

SUBCUTANEOUS INSULIN THERAPY IN THE HOSPITAL SETTING: ISSUES, CONCERNS, AND IMPLEMENTATION

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ABSTRACT

Objective: To summarize issues and recommendations regarding subcutaneous insulin therapy in various clinical settings in the hospital.

Results: The inpatient insulin regimen must be tailored to the specific clinical circumstance of the individual patient. Because nutritional intake is not necessarily provided as discrete meals in the hospital, the insulin dose requirement can be subclassified into “basal” and “nutritional” needs. In addition, the insulin requirement is generally increased in the presence of acute illness and stress. Thus, components of the insulin requirement are divided into basal, nutritional, and correction insulin. When the physician writes insulin orders, the basal and nutritional components are written as programmed or scheduled insulin, and the correction-dose insulin is written as an algorithm to supplement the scheduled insulin. Total insulin requirements may vary widely. Practical guidelines and suggestions are presented for selection of appropriate insulins, the delivery route, and the logical apportionment to programmed and correction insulin doses for hospitalized patients who are eating or not eating. Moreover, the role of bedside blood glucose monitoring in the hospital setting is discussed.

Conclusion: Strict glycemic management in hospitalized patients has been shown to improve outcomes. Development and implementation of specific strategies for insulin delivery and improved methods for blood glucose monitoring should help to achieve target blood glucose levels safely. (*Endocr Pract.* 2004;10[Suppl 2]:81-88)

Abbreviation:

NPO = nothing by mouth

INTRODUCTION

In the hospital, as in the outpatient setting, a thorough understanding of normal insulin function and the pharmacokinetics of exogenous insulin is essential for providing effective insulin therapy. The inpatient insulin regimen must be matched or tailored to the specific clinical circumstance of the individual patient.

Components of the Insulin Dose Requirement Defined Physiologically

In the outpatient setting, it is convenient to think of the insulin dose requirement in physiologic terms as consisting of the *basal* and *prandial* needs of the patient. In the hospital, nutritional intake is not necessarily provided as discrete meals; hence, the insulin dose requirement may be categorized into *basal* and *nutritional* needs. The term *nutritional insulin requirement* refers to the amount of insulin necessary to cover intravenously administered dextrose, total parenteral nutrition, enteral feedings, nutritional supplements administered, and discrete meals. When patients eat discrete meals without receiving other nutritional supplementation, the nutritional insulin requirement is equivalent to the *prandial* requirement. The term *basal insulin requirement* refers to the amount of exogenous insulin per unit of time necessary to prevent unchecked gluconeogenesis and ketogenesis.

An additional variable that determines total insulin needs in patients in the hospital is an increase in insulin requirement that generally accompanies acute illness. Insulin resistance occurs as a result of counterregulatory hormone responses to stress (for example, surgical procedures or illness) and the use of corticosteroids, pressor agents, or other diabetogenic drugs. The net effect of these factors is an increase in insulin requirement, in comparison with the requirement in a nonsick population. This portion of the insulin requirement specific to illness is referred to as illness- or stress-related insulin and varies between individuals (Fig. 1).

Components of the insulin requirement are classified as basal, prandial or nutritional, and correction insulin. When insulin orders are provided, the basal and prandial or nutritional insulin doses are written as programmed (scheduled) insulin, and correction-dose insulin is written

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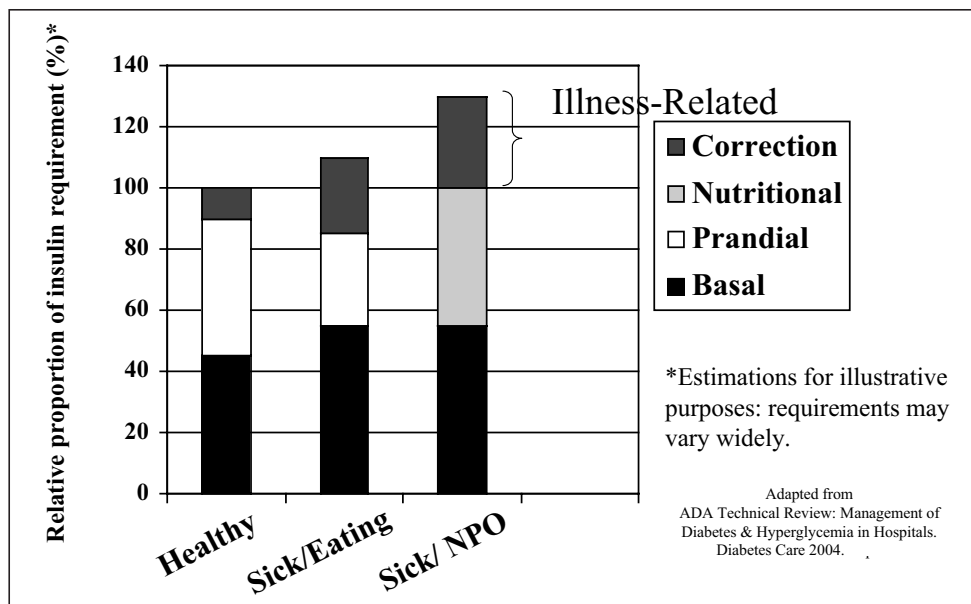


Fig. 1. Insulin requirements in health and illness. *NPO* = nothing by mouth.

as an algorithm to supplement the scheduled insulin (Appendix 1). Programmed and correction insulin are increased to meet the higher daily basal and prandial or nutritional requirements in the hospital setting. Total insulin requirements may vary widely.

Does the Patient Have Insulin Deficiency?

As in the outpatient setting, the key to providing effective insulin therapy in the hospital setting is determining whether a patient has the ability to produce endogenous insulin. Patients with a known history of type 1 diabetes have, by definition, insulin deficiency. In addition, other clinical features may be helpful in determining the level of insulin deficiency (Table 1). Patients verified as having insulin deficiency require basal insulin replacement to prevent iatrogenic diabetic ketoacidosis (that is, they must be treated with insulin at all times).

SUBCUTANEOUS INSULIN THERAPY

In most hospitalized patients with diabetes, subcutaneous insulin therapy may be used to attain glucose control. The components of the daily insulin dose requirement can be met by use of a variety of insulins, depending on the particular hospital situation. Subcutaneous insulin therapy is subdivided into programmed or scheduled insulin and supplemental or correction insulin (Appendix 1).

This review will use the term *programmed* or *scheduled insulin requirement* to refer to the dose requirement in the hospital necessary to cover both the basal and the nutritional needs. For patients who are eating discrete meals, separate consideration of the basal and the prandial components of the insulin requirement is appropriate.

Basal Insulin Therapy for Patients Who Are Eating

Subcutaneous basal insulin therapy can be provided by any one of several strategies. These options include continuous subcutaneous insulin infusion or subcutaneous injection of intermediate-acting insulin (including premixed insulin) or of long-acting insulin analogues. Some of these methods result in peaks of insulin action that may exceed the basal needs of the patient, causing hypoglycemia. Such an occurrence is most likely when the acute illness begins to resolve and basal insulin requirements that were increased because of stress or illness (or both) begin to return to normal levels. Although selected in part for basal coverage, NPH, Lente, and (to some extent) Ultralente insulin also deliver peaks of insulin that potentially can cover prandial needs, albeit with variable capability for matching the timing of nutritional intake. When NPH insulin is used in very low doses, it can also be administered four times daily as an alternative way to provide basal insulin action (2).

Prandial Insulin Therapy for Patients Who Are Eating

Prandial insulin replacement has its main effect on peripheral glucose disposal into muscle. Also referred to as *bolus* or *mealtime* insulin, prandial insulin is usually administered before eating. Occasionally—such as when it is unclear how much food will be eaten—this insulin may be injected immediately after eating. In such situations, the quantity of carbohydrates ingested can be counted, and an appropriate amount of rapid-acting insulin analogue can be injected. The technique of carbohydrate counting may be useful for patients practicing insulin self-management. The rapid-acting insulin analogues, insulin lispro and aspart, are excellent prandial insulins. Regular insulin is more accurately considered to have both basal and pran-

Table 1
Clinical Characteristics
of Patients With Insulin Deficiency

Known type 1 diabetes
 History of pancreatectomy or pancreatic dysfunction
 History of wide fluctuations in blood glucose levels
 History of diabetic ketoacidosis
 History of insulin use for >5 years, diabetes for >10 years, or both

Adapted from the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1) and based on consensus of the authors.

dial components because of its longer duration of action. Similarly, NPH and Lente insulins, with their distinct peaks and prolonged action, can be used for both their basal and prandial insulin effects. For hospitalized patients with severe insulin deficiency, this approach can be a disadvantage because the timing of meals and the quantity of food are often inconsistent.

Basal Insulin Therapy for Patients Who Are Not Eating

While not eating, patients without insulin deficiency may not require basal insulin. Because reduction of caloric intake may alter insulin resistance substantially in patients with type 2 diabetes, sometimes allowing previously insulin-requiring patients to maintain control of blood glucose with endogenous insulin production alone, the basal requirement is not easily determined. Withholding basal insulin in insulin-deficient patients, however, results in a rapid increase in blood glucose level by 45 mg/dL (2.5 mmol/L) per hour until ketoacidosis occurs (for review of related studies, see Clement et al [3]). This situation can occur when *sliding-scale* insulin therapy is the sole method of insulin coverage. Scheduled basal insulin therapy for patients who are not eating can be provided by many insulin types and methods.

Insulin for Patients With Intermittent Nutritional Intake

Hospitalized patients may receive nutrition intermittently. Included in this category are patients who are being transitioned between a status of nothing by mouth (NPO) and regular diet, patients with anorexia or nausea, and patients receiving overnight cycling of enteral feedings. Appropriate insulins used in combination therapy might include regular, intermediate, and long-acting insulins or insulin analogues, administered to cover basal needs and timed to match the intermittent nutritional intake.

Illness-Related or Stress Dose Insulin Therapy

The illness-related insulin can be apportioned among the basal insulin, the nutritional or prandial insulin, and the

correction doses. An important point is that illness-related insulin requirements decrease as the patient's condition improves; thus, in many situations, precise replacement of insulin may be difficult (Fig. 1). In attempting to meet the illness-related insulin requirement, and later to return to lower doses, it is important to recall that intravenous insulin infusion allows the greatest flexibility, and long-acting insulin analogue provides the least flexibility; other preparations or routes are intermediate. Rapid changes in illness-related insulin requirements necessitate close blood glucose monitoring and daily changes in the scheduled insulin doses, as the blood glucose levels dictate.

Correction-Dose or Supplemental-Dose Insulin Therapy

Also called *supplemental* insulin, correction-dose insulin therapy usually refers to the insulin used to treat hyperglycemia that occurs before meals or between meals. At bedtime, correction-dose insulin often is administered in a reduced dose in comparison with other times of day in order to avoid nocturnal hypoglycemia. Correction-dose insulin may also refer to insulin used to correct hyperglycemia in the NPO patient or in the patient who is receiving scheduled nutritional and basal insulin but not eating discrete meals. Correction-dose insulin should not be confused with *sliding-scale insulin*, which usually refers to a set amount of insulin administered for hyperglycemia without regard to the timing of the food intake, the presence or absence of preexisting insulin administration, or even individualization of the patient's sensitivity to insulin.

The traditional sliding-scale insulin regimens, usually consisting of regular insulin without any intermediate or long-acting insulins, have been shown to be ineffective at best and dangerous at worst (4-6). Problems cited with sliding-scale insulin regimens are, first, that the sliding-scale regimen prescribed on admission to the hospital is likely to be used throughout the hospital stay without modification (4). Second, a sliding-scale insulin regimen treats hyperglycemia after it has already occurred, rather than attempting to prevent the occurrence of hyperglycemia. This reactive approach can lead to rapid changes in blood glucose levels, exacerbating both hyperglycemia and hypoglycemia.

Correction-dose insulin therapy is an important adjunct to scheduled insulin, both as a dose-finding strategy and as a supplement when rapid changes in insulin requirements lead to hyperglycemia. If correction doses are frequently required, the scheduled insulin doses for the following day should be increased to accommodate the increased insulin needs.

PRACTICAL GUIDELINES AND WRITING INSULIN ORDERS

Practical guidelines for using insulin in various clinical settings in the hospital, including when the patient is

eating or not eating (NPO), are summarized in Appendix 1. Suggestions are also provided for selection of appropriate insulins, the delivery route, and their logical apportionment to programmed/scheduled insulin and supplemental/correction insulin doses.

When writing an insulin order for hospitalized patients, the physician should address all three components of insulin therapy—basal, prandial/nutritional, and correction dose. An example of a form that could be incorporated into computerized order sets to reduce errors is available (as “Appendix 1”) at <http://care.diabetesjournals.org/cgi/content/full/27/2/553/DC2>.

PREVENTION OF HYPOGLYCEMIA

Hypoglycemia, especially in insulin-treated patients, is the leading limiting factor in the management of blood glucose control in patients with type 1 and type 2 diabetes. The risk factors, treatment, and practical steps for minimizing the risk of hypoglycemia are discussed elsewhere in this publication (see Braithwaite et al, page 89).

ROLE OF BEDSIDE GLUCOSE MONITORING IN HOSPITALIZED PATIENTS

Implementation of intensive diabetes therapy in the hospital setting necessitates frequent and accurate blood glucose data. The blood glucose value is analogous to an additional “vital sign” for hospitalized patients with diabetes. Bedside glucose monitoring with use of capillary blood has advantages over laboratory venous glucose testing in that the results can be obtained rapidly at the “point of care,” where therapeutic decisions are made. Overall, the terms *bedside* and *point of care* glucose monitoring are used interchangeably.

To date, no hospital study has been conducted to test the effect of frequency of bedside glucose testing on the incidence of hyperglycemia or hypoglycemia in hospitalized patients. In the absence of such data, recommendations are based only on expert and consensus opinions. For patients who are eating, commonly recommended glucose testing frequencies are premeal and at bedtime. For patients who are not eating (NPO), glucose testing every 4 to 6 hours is usually sufficient for determining correction insulin doses. Patients in whom blood glucose is controlled with continuous intravenous insulin therapy typically require hourly blood glucose testing until the blood glucose levels are stable; then, measurements every 2 hours will suffice.

Bedside blood glucose testing is usually performed with portable glucose devices that are identical or similar to home devices for self-monitoring of blood glucose. Characteristics unique to hospitalized patients and common to nonhospitalized patients can lead to erroneous bedside blood glucose testing results (Table 2). Most of these errors can be prevented by implementing and maintaining a strong hospital quality control program (7,8). The effect of specific interfering substances or hematocrit depends on the device used (9-13). High levels of multiple interfering substances may alter bedside glucose results, even though each substance, by itself, may be below the interference threshold specified by the manufacturer (14).

New bedside glucose monitoring devices allow for identification of both the patient and the provider by reading a unique bar code. The glucose results also can be automatically downloaded into the hospital’s central laboratory database; this option expedites access to serial data and allows monitoring for quality control purposes. Most currently available bedside glucose meters use capillary whole blood samples for testing, but they are calibrated to

Table 2
Conditions Causing Erroneous Bedside Blood Glucose Results

Sources of analytical error	Sources of user error
Low hematocrit*	Inadequate meter calibration
High hematocrit†	Use of a test strip that does not match the meter code or that has passed the expiration date
Shock and dehydration†	Inadequate quality control testing
Hypoxia‡	Poor meter maintenance
Hyperbilirubinemia, severe lipemia*	Poor technique in performing finger prick
Specimen additives: sodium fluoride†	Poor technique of applying drop of blood to the test strip
Drugs—acetaminophen overdose, ascorbic acid, dopamine, fluorescein, mannitol, salicylate‡	Failure to record results in patient’s chart or to take action if blood glucose is out of target range

*Falsely increases result.

†Falsely lowers result.

‡Can either falsely lower or falsely increase result, depending on device used.

report results compatible to plasma, a feature that facilitates reliable comparison with the laboratory glucose tests. For critically ill patients, hypotension, dehydration, anemia, and interfering substances in the blood may render the results of capillary blood glucose testing inaccurate (10). Use of arterial or venous blood with bedside glucose meters in these situations is likely more reliable, but frequent comparison with the laboratory glucose test is recommended to avoid errors in insulin therapy. Arterial concentrations are approximately 5 mg/dL (0.3 mmol/L) higher than capillary concentrations and approximately 10 mg/dL (0.6 mmol/L) higher than venous concentrations. In the study by Van den Berghe et al (15), in which very strict glucose targets were maintained in critically ill patients, all blood glucose determinations were performed with a glucose analyzer at 1- to 4-hour intervals. The use of alternate-site blood glucose testing (for example, arm, leg, or palm) in the hospital has not been studied. The use of alternate-site glucose testing may cause erroneous results when the blood glucose level is rapidly increasing or decreasing and when hypoglycemia occurs (16).

As with any procedure in which blood is handled, the use of protective gloves is essential for health-care personnel performing bedside glucose monitoring. The use of self-retracting lancet devices has the potential to eliminate the possibility of needle-stick injury and risk for infection. Specific elements of a quality control program found to be necessary for appropriate use of bedside blood glucose testing in the hospital are outlined in Table 3 (17). Key participants in the program are representatives from the clinical laboratory, nurses, physicians, and hospital administrators. Additional guidelines are published by the National Committee for Clinical Laboratory Standards (18). For patients practicing diabetes self-management in the hospital, a quality control program to assess the patient's blood glucose device and the patient's testing technique is necessary to ensure accurate results.

SUGGESTIONS FOR FUTURE RESEARCH

Although outcome studies that provide evidence for a clear role for targeted glucose control in the hospital management of diabetes are beginning to accumulate in the scientific literature, numerous questions regarding optimal management of diabetes in the hospital setting remain to be addressed. These questions may be grouped into three main areas: (1) health-care outcomes attributable to glycemic control, (2) specific strategies for insulin delivery, and (3) processes for optimizing diabetes care and education in the hospital setting.

Specific Strategies for Insulin Delivery

Development and implementation of specific strategies for insulin delivery, based on knowledge of the pharmacokinetics of the currently available insulins, will enable physicians and nurses to overcome barriers to the effective use of insulin in managing blood glucose. Such

strategies will need to demonstrate the safety and efficacy of specific applications of insulin therapies that address known areas of need, including the following:

- Identifying optimal methods for delivering basal insulin under various clinical conditions
- Ascertaining the feasibility of using subcutaneously administered glargine or detemir insulin to meet basal insulin requirements (for example, on medicine services, in the operating room, and for periprocedural management)
- Determining the role of standardization of diabetes management and algorithmic care and validating such pathways and tools
- Assessing the safety and practicality of delivering insulin infusion therapy outside the intensive-care unit

Table 3
Characteristics of an Effective
Bedside Glucose Monitoring
Quality Control Program*

A specifically designated person, preferably a laboratory professional, responsible for administration and quality assurance of BGM program
A written procedure for BGM program
An organized training program that involves laboratory personnel and nursing staff
Defined frequencies and requirements for maintenance and cleaning of BGM instruments
Regular performance of quality control testing on each instrument (daily or by shift), depending on frequency of patient testing
A policy for regular comparison of BGM results from each operator and instrument with results from a corresponding sample tested in the clinical laboratory. (All BGM results should be within $\pm 15\%$ of the clinical laboratory results)
Participation in an external proficiency testing program
Acknowledgment of limitations of BGM and requirement of a clinical laboratory glucose determination when a BGM result is outside a defined range
Acknowledgment of effect of hematocrit value variation on BGM results and establishment of hematocrit value limitations for instrument in use
Determination of bias of instrument in use and communication of this information to physicians and institutional quality assurance program

*BGM = bedside glucose monitoring.
Adapted from Jones et al (17).

- Formulating simple algorithms for subcutaneous delivery of programmed basal, prandial or nutritional, and correction doses of insulin as well as algorithms for insulin infusion

Improved Methods for Glucose Monitoring

Current methods for blood glucose monitoring can be painful and time-consuming. Improved methods for frequent and accurate blood glucose monitoring would enhance the ability to reach target blood glucose levels safely. Development of continuous glucose monitoring systems that are safe and accurate is encouraged.

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APPENDIX 1
Practical Guidelines for Hospital Use of Insulin*

Clinical setting	Programmed/ scheduled insulin option(s)		Supplemental/ correction insulin option(s)	Comments
	Basal	Prandial &/or nutritional		
				Total daily insulin requirement may be calculated on basis of prior insulin doses or as 0.6 U/kg per day Basal insulin generally accounts for 40-50% of daily insulin requirement Prandial &/or nutritional or supplemental/correction doses may be calculated as 10-20% of total daily insulin requirement for each dose Patients with type 1 DM always require continuous insulin coverage to avoid ketosis
<i>Nutritional status</i>				
Eating meals	Int-I bid or hs LA-I hs or AM Insulin drip	Reg-I or RA-I ac—B & D or B, L, & D	Reg-I or RA-I ac ± hs	Give reg-I 30-45 min ac or RA-I 0-15 min ac Give glargine as once-daily dose, usually at hs Avoid/minimize reg-I & RA-I doses at hs to decrease risk of nocturnal hypoglycemia 70/30 or 75/25 insulin may be used ac (B & D) to meet both basal & prandial needs Insulin drip is Rx of choice in severely decompensated type 1 DM ± DKA and in type 2 DM with HHS
Not eating	Insulin drip Int-I bid or hs LA-I hs or AM	NA	Reg-I q 4-6 h RA-I q 4 h	Insulin drip is Rx of choice in severely decompensated type 1 DM ± DKA and in type 2 DM with HHS
<i>Perioperative or periprocedural</i>				
Will eat postop or after procedure (eg, cataract extraction, cardiac catheterization, endoscopy)	Based on prior insulin Rx: Int-I, give 1/2-2/3 usual AM dose LA-I glargine, continue usual dose PM prior	When eating resumed: Restart prior doses of reg-I or RA-I ac	Until eating resumed: Reg-I q 4-6 h RA-I q 4 h	Usual insulin &/or oral agent doses given PM preop to ensure adequate glycemic control on AM of procedure Patients with DM should be on OR list for early AM to minimize the time kept NPO. This decreases risk of hypoglycemia & allows maintenance of optimal metabolic homeostasis
Will not eat (eg, major surgical procedure)	Insulin drip Reg-I q 4-6 h RA-I q 4 h Int-I, give 1/2 usual AM dose LA-I glargine, give usual daily dose	NA	Until eating resumed: Reg-I q 4-6 h RA-I q 4 h	Where a prolonged postop NPO period is anticipated (eg, cardiothoracic, major abdominal, CNS cases), insulin drip Rx is recommended Starting dose for perioperative maintenance insulin drip is 0.2 U/kg per hour
<i>ICU</i>				
	If NPO &/or clinically unstable: Insulin drip Reg-I q 4-6 h RA-I q 4 h If eating: Continue prior Int-I or LA-I	If NPO: NA If eating: Reg-I or RA-I ac & hs	Reg-I q 4-6 h RA-I q 4 h	Evidence-based outcome studies support use of insulin drip as Rx of choice for decompensated DM in ICU setting, including coronary care (acute myocardial infarction) and surgical ICU
<i>Enteral tube feeding</i>				
Continuous	24 h: Int-I bid LA-I hs or AM Daytime only: Int-I AM	Reg-I q 4-6 h RA-I q 4 h During tube feeding only: Reg-I q 4-6 h RA-I q 4 h	Reg-I q 4-6 h RA-I q 4 h	Basal insulin dose generally no more than 40% of total daily insulin requirement to avoid hypoglycemia if enteral feeding interrupted Nutritional insulin requirements met with programmed doses of reg-I or RA-I May use low-dose int-I at hs to control fasting hyperglycemia If tube feeding interrupted (eg, for procedure or intolerance), increase finger-stick BG checks
Bolus	24 h: Int-I bid LA-I hs or AM Daytime only: Int-I AM	Reg-I q 4-6 h RA-I q 4 h During bolus delivery period only: Reg-I q 4-6 h RA-I q 4 h	Reg-I q 4-6 h RA-I q 4 h	Give reg-I 30-45 min or RA-I 0-15 min before bolus to control post-bolus BG excursions Check finger-stick BG 2 h after reg-I or 1 h after RA-I to determine dose adjustments for post-bolus target BG <180 mg/dL May use low-dose int-I at hs to control fasting hyperglycemia

APPENDIX 1 (Continued)
Practical Guidelines for Hospital Use of Insulin*

Clinical setting	Programmed/ scheduled insulin option(s)		Supplemental/ correction insulin option(s)	Comments
	Basal	Prandial &/or nutritional		
<i>TPN</i>	Reg-I added to TPN bags		Reg-I q 4-6 h	Basal & nutritional insulin needs met with reg-I added to TPN bag directly To determine daily dose of insulin to add to TPN bag: use separate IV insulin infusion for 24 h to determine daily insulin requirement & then add 2/3 of this amount to subsequent TPN bags <i>or</i> add 2/3 of total units of insulin administered SQ the previous day to the next day's TPN bag as reg-I, until daily dose determined Use SQ insulin Rx with caution with TPN. Lack of correlation of insulin peaks & troughs with nutrient delivery may lead to erratic BG control
<i>Transition to oral intake</i>	Int-I bid LA-I hs or AM	Reg-I or RA-I ac	Reg-I or RA-I ac ± hs	Give reg-I 30-45 min or RA-I 0-15 min before meal to control postprandial BG excursions Postprandial target BG <180 mg/dL Check finger-stick BG 2 h after reg-I or 1 h after RA-I to determine prandial insulin dose adjustments
<i>High-dose GC Rx</i>	Insulin drip Int-I bid LA-I hs or AM	Reg-I or RA-I: ac (B & D) or ac (B, L, & D) if eating or q 4-6 h if NPO	Reg-I or RA-I: ac & hs if eating or q 4-6 h if NPO	High-dose GCs raise insulin requirements Adjust/increase insulin doses to counter postprandial hyperglycemia & BG peak that may occur 8-12 h after once-daily GC dose Alternate-day GC doses necessitate alternate-day insulin doses

*ac = before meals; AM = morning; B = breakfast; BG = blood glucose; bid = twice a day; CNS = central nervous system; D = dinner; DKA = diabetic ketoacidosis; DM = diabetes mellitus; GC = glucocorticoid; HHS = hyperglycemic hyperosmolar state; hs = bedtime; ICU = intensive-care unit; Int-I = intermediate-acting insulin (NPH or Lente); IV = intravenous; L = lunch; LA-I = long-acting insulin (glargine or Ultralente); NA = not applicable; NPO = nothing by mouth; OR = operating room; PM = evening; postop = postoperatively; preop = preoperatively; q = every; RA-I = rapid-acting insulin (lispro or aspart); reg-I = regular insulin; Rx = therapy; SQ = subcutaneously; TPN = total parenteral nutrition; ± = with or without.