Practical management of inpatient diabetes regimens

Introduction

People with diabetes may be admitted to hospital as a result of diabetic emergencies such as diabetic ketoacidosis or hyperosmolar non-ketotic hyperglycaemic syndrome, or for illness or surgery unrelated to diabetes. Hospitalized people with diabetes need good glycaemic control as much as they do at home, or perhaps even more, considering the stresses associated with illness or surgery.

In fact, whether a person has diabetes or not, hyperglycaemia in hospital is associated with increased morbidity and mortality that can be reduced if it is controlled (Van Den Berghe et al, 2001; Umpierrez et al, 2002). Most studies show similar benefits in controlling blood glucose in hyperglycaemia whatever the subsequent formal diagnosis, but for longer term management, formal diagnosis should be pursued or passed to the GP to pursue.

On admission to hospital, patients should be questioned to see if they have a history of diabetes or glucose intolerance. Individuals at risk of diabetes include those from susceptible ethnic minorities (such as south Asians), those who are obese, have hypertension or who have a first-degree relative with diabetes. All such patients should have a laboratory blood glucose estimation performed on admission or at a pre-admission visit for a planned procedure.

Although it is desirable to have inpatient review by a diabetes team for patients whose diabetes is causing problems, in reality this is not always possible, and members of other teams can do a great deal to manage their diabetes. One of the most contentious areas is to what degree treatment regimens should be altered before a specialist team needs to be involved.

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Some patients will manage on their previous diabetes treatment, but others will need to start or intensify an insulin regimen (*Table 1*). Realistic choices will be between no insulin, subcutaneous insulin or intravenous insulin.

Intravenous insulin regimens

The goals of treatment are to maintain adequate glycaemia, keep a normal level of hydration, eliminate ketone production and reverse or prevent electrolyte imbalances. To this end, insulin may be given alone, with saline or as insulin plus dextrose and possibly potassium in combined infusions (*Table 2*).

Almost every hospital in the UK has protocols for the use of intravenous insulin regimens in the acute situation (Scottish Diabetes Group, 2005; Sampson et al, 2007). These may vary in their exact details, but it is important to use local, agreed protocols that your colleagues are familiar with to reduce clinical risk. However, the decision to start someone on intravenous insulin can be rather less clearly defined.

Deciding who needs intravenous insulin in hospital

A reasonable list of indications for intravenous insulin therapy for inpatients with diabetes is (based on the American College of Endocrinology Consensus statement; Garber et al, 2004):

Well-defined emergency situations

- Diabetic ketoacidosis or hyperosmolar state
- Critical illness (admission to a critical care unit)
- Myocardial infarction.

Planned procedures

- Planned major surgery (any which results in prolonged fasting)
- Following organ transplantation
- Total parenteral nutrition
- Labour and delivery.

General management of difficult control

- Prolonged fasting (>12 hours) in type 1 diabetes
- Any situation requiring rapid control of blood glucose.

Any inpatients with diabetes presenting with any of the above indications should be taken off their standard regimen and transferred to intravenous insulin.

If the situation is less clear, a fasting blood glucose test can be taken. A fasting glucose >9 mmol/litre should be a signal to monitor blood glucose more closely and to determine the direction of any glycaemic trend. If blood glucose levels are rising, or if there is any concern over the clinical situation of the patient, an intravenous insulin regimen is an acceptable and safe approach.

Choice of regimen

Once an acutely raised blood glucose has fallen in response to insulin and fluids, or

Table 1. If a procedure is planned, can patients manage on their current diabetes treatment?

If the procedure is not likely to result in prolonged >12-hour fasting (interventional radiology, day case procedure, laparoscopic or minor surgery)	Yes
If patients do not have frequent hypoglycaemic episodes (glucose <4 mmol/litre) on treatment (insulin or sulphonylureas)	Yes
If patients have a fasting plasma glucose < 10 mmol/litre, random premeal glucose <15 mmol/litre	Yes
If surgery is emergency or prolonged or likely to require postoperative admission to critical care	No*
If there is a likelihood of prolonged fasting (e.g. postoperative ileus, sepsis)	No*
If there is concern about hypoglycaemia as a result of long-acting treatment (basal insulin analogues or long-acting sulphonylureas)	No*

*If the answer is no, patients require intravenous insulin and fluids, started at least 6 hours before surgery, to allow for blood glucose stabilization before the procedure commences. Usual treatment can be restarted after the procedure if previously effective

Table 2. Intravenous insulin and fluid regimens

Regimen	Purpose	Typical regimen
Hyperglycaemia reduction	To correct a high blood glucose and clear ketones where blood glucose over 20 mmol/litre (e.g. diabetic ketoacidosis, hyperosmolar state)	Use local protocols if available: 6 units/hour rapid-acting insulin or analogue, or with physiological (normal) saline at least 120 ml/hour (3 litres/day), to compensate for osmotic diuresis. Rate judged on clinical state Use potassium-containing fluids if serum potassium <4 mmol/litre. Check glucose hourly by finger prick. When blood glucose <15 mmol/litre, reduce insulin to 3 units/hour and change fluids to dextrose-containing preparations (see below)
Glucose maintenance	To maintain blood glucose at target level (locally determined) and prevent starvation ketones and hypokalaemia (e.g. starvation of insulin-treated patient for procedure)	Use local protocols if available: fixed infusion of dextrose containing fluid at predetermined rate (30–120 ml/hour). Rates will depend whether anuria, heart failure, post myocardial infarction. Commonly used are 10% dextrose, 5% dextrose or 'dextrose saline'. Variable insulin (or analogue) infusion (typically 0.5–3 units/hour) with adjustment algorithm to maintain blood glucose close to target. Usually 1 unit/ml in syringe driver
		Alternatively, if syringe drivers or infusion systems are not available, a combined 'GKI' (glucose-potassium-insulin) infusion can be used. This is a 500 ml bag of dextrose-containing fluid (typically 10% dextrose with potassium) with 10–20 units of insulin injected into bag. Infusion rate is 6–8-hourly (60–80 ml/hr), and need not be through an infusion pump, since the insulin and dextrose are delivered together and overall infusion rate is not critical. If glucose falls outside predetermined range, the bag is discarded and replaced by one with 2 or 4 units less or more insulin injected into the bag

after surgery has been carried out, there may be a period in which maintenance of a fasted state is required. The target level for blood glucose in this state is debated, with a wide range of values suggested, depending on clinical context. A consensus statement from the American College of Endocrinologists recommends specific glycaemic targets for inpatients (*Table 3*) (Garber et al, 2004).

Common problems of intravenous insulin treatment are hypokalaemia and hypoglycaemia, both of which are predictable from the physiological action of insulin. Hypoglycaemia becomes more of a risk as tight target blood glucose levels are approached, while hypokalaemia can be more of an issue with prolonged starvation.

A dextrose/potassium drip at 3–8 g/hour (e.g. 30–80 ml/hr 10% dextrose with potassium) can be used as a source of electrolytes, calories (4 kcal/g) and water, and may reduce the risk of both hypoglycaemia and hypokalaemia. In addition, this may allow a higher dose of insulin to be used, which may have benefits in clearing ketonaemia, either from starvation or from resolving ketoacidosis. As with all infusions, infections at the site of the intravenous line are a potential problem to be dealt with in part by prompt return to subcutaneous regimens.

Table 3. Glycaemic targets for inpatients

Patient		Plasma glucose target
Intensive care unit		6.1 mmol/litre
Non-critical patients	Preprandial	6.1 mmol/litre
	Maximal	10.0 mmol/litre

From Garber et al (2004)

Subcutaneous insulin regimens

Transition from intravenous to subcutaneous insulin therapy

Once blood glucose has stabilized, and the patient has started eating and drinking, it is necessary to transfer from intravenous insulin to a subcutaneous insulin regimen. This should occur well before patient discharge (*Table 4*). When the transfer is done effectively, there is evidence of improved outcome in postoperative patients (Schmeltz et al, 2007). For patients who were previously taking insulin, the aim should be to get them back onto their previous regimen, or close to it. Patients should ideally receive pre- and postprandial (1.5–2 hours) glucose monitoring so that the insulin dose can be adjusted to take into account the level of patient stress, oral intake, intravenous or enteral feeding, dietary supplements and any new medications that are being taken (e.g. steroids).

In patients who were not previously on insulin but who are to continue insulin

Table 4. How to transfer to subcutaneous insulin

Step	Action
1	Estimate 24-hour insulin requirements from previous 6–8 hours of infusion rate
2	Give approximately two-thirds of this as the next 24 hours subcutaneous insulin total a. Premix regimen (any 30/70 or 25/75 premix insulin): Divide insulin 60% morning pre breakfast, 40% evening pre evening meal b. 'Basal bolus' regimen (short-acting analogue premeal, basal analogue daily): Divide insulin 20% with each of three meals, 40% basal
3	Time first subcutaneous injection before a meal. Give insulin half an hour before food if possible. (first premix dose if using twice daily premix regimen, or both first mealtime bolus and first basal injection if using basal bolus regimen)
4	Run infusion for an hour after the meal finishes to ensure overlap of intravenous and subcutaneous insulin effect
5	Check fingerprick glucose at least four times a day (premeal and pre-bed) Adjust insulin doses by 10% per day for type 1 patients, 20–25% for type 2
6	If new to insulin or problems with self care on the ward are apparent, ensure the diabetes specialist nurse sees the patient before discharge, or if that is not possible, that the patient is given instruction by ward nurses, and has home supervision (at least initially) by the district nurse

treatment once intravenous therapy is withdrawn, a reasonable regimen must be determined. However, choosing a suitable regimen is relatively complex, as there will be a rapid reduction in insulin requirements as the patient improves from the acute illness that originally led to the decision to initiate intravenous insulin. The clinician is attempting to predict a falling insulin requirement. A good starting point is to calculate the insulin required for 24 hours by looking at the average hourly insulin infusion rate/dose for 6–8 hours before terminating the intravenous insulin regimen, using this to calculate a 'snapshot' 24-hour requirement and to give half to two thirds of this as subcutaneous insulin for the next 24 hours.

In a basal bolus regimen (four injections per day), 40–50% of the 24-hour insulin dose is given as a basal dose once per day and half as preprandial short-acting insulin doses, divided between the number of meals taken per day. Many people divide this up as mealtime 20/20/20%, basal 40% of the total insulin dose. The patient should have regular preprandial (and, ideally, postprandial) blood glucose tests taken and this starting dose should be adjusted pragmatically every 2–3 days to achieve the target level of glycaemia.

In a premix-based regimen (two injections per day), this total insulin dose is given as 30/70 or 25/75 mixed insulin, split two-thirds in the morning and one third in the afternoon.

Starting subcutaneous insulin if intravenous insulin has not been used

If intravenous insulin is not being used but control is inadequate, such as in a new type 1 patient or a type 2 individual on maximal tolerated oral agents, subcutaneous insulin regimens can be started directly. These can be either basal insulin or premixed insulin regimens alone or separate basal and mealtime insulins given at various points throughout the day, depending on patient need or preference.

Basal insulins (glargine, levemir) added to oral treatment in type 2 diabetes make once-daily insulin supplementation relatively straightforward. One approach is to start with 10 units daily, administered with the evening meal, and titrate the dose by two units every 3 days to achieve a fasting blood glucose value of around 6 mmol/litre. This has the advantage that the patient can be taught to self-titrate after discharge to optimize the fasting glucose.

Basal insulin may be sufficient for patients who retain mealtime insulin response, but when monitored in hospital it may become apparent that postprandial blood glucose runs high, particularly later in the day. 'Basal bolus' and 'basal plus' regimens provide more intensive insulin therapy for those who are uncontrolled on oral agents alone or oral agents plus a basal insulin.

In the basal plus regimen, patients use a basal insulin analogue plus a single mealtime dose of a short-acting insulin analogue, adjusted to keep the pre-meal glucose level around 6 mmol/litre and postprandial glucoses <10 mmol/litre. Further mealtime insulin injections can be added in as needed. The basal bolus regimen takes this further, with administration of a basal insulin analogue plus a short-acting insulin analogue with every meal (Nathan et al, 2006).

Premixed insulin regimens consist of a short-acting insulin analogue plus an intermediate- or long-acting insulin in a fixed ratio, usually with 25–30% of rapid-acting analogue. Until recently, these were a common choice for initiating insulin when a patient was uncontrolled on oral agents alone. Premixed insulins are still a treatment choice for patients who are unwilling or unable to progress to a basal bolus insulin regimen, as these are either given as a single injection up to three times per day, depending on patient need.

Inpatients with chronic hyperglycaemia on insulin treatment

If an inpatient's fasting and pre-meal blood glucose results are consistently elevated despite insulin treatment, investigative and remedial action is needed. An important initial strategy is to determine the direction and timing of blood glucose changes – i.e. to decide whether the glucose is increasing or decreasing during the time-course of insulin injections.

If intensification of insulin treatment is warranted, an increment of 5–10% of a particular dose should be given to people with type 1 diabetes, and 20–25% for those with type 2 diabetes. This should be followed by regular fasting, pre- and postprandial glucose testing and further increments considered if glycaemia remains uncontrolled. Often it helps to focus on and correct one part of the 24-hour glucose profile at a time. If all else fails, and blood glucose levels are still above 20 mmol/litre an overnight (16–20 hr) intravenous insulin regimen should be given and a subcutaneous insulin regimen re-initiated the following day, as suggested above, with recalculation of insulin doses from the intravenous requirements.

Inpatients with recurrent hypoglycaemia

Occasionally, because of errors in doses or poor intake, a patient will run with recurrent low blood glucose readings and frequent symptomatic hypoglycaemia. Counter-regulation to raise blood glucose and the frequent need to treat with glucose with 'rebound' higher readings makes a pattern hard to determine. Under these circumstances, it is best to reduce insulin doses substantially (25–50%, depending on the severity of hypoglycaemic events) across all dose times to re-establish a pattern, even if the blood glucose levels run high for the next few days. Dealing with the pattern of high glucose readings is easier because counter-regulation does not interfere.

Inpatients with 'unstable' sugars

This phrase is used by nurses and junior doctors to describe a mix of high and low glucose readings with no discernable pattern. This state of affairs is usually iatrogenic: over-compensation for hypoglycaemia by giving too much glucose, missing doses of insulin if the glucose is low and erratic mealtimes and snacks to avoid hypoglycaemia. The worst offence is arbitrary use of fixed doses of subcutaneous human insulin to treat blood glucose readings over 20 mmol/litre, with consequent late hypoglycaemia. This can usually be dealt with as for recurrent hypoglycaemia, by a substantial insulin dose reduction, but ensuring that the regular dose of insulin is actually given. If that leads to high glucose readings, it can be helpful to use an overnight intravenous regimen, and start with recalculation of insulin doses, as above.

Optimizing oral agents

There are four classes of oral agents frequently used to manage diabetes, all with additive effects, but individual strengths. Most type 2 patients seen in hospital will be on one or more class of oral agent, with or without insulin.

Metformin is the mainstay of treatment regimens in type 2 diabetes, but is contraindicated in individuals with chronic kidney disease worse than grade 3 (glomerular filtration rate <30 ml/min), and may not be tolerated in 20% of patients because of gastrointestinal side-effects. After metformin, there is no firm consensus as to which agent should be used next (Nathan et al, 2006). A systematic review found each class to be safe, similarly effective, with no evidence of difference in outcomes between classes (Bolen et al, 2007).

Secretagogues, such as sulphonylureas (gliclazide, glimepiride) or glinides (repaglinide, nateglinide), are often used in combination or as monotherapy, but do have a risk of hypoglycaemia. Glitazones (pioglitazone, rosiglitazone) are also often used in combination, but congestive heart failure is the main contraindication. The dipeptidyl peptidase inhibitors, a new class of which sitagliptin is a member, have recently been launched in the UK.

All can be used together, in theory, but some are more favoured by guidelines than others. Common combinations are metformin with another one or two classes. The principles of their use are:

- Half-maximal doses will achieve almost the full effect of each agent
- The effect of the agents is additive
- Sulphonylureas added at half maximal doses will reduce average blood glucose by 3–4 mmol/litre, within a day or two
- Metformin at 2 g/day will reduce blood glucose by a similar amount over a week or more (to reduce risk of intolerance, start at 500 mg twice daily for a week)
- Glitazones may be less potent and show their effects over weeks to months
- Sitagliptin has a modest effect on average blood glucose (1–2 mmol/litre).

What to do on discharge

Most inpatient diabetes specialist teams are keen to review or discuss patients with diabetes before discharge if there have been problems with control or major adjustments in treatment. There is good evidence that early input from these teams can shorten length of stay of inpatients with diabetes (Sampson et al, 2007).

The help of a diabetes specialist nurse or other experienced educator is invaluable if there have been changes to regimens, especially if insulin has been newly started. A promise of early review clinic often gives both the patient and the clinician confidence to discharge early. A review of home blood glucose readings a few days after discharge, and the review of an up-to-date haemoglobin A1c (most conveniently taken before discharge) ensures that treatment can be optimized soon after discharge and reduces the temptation to keep a patients in for a few more days 'just in case'. This visit to the diabetes nurse might occur within a week for patients new to insulin, or within a month for those who were taking insulin before admission to hospital but had major insulin dose adjustments.

Conclusions

Insulin regimens for diabetes do not present major problems thanks to modern delivery devices and the development of insulin analogues that can closely mimic physiological insulin secretion. Insulin pen delivery devices are used mainly for convenience, but can be easier to learn and may be more accurate than syringes, depending on the dose being given and the amount of education that the user has received.

Although there are strict targets for glycaemia for people with diabetes and inpatients at risk of poor glycaemic control, the principles of dose adjustment are mostly pragmatic. Depending upon the patient's health, the glycaemic target might need to be reviewed, so care should be taken to ensure that adequate monitoring of blood glucose is undertaken and that treatment reflects a global view of the patient's health and context. **BJHM**

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KEY POINTS

- So many people with diabetes attend hospital that all medical and surgical doctors should be confident in their management during their stay.
- The period of inpatient observation may provide an opportunity to improve blood glucose control in diabetic patients.
- Use an intravenous insulin infusion regimen to manage diabetes in all but the most minor procedures or if diet controlled.
- Occasionally erratic control can be caused by over treatment with insulin with hypoglycaemia and rebound hyperglycaemia, reducing doses may paradoxically improve control.