


## POSITION STATEMENT

# A guideline for the outpatient management of glycaemic control in people with cancer

Nalinie Joharatnam-Hogan<sup>1</sup>  | Pinkie Chambers<sup>2</sup> | Ketan Dhatariya<sup>3</sup>  | Ruth Board<sup>4</sup> | the Joint British Diabetes Society for Inpatient Care (JBDS), UK Chemotherapy Board (UKCB)

<sup>1</sup>Institute of Clinical Trials and Methodology, MRC Clinical Trials Unit, UCL, London, UK

<sup>2</sup>University College London Hospital NHS Foundation Trust, London, UK

<sup>3</sup>Norfolk and Norwich Hospitals NHS Foundation Trust, London, UK

<sup>4</sup>Lancashire Teaching Hospitals NHS Foundation Trust, London, UK

## Correspondence

Nalinie Joharatnam-Hogan, Institute of Clinical Trials and Methodology, MRC Clinical Trials Unit, UCL, London, UK.  
Email: n.j-hogan@ucl.ac.uk

## Present address

Nalinie Joharatnam-Hogan, Royal Marsden NHS Foundation Trust, London, UK

## Abstract

Individuals with cancer are at increased risk of developing new-onset diabetes mellitus and hyperglycaemia, and an estimated 20% of people with cancer already have an underlying diagnosis of diabetes mellitus. People with both cancer and diabetes may have an increased risk of toxicities, hospital admissions and morbidity, with hyperglycaemia potentially attenuating the efficacy of chemotherapy often secondary to dose reductions and early cessation. Numerous studies have demonstrated that hyperglycaemia is prognostic of worse overall survival and risk of cancer recurrence. These guidelines aim to provide the oncology/haemato-oncology and diabetes multidisciplinary teams with the tools to manage people with diabetes commencing anti-cancer/glucocorticoid therapy, as well as identifying individuals without a known diagnosis of diabetes who are at risk of developing hyperglycaemia and new-onset diabetes.

## KEYWORDS

cancer, diabetes, glycaemic control, guideline, oncology, systemic anti-cancer therapy

## 1 | INTRODUCTION

Individuals with a diagnosis of diabetes mellitus are at higher risk for developing several cancers, potentially due to shared risk factors between the two diseases.<sup>1</sup> It is estimated that approximately 20% of people with cancer have concurrent diabetes,<sup>2</sup> with cancer now the leading cause of death in people with diabetes.<sup>3</sup> Individuals with cancer are also at an increased risk of developing new-onset diabetes mellitus or hyperglycaemia, independent of an underlying diagnosis of diabetes, as well as worsening control of their pre-existing diabetes mellitus.<sup>4</sup>

A number of observational studies have demonstrated an increased risk of cancer among individuals with diabetes. An umbrella review of meta-analyses of observational

studies reported an increased risk of developing cancer for participants with versus without diabetes.<sup>5</sup> The evidence was demonstrated to be most robust for breast cancer, intrahepatic cholangiocarcinoma, colorectal cancer and endometrial cancer, although most included studies demonstrated substantial heterogeneity. Data are also emerging to suggest that hyperglycaemia may be associated with worse overall survival (OS) and increased risk of cancer recurrence in a number of cancer subtypes, including both solid and haematological malignancies.<sup>4,6-15</sup> One of the largest of these reviewed 12 retrospective studies comprising of 9,872 people with cancer and without known diabetes. Individuals with hyperglycaemia were found to have a significantly worse disease-free survival (hazard ratio [HR] 1.98, 95% confidence interval [CI]

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1.20–3.27) compared with those with normo-glycaemia, as well as worse OS (HR 2.05, 95% CI 1.67–2.551).<sup>16</sup> Moreover a number of preclinical studies have suggested that hyperglycaemia may specifically attenuate the efficacy of chemotherapy in people with cancer, with or without diabetes,<sup>17</sup> perhaps accounting in part for these worse outcomes. However, the majority of the evidence base is derived from observational data, and there have been no randomised controlled trials to date to support the contention that better glucose control improves outcomes in cancer, although several trials are currently underway evaluating the role of glucose-lowering therapies as cancer therapeutic agents.

Several anti-cancer agents are known to increase the risk of hyperglycaemia, even in individuals without a known diagnosis of diabetes (Table 1). Hyperglycaemia during chemotherapy can occur in approximately 10%–30% of people with cancer,<sup>18–20</sup> and although is frequently transient during treatment, can become long term. A number of observational studies have shown that poor glycaemic control can increase the risk for infections and hospitalisation, particularly in individuals with metastatic or advanced cancers on chemotherapy.<sup>21,22</sup> This, in turn, can lead to avoidable treatment interruptions and dose reductions, as well as significant morbidity, and even mortality.<sup>23</sup> Review of all admissions at a specialist cancer hospital in London demonstrated that 11% of inpatients had either diabetes or hyperglycaemia,<sup>24</sup> and individuals with hyperglycaemia have been shown to have higher rates of emergency hospital admissions during cancer therapy than those without.<sup>25</sup> In these individuals particularly, early intervention to manage glycaemic control is much more likely to be beneficial.<sup>26</sup>

Immune checkpoint inhibitors (ICPs), such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) inhibitors, may induce *de novo* diabetes, although this occurs at a low frequency (<1%).<sup>27</sup> PD-1 inhibitors, PD-L1 inhibitors and combination CTLA-4/PD-1 therapy have been found to precipitate diabetes more commonly than CTLA-4 inhibitors alone. ICP-induced insulin deficiency may present both as new-onset, insulin-dependent diabetes or worsening pre-existing type 2 diabetes; however, the underlying mechanism is considered similar to that of type 1 diabetes.<sup>28</sup>

The use of glucocorticoids (GCs) in high doses is common in advanced cancer, GCs are the backbone of many haematological cancer treatment regimens and are frequently used for symptom control in palliative care.<sup>29</sup> They are frequently used as an anti-emetic alongside systemic treatments and are the main treatment for the management of immunotherapy toxicity (Table 2). GCs have a direct hyperglycaemic effect, which starts very early after ingestion.<sup>29,30</sup> They typically cause an increase in blood glucose levels 4–8 h after ingestion leading to a peak blood glucose level between mid-day meal and evening meal.<sup>30,31</sup> One in ten people not known

### What's new?

- These national guidelines are the first attempt to provide a good clinical practice approach to diabetes care for people with cancer, with the aim of reducing the risk of glucose-related emergencies.
- An estimated one in five people with cancer have an underlying diagnosis of diabetes mellitus, and anti-cancer therapy increases the risk of developing new-onset hyperglycaemia and diabetes, demonstrated to worsen cancer outcomes.
- We look at the acute management of those known to have diabetes and those at risk of developing hyperglycaemia, particularly when commencing anti-cancer therapy in the setting of the oncology/haemato-oncology clinic.

to have diabetes develop GC-induced diabetes,<sup>32</sup> an effect which is dose dependent.<sup>33</sup>

Supra-physiological doses of GCs approximates to a dose of prednisolone greater than 5 mg per day—or an equivalent dose of the alternative synthetic GC (Table 3). With increasing dose of GC, the risk of potential hyperglycaemia increases. This hyperglycaemia may or may not resolve once the GCs are withdrawn.

It is evident that hyperglycaemia and diabetes are common among people with cancer. Although further high-level evidence is required to better understand the importance of glycaemic control in people with cancer, improved recognition and potentially more complex diabetes care is required in these individuals.<sup>24</sup> There is a sparsity of guidance in the management of these individuals. We, therefore, developed multidisciplinary guidelines and propose the principles of management to facilitate clinical practice, based on consensus expert opinion. This piece of work has been produced by a multidisciplinary working party on behalf of the UK Chemotherapy Board (UKCB) and Joint British Diabetes Society for Inpatient Care (JBDS), which includes specialist representation from medical, diabetes, pharmacy and dietetic teams across the United Kingdom. The UKCB is the national overarching body that provides guidance, oversight and support for the continuing development of chemotherapy (systemic anti-cancer therapy—SACT) services in the United Kingdom. The JBDS group was created in 2008 to ‘deliver a set of diabetes inpatient guidelines and proposed standards of care within secondary care organisations’, with the overall aim of improving inpatient diabetes care through the development and use of high-quality, evidence-based guidelines and through better inpatient care pathways.

This guidance aims to provide advice for the oncology/haemato-oncology and diabetes multidisciplinary teams to manage people with diabetes, commencing anti-cancer/

TABLE 1 SACT used in the treatment of cancer demonstrated to be associated with worsening glycaemic control

Type of SACT	Drug examples	Risk of diabetes/hyperglycaemia (range of any grade)	Type of diabetes most likely to develop
<b>Targeted therapy</b>			
mTOR inhibitors	Everolimus <sup>49,50</sup>	12%–50%	T2DM
	Temsirolimus <sup>50</sup>	26%	
PI3K inhibitors	Alpelisib <sup>51</sup>	37%	T2DM
	Idelalisib <sup>52</sup>	28%/30%	
EGFR inhibitor	Osimertinib <sup>53</sup>	2%	T2DM
	Panitumumab <sup>54,55</sup>	1%–10%	
Multikinase inhibitor	Sunitinib <sup>56–58</sup>	0%–8%	Reverses T1/T2DM but also causes hyperglycaemia
	Pazopanib <sup>58</sup>	Risk of hypoglycaemia	
Tyrosine kinase inhibitor (TKI)	Nilotinib <sup>59</sup>	6%	T2DM
	Ponatinib <sup>60</sup>	3%	
ALK inhibitor	Ceritinib <sup>61</sup>	49%	T2DM
FLT3 inhibitor	Midostaurin <sup>62,63</sup>	7%–20%	T2DM
	Gilteritinib <sup>64</sup>	13%	
Monoclonal antibody	Gemtuzumab (anti-CD33) *inpatient use <sup>65</sup>	10%	T2DM
Somatostatin analogues	Octreotide, lanreotide <sup>66</sup>	Up to 30%	T2DM, but risk of hypoglycaemia
<b>Chemotherapy</b>			
Anti-metabolite	5-fluorouracil <sup>67,68</sup>	Up to 10%	T2DM
	Pemetrexed <sup>69,70</sup>	4%	
	Decitadine/azacitidine <sup>71</sup>	6%–33%	
Alkylating agents	Busulfan <sup>72</sup>	66%–67%	
Platinum based	Oxaliplatin <sup>73,74</sup>	4%	
Anthracyclines	Doxorubicin <sup>68,75</sup>	Up to 10%	
Other	Arsenic trioxide <sup>76</sup>	45%	
<b>ICPs</b>			
PD-1	Nivolumab <sup>27</sup>	<1%	T1DM
	Pembrolizumab <sup>28</sup>	1%–2.2%	
CTLA-4	Ipilimumab <sup>27</sup>	0.02%	
	Combination ICP <sup>77</sup>	4%	
<b>Hormone therapy</b>			
Hormone treatment	ADT <sup>52,78</sup>	Risk ratio 1.39 (95% CI 1.27–1.53) <i>n</i> = 65,595 cases	T2DM
	Tamoxifen <sup>79</sup>	Diabetes risk adj. odds ratio 1.24 (95% CI 1.08–1.42)	

Abbreviations: ADT, androgen deprivation therapy; ALK, anaplastic lymphoma kinase; CTLA-4, cytotoxic T-lymphocyte protein-4; EGFR, epidermal growth factor receptor; FLT3, FMS-like tyrosine kinase-3; ICP, immune checkpoint inhibitor; mTOR, mechanistic target of rapamycin; PD-1, programmed cell death protein-1; PI3K, phosphoinositide-3 kinase; SACT, systemic anti-cancer therapy; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TKI, tyrosine kinase inhibitor.

steroid therapy, as well as identifying individuals without a known diagnosis of diabetes who are at risk of developing hyperglycaemia and new-onset diabetes. These guidelines are intended for the outpatient management of people with cancer, particularly in the setting of the oncology/haemato-oncology clinic, and provision of advice for individuals at home, but where necessary, may be applied to inpatients as well.

## 2 | RECOMMENDATIONS

All people with cancer should have HbA<sub>1c</sub> and a random plasma glucose checked in the outpatient clinic at baseline, prior to commencing anti-cancer treatment. Individuals should be provided with a capillary blood glucose (CBG) meter and glucose testing strips if individuals are at high

TABLE 2 Use of glucocorticoids in oncology/haemato-oncology

Metastatic spinal cord compression
Multiple myeloma/lymphoma
Immunotherapy toxicity
Superior vena cava obstruction
Graft versus host disease
Symptomatic brain metastases
Supportive treatment during chemotherapy (chemotherapy induced nausea and vomiting, prevention of allergic reactions etc.)

TABLE 3 Glucocorticoid dose equivalent<sup>30</sup>

Glucocorticoid (steroid)	Potency (equivalent doses)	Duration of action (half-life, in hours)
Hydrocortisone	20 mg	8
Prednisolone	5 mg	16–36
Methylprednisolone	4 mg	18–40
Dexamethasone	0.8 mg	36–54
Betamethasone	0.8 mg	26–54

TABLE 4 Risk factors for glucocorticoid induced diabetes.

<b>Pre-existing type 1 or type 2 diabetes</b>
Family history of diabetes
Obesity
Increasing age
Ethnic minorities
Impaired fasting glucose or impaired glucose tolerance
Polycystic ovarian syndrome
Previous gestational diabetes
Previous development of hyperglycaemia on glucocorticoid therapy
Concurrent cytotoxic therapy known to cause hyperglycaemia

risk of GC-induced diabetes (Table 4), or if baseline plasma glucose is  $\geq 12$  mmol/L (contact the primary care diabetes provider). Those individuals identified as having a raised baseline HbA<sub>1c</sub> ( $>47$  mmol/mol/6.5%) should be referred to primary care for the management of hyperglycaemia prior to any follow-up visits; however, anti-cancer therapy start dates should not be delayed, especially if clinically urgent and they are otherwise fit for SACT treatment. In asymptomatic individuals, an elevated HbA<sub>1c</sub> should be repeated. There are no data to guide the management of individuals with cancer who have an HbA<sub>1c</sub> of 42–47 mmol/mol, and this issue remains outside of the remit of this document. However, in line with guidance for the general population individuals should be referred to their local diabetes prevention programme. When initiating SACT/GCs, individuals must be informed of the risk of developing hyperglycaemia/diabetes and potential symptoms to expect (including polyuria, nocturia, fatigue, thirst, blurred vision, headaches, confusion, weight loss).

## 2.1 | Individuals without a prior diagnosis of diabetes

### 2.1.1 | Commencing glucocorticoid/systemic anti-cancer therapy (without immune checkpoint inhibition) (Algorithm 1)

Algorithm 1 outlines the treatment regimen for people with cancer commencing SACT or GC therapy without a prior diagnosis of diabetes.

1. A random plasma glucose should be checked at each outpatient visit. If plasma glucose or CBG results are consistently  $<10$  mmol/L consider cessation of testing (until a new/change in therapy is initiated or if on concurrent ICP).
2. Where plasma glucose is  $\geq 12$  mmol/L on two occasions in the outpatient setting, screen for symptoms of hyperglycaemia, for example, thirst, polyuria and ketonuria/blood ketones to rule out ketoacidosis.
3. Commence gliclazide 40 mg in the morning and prescribe a blood glucose meter and glucose testing strips (if possible), and/or promptly refer to primary care to discuss initiating treatment and provide education on blood glucose meter use (see Appendix 7 for template letter). Provide a copy of these guidelines for the suggested treatment regimen. Counsel the individual on symptoms and management of potential hypoglycaemia secondary to gliclazide (see JBDS hypoglycaemia guidelines<sup>34</sup>).
4. The original JBDS steroid guideline was written with the use of once-daily prednisolone as the main steroid being used.<sup>30</sup> It was the effect of prednisolone on glucose that guided the use of gliclazide. However, with other, longer-acting GCs used in people with cancer, for example, dexamethasone, gliclazide may not be chosen as the sulfonylurea of choice. We acknowledge variations in local practice and differences in sulfonylurea regimes used, and local input may be sought where appropriate.
5. Gliclazide should be avoided in those with severe hepatic or renal impairment ( $<30$  ml/min/1.73 m<sup>2</sup>). In these situations, insulin will almost always be the treatment of choice, and advice should be sought from the diabetes team regarding commencement.
6. The dose of gliclazide may need incrementing by 40 mg per day if random plasma glucose remains  $\geq 12$  mmol/L or if targets are not reached. Individuals on high-dose GCs (i.e. prednisolone  $\geq 20$  mg per day or equivalent) may need larger incremental increase. Gliclazide may be titrated to a maximum of 240 mg in the morning, and an evening dose of gliclazide may also be initiated to achieve a maximum daily dose of 320 mg. (You may wish to seek specialist advice on dose titration at this stage.) The JBDS have specific guidelines on the management of hyperglycaemia

and GC therapy and provide details on further dose increments of gliclazide or addition of insulin if blood glucose remain high.<sup>35</sup>

- Should plasma glucose rise above 20 mmol/L, or if the individual is unwell with vomiting, abdominal pain or stupor, rule out ketoacidosis/hyperosmolar hyperglycaemic state (HHS). The JBDS have specific guidelines on the management of ketoacidosis and HHS in adults, or consult local hospital guidelines.<sup>36,37</sup> Where ketoacidosis/HHS has been excluded, refer the individual to the diabetes team for further management.

## 2.1.2 | Commencing immune checkpoint inhibitors (Algorithm 2)

Algorithm 2 outlines the treatment regimen for people with cancer commencing ICP without a prior diagnosis of diabetes.

It has been demonstrated that up to 75% of people who develop ICP-induced hyperglycaemia/diabetes present with ketoacidosis<sup>38–40</sup> and tend to present acutely with a severe increase in blood glucose.<sup>41</sup> Up to a third of individuals receiving ICP may receive high-dose steroids for non-endocrine immune related adverse events (IRAEs), and these individuals are also at risk for steroid induced hyperglycaemia. Compared to ‘standard’ type 1 diabetes mellitus, ICP-induced diabetes tends to have a faster onset, fulminant course and high degree of antibody negativity.<sup>41</sup>

- Prior to initiating ICP treatment individuals should be educated about the rare but potentially serious risk of diabetes mellitus. The signs and symptoms of hyperglycaemia should be explained to people in detail and advise them to seek medical attention immediately, to avoid potential life-threatening emergencies.<sup>41</sup>
- A random plasma glucose should be checked with each treatment cycle and/or if symptoms of hyperglycaemia develop for the duration of ICP treatment.
- If plasma glucose is  $\geq 20$  mmol/L or there are suggestive symptoms, rule out ketoacidosis/HHS (see JBDS ketoacidosis/HHS guidelines).<sup>36,37</sup> Whilst most cases of ketoacidosis occur with hyperglycaemia, about 1 in 20 cases occur with glucose concentrations less than 13 mmol/L. If individuals have other symptoms (e.g. acetone on the breath, deep (Kussmaul) breathing) then consider ketoacidosis, irrespective of the glucose.
- Pancreatic antibodies (e.g. GAD65, Zn transporter 8 or anti-islet cell) should be measured.<sup>42</sup>
- Commencement of insulin therapy is almost always required, and therefore early/prompt referral to the specialist diabetes team is required. Given the risk of precipitous hyperglycaemia, urgent management of hyperglycaemia

is necessary. Urgent hospital admission is necessary when ketoacidosis or HHS is diagnosed.

- High-dose GCs have not been demonstrated to reverse ICP-induced pancreatic toxicity and diabetes unlike other ICP-related toxicities. There is also the potential that any high-dose GCs will worsen hyperglycaemia and they should be used with caution in this setting, if at all.<sup>27,42</sup>
- Withhold ICP if there is evidence of an ICP-induced diabetic emergency. Consider restarting the ICP once management for hyperglycaemia has been instigated.<sup>42</sup>

The management of ICP induced hyperglycaemia algorithm (algorithm 2) should be prioritised over the management of SACT induced hyperglycaemia algorithm (algorithm 1) in those individuals on dual ICP and chemotherapy regimens.

## 2.2 | Individuals with pre-existing diabetes

It is estimated that up to 20% of all people with cancer have pre-existing diabetes.<sup>2,24</sup> Undergoing cancer treatment can be stressful for these individuals; however, it is essential that they are adequately supported to appropriately manage their diabetes to optimise both treatment and quality of life.

### 2.2.1 | Prior to commencing SACT/ glucocorticoid therapy

- Document the type of diabetes the person with diabetes has, the presence of any pre-existing diabetes related complications and if they have hypoglycaemic awareness.
- A baseline random plasma glucose should be checked in all people with diabetes, as well as a HbA1c in those individuals in whom this has not been tested within 3 months.
- If plasma glucose is  $\geq 20$  mmol/L rule out ketoacidosis or HHS (see JBDS ketoacidosis/HHS guidelines).<sup>36,37</sup> Whilst most cases of ketoacidosis occur with hyperglycaemia, about 1 in 20 cases occur with glucose concentrations less than 13 mmol/L. If someone has other symptoms (e.g. acetone on the breath, deep (Kussmaul) breathing) then consider ketoacidosis, irrespective of the glucose.
- During pre-chemotherapy treatment counselling a health professional must ensure that the individual is in contact with their usual diabetes care provider (usually primary care), who should be made aware that systemic anti-cancer treatment is being commenced (Appendix 7 for referral letter to usual diabetes care provider). The diabetes care provider should provide urgent advice or appropriately refer to a specialist diabetes team in the event of deterioration of glycaemic control.



5. People with pre-existing diabetes should be made aware of the likely exacerbation of hyperglycaemia whilst on GC containing anti-emetic therapy. People with known diabetes may need to be supplied with a blood glucose meter, as they may not have tested their CBG previously. The blood glucose meter supply and education on use should be arranged by their usual diabetes care provider (usually primary care) upon liaison with the oncology/haematology specialist teams. Those who already test CBG should undertake more frequent capillary glucose testing. These glucose readings can be reviewed by a specialist nurse, clinician or pharmacist. People with diabetes should be counselled on careful self monitoring of glucose levels and retaining liaison with their usual diabetes care provider.

### 2.2.2 | For non-insulin-treated individuals with type 2 diabetes (Algorithm 3)

Algorithm 3 outlines the treatment regimen for people with cancer commencing SACT or GC therapy with a history of diabetes receiving oral glucose-lowering therapies.

1. Where plasma glucose is  $\geq 12$  mmol/L on two occasions, initially screen for symptoms of hyperglycaemia (polyuria, nocturia, fatigue, thirst, blurred vision, headaches, confusion, weight loss) and ketonuria/blood ketones to rule out ketoacidosis.
2. If the individual is already on a sulfonylurea such as gliclazide or meglitinides (the insulin secretagogues), up-titrate the morning dose of gliclazide to a maximum dose of 240 mg, and an evening dose of gliclazide may also be initiated to achieve a maximum daily dose of 320 mg. Titration of metformin may also be beneficial. People not using insulin for their diabetes may require switching to insulin therapy, especially those people already on more than one non-insulin glucose-lowering agent (including sulfonylureas) or in individuals receiving GCs.
3. Ensure the individual has no symptoms of hypoglycaemia, day or night. If the person is already on a maximum dose, or plasma glucose remains  $\geq 12$  mmol/L despite increasing the dose, contact their usual diabetes care provider (usually primary care).
4. If the individual is on a diet controlled regimen only, or on other non-sulfonylurea treatments (e.g. metformin, DPP 4 inhibitors, pioglitazone, SGLT2 inhibitors) commence gliclazide 40 mg daily in the morning, and refer the individual back to their usual diabetes care provider (usually primary care). Consider incrementing by 40 mg at treatment visits if blood glucose levels are persistently above the target range 6–12 mmol/L. People on

high-dose GCs may need larger incremental increases: gliclazide may be titrated to a maximum of 240 mg in the morning and an evening dose of gliclazide may be initiated to achieve a maximum daily dose of 320 mg. Seek specialist advice if you are concerned about dose titration in those taking 160 mg with no improvement in glycaemic control.

5. A number of anti-cancer therapies are known to cause nephrotoxicity and hepatotoxicity, and both complications may require adjustments to diabetes treatment. These cases may require specific input from diabetes teams.
6. In individuals receiving ICP with a prior history of type 2 diabetes, a sudden change in blood glucose levels/symptoms may indicate immunotherapy induced pancreatic dysfunction and these individuals need initiation of insulin treatment.

### 2.2.3 | For insulin-treated individuals (Algorithm 4)

Algorithm 4 outlines the treatment regimen for people with cancer commencing SACT or GC therapy with a history of diabetes treated with insulin.

1. As above, where plasma glucose is  $\geq 12$  mmol/L on two occasions, initially screen for symptoms of hyperglycaemia and ketonuria/blood ketones to rule out ketoacidosis.
2. In all cases, contact the diabetes team for support in titrating insulin. However when unable to contact the team, and whilst in the outpatient setting, titrate insulin by 10%–20% of the original dose daily; however, an increase in insulin dose by up to 40% may be required particularly with the first dose of high-dose GCs to maintain euglycaemia<sup>43</sup> (see JBDS guidelines on the management of hyperglycaemia and GCs).<sup>35</sup> Algorithm 4 provides further detail of insulin titration according to the type of insulin received.
3. People with type 1 diabetes are at a particularly high risk of uncontrolled hyperglycaemia, and close liaison with the diabetes team is essential.
4. Individuals should be aware of ‘sick day rules’ with insulin administration (including testing CBG and blood ketones every 4–6 h and to continue insulin regimen when unwell/reduced oral intake) and may need careful reminders at the initiation of therapy (see ‘Trend Diabetes sick day rules’ leaflets for specific type 1 and 2 diabetes guidance<sup>44</sup>). People with type 1 diabetes should be encouraged to seek early advice and treatment when unwell with hyperglycaemia  $\pm$  ketones.
5. The importance of not omitting basal insulin in people with type 1 diabetes should be emphasised in individuals not eating/with cachexia to avoid ketoacidosis.

## 2.2.4 | Management of nausea and vomiting

The majority of anti-emetic regimens given alongside SACT involve the use of a GC. GCs have demonstrated efficacy in the control of emesis in acute nausea and vomiting. Over the past few decades, neurokinin 1 (NK1) antagonists (e.g. aprepitant) have improved emesis outcomes for people with cancer. Their licensing has meant that they can be used with a lower GC dose, with equivalent efficacy, due to an interaction in their mechanisms. There have been some studies involving the new-generation NK1 antagonists that have demonstrated an effect without GCs.

Individuals receiving highly emetogenic and moderately emetogenic chemotherapy should be offered an NK1 antagonist (e.g. aprepitant) with a long-acting 5HT3 inhibitor (e.g. ondansetron). In the highly emetogenic category, clinicians should consider the use of a GC in the first cycle and reduce doses or withdraw completely based on the individual's emetic control and on blood glucose management.<sup>45</sup>

Seek advice on diabetes management from specialist service when nausea and vomiting is unpredictable and poorly managed.

## 3 | GLUCOSE TARGETS

The recommended target level is 6.0–10.0 mmol/L, allowing a range of 6.0–12.0 mmol/L. However, people with cancer receiving end-of-life care do not require such tight control,<sup>46</sup> with levels targeted at no lower than 6.0 mmol/L and no higher than 15 mmol/L.<sup>35</sup>

## 4 | BLOOD GLUCOSE MONITORING

During treatment with GCs or treating individuals at high risk of hyperglycaemia (Table 4), CBG monitoring should occur at least once daily.<sup>35</sup>

Although readings remain over 12 mmol/L individuals should be advised to increase the frequency of CBG monitoring to four times daily for 48 h, a mix of pre-meals, 1–2 h post-meals and before bed, and enter the treatment algorithm (Appendix 1–4).<sup>35</sup> CBG testing should continue daily while remaining on GCs/SACT or after a dose increase. CBG testing should continue ever after treatment discontinuation while readings remain over 12 mmol/L.

If CBG tests are persistently below 10 mmol/L and SACT/GCs have been discontinued, then blood glucose testing can be stopped (unless receiving ICP).

As steroid doses or SACT reduce or are discontinued, the treatment of hyperglycaemia will similarly need to be titrated

down, for example, a weekly 5 mg reduction of prednisolone from 20 mg may require a 20%–25% reduction in insulin dose, or a 40 mg reduction in gliclazide.

## 5 | RISKS OF HYPOGLYCAEMIA

Poor oral intake and nausea/vomiting from the underlying cancer or treatments put individuals at risk for hypoglycaemia.

Symptoms of hypoglycaemia include perspiration, fatigue, dizziness, hunger, palpitations, mood change, pallor and confusion.

People with new-onset, ICP-induced insulin deficiency often have labile glucose control; therefore, they should be counselled on the risks and symptoms of hypoglycaemia.<sup>41</sup> More relaxed glucose targets may be required to avoid hypoglycaemia wherever possible. ICPs can also induce hypopituitarism leading to secondary adrenal insufficiency. This may lead to hypoglycaemia (together with any of the following—hyponatraemia, hyperkalaemia and hypotension). Adrenalitis leading to primary adrenal insufficiency is very rare. Presentation of adrenal insufficiency ranges from asymptomatic laboratory alterations to the acutely unwell, with management depending on the severity. The local endocrine team should be involved and referral made to local immunotherapy related toxicity guidelines for management. Oncology teams should be aware of other causes of adrenal or pituitary deficiency leading to hypoglycaemia, including metastases at these sites, surgery, irradiation,azole class of anti-fungal medication and inappropriate abrupt cessation of GC medication.

Individuals on gliclazide should also be counselled on symptoms and management of potential hypoglycaemia secondary to gliclazide.

Please refer to the JBDS hypoglycaemia guidelines or local hospital guidelines for the management of hypoglycaemia in adults with diabetes.<sup>47</sup>

## 6 | IMAGING CONSIDERATIONS

**Contrast scans:** In individuals already on metformin, this should only be discontinued (temporarily) if contrast media for imaging is being used, or if renal function deteriorates significantly (estimated GFR <30 ml/min).

**PET scanning:** Glycaemic excursions affect scan quality and can be a reason for cancelling the scan on the day. Aim for a stable glucose within the range of 4–11 mmol/L. Avoid antidiabetic agents in the 4–6 hs prior to scanning. Consider adding a corrective dose of rapidly acting insulin analogue for those with a blood glucose above 12 mmol/L prior to scan.

## 7 | DIETETIC RECOMMENDATIONS

Guidance on appropriate first-line nutritional advice and when to refer to dietetic services to support people with diabetes (established, newly diagnosed or GC-induced) undergoing SACT is available from the full version of these guidelines, available from the JBDS website, as well as JBDS' 'Glycaemia management during enteral feeding' guidelines.<sup>48</sup>

## 8 | END-OF-LIFE DIABETES CARE

Glycaemic targets in individuals receiving end-of-life care tend to be different to those traditionally given because treatment often focuses on symptomatic relief, although should be balanced with the glycaemic control required to manage symptoms. Glucose levels should be targeted at no lower than 6.0 mmol/L and no higher than 15 mmol/L.<sup>35</sup> Diabetes UK provide detailed guidance for the management of diabetes in individuals approaching the end of life.<sup>46</sup>

## 9 | FOLLOW-UP

It is anticipated that primary care will provide the majority of diabetes follow-up for the people described in this guideline. This will require regular communication between the oncology, diabetes and primary care teams (see Appendix 3 for template referral letter). These individuals should be placed on the diabetes register to ensure that they receive regular appropriate care for diabetes, including foot checks and retinal photograph.

## 10 | SUMMARY

It is common practice in oncology to start anti-cancer therapy (including chemotherapy, targeted treatment, immunotherapy and steroids) in people with pre-existing diabetes for a range of cancers. These guidelines call for recognition of the risks of developing hyperglycaemia and new-onset diabetes in people with cancer by the multidisciplinary team and provide the tools to appropriately manage these individuals and reduce the risks of complications. Each individual hospital and service is recommended to adopt these guidelines and template information sheets for local use (Appendix). We encourage good practice through collaborative working, and it is recommended that local oncology services develop strategic and operational links with their local diabetes specialist teams including nurses and dietetics, both within the hospital and community settings.

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Writing group: Safwaan Adam (The Christie NHS Foundation Trust); James Aries (Barts Health NHS Trust); Jason Cheung (Norfolk and Norwich University Hospitals NHS Foundation Trust); Saira Chowdhury (Guys and St Thomas' Hospital); Umesh Dashora (East Sussex Healthcare NHS Trust); Parijat De (Sandwell and West Birmingham NHS Trust); Shreya Dhar (General Practitioner); Sarah Gane (Kings College London); Kerry Guile (Royal Free London NHS Foundation Trust); Claire Higham (The Christie NHS Foundation Trust); Louise Hopewell (The Christie NHS Foundation Trust); Adele Hug (Royal Surrey County Hospital NHS Foundation Trust); Apostolos Konstantis (Princess Alexandra Hospital and UCL NHS Trust); Susan Mason-Cave (The Christie NHS Foundation Trust); Laura Morrison (Royal Free London NHS Foundation Trust); Neil Reynolds (University College London Hospital NHS Foundation Trust); Katherine Walton (General Practitioner) and Edna Young (Patient Representative).

## ORCID

Nalinie Joharatnam-Hogan  <https://orcid.org/0000-0001-8406-2732>

<https://orcid.org/0000-0001-8406-2732>

Ketan Dhatriya  <https://orcid.org/0000-0003-3619-9579>

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.