Tight glycaemic control: clinical implementation of protocols

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Implementation of tight glycaemic control in hospitalised patients presents a huge challenge. It concerns many patients, there are many interfering factors and many health-care professionals are involved. The current literature provides little practical guidance. This article offers the clinical anesthesiologist direction for the organisation of inpatient blood glucose control in acute situations, in the perioperative setting and in the intensive care unit. An effective, safe and user-friendly algorithm for intravenous insulin administration is presented that can be executed by regular nurses and used in many situations. Practical advice is offered for the use of subcutaneous basal–bolus insulin, for fasting orders and for transition to discharge care. The main safety considerations are discussed.

Many hospitals seek to institute intensive glucose control, inspired by the results of the Leuven trials and by observational data showing a relation between elevated blood glucose levels during hospitalisation and adverse clinical outcomes.\textsuperscript{1–3} They are confronted with great difficulties, however, due to a high number of patients, many interfering factors and scarcity of practical guidance in the available literature. In acute settings, hyperglycaemia occurs very frequently, mainly due to elevated concentrations of stress hormones. With a conservative blood glucose target of $\leq 180$ mg dl\textsuperscript{-1} nearly three-fourths, and with an intensive target of $\leq 110$ mg dl\textsuperscript{-1} nearly all critically ill patients require exogenous insulin.\textsuperscript{1,2,4} Many published intravenous (IV) insulin protocols use complex algorithms that...
are neither safe nor simple enough for routine use. The blood glucose targets are frequently not reached because of poor algorithm performance and the incidence of severe hypoglycaemia (≤40 mg dl\(^{-1}\)) is high.\(^{1-4,6}\) The quality of point of care (POC) blood glucose measurements, needed to feed the algorithms, is often weak.\(^{7,8}\) Finally, the transition to subcutaneous (sc) insulin is often difficult, due to lack of expertise in using basal–bolus insulin regimens.\(^9\)

We are convinced that effective and safe glycaemic control is feasible, however, both in acute and perioperative situations and in the intensive care unit (ICU), with smooth transition to post-acute care. This article offers guidance for the clinical anaesthesiologist in charge of these patients. First, essential ‘building blocks’ for glycaemic control are presented. Then safety considerations are discussed. Finally, perioperative care is used as a practical example of integration of the different elements in a workable system.

### Building blocks

For effective and safe in-hospital blood glucose regulation, a systematic approach is needed. A clinical path should be developed with protocolar guidance for every situation that can be encountered during hospitalisation. Key stakeholders should be identified, working groups appointed, protocols and algorithms created and educational programmes developed. The protocols should be as simple as possible, taking into account staffing requirements and safety. It is recommended to use as few ‘building blocks’ as possible that can be used in different situations. This facilitates education of the nursing and medical staff and allows experience gained in a certain situation to be used in other protocols. Our hospital management consists of the following principal building blocks:

1. A dynamic IV insulin infusion algorithm that can be used for different blood glucose targets,
2. A sc basal–bolus insulin scheme for patients recovering from an acute situation,
3. A transition scheme to make the link from a basal–bolus insulin scheme to a treatment plan for discharge and
4. A protocol for blood glucose regulation when fasting for an investigation or treatment.

### IV insulin infusion algorithm

An essential condition for obtaining good glycaemic control in acute situations, during major surgery and in critical illness, is the availability and creative use of a good IV insulin-infusion protocol. It should be effective, safe and simple enough to be used throughout the hospital by regular nurses, keeping the need for expert supervision to a strict minimum. Most of the published algorithms do not meet these requirements. Hypoglycaemia is a particular concern. In the Leuven studies, the incidence of severe hypoglycaemia (defined as a blood glucose level ≤40 mg dl\(^{-1}\)) in the intensively treated patients was 5.2% in the surgical and 18.7% in the medical ICU.\(^{1,2}\) The Glucontrol and VISEP studies were stopped early due to the incidence of hypoglycaemia, at 9.8% and 17.0%, respectively, in their tightly controlled groups.\(^5,6\) In the Normoglycemia in intensive care evaluation and survival using glucose algorithm regulation (NICE-SUGAR) study, the incidence was lower, but still too high at 6.8% in the intensive group.\(^4\)

During the past years, better protocols for IV insulin administration were published, based on the principle, initially published by Markovitz et al., that the insulin infusion rate is gradually adapted to the individual insulin sensitivity of the patient.\(^{10-12}\) Davidson et al. created a computer algorithm inspired on this principle, using the formula: insulin dose/h = (blood glucose in mg dl\(^{-1}\)-60) × multiplier.\(^{12}\) When the blood glucose level is not decreasing fast enough, the insulin administration can be made more aggressive by increasing the multiplier and vice versa. This can be expressed visually in a grid (Fig. 1), with rows representing blood glucose ranges and columns insulin doses, moving from left to right to more aggressive administration (higher multiplier). The insulin infusion is usually started in column 2 (multiplier 0.02) at a rate corresponding to the current blood glucose. When the blood glucose has decreased significantly (≥1 range) at the next measurement, the same column is used for the insulin administration, and the dose is decreased according to the new blood glucose level. When
the blood glucose fails to decrease, the insulin dosage is increased by moving one column to the right (increasing the multiplier with 0.01). By repeating this, a column corresponding to the individual insulin sensitivity of the patient is gradually reached. Once the blood glucose target (green zone in Fig. 1) has been reached, the insulin administration stays in the same column, but, unlike in most other protocols, small adaptations can still be made. If the blood glucose falls below the target (orange zone in Fig. 1), the aggressiveness of the insulin algorithm is decreased to avoid hypoglycaemia, by moving a column to the left.

Davidson et al. published data of 5080 IV insulin runs with this protocol. They achieved a mean glucose level $< 150$ mg dl$^{-1}$ in 3 h, that remained stable for as long as the run continued (mean 24 h). The prevalence of severe hypoglycaemia ($< 40$ mg dl$^{-1}$) was 2.6%.

We have adapted this protocol in our institution to make it even more efficient and safe. The goal of our adaptations was to proactively react to rapidly changing insulin needs in cardiac surgical patients, both during the operation as later in the ICU. During cardiac surgery with cardiopulmonary bypass, we proactively increase the insulin dosage by moving three columns to the right during rewarming, because this induces a sudden, transient increase in insulin resistance. We return three columns to the left when the oesophageal temperature reaches $36^\circ$C. We move a further column to the left at the end of the operation to anticipate a decrease in insulin requirements when surgical stress fades. Similarly, we anticipate the effect of stress induced by stopping the sedation for extubation by moving insulin one column to the right.

Fig. 1. Protocol for continuous IV insulin administration for BG target 80–110 mg/dl (O.L.V. hospital Aalst, Belgium, 2009).
In 745 patients undergoing cardiac surgery with cardiopulmonary bypass, blood glucose remained \( \leq 130 \, \text{mg} \, \text{dl}^{-1} \) during surgery and in the first 24 h in the ICU in, respectively, 92% and 95% of the measurements in non-diabetic patients and 84% and 91% in diabetic patients.\(^{14}\) All blood glucoses remained above 40 mg dl\(^{-1}\).

Recently, we created a computerised expert system including these adaptations, allowing nurses to safely use this IV insulin protocol. We included anticipation to sudden changes in carbohydrate supply, and also used the computer system to calculate the anticipated sc insulin dosage when the patient is transferred from ICU to the ward. The computer expert system also allows us to study changes in the protocol without increasing the workload for the nurses. We are currently investigating whether moving to the left when the blood glucose decreases too fast between two successive measurements, even when it is still above target, better avoids hypoglycaemia without jeopardising the effectiveness of the protocol.

The algorithm is designed for glucose measurements every 60 min, but measurements every 30 min may be necessary when the insulin sensitivity is changing rapidly. When in a stable patient the blood glucose remains in target at four successive measurements, checking can be decreased to every 120 min.

This protocol is not only effective and safe, but also very user-friendly. Since it automatically searches the most effective insulin dosage, it can operate with all infusion fluids and fluid administration rates. The same protocol can be used for different blood glucose targets by changing the upper and/or lower target levels (green zone in Fig. 1). It can easily be taught to nurses of all units. All these advantages allow its use in different situations and/or hospital units.

\textit{Sc basal–bolus insulin scheme}

When the patient starts to eat, the IV insulin protocol will induce up-titrating of the insulin dose, increasing the risk of hypoglycaemia after a few hours. This could be avoided by giving a 2-h square bolus of IV insulin, but this would make the treatment more complex. It is easier to convert to a basal–bolus scheme with sc administration of short-acting insulin before the meals and intermediate- or long-acting insulin, usually at bedtime.\(^3,15\) In patients whose medical stress still induces high insulin requirements, the IV insulin infusion can be continued to provide basal insulin, with sc short-acting insulin covering the meals.

Although rapid- and long-acting insulin analogues theoretically offer a more physiologic profile,\(^{16}\) it is easier to work with standard regular and NPH insulins in the ICU setting. Critically ill patients have slower gastric emptying, start out by eating poorly and usually receive between-meal nutritional supplements.\(^{17}\) This can better be covered with regular insulin than with rapid-acting analogues. Their insulin needs usually change rapidly during the first days, due to fading of medical stress, tapering medication with hyperglycaemic effect (inotropics and corticosteroids) and fasting for technical investigations. In these circumstances, the ultra-long action (20–24 h) of the analogues glargine and levemir is disadvantageous in comparison with the shorter action (12–18 h) of NPH insulin. Regular and NPH are also more convenient for transitioning from IV to sc therapy. The action of regular insulin is long enough to be able to jump to the next meal. This is not the case with rapid-acting analogues, necessitating simultaneous injection of basal insulin, usually at a time of the day when the basal insulin would normally not yet be injected.

Since regular insulin covers approximately one-fourth of the day, an easy rule of thumb to determine the starting dose is to sum up the insulin administered during the last 6 h and add 20% for the prandial requirements. For example, when the insulin pump provided a mean dose of 2 U h\(^{-1}\) during the past 6 h, \((6 \times 2) + 20\%\) that is, approximately 14 U of regular insulin can be given before the first meal. This should be considered as a test dose, helping to determine the next doses on the basis of its effect. When during the past hours blood glucose levels were well controlled with \(\leq 0.5\) units of IV insulin per hour, insulin can usually be stopped, except in type 1 diabetes. Stopping insulin in type 1 diabetes will rapidly cause ketosis. When in doubt about the type of diabetes, it is wise to continue insulin to avoid problems.

Regular insulin has a delay to onset of action of 30 min, requiring sc injection at least 30 min before stopping the IV insulin pump.\(^{15}\) It should also be injected 30 min prior to meals, a goal that may be
difficult to meet in a busy unit. Since a regimen with regular and NPH insulin induces high insulin levels in the early night, a bedtime snack is needed to prevent nocturnal hypoglycaemia.

Bedside glucose monitoring should be performed before meals and at bedtime. It can also be useful to measure between 2:00 and 3:00 a.m. to assess for nocturnal hypoglycaemia, particularly if the patient just converted to sc insulin, or if a correction dose was used at bedtime.

All data concerning blood glucose levels and insulin administration should be noted on a summary chart or computer file (example in Fig. 2). Good communication is very important, because the blood glucose treatment of these patients will be executed by different caregivers. On the basis of the patient’s response to prior insulin doses, the responsible physician (or diabetes nurse) can determine the next doses. The nurse who administers the insulin should adapt the scheduled dose with a correction algorithm. This should take into account the insulin sensitivity of the patient by providing larger corrections at higher insulin doses. At our institution, we use the algorithm shown in Fig. 2, based on the formula developed by Davidson: (actual blood glucose – target blood glucose)/correction factor.\(^{18,19}\) The correction factor corresponds to how much the blood glucose level is lowered by 1 unit of short-acting insulin. This is usually estimated with the formula 1700/total daily insulin dose. We use a somewhat more conservative estimation of 2200/total daily insulin dose to avoid hypoglycaemia. At bedtime, we use even more conservative correction doses to avoid nocturnal hypoglycaemia.

It should be stressed that there is no place for traditional sliding-scale insulin regimens, that provide a fixed dose of short-acting insulin administered for a certain level of hyperglycaemia, without basal insulin and without any individualisation. This ‘reactive’ approach treats hyperglycaemia after it has already occurred, instead of preventing it. It results in a saw-tooth curve, exacerbating both hyperglycaemia and hypoglycaemia.\(^{20,21}\)

### Transition scheme

Before the patient is discharged, the insulin regimen may need to be simplified, oral anti-diabetics (re-)introduced or glycaemic treatment tapered off and stopped. One should proceed with this

<table>
<thead>
<tr>
<th>3-4 injections/dl:</th>
<th>adaptations of short-acting insulin</th>
<th>long-acting insulin(^{[1]})</th>
<th>reason for admittance:</th>
</tr>
</thead>
<tbody>
<tr>
<td>scheduled insulin:</td>
<td>0-6 U</td>
<td>7-12 U</td>
<td>13-18 U</td>
</tr>
<tr>
<td>BG (mg/dl):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 70(^{[2]})</td>
<td>-1 U</td>
<td>-2 E</td>
<td>-3 U</td>
</tr>
<tr>
<td>71 – 100</td>
<td>OK</td>
<td>-1 E</td>
<td>-2 U</td>
</tr>
<tr>
<td>101 – 150</td>
<td>OK</td>
<td>OK</td>
<td>OK</td>
</tr>
<tr>
<td>151 – 200</td>
<td>OK</td>
<td>OK</td>
<td>OK</td>
</tr>
<tr>
<td>201 – 250</td>
<td>+1 U</td>
<td>+2 U</td>
<td>+3 U</td>
</tr>
<tr>
<td>251 – 300</td>
<td>+3 U</td>
<td>+5 U</td>
<td>+6 U</td>
</tr>
<tr>
<td>301 – 350</td>
<td>+6 U</td>
<td>+8 U</td>
<td>+11 U</td>
</tr>
<tr>
<td>351 - 400(^{[1]})</td>
<td>+8 U</td>
<td>+10 U</td>
<td>+13 U</td>
</tr>
</tbody>
</table>

**BG** (or blood glucose); **BG** (or blood glucose); **BP** (or blood pressure); **EN, PN** (or enteral nutrition, or parenteral nutrition); **CORT** (or corticosteroids).

**Fig. 2.** Glucose summary chart for patients on sc insulin and/or oral antidiabetic agents (O.L.V. hospital Aalst, Belgium, 2009).
planning as early as possible, when the patient eats discrete meals. Waiting too long can cause longer hospital stay or discharge with an inappropriate treatment regimen.\textsuperscript{22,23} The timely involvement of a hospital diabetes nurse educator can facilitate this transition and reduce length of stay in the hospital.\textsuperscript{22,23} Discharge planning demands assessment of the patient’s history of diabetes, previous treatment and metabolic control (HbA1c), emergence of contraindications for oral anti-diabetic agents, adaptations of treatment goals related to prognosis and need for extra education. Every member of the treatment team – physicians, nurses and dieticians – should contribute information to aid the responsible physician in his decision-making process. The design of the patient glucose summary chart or computer file (example in Fig. 2) should facilitate this information gathering and provide help for structuring the decision process.

At discharge, one should anticipate that blood glucose levels can decrease at home when physical activity increases, medication with hyperglycaemic effect (e.g., corticosteroids) is tapered and medical stress abates. A recent hospitalisation is a strong predictor of subsequent serious outpatient hypoglycaemia.\textsuperscript{24} This should lead to caution in the dosing of glycaemic therapy at discharge and to careful communication with general practitioners.

**Fasting protocol**

There are no fixed guidelines to adapt sc insulin or oral anti-diabetic drugs when a patient skips meals for an investigation or treatment. One must resort to some simple rules of thumb and common sense.\textsuperscript{3,15} In our institution we use the following general rules:

- Hold oral anti-diabetic drugs when fasting.
- In patients on a regimen including a long-acting insulin analogue: Continue this analogue, and give the usual dose of short-acting insulin before a meal.
- In patients on other insulin regimens: Provide basal insulin using an intermediate-acting insulin, such as NPH. When breakfast is omitted, give half of the breakfast plus lunch insulin dose as a single morning injection of NPH (e.g., when 18 U of a 30/70 premixed insulin would have been given before breakfast, replace it by 9 U of NPH). Provide some extra regular insulin before the lunch. When the patient receives breakfast but skips lunch, give two-thirds of the breakfast plus lunch insulin dose as two-thirds regular and one-thirds NPH insulin before breakfast (e.g., when 18 U of a 30/70 premixed insulin would have been given before breakfast, replace it by 8 U regular and 4 U NPH before breakfast).
- Adapt the dose for hypo- and hyperglycaemia using an algorithm that takes into account the insulin sensitivity of the patient by providing larger corrections at higher insulin doses.
- In patients receiving a bolus dose of corticosteroids (e.g., as prevention of contrast reaction) use higher insulin doses and a more aggressive correction algorithm.

Since these rules are rather complex, we cast them in four visual diagrams to give the nurses more guidance. We use two diagrams for patients on a regimen including a long-acting insulin analogue, one for skipping breakfast and one for skipping lunch, and similarly, two diagrams for other insulin regimens (see example in Fig. 3).

**Safety considerations**

Any attempt at better in-hospital glycaemic control should focus on prevention, immediate recognition and appropriate treatment of hypoglycaemia. Hypoglycaemia is a major safety concern, especially in patients with impaired mental status. On the other hand, fear of hypoglycaemia is a major barrier to achieve tight control.\textsuperscript{9,25} In the trials of tight glycaemic control in the ICU, high rates of major hypoglycaemia (≤40 mg dl\textsuperscript{-1}) were reported.\textsuperscript{1,2,4–6} The ensuing discussion was mainly focussed on the safety of the strict blood glucose target of 80–110 mg dl\textsuperscript{-1}. Although hypoglycaemia occurs less frequently with less strict targets of for example, 140–180 mg dl\textsuperscript{-1}, this offers no guarantee. More important than the choice of the blood glucose target is the organisation of the blood glucose control, with attention to the following essential components.\textsuperscript{26–28}
FASTING PROTOCOL: SKIPPING BREAKFAST for patients on an insulin regimen NOT including glargine or detemir

Determine the row that should be followed:

- STEP 1: add scheduled breakfast and lunch insulin dose; indicate in column 1.
- STEP 2: omit oral antidiabetic drugs. Replace them by insulin by moving down a row.
- STEP 3: if the patient receives a bolus dose of corticosteroids move 2 rows down.
- Mark the obtained row with a fluorescent marker: give sc insulin as indicated.
- Reg = Regular insulin, COR = correction dose, 2x(COR) = double correction dose.

<table>
<thead>
<tr>
<th>STEP 1</th>
<th>STEP 2</th>
<th>STEP 3</th>
<th>sc insulin at 0 h</th>
<th>sc insulin at 12 h if NO lunch (according to BG)</th>
<th>sc insulin at 12 h if lunch (according to BG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6 U</td>
<td></td>
<td></td>
<td>0 NPH + COR</td>
<td>0 Reg 0 Reg 2 Reg 4 Reg 0 Reg 0 Reg 0 Reg 0 Reg 2 Reg</td>
<td>≤ 70 71-100 101-150 151-200 201-250 251-300 301-350</td>
</tr>
<tr>
<td>7-11 U</td>
<td></td>
<td></td>
<td>5 NPH + COR</td>
<td>0 Reg 0 Reg 2 Reg 4 Reg 0 Reg 0 Reg 0 Reg 2 Reg 2 Reg</td>
<td></td>
</tr>
<tr>
<td>12-19 U</td>
<td></td>
<td></td>
<td>8 NPH + COR</td>
<td>0 Reg 0 Reg 3 Reg 6 Reg 0 Reg 2 Reg 2 Reg 3 Reg 4 Reg</td>
<td></td>
</tr>
<tr>
<td>20-27 U</td>
<td></td>
<td></td>
<td>12 NPH + COR</td>
<td>0 Reg 2 Reg 4 Reg 7 Reg 2 Reg 2 Reg 3 Reg 5 Reg 6 Reg</td>
<td></td>
</tr>
<tr>
<td>28-45 U</td>
<td></td>
<td></td>
<td>16 NPH + COR</td>
<td>0 Reg 2 Reg 5 Reg 9 Reg 2 Reg 3 Reg 5 Reg 5 Reg 6 Reg</td>
<td></td>
</tr>
<tr>
<td>46-60* U</td>
<td></td>
<td></td>
<td>20 NPH + 2x(COR)</td>
<td>0 Reg 3 Reg 7 Reg 11 Reg 3 Reg 4 Reg 6 Reg 5 Reg 8 Reg</td>
<td></td>
</tr>
<tr>
<td>61-66 U</td>
<td></td>
<td></td>
<td>23 NPH + 2x(COR)</td>
<td>0 Reg 4 Reg 9 Reg 14 Reg 4 Reg 8 Reg 7 Reg 10 Reg 12 Reg</td>
<td></td>
</tr>
<tr>
<td>&gt; 60 U</td>
<td></td>
<td></td>
<td>31 NPH + 2x(COR)</td>
<td>0 Reg 9 Reg 14 Reg 24 Reg 4 Reg 24 Reg 10 Reg 15 Reg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>36 NPH + 2x(COR)</td>
<td>0 Reg 9 Reg 10 Reg 16 Reg 5 Reg 7 Reg 10 Reg 14 Reg</td>
<td></td>
</tr>
</tbody>
</table>

* if > 60 U: contact diabetologist

Fig. 3. Fasting protocol for skipping breakfast for patients on an insulin regimen not including glargine or detemir (O.L.V. hospital Aalst, Belgium, 2009). (example used: patient on 24 U of a 30/70 insulin mixture and 1 tablet of gliclazide before breakfast, receiving a bolus dose of corticosteroids for prevention of contrast reaction).

1. Accurate bedside measurement of blood glucose,
2. The choice of an effective and safe system of insulin administration,
3. Matching of the therapy to carbohydrate deliverance,
4. Early detection and treatment of hypoglycaemia and
5. Expert handling of errors.

With a policy that pays attention to these elements, severe hypoglycaemia can be drastically reduced.

Accurate bedside measurement of blood glucose

In addition to the source of the blood sample, the choice of the meter and the expertise of the person who performs the measurement are important. In circumstances of tight glycaemic control, using IV insulin infusion, measurements on blood obtained through an arterial catheter are preferable. Capillary sampling is less reliable in severely ill patients with peripheral vasoconstriction or oedema. In the case of venous sampling, admixture of dextrose from an infusion can give erroneous results. In the ICU setting, measurement with an arterial blood gas analyser is preferred, as its reliability closely approximates that of a central laboratory, and it also provides potassium levels, facilitating the prevention of hypokalaemia induced by glucose–insulin administration. Classical glucose meters, similar to devices for home self-monitoring of blood glucose, are less precise and more influenced by haematocrit and oxygen tension. They are well suited for use outside the ICU and equivalent settings, provided that quality assurance is organised.

The choice of an effective and safe system of insulin administration

The above-explained characteristics of effective IV or sc insulin administration are important not only to reach the blood glucose targets but also to minimise the risk of hypoglycaemia. This includes the proactive use of a good IV insulin infusion protocol, the use of scheduled sc insulin with provision of basal coverage instead of a sliding scale and the use of algorithms for adaptation of IV and sc insulin.
that take into account the insulin sensitivity of the patient. The physician who schedules the doses of sc insulin and oral anti-diabetic agents should take care to proactively diminish them in case of recovery of an acute medical situation, deterioration of kidney function or tapering of corticosteroids. This can be facilitated by including information on kidney function and use of corticosteroids on the patient glucose summary chart (Fig. 2).

The way in which insulin is administered IV is also important. When using an IV pump, insulin should be administered through a central venous line, using an accurate syringe-driven infusion pump, avoiding the variability induced by peripheral venous infusion and volumetric pumps. In our institution, we only use IV pumps in units with intensive nursing supervision, that is, ICU, medium-care units, operating theatre and recovery unit. Outside these units, we give insulin only through a graduated burette, connected between the infusion and the patient. This is filled every hour with 100 cc glucose and the amount of insulin that is needed for the next hour. This provides the safety that the insulin is always administered together with the glucose, contrary to a separate insulin pump that continues giving insulin when the glucose administration is hampered.

**Matching of the therapy to carbohydrate delivery**

Failure to adjust anti-hyperglycaemic medication appropriately for sudden loss of caloric exposure is a major cause of iatrogenic hypoglycaemia. Nurses should receive repeated education on the synchronisation of nutrition and blood glucose regulation. With IV insulin, the rate should immediately be reduced when enteral or parenteral nutrition is interrupted. In the ICU, we use a computerised expert system that requires input of information on nutritional intake before an IV insulin rate is suggested. With sc insulin and/or oral anti-diabetic agents, nausea and emesis should immediately launch more frequent monitoring of glucose and appropriate adaptation of the treatment. Nutrition should be included as a parameter on the patient glucose summary chart, reminding the nurses to consider the nutritional intake each time they administer insulin or oral anti-diabetic agents.

**Early detection and treatment of hypoglycaemia**

Early detection requires increased alertness in the presence of risk factors for hypoglycaemia. Major risk factors are decreased carbohydrate intake, reduction of corticosteroids and prior hypoglycaemia. A previous hypoglycaemia greatly increases the chance of a new one. In these situations more frequent blood glucose monitoring is needed.

Clear guidelines should be provided on how to treat a hypoglycaemic event. Adherence to these guidelines should be promoted regularly and monitored. As in most patients with diabetes, nurses also tend to overcorrect hypoglycaemia, giving excess carbohydrates and withholding insulin. The correction of the ensuing hyperglycaemia can again induce hypoglycaemia, leading to a saw-tooth curve.

**Expert handling of errors**

Errors in the administration of insulin or oral anti-diabetic drugs should immediately be reported to the supervising physician or diabetes nurse, who should take on a non-reprimanding, positive and supporting attitude. For some frequently occurring errors guidance can be offered in the protocols. For example, patients who must present fasted for small surgery or an examination often mistakenly take their diabetes medications at home before presenting in the hospital. Recommendations on how this can be compensated with additional IV glucose infusion can be included in the protocols.

**System design**

By creatively combining the above-presented building blocks, and taking into account the safety considerations, any situation that a patient with diabetes or transient hyperglycaemia can be confronted with during hospitalisation, can be handled. The use of the same elements in different situations, facilitates the education of the users and minimises the risk of errors. All well trained nurses can
run these protocols, reducing the need for expert supervision. We illustrate this with the perioperative blood glucose policy used in our institution.

Surgery offers a complex situation with many variables. The patient can present with stress hyperglycaemia, unknown or known diabetes, either well or badly controlled. The preoperative blood glucose treatment can consist of many different oral anti-diabetic drugs and/or insulin types and schemes. On the day of surgery, the patient may need to remain fasting from the morning on or may be allowed to take breakfast. Eating can be resumed immediately after the operation or be postponed for several days. The surgery can vary from a minimal procedure, only requiring a few hours hospitalisation, to major surgery requiring transfer to ICU. The effect on the blood glucose control can vary considerably, depending on the endogenous insulin reserve of the patient, on the ‘stress response’ induced by the procedure and on the use of medications with hyperglycaemic effect. For some operations, very strict glycaemic control is desirable, whereas for others a more conservative approach can be justified. Many services are involved, some with standard, some with intensive staffing. A systematic approach, with as much simplification as possible, is essential to get a grip on such a complex situation.

We start the day of surgery with our fasting protocol. This allows us to 'jump' to the surgery using SC insulin, even when the surgical procedure starts late in the afternoon. It is a simple scheme with minor workload. Blood glucose is only measured every 4–6 h with a classical blood glucose meter on a capillary blood sample. If a switch to IV insulin is needed, the insulin that is already on board from the fasting protocol poses no problem, since our IV insulin protocol automatically adapts to this situation, searching the most suitable column for insulin administration. Our fasting protocol allows correction of hyperglycaemia with SC insulin up to a value of 350 mg dl$^{-1}$. For blood glucose levels above 350 mg dl$^{-1}$, we switch to IV insulin on the surgical ward, safely administered with a graduated burette.

In the operating theatre the policy depends on the blood glucose goal. In high-risk surgery we aim at blood glucose levels between 85 and 110 mg dl$^{-1}$. We define high-risk surgery as any intervention that routinely leads to postoperative transfer to ICU (e.g., cardiac surgery, brain surgery and major gastrointestinal surgery). In these patients we immediately switch to IV insulin upon arrival in the operating theatre, and continue this in the ICU (results, see section on IV insulin infusion algorithm). The insulin is administered with a syringe-driven infusion pump, and blood glucose is measured in arterial blood with an on-site blood gas analyser.

In all other interventions we aim at blood glucose levels below 200 mg dl$^{-1}$. In these patients, blood glucose is measured hourly during long operations, using a classical blood glucose meter on a capillary blood sample. If the blood glucose exceeds 200 mg dl$^{-1}$ an IV insulin pump is started. If not, the fasting protocol is continued. We use the same insulin infusion protocol as for high-risk surgery, but with a higher target zone of 90–140 mg dl$^{-1}$ (green zone in Fig. 1). When the patient returns to the surgical ward, we switch to an IV insulin burette. On the ward most patients can be converted to SC insulin, using a basal–bolus scheme, the evening after the operation. Patients who return home the day of the operation immediately switch to their home treatment. An audit of all 917 low- and medium-risk interventions in December 2008, in patients with diabetes and/or stress hyperglycaemia, showed that with this approach 89.7% of the measurements ranged between 70 and 200 mg dl$^{-1}$, with only 0.1% <50 mg dl$^{-1}$ and 1.2% >300 mg dl$^{-1}$.

**Quality assurance**

It is important to regularly evaluate whether the protocols are effective enough, and whether they are systematically and properly used. One would especially like to know whether blood glucose is measured sufficiently frequently, how many measurements fall within the set targets, how large the blood glucose variations are and how often hypoglycaemia and significant hyperglycaemia occur. For comparison between different centres, the Yale group proposes to organise this in a standardised manner, and makes guidelines and a computer program available on the Web under the name ‘glucometrics’. These data can be looked at hospital-wide, for a general overview of the inpatient blood glucose control, and also per situation (e.g., perioperative) or per unit. Regular feedback of the results is important to motivate staff to continue to follow the protocols. In case of unsatisfying results, the process should be analysed to determine what can be improved. Besides parameters of blood glucose
control, it is also useful to follow outcome parameters. Since we introduced tight glycaemic control in our ICUs we see a reduction of mortality and of cardiac, renal and infectious complications.14

In brief, effective and safe inpatient glycaemic control is feasible, with the creative use of a few well-chosen building blocks, and careful attention to safety. An essential element is a well-designed algorithm for IV insulin administration that gradually adapts the insulin infusion rate to the individual insulin sensitivity of the patient. For smooth transition to post-acute care a sc basal–bolus scheme, preferably using regular and NPH insulin, offers flexibility, but avoids the fluctuations induced by a traditional sliding-scale regimen. It should be used with a correction algorithm that provides larger corrections at higher insulin doses and vice versa. Other essential elements are fasting rules, and agreements on transitioning to discharge care. Hypoglycaemia can be reduced to a strict minimum by proactive adaptation of the treatment in situations of diminishing insulin needs, especially in case of sudden reduction of calorie intake. These different building blocks and safety considerations can be integrated in effective and safe protocols for the organisation of tight glycaemic control in different hospital environments and situations. More research is needed, however, on several components of this practical approach. It is surprising how little practical guidance is available in the current literature. Hospitals should be encouraged to make their protocols and results more readily available.

**Practice points**

- When developing protocols for inpatient blood glucose control, use as few building blocks as possible. With the creative use of an IV insulin algorithm, a sc basal–bolus system, fasting orders and agreements on transitioning to discharge care, most situations can be handled.
- Use an IV insulin algorithm that gradually adapts the insulin infusion rate to the individual insulin sensitivity of the patient.
- For sc use, avoid sliding scales, but use scheduled insulin with provision of basal coverage. Use a correction algorithm that provides larger corrections at higher insulin doses.
- To avoid hypoglycaemia, pay major attention to immediate reduction of blood glucose medication in case of sudden reduction of calorie intake or dose of corticosteroids.
- The tighter the blood glucose goals, the more accurate the glucose monitoring and IV insulin administration should be.
- Good communication is an important element of inpatient blood glucose treatment. Include information on nutrition intake, corticosteroid use and kidney function on the glucose charts.

**Research agenda**

- More research is needed to optimise the effectiveness and safety of insulin infusion algorithms.
- The accuracy of bedside monitoring in the ICU setting should be improved.
- Accurate and safe continuous glucose monitoring should be developed, that can be used to create closed-loop glycaemic control.
- Expert systems should be created that integrate information on blood glucose evolution, insulin pharmacology and determinants of insulin needs (such as carbohydrate supply) to drive an IV insulin pump, creating a ‘smart closed-loop system’.
- Research is needed on the essential components of sc insulin delivery, such as transitioning from IV to sc delivery, use of correction doses and fasting rules.
- Nursing policies for effective hypoglycaemia prevention should be examined.
- Outcome research of tight glycaemic control in the ICU and perioperative settings should be repeated with algorithms that provide accurate blood glucose control with a low incidence of severe hypoglycaemia.


