PERSPECTIVES

# Inpatient Diabetology

## The New Frontier

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**Tight glycemic control is now an imperative of outpatient diabetes care. The inpatient arena remains under the influence of an ineffective paradigm characterized by tolerance for hyperglycemia and a reluctance to use insulin intensively. This article is a call to action against the lip service paid to inpatient diabetes care. The compelling in vitro and in vivo evidence for the benefit of intensive insulin-mediated glycemic control is summarized. The linchpin of current inpatient care is a commonly used insulin sliding scale. This autopilot approach as the sole mode of treatment for inpatient hyperglycemia has been strongly condemned. Nevertheless, it continues to survive. The evidence supports the compelling argument that the adverse effect of hyperglycemia on hospital length of stay, morbidity, and mortality is substantial. Clinicians, nurses, administrators, and insurers ought to look critically at the prevailing paradigm and spearhead the much-needed revolution in inpatient diabetology. The issue of glycemic targets, the need for noninvasive blood glucose monitoring, and the role of nursing staff in this revolution are raised. We call for the banning of the insulin sliding scale use as the sole diabetes order. Also, the use of basal insulin via continuous intravenous insulin infusion or subcutaneous insulin analogs should be embraced. Educating nurses, house staff, and other frontline professionals in the adverse consequences of the current paradigm is essential. Inpatient glycemic control matters; clinical and financial outcomes are at stake. It behooves the health care system and the diabetic public to address the contemporary state of inpatient diabetology as soon as possible.**

***KEY WORDS:*** **inpatient diabetes; intensive insulin; sliding scale insulin.**
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Today a new frontier in diabetology beckons. Its landscape is the inpatient arena, a place where an ineffective paradigm still holds sway. Despite mounting evidence and maverick voices, attitudes toward inpatient diabetes care remain steeped in the historical use of "the insulin sliding scale," the reluctance to use insulin intensively, and the tolerance for inpatient hyperglycemia except when it reaches extreme magnitudes. The emerging evidence, however, puts this area of diabetes care on the verge of a much-needed revolution with a potentially enormous impact on hospitalization expenditures, inpatient morbidity, and mortality.

This article is a call to action against the lip service paid to inpatient diabetes care, and for advancing a philosophy that embraces inpatient intensive insulinization. The literature contains myriad protocols for such intensive approach and the evidence supporting their use is very compelling.[1–5] Based on the strength of the evidence, a new inpatient paradigm is needed where aggressive insulin therapy is a clinical imperative not only for those who are in severe glycemic crises, but for all postoperative and critically ill inpatient diabetics. As to general medical inpatients, the available evidence points in the direction of the new paradigm, but is not yet strong enough, as randomized, controlled trials are still lacking.

### COMPELLING LITERATURE EVIDENCE

Table 1 summarizes some of the in vitro evidence detailing the adverse effects of hyperglycemia on host defenses, and their amelioration by insulin and euglycemia.[6–20] Table 2 summarizes the clinical evidence (including study design, sample size, and findings) showing a strong salutary effect of intensive insulinization and euglycemia on clinical outcomes in hospitalized diabetics.[21–40] The evidence for the benefits of this intensive approach is shown mostly in critically ill, post-operative, and post-myocardial infarction diabetic patients (Table 2).[21–34] The American College of Cardiology and the American Heart Association have recently made tight glucose control a class I recommendation in managing diabetics with acute coronary syndrome.[41] In general medical inpatients with hyperglycemia, no prospective, randomized controlled studies are available to date showing that intensive insulin therapy via either continuous intravenous insulin infusion (CIII) or subcutaneous insulin analogs, and/or tight glycemic control will reduce morbidity, mortality, and length of hospital stay. However, preliminary data from the retrospective study by

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**Table 1. In Vitro Studies**

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| Hansen et al. (2003)[6] | Intensive insulin therapy has profound effects on markers of inflammation as shown by a decrease in C-reactive protein and an increase in mannose-binding lectin, both indicators of the presence and extent of inflammation and intrinsic antimicrobial properties, respectively. The improvement in morbidity and mortality is attributed to maintaining normoglycemia and the beneficial properties of insulin. |
| Tenenberg et al. (1999)[7] | A high-glucose environment prevented lipopolysaccharide (LPS)-induced inhibition of apoptosis in normal neutrophils. The high-glucose environment may mediate the apparent lack of LPS responsiveness in diabetic neutrophils, resulting in their more rapid rate of clearance from infection sites and decreased functional longevity. |
| Rassias et al. (1999)[8] | Neutrophil function in diabetic patients on conventional insulin treatment had a 54% decrease in phagocytic function versus 25% in those on aggressive insulin treatment. Secondary outcome: increased infection in the conventional insulin group. |
| Alexiewicz et al. (1995)[9] | Polymorphonuclears (PMNs) from diabetic patients showed elevated basal levels of cytosolic calcium, reduced ATP content, and impaired phagocytosis compared with controls, which improved with treatment with glyburide. |
| Marhoffer et al. (1992)[10] | PMNs of diabetic patients showed a significant reduction in the uptake of $^{3}$H-thymidine-labeled *S. aureus*, which represented ingestion of *S. aureus* and bacterial killing, compared with healthy nondiabetic controls. |
| Hostetter et al. (1990)[11] | Expression of a surface protein by *Candida albicans* is increased in a dose-dependent fashion as hyperglycemia increases from 1 to 20 mM with an abrupt increase from 10 to 20 mM (180–360 mg/dl), resulting in impaired phagocyte recognition and adhesion of the yeast to endothelial surfaces. |
| Nielson et al. (1989)[12] | PMNs incubated with higher glucose concentrations had a marked reduction in the magnitude of respiratory burst induced by the chemotactic peptide N-formylmethionyl-leucine-phenylalanine. The respiratory burst was impaired in all specimens of PMNs incubated in plasma containing any concentration of glucose >11.11 mM (200 mg/dl). |
| MacRury et al. (1989)[13] | Phagocytic function in poorly controlled diabetic patients over 12 weeks improved with enhanced glycemic control. |
| Sima et al. (1989)[14] | The ability of alveolar macrophages in the diabetic BB rat to phagocytize and kill *S. aureus* was decreased in hyperglycemic diabetic rats, and was corrected after glycemic control was achieved with insulin. |
| Naghibi et al. (1987)[15] | Defective bactericidal capability of white blood cells against *P. aeruginosa* in diabetic patients improved after intensified glycemic control. |
| Bagdade et al. (1978)[16] | Granulocyte adherence in hyperglycemic diabetic patients was 53% of nondiabetic controls, which improved after initiation of antidiabetic regimen. |
| Tan et al. (1975)[17] | The amount of killed intracellular bacteria (% of initial inoculum): 95.4% in controls versus 72.8% in diabetic patients. Further evaluation showed impaired phagocytosis, impaired intracellular killing, and combination of both in those with severe bacterial infections with diabetes. |
| Bagdade et al. (1974)[18] | Uncontrolled diabetic subjects demonstrated a marked impairment in phagocytosis and a significant decrease in the rate of bacterial killing by granulocytes, which improved remarkably in controlled diabetics to levels similar to control values. |
| Mowat et al. (1971)[19] | Utilized an in vitro method of measuring chemotaxis of PMNs to show a relative deficiency in diabetics as compared to normal controls, which was corrected by incubation of the cells with insulin. |
| Bybee et al. (1964)[20] | Leukocytes from diabetic patients in ketoacidosis showed a statistically significant decrease in uptake of pathogenic Staphylococci that disappeared upon correction of the ketoacidotic state. |

Umpierrez et al. included adult admissions to general medical non-intensive care unit (ICU) floors and showed poor outcomes in those with newly diagnosed hyperglycemia as well as in those with hyperglycemia and known diabetes, compared to normoglycemic patients.[25] Also, hyperglycemia per se seems to predict poor prognosis in patients without known diabetes admitted with acute stroke.[37]

## THE INPATIENT ARENA

The current paradigm for handling hospitalized diabetic patients is transmitted from elder to younger generations of clinicians, and remains ingrained in the clinical culture. It is typified by one order within the all-familiar order set for the insulin sliding scale, which simply states: "call MD if BG >400 mg/dl." The message is that clinicians need not be actively involved until extreme hyperglycemia sets in, and that the sliding scale insulin orders will automatically handle the diabetes while they are freed to deal with the illness(es) at hand.

This is not the message that the recent literature carries. Nevertheless, the old paradigm remains dominant and unscathed despite the many authoritative voices denouncing it, calling for active euglycemic intervention, showing the deleterious effects of current practices, and documenting the poor glycemic control in hospitalized diabetics.[42–47] This is a problem of potentially large magnitude because it involves a substantial proportion of the hospital population. In our hospital, approximately 25% of inpatients carry the diagnosis of diabetes. This obviously underestimates the proportion of hyperglycemic inpatients who are not labeled as, or previously known to be, diabetic. The emerging evidence of a deleterious effect of hyperglycemia on hospital morbidity, recovery, and mortality argues for calling on providers (primary care and specialists), nurses, administrators, and insurers among others to look critically at the prevailing paradigm.

**Table 2. Clinical Studies**

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| Van den Berghe et al. (2001)[21] | Prospective, randomized, controlled study of intensive insulin therapy aiming at glycemic goal of 4.5–6.1 mM (81–110 mg/dl) in critically ill surgical adult patients ($n$ = 1,548) led to:<br>Mortality reduction: 32%<br>Acute renal failure requiring dialysis: 41% reduction<br>Septicemia: 46% reduction in recurrent episodes<br>Antibiotic use: group with intensive insulin therapy less likely to require prolonged use of antibiotics<br>Critical care polyneuropathy: significantly lower incidence than conventional group. It resolved rapidly in intensive insulin therapy group. |
| Malmberg et al. (1999)[22] | Long-term mortality postmyocardial infarction in diabetics: a randomized controlled study (DIGAMI), $n$ = 620: intensive insulin treatment for at least 24 hours reduced long-term mortality by 28%. |
| Sala et al. (2002)[23] | Cohort study of 28-day mortality in 662 consecutive MI patients. On admission, 457 had BG > 6.67 mM (120 mg/dl), and 195 had known diabetes. Admission BG > 6.67 mM (120 mg/dl) is an independent predictor of 28-day mortality. |
| Carson et al. (2002)[24] | Retrospective study ($n$ = 146,786) undergoing CABG: 41,663 with diabetes, 105,123 without. Diabetics had a significant increase in 30-day mortality and post-op complications. |
| Umpierrez et al. (2002)[25] | A retrospective study of 886 adult admissions to ICU and non-ICU floors: new hyperglycemic inpatients had high in-hospital mortality, long length of hospital stay, and were less likely to be discharged to home. |
| Nieto-Rodriguez et al. (1996)[26] | A case-control study of 78 adult liver transplant recipients (26 with candidemia vs 52 control): hyperglycemia is one of 2 factors associated with the development of candidemia after liver transplant. |
| Latham et al. (2001)[27] | Prospective cohort and case-control study of 1,000 patients undergoing cardiothoracic surgery. Seventy-four had surgical site infections, which were independently associated with diabetes and post-op hyperglycemia. |
| Pomposelli et al. (1998)[28] | Prospective uncontrolled study of 100 diabetics undergoing elective cardiovascular or abdominal surgery. Relative risk for post-op infections increased to 5.7 when BG on post-op day 1 was >12 mM (216 mg/dl). |
| Golden et al. (1999)[29] | Retrospective study of 411 diabetics undergoing coronary artery surgery. Post-op hyperglycemia is an independent predictor of short-term infections. |
| Thomas et al. (2001)[30] | Retrospective study of diabetics undergoing their first renal transplant, $n$ = 50: perioperative poor glycemic control (BG > 11.2 mM; 202 mg/dl) was associated with an increased incidence of infection and acute rejection. Eleven percent with reasonable glycemic control during the 100 hours following surgery (mean <11.2 mmol/L; 202 mg/dl) had rejection episodes compared with 58% of patients with poor control (>11.2 mmol/L; 202 mg/dl). All patients with poor glycemic control experienced postoperative infection. |
| Furnary et al. (1999)[31] | Prospective 7-year study of the effect of perioperative CIII on deep sternal wound infections in diabetics ($n$ = 1,499) undergoing open-heart surgery. The control group was a historical cohort of diabetics ($n$ = 968) operated upon in the 4 years prior to study. CIII resulted in significant reduction in glycemic level and a striking reduction in incidence of deep sternal wound infections. |
| Trick et al. (2000)[32] | Retrospective case control study of deep sternal wound infection ($n$ = 30) post-CABG: diabetes with pre-op BG >11 mM (198 mg/dl) was an independent risk factor for deep sternal wound infection. |
| Gore et al. (2001)[33] | Retrospective study of 58 pediatric severely burned patients. Patients with poor glucose control (more than 40% of plasma glucose values >8 mmol/L; 144 mg/dl) had a significantly greater incidence of positive blood cultures, less percentage of skin graft take, and greater mortality than tightly controlled patients. |
| Mowlavi et al. (2000)[34] | Retrospective study of burn patients ($n$ = 74) undergoing skin grafts showed significant reduction in graft survival on post-op day 4 in hyperglycemic versus normoglycemic patients. |
| Suskin et al. (2000)[35] | Cross-sectional study of patients with CHF ($n$ = 663): hyperglycemia was found in 43% and was associated with more severe symptoms but not worse LV function. |
| Cottin et al. (2002)[36] | Noncontrolled intervention study showed improved systolic function in male patients ($n$ = 12) with coronary disease and ejection fraction <45%, when treated with glucose-insulin-potassium infusion. |
| Weir et al. (1997)[37] | Three-month follow-up study of 750 patients admitted with acute stroke. Hyperglycemia >8 mM (144 mg/dl) predicted a poor prognosis. The effect of hyperglycemia on mortality was largest in the first month poststroke. |
| Williams et al. (2002)[38] | Retrospective study, $n$ = 656 patients hospitalized with acute ischemic stroke. Admission hyperglycemia was common and was associated with increased short-term and long-term mortality and increased hospital charges. |
| Scott et al. (1999)[39] | Demonstrated safety and feasibility of CIII for 24 hours after a stroke event. |
| Pulsinelli et al. (1983)[40] | Retrospective study of admissions with ischemic stroke in diabetics ($n$ = 35) versus nondiabetics ($n$ = 72). Diabetics had worse neurologic outcome and greater stroke-related deaths. Poorer neurologic outcome related to admission BG > 6.6 mM (119 mg/dl). |

*MI, myocardial infarction; BG, blood glucose; CABG, coronary artery bypass graft; CIII, continuous intravenous insulin infusion; ICU, intensive care unit; CHF, congestive heart failure; LV, left ventricle.*

## THE MYSTERY OF THE CONTINUED SURVIVAL OF THE SLIDING SCALE

The ubiquitous use of the insulin sliding scale as the single routine response to diabetes in inpatients has been discredited for a long time, but to no avail.[47–52] Strong terms have been used in its condemnation: for example, "mindless medicine" and "paralysis of thought."[49] A vivid description by a leading endocrinologist summarized the current sliding scale paradigm as follows: "…it is passed along by word of mouth through a chain of successive cohorts of house officers, who also use it later as attending physicians.

It has become a part of the practical store of knowledge that is rapidly absorbed by first-year residents and then often employed by them in knee-jerk fashion as a quick fix to a problem."[49]

Proper insulinization is about achieving a basal level of insulin with pulses of quick-acting insulin entrained by any glycemic rise. It is not about injecting regular insulin after the fact! The need to use a long-acting or basal insulin or CIII cannot be overemphasized. Despite several voices rising in opposition to the above-described state of affairs, inpatient diabetology remains bogged down in the sliding scale practice, and in the aversion to the use of either basal insulin (e.g., glargine) or CIII. Even when used, the CIII method is quickly discontinued once blood glucose is normal.

Making available CIII protocols on general medical and surgical floors, and DIGAMI protocols[53] in coronary care units, is important. But availability does not always lead to usage. The polemics against the sliding scale practice as a sole way to treat hyperglycemia has not been sufficient to halt the practice. The reluctance to use basal insulin or CSIII stems in part from the historical tolerance of hyperglycemia, concerns about hypoglycemia, and from the lack of definitive randomized controlled trials in non-intensive care, nonsurgical general medical inpatients demonstrating its effectiveness, safety, and cost-saving effects. To some extent it also stems from the comfort of steady habits. A recent 4-year study of an inpatient program designed to minimize the use of the regular insulin sliding scale and to introduce a more physiologic insulin therapy showed how "recalcitrant" the sliding scale use remains.[54]

## ISSUES AND QUESTIONS

The current paradigm will shift when clinical and financial outcomes are shown to be at stake. In the critical care arena, the favorable decrease in ICU days resulting from intensive insulin therapy is calculated to yield an annual cost saving of $40,000.00 per ICU bed.[55] No such data exist for general medical inpatients. Protocols for safely administering CIII in general medical floors are feasible and effective and should be developed and approved hospital-wide. The use of CIII in a large segment of hospitalized diabetics could pose the logistic question of human power needed to obtain frequent invasive finger stick blood glucose data necessary to drive and clamp such drips. However, once normoglycemic levels are achieved and clamped at a stable CIII rate, the frequency of finger stick glucose measurements can be decreased from every 1 to every 4 hours. As expertise is built with training, this barrier can be surmounted. Moreover, new generations of minimally invasive glucose sensors (whether subcutaneous or by iontophoresis) are being refined and their use as inpatient tools should be tested. This will also be an important step in facilitating the routine use of CIII. With the widespread outpatient use of pump-driven continuous subcutaneous insulin infusion as an effective mode of insulin delivery, experience needs to be developed on medical floors to handle those cases when they are hospitalized and are in a stable condition without resorting to discontinuing the pump.

There are several issues and questions that need to be resolved. 1) Randomized controlled trials akin to that by Van den Berghe et al. are needed to show similar benefits in general medical inpatients outside the ICUs.[21] Those investigators aimed at a glycemic goal of 4.5–6.1 mM (81–110 mg/dl) with remarkable outcome. This range seems reasonable to adopt for all patients. However, no consensus exists yet on the inpatient glycemic target. 2) Should all hospitalized diabetics be put on CIII? Does the mode of insulin delivery matter (CIII versus subcutaneous basal/bolus)? 3) What about hypoglycemia? In the controlled randomized trial of Van den Berghe et al., those with very tight glycemic control experienced significantly more hypoglycemic episodes, defined as blood glucose <2.2 mM (39.6 mg/dl), compared to those with uncontrolled hyperglycemia (5% versus 0.7%). However, those investigators reported no occurrence of untoward cardiovascular events or seizures. With training, the use of CIII is associated with minimal occurrence of hypoglycemia. Also, the availability of basal insulin analogs, such as glargine, has been associated with decreased hypoglycemia due to the virtual absence of insulin peaks. 4) It is crucial to document the cost-saving effect of inpatient euglycemic intervention. Based on current evidence from critically ill and surgical patients, it is plausible to think that CIII or intensive basal/bolus subcutaneous insulin will be shown to have significant impact on length of hospital stay and health care cost for the general medical inpatient. Such data when available will be part of the springboard for the new inpatient revolution. 5) Developing new generations of reliable noninvasive or minimally invasive glucose monitors is critical if CIII is to be used routinely. 6) Studies have already hinted that intensive insulin therapy per se has a salutary role beyond its normoglycemic effect.[6] This area needs to be further elucidated. 7) The role of the nursing staff (especially general medical/surgical) in promulgating tight glycemic control in the inpatient arena cannot be overemphasized. They are important team members under the new paradigm and they need to be provided with the necessary inservices and training. They should be empowered to become advocates for their patients' normoglycemia.

## ACTION

This article is a call to reassess the prevailing philosophy of inpatient diabetes management in view of emerging data. The evidence for tight intensive insulinization in critical care arenas is compelling, and the urgent call to adopt protocols for CSIII is justified as mortality, morbidity, as well as cost of hospitalization are all at stake. Mandating intensive insulin therapy for general medical inpatients awaits stronger clinical evidence, and the time is now to call for clinical trials that might solidify this evidence. However, extrapolating from critically ill diabetic patients to

general medical inpatients is not unreasonable as they all share an accelerated catabolic, hyperglycemic state. The evidence from in vitro data and from numerous uncontrolled trials strongly suggests that tight glucose control matters and tolerance of hyperglycemia is not in the best interest of diabetic inpatients. With the evidence amassed so far, and pending the resolution of the above-mentioned issues, we urge clinicians to examine all diabetes orders on all hospitalized patients from day one and intensively intervene to achieve tight, nonfluctuating glycemic control at least via subcutaneous basal/bolus insulin. The use of the "sliding scale autopilot approach" hospital-wide as the sole diabetes order should be banned. Rare exceptions exist when euglycemia is achieved without basal insulin. However, there is nothing wrong with the use of a sliding scale as an adjunct to a long-acting insulin regimen. All "sliding scale orders" and the concurrent glycemic status should be reviewed on day one of admission. If blood glucose exceeds a set level (no consensus yet but we suggest 6–8 mM; 108–144 mg/dl), then a physiologic regimen (based on either intermediate-acting insulin or glargine or CIII) should be started. It is crucial that the house staff be educated in the adverse consequences of the current paradigm, for they will be the agents of change. The transmission of the sliding scale autopilot across generations of clinicians needs to be halted. We urge that CIII protocols be developed for use on general floors—a necessary, but not sufficient step for its use!

## CONCLUSION

The last decade brought compelling evidence leading to the universal embracing of tight diabetes control in the outpatient arena. The inpatient arena still flounders in a state analogous to where outpatient diabetology was prior to that decade. Whether via normoglycemia and/or a unique insulin effect, intensive insulin treatment can improve inpatient outcome.[55,56] Inpatient glycemic control matters—a powerful message defining the new frontier. It should be addressed by the health care system and the diabetic public as soon as possible.

*Editor's Note: The American College of Endocrinology and the American Association of Clinical Endocrinologists released a position statement on "Inpatient Diabetes and Metabolic Control" calling for aggressive and tight glycemic control in the inpatient arena and setting target blood glucose levels for hospitalized diabetics. This is a happy development and lends a great deal of support to our call to action limned in our paper. The position statement can be accessed at http://www.aace.com/pub/ICC and will be published in the January/February 2004 issue of Endocrine Practice.*

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