Insulin Use in the Hospital: An Evolving Therapeutic Paradigm

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Abstract
As evidence has accumulated confirming the importance of carefully managing inpatients with hyperglycemia, hospitals are facing the challenge of developing safe protocols for insulin administration. Standard protocols with multidisciplinary input are essential, but implementation can occur only after all hospital departments have completed an educational program. The subsequent increased use of intravenous insulin infusions and increased monitoring of hyperglycemia in patients throughout the hospital has led to a greater demand for laboratory services, particularly point-of-care glucose monitoring systems. Involving clinical laboratory personnel is critical to the implementation process to ensure that resources are appropriately allocated. Successful implementation requires coordination and communication between the clinical laboratory and other hospital departments that deliver bedside care to the hyperglycemic patient.

Hospital systems are now facing the task of caring for significant numbers of patients with diabetes and hyperglycemia—perhaps 20% to 30% of adult inpatients—at a time when usual management practices are being challenged.1 Managing hyperglycemia in hospitalized patients has typically been handled in a casual fashion with either indifference or default “retroactive” sliding-scale insulin regimens.2 This pattern of care has been underpinned by a fear of hypoglycemia and the impression that hyperglycemia, unless dangerously high, will not affect outcomes during a hospital stay. As evidence to the contrary began to mount, the American College of Endocrinology (ACE) convened the initial multidisciplinary task force in 2003 and subsequently published recommended standards of care.3 In 2004, the American Diabetes Association (ADA) published a technical review on managing diabetes and hyperglycemia in the hospital and included standards of care for inpatients as a part of their annual clinical practice recommendations in 2005.4,5 As hospitals began to examine their methods of managing hyperglycemia, they faced a number of logistical challenges, including an increased demand on staff and resources, plus the need to develop multidisciplinary consensus and educational resources to implement common protocols. The ADA, in its latest practice recommendations, has acknowledged these difficulties and added qualifying phrases and somewhat less stringent glycemic goals to the guidelines, providing flexibility to hospitals in their implementation of tight glycemic control practices.5 This review will discuss the evidence that led to these recommendations and then focus on contemporary guidelines for insulin use in the hospital, including intravenous infusions and subcutaneous insulin in the non-critically ill patient.

Evidence Favoring Tight Glycemic Control
Malmberg and colleagues reported an overall reduction in mortality of 29% at 1 year in diabetics with acute myocardial infarction treated with intravenous insulin for 24 hours followed by 3 months with multiple subcutaneous insulin injections in the Diabetes Mellitus Glucose Insulin in Acute Myocardial Infarction (DIGAMI) study published in 1995.6 The subjects in the DIGAMI trial with a lower cardiovascular risk profile and no previous insulin exposure had a 52% mortality rate reduction. Beginning in 1992, Furnary and colleagues initiated the Portland Diabetes Project in patients undergoing open-heart surgery. Progressive lowering of the target blood glucose goals to 100 to 150 mg/dL using intravenous insulin reduced the risk of death by 57% and deep sternal wound infections by 66%.7

The report that attracted the greatest attention was the landmark Van den Berghe study in 2001 that randomly assigned surgical intensive care unit (ICU) patients to either an intensive intravenous insulin protocol with a goal of normalizing glucose levels to 80 to 110 mg/dL or a conventional regimen that used intravenous insulin only if glucose levels exceeded 220 mg/dL.8 Overall, hospital mortality was reduced by 34% in the intensively managed group with additional reductions in acute renal failure (41%), sepsis (46%), transfusions (50%), and polyneuropathy (44%). Severe hypoglycemia, defined as a glucose <40 mg/dL, occurred in 5.2% of the intensively managed patients compared with 0.8% of the conventionally managed patients, but there were no associated adverse outcomes. Van den Berghe then evaluated the same intensive insulin protocol in the medical ICU in a similar randomized controlled clinical trial.9 In this second study, intensive insulin did not reduce overall hospital mortality, but again reduced the risk of acute renal failure and shortened ventilator dependency and ICU and hospital length of stay. Further analysis...
revealed that those subjects in the ICU for at least 3 days treated intensively did have a reduction in mortality, similar to the surgical ICU study, but those in the ICU less than 3 days treated intensively appeared to have a higher mortality rate. Further post hoc analysis of the short-stay group demonstrated that admission risk factors caused a selection bias and that the mortality rate was not significantly increased in those treated with the intensive regimen. Concern regarding the benefit-versus-harm of intensive insulin therapy caused Van den Berghe to critically review the pooled database of 2,700 patients to address this question.\textsuperscript{10} Mortality was highest in those patients with mean glucose levels >150 mg/dL and lowest in those with glucose levels <110 mg/dL.

Two more recent studies of intravenous insulin, VISEP and Glucontrol, were stopped early due to hypoglycemia but were underpowered to demonstrate a mortality rate difference.\textsuperscript{11-13} Other notable published trials, including DIGAMI-2, CREATE-ECLA, and GIST trials, all failed to achieve glucose targets in the intensive groups so that outcome differences could not be demonstrated.\textsuperscript{14-16}

The evidence regarding outcomes associated with inpatient hyperglycemia outside the critical care unit is based primarily on analyses of patient groups based on admission glucose levels. Patients admitted to a general medical surgical unit with newly discovered hyperglycemia had a higher mortality rate (16%) than those with diagnosed diabetes (3%) or those with normal blood glucose levels (1.7%).\textsuperscript{17} Patients with community-acquired pneumonia with admission hyperglycemia had a mortality risk that was 73% higher and a hospital complication risk that was 52% higher than those with normoglycemia.\textsuperscript{18} Stroke patients with admission hyperglycemia had higher inpatient mortality rates and poorer functional recovery at 1 year.\textsuperscript{19} Other patient groups with worse outcomes linked to hyperglycemia include diabetes undergoing surgery, chronic lung disease patients with exacerbations, and those on total parenteral nutrition.\textsuperscript{20-22}

**Current ADA Recommendations for Inpatient Care**

In January 2008, the ADA published their annual supplement to *Diabetes Care* with an updated section on caring for diabetic patients in the hospital.\textsuperscript{5} It should be noted, however, that these guidelines do not specifically address managing hyperglycemia in nondiabetics. Many hospitals do apply these recommendations to managing patients who have persistent hyperglycemia in the hospital. See Table 1 for a summary of these recommendations. Based on the evidence available on critically ill patients, the standard of care in these patients has been intravenous insulin infusions to maintain glucose levels as close to 110 mg/dL as possible with the modifier in 2008, “generally <140 mg/dL.” An additional qualifier is a requirement for a protocol with proven efficacy and safety that will not increase the risk of severe hypoglycemia. The 2008 ADA guidelines emphasize safety and appear to provide less stringent glycemic goals to reduce the risks of hypoglycemia.

For noncritically ill patients, glycemic goals include fasting glucose levels <126 mg/dL and random glucose levels <180 to 200 mg/dL. “If these ranges can be safely reached.” The ADA recommendations also include statements addressing the need for prandial insulin in patients who are being fed and discourage the use of stand-alone, sliding-scale insulin regimens in diabetic patients. Other key pieces are recommendations for A1c testing, diabetes education, and planning for follow-up testing in patients not previously known to have diabetes. The results of A1c tests can be particularly helpful in the decision process regarding the need for continued insulin immediately upon discharge versus resuming previously prescribed oral antidiabetic therapies.

**Implications for the Clinical Laboratory**

Increased use of intravenous insulin infusions and greater awareness of the implications of hyperglycemia in patients throughout the hospital has led to an increased demand for laboratory services, particularly point-of-care glucose monitoring systems. The ADA recommendation that current hemoglobin A1c test results are integral to the discharge planning process has also increased laboratory workloads. Recognizing that involvement of the clinical laboratory was critical to our intensive glycemic control initiative meant including the clinical laboratory director in the planning process from the outset. This facilitated communication between all involved departments and ensured that resources were appropriately allocated. The clinical laboratory was instrumental in evaluating newer technologies and advising the multidisciplinary committee regarding facility needs. This communication facilitated a teamwork approach necessary in an initiative affecting all hospital departments that deliver bedside care to the hyperglycemic patient.

The rapid availability of glucose values is critical to managing tight glycemic control and requires using point-of-care bedside meter systems. The increased focus on glucose monitoring has required our hospital to triple its meter inventory and test-strip usage over the past 3 years, and the laboratory point-of-care manager has been instrumental in maintaining the system. Accuracy in methodology mandates robust quality control systems to prevent errors in technique and documentation. The laboratory is critical to advising clinical personnel regarding point-of-care testing shortcomings when there are large variations in hematocrit and interferences from mannitol, dopamine, salicylate, marked hyperbilirubinemia, and hyperlipemia.\textsuperscript{1} The laboratory can also advise when there are discrepant point-of-care glucose values in patients with poor peripheral perfusion on pressor agents or in severe congestive failure. Our laboratory has been helpful in providing rapid glucose results on blood samples obtained from a central source such as an arterial line.

**Intravenous Insulin Implementation**

Multiple intravenous insulin protocols have been published in recent years, but no comparison trials have been completed. Most hospitals limit intravenous insulin use to critical care units or dedicated intermediate care units that have a higher level of staffing compared with usual medical surgical care units. The greater

### Table 1. ADA Inpatient Care Guidelines

<table>
<thead>
<tr>
<th>Blood glucose goal</th>
<th>Requirements</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Close to 110 mg/dL as possible and generally &lt;140 mg/dL</td>
<td>Requires an IV protocol with efficacy and safety without increased risk for severe hypoglycemia.</td>
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- **Critically Ill Patients:**
  - Blood glucose goal: as close to 110 mg/dL as possible and generally <140 mg/dL.
  - Requires an IV protocol with efficacy and safety without increased risk for severe hypoglycemia.

- **Noncritically Ill Patients:**
  - Fasting glucose levels <126 mg/dL.
  - Random glucose levels <180–200 mg/dL.
  - Insulin is the preferred drug in most patients.
  - Scheduled prandial insulin doses should be given in relation to meals and adjusted according to point-of-care glucose levels.
  - Traditional sliding-scale regimens are not recommended.
intensity of monitoring and closer degree of observation required in these patients usually exceeds the capabilities of the staff on contemporary medical surgical units with high patient-nurse ratios. Successful implementation of a tight glycemic control initiative requires multidisciplinary input and administrative support. Table 2 lists the key components to protocol implementation. Staff and resource assessment and allocation are critical as managing intravenous protocols is labor intensive. Important, clearly defined components of an intravenous protocol are glycemic targets, monitoring frequency, provisions for nutritional support, and an algorithm for adjusting the insulin infusion rate. Hypoglycemia management and guidelines for dealing with changes in enteral feeding are important additional components.

The importance of using a standard protocol cannot be overemphasized. This will reduce confusion and errors and result in a safer environment for the critically ill patient. At least 2 published studies evaluating implementing a standard protocol demonstrated improved glycemic control and less hypoglycemia. Our hospital and others have implemented a protocol in a single nursing unit after preparatory education and supervision. Piloting the protocol allowed for adjustments in the algorithm based on practicality, but also demonstrated improved outcomes with adherence to the protocol. The frequency of hypoglycemia was reduced by adjustments in the initial algorithm, such as less aggressive up-titration of infusions as patients approached glycemic goals. Hospitals have found that tight glycemic control initiatives have led to using insulin infusions in the majority of critically ill patients during their stays in critical care units. The logistical challenges include a greater demand for infusion pumps, staffing increases such as nursing technicians, and increased numbers of bedside meters and test strips as noted previously. Ongoing staff education is critical to maintain the integrity of the standard protocol. Some centers have employed computer-based systems to deliver insulin infusions, but this requires an even greater commitment of resources than the usual nurse-driven algorithms. Administrative support and working within the limits of resources are therefore critical to implementing tight glycemic control practices.

**Transition to Subcutaneous Insulin**

The majority of patients on intravenous insulin will require transition to scheduled subcutaneous insulin upon transfer out of the critical care unit. The exceptions are those nondiabetics on low infusion rates of <0.5 units/hour. For the patient requiring high infusion rates of >2 units/kg/24 hours, it may be very difficult to properly manage on subcutaneous insulin until insulin requirements have declined somewhat. The brief duration of action of intravenous insulin requires that subcutaneous insulin be given prior to cessation of the insulin infusion. Protocols for transition extrapolating from intravenous infusion rates have been published and tested with reasonable success. The rationale for providing approximately 80% of infused insulin with subcutaneous insulin is based on the premise that insulin requirements are decreasing with the reduction in the stress of illness. If the patient has been receiving minimal nutrition while on the infusion, the initial calculation of converting to 80% of the infused rate provides only basal insulin coverage. Patients will also need an equivalent amount of insulin to cover meal or prandial needs, usually equally divided among the 3 main meals. If there is uncertainty regarding oral intake, then basal insulin plus supplemental insulin can be ordered until oral intake is established.

**Subcutaneous Insulin Protocols**

In our hospital, the next challenge after establishing tight glycemic control practices in the critical care units was transitioning to the floor and maintaining reasonable glycemic control despite the vagaries of unpredictable intake and less intense monitoring. Reliance on sliding-scale insulin alone has been an established practice due primarily to convenience and familiarity, contrary to evidence that this method is ineffective and sometimes dangerous. Our task was therefore to follow a pathway similar to that developed in the critical care units with establishment of a standard subcutaneous insulin order set and implementation of an intense educational program for all staff. Table 3 highlights the key components of the implementation process. During the process, we realized that the hospital formulary included 14 insulin products. With the involvement of the Pharmacy and Therapeutics Committee, a streamlined insulin formulary was approved. This included regular human insulin, neutral protamine hagedorn (NPH), a basal analog, a rapid-acting analog, and a premixed 70/30 insulin.

With the assistance of information systems staff, a subcutaneous insulin order set was activated in our computer order-entry system. Components of the order set included orders for A1c testing, frequency and timing of point-of-care testing, basal insulin, prandial insulin, correction algorithms, hypoglycemia protocols, and consents. Our nutrition department converted the diabetic diet options to carbohydrate-consistent diets to facilitate the integration of scheduled prandial insulin orders. The order set provides guidelines to the practitioner regarding insulin dose calculations for basal and prandial insulins similar to those recommended by Inzucchi. We strongly discouraged using stand-alone, sliding-scale or correction insulin orders, except in the nondiabetic individual for 1 to 2 days and eliminated the embedded sliding-scale insulin orders from existing order sets. We have established guidelines for the nursing staff addressing common dilemmas, such as poor intake, hypoglycemia at meal times, and interruption

**Table 2. Keys to Protocol Implementation**

- Multidisciplinary input
- Administration support
- Assessing resource/staff needs
- Standardizing procedures
- Clarifying treatment goals
- Staff education
- Pilot test procedures
- Incorporating feedback
- Revising/adapting protocol
- Ongoing education

**Table 3. Facilitating Improvements in the Hospital**

- Staff education: preemptive and ongoing
- Common protocols
- Accessible documentation of insulin/glucose values
- Streamlining the insulin formulary
- Incremental implementation
- Eliminating the sliding scale as a stand-alone order
- Teamwork approach
- Considering errors and hypoglycemic events as educational opportunities
in enteral feedings. A major challenge that required interdepartmental cooperation was the coordination of point-of-care testing, delivery of meal trays, and prandial insulin administration.

Our subcutaneous order set places analog insulins in preferential positions over NPH and regular insulin for basal, prandial, and correction usage because the pharmacokinetic profiles of analogs more closely mimic physiologic patterns.\textsuperscript{36} We prefer basal analog insulins, such as glargine or detemir, to NPH because of their longer duration of action and relatively flat-peak action curves. Both glargine and detemir have been shown to be associated with a lower risk of nocturnal hypoglycemia than NPH insulin, presumably due to a near peakless pharmacokinetic profile.\textsuperscript{37,38}

Regular insulin injected subcutaneously results in a delayed peak action of 2 to 3 hours with a relatively long duration of action of at least 6 hours. This means that mealtime injections should be given at least 30 minutes prior to eating to avoid immediate post-meal hyperglycemia and late post-meal hypoglycemia. If regular insulin is given at 4- to 5-hour intervals with meals in the hospital, then overlap of insulin effect can occur, resulting in a greater risk of hypoglycemia in the afternoon and evening hours. On the other hand, the newer rapid-analog insulins (lispro, aspart, and glulisine) have an onset of action within minutes and a relatively shorter duration of action of 4 to 5 hours. This results in less post-meal hyperglycemia and a lower risk of later hypoglycemia with the rapid analogs compared with regular insulin.\textsuperscript{39–41} Because of the rapid onset of action of the newer analogs, prandial injections should be given only when the patient has been delivered a meal tray. The rapid analogs can also be given at the completion of a meal in the case of uncertainty regarding the patient’s intake. In the interest of safety, our nursing guidelines provide for omitting a scheduled prandial insulin dose if a patient eats <50% of any given meal. Our orders also clearly indicate that patients who are being fed should be given their prandial and correction insulins together, reducing the frequency of injections and providing for correction insulin only at mealtime if food intake is limited. This clearly necessitates that the prandial and correction insulins are of the same type, and this point has required additional staff education. The rapid analogs have an earlier peak than regular insulin and more predictable absorption, making them also more desirable than regular insulin for correction purposes.\textsuperscript{46} Table 4 lists the more common errors we have encountered with the insulin order set.

In the situation of the diabetic patient admitted to the hospital with an acute illness and previously managed with oral antidiabetic medications, we strongly advise converting to a subcutaneous insulin regimen, unless critically ill. The rationale is clearly presented in the ADA practice guidelines, including risks of hypoglycemia with sulfonylureas and contraindications to metformin acquired pneumonia.

| Table 4_Mismanagement Scenarios in the Hospital |

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Cause</th>
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<tbody>
<tr>
<td>Indifference to hyperglycemia</td>
<td>Failure to provide scheduled prandial insulin</td>
</tr>
<tr>
<td>Different insulins for prandial and correction needs</td>
<td>Overly aggressive correction insulin at HS or 3 AM</td>
</tr>
<tr>
<td>Omitting basal insulin</td>
<td>Using oral agents in acutely ill patients</td>
</tr>
<tr>
<td>Failure to adjust insulin for enteral feeding changes</td>
<td>Lack of diabetes self-care skill assessment and education</td>
</tr>
</tbody>
</table>

Mismanagement Scenarios in the Hospital

13. Van den Berge G. Insulin therapy in the intensive care unit should be targeted to maintain blood glucose between 4.4 mmol/l and 6.1 mmol/l. Diabetologia. 2007 Nov 27. Epub ahead of print.


