Inpatient insulin therapy
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Purpose of review
In a 2001 report from a surgical intensive care unit in Leuven, Belgium [1], intravenous insulin infusion targeting blood glucose 80–110 mg/dl reduced patient mortality and morbidities. Subsequent research has failed to define glycemic targets necessary or sufficient for attainment of desired health outcomes in other inpatient settings, but a large body of evidence suggests hospital outcomes are related to hyperglycemia.

Recent findings
Recent literature describes observational evidence for hypoglycemia as an independent predictor of mortality in a general medical intensive care unit; superiority of performance of computerized intravenous insulin algorithms in comparison to earlier manual algorithms; acceptability of early transition to scheduled basal prandial correction subcutaneous insulin analog therapy for maintenance of glycemic targets after induction of euglycemia by intravenous insulin infusion, among cardiothoracic surgery patients; inferiority of sliding scale insulin compared to basal prandial correction therapy; and feasibility of diabetes patient self-management in the hospital setting.

Summary
With development of improved insulin administration strategies problems of hypoglycemia and variability of glycemic control are reduced. Investigators and care providers need to achieve glycemic targets to optimize patient outcomes.

Keywords
basal-prandial-correction therapy, diabetes patient self-management, hypoglycemia, insulin analogs, intravenous insulin infusion

Introduction
In a groundbreaking randomized trial reported in 2001 from Leuven, Belgium [1], a policy of strict glycemic control, targeting blood glucose 80–110 mg/dl compared to conventional control, achieved reduction of mortality and morbidities in the surgical ICU. In the medical ICU, however, the same center was unable to demonstrate a mortality advantage in the intention-to-treat group [2,3]. The European VISEP and Glucontrol studies were both terminated without having shown outcome advantage, but with evidence of increased hypoglycemia in groups randomized to strict glycemic control [4,5]. Hypoglycemia has limited the ability of other investigators to reproduce the level of control shown to be beneficial in the Leuven, Belgian surgical ICU study [6]. Nevertheless, the DIGAMI 1 trial, the long-running Portland cardiac surgery trial, and a large amount of observation evidence support the possibility that strict glycemic control may be important to hospital outcomes [7,8].

Evidence and controversy surround selection of patients for strict glycemic control, potential benefits and mechanisms [9,10], glycemic targets, and treatment strategies in the settings of critical care [2–4,6,11–17], heart surgery [18–20,21,22,23,24,25], noncardiac, nonvascular surgery [26,27], myocardial infarction [28–32], trauma [33–38], heart failure [39,40], pneumonia [41,42], chronic obstructive lung disease [43,44], and stroke [45–48]. Concerning glycemic targets, it is important to recognize that plasma-correlated measurements used in many US hospitals are higher than whole blood results used in the Leuven trial [49].

Improvement of glycemic control will require consensus on standards of care [50,51], assessment of performance (glucometrics) [52,53], and cost–benefit analysis [54,55,56]. Hypoglycemia, the principal factor limiting attainment of glycemic targets, has been shown repeatedly to be associated with increased mortality [57,58,59]. Nonfatal sequelae to hypoglycemia are recognized [60]. Correct attribution and causal dependence of population fatality rate upon hypoglycemia may be difficult to prove. In a case–control analysis from a mixed adult ICU, mortality rates observed retrospectively were 55.9% among 102 patients with severe hypoglycemia and...
39.5% among 306 controls ($P = 0.0057$). Severe hypoglycemia (plasma glucose below 40 mg/dl) in a multivariable logistic regression analysis emerged as an independent predictor of mortality in this study (odds ratio, 2.28; 95% confidence interval, 1.41–3.70; $P = 0.0008$) [58**]. Instances of severe hypoglycemia were associated with the preceding 12h with subcutaneous regular insulin (55.9%), intravenous regular insulin (17.5%), glargine (5.9%), any insulin (72.5%), and oral antihyperglycemic agents (2.9%). A high priority is to develop insulin treatment strategies that reduce hyperglycemia without introducing increased risk of hypoglycemia.

**Strategies for intravenous insulin infusion**

In general insulin infusion algorithms are rules that use previous blood glucose, insulin infusion rate, current blood glucose, and time between tests in order to assign the next insulin infusion rate and blood glucose test time in order to achieve glycemic targets [61,62**,63–71,72**,73–87]. Head-to-head comparisons of protocols used in the same population have not been published. Many of the existing algorithms might be classified as targeting the infusion rate or maintenance rate of insulin infusion for repetitive correction (infusion rate and maintenance rate algorithms, respectively) [65].

The infusion rate algorithms assign each insulin infusion rate by making an incremental adjustment of the previous infusion rate and sometimes require qualitative assessments by nursing staff [1,8,77]. The more elaborate algorithms of the infusion rate design incorporate a step-wise dependency of the increment to the previous infusion rate upon the magnitude of the previous infusion rate and rate-of-change of blood glucose [69]. Implementation of the Leuven, Belgium algorithm in another hospital resulted in hypoglycemia 60 mg/dl or below in 1.8% of the measurements occurring among 18 of 30 patients, and blood glucose 40 mg/dl or below in 0.1% of measurements occurring among six patients; only 42% of total protocol implementation time was spent within the target range 81–110 mg/dl [77]. Researchers using an algorithm of infusion rate design to treat 20 patients reported both hypoglycemia under 2.5 mmol/l occurring seven times in five patients and a 38.7% rate of measurements in the range of 8–10 mmol/l, concluding that a larger trial of glycemic control would require a refined insulin algorithm [6]. Despite computerization, tight control using an infusion rate algorithm may be difficult to achieve with safety among critically ill patients, especially during the early stages of therapy [82].

The maintenance rate algorithms seek first to establish a maintenance requirement under ambient conditions of medical illness, carbohydrate exposure, and concomitant therapy, or seek to define the next multiplier or column assignment under the algorithm. The rule for assigning the maintenance rate, multiplier or column assignment incorporates rate of change or fractional change of blood glucose, requires the previous infusion rate or previous multiplier, and consists of determining a new multiplier, column assignment, or calculated maintenance rate at the end of every iteration. The next infusion rate then is assigned to be commensurate to the maintenance rate, or is assigned according to multiplier or column assignment, and is also commensurate with the distance of current blood glucose from target. Maintenance rate algorithm usually are dose-defining, such that the burden of interpretation by nursing staff may be reduced. Maintenance rate algorithms do not predict coverage necessary for intermittent carbohydrate exposure, but rather they discover the maintenance needs during continuous exposure or no exposure to carbohydrate and advise commensurate corrective action when necessary.

Computerization of maintenance rate algorithms has yielded satisfactory glycemic results in the treatment of surgical ICU, medical-surgical ICU, and cardiothoracic patients [62**,70,72**,88]. In comparison to a manual protocol of infusion rate design, a computer-based protocol of maintenance rate design, representing Vanderbilt University’s modification of the earlier protocol of Bode et al. [89], hastened the initiation of insulin infusion and, over five measurement days, improved the overall percentage of glucose readings between 70 and 109 mg/dl from 29.3% to 37.7% ($P = 0.006$), with occurrence of hypoglycemia (<40 mg/dl) at 0.2% in each group [62**]. Computerization of the Clarion maintenance rate algorithm, using a multiplier method, in a comparison of 3 months of ICU measurements before and after protocol introduction, demonstrated improvement in percentage of blood glucose measurements $>$(above) 110 mg/dl from 51.5% to 31.5% ($P < 0.001$). Overall efficacy and safety in attaining glycemic control among 2398 ICU patients at two hospitals between October 2004 and March 2006 was indicated by the findings of 61.0% of 177.279 blood glucose measurements between 80 and 110 mg/dl, mean blood glucose 106.5% (median 98.0, SD 39.1 mg/dl), and frequency of hypoglycemia under 50 mg/dl 0.4% [72**].

Some algorithms require preemptive bolus dextrose infusion for hypoglycemia prevention. Relative inflexibility of algorithm parameters is an unfavorable design feature. Revision to seek a markedly higher target range does not seem to be readily encompassed under the design of most multiplier algorithms, and applicability for initial treatment of ketoacidosis and hyperosmolar hyperglycemic state has not been specifically reported. Inability to anticipate changes of carbohydrate exposure is the Achilles heel of most algorithms for intravenous insulin infusion. For the future, model predictive algorithms and algorithms incorporating responsiveness to variation in
Strategies for ordering subcutaneous insulin

It is probable that the subcutaneous route will continue to be the dominant method of administration of insulin in the hospital. A small literature demonstrates efficacy of scheduled regimens and lack of efficacy of sliding scale insulin in achieving glycemic targets [80,90,91,92*,93,94*,95–99,100*,101].

Patients eating discrete meals or receiving bolus enteral feedings

For patients who are eating, an optimal method of management of hospital hyperglycemia or diabetes is to meet insulin requirements between meals and overnight by providing intermediate-acting insulin twice daily or long-acting insulin analog once or twice daily for coverage of basal needs, and to provide rapid-acting insulin analog for coverage of meals and correction of premeal hyperglycemia. The prescribing style is termed ‘basal-prandial-correction’ therapy [102,103]. The orders for basal insulin may be entered with a provision to withhold or reduce the dose for nihil-per-orem (NPO) status in the case of type 2 diabetes, or with a provision to not withhold the dose despite NPO status in the case of type 1 diabetes. The orders for prandial insulin may be entered with a provision to withhold the dose for NPO status and, in some cases, to reduce the dose at a specified threshold of premeal blood glucose. The orders for correction dose insulin are timed such that the correction dose will be delivered together with prandial insulin and, sometimes, perhaps in modified dosage, at bedtime and again during mid-sleep, with care to avoid stacking. In deciding whether to administer correction dose insulin at bedtime and mid-sleep, the benefits of achieving rapid control are weighed against the risk of hypoglycemia. The appropriate doses of correction insulin are proportionate to both blood glucose elevation and also total daily dose of insulin, with additional consideration for time of day and individual patient risk factors for hypoglycemia. The prandial and correction dose may be delayed until 20 min after the beginning of a meal in cases of uncertainty concerning oral intake [92*]. Insulin is ordered as nutritional insulin for patients receiving intermittent scheduled doses of basal and prandial insulin are estimated upon transition from intravenous insulin infusion or upon admission but must be revised during the remainder of the admission. The apportionment of scheduled insulin usually is up to 50% as basal insulin and at least 50% as prandial insulin for most patients. Patients having renal or hepatic failure or receiving corticosteroid therapy often require greater than 50% as prandial insulin.

The Northwestern group in Chicago reports targeting a blood glucose of 80–150 mg/dl, and using an initial dosing guideline based on body weight for patients having unknown requirements (0.5 units/kg for patients having type 2 diabetes and 0.3 units/kg for patients having type 1 diabetes or those without a prior history of diabetes), with apportionment of the daily scheduled insulin dose to be 50% basal insulin delivered as glargine and 50% prandial insulin equally divided between three meals delivered as apart. In the individualization of doses, the investigators emphasized the importance of considering clinical variables, including prior history of diabetes, outpatient hypoglycemia regimen, surgical stress, concomitant medications, and caloric intake. From a time interval between June 2004 and June 2005, after initiation of a program of consultation with an inpatient glucose management service (GMS), 18 067 capillary blood glucose measurements obtained during subcutaneous insulin treatment, obtained from 922 patients of whom 61% were male and 42% were seen in consultation for the cardiovascular surgery service, were compared to the results of 2379 capillary blood glucose measurements on the same surgical services between September 1 and September 30, 2003 during an historical comparison period before development of the GMS. The percentage of measurements in the hypoglycemic range (≤60 mg/dl) were 1.3% and 1.4%, measurements in the target range were 58.6% versus 48.4%, and the means of blood glucose were 145.6 ± 55.8 and 163.5 ± 68.3, in the intervention and the historical control groups respectively [94*].

Longer acting insulins such as glargine or detemir, prescribed in excessive dosage in order to correct hyperglycemia that arose during the day, may deliver greater than hourly basal requirements overnight. Hyperglycemia, occurring in a quotidian pattern of meal-related exacerbation with overnight correction, might be better prevented by administration of premeal prandial insulin [92*,93]. Hypoglycemia and failure to achieve glycemic goals in both the inpatient and outpatient setting may be attributable to omission of appropriate prandial dosing, or to the compromise use of ‘umbrella’ prandial coverage with premixed insulin [98].

Grainger and colleagues [97] at the Barnes Hospital in St. Louis describe a regimen for provision of basal and nutritional insulin for patients receiving intermittent...
bolus enteral tube feedings. Insulin was initiated with a daily glargine dose of 10 units for patients with BMI under 30 kg/m² and 20 units for patients with BMI 30 kg/m² or higher. Bolus tube feedings were given every 4 h, and each feeding was treated as a meal with insulin administered. Patients received baseline nutritional doses of lispro according to carbohydrate intake and body weight. Patients also received correction doses related to the magnitude of blood glucose elevation and their body weight. The baseline dose of lispro was calculated as 1 unit per 15 g carbohydrate for patients with BMI 30 kg/m² or higher. The baseline lispro but not the glargine dose was withheld in case of tube feeding interruption. An intervention group of 28 patients was compared to an historical control group of 24 patients in the cardiovascular intensive care unit. Hypoglycemia (glucose ≤79 mg/dl) was more common in the intervention group (4.1%) than in the control group (1.7%, *P* = 0.02), but no sequelae of hypoglycemia were reported, and only 1% of hypoglycemic episodes were associated with blood glucose under 65 mg/dl. The percentages of blood glucose measurements within the target range of 80–140 mg/dl were 48.6% versus 8.26% (*P* value 0.01), and the means of blood glucose values were 148.9 ± 51 versus 225.1 ± 72 mg/dl (*P* < 0.0001) respectively.

**Continuous enteral feedings**

Long acting insulin analogs present special risks when used for coverage of enteral feedings. If feedings are abruptly interrupted, outside of the ICU a patient is at risk for unrecognized hypoglycemia potentially for many hours. A safety precondition is to have a policy of the hospital, ward, or service to deal with abrupt interruption of continuous enteral feedings during any kind of subcutaneous insulin therapy, providing for increased frequency of testing and intravenous infusion of 10% dextrose for the duration of expected insulin action, or equivalent precautions.

Intensivists commonly favor intermediate acting insulin for coverage of basal and nutritional needs during continuous enteral feedings of relatively stable patients. Mixtures of intermediate and short acting insulin, or intermediate acting insulin alone given in equal dosage every 6–8 h, may achieve deliberate stacking, with continuous flat-line delivery of the hypoglycemic effect of insulin [92*,99].

**Transferring from intravenous to subcutaneous insulin**

Several opinions have been presented on strategies for transferring [92*,94*,103]. It had been argued that delivery of intravenous insulin through the morning of the third postoperative day after cardiac surgery was an important component of an insulin protocol that over time markedly reduced the mortality disadvantage for patients having diabetes [8]. Nevertheless, maintenance of intravenous insulin therapy outside of the critical care unit, or detention of a patient in critical care unit for the sole purpose of maintaining postoperative intravenous insulin infusion, have proven to be beyond the reach of many hospitals.

Northwestern recently described outcomes among patients who were transitioned after cardiothoracic surgery from intravenous insulin to subcutaneous basal-prandial-correction therapy on the day of discharge from the intensive care unit. In this cohort with diabetes undergoing coronary artery bypass grafting alone the mortality was zero percentage. According to the National Society of Thoracic Surgeons 2005 database, which adjusts for patient risk factors, the expected mortality for those undergoing coronary artery bypass grafting with a prior diagnosis of diabetes was 2.1% (0–8.2%). In the entire cardiothoracic surgery group of the Northwestern study treated with early transitioning, diabetic patients in comparison to nondiabetics had higher rates of postoperative mortality (*P* = 0.04) and pulmonary complications (*P* = 0.02), but in multivariate analysis diabetes was not an independently associated factor. For the institution, preinterventional historical mortality was not stated, and there was no control group for the study, so that direct demonstration of improvement was not possible. Hyperglycemia-related excess mortality, reported in other series, was not seen, and excellent results were reported, during use of a strategy of induction of euglycemia by intravenous insulin infusion therapy followed by scheduled subcutaneous insulin for maintenance of glycemic control [24**].

**Abolition of sliding scale**

The use of sliding scale insulin management has never been shown to be effective [90,96,100**,104]. One-step computerized sliding scale order entry may have the unfortunate consequence that prescribing of sliding scale monotherapy becomes the pathway of least resistance for entering diabetes related orders.

In the first randomized study [100**] designed to compare sliding scale management with basal-prandial-correction therapy, at Grady Hospital in Atlanta, patients having a known history of diabetes and admitted with blood glucose between 140 and 400 mg/dl were randomized to sliding scale regular insulin four times daily or basal-bolus therapy using glargine and glulisine. In each limb of the study, dosing was tailored to body weight and to severity of hyperglycemia according to algorithm. In the basal-bolus group, 50% of the weight-based total daily dose of insulin was to be prandial glulisine, which was withheld in case patients were unable to eat. In the basal-bolus group, there were dose titration rules
for the scheduled glargine insulin but not for the glulisine, and supplemental glulisine dosing was provided for hyperglycemia, with dosing and timing according to the sliding scale algorithm. Under the sliding scale algorithm the timing of insulin was appropriate to the conditions of either eating (insulin given with meals and at bedtime) or lack of oral intake (insulin given at 6 h intervals). There were three columns for display of the sliding scale, according to insulin sensitivity, with a column-change rule for reassignment of the patient to a new column according to patient response. A rescue plan was pre-specified for the group assigned to sliding scale switching to scheduled insulin if sliding scale management resulted in mean daily glucose over 240 mg/dl or three consecutive values over 240 mg/dl. The goal of therapy was to maintain fasting and premeal blood glucose under 140 mg/dl without hypoglycemia.

Nine patients in the sliding scale group required the rescue therapy for blood glucose over 240 mg/dl and, after conversion from sliding scale to scheduled insulin management, experienced prompt improvement of blood glucose. Comparison of the basal-bolus and the sliding scale groups respectively showed mean length of stay 5.3 ± 4 versus 5.1 ± 6 days, mean admission blood glucose 229 ± 71 versus 225 ± 60 mg/dl (NS), percentages of patients achieving target blood glucose under 140 mg/dl 66% versus 38%, and mean glucose during the hospital stay 166 ± 32 versus 193 ± 54 mg/dl (P < 0.001). The mean insulin daily dose administered was higher, 22 ± 2 units glargine and 20 ± 1 unit glulisine in the basal-bolus group versus 12.5 ± 2 units regular insulin per day in the sliding scale group. Hypoglycemia under 60 mg/dl occurred in two patients in each group.

Diabetes self-management

Increasing numbers of patients address their diabetes at home with multiple daily injections of insulin or wear insulin pumps for continuous subcutaneous insulin infusion. One of the principal benefits is the facilitation of appropriate timing and dosing of prandial and correction doses of insulin, and another advantage specific to insulin pumps is the possibility of entering variable basal rates. These considerations are of greatest importance to insulin-deficient patients and others who are very sensitive to insulin, but may also be important to patients using insulin for treatment of insulin-resistant type 2 diabetes. With the availability of ‘smart’ pumps, the daily use of advanced carbohydrate counting to determine prandial insulin dosing has become a widespread skill. Continued in-hospital self-management may be facilitated when an institution has had the foresight to create enabling policies and procedures that will ensure safety and meet regulatory requirements while enhancing patient satisfaction [93,105,106].

A patient must be willing and judged competent by physician and nursing staff to participate in a self-management program. Removal of an insulin pump during anesthesia is not necessary unless the cannula insertion site is in the operative field, but insertion of a new cannula and infusion set by the patient upon awakening is a prudent requirement. Participation of the patient in a self-management program does not relieve the physician of the duty to monitor and treat the patient. A decision to rely upon self-management can be revised during the course of the hospital stay. A patient who does not know how to conduct self-management is not a candidate for participation in the program. The hospital could specify that a patient who does not carry the necessary supplies into the hospital is not a candidate. It is reasonable to require an endocrine consultation. Nursing education and patient information on the program should be offered.

Conclusion

Future research should lead to discovery of the mechanisms of benefit of strict glycemic control, and technological development should result in improvement of strategies for safely attaining control among hospitalized patients. Research should be directed to the definition of glycemic targets that are necessary and sufficient for assurance of desired medical outcomes, and to discerning the relationship between treatment modality, attainment of glycemic targets, and medical outcomes among hospitalized patients.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

** of special interest
*** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 194).

Diabetes and the endocrine pancreas


21 Gandhi GY, Nutall GA, Abel MD, et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. Ann Intern Med 2007; 146:233–243. This provocative paper will require confirmation at other sites and in other patient populations in order to generalize the findings of the risk–benefit analysis of strict intraoperative glucose control.


24 Schmelz LR, DeSantis AJ, Thiagarajan V, et al. Reduction of surgical mortality and morbidity in diabetic patients undergoing cardiac surgery with a combined intravenous and subcutaneous insulin glucose management strategy. Diabetes Care 2007; 30:823–828. The authors showed no excess of hyperglycemia-related mortality or morbidity after heart surgery during use of a sequentially applied regimen consisting of induction of euglycemia by the use of intravenous insulin infusion, followed by maintenance of euglycemia through early transition to basal-prandial-correction subcutaneous insulin therapy. The study is of practical importance because maintenance of intravenous insulin infusion after heart surgery when patients are otherwise ready for transfer out of the ICU is beyond the reach of many hospitals.


53 Overall glycemic management was suboptimal in 44 US hospitals.


56 Cost-effectiveness of a diabetes management program is discussed.


Superiority of a computerized multiplier algorithm over a manual algorithm for intravenous insulin infusion is demonstrated.


Computation assisted implementation of a multiplier algorithm. Improvement of glycemic control during intravenous insulin infusion was demonstrated at two hospitals.


The discussion of transitioning from intravenous insulin to subcutaneous management, outlining a plan for basal-prandial-correction therapy using insulin analogs, emphasizes the common error of omission of adequate prandial coverage for patients who are eating, and the paper also discusses a plan for insulin coverage for patients who are not eating.


A program of basal-prandial-correction therapy is outlined together with description of performance.


The study was the first randomized trial to demonstrate inferiority of sliding scale insulin regimens in comparison to basal–prandial–correction therapy. A treatment regimen utilizing scheduled insulin is outlined for patients who are eating or not eating.


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