=671)

- **DM HbA1c ≥ 6.5%**
- **Uncontrolled hyperglycemia ≥ 2 BG > 180 mg/dL within 24h**
- **Mortality rate 28.8% in DM or uncontrolled hyperglycemia patients vs. 6.2% (p< 0.01)**
- **Longer LOS (5.7 vs. 4.3 days, p<0.01)**

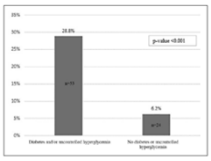
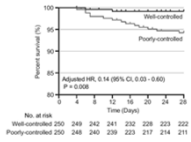


Figure 3. Mortality rates among patients who were discharged or died comparing diabetes and/or uncontrolled hyperglycemia (n = 184) with patients without diabetes or hyperglycemia (n = 386).

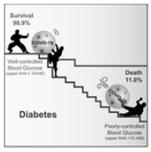
Bode B et al. J Diabetes Sci Technol. 2020 Jul;14(4):813-821

In Hospital Glycemic Control Matters



Lower mortality in well-controlled (3.9-10 mmol/L; 70-180 mg/dL)

Retrospective, multicenter study
Hubei Province, China (n=7337)
Patients with and without DM
Hospitalized for COVID-19



Zhu L et al. Cell Metab. 2020 Jun 2;31(6):1068-1077

Duration of Hyperglycemia Matters

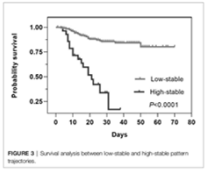


FIGURE 3 | Survival analysis between low-stable and high-stable pattern trajectories.

Retrospective (n=230)
Patients hospitalized for COVID-19
WITHOUT prior history of DM (SH)

"low stable"
6.63-7.54 mmol/L (119-136 mg/dL)

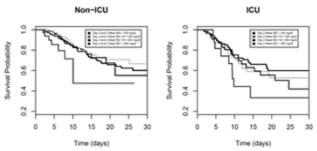
"high stable"
12.59-14.02 mmol/L (227-252 mg/dL)

"High stable" pattern was an independent predictor of mortality

Song S et al. Front Endocrinol. 2021 Mar 30;12:640529

Glycemic Control Matters: *window of opportunity*

Patients hospitalized for COVID-19 in critical care and non-critical care units
Glytec Database: 91 hospitals, 12 US states (N=1544)



BG >13.88 mmol/L (250 mg/dL) on days 2-3 was independently associated with mortality [HR] 7.17;95%CI 2.62–19.62) compared with patients with BG<7.77 mmol/L (140 mg/dL).

Klonoff DC et al. Diabetes Care. 2021 Feb;44(2):578-585.

Hyperglycemic Crisis and COVID-19

19 articles reporting 110 patients

Table 2
Showing demographic parameters of the COVID-19 patients with DKA (and combined DKA/HHS).

Parameter	Value
Age (years) [Median (IQR)]	45.5 (36.2–57.7) [2,6,10–16,18–21,23,24,28] 57.0 (48.0–64.0) [22] 59.0 (42.3–70.0) [1]
Sex (N = 102) [1]	Male (n = 67, 65%) Female (n = 35, 35%)
Ethnicity[2] (N = 84)	Black (n = 30, 36%) Hispanic (n = 19, 23%) White (Caucasian) (n = 10, 12%) Asian (n = 6, 7%) Mixed (n = 4, 5%) Others (n = 6, 9%) Unknown (n = 7, 8%)
Type of diabetes [3] (N = 97)	Pre-existing T1DM (n = 12, 12%) Pre-existing T2DM (n = 74, 77%) Newly diagnosed (n = 10, 10%) Gestational DM (n = 1, 1%)
Use of SGLT2 inhibitors [4]	7
BMI (kg/m^2) [Median (IQR)]	26.6 (23.7–32.3) [2,11–13,16,24] 24.7 (21.3–28.5) [22] 27.1 (23.2–33.0) [1]

91 (83%) DKA
19 (17%) DKA/HHS

majority were:
male (63%)
Black (77%)
Preexisting DM

~10% newly diagnosed DM

In hospital mortality 45% higher in DKA/HHS group vs. DKA group (67% vs, 29%)

Pal R et al Diabetes Metab Syndr. Nov-Dec 2020;14(6):1563-1569.