Inpatient Management of Hyperglycemia

Guillermo Umpierrez, MD, CDE Saturday, February 10, 2018 10:30 a.m. – 11:15 a.m.

There are over 7.5 million hospital admissions for patients with diabetes in the US. About 20 to 30% of patients have prior history of diabetes. The prevalence of hyperglycemia is even higher and reported in 38% of patients in community hospitals, 41% of critically ill patients with acute coronary syndromes, and in 80% of patients after cardiac surgery. Diabetes imposes a substantial economic burden on society. The total estimated cost of diagnosed diabetes in 2012 in the US was \$245 billion, of which \$76 billion (41%) represented inpatient medical care. Extensive data from observational and randomized controlled trials indicate that inpatient hyperglycemia, in patients with or without a prior diagnosis of diabetes, is associated with an increased risk of complications and mortality. It is also well established that improvement in glucose control with goal-directed insulin regimens reduces hospital complications and mortality in critically ill, as well as in general medicine and surgery patients. Recent studies and meta-analyses have shown that intensive insulin therapy is associated with increased risk of hypoglycemia, which has been independently associated with increased morbidity and mortality in hospitalized patients.

In patients with adequate oral intake, the basal bolus approach is the preferred regimen as it addresses the three components of insulin requirement: basal, nutritional, and correctional doses. The use of basal-bolus insulin had greater improvement in blood glucose control than sliding scale alone. In general surgery patients, the basal bolus regimen resulted in significant improvement in glucose control and in a reduction in the frequency of the composite of postoperative complications including wound infection, pneumonia, respiratory failure, acute renal failure and bacteremia. In patients with reduced total caloric intake due to lack of appetite, acute illness, medical procedures or surgical interventions, the Basal Plus trial in patients with type 2 diabetes compared a standard basal bolus regimen with glargine once daily and glulisine before meals and a single daily dose of glargine and supplemental doses of glulisine for correction of hyperglycemia (>140 mg/dL) per sliding scale. There was similar improvement in glycemic control and in the frequency of hypoglycemia with Basal Plus regimen compared to basal bolus regimen.

The use of oral antidiabetic agents is generally not recommended in hospitalized patients due to the limited data available on their safety and efficacy. The safety and efficacy of sitagliptin, a DPP-4 inhibitor, for the management of inpatient hyperglycemia was recently evaluated in 3 randomized controlled studies in general medicine and surgery hospitalized patients with type 2 diabetes. These studies indicate that in patients with mild to moderate hyperglycemia (BG < 200 mg/dl), there was no difference in the mean BG concentration or in the occurrence of hospital complications.

Transition to an outpatient setting requires planning and coordination. Although insulin is used for most patients with diabetes in the hospital, many patients do not require insulin after discharge. Patients with acceptable diabetes control could be discharged on their pre-hospitalization treatment regimen (oral agents and/or insulin therapy). Patients with suboptimal control should have intensification of therapy, either by addition or increase in oral agents, addition of basal insulin, or a more complex insulin regimen as warranted by their admission glucose control. Our preliminary experience indicates that measurement of HbA1c on admission is useful in guding treatment regimen at the time of hospital discharge in patients with type 2 diabetes. Patients admitted with a HbA1c <7% can be discharged on the same pre-admission diabetes therapy. Those with HbA1c between 7%-9% can be discharged on oral agents plus basal insulin at 50% of the hospital basal insulin and patients with HbA1c >9% should be discharged on basal bolus insulin or in the combination of metformin plus basal insulin at 80% of hospital dose.

This lecture will i) review the results of recent randomized control studies, in non-ICU patients with hyperglycemia and diabetes, ii) will present easy to follow insulin- and non-insulin-based treatment regimens for the management of inpatient hyperglycemia; iii) will discuss treatment regimens for the management of patients with diabetes after hospital discharge

Management of Hyperglycemia and Diabetes in Non-ICU Settings: Current and Future Recommendations

Guillermo E. Umpierrez, MD, FACP, FACE Professor of Medicine Director, Clinical Research Diabetes & Metabolism Center Emory University School of Medicine

> Director, Diabetes & Endocrinology Section Grady Health System

Dr. Guillermo Umpierrez, MD, CDE, FACE, FACP Personal/Professional Financial Relationships with Industry

External Industry Relationships *	Company Name(s)	Role
Equity, stock, or options in biomedical industry companies or publishers	BMJ Open Diabetes Research & Care	Editor-in-Chief
	ADA	Professional Practice Committee
	AACE	Board of Directors Diabetes Council Committee
Industry funds to Emory University for my research	Merck, Sanofi, Novo Nordisk Boehringer Ingelhein Astra Zeneca	Investigator-Initiated Research Projects
Industry Advisory/Consultant activities	Sanofi, Intarcia	Advisory Board Member

Lecture Agenda

- Scope of the Problem
 - Prevalence and impact of hyperglycemia
 - Glycemic targets in non-ICU
- Management of Hyperglycemia in Non-ICU
 - Basal Bolus Insulin Regimen
 - Alternatives to Basal Bolus
 - Basal Plus (basal + correction)
 - DPP4-inhibitors
 - Hospital Discharge Regimens

Case Presentation:

- 68 y/o male with an 8 yr history of DM admitted with SOB and CHF.
- Treated with metformin and sitagliptin.
- Lab: BG 172 mg/dL, A1c: 7.8%; serum creatinine 1.3 mg/dL, eGFR: 45 ml/min
- 42 y/o male with an 10 yr history of DM with diabetic foot and osteomyelitis left toe.
 Treated with metformin and glipizide.
- Lab: BG 294 mg/dL, A1c: 9.2%; serum creatinine 1.4 mg/dL, eGFR: 60 ml/min

What is the best treatment option for glycemic control? Should both patients be treated with insulin and to the same glucose target?





Distribution of patient-day-weighted mean POC-BG values for ICU





Adverse Events Stratified by Perioperative Hyperglycemia Diabetes No Diabetes Hospital Deaths **Re-operations** ÷ Composite Infections * * BG > 180 mg/dL BG < 180 mg/dL 0 3 9 12 15 0 q 15 3 12 * P <0.01 § p <0.05 Proportion of Patients (%) BG at any point on the day of surgery, post-op day 1 and 2 N= 11,633, colorectal and bariatric surgery; 29.1% with hyperglycemia Known et al. Ann Surg 2013



<u>Glycemic Targets</u> in Non-Critical Care Setting

- 1. Premeal BG target of <140 mg/dl and random BG <180 mg/dl for the majority of patients
- 2. 2016 American Diabetes Association glucose target 140-180 mg/dl for most patients with T2D
- 3. Glycemic targets be modified according to clinical status. - Patients with terminal illness <180-200 mg/dl
- 4. For avoidance of hypoglycemia, therapy should be reassessed when BG<100 mg/dl

ADA/AACE Guidelines, Diabetes Care 2009; Endocrine Society. J Clin Endocrinol Metabol, 2012; Under Revision 2018 2018 Standard of Diabetes Care, # 14, Hospital Management of Diabetes, Diabetes Care 2018

Diagnosis & recognition of hyperglycemia and diabetes in the hospital setting



A1C for Diagnosis and Management of Hyperglycemia in the Hospital

- Measure HbA1c in non-DM subjects with persistent BG >140 mg/dl and in DM subjects if not done within 2-3 mo.
- > Implementation of A1C testing can be useful:
 - > Assess glycemic control prior to admission
 - Assist with differentiation of newly diagnosed diabetes from stress hyperglycemia
 - > Predicts inpatient glycemic control and hypoglycemia
 - > Design an optimal regimen at hospital discharge

ADA Standard of Care, 14. Hospital Management of Diabetes. Diabetes Care January, 2018 Umpierrez et al, J Clin Endocrinol Metabol, February 2012 Pasquell et al. Diabetes Care 2014

Recommendations for Managing Patients With Diabetes in Non-ICU Setting



Management of Patients With Diabetes in Non-ICU Settings

- > Discontinue oral antidiabetic agents
- Insulin naïve: starting total daily dose (TDD):
 0.3 U/kg to 0.5 U/kg
 - Lower doses in the elderly and renal insufficiency
- Previous insulin therapy: reduce outpatient insulin dose by 20-25%
- Basal bolus regimen: Half of TDD as basal and half as rapid-acting insulin before meals

Umpierrez et al, Diabetes Care 30:2181-2186, 2007; Baldwin et al, Diabetes Care 10:1970-4, 2011; Rubin et al, Diabetes Care 34:1723-8, 2011; Umpierrez et al. J Clin Endocrinol Metabol. 97(1):16-38, 2012

SC Insulin Administration







Randomized Basal Bolus versus Sliding Scale Regular Insulin in patients with type 2 Diabetes Mellitus (RABBIT-2 Trial)

- D/C oral antidiabetic drugs on admission
- > Starting total daily dose (TDD):
 - 0.4 U/kg/d x BG between 140-200 mg/dL
 - 0.5 U/kg/d x BG between 201-400 mg/dL
- Half of TDD as basal insulin and half as rapidacting insulin
 - Insulin glargine once daily, at the same time/day.
 - Glulisine- three equally divided doses (AC)

Umpierrez et al, Diabetes Care 30:2181-2186, 2007

Sliding Scale Insulin Regimen

Before meal: Supplemental Sliding Scale Insulin (number of units)
 Add to scheduled insulin dose

Bedtime: Give half of Supplemental Sliding Scale Insulin

Blood Glucose (mg/dL)	Insulin Sensitive	Usual	Insulin Resistant
>141-180	2	4	6
181-220	4	6	8
221-260	6	8	10
261-300	8	10	12
301-350	10	12	14
351-400	12	14	16
>400	14	16	18

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









Lunch

Dinner

Bedtime

120

*p<0.001

Breakfast

z et al, Diabetes Care 34 (2):1-6, 2011



	All (n= 180)	Basal Bolus (n= 88)	SSI (n= 92)	p valu
Length of hospital stay, days	7.9 ± 5.5	7.3 ± 5.1	8.5 ± 5.9	0.15
Patients with complications, n (%)*	28 (16%)	6 (7%)	22 (24%)	0.00
Postsurgical ICU admission, n (%)	23 (13%)	10 (11%)	13 (14%)	0.66
Total hospitalization costs, USD	24457 ± 18359	23226 ± 18745	25641 ± 17991	0.09
Inpatient cost per day	4541 ± 18359	3907 ± 6606	3724 ± 4020	

*Wound infections, pneumonia, acute respiratory failure, acute renal failure, bacteremia Phillips VL et al. PharmacoEconom Open, 1(2):109-115, 2017



Umpierrez et al, Diabetes Care 34 (2):1-6, 2011











Prevalence of Hypoglycemia in Patients Treated with Human and Analogs





Bueno, Benitez eta al. Endocrine Practice, July 2015

Management of Patients With Diabetes in the Non-ICU Setting



Alternatives to Basal Bolus Insulin Regimen in Non-ICU Settings

- Basal Plus (basal + correction)
- DPP4-inhibitors



Basal Plus Trial Basal + Correction vs. Basal Bolus				
 Basal plus Correction Start glargine: 0.25 U/kg once daily Correction for BG >140 mg/dl per sliding scale 	Basal Bolus Regimen Start TDD: 0.5 U/kg Glargine: 0.25 U/kg Glulisine: 0.25 U/kg (AC) Correction for BG >140 mg/dl per sliding scale 			
* Reduce TDD to 0.15 U/kg in patients ≥70 yrs and/or serum creatinine ≥ 2.0 mg/dL	* Reduce TDD to 0.3 U/kg in patients ≥70 yrs and/or serum creatinine ≥ 2.0 mg/dL			



Patients treated with diet, oral agents or with low-dose insulin ≤ 0.4 U/Kg/Day Umpierrez et al. Diabetes Care. 2013 Aug.36(8):2169-74.

Basal-PLUS vs Basal Bolus: Medicine and Surgery Patients









DPP-4 Therapy in Hospitalized Patients

- <u>Study Type:</u> Multicenter, prospective, open-label randomized clinical trial
- <u>Patient Population</u>: Patients with T2D admitted to general medicine and surgery services at 3 hospitals: Emory University, Grady, and University of Michigan
- Treatment Groups*
- Group 1. Sitagliptin once daily (n=30)
- Group 2. Sitagliptin plus glargine insulin once daily (n=30)
- Group 3. Basal bolus regimen with glargine once daily and lispro before meals (n=30)

* All groups received supplemental doses of lispro for BG > 140 mg/dl before meals

Umpierrez et al. Diabetes Care. 2013 Nov;36(11):3430-5.

Mean Daily BG During Treatment





Sita Hospital Trial Research Design and Methods

- <u>Study Type:</u> Multicenter, prospective, open-label randomized clinical trial
- <u>Patient Population</u>: Patients with T2DM admitted with BG between 140-400 mg/dl, treated with diet, OADs and insulin at TDD < 0.6 Unit/kg
- Treatment Groups*
 - Group 1. Sitagliptin plus glargine once daily (n=140)
 Group 2. Basal bolus regimen with glargine once daily and
- rapid-acting insulin before meals (n=140)
- * Both groups received supplemental (correction) doses of rapid-actin insulin for BG > 140 mg/dl before meals

Pasquel et al. Lancet Diabetetes & Endocrinology, 5 (2) 125-133, 2017



	Sitagliptin + Basal	Basal Bolus	P-value
Total daily dose, U/kg/day	0.2 ± 0.1	0.3 ± 0.2	< 0.001
Total daily dose, U/day	24.1 ± 16.2	34.0 ± 20.1	< 0.001
Basal- Glargine, U/day	17.9 ± 12.5	16.8 ± 10.4	0.94
Prandial- aspart/lispro, U/day		11.7 ± 7.9	< 0.001
Supplements- U/day*	5.8 ± 5.7	5.5 ± 4.7	0.91
Number of Injections			
<pre># injections/day (Hospital stay)</pre>	2.2 ± 1.0	2.9 ± 0.9	< 0.001
# injections/ day (Day 2-10)	2.1 ± 1.4	2.9 ± 1.1	< 0.001

 Linagliptin Surgery Trial

 Aradomized Controlled Trial on the Safety and Efficacy of Linagliptin Surgery for the Inpatient Surgery of General Surgery Patients "Type 2 Diabetes

 General Surgery Patients

 Basal Bolus
 Linagliptin

 Cherral surgery (non-cardiac) patients with T2DM admitted with BC between 146 to myd/l, treated with diet, OADs and insulin at TDD < 0.5 Unit/kg</td>

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Linagliptin Inpatient Trial

A Randomized Controlled Trial on the Safety and Efficacy of Linagliptin Therapy for the Inpatient Management of General Surgery Patients with Type 2 Diabetes

Linagliptin*:

Linagliptin : 5 mg/day

Basal Bolus Regimen*:

- Total daily insulin dose: 0.4 unit/kg/day for BG between 140-200 mg/dl and 0.5 unit/kg/day for BG between 201-400 mg/dl
- Half of total daily dose (TDD) given as glargine once daily
- · Half of TDD given as lispro in three equal doses before meals

* Supplemental (correction) doses of rapid-acting insulin analog per sliding scale given as needed before meals for BG > 140 mg/dl or bedtime > 200 mg/dl

Vellanki & Umpierrez et al. ADA 2017 Scientific Meeting



Lina Surgery Trial: Daily Glucose Levels

+	Basal Bolus			
Innationt PG, days 2-10	Linaglintin	acal Polyc		
All patients mg/dl			0.04	
Pandomization RG <200 mg/dl	156 ± 41	160 ± 41	0.04	
- Randomization BG >200 mg/dL	165 ± 40	100 ± 41	0.43 6	3%
	105140	150 1 47	0.001	
- BG <70 mg/dL n (%)	14 (11)	2 (1.6)	0.001	
- BG <40 mg/dL, n (%)	0 (0)	1 (0.8)	>0.99	
Treatment failures, n (%)	10 (8.2)	19 (15)	0.12	
Composite complications, n (%)	11 (9)	14 (11)	0.63	
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Raliu 1 2	3 4 5	0 / 0 9	10	
Days				
Vallanki & Umpiorraz et al ADA 2017 Selentilio IV	laatina			







Recommendations for Managing Patients With Diabetes After Hospital Discharge





Hospital Discharge Algorithm Based on Admission HbA1C for the Management of Patients with T2DM



Hospital Discharge Algorithm Based on Admission HbA1C for the Management of Patients with T2DM

Primary outcome:

- change in A1C at 4 wks and 12 wks after discharge

	All Patients	OAD	OAD + Glargine	Glargine+ Glulisine	Glargine
# patients, n (%)	224	81 (36)	61 (27)	54 (24)	20 (9)
A1C Admission, %	8.7±2.5	6.9±1.5	9.2±1.9	11.1±2.3	8.2±2.2
A1C 4 Wks F/U, %	7.9±1.7*	7.0±1.4	8.0±1.4ψ	$8.8 \pm 1.8 \psi$	7.7±1.7
A1C 12 Wks F/U, %	7.3±1.5*	6.6±1.1	7.5±1.6*	8.0±1.6*	6.7±0.8*

* p< 0.001 vs. Admission A1C; wp=0.08

Umpierrez et al, ADA Scientific Sessions, 2012









Management of diabetes in non-critical care setting

So... What really have we learned?

Case Presentation:

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 - What is the best treatment option for glycemic control? Should both patients be treated with insulin and to the same glucose target?
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