Inpatient insulin therapy

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Purpose of review

In a 2001 report from a surgical intensive care unit in Leuven, Belgium, 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

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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, Belgium 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 within the preceding 12 h 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 stepwise 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 algorithms 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

carbohydrate exposure offer excellent promise of further improvement [71,73,87].

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 threshhold 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 midsleep, with care to avoid stacking. In deciding whether to administer correction dose insulin at bedtime and midsleep, 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 part of a management plan that requires additional orders for blood glucose monitoring, usually premeal and at bedtime, and sometimes midsleep; alert parameters specifying conditions for calling the provider; a treatment protocol for hypoglycemia; patient education orders; and orders for measurement of an A1C test. The management plan at some institutions is communicated on an order set by entering numbers and checking boxes [94•,103].

Correction dose therapy is the least important component of basal-prandial-correction dose therapy. The required 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 aspart. 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 ($\leq$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/m^2 and 20 units for patients with BMI 30 kg/m^2 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 under 30 kg/m^2 and 1 unit per 10 g of carbohydrate for those with BMI 30 kg/m^2 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 $\leq$79 mg/dl) was more common in the intervention group (4.1%) than in the control group (1.7%, $P = 0.02$), but no sequellae 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 $\pm$ 51 versus 225.1 $\pm$ 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].

Transitioning from intravenous to subcutaneous insulin

Several opinions have been presented on strategies for transitioning [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% (0–8.24%). 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 prespecified for the group assigned to sliding scale switching patients 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).

1 Van den Berghe G, Wouters P, Weekers F, *et al.* Intensive insulin therapy in critically ill patients. N Engl J Med 2001; 345:1359–1367.

2 Van den Berghe G, Wilmer A, Hermans G, *et al.* Intensive insulin therapy in the medical ICU. N Engl J Med 2006; 354:449–461.

3 Van den Berghe G, Wilmer A, Milants I, *et al.* Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. Diabetes 2006; 55:3151–3159.

4 Devos P, Preiser JC. Current controversies around tight glucose control in critically ill patients. Curr Opin Clin Nutr Metab Care 2007; 10:206–209.

5 Brunkhorst FM, Engel C, Bloos F, *et al.* Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358:125–139.

6 McMullin J, Brozek J, McDonald E, *et al.* Lowering of glucose in critical care: a randomized pilot trial. J Crit Care 2007; 22:112–118; discussion 8–9.

7 Braithwaite SS. Defining the benefits of euglycemia in the hospitalized patient. J Hosp Med 2007; 2 (S1):5–12.

8 Furnary AP, Wu Y. Eliminating the diabetic disadvantage: the Portland Diabetic Project. Semin Thorac Cardiovasc Surg 2006; 18:302–308.

9 Ellger B, Debaveye Y, Vanhorebeek I, *et al.* Survival benefits of intensive insulin therapy in critical illness: impact of maintaining normoglycemia versus glycemia-independent actions of insulin. Diabetes 2006; 55:1096–1105.

10 Monge M, Ledeme N, Mazouz H, *et al.* Insulin maintains plasma antioxidant capacity at an early phase of kidney transplantation. Nephrol Dial Transplant 2007; 22:1979–1985.

11 Ligtenberg JJ, Meijering S, Stienstra Y, *et al.* Mean glucose level is not an independent risk factor for mortality in mixed ICU patients. Intensive Care Med 2006; 32:435–438.

12 Nasraway SA Jr. Hyperglycemia during critical illness. JPEN J Parenter Enteral Nutr 2006; 30:254–258.

13 Pittas AG, Siegel RD, Lau J. Insulin therapy and in-hospital mortality in critically ill patients: systematic review and meta-analysis of randomized controlled trials. JPEN J Parenter Enteral Nutr 2006; 30:164–172.

14 Thomas G, Rojas MC, Epstein SK, *et al.* Insulin therapy and acute kidney injury in critically ill patients a systematic review. Nephrol Dial Transplant 2007; 22:2849–2855.

15 Vanhorebeek I, Langouche L, Van den Berghe G. Tight blood glucose control with insulin in the ICU: facts and controversies. Chest 2007; 132:268–278.

16 Wintergerst KA, Buckingham B, Gandrud L, *et al.* Association of hypoglycemia, hyperglycemia, and glucose variability with morbidity and death in the pediatric intensive care unit. Pediatrics 2006; 118:173–179.

17 Lacherade JC, Jabre P, Bastuji-Garin S, *et al.* Failure to achieve glycemic control despite intensive insulin therapy in a medical ICU: incidence and influence on ICU mortality. Intensive Care Med 2007; 33:814–821.

18 Brown JR, Edwards FH, O'Connor GT, *et al.* The diabetic disadvantage. Historical outcomes measures in diabetic patients undergoing cardiac surgery: the preintravenous insulin era. Semin Thorac Cardiovasc Surg 2006; 18:281–288.

19 Furnary AP, Wu Y. Clinical effects of hyperglycemia in the cardiac surgery population: the Portland diabetic project. Endocr Pract 2006; 12 (Suppl 3):22–26.

20 Gandhi GY, Nuttall GA, Abel MD, *et al.* Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. Mayo Clin Proc 2005; 80:862–866.

21 • Gandhi GY, Nuttall 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 glycemic control.

22 Hirsch IB. Inpatient diabetes: review of data from the cardiac care unit. Endocrine Practice 2006; 12 (Suppl 3):27–34.

23 Quinn DW, Pagano D, Bonser RS, *et al.* Improved myocardial protection during coronary artery surgery with glucose-insulin-potassium: A randomized controlled trial. J Thorac Cardiovasc Surg 2006; 131:34–42.

24 •• Schmeltz LR, DeSantis AJ, Thiyagarajan 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 morbidity or mortality 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.

25 Ingels C, Debaveye Y, Milants I, *et al.* Strict blood glucose control with insulin during intensive care after cardiac surgery: impact on 4-years survival, dependency on medical care, and quality-of-life. Eur Heart J 2006; 27:2716–2724.

26 Dronge AS, Perkal MF, Kancir S, *et al.* Long-term glycemic control and postoperative infectious complications. Arch Surg 2006; 141:375–380.

27 Noordzij PG, Boersma E, Schreiner F, *et al.* Increased preoperative glucose levels are associated with perioperative mortality in patients undergoing noncardiac, nonvascular surgery. Eur J Endocrinol 2007; 156:137–142.

28 Ainla T, Baburin A, Teesalu R, Rahu M. The association between hyperglycaemia on admission and 180-day mortality in acute myocardial infarction patients with and without diabetes. Diabet Med 2005; 22:1321–1325.

29 Cheung NW, Wong VW, McLean M. The Hyperglycemia: Intensive Insulin Infusion In Infarction (HI-5) Study: A randomized controlled trial of insulin infusion therapy for myocardial infarction. Diabetes Care 2006; 29:765–770.

30 Goyal A, Mahaffey KW, Garg J, *et al.* Prognostic significance of the change in glucose level in the first 24 h after acute myocardial infarction: results from the CARDINAL study. Eur Heart J 2006; 27:1289–1297.

31 Kosiborod M, Rathore SS, Inzucchi SE, *et al.* Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. Circulation 2005; 111:3078–3086.

32 van der Horst IC, Nijsten MW, Vogelzang M, Zijlstra F. Persistent hyperglycemia is an independent predictor of outcome in acute myocardial infarction. Cardiovasc Diabetol 2007; 6:2.

33 Ahmad R, Cherry RA, Lendel I, *et al.* Increased hospital morbidity among trauma patients with diabetes mellitus compared with age- and injury severity score-matched control subjects. Arch Surg 2007; 142:613–618.

34 Gale SC, Sicoutris C, Reilly PM, *et al.* Poor glycemic control is associated with increased mortality in critically ill trauma patients. Am Surg 2007; 73:454–460.

35 Reed CC, Stewart RM, Sherman M, *et al.* Intensive insulin protocol improves glucose control and is associated with a reduction in intensive care unit mortality. J Am Coll Surg 2007; 204:1048–1054; discussion 54–5.

36 Shin S, Britt RC, Reed SF, *et al.* Early glucose normalization does not improve outcome in the critically ill trauma population. Am Surg 2007; 73:769–772; discussion 72.

37 Vogelzang M, Nijboer JM, van der Horst IC, *et al.* Hyperglycemia has a stronger relation with outcome in trauma patients than in other critically ill patients. J Trauma 2006; 60:873–877; discussion 8–9.

38 Sung J, Bochicchio GV, Joshi M, *et al.* Admission hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma 2005; 59:80–83.

39 Barsheshet A, Garty M, Grossman E, *et al.* Admission blood glucose level and mortality among hospitalized nondiabetic patients with heart failure. Arch Intern Med 2006; 166:1613–1619.

40 Eshaghian S, Horwich TB, Fonarow GC. An unexpected inverse relationship between HbA1c levels and mortality in patients with diabetes and advanced systolic heart failure. Am Heart J 2006; 151:91.

41 Kornum JB, Thomsen RW, Riis A, *et al.* Type 2 diabetes and pneumonia outcomes: A population-based cohort study. Diabetes Care 2007; 30:2251–2257.

42 McAlister FA, Majumdar SR, Blitz S, *et al.* The relation between hyperglycemia and outcomes in 2,471 patients admitted to the hospital with community-acquired pneumonia. Diabetes Care 2005; 28:810–815.

43 Baker EH, Janaway CH, Philips BJ, *et al.* Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. Thorax 2006; 61:284–289.

44 Finney SJ, Evans TW. Tight glycaemic control in acute exacerbations of COPD. Thorax 2006; 61:275–279.

45 Burroughs V, Weinberger J. Diabetes and stroke. Part two: treating diabetes and stress hyperglycemia in hospitalized stroke patients. Curr Cardiol Rep 2006; 8:29–32.

46 Frontera JA, Fernandez A, Claassen J, *et al.* Hyperglycemia after SAH: predictors, associated complications, and impact on outcome. Stroke 2006; 37:199–203.

47 Garg R, Chaudhuri A, Munschauer F, Dandona P. Hyperglycemia, insulin, and acute ischemic stroke: a mechanistic justification for a trial of insulin infusion therapy. Stroke 2006; 37:267–273.

48 Gentile NT, Seftchick MW, Huynh T, *et al.* Decreased mortality by normalizing blood glucose after acute ischemic stroke. Acad Emerg Med 2006; 13:174–180.

49 Dungan K, Chapman J, Braithwaite SS, Buse J. Glucose measurement: confounding issues in setting targets for inpatient management. Diabetes Care 2007; 30:403–409.

50 ACE/ADA Task Force on Inpatient Diabetes. American College of Endocrinology and American Diabetes Association Consensus Statement on Inpatient Diabetes and Glycemic Control. Endocrine Practice 2006; 12 (Suppl 3):3–13.

51 American Diabetes Association. Standards of medical care in diabetes: 2007. Diabetes Care 2008; 30 (Suppl 1):S12–S54.

52 • Goldberg PA, Bozzo JE, Thomas PG, *et al.* "Glucometrics": assessing the quality of inpatient glucose management. Diabetes Technol Ther 2006; 8:560–569.

A method of analysis of hospital performance is proposed for assessment hyperglycemia and hypoglycemia.

53 • Wexler DJ, Meigs JB, Cagliero E, *et al.* Prevalence of hyper- and hypoglycemia among inpatients with diabetes: a national survey of 44 U.S. hospitals. Diabetes Care 2007; 30:367–369.

Overall glycemic management was suboptimal in 44 US hospitals.

54 Krinsley JS, Jones RL. Cost analysis of intensive glycemic control in critically ill adult patients. Chest 2006; 129:644–650.

55 • Newton CA, Young S. Financial implications of glycemic control: results of an inpatient diabetes management program. Endocr Pract 2006; 12 (Suppl 3): 43–48.

Cost-effectiveness of a diabetes management program is discussed.

56 Zijlstra JG, Corstjens AM, Tulleken JE, *et al.* Cost analysis of intensive glycemic control in critically ill adult patients. Chest 2006; 130:1953–1954.

57 Bhatia A, Cadman B, Mackenzie I. Hypoglycemia and cardiac arrest in a critically ill patient on strict glycemic control. Anesth Analg 2006; 102:549–551.

58 •• Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. Crit Care Med 2007; 35:2262–2267.
The serious concomitants of hypoglycemia and the associated increase of mortality among critically ill patients are confirmed.

59 Vriesendorp TM, van Santen S, DeVries JH, *et al.* Predisposing factors for hypoglycemia in the intensive care unit. Crit Care Med 2006; 34:96–101.

60 Varghese P, Gleason V, Sorokin R, *et al.* Hypoglycemia in hospitalized patients treated with antihyperglycemic agents. J Hosp Med 2007; 2:234–240.

61 Barth M, Oyen L, Warfield K, *et al.* Comparison of a nurse initiated insulin infusion protocol for intensive insulin therapy between adult surgical trauma, medical and coronary care intensive care patients. BMC Emergency Medicine 2007; 7:14.

62 •• Boord JB, Sharifi M, Greevy RA, *et al.* Computer-based insulin infusion protocol improves glycemia control over manual protocol. J Am Med Inform Assoc 2007; 14:278–287.
Superiority of a computerized multiplier algorithm over a manual algorithm for intravenous insulin infusion is demonstrated.

63 Boulkina LS, Braithwaite SS. Practical aspects of intensive insulinization in the intensive care unit. Curr Opin Clin Nutr Metab Care 2007; 10:197–205.

64 Braithwaite SS, Edkins R, Macgregor KL, *et al.* Performance of a dose-defining insulin infusion protocol among trauma service intensive care unit admissions. Diabetes Technol Ther 2006; 8:476–488.

65 Braithwaite SS, Clement S. Algorithms for intravenous insulin delivery. Curr Diabetes Rev (in press).

66 Button E, Keaton P. Glycemic control after coronary bypass graft: using intravenous insulin regulated by a computerized system. Crit Care Nurs Clin North Am 2006; 18:257–265; xi.

67 Clayton SB, Mazur JE, Condren S, *et al.* Evaluation of an intensive insulin protocol for septic patients in a medical intensive care unit. Crit Care Med 2006; 34:2974–2978.

68 Fabietti PG, Canonico V, Orsini-Federici M, *et al.* Clinical validation of a new control-oriented model of insulin and glucose dynamics in subjects with type 1 diabetes. Diabetes Technol Ther 2007; 9:327–338.

69 Goldberg PA, Roussel MG, Inzucchi SE. Clinical results of an updated insulin infusion protocol in critically ill patients. Diabetes Spectrum 2005; 18:188–191.

70 Hermayer KL, Neal DE, Hushion TV, *et al.* Outcomes of a cardiothoracic intensive care web-based online intravenous insulin infusion calculator study at a medical university hospital. Diabetes Technol Ther 2007; 9:523–534.

71 Hovorka R, Kremen J, Blaha J, *et al.* Blood glucose control by a model predictive control algorithm with variable sampling rate versus a routine glucose management protocol in cardiac surgery patients: a randomized controlled trial. J Clin Endocrinol Metab 2007; 92:2960–2964.

72 •• Juneja R, Roudebush C, Kumar N, *et al.* Utilization of a computerized intravenous insulin infusion program to control blood glucose in the intensive care unit. Diabetes Technol Ther 2007; 9:232–240.
Computerization assisted in the implementation of a multiplier algorithm. Improvement of glycemic control during intravenous insulin infusion was demonstrated at two hospitals.

73 Lonergan T, Compte AL, Willacy M, *et al.* A pilot study of the SPRINT protocol for tight glycemic control in critically Ill patients. Diabetes Technol Ther 2006; 8:449–462.

74 Lonergan T, Le Compte A, Willacy M, *et al.* A simple insulin-nutrition protocol for tight glycemic control in critical illness: development and protocol comparison. Diabetes Technol Ther 2006; 8:191–206.

75 Malesker MA, Foral PA, McPhillips AC, *et al.* An efficiency evaluation of protocols for tight glycemic control in intensive care units. Am J Crit Care 2007; 16:589–598.

76 Meynaar IA, Dawson L, Tangkau PL, *et al.* Introduction and evaluation of a computerised insulin protocol. Intensive Care Med 2007; 33:591–596.

77 Oeyen SG, Hoste EA, Roosens CD, *et al.* Adherence to and efficacy and safety of an insulin protocol in the critically ill: a prospective observational study. Am J Crit Care 2007; 16:599–608.

78 Osburne RC, Cook CB, Stockton L, *et al.* Improving hyperglycemia management in the intensive care unit: preliminary report of a nurse-driven quality improvement project using a redesigned insulin infusion algorithm. The Diabetes Educator 2006; 32:394–403.

79 Plank J, Blaha J, Cordingley J, *et al.* Multicentric, randomized, controlled trial to evaluate blood glucose control by the model predictive control algorithm versus routine glucose management protocols in intensive care unit patients. Diabetes Care 2006; 29:271–276.

80 Quinn JA, Snyder SL, Berghoff JL, *et al.* A practical approach to hyperglycemia management in the intensive care unit: evaluation of an intensive insulin infusion protocol. Pharmacotherapy 2006; 26:1410–1420.

81 Rea RS, Donihi AC, Bobeck M, *et al.* Implementing an intravenous insulin infusion protocol in the intensive care unit. Am J Health Syst Pharm 2007; 64:385–395.

82 Shulman R, Finney S, O'Sullivan C, *et al.* Tight glycaemic control: a prospective observational study of a computerised decision-supported intensive insulin therapy protocol. Critical Care 2007; 11:R75.

83 Smith AB, Udekwu PO, Biswas S, *et al.* Implementation of a nurse-driven intensive insulin infusion protocol in a surgical intensive care unit. Am J Health Syst Pharm 2007; 64:1529–1540.

84 Taylor BE, Schallom ME, Sona CS, *et al.* Efficacy and safety of an insulin infusion protocol in a surgical ICU. J Am Coll Surg 2006; 202:1–9.

85 Wilson M, Weinreb J, Soo Hoo GW. Intensive insulin therapy in critical care: a review of a dozen protocols. Diabetes Care 2007; 30:1005–1011.

86 Wintergerst KA, Deiss D, Buckingham B, *et al.* Glucose control in pediatric intensive care unit patients using an insulin and glucose algorithm. Diabetes Technol Ther 2007; 9:211–222.

87 Wong XW, Singh-Levett I, Hollingsworth LJ, *et al.* A novel, model-based insulin and nutrition delivery controller for glycemic regulation in critically ill patients. Diabetes Technol Ther 2006; 8:174–190.

88 Dortch MJ, Mowery NT, Ozdas A, *et al.* A computerized insulin infusion titration protocol improves glucose control with less hypoglycemia compared to a manual titration protocol in a trauma intensive care unit. JPEN J Parenter Enteral Nutr 2008; 32:18–27.

89 Bode BW, Braithwaite SS, Steed RD, Davidson PC. Intravenous insulin infusion therapy: indications, methods, and transition to subcutaneous insulin therapy. Endocr Pract 2004; 10 (Suppl 2):71–80.

90 Baldwin D, Villanueva G, McNutt R, Bhatnagar S. Eliminating inpatient sliding-scale insulin: a reeducation project with medical house staff. Diabetes Care 2005; 28:1008–1011.

91 Boullu-Sanchis S, Ortega F, Chabrier G, *et al.* Efficacy of short term continuous subcutaneous insulin lispro versus continuous intravenous regular insulin in poorly controlled, hospitalized, type 2 diabetic patients. Diabetes Metab 2006; 32:350–357.

92 • Braithwaite SS. The transition from insulin infusions to long-term diabetes therapy: the argument for insulin analogs. Semin Thorac Cardiovasc Surg 2006; 18:366–378.
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.

93 Braithwaite SS, Mehrotra HP, Robertson B, *et al.* Managing hyperglycemia in hospitalized patients. Clinical Cornerstones 2007; 8:44–57.

94 • DeSantis AJ, Schmeltz LR, Schmidt K, *et al.* Inpatient management of hyperglycemia: the Northwestern experience. Endocr Pract 2006; 12:491–505.
A program of basal-prandial-correction therapy is outlined together with description of performance.

95 Donaldson S, Villanueva G, Rondinelli L, Baldwin D. Rush University guidelines and protocols for the management of hyperglycemia in hospitalized patients: elimination of the sliding scale and improvement of glycemic control throughout the hospital. Diabetes Educ 2006; 32:954–962.

96 Golightly LK, Jones MA, Hamamura DH, *et al.* Management of diabetes mellitus in hospitalized patients: efficiency and effectiveness of sliding-scale insulin therapy. Pharmacotherapy 2006; 26:1421–1432.

97 Grainger A, Eiden K, Kemper J, Reeds D. A pilot study to evaluate the effectiveness of glargine and multiple injections of lispro in patients with type 2 diabetes receiving tube feedings in a cardiovascular intensive care unit. Nutr Clin Pract 2007; 22:545–552.

98 Holman RR, Thorne KI, Farmer AJ, *et al.* Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med 2007; 357:1716–1730.

99 Thompson CL, Dunn KC, Menon MC, *et al.* Hyperglycemia in the Hospital. Diabetes Spectr 2005; 18:20–27.

100 •• Umpierrez GE, Smiley D, Zisman A, *et al.* Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). Diabetes Care 2007; 30:2181–2186.
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.

101 Yeldandi RR, Lurie A, Baldwin D. Comparison of once-daily glargine insulin with twice-daily NPH/regular insulin for control of hyperglycemia in inpatients after cardiovascular surgery. Diabetes Technol Ther 2006; 8:609–616.

102 Hirsch IB. Insulin analogues. N Engl J Med 2005; 352:174–183.

103 Trence DL, Kelly JL, Hirsch IB. The rationale and management of hyperglycemia for in-patients with cardiovascular disease: time for change. J Clin Endocrinol Metab 2003; 88:2430–2437.

104 Schoeffler JM, Rice DAK, Gresham DG. 70/30 Insulin algorithm versus sliding scale insulin. Ann Pharmacother 2005; 39:1606–1609.

105 White WA Jr, Montalvo H, Monday JM. Continuous subcutaneous insulin infusion during general anesthesia: a case report. AANA J 2004; 72:353–357.

106 Cook CB, Boyle ME, Cisar NS, *et al.* Use of continuous subcutaneous insulin infusion (insulin pump) therapy in the hospital setting: proposed guidelines and outcome measures. Diabetes Educ 2005; 31:849–857.