Glycaemic management in patients with diabetes in hospital

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Abstract

The prevalence of diabetes mellitus in the inpatient population is three times greater than in the general population. A significant proportion of inpatient expenditure in the UK is spent on the care of patients with diabetes. Despite this, patients with diabetes stay longer in hospital than patients without diabetes, and have increased mortality and morbidity. The emerging evidence is in favour of good glycaemic control, which requires control of hyperglycaemia and avoidance of hypoglycaemia. Although insulin is the preferred therapy in the inpatient setting, there remain serious concerns about its safe use. Newer agents such as incretin-based therapies appear promising in the context of inpatient diabetes care, but more research is required before they can be recommended in the inpatient setting. Healthcare professionals caring for inpatients with diabetes continue to demonstrate suboptimal expertise, and their training needs to be addressed.

Keywords Hyperglycaemia; hypoglycaemia; inpatient diabetes mellitus; insulin; MRCP; safe discharge

Key points

- Good glycaemic control in hospital requires control of hyperglycaemia and avoidance of hypoglycaemia; both are associated with increased morbidity, mortality and increased length of stay
- Staff inexperience, hospital meals and medication errors are major barriers to achieving good glycaemic control
- Insulin remains the preferred method of achieving good glycaemic control, although serious concerns exist about its safe use in hospitals
- Newer agents such as incretin-based therapies appear promising in the inpatient setting, but more research is required before they can be recommended
- Sodium glucose co-transporter 2 inhibitors should be temporarily discontinued in patients undergoing major surgery or in hospital with severe illness because of the risk of euglycaemic diabetic ketoacidosis

Introduction

The most recent (2017) English National Inpatient Diabetes Audit (NaDIA) has shown a prevalence of diabetes mellitus in the hospital inpatient population of 18%. People with diabetes are twice as likely to be hospitalized, and have longer hospital stays, than people of the same age without diabetes. It is estimated that the NHS in England spends >£2 billion a year on inpatient care for people with diabetes alone – around 11% of its total inpatient care expenditure.

Importantly, >90% of inpatients with diabetes are admitted because of other illnesses rather than diabetes per se, often under specialty teams that may not have the expertise to manage diabetes in the complex inpatient setting. Driven by evidence of suboptimal hospital management of diabetes, inpatient diabetes care including management of diabetic emergencies, glycaemic control in inpatients and perioperative diabetes care is now a major focus of attention in the UK. Here we discuss the control of hyperglycaemia and the avoidance of hypoglycaemia in adult inpatients with diabetes mellitus. The specific requirements of children and pregnant women will not be covered here.

Hyperglycaemic patterns in inpatients

Hyperglycaemic patients in hospital can have pre-existing diabetes, hospital-related diabetes (stress hyperglycaemia) that resolves after discharge, or newly diagnosed diabetes that persists after discharge. Glycated haemoglobin (HbA_{1c}) reflects glycaemia over the previous 6–12 weeks and can be of use in distinguishing the latter two categories: HbA_{1c} ≥48 mmol/mol (≥6.5%) is diagnostic of diabetes. Measuring HbA_{1c} in hospital also predicts clinical outcomes in surgical patients, and can inform the choice of diabetes therapy at discharge. All three categories of hyperglycaemia influence outcome of hospital stay and should be managed with equal care. Poorly managed inpatient hyperglycaemia or insulin omission can lead to diabetic ketoacidosis (DKA) in type 1 diabetes; the latest NaDIA report shows that 1 in 25 inpatients with type 1 diabetes (4.3%) develop DKA during their hospital stay, and disappointingly, the incidence has remained the same in the last few years.

Hypoglycaemia in hospital

Hypoglycaemia is widely defined as a blood glucose concentration <4.0 mmol/litre, which is the concentration at which most people with diabetes develop hypoglycaemic symptoms. Self-treated hypoglycaemic episodes are classified as 'mild', whereas those requiring assistance by a third party are classified

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as 'severe'. This classification is blurred in the inpatient setting as most patients do not have access to glucose-increasing therapies and therefore require assistance even if well enough to treat themselves. The Joint British Diabetes Societies (JBDS) recommend that all adults with diabetes with a blood glucose <4.0 mmol/litre in hospitals should be treated, whether or not symptomatic. One of the key concerns highlighted by NaDIA over 7 years has been the unacceptably high rate of hypoglycaemia in hospital, affecting up to 18% of all inpatients with diabetes and up to half of all insulin-treated inpatients.

Evidence in favour of controlling glycaemia in hospitalized patients

A wealth of observational evidence associates both hyperglycaemia and hypoglycaemia in hospitalized patients with increased length of stay and higher morbidity and mortality. However, the promise of reduced morbidity and mortality with tight glycaemic control in critically ill inpatients implied by intervention trials early in this century has been disputed by subsequent trials and meta-analyses, some of which have found higher mortality rates. In all these trials, patients with tight glycaemic control have had more hypoglycaemia, which may have led to poorer outcomes. Good glycaemic control in hospital should avoid both excessive hyperglycaemia and hypoglycaemia.

Barriers to achieving good glycaemic control in hospital

The stress of illness worsens hyperglycaemia by stimulating the release of counter-regulatory hormones, which increase hepatic gluconeogenesis and glycogenolysis and inhibit peripheral glucose uptake.

Controlling hyperglycaemia and avoiding hypoglycaemia is particularly difficult in hospitalized patients because of both patient factors, such as co-morbidity (renal and liver disease), sepsis, abnormal nutritional states and changing drug therapies, as well as hospital environment factors, such as meal quality and timing, staff expertise and confidence in treating people with diabetes, and medication errors. It has been consistently reported that there is a high degree of dissatisfaction among patients with diabetes with the quality, quantity and timing of hospital meals; those who reported higher dissatisfaction were significantly more likely to experience severe hypoglycaemia in hospital.

Moreover, one of the largest surveys of junior doctors in the UK found that most felt their diabetes training did not allow them to safely manage inpatients with diabetes, and that only 40% would take the initiative to optimize glycaemic control for patients under their care >80% of the time. Inpatients experiencing medication errors are also twice as likely to experience hypoglycaemia.

Recommended glycaemic targets in hospitalized patients

Because of the conflicting evidence on tight glycaemic control, the American Diabetes Association (ADA) expert panel now recommends the following blood glucose targets:

- critically ill inpatients — 7.8–10.0 mmol/litre
- non-critically ill inpatients — pre-meal <7.8 mmol/litre, random <10.0 mmol/litre
- less stringent targets for those with severe co-morbidities.

The UK JBDS recommends an ideal blood glucose target range of 6.0–10.0 mmol/litre (acceptable range 4.0–12.0 mmol/litre) in the perioperative period. It is possible that these targets may be revised when new evidence emerges.

Treatment strategies: non-insulin or insulin therapy?

Use of insulin to control inpatient hyperglycaemia remains a subject of debate. The JBDS does not currently recommend a preferred method of achieving good glycaemic control in non-critically ill inpatients. The ADA, however, recommends insulin therapy for both critically and non-critically ill inpatients as the preferred method of achieving and maintaining glycaemic control.

Non-insulin therapy in the hospital setting

In the hospital setting, oral anti-hyperglycaemic agents may not be the best option for achieving good glycaemic control, especially when glucose concentrations are changing rapidly because of the patient factors described earlier. Metformin may need to be discontinued temporarily as a result of declining renal function and administration of intravenous contrast for imaging procedures. The effects of sulfonylureas are unpredictable in critically ill patients, especially in individuals who are elderly or have renal impairment, and can lead to prolonged and recurrent hypoglycaemia. Oral incretin-based therapies appear to achieve similar glycaemic control to insulin therapy in a subgroup of inpatients with diabetes, with lower rates of hypoglycaemia, but larger trials in a wider inpatient population are required to confirm this.

There is lack of evidence supporting the use of injectable incretin-based therapies in the acute inpatient setting. Sodium glucose co-transporter 2 (SGLT-2) inhibitors are a relatively new group of oral medications currently indicated only in type 2 diabetes, but they carry a risk of precipitating euglycaemic DKA in patients with poor control. Hence the current recommendation is to temporarily stop SGLT-2 inhibitors in patients who are undergoing major surgery or are in hospital because of serious illness.

Insulin therapy in the hospital setting

Insulin therapy, either subcutaneous or intravenous depending on the situation, is often the most effective method of controlling blood glucose in hospital, even in insulin-naive patients. Subcutaneous insulin is preferred in most inpatients who are able to eat and drink normally. It is often difficult to optimize control using twice-daily pre-mixed insulin in hospital settings because of the patient and hospital factors described above, although this approach is still widely used.

There is now good evidence that better glycaemic control and lower rates of hypoglycaemia are associated with the use of basal bolus or basal plus correction regimens. Figure 1 is an example of a subcutaneous insulin therapy regimen in hospital for hyperglycaemic patients. In the USA, basal bolus insulin therapy is recommended for all hospitalized patients with diabetes. In the UK, it is not possible to advocate this as first-line therapy for those taking oral therapies on admission, as up to a third of all NHS hospitals in England still do not have a dedicated inpatient diabetes nurse to facilitate this.

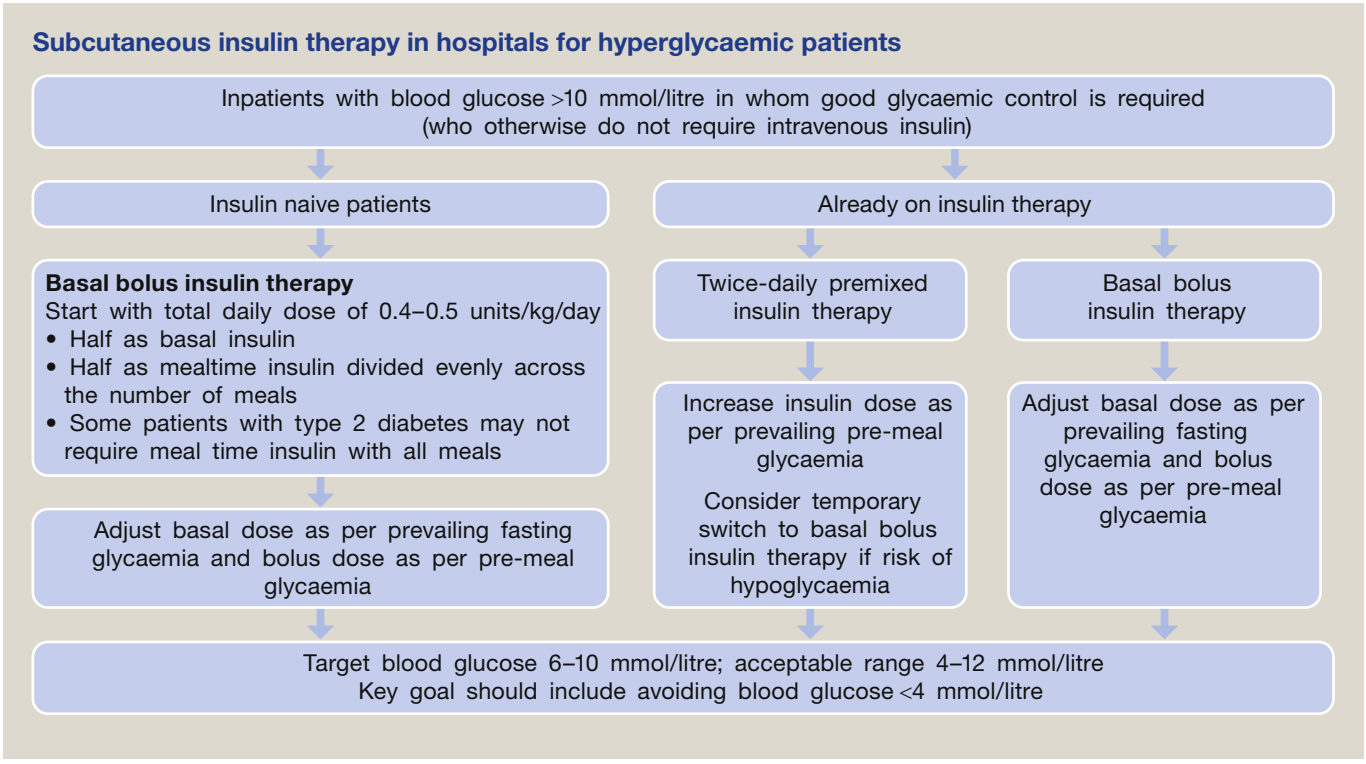

Figure 1

Of note, the term 'sliding scale' is used loosely in the literature with no specific definition and should be abandoned, to avoid confusion. In the USA, it refers to the use of a predefined subcutaneous insulin bolus regimen according to the prevailing blood glucose, whereas in the UK it refers to a variable-rate intravenous insulin infusion (VRIII). Subcutaneous 'sliding scale' insulin regimens are now widely considered by most experts to be inappropriate for achieving good glycaemic control as they can result in a high degree of glycaemic variability.

Intravenous insulin has a half-life of only a few minutes and must be administered continuously, either as a fixed-rate intravenous insulin infusion (FRIII) or VRIII. FRIIIs are used in the management of diabetic emergencies such as DKA and hyperosmolar hyperglycaemic states (see pages 46–51 of this issue). In some situations, as shown in Table 1, VRIII is often the only appropriate therapy for achieving good glycaemic control.

Indications for VRIII

Hyperglycaemia (capillary blood glucose >10 mmol/litre) in the following situations:

- Vomiting and/or intolerance of oral fluid/food (especially in type 1 diabetes after ketoacidosis has been excluded)
- Nil-by-mouth for more than one meal (e.g. perioperative patients, critical care unit patients)
- Severe systemic illness (e.g. sepsis)
- Special circumstances such as acute coronary syndrome, stroke and artificial feeding

Table 1

However, it can cause harm if used inappropriately — as in the treatment of isolated hyperglycaemia in a patient who is otherwise well and able to eat and drink, or in the treatment of hyperglycaemia after hypoglycaemia. It is important that glucose monitoring is undertaken hourly during administration of VRIII to permit insulin dose titration and to avoid inadvertent hypoglycaemia.

VRIII protocols vary among hospitals, but it is essential that only one safe, simple and workable protocol is used in an individual hospital (except in intensive care units, where more intensive monitoring permits more complex protocols). A typical VRIII chart is shown in Table 2. The recommended first-line concurrent fluid therapy is sodium chloride 0.45% with glucose 5% (containing potassium chloride 20 or 40 mmol/litre). If this is not readily available, acceptable alternatives are sodium chloride 0.18% with glucose 4% (containing potassium chloride 20 or 40 mmol/litre), and glucose 5% alone (with potassium chloride 20 or 40 mmol/litre). Prolonged infusion of either sodium chloride 0.18% with glucose 4% or only glucose 5% carries a risk of hyponatraemia.

Conversion back to subcutaneous insulin or oral medications should be undertaken at mealtimes, as soon as VRIII is no longer required and the patient is able to eat and drink as normal. To avoid hyperglycaemia, VRIII should be discontinued 30 minutes after subcutaneous insulin therapy has been commenced. VRIII should never be discontinued at bedtime, especially in patients with type 1 diabetes, because of the risk of ketoacidosis. It is now universally recommended that basal subcutaneous insulin be continued even during administration of VRIII to minimize the risk of rebound hyperglycaemia and ketosis after discontinuing the VRIII.

Recommended insulin infusion rates for variable rate insulin infusion (VRII) as per scale

Glucose (mmol/litre)	Insulin infusion rate (U/hour)		
	Scale 1	Scale 2	Scale 3
	If already insulin-treated, daily insulin dose <30 units If insulin-naive, consider in likely insulin-sensitive patients (e.g. BMI <20 kg/m^2, frail, elderly, renal failure)	If already insulin-treated, daily insulin dose 30–60 units If insulin-naive, consider in patients not requiring scale 1 or scale 3 First choice in most patients	If already insulin-treated, daily insulin dose >60 units If insulin-naive, consider in patients with likely insulin resistance (e.g. BMI >35 kg/m^2, corticosteroid therapy)
<4[a]	0[a]	0[a]	0[a]
4–6.9	0.5	1	2
7–9.9	1	2	3
10–14.9	2	3	4
15–19.9	3	4	5
>20	4	5	6

Target blood glucose 6–10 mmol/litre in most patients; acceptable range 4–12 mmol/litre. BMI, body mass index.
NB. Continue *basal* subcutaneous insulin in patients already having this treatment.
[a] Treat hypoglycaemia and restart the intravenous insulin infusion in 20 minutes.

Table 2

An exciting new development in the management of inpatient diabetes has been automated, closed-loop insulin delivery systems. These have been shown to significantly improve glycemic control compared with conventional subcutaneous insulin therapy, without a higher risk of hypoglycaemia. To date, these have only been used in research studies of inpatients with type 2 diabetes. Although attractive, such systems currently require considerable expertise in the use of closed-loop technology, as well as the involvement of trained diabetes staff. Further work is necessary to improve the ease of use of these systems before they can be used on busy general wards.

Safe use of insulin

Worldwide, insulin has been identified as one of the top 10 high-risk medicines. It has a low therapeutic index, and requires precise dose adjustment, careful administration and monitoring of its effect. Correct prescription of insulin involves appropriate timing in relation to meals, dose titration to the prevailing blood glucose concentration, and knowledge of its pharmacodynamics and altered sensitivity caused by illness. This requires considerable expertise, which is often lacking among healthcare professionals in inpatient settings, resulting in errors that sometimes lead to serious harm, including death.

Common insulin errors

Errors typically involve omitted doses, incorrect doses and inaccurate transcription of the type, dose or timing of insulin. Examples of and reasons for commonly encountered errors are:

- Confusing insulin preparations (e.g. Humalog and Humalog Mix25; NovoRapid and NovoMix 30)
- Incomplete insulin names on prescription chart (e.g. 'Humulin' instead of 'Humulin S' or 'Humulin I')
- Use of the wrong syringe for delivery — in 2005 a junior doctor and in 2007 a registered nurse used the wrong syringe, believing that 1 ml contained 1 U of insulin, both with fatal consequences
- Use of 'U' on prescription forms to denote units, easily mistaken for '0', leading to overdose, e.g. 60 units for '6U', or use of 'IU' to denote international units, with 'I' easily mistaken for '1', e.g. 61 units for '6IU'
- Use of '/' to separate doses e.g. '10/5 units' to denote 10 units in the morning and 5 units in the evening misinterpreted as 10 units in the morning and 15 units in the evening or 1015 units as a single dose

Key recommendations to prevent insulin errors

- Prescribe the full, correct name of the insulin product (usually brand name) including strength and origin (e.g. human, animal or analogue). Prescribe doses for different times of day separately
- Never use abbreviations such as U or IU for the terms 'units' or 'international units' on prescription forms. Always write 'units' in full
- Include the administration method in the prescription when possible (i.e. vial, cartridge or pre-filled pen)
- Use insulin syringes only for insulin administration
- Use an insulin syringe to measure and prepare insulin for intravenous insulin infusion, or a safer alternative such as ready-to-use infusion products
- Whenever unsure refer to British National Formulary (http://www.bnf.org/bnf/index.htm)
- All healthcare professionals prescribing or administering insulin must have evidence of training in its safe use

Table 3

In the UK, the National Patient Safety Agency identified 16,600 incidents involving insulin alone between November 2003 and November 2009; 24% resulted in harm to the patient, and 18 were associated with fatal or other severe outcomes. The large majority were considered readily preventable. Despite this high documented prevalence of harm, recent UK data suggest that errors are still grossly under-reported, with one estimate of insulin-related inpatient harm 4-fold higher than the previously reported rate.

A range of initiatives and resources is available in the UK to reduce harm from insulin errors. They include Think Glucose, national patient safety campaigns and Insulin Passports, the 'Safe use of insulin' e-learning module and the yearly NaDIA reports. Death or severe harm from maladministration of insulin by a healthcare professional is deemed a 'never event' by the UK Department of Health. Nevertheless, patients continue to suffer serious harm because of insulin errors. Table 3 lists some of the common preventable errors in insulin use in hospitals, with recommendations for prevention.

Figure 2 shows examples of diabetes cards given to healthcare professionals in hospitals to highlight safety measures regarding both oral hypoglycaemic drugs and appropriate use of insulin.

Safe discharge from hospital

Readmission rates within 28 days for people with diabetes are 59% higher than those without diabetes. A proportion of these can be prevented by a 'safe diabetes discharge policy'. This should include a formal review of diabetes therapy before discharge, which can be informed by HbA_{1c} measured on admission. Care should be taken to avoid transcription errors

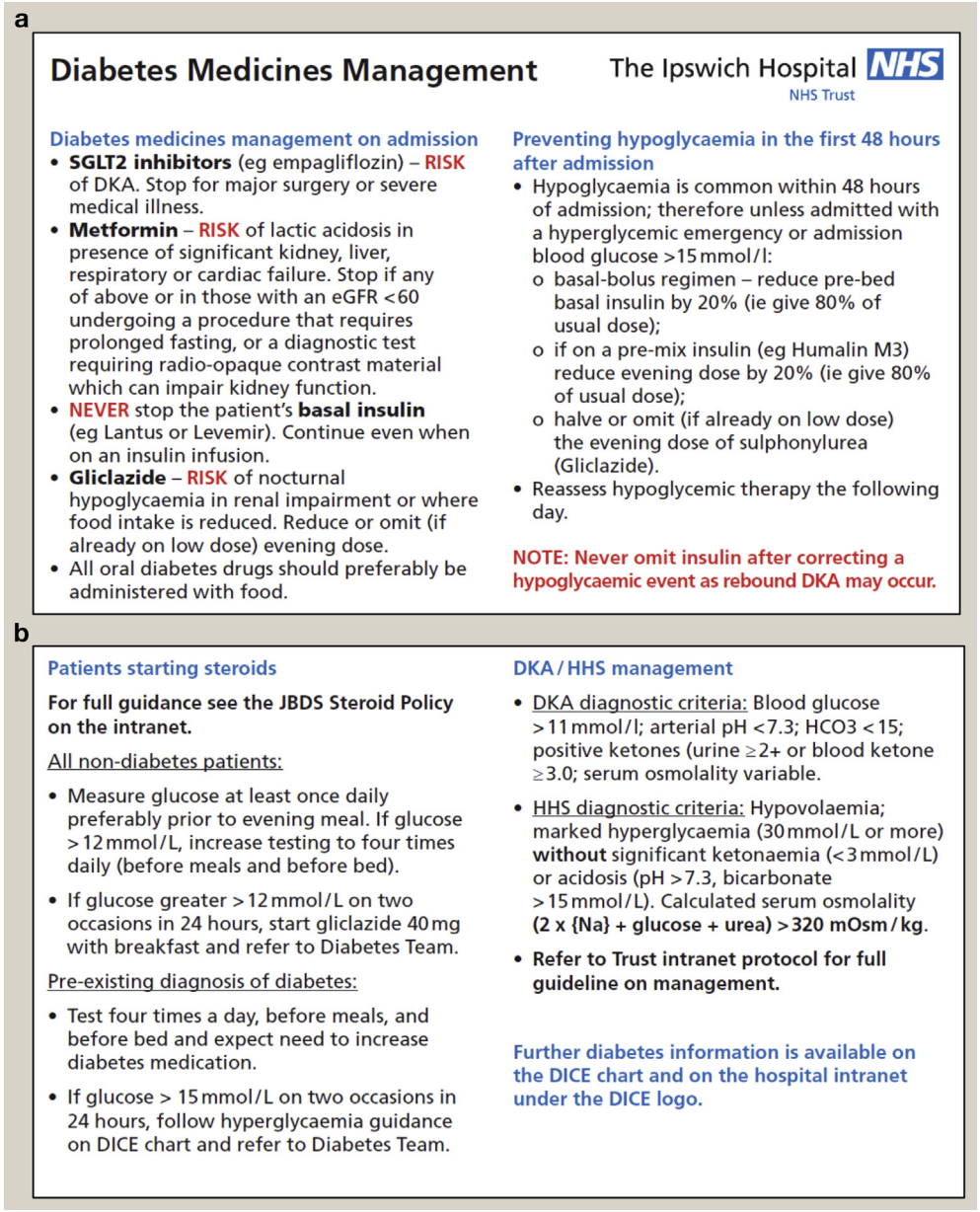

Figure 2 Examples of health cards used to improve inpatient diabetes management. Reproduced with permission of Ipswich Hospital.

when communicating medication dosages. In the UK, the inpatient diabetes specialist nurse is the key member of the team in this discharge policy as well as patient/carer support and education. ◆

FURTHER READING

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 55-year-old man was admitted with cellulitis of the lower legs. He had type 2 diabetes and was taking isophane basal insulin, metformin 2 g daily and empagliflozin 10 mg daily. His capillary blood glucose as an inpatient varied between 7 and 11 mmol/litre.

Investigations

- Estimated glomerular filtration rate at 61 ml/minute
- HbA_{1c} 9.2% (77 mmol/mol) (4–6)

How should his diabetes be best managed as an inpatient?

A. Continue the above regimen, including titration of the basal isophane insulin dose
B. Stop all his medications and start him on an intravenous insulin infusion
C. Stop the metformin but continue the isophane insulin and empagliflozin
D. Continue the basal isophane and metformin but stop the empagliflozin
E. Change the insulin to a twice-daily biphasic (pre-mixed) insulin regimen and continue the oral drugs

Question 2

A 69-year-woman was admitted with new-onset ocular symptoms suggestive of a relapse of multiple sclerosis. She had a past medical history of well-controlled type 2 diabetes (HbA_{1c} 7.2%; (55 mmol/mol)) and was taking metformin 1 g daily and gliclazide 80 mg 12-hourly. She had been treated with methyl prednisolone 1 g intravenously for 3 days because of her relapse. On day 3 she started to vomit, her capillary blood glucose was 24.2 mmol/litre, and fingerprick ketone concentrations were 3.1 mmol/litre (<0.6).

What is the best step to use next in her management?

A. Continue the oral drugs she has been taking and start subcutaneous insulin
B. Start a subcutaneous 'sliding scale insulin' regimen
C. Stop oral medications and start a fixed-rate insulin intravenous infusion
D. Stop oral medications and start a variable-rate insulin intravenous infusion
E. Continue oral medications and start a variable-rate insulin intravenous infusion

Question 3

A 28-year-old man was admitted because of further worsening of gastroparetic symptoms. He had a long-standing history of poorly controlled type 1 diabetes (HbA_{1c} 12.2%; (110 mmol/mol)). He was taking a night-time basal insulin and three mealtime rapid-acting insulin doses. He was started on total parenteral nutrition because of an inability to retain meals. In the first 24 hours, he had a severe hypoglycaemic episode at 3 am, needing intravenous glucose and subcutaneous glucagon.

What is the ideal way to manage his diabetes?

A. Reduce his night-time basal insulin dose
B. Reduce all his insulin doses and aim to maintain a higher blood glucose concentration of 10–15 mmol/litre
C. Stop his subcutaneous insulin and start a variable-rate intravenous insulin regimen
D. Continue basal insulin at a lower dose but replace the bolus insulin with a variable-rate intravenous insulin regimen
E. Start an insulin pump (continuous subcutaneous insulin infusion) and use a subcutaneous glucose sensor to monitor the glucose levels