23 Mar 2018

PROTOCOL FOR THE MANAGEMENT OF DIABETIC KETOACIDOSIS (DKA) OR HYPEROSMOLAR HYPERGLYCEMIA STATE (HHS) IN CRITICALLY ILL PATIENTS AT WRNMMC

SUBJECT: Diabetic Ketoacidosis (DKA) Hyperosmolar Hyperglycemic State represents an acute decompensation of Diabetes Mellitus (usually Type 1 DM for DKA and Type II for HHS), wherein absolute or relative insulin deficiency prevents cells from taking up glucose from the serum; this results in cellular oxidation of fatty acids for energy, generating ketones and subsequent acidemia. Diagnostic criteria of DKA / HHS include Hyperglycemia, Ketosis, Acidosis and Volume depletion. HHS will often present with blood glucose levels ranging from 500 to 1000mg/dL and markedly elevated serum osmolarities. DKA most commonly occurs in patients with known insulin-dependent DM and blood glucose levels <500 with normal osmolarities. DKA may be the initial presentation of diabetes in an undiagnosed patient. Severity of DKA can range from mild dehydration and ketoacidosis to a profound shock state, requiring aggressive goal-directed management.

REFERENCES:

1. Kitabchi AE, et al, Hyperglycemic Crises in Adult Patients with Diabetes. Diabetes Care 2009 32(7):1335-43.
2. Van Ness-Otunnu, et al, Hyperglycemic Crisis. J Emerg Med 2013 45(5):797-805.
3. Pasqual, et al, Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State, Endocrinology Adult and Pediatric, 7th edition 2016.
4. Eledrisi MS, et al. *Overview of the diagnosis and management of diabetic ketoacidosis*. Am J of Med Sci 331(5): 243–51.
5. Heber D, et al. *Low-dose continuous insulin therapy for diabetic ketoacidosis*. Arch Intern Med 137:1377-1380
6. Umpierrez GE, et al. *Narrative review: ketosis-prone type 2 diabetes mellitus.* Annals of Internal Medicine 144(5): 350–7.

PURPOSE: This protocol establishes guidelines for the management of patients with Diabetic Ketoacidosis (DKA) or Hyperosmolar Hyperglycemic State (HHS) in the Critical Care units at Walter Reed National Military Medical Center (WRNMMC). This protocol is not a substitute for, nor does it countermand the attending physician's clinical judgment; rather it is to be used as an evidence-based guideline.

SCOPE: This Protocol applies to all physicians and nurses caring for patients with DKA or HHS in the Critical Care Units of Walter Reed National Military Medical Center.

ENCLOSURE: See attached algorithm and flow sheet

INDICATIONS:

1. Patients admitted from the Emergency Department (ED), Inpatient Wards or outlying hospitals with Diabetic Ketoacidosis or HHS.
2. Patients already in the Critical Care unit who develop signs/symptoms of DKA.

3. Patients already in the Critical Care unit who develop signs/symptoms of Hyperosmolar Hyperglycemic State.

CONTRAINDICATIONS:

1. Patients with extremely low likelihood of survival or meaningful recovery
2. Patients currently receiving palliative care.
3. Apply carefully in patients with cardiomyopathy, end-stage renal disease or liver failure.
4. This protocol is not intended to be used for the management of stress hyperglycemia

PROCEDURE:

1. <u>Establish Diagnosis of Diabetic Ketoacidosis (DKA)</u>: The diagnostic criteria of DKA include:

i. Hyperglycemia (>250 mg/dL)

ii. Anion Gap Metabolic Acidosis (AGMA)
pH<7.3, CO2<18 mEq/L
Anion gap >14 mEq/L

iii. Ketonemia (beta-hydroxybutyrate >3 mosm/L or +acetoacetate)

iv. Dehydration

Other causes of AGMA (i.e. lactic acidosis, uremia) should be considered and excluded.
Signs and symptoms of DKA include Nausea/Vomiting, Polyuria/ Polydypsia, Tachypnea (i.e. Kussmaul respiration) and Altered Mental Status.
Initial laboratory studies to establish the diagnosis of DKA (if not already done so) include:

a. Comprehensive Chemistry
b. Arterial Blood Gas (ABG) with Lactate
c. Serum Ketones
d. Serum osmolarity

2. <u>Determine Severity:</u>

	Mild (plasma glucose >250 mg/dl)	**Moderate** (plasma glucose >250 mg/dl)	**Severe** (plasma glucose >250 mg/dl)
Arterial pH	7.25 – 7.30	7.0 – 7.24	<7.0
Serum bicarb (meq/L)	15 - 18	10 to <15	<10
Urine ketones	Positive	Positive	Positive
Serum ketones	Positive	Positive	Positive
Serum osmolality	Variable	Variable	Variable
Anion gap	> 10	> 12	> 12
Mental status	Alert	Alert/drowsy	Stupor/coma

Place A-line for pH <7.25

3. <u>Determine the Precipitating Cause</u>: DKA represents an acute decompensation of Insulin-dependent diabetes mellitus; as such, there is usually a precipitating cause, most commonly infection, which should be sought and managed. The following are the most common precipitating causes of DKA and some applicable diagnostic tests:

a. <u>Infection</u>:
   i. Complete Blood Count (CBC) with differential
   ii. Urinalysis with micro
   iii. Blood Cultures x 2, Urine Cultures
   iv. Chest X-Ray (CXR)

b. Acute Coronary Syndrome (ACS):
    i. Electrocardiogram (EKG)
    ii. Creatinine Kinase (CK), CK-MB, Myoglobin, Troponin (q8hrs x 3)
    iii. CXR
c. Insulin Deficiency (Outpatient Management Failure):
    i. Regimen Non-compliance
    ii. Insulin Pump failure
    iii. New or worsening insulin deficiency or resistance

4. Assess and Manage Volume and Hemodynamic Status: DKA can result in volume depletion through multiple mechanisms; the volume deficit can range from mild hypovolemia to hypovolemic shock. The latter is more likely in patients presenting to the ED. As such, an assessment of volume status and prompt, appropriate volume resuscitation are paramount in DKA management:

a. Severe Hypovolemia to Hypovolemic Shock:
    i. Administer crystalloid boluses (10-20 mL/kg bolus, usually 1 -2 liters of NS or LR over 15 – 20 minutes) as needed to correct shock
    ii. Start initial infusion of maintenance fluid at 250 – 500 ml/hr until volume depletion is considered mild. Choice of maintenance fluids should be based on corrected Na (**Estimated (corrected) plasma sodium* = Measured plasma or serum sodium concentration + (2 * (Serum glucose - 100) / 100)**. (Emmett, M et al. *The American Society of Nephrology*. 2013; 12 (3):191)
        1. Na >140 use 0.45% NaCl @125-250 ml/hr
        2. Na <140 use 0.9% NaCl @125-250 ml/hr
    iii. Consider invasive or noninvasive assessment of volume responsiveness. Other shock states may co-exist with hypovolemic shock, (i.e. Cardiogenic shock from ACS).
    iv. Once shock is corrected, continue volume repletion with isotonic crystalloid with close reassessment to correct hypovolemia
    v. Once hypovolemia is mild, proceed to subsection 3b, below.
b. Mild Hypovolemia:
    i. If Corrected Serum Sodium (Na) is Low: administer isotonic crystalloid
    ii. If Corrected Serum Na is Normal or High: administer hypotonic crystalloid
    iii. Reassess volume status and adjust fluid rate appropriately
    iv. Once shock is corrected, continue volume repletion with isotonic crystalloid with close reassessment to correct hypovolemia

5. Assess and Manage Ketoacidosis and Hyperglycemia: Once any shock state has been reversed, the next focus is correcting the Acidosis and Hyperglycemia. This goal is achieved by low-dose continuous insulin infusion:

a. Closely monitor Anion gap, Blood glucose and Electrolytes:
    i. Q1h Fingerstick glucose
    ii. Q2h Basic Chemistry with q2h Magnesium (Mg), Phosphate (Phos)
b. Start low-dose Regular Insulin infusion:
    i. Start drip (gtt) at 0.1 Units/kg/hr: the primary goal of insulin infusion is correction of the ketosis and, thus, "closure" of the Anion gap; the infusion rate can be modified, however, based on the blood glucose. Please follow the chart for titration (If Potassium <3.3 mEq/L, replete potassium prior to starting insulin drip)
    ii. When fingerstick glucose reaches 250 mg/dl maintenance fluids should be switched to D5 ½ NS or D5NS at 150 – 250 ml/hr to maintain serum glucose of 200 – 250 mg/dl. **Recalculate Insulin infusion rate to 0.05 u/kg/hr, resume titration using table with goal serum glucose of 200 – 250 mg/dl**

iii. If serum glucose is >250 mg/dl for greater than 1 hour, change maintenance fluids to D5NS, if running D10 and recheck glucose in 1 hour. If glucose remains >250 for 2 hours, recalculate insulin infusion rate to 0.1 Units/Kg/hr and reassess in 1 hour. Once glucose reaches 250 mg/dl for 1 hour, recalculate insulin infusion rate to 0.05 Units/Kg/hr and resume titration using table with goal serum glucose of 200 – 250 mg/dl.

iv. If serum glucose is <200 for greater than 1 hour, change maintenance fluids to D10NS or D10 ½ NS.

v. Insulin gtt to remain on while D5 ½ NS or D5 NS or D10 ½ NS or D10 NS is infused, until resolution of DKA.

vi. Resolution of DKA:

Serum glucose <200 mg/dl AND 2 of the following,

Bicarbonate >18 mEq/L

pH > 7.3

Anion gap < 14

vii. DKA has resolved, and patient is able to eat, administer long acting insulin (glargine) (glargine dose is calculated as 50% of 24 hr insulin gtt requirement, if insulin gtt is on for less than 24hrs, the total amount of insulin needs to be calculated as a U/hr, then multiplied by 24. To obtain total requirement for a 24hr period (i.e. insulin gtt on for 6hrs, with a total of 30U. Translates to 5U/hr of insulin. Take 5U/hr x 24, to obtain total requirement in 24hrs) (in this example total requirement in 24hrs would be 120U) take total requirement of insulin and divide by 2, this is your basal dose, then take 50% of total requirement and divide by 3. This is your short acting AC/HS/Snack requirement.)

viii. Insulin gtt to remain at current dose, when glargine administered, for an additional 2 hrs, then gtt may be turned off.

ix. Order Diabetic diet and begin QAC dosing for short acting insulin (aspart). Aspart dose is calculated based on 1/3 of 50% of total daily dose (TDD) (ie. TDD = 90U, glargine dose = 45U, QAC aspart dose = 15U with meals)

BG has changed less than 50 mg/dl in the previous hour			BG has DECREASED BG has decreased 50 mg/dl or more in the previous hour			BG has INCREASED BG has increased 50 mg/dl or more in the previous hour	
150 - 199	↓ 0.5 U/hr		150 - 199	↓ 1 U/hr		150-199	No change
200 - 250	No change		200- 250	↓ 0.5 U/hr		200- 250	↑ 0.5 U/hr
251- 300	↑ 1 U/hr		251- 300	↑ 0.5 U/hr		251- 300	↑ 1 U/hr
> 301 *	↑ 2 U/hr		> 301 *	↑ 1.5 U/hr		> 301 *	↑ 2 U/hr
*Notify provider if BG > 301 mg/dl for 3 consecutive readings			*Notify provider if BG > 301 mg/dl for 3 consecutive readings			*Notify provider if BG > 301 mg/dl for 3 consecutive readings	

* Glucose < 40 mg/dl should be repeated to ensure accuracy, *without* delaying treatment for hypoglycemia. Values < 40 mg/dl and > 400 mg/dl should be repeated on another machine to ensure accuracy and reported to the physician. The provider should order a STAT venous sample for glucose testing to be sent to the Core Lab.

Hypoglycemia: While on a continuous IV infusion of insulin, the patient is at risk for hypoglycemia. Hourly glucose measurement and addition of dextrose to the IV solution when blood glucose falls to < 250 mg/dl should prevent the problem. It is appropriate to use D10 dextrose if glucose levels are <200 mg/dl for next one to two hours on D5 and not yet appropriate to discontinue IV insulin (AG still open). For acute hypoglycemia (<150), the insulin infusion may be discontinued for 15 minutes, then recheck the serum glucose. If glucose remains <150, increase D10 by 50% until >150 and restart insulin drip at 75% the previous rate. **The insulin drip should not be decreased to less than 0.02u/kg/hr as insulin is essential for preventing continued ketogenesis.**

Ketoacidosis/AG persists & BG < 70: Hold insulin for 15 min & give 1/2 AMP D_{50}. Re-check glucose every 15 min and if still < 70 give and additional 1/2 AMP D_{50}. Once BG > 70 mg/dL restart insulin gtt at 50% of rate prior to holding insulin gtt. Increase $D_{10}W$ or $D_{10}NS$ to 300-350 mL/hr, to maintain serum glucose between 200-250 mg.

c. Bicarbonate Therapy: Evidence suggests that there is no clinical benefit to the administration of Bicarbonate for severe acidemia in DKA unless pH < 7.0.
d. If pH 6.9 and below, administer Sodium Bicarbonate 100 meq in 400 ml D5W with 20 meq Potassium Chloride over 2 hrs. May repeat in 2 hrs if pH remains <7.0.

6. **Assess and Manage Electrolyte Disturbances:** DKA and its treatment are associated with dramatic and potentially life-threatening electrolyte disturbances. In particular, DKA is characterized by total body deficiencies in Potassium, Magnesium and Phosphate. Electrolytes must be closely monitored and deficits proactively corrected:
   a. Closely monitor electrolytes with Q2h Basic Chemistry and q2h Mg, Phos during the acute phase.
   b. Correct any Potassium, Phosphate and Magnesium deficiencies with IV supplementation (taking into account renal function).
   c. Further prevent Potassium deficiency by adding K^+ to the maintenance fluids (taking into account renal function). Even in the setting of normal or elevated serum K+, total body K+ is typically low, requiring continued supplementation.
      i. Suggested potassium replacement below
      ii. If Serum K >5.5, do not add K to maintenance fluid. Check EKG for evidence of hyperkalemia-induced conduction abnormalities. (Serum hyperkalemia typically autocorrects as acidosis is corrected.)

Serum Potassium	Total Replacement Dose	Replacement based on SCr >2
<3 mEq/L	Hold insulin gtt 40 – 80 mEq/L	40 mEq/L
3.1 – 3.4 mEq/L	40 – 60 mEq/L	20 mEq/L
3.5 – 3.9 mEq/L	20 – 40 mEq/L	No potassium replacement
4 – 5 mEq/L	Add KCL 20 mEq/L to each liter of MIVF	No potassium replacement
> 5.5 mEq/L	No potassium replacement	No potassium replacement

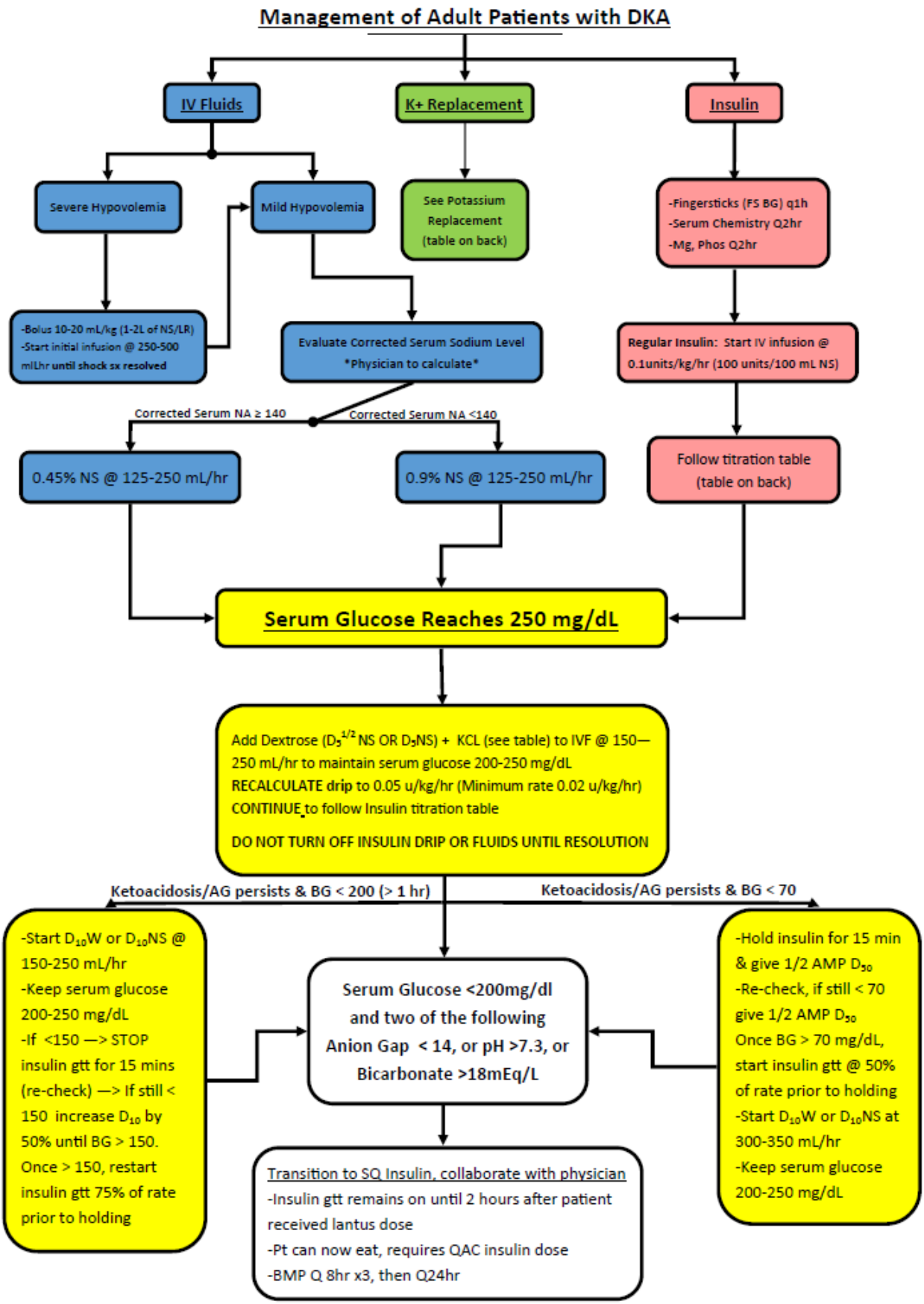
7. **<u>Manage Associated Symptoms</u>:** Nausea and vomiting are classically present in DKA, reflecting acidemia and potentially gastroparesis. Significant nausea/vomiting can potentially stymie attempts to correct hypovolemia and delay the initiation of enteral feeding. Nausea/vomiting should be treated with anti-emetics (i.e. Ondansetron) or, if gastroparesis is suspected, agents that promote gastric emptying (i.e. Metoclopramide). Ensure that bowel obstruction is excluded before administering pro-motility agents.

8. **<u>Obtain Appropriate Consults</u>:** Consultation from the following services can facilitate patient care as they transition to the wards and to the outpatient setting:
    a. Endocrinology
       Mandatory consult required for patients previously on Insulin Pumps
       (Ensure Endocrine is consulted prior to stopping Insulin infusion)
    b. Nutrition

Prepared by:

Madalyn Hise, PharmD, BCNSP, BCCCP
Clinical Pharmacist-Critical Care

Paul Clark, D.O.
MAJ, MC, USA
Staff Physician, Critical Care Medicine


Management of Adult Patients with DKA
IV Fluids
K+ Replacement
Insulin
Severe Hypovolemia
Mild Hypovolemia
See Potassium Replacement (table on back)
-Fingersticks (FS BG) q1h
-Serum Chemistry Q2hr
-Mg, Phos Q2hr
-Bolus 10-20 mL/kg (1-2L of NS/LR)
-Start initial infusion @ 250-500 mlLhr until shock sx resolved
Evaluate Corrected Serum Sodium Level
Physician to calculate
Regular Insulin: Start IV infusion @ 0.1units/kg/hr (100 units/100 mL NS)
Corrected Serum NA ≥ 140
Corrected Serum NA <140
0.45% NS @ 125-250 mL/hr
0.9% NS @ 125-250 mL/hr
Follow titration table (table on back)
Serum Glucose Reaches 250 mg/dL
Add Dextrose ($D_5^{1/2}$NS OR D_5NS) + KCL (see table) to IVF @ 150—250 mL/hr to maintain serum glucose 200-250 mg/dL
RECALCULATE drip to 0.05 u/kg/hr (Minimum rate 0.02 u/kg/hr)
CONTINUE to follow Insulin titration table
DO NOT TURN OFF INSULIN DRIP OR FLUIDS UNTIL RESOLUTION
Ketoacidosis/AG persists & BG < 200 (> 1 hr)
Ketoacidosis/AG persists & BG < 70
-Start D_{10}W or D_{10}NS @ 150-250 mL/hr
-Keep serum glucose 200-250 mg/dL
-If <150 —> STOP insulin gtt for 15 mins (re-check) —> If still < 150 increase D_{10} by 50% until BG > 150. Once > 150, restart insulin gtt 75% of rate prior to holding
Serum Glucose <200mg/dl and two of the following Anion Gap < 14, or pH >7.3, or Bicarbonate >18mEq/L
-Hold insulin for 15 min & give 1/2 AMP D_{50}
-Re-check, if still < 70 give 1/2 AMP D_{50}
Once BG > 70 mg/dL, start insulin gtt @ 50% of rate prior to holding
-Start D_{10}W or D_{10}NS at 300-350 mL/hr
-Keep serum glucose 200-250 mg/dL
Transition to SQ Insulin, collaborate with physician
-Insulin gtt remains on until 2 hours after patient received lantus dose
-Pt can now eat, requires QAC insulin dose
-BMP Q 8hr x3, then Q24hr

POTASSIUM REPLACEMENT (Serum Chemistry q 2-4 hours)(Excludes ESRD/Anuria)		
Serum Potassium	Total Replacement Dose (Consider lower dose for renal insufficiency/AKI)	Replacement based on SCr > 2
<3 mEq/L	Hold insulin gtt 40-80 mEq/L	40 mEq/L
3.1 - 3.4 mEq/L	40-60 mEq/L	20 mEq/L
3.5 - 3.9 mEq/L	20-40 mEq/L	No potassium replacement
4 - 5 mEq/L	Add KCL 20 mEq/L to each liter of MIVF	No potassium replacement
> 5.5 mEq/L	No potassium replacement	No potassium replacement

Titration Table					
BG has **changed less than 50** mg/dL in the previous hour **(RECALCULATE RATE WHEN BG ≤250, SEE ALGORTIHM)**		**BG has DECREASED** BG has decreased 50mg/dL or more in the previous hour **(RECALCULATE RATE WHEN BG ≤250, SEE ALGORTIHM)**		**BG has INCREASED** BG has increased 50 mg/dL or more in the previous hour	
150 - 199	↓ 0.5 U/hr	150 - 199	↓ 1 U/hr	150 - 199	No change
200 - 250	No change	200 - 250	↓ 0.5 U/hr	200 - 250	↑ 0.5 U/hr
251 - 300	↑ 1 U/hr	251 - 300	↑ 0.5 U/hr	251 - 300	↑ 1 U/hr
> 301 *	↑ 2 U/hr	> 301 *	↑ 1.5 U/hr	> 301*	↑ 2 U/hr
*Notify provider if BG > 301 mg/dL for 3 consecutive readings		*Notify provider if BG > 301 mg/dL for 3 consecutive readings		*Notify provider if BG > 301 mg/dL for 3 consecutive readings	

Do NOT infuse drip below 0.02 U/kg/hr. MINIMUM calculated rate:___ Units/ hour

Date/Time	BG	Rate Change	Actual Rate	K+ (q2h)	IV Fluid

Titration Table

BG has **changed less than 50** mg/dL in the previous hour (**RECALCULATE RATE WHEN BG ≤250, SEE ALGORTIHM)**		**BG has DECREASED** BG has decreased 50mg/dL or more in the previous hour (**RECALCULATE RATE WHEN BG ≤250, SEE ALGORTIHM)**		**BG has INCREASED** BG has increased 50 mg/dL or more in the previous hour	
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251 - 300	↑ 1 U/hr	251 - 300	↑ 0.5 U/hr	251 - 300	↑ 1 U/hr
> 301 *	↑ 2 U/hr	> 301 *	↑ 1.5 U/hr	> 301*	↑ 2 U/hr
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Date/Time	BG	Rate Change	Actual Rate	K+ (q2h)	IV Fluid