OXFORD

Revalidation FOR ANAESTHETISTS RCA Revalidation matrix Matrix reference 1A01, 2C01, 3J02

BJA Education, 17 (11): 370–376 (2017)

doi: 10.1093/bjaed/mkx024
Advance Access Publication Date: 19 June 2017

Endocrine problems in the critically ill 1: diabetes and glycaemic control

Deborah Elizabeth Kerr MBChB FRCA MRCEM[1], Tim Wenham MBChB FRCA DICM FFICM[2,*] and Alia Munir MBBCh PhD FRCP[3]

[1]ST6 Anaesthesia and Intensive Care Medicine, Department of Anaesthesia, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK, [2]Consultant in Anaesthesia and Intensive Care Medicine, Department of Anaesthesia, Barnsley Hospital NHS Foundation Trust, Barnsley S75 2EP, UK and [3]Consultant Endocrinologist, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

*To whom correspondence should be addressed. Tel: +44 1226 730000; E-mail: t.wenham@nhs.net

Key points

- Dysglycaemia occurs frequently in critical illness, both in diabetic and in non-diabetic patients, often reflecting underlying disease severity.
- Aggressive insulin therapy may be harmful and is associated with an increased incidence of severe hypoglycaemia; therefore, a pragmatic approach to glycaemic control is necessary.
- Hypoglycaemia is common, and the clinical features are frequently masked in critical illness.
- Immediate insulin therapy is not indicated in the hyperosmolar hyperglycaemic state (HHS) and may precipitate cardiovascular collapse.
- A mixed picture of diabetic ketoacidosis and HHS can occur; treatment should be directed at the predominant element.

Disorders of glycaemic control represent a common problem in patients with and without diabetes, who present with critical illness. Diabetic emergencies also account for a considerable portion of critical care workload, with approximately 13% of diabetic ketoacidosis (DKA) patients requiring critical care admission.[1] The hyperosmolar hyperglycaemic state (HHS), although less frequent, carries a significant mortality risk, warranting early recognition and treatment.

In this review, we discuss glycaemic control in critical illness and the management of diabetic emergencies. An accompanying article, 'Endocrine problems in the critically ill 2: endocrine emergencies' covers other endocrine emergencies, including abnormalities of adrenal and thyroid function.[2]

Glycaemic control in critical illness

Dysglycaemia is common in critical illness. During the stress response, increased cortisol levels promote gluconeogenesis but also impair peripheral glucose uptake. Growth hormone is released: this also impedes glucose uptake, and antagonizes the effects of insulin. Catecholamines inhibit insulin release. Consequently, the body cannot use glucose effectively for energy production, creating a state of hyperglycaemia, insulin resistance, and glucose intolerance. Pharmacological therapies (e.g. steroids, beta agonists, and enteral/parenteral nutrition) and underlying disease processes (e.g. hepatic dysfunction) can compound these effects.

Dysglycaemic states (hyper or hypo) are both associated with increased mortality, particularly if occurring in the same patient. Such fluctuations are likely to be the consequence of underlying severity of illness, and controversy surrounds how actively we should interfere with these pathophysiological processes.[3–5]

The landmark Leuven I study suggested that tight glycaemic control [blood glucose (BG) 4.4–6.1 mmol litre^{-1}] using variable rate intravenous insulin infusion (VRIII) significantly reduced

Editorial decision: April 13, 2017; **Accepted:** April 26, 2017

morbidity and mortality among surgical intensive care unit (ICU) patients, compared to a more liberal target (BG 10–11.2 mmol litre^{-1}).[6] This was a single-centre trial of surgical patients in an expert centre, leading to concerns about the external validity of the results. Subsequent studies (Table 1) have demonstrated variable outcomes with respect to tight glycaemic control. Notably, the multicentre NICE-SUGAR trial found significantly increased 90 day mortality with 'intensive' insulin therapy. All trials reported a significant risk of severe hypoglycaemia (BG <2.2 mmol litre^{-1}) with intensive treatment, despite the mean BG levels achieved in the 'conventional' therapy groups being lower than targeted.[6–10]

Current ICU management of BG levels is therefore pragmatic, aiming to avoid excessive fluctuations and extremes while targeting a more manageable BG range (around 5–10 mmol litre^{-1}). Targets and VRIII regimens will vary from centre to centre.

BG levels should be monitored via arterial blood gas sampling in the ICU as capillary levels are inaccurate.[4,11] Care must be taken to avoid contamination of sampling lines with glucose-containing solutions; close monitoring for intravenous insulin extravasation is also prudent.

Stress-induced hyperglycaemia will resolve as the patient recovers from the underlying illness, therefore most do not have an ongoing insulin requirement at critical care discharge. In patients known to have diabetes, recovery usually provides an opportunity to convert the patient to oral or subcutaneous therapies.

Hypoglycaemia

Hypoglycaemia (defined as BG <4 mmol litre^{-1}) occurs in approximately 2–3% of critical care patients,[3] including many non-diabetics. This is usually a consequence of insulin therapy/diabetic medications, but other causes (e.g. liver failure, adrenal insufficiency, hypothyroidism, and excessive alcohol intake) should be considered. Lack of recognition can result in profound neurological deficits, even death.

Clinical features

The clinical features that occur secondary to autonomic stimulation (sweating, tachycardia, and tremor) and cerebral glucose deprivation (altered consciousness, speech changes, and ataxia) may be masked in sedated/unconscious patients; therefore frequent BG monitoring is essential. Patients receiving enteral or parenteral feeding (usually alongside a VRIII) are particularly susceptible following changes to feeding regimens or with disruptions to feed delivery/absorption. Patients should never receive unopposed insulin therapy; a 10% i.v. glucose infusion (usually administered at 50–100 ml h^{-1}) should be given until continuous/regular feeding is established.

Management

Most critical care departments have local protocols for managing hypoglycaemia, and the Joint British Diabetes Societies (JBDS) have produced guidelines for diabetic inpatients.[12] Since critically ill patients often have impaired enteral intake, this article will focus on i.v. glucose replacement.

The management principles described are applicable to hypoglycaemic episodes in both diabetic and non-diabetic patients. The main treatment aims are:

- Stop insulin infusions where applicable.
- Restore normoglycaemia: 75–100 ml 20% glucose (or 150–200 ml 10% glucose) i.v., for 15 min.
- Check BG after 10–15 min, and repeat i.v. glucose boluses as necessary to achieve BG > 4 mmol litre^{-1}.
- Identify and treat any causes; ensure unopposed insulin is not being given. VRIII should be recommenced per local protocols.

Note that 50% i.v. glucose is no longer recommended, as it is associated with extravasation injury and post-treatment hyperglycaemia.[12] Glucagon 1 mg i.m. is an alternative to i.v. glucose.[12] This mobilizes liver glycogen stores, and so will be less effective in malnourished patients or those with significant liver disease.

Diabetic ketoacidosis

DKA is characterized by the combination of hyperglycaemia and ketoacidosis. Over the last 20 years, mortality rates have fallen from 7.96% to 0.67%, likely attributable to improved understanding of the pathophysiology, along with closer monitoring and correction of electrolyte abnormalities.[13]

Although historically associated only with type 1 diabetes, 'ketone prone type 2 diabetes mellitus (T2DM) syndrome' is now increasing in prevalence across all ethnicities.[14,15] Furthermore, sodium/glucose co-transporter 2 inhibitors (e.g. canagliflozin and dapagliflozin) for T2DM management may precipitate a severe form of DKA in which patients present atypically, with only moderately raised glucose levels, so a high index of suspicion is required.[16]

An overview of the pathogenesis of DKA can be seen in Figure 1.

Clinical features

Underlying infection often triggers DKA, although treatment non-compliance, or any major physiological stressor, may contribute. Features include polyuria, polydipsia, weight loss, vomiting, and abdominal pain and signs/symptoms of any precipitating illness. Hypotension, tachycardia, and tachypnoea (Kussmaul respiration) are common.

Investigations and management

The JBDS recommend the following diagnostic criteria:[13]

- Ketonaemia >3 mmol litre^{-1} or significant ketonuria (>2+ on urine dipstick).
- BG > 11 mmol litre^{-1} or known diabetic patient.
- Serum bicarbonate <15 mmol litre^{-1} or venous pH < 7.3.

BG levels rarely exceed 40 mmol litre^{-1} in DKA when compared with HHS. This may be because of earlier presentation and reduced incidence of kidney injury. Further investigations should focus on identifying any precipitating illness or biochemical derangements (e.g. hypokalaemia) requiring correction. Of note, markedly elevated serum creatinine levels may be seen in DKA, disproportionate to contemporaneous blood urea levels. Ketone bodies (particularly acetoacetate) interfere with some automated laboratory assays, producing spurious results; advice from the clinical chemistry department should be sought in these cases.

Critical care admission should be considered in those with indicators of severe DKA (Table 2).[13]

The primary management goals are:

- treatment of the precipitating cause;
- restoration of circulating volume;

Table 1 Summary of trials comparing intensive insulin therapy (IT) regimens against conventional therapy (CT) in critical care

Authors	Study type	Patient groups	Target blood glucose (mmol litre^{-1})		Mean blood glucose (mmol litre^{-1})		Primary outcome measure	Result	Significant hypoglycaemia (<2.2 mmol litre^{-1}) seen with IT?	Other outcomes
			IT	CT	IT	CT				
Van den Berghe *et al.*[6] (Leuven I)	Prospective single-centre RCT	Surgical (mainly cardiac) ICU	4.4–6.1	10.0–11.2	5.7	8.5	ICU mortality	Significant mortality reduction with IT: 4.6% IT *vs* 8% CT deaths, $P < 0.04$	Y	IT: ↓ in-hospital death. ↓ duration of ventilation and RRT requirement; ↓ ICU acquired weakness
Van den Berghe *et al.*[7] (Leuven II)	Prospective single centre RCT	Medical ICU	4.4–6.1	10.0–11.2	6.2	8.5	In-hospital mortality	Significant mortality benefit in IT only seen when ICU stay >3 days	Y	
Brunkhorst *et al.*[8] (VISEP)	Prospective multicentre 2 × 2 factorial RCT	Early sepsis/ severe septic shock	4.4–6.1	10.0–11.1	6.2	8.4	28 day mortality	No significant difference, but IT arm terminated early due to frequent hypoglycaemic episodes	Y	Hypoglycaemia independently associated with death
NICE-SUGAR Investigators[9]	Prospective multicentre RCT	Medical and surgical ICU	4.5–6.0	<10.0	6.4	8.0	90 day mortality	Significant mortality increase with IT: OR for death 1.14 (95% CI 1.02–1.28, $P = 0.02$)	Y	2012 *post hoc* analysis: Dose–response relationship between severe hypoglycaemia and mortality
COIITSS Investigators[10]	Prospective 2 × 2 factorial RCT	Septic shock receiving regular i.v. hydrocortisone	4.4–6.1	<8.3	*(Data unavailable)*		In-hospital mortality	No significant difference	Y	

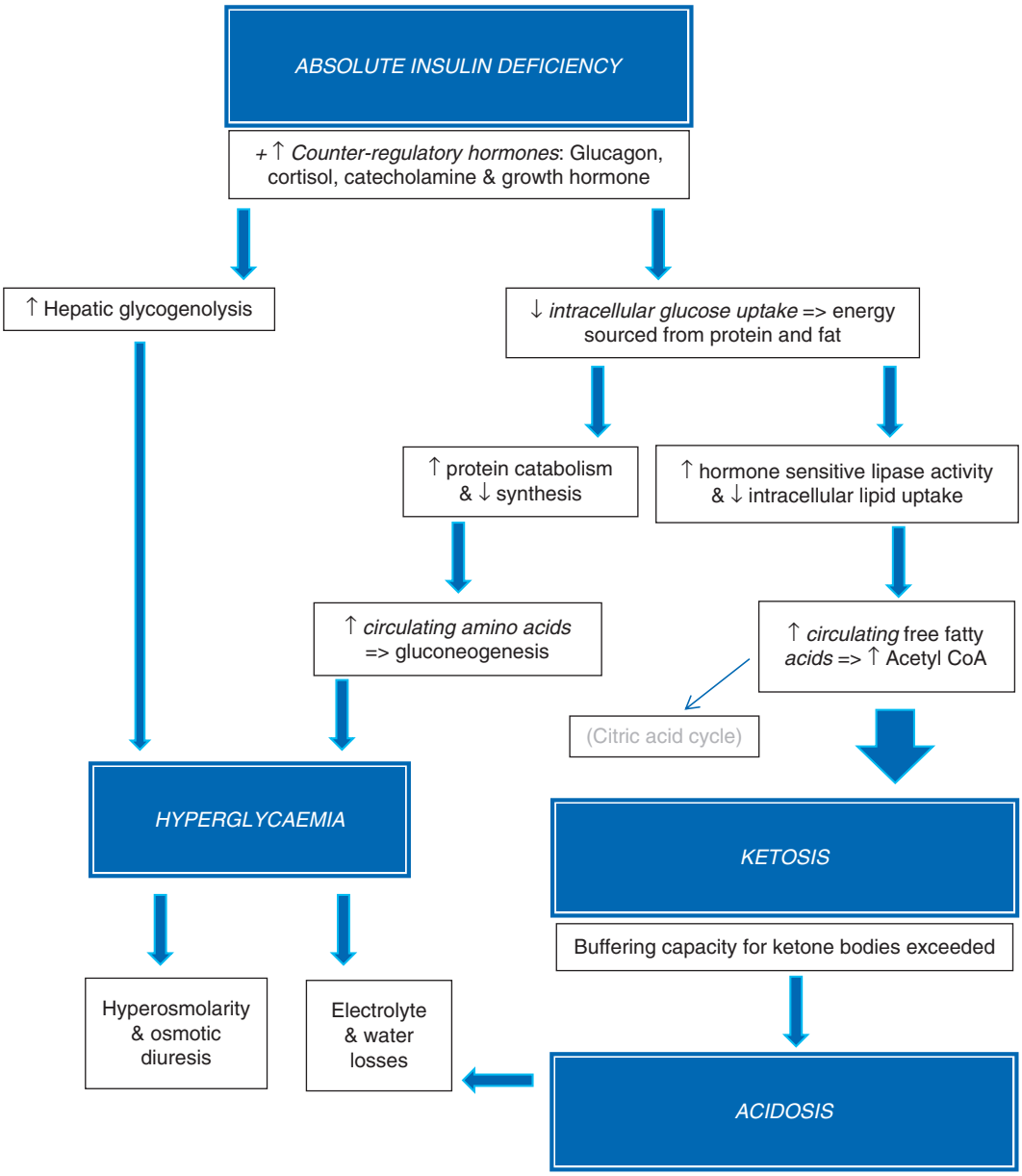

Fig 1 Overview of the pathophysiology of diabetic ketoacidosis.

- correction of electrolyte disturbances; and
- suppression of ketonaemia.

For a haemodynamically stable patient, an example of a typical fluid regimen is given in Table 3.[13] Note that sodium chloride 0.9%, Hartmann's solution, or equivalent are all appropriate choices in DKA.

Potassium supplementation will usually be required from the outset, even if initial serum levels are high, as total body potassium is low. With insulin therapy, potassium is driven intracellularly and will fall precipitously without adequate supplementation. For a serum potassium 3.5–5.5 mmol litre^{-1}, 40 mmol potassium chloride should be added to the crystalloid infusion, ensuring administration rates do not exceed 20 mmol h^{-1}. For significant hypokalaemia (<3.5 mmol litre^{-1}), central venous potassium infusion must be considered and will also allow potassium delivery in a more concentrated form, avoiding excessive fluid administration once euvolaemia is achieved.

More aggressive fluid resuscitation may be necessary in the shocked patient, though caution must be observed due to the small risk of precipitating cerebral or pulmonary oedema. The former is much more common in the paediatric population, though young adults are still susceptible. Pulmonary oedema may rarely occur in those with impaired cardiac function. Cardiac output monitoring should be considered in such cases.

Once fluid therapy is established, a fixed-rate intravenous insulin infusion (FRIII) should be commenced at 0.1 U kg^{-1} h^{-1}. This regimen has gained favour over VRIII due to improved blood ketone clearance.[13] Bedside testing for 3-beta-hydroxybutyrate (a ketone body) is now widely available and has largely superseded BG measurements in guiding intravenous insulin therapy. Ketone and BG measurements should be performed hourly, with 2 hourly measurement of pH, potassium and bicarbonate levels,

over the first 6 h of treatment. Patients already taking long-acting insulin should continue this, alongside the FRIII.

The aim is to reduce ketones by 0.5 mmol l^{-1} h^{-1}—the FRIII can be increased by 1 U h^{-1} as required and should continue until ketones reach <0.6 mmol $litre^{-1}$, venous pH >7.3, and venous bicarbonate >18 mmol $litre^{-1}$. Glucose 10% infusion is commenced at 125 ml h^{-1} (in addition to crystalloid) once BG falls below 14 mmol $litre^{-1}$.

Patients should be managed jointly with the diabetes team. Acid–base disturbances and ketonaemia usually resolve within 24 h. Following this, patients can convert to VRIII, or even their previous subcutaneous regimen, if a normal diet has resumed.[13] In previously undiagnosed diabetics, once a stable i.v. insulin infusion rate is established, the 6 hourly i.v. requirement can be quadrupled to calculate a total daily dose (TDD) for subcutaneous therapy. Initially, a basal dose of long-acting human insulin/analogue is prescribed at 60–80% of the TDD, with a bolus dose at 10%; these can then be titrated accordingly.[17] Intravenous insulin should stop 4 h after the administration of the first basal dose to smooth the transition. Adjunctive therapy (e.g. metformin) may be considered in patients with a body mass index >25 kg m^{-2} (or >23 kg m^{-2} in Black and ethnic minority groups) to minimize their effective insulin requirement.

Table 2 Possible indications for critical care admission

DKA[13]	HHS[18]
Serum osmolality >350 mOsmol kg^{-1}	Serum pH <7
Sodium >160 mmol $litre^{-1}$	Serum bicarbonate <5 mmol $litre^{-1}$
Venous/arterial pH <7.1	Blood ketones >6 mmol $litre^{-1}$
Potassium <3.5 or >6 mmol $litre^{-1}$ on admission	Serum potassium <3.5 mmol $litre^{-1}$ on admission
GCS <12 or abnormal AVPU score	GCS <12
SpO_2 <92% breathing room air	Oxygen saturation (SpO_2) <92% in air (without significant respiratory disease)
Systolic blood pressure <90 mm Hg	Systolic BP <90 mm Hg
Heart rate <60 or >100 beats min^{-1}	Heart rate >100 or <60 beats min^{-1}
Urine output <0.5 ml kg^{-1} h^{-1}	Anion gap >16
Serum creatinine >200 μml $litre^{-1}$	
Hypothermia	
Macrovascular event—stroke, myocardial infarction	
Other serious co-morbidity	

Hyperosmolar hyperglycaemic state

Although less common than DKA, HHS carries a significantly higher mortality of 15–20%.[17] Historically, this condition affected elderly T2DM patients, but increasingly younger patients are being seen, sometimes without a prior diabetes diagnosis.

Clinical features

Precipitants are similar to those for DKA. However, symptoms tend to progress over days, causing more profound dehydration and metabolic disturbance. The pathophysiology has many common elements with DKA—except that HHS represents a relative, not absolute, insulin deficiency. Patients generally have enough residual insulin to prevent exaggerated lipolysis and subsequent ketoacidosis. Severe hyperosmolality may also inhibit lipolysis, by attenuating the response of adipose tissue to circulating catecholamines. Occasionally, a mixed picture of HHS and DKA may occur: subsequent treatment must reflect the predominant element.[18,19] If doubt exists, manage as DKA initially and seek early specialist input.

Clinical presentation includes malaise, polydipsia, polyuria, weakness, sunken eyes, and tachycardia. Altered mental status is common, in contrast to DKA. The features often reflect the hyperosmolar state of the patient, but other factors, such as electrolyte disturbances and concurrent illness, may contribute. The hypertonicity observed may mask the severity of dehydration, as the intravascular volume remains relatively well preserved due to water shift from the intracellular space.

Investigations and management

Initial investigations should include BG, urea, and electrolytes, measured (or calculated) serum osmolality, serum ketone and lactate levels, venous/arterial blood gas, and full blood count. In addition, an electrocardiograph, chest radiograph, blood/urine/sputum cultures, serum troponin, and C-reactive protein may be useful in identifying precipitating causes.[19]

The JBDS recommend the following criteria to distinguish HHS from other hyperglycaemic states:[18]

- hypovolaemia;
- marked hyperglycaemia (>30 mmol $litre^{-1}$) without significant ketonaemia (<3 mmol $litre^{-1}$), or acidosis (pH > 7.3, HCO_3 >15 mmol $litre^{-1}$); and
- osmolality >320 mOsmol kg^{-1}.

The main treatment aims are:

- treatment of precipitating causes;
- replacement of fluid and electrolyte losses;
- normalization of BG and osmolality; and

Table 3 Examples of fluid replacement regimens in DKA and HHS[13,18]

DKA		HHS	
Infusion fluid (Note that Hartmann's solution or equivalent may also be used in DKA)	Infusion rate (ml h^{-1})	Infusion fluid	Infusion rate (ml h^{-1})
Sodium chloride 0.9%, 1 litre	1000	Sodium chloride 0.9% 1 litre + KCl 40 mmol	1000
Sodium chloride 0.9% 1 litre+ KCl 40 mmol	500	Sodium chloride 0.9% 1 litre + KCl 40 mmol	500–1000
Sodium chloride 0.9% 1 litre + KCl 40 mmol	250	Sodium chloride 0.9% 1 litre + KCl 40 mmol	500–1000
Sodium chloride 0.9% 1 litre + KCl 40 mmol	250	Sodium chloride 0.9% 1 litre + KCl 40 mmol	500–1000
Sodium chloride 0.9% 1 litre + KCl 40 mmol	167	Sodium chloride 0.9% 1 litre + KCl 40 mmol	250–500

- prevention of complications, such as thrombosis and foot ulceration.

Because of the multitude of physiological disturbances seen, HHS patients can be difficult to manage, and early specialist input should be sought. Critical care admission should be considered for patients meeting any of the conditions listed in Table 2.[18]

Fluid replacement regimens should aim to restore 50% of the total losses within the first 12 h and an example is shown in Table 3.[18] Patients often have a profound fluid deficit in the range of 10–20 litre at presentation, typically requiring 3–6 litre fluid over the first 12 h. Note that sodium chloride 0.9% is the crystalloid of choice, as these patients have significant sodium and chloride losses.

Treatment should aim for a fall in osmolality of 3–8 mOsmol kg^{-1} h^{-1}.[18] Serum osmolality (measured or calculated), BG, and sodium should be checked hourly during this phase. It is important that a consistent method is used for calculation/measurement of osmolality. If the desired rate of correction is not being achieved, adjustments to the rate of infusion fluid (and/or insulin—see below) can be made accordingly.

Fluid replacement lowers osmolality by reducing BG, thus allowing water to diffuse intracellularly. This fluid shift creates a modest rise in serum sodium of 2.4 mmol $litre^{-1}$ for every 5.5 mmol $litre^{-1}$ reduction in BG.[18] Thus, an initial rise in sodium is only concerning if it exceeds that which is expected or if it is not associated with falling osmolality. In these circumstances, more aggressive fluid replacement is usually necessitated. However, if fluid balance is adequate, sodium chloride 0.45% can be used. Once serum sodium starts to fall, the reduction should be no greater than 10 mmol $litre^{-1}$ over a 24 h period. If falling more rapidly, then the concentration of the sodium chloride solution should be increased temporarily to slow the rate of fall. This situation requires close and careful monitoring.

For the above reasons, immediate insulin therapy is *not* recommended in HHS, the uncommon exception being where significant ketonaemia (>1 mmol $litre^{-1}$) is present. When given prior to appropriate fluid resuscitation, insulin can rapidly reduce osmolality, which may precipitate cardiovascular collapse. Once clinically euvolaemic and the BG fall ceases, FRIII can be commenced at 0.05 U kg^{-1} h^{-1}, aiming to reduce BG levels by up to 5 mmol l^{-1} h^{-1}. If FRIII is already running, the infusion rate can be increased by 1 U h^{-1} at this point.

Once BG levels reach <14 mmol $litre^{-1}$, a 5% or 10% glucose infusion should be commenced at 125 ml h^{-1} in addition to the ongoing saline replacement.[18]

Potassium can be administered either centrally or peripherally and should be closely monitored. Any underlying causes should be identified and managed appropriately.

Patients with HHS are at increased risk of thrombosis due to their hyperosmolar state and should receive thromboprophylaxis unless contraindicated.

During recovery, i.v. insulin can usually be discontinued once oral intake is established. Most patients require conversion to s.c. insulin initially. However, previously undiagnosed diabetics, or those well controlled with oral hypoglycaemics prior to admission, may be managed on appropriate oral therapies.[18]

Conclusion

Dysglycaemia is common in the critically ill, often indicating underlying disease severity. Significant BG fluctuations have been linked to poorer outcomes, yet strict glycaemic control regimens carry their own risks, particularly that of hypoglycaemia. Therefore, current consensus supports a more liberal approach, minimizing BG variability while still targeting a BG range that can be achieved in 'real-world' settings.

Diabetic emergencies require prompt recognition and treatment. Correction of fluid, electrolyte, and acid–base disturbances can be complex, and critical care admission for invasive monitoring may be appropriate for a proportion of these cases.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at http://www.oxforde-learning.com/journals/ by subscribers to *BJA Education*.

References

1. Kohler K, Levy N. Management of diabetic ketoacidosis: a summary of the 2013 Joint British Diabetes Societies guidelines. *JICS* 2014; **15**: 222–6
2. Accompanying BJA Education article. In press. Kerr DE, Wenham T, Newell-Price JA. Endocrine problems in the critically ill 2. Endocrine emergencies. BJA Educ 2017; **17**: 1–6
3. Badawi O, Waite MD, Fuhrman SA, Zuckerman IH. Association between intensive care unit-acquired dysglycaemia and in-hospital mortality. *Crit Care Med* 2012; **40**: 3180–8
4. Mesotten D, Preiser JC, Kosiborod M. Endocrine and metabolic considerations in critically ill patients 1: glucose management in critically ill adults and children. *Lancet Diabetes Endocrinol* 2015; **3**: 723–33
5. Marik PE, Bellomo R. Stress hyperglycaemia: an essential survival response! *Crit Care* 2013; **17**: 305–12
6. Van den Berghe G, Wouters P, Weekers F *et al*. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; **345**: 1359–67
7. Van den Berghe G, Wilmer A, Hermans G *et al*. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; **354**: 449–61
8. Brunkhorst FM, Engel C, Bloos F *et al*. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; **358**: 125–39
9. The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; **360**: 1283–97
10. The COIITSS Study Investigators. Corticosteroid treatment and intensive insulin therapy for septic shock in adults. *JAMA* 2010; **303**: 341–8
11. Finfer S, Wernerman J, Preiser JC *et al*. Clinical review: consensus recommendations on measurement of blood glucose and reporting glycaemic control in critically ill adults. *Crit Care* 2013; **17**: 229–39
12. Joint British Diabetes Societies for Inpatient Care. The hospital management of hypoglycaemia in adults with diabetes mellitus. Available from https://www.diabetes.org.uk/Documents/About%20Us/Our%20views/Care%20recs/JBDS

%20hypoglycaemia%20position%20(2013).pdf (accessed 31 October 2016)
13. Joint British Diabetes Societies for Inpatient Care. The management of diabetic ketoacidosis in adults, second edition. Available from http://www.diabetes.org.uk/Documents/About%20Us/What%20we%20say/Management-of-DKA-241013.pdf (accessed 9 July 2016)
14. Balasubramanyam A, Nalini R, Hampe CS, Maldonado M. Syndromes of ketosis-prone diabetes mellitus. *Endocr Rev* 2008; **29**: 292
15. Seok H, Jung CH, Kim SW *et al*. Clinical characteristics and insulin independence of Koreans with new-onset type 2 diabetes presenting with diabetic ketoacidosis. *Diabetes Metab Res Rev* 2013; **29**: 507
16. Medicines and Healthcare Products Regulatory Agency. Drug safety update. SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis. Available from https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-the-risk-of-diabetic-ketoacidosis (accessed 15 May 2016)
17. Schmeltz LR, DeSantis AJ, Schmidt K *et al*. Conversion of intravenous insulin infusions to subcutaneously administered insulin glargine in patients with hyperglycemia. *Endocr Pract* 2006; **12**: 641–50
18. Scott AR; Joint British Diabetes Societies (JBDS) for Inpatient Care, JBDS hyperosmolar hyperglycaemic guidelines group. Management of hyperosmolar hyperglycaemic state in adults with diabetes. *Diabet Med* 2015; **32**: 714–24
19. Maletkovic J, Drexler A. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Endocrinol Metab Clin North Am* 2013; **42**: 677–95