Glycemic Control in the Intensive Care Unit

Jorie Frasiolas, Pharm.D., BCPS
Clinical Pharmacy Manager, CTICU
NewYork-Presbyterian Hospital
Columbia University Medical Center
August 23, 2013

Disclosures

- No disclosures

Objectives

- Identify the importance of inpatient glycemic control in critically ill patients
- Discuss key recommendations from the Society of Critical Care Medicine Guidelines for the Use of Insulin Infusions for the Management of Hyperglycemia in Critically Ill Patients
- Describe the components of an optimal insulin dosing protocol
- Review electronic systems that provide computerized decision-support regarding glycemic control

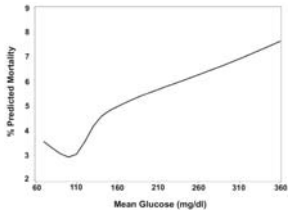
Hyperglycemia

- Up to 80% of critically ill patients
  - Diabetes
  - Unrecognized diabetes
  - Stress-induced
  - Contributing factors (i.e. nutrition, medications, infection)
- Causes tissue abnormalities
  - Mitochondrial injury
  - Neutrophil and endothelial dysfunction
  - Oxidative injury
  - Complement inhibition
- Independent predictor of hospital morbidity and mortality

Crit Care Med 2009;37:463-70. *Crit Care Med* 2009;37:3001-9.
JAMA 2002;288:2167-9. *N Engl J Med* 2010;363:2540-6.

Hyperglycemia

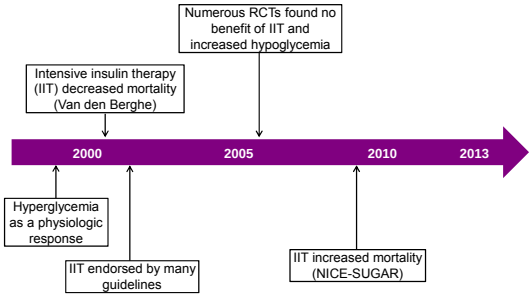
- Retrospective review of 259,040 admissions to 173 U.S. medical, surgical, and cardiac ICUs



- Acute coronary syndrome, heart failure, arrhythmia, stroke, gastrointestinal bleeding, acute renal failure, pneumonia, pulmonary embolism, and sepsis

Crit Care Med 2009;37:3001-9.

History



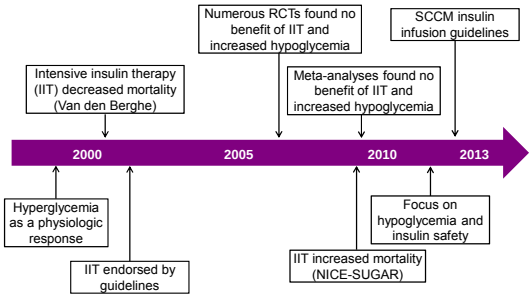
Randomized Controlled Trials

	Van den Berghe	Van den Berghe, MICU	VISEP	Glucontrol	NICE-SUGAR
Population	Surgical (cardiac); 13% diabetics	Medical; 17% diabetics	Sepsis/mixed; 30% diabetics	Mixed; 19% diabetics	Mixed; 20% diabetics
Intensive target BG (mg/dL)	80-110	80-110	80-110	80-110	81-108
Intensive actual BG (mg/dL)	103 ± 19	111 ± 29	130 (108-167)	117 (108-130)	115 ± 18
Conventional target BG (mg/dL)	180-200	180-200	180-200	140-180	144-180
Conventional actual BG (mg/dL)	153 ± 33	153 ± 31	138 (111-184)	144 (128-162)	144 ± 23
BG measurement	Every 1-4 hrs; arterial; blood gas analyzer	Every 1-4 hrs; Arterial preferred; POC	Every 1-4 hrs: arterial preferred; POC	Every 1-4 hrs; arterial/venous preferred; POC/ blood gas/lab	Every 1-4 hrs; arterial preferred; POC/blood gas/lab
BG value(s)	Mean morning	Mean morning	Mean morning	Median of all values, median morning	Time-weighted
Comments	IV glucose; single center	Single center	Terminated early	Terminated early; protocol violations	Intensive group didn't achieve target; enteral nutrition

BG = blood glucose; POC = point of care

N Engl J Med 2001;345:1359-67. *N Engl J Med* 2006;354:449-61. *Intensive Care Med* 2009;35:1738-48. *N Engl J Med* 2009;360:1283-97. *N Engl J Med* 2008;358:125-39.

History



SCCM Guideline Methodology

- Target population: adult medical and surgical ICU patients
- Published clinical trials
- Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system
- Recommendation for strong (Grade 1) evidence
- Suggestion for weak (Grade 2) evidence
- Quality of evidence
  - High: Further research is very unlikely to change their confidence in the estimate of the effect
  - Moderate: Further research is likely to impact their confidence in the estimate of the effect and may change the estimate
  - Low: Further research is very likely to impact their confidence in the estimate of the effect and is likely to change the estimate
  - Very low: Any estimate of effect is very uncertain
- Meta-analyses

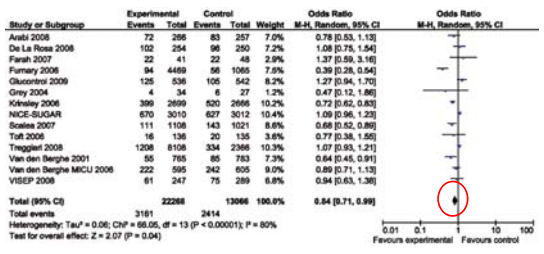
Crit Care Med 2012;40:3251-76.

Glycemic Targets

We suggest blood glucose (BG) ≥ 150 mg/dL should trigger initiation of insulin therapy, titrated to keep BG < 150 mg/dL for most adult ICU patients and to maintain BG values absolutely < 180 mg/dL using a protocol that achieves a low rate of hypoglycemia (BG ≤ 70 mg/dL) despite limited impact on patient mortality. [Quality of evidence: very low]

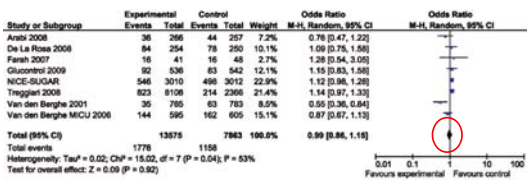
Crit Care Med 2012;40:3251-76.

Hospital Mortality



Crit Care Med 2012;40:3251-76.

ICU Mortality



Crit Care Med 2012;40:3251-76.

Special Patient Populations

Patient Population	Recommendation
Postoperative cardiac surgery	We suggest moderate glycemic control (BG < 150 mg/dL) to achieve a reduced risk of deep sternal wound infection and mortality. [Quality of evidence: very low]
Trauma	We suggest that BG ≥ 150 mg/dL should trigger initiation of insulin therapy, titrated to keep BG < 150 mg/dL to maintain values absolutely < 180 mg/dL, using a protocol that achieves a low rate of hypoglycemia. [Quality of evidence: very low]
Neurologic injury	We suggest that BG ≥ 150 mg/dL triggers initiation of insulin therapy, titrated to achieve BG values absolutely < 180 mg/dL with minimal BG excursions < 100 mg/dL. [Quality of evidence: very low]

Crit Care Med 2012;40:3251-76. *N Engl J Med* 2001;345:1359-67. *Eur Heart J* 2006;27:2716-24. *Ann Thorac Surg* 2010;90:1825-32. *N Engl J Med* 2009;360:1283-97.

A Moving Target

Year	Organization	Treatment Threshold (mg/dL)	Target BG (mg/dL)
2013	Surviving Sepsis Campaign	180	≤ 180
2012	Society of Critical Care Medicine	150	100-150
2011	Institute for Healthcare Improvement	180	< 180
2011	American Diabetes Association	180	140-180 (100-140)
2010	American Heart Association	180	140-180
2009	American Association of Clinical Endocrinologists and American Diabetes Association	180	140-180

Crit Care Med 2012;40:3251-76. *Crit Care Med* 2013;41:580-637. *Diabetes Care* 2011;34(Suppl 1):S11-61. *Circulation* 2010;122:2736-44. *Endocr Pract* 2009;14:1-17. http://www.ihi.org

Hypoglycemia

We suggest BG ≤ 70 mg/dL is associated with an increase in mortality and even brief severe hypoglycemia (BG ≤ 40 mg/dL) is independently associated with a greater risk of mortality, which increases with prolonged or frequent episodes.

[Quality of evidence: low]

Crit Care Med 2012;40:3251-76.

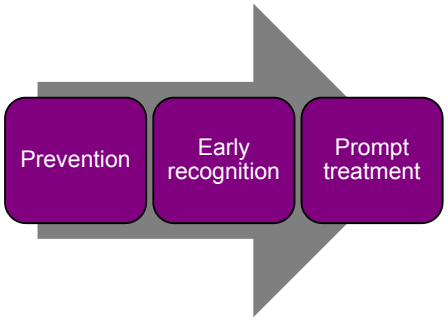
Hypoglycemia and Mortality

- Severe hypoglycemia (≤ 40 mg/dL)
  - OR 2.28 (95% CI, 1.41-3.7; p = 0.0008)
- Mild to moderate hypoglycemia (< 70 mg/dL)
  - RR 2.18 (95% CI, 1.87, 2.53; p < 0.001)
- Mortality related to severity of hypoglycemia
- Increased risk with frequent episodes

	ICU Mortality OR (95% CI)	Hospital Mortality OR (95% CI)
2 episodes	2.4 (2-2.8)	2.2 (1.9-2.5)
1 episode	1.3 (1.2-1.4)	1.2 (1.1-1.3)

Crit Care 2011;15:R173. *Crit Care Med* 2007;35:2262-7. *Crit Care* 2009;13:R91.

Hypoglycemia Management



Crit Care Med 2012;40:3251-76.

Risk Factors

- Diabetes
- Renal failure
- Continuous renal replacement therapy
- Hepatic impairment
- Sepsis with vasoactive agents
- Mechanical ventilation
- Greater severity of illness
- Tight glycemic control
- Nutrition interruptions
  - 62% of hypoglycemic events in the initial Van den Berghe study

Crit Care Med 2012;40:3251-76. *Crit Care Med* 2003;31:359-66. *Crit Care Med* 2006;34:96-101. *Crit Care Med* 2007;35:2262-7.

Hypoglycemia Prevention

We suggest that glycemic control protocols should include instructions to address unplanned discontinuation of any form of carbohydrate infusion.

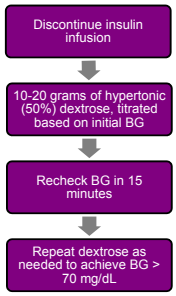
[Quality of evidence: low]

- Dextrose 5% at rate equal to enteral feeds
- Dextrose 10% to minimize free water

Crit Care Med 2012;40:3251-76.
Nutrition 2008;24:536-45.

Hypoglycemia Treatment

We suggest BG < 70 mg/dL (< 100 mg/dL in neurologic injury patients) be treated immediately. [Quality of evidence: very low]



Crit Care Med 2012;40:3251-76.

Hypoglycemia Treatment

- Avoid rebound hyperglycemia
- Dextrose 50% (g) = (100-BG) x 0.2 g
  - Example
    - Dextrose 50% (g) = (100-60) x 0.2 g = 8 g
    - Dextrose 50% (g) = (100-40) x 0.2 g = 12 g
  - Glucommander™ study
    - Mean hypoglycemic value 49 ± 10 mg/dL
    - Repeat BG in a mean of 33 min = 83 ± 10 mg/dL
- Dextrose 10% in 50 mL aliquots

Crit Care Med 2012;40:3251-76.
Diabetes Care 2005;28:2418-23.
Emerg Med J 2005;22:512-5.

Hypoglycemia Treatment

- Glucagon
  - 1 mg IM/subQ, may repeat in 15-20 minutes
  - IV dextrose is preferred over glucagon
  - May cause significant nausea and vomiting
- Oral dextrose replacement
  - Not studied in critically ill patients
  - Must be responsive and tolerating an oral diet
  - Dextrose or sucrose tablets or solutions preferred over viscous gels or orange juice

Crit Care Med 2012;40:3251-76.
Arch Intern Med 1990;150:589-93.
Prehosp Disaster Med 1998;13:44-50.

Blood Glucose Monitoring

We suggest monitoring BG every 1-2 hours for most patients receiving an insulin infusion. Unstable patients should be monitored at least every hour.

[Quality of evidence: very low]

- No prospective data
- Most published protocols begin with hourly
- Delays in monitoring contribute to hypoglycemia
- Protocols with every four hour BG monitoring report the highest rates of severe hypoglycemia (~10%)
- Continuous glucose sensors

Crit Care Med 2012;40:3251-76.
Crit Care 2009;13:R163.

Point of Care Meters

We suggest most point of care glucose meters are acceptable but not optimal.

[Quality of evidence: very low]

- Advantages
  - Ease of use, availability, rapid results
- Disadvantages
  - Standards allow up to 15-20% error between point of care and laboratory results
  - Not designed for use in the ICU
  - Lack of accuracy in critically ill patients (i.e. anemia, hypoxia, medications)
  - Operator error

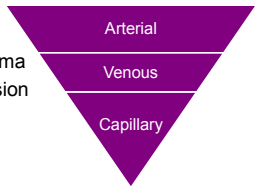
Crit Care Med 2012;40:3251-76. *Diabetes Care* 2007;30:403-9.
Crit Care Med 2012;40:3251-76. *Chest* 2011;140:212-20.

Blood Glucose Sampling

We suggest arterial or venous whole blood sampling be used instead of finger-stick capillary BG testing for the following patients:

[Quality of evidence: moderate]

- Shock
- Vasopressors
- Severe peripheral edema
- Prolonged insulin infusion



Crit Care Med 2012;40:3251-76.

Insulin Safety

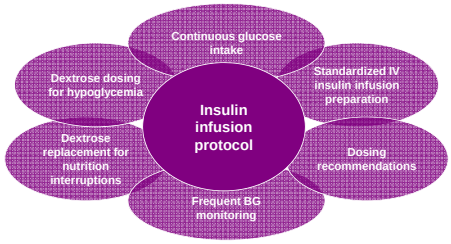
We suggest that insulin is a high-risk medication, and that a systems-based approach is needed to reduce errors.

[Quality of evidence: very low]

- Top 5 high-risk medications that account for one third of major medication errors
- One third of errors resulting in death within 48 hours involve insulin

Crit Care Med 2012;40:3251-76.
Endocr Pract 2005;11:197-202.

Insulin Infusion Protocols



[Quality of evidence: very low]

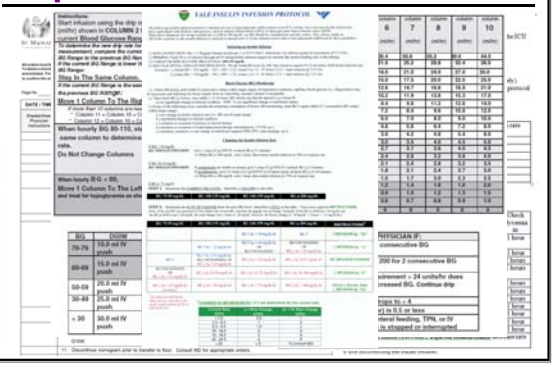
Crit Care Med 2012;40:3251-76.

Insulin Infusion Protocols

- Structure
  - "If-then" decision model
  - Column method
  - Algebraic formula
- Bolus dosing
- Basis for insulin titration
  - BG value
  - Direction of BG trend
  - Rate of BG change
  - Insulin sensitivity
  - Patient specific variables
- Dose adjustments
  - Units
  - Percent change
- Paper vs computerized

J Hosp Med 2008;5 Suppl:42-54.
Crit Care 2009;13:223-9.
Diabetes Care 2007;30:1005-11.

Paper Protocols



Paper Protocols

Advantages

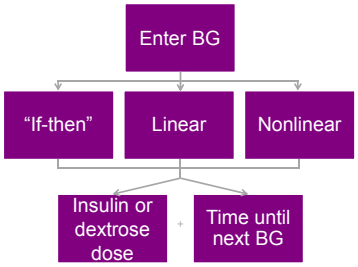
- Accessible
- Tangible
- Clinical judgment
- No direct cost

Disadvantages

- Complexity
- High-level training
- Operator error
- Time intensive
- No reminder system
- Reactive
- Protocol violations

Crit Care Med 2012;40:3251-76.

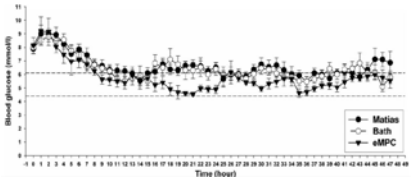
Computerized Protocols



Intensive Care Med 2009;35:1505-17. *Diabetes Tech &Ther* 2010;12:S51-8.
J Diabetes Sci Technol 2009;3:125-40. *Crit Care* 2009;13:223-9.

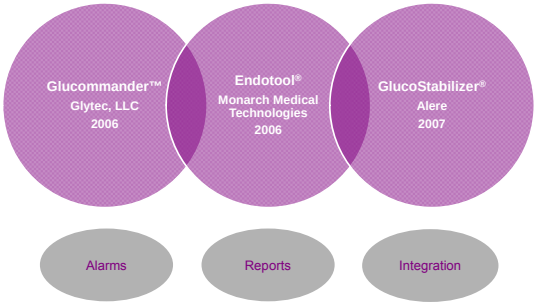
Computerized vs Paper Protocols

- Elective cardiac surgery ICU patients randomized to one of two paper protocols or a computerized protocol to achieve target BG of 80-110 mg/dL (n = 120)
  - Matias protocol = "If-then" decision model based on absolute BG value
  - Bath protocol = "If-then" decision model based on relative BG change
  - Computerized protocol = nonlinear algebraic formula



Diabetes Care 2009;32:757-61.

Commercial Systems

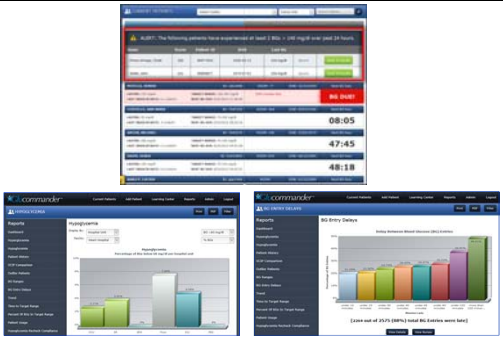


Glucommander™

- Web-based
- Optimized for handheld devices
- Linear formula: (BG-60) x multiplier
- Additional features
  - Nutritional adjustments to insulin infusion dose
  - Patient-specific transition to subcutaneous insulin
  - FDA clearance for subcutaneous (2010) and pediatric (2012) dosing
  - Customized alerts
- Clinical outcomes
  - Mean time to target ~ 3-6 hours
  - 0.1-0.6% of values < 50 mg/dL

Diabetes Care 2005;28:2418-23.
J Diabetes Sci Technol 2008;2:369-75.

Glucommander™



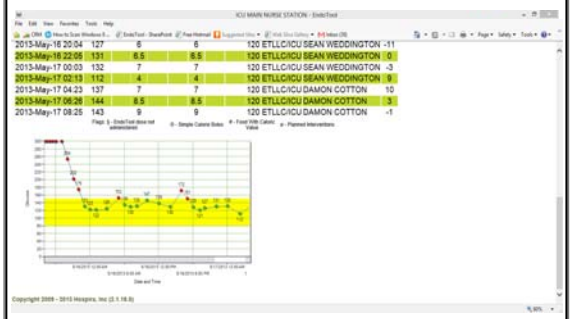
Glytec, LLC.

EndoTool®

- Web and/or thick client based
- Nonlinear formula
- Additional features
  - Accounts for patient specific variables
  - Nutritional adjustments to insulin infusion dose
  - Patient specific transition to subcutaneous insulin
  - Clinical advisories
- Clinical outcomes
  - Mean time to target ~ 1 hour
  - 84% of values within target range
  - 0.3% of BG readings < 60 mg/dL
  - 0.05% BG readings < 40 mg/dL

J Cardiothorac Vasc Anesth 2008;22:377-82.
J Am Coll Surg 2013;216:828-33.
http://www.hospira.ae/english/endotool.aspx#PRDFTR

EndoTool®



Monarch Medical Technologies

GlucoStabilizer®

- Network based
- Linear formula: (BG-60) x multiplier
- Additional features
  - Regular insulin IV boluses for meal coverage
  - General guidance for transition to subcutaneous insulin
  - Alerts for BG due
- Clinical outcomes
  - Median time to target 6 hours
  - 97.5% achieved target
  - 75% of time spent in target once achieved
  - 0.1% of values < 40 mg/dL

Diabetes Tech & Ther 2007;9:232-40.
Crit Care 2009;13:R163.

GlucoStabilizer®

http://www.glucostabilizer.net/Multimedia.htm

Comparison

	Glucommander™	EndoTool®	GlucoStabilizer®
Formula	Linear	Nonlinear	Linear
Insulin infusion dosing	+	+	+
Dextrose dosing	+	+	+
Nutritional adjustments	Infusion dose increase	Infusion dose increase	IV bolus
Transition to subcutaneous	Patient specific	Patient specific	General guidance
Subcutaneous dosing FDA clearance	+	-	-
Pediatric dosing FDA clearance	+	-	-
Interfaces with HIS	+	+	+
Alert notifications	+	+	BG due
Report generation	+	+	+

HIS = hospital information system

Computerized Protocols

Advantages

- Low complexity
- Less time intensive
- Minimal training
- Low operator error
- Patient specific variables
- Proactive
- Reminder system
- Report generation

Disadvantages

- Commercial fees
- Need for computer
- IT support
- Back-up protocol
- Intangible

Crit Care Med 2012;40:3251-76.
Crit Care 2009;13:223-9.

Implementation

- Develop a multidisciplinary committee/task force
- Recognize key stakeholders
- Evaluate current policies/procedures
- Select an insulin infusion protocol and glycemic targets
- Obtain necessary equipment
- Educate/train staff
- Identify and address local barriers

Crit Care Med 2012;40:3251-76.
J Hosp Med 2008;5 Suppl:42-54.

Quality Improvement

- Efficacy
  - Mean (SD)
  - Median (interquartile range)
  - Percent of BG < 150 mg/dL and < 180 mg/dL
  - Glycemic variability
- Safety
  - Events per patient
  - Percentage of all BG values
  - Events per 100 hours of infusion
- [Quality of evidence: very low]

Crit Care Med 2012;40:3251-76.

Subcutaneous Insulin

We suggest that stable ICU patients be transitioned to a protocol-driven basal/bolus insulin regimen before the insulin infusion is stopped.

[Quality of evidence: very low]

- Advantages
  - Decreased workload
  - Less frequent monitoring
  - Cost
- Exclusions
  - Not receiving sufficient nutrition
  - Planned interruptions of nutrition
  - Peripheral edema
  - Hemodynamic instability

Crit Care Med 2012;40:3251-76.
Endocr Pract 2006;12:641-50.

Subcutaneous Insulin

- Basal/bolus regimen
  - Type 1 diabetes mellitus
  - Type 2 diabetes mellitus on insulin as outpatient
  - Type 2 diabetes mellitus on insulin > 0.5 unit/hr
  - Stress hyperglycemia on insulin > 1 unit/hr
- Bolus only
  - Type 2 diabetes mellitus on insulin < 0.5 unit/hr
  - Stress hyperglycemia on insulin < 1 unit/hr

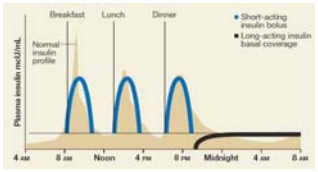
Crit Care Med 2012;40:3251-76.
J Hosp Med 2008;3:S55-65.

Subcutaneous Insulin

We suggest that calculation of basal and bolus insulin dosing requirements should be based on IV insulin infusion history and carbohydrate intake.

[Quality of evidence: very low]

- Components: basal, nutritional, and correction



Crit Care Med 2012;40:3251-76.
J Hosp Med 2008;3:S55-65.
Clin Diabetes 2011;29:3-9.

Initiating Subcutaneous Insulin

- Intermediate or long acting insulin 2-4 hours prior to discontinuation of the insulin infusion

  OR

- Rapid acting insulin (~ 10% of basal dose) with long acting insulin at discontinuation

Crit Care Med 2012;40:3251-76.
J Hosp Med 2008;3:S55-65.
Clin Diabetes 2011;29:3-9.

Summary

- The optimal target blood glucose is unknown; however, for most adult ICU patients a goal of < 150 mg/dL is reasonable and may decrease hospital mortality
- When hypoglycemia cannot be prevented, early recognition and prompt treatment are critical
- Insulin infusion protocols should be implemented to improve the efficacy and safety of insulin therapy
- Computerized protocols may be more effective than paper protocols
- Protocols should be evaluated and updated at regular intervals

Glycemic Control in the Intensive Care Unit

Jorie Frasiolas, Pharm.D., BCPS
jog9104@nyp.org