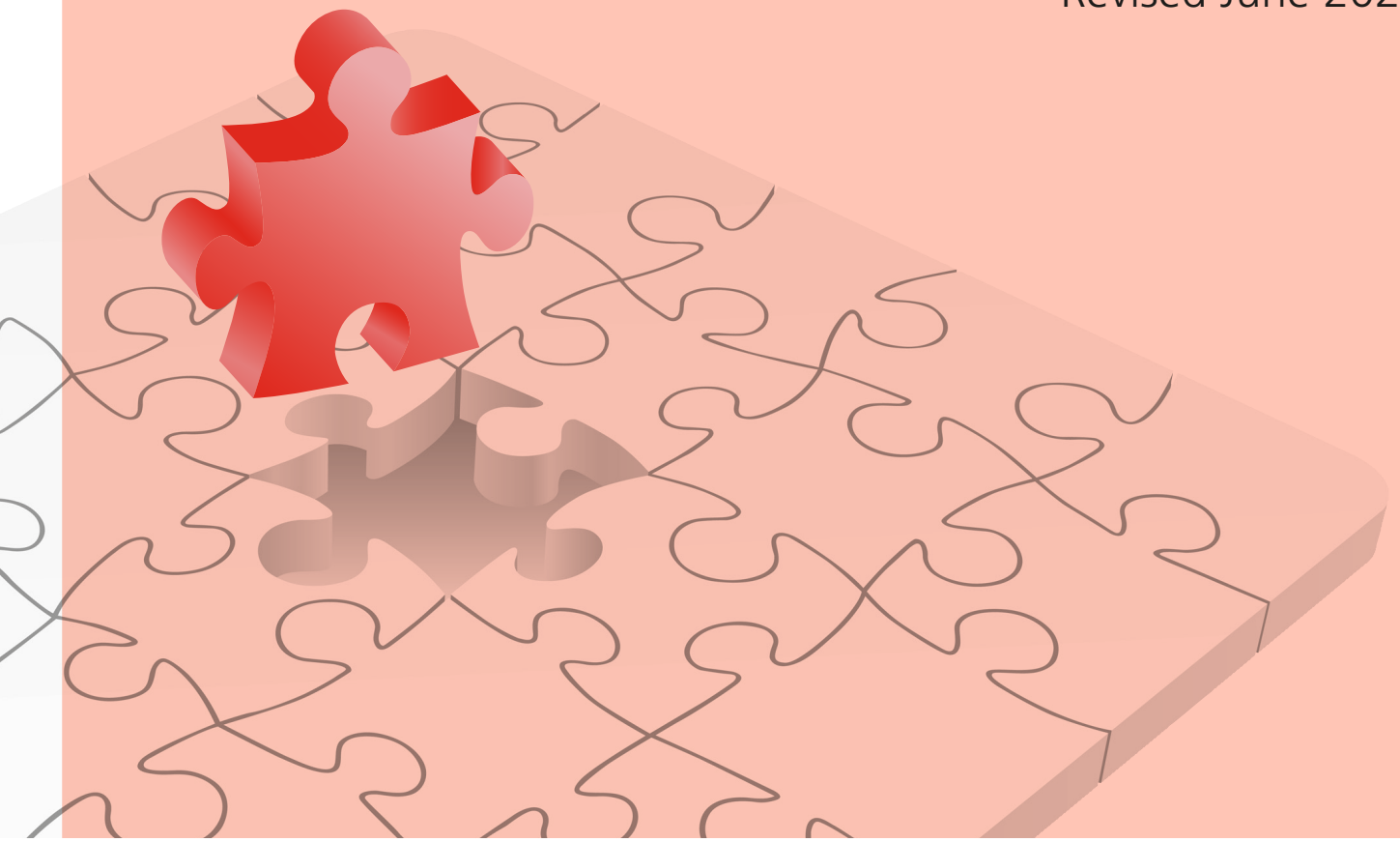
JBDS-IP Joint British Diabetes Societies for inpatient care

Management of Hyperglycaemia and Steroid (Glucocorticoid) Therapy

Revised June 2022



ABCD Association of British Clinical Diabetologists

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This document is coded JBDS 08 in the series of JBDS documents:

Other JBDS documents:

The hospital management of hypoglycaemia in adults with diabetes mellitus	*JBDS 01*
The management of diabetic ketoacidosis in adults	*JBDS 02*
Management of adults with diabetes undergoing surgery and elective procedures: improving standards	*JBDS 03*
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Diabetes at the front door	*JBDS 16*
The Management of Glycaemic Control in Patients with Cancer	*JBDS 17*

These documents are available to download from the ABCD website at https://abcd.care/joint-british-diabetes-societies-jbds-inpatient-care-group , the Diabetes UK website at www.diabetes.org.uk/joint-british-diabetes-society and the chemotherapy board website at www.ukchemotherapyboard.org

These guidelines can also be accessed via the Diabetologists (ABCD) app (need ABCD membership to access the app)

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Disclaimer

The information contained in this guidance is a consensus of the development and consultation groups' views on current treatment. It should be used in conjunction with any local policies/procedures/guidelines and should be approved for use according to the trust clinical governance process. Care has been taken in the preparation of the information contained in the guidance. Nevertheless, any person seeking to consult the guidance, apply its recommendations or use its content is expected to use independent, personal medical and/or clinical judgement in the context of the individual clinical circumstances, or to seek out the supervision of a qualified clinician. The group makes no representation or guarantee of any kind whatsoever regarding the guidance content or its use or application and disclaim any responsibility for its use or application in any way.

To enable the guideline to stay relevant, it is envisaged that all of the JBDS guidelines will be updated or reviewed each year. As such these are 'living' documents – designed to be updated based on recently published evidence or experience. Thus, feedback on any of the guidelines is welcomed. Please email christine.jones@nnuh.nhs.uk with any comments, suggestions or queries.

Conflict of interest statement

The authors declare no conflicts of interest

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Training, Research and Education for Nurses in Diabetes (Trend Diabetes)

What has changed since the previous guideline?

- The major change has been to move the management and management algorithm to the front of the document. This is to make it easier for people to access the most frequently used sections of the guideline.
- Clinical targets have been revised to reduce the risk of hypoglycaemia.
- A new section on the impact of dexamethasone in people diagnosed with the Coronavirus-19 has been included. This includes specific algorithms produced by the ABCD.
- Updates have been made to the section relating to "special groups", including, pregnancy, oncology and the management of people who are frail.
- The term glucose has been consistently applied to glucose containing preparations suitable for intravenous administration.
- We have used the term "people or individual with diabetes" in line with Language Matter documentation from Diabetes UK.

Foreword

This is the 2nd edition of the Joint British Diabetes Societies for Inpatient Care (JBDS-IP) guideline for the management of steroid induced hyperglycaemia and steroid induced diabetes. This document is evidence-based where possible but also draws from accumulated professional knowledge and consensus agreement. A new section on care of people undergoing cancer treatment has been added. The impact that the Coronavirus pandemic has had on the use of steroids is acknowledged and a section relating to this is included.

The use of steroids in patients with established diabetes is a common clinical problem and many teams have developed their own guidelines based on the original document. Since the original JBDS guideline document was published over 10,000 downloads have been reported in the UK and the more concise version published in Diabetic Medicine was in the top 10 of article downloads in 2019. This edition will provide further evidence-based information to assist healthcare professionals working in the hospital and when reviewing people in hospital clinics and GP practices following a hospital admission.

There is no generally accepted management strategy but there is now more clarity over the impact the use of steroids can have on people already known to have diabetes and those without a previous diagnosis of the condition. Steroid induced diabetes may be frequently undiagnosed and only discovered on the emergence of symptoms or complications of acute hyperglycaemia.

This guideline constructs a framework for the recognition and management of steroid induced hyperglycaemia and steroid induced diabetes and is designed for use by general physicians. As with all of the JBDS-IP documents, this document is dynamic and will be reviewed in response to feedback with a view to incorporating emerging evidence. This document has been produced by the Joint British Diabetes Societies for Inpatient Care on behalf of Diabetes UK, the Association of British Clinical Diabetologists, (ABCD), the Diabetes Inpatient Specialist Nurse (DISN) UK Group and Training Research and Education for Nurses in Diabetes (Trend Diabetes).

Introduction

This document aims to guide the management of hyperglycaemia in people given steroids as a hospital inpatient and following discharge. Glucocorticoids (steroids) are potent anti-inflammatory and immunosuppressive drugs; they were first used for therapeutic purposes in the mid-20th century (1). The prevalence of steroid use in people with diabetes is common and in hospital inpatients may be between 25-40% of the population. In the outpatient population, short courses of oral corticosteroids are often used to treat conditions such as asthma, chronic obstructive pulmonary lung disease, rheumatoid arthritis, and inflammatory bowel disease (2). The highest use of steroids (40%) is for respiratory disease, with most of the rest being used in musculoskeletal and cutaneous diseases, and conditions requiring immunosuppression. Dexamethasone has been shown to be used in up to 50% of individuals undergoing palliative care but most often for short courses of 5-7 days (3). The Coronavirus pandemic starting in 2020 led to the use of dexamethasone in those with life threatening symptoms associated with the virus (4; 5); this guideline includes a new section on management in these cases.

Most steroid use is for less than 5 days, but 22% is for greater than 6 months and 4.3% for longer than 5 years (6). Nearly one-quarter of people may need to use corticosteroids for more than 6 months (7). Screening for glucocorticoid induced diabetes should be considered in all those treated with medium to high doses of glucocorticoids. The meta-analysis by Suh et al (7) demonstrated that rates of glucocorticoid induced hyperglycaemia and diabetes were 32.3% and 18.6%, respectively. This is related to the duration of time on steroids, the potency of the drug used and the doses given, the length of time on glucocorticoids, and the relative potency and dose of the glucocorticoid.

A rise in glucose related to steroid therapy occurring in people without a known diagnosis of diabetes is termed steroid induced diabetes. This may or may not resolve when the steroids are withdrawn.

The use of steroid treatment in people with pre-existing diabetes will undoubtedly result in worsening glucose control; this may be termed steroid induced hyperglycaemia. This warrants temporary additional and more active glycaemic management.

Steroid treatment may be administered as a single high dose for a defined period and titrated down slowly. It can also be used as maintenance therapy for a prolonged period, may be given in high doses when a malignancy is identified or at the end of life and can be administered orally or intravenously. The management of adrenal suppression due to long-term steroid use is beyond the remit of this document and advice on how to manage this condition should be sought from local endocrine services. There is little evidence to guide how individuals with hyperglycaemia related to steroid use should be managed (8). Short courses of steroids resulting in minimal periods of hyperglycaemia may not warrant intervention. Higher dose steroids for longer periods may result in significant symptomatic hyperglycaemia including fatigue, polyuria, and polydipsia with the potential for acute complications related to hyperglycaemia (9). The control of hyperglycaemia in such circumstances will ameliorate symptoms, reduce the risk of acute complications, and lessen the increased risk of infections and other complications associated with hyperglycaemia. It is also important to note that acute illness may result in "stress hyperglycaemia" independent of steroid administration (10).

This document is aspirational, and the guidance outlined is a consensus based on best practice collated from around the United Kingdom. Where evidence is available, this is referenced. The entry point to the treatment algorithms indicated within this document would be any supraphysiological dose of steroid, approximating to a dose of prednisolone of greater than 5mg – or equivalent dose of the alternative synthetic glucocorticoids. Some individuals may develop hyperglycaemia at a lower steroid dose, so clinical vigilance is therefore recommended with steroid therapy at any dose.

This document is presented as "how to" pages to enable ease of access at the beginning and the accompanied evidence follows.

The assessment of hyperglycaemia in individuals is presented in 3 separate arms:

1. Management in people with steroid induced diabetes (no known diabetes diagnosis)
2. Management of people with steroid induced hyperglycaemia in those with a pre-existing diabetes diagnosis
3. End of life care

Table 1. Assessment of hyperglycaemia in people taking steroids

No previous diagnosis of diabetes

- Check HbA1c prior to the commencement of steroids in individuals perceived to be at high risk.
- On commencement of steroid, recommend capillary blood glucose (CBG) once daily pre or post lunch or evening meal, in those at "high risk" or with symptoms suggestive of "hyperglycaemia".
- If CBG is below 12mmol/L consider the person to be at low risk and record the CBG daily post breakfast or post lunch
- If CBG consistently <10mmol/L consider cessation of CBG testing.
- If a capillary blood glucose is found to be greater than 12mmol/L the frequency of testing should be increased to four (4x) times a day.
- If a capillary blood glucose is found to be consistently greater than 12mmol/L (i.e. on 2 occasions during a 24hr period), then the individual should enter the treatment algorithm below.

Known diagnosis of diabetes

- Reassess glucose control and current therapy.
- Set target blood glucose e.g. 6-10mmol/L.
- Check CBG 4 times a day and use this flowchart to adjust diabetes medication accordingly.
- In Type 1 diabetes also check daily for ketones if CBG >12mmol/L.
- Aim for 6-10mmol/L (acceptable range 6-12mmol/L).

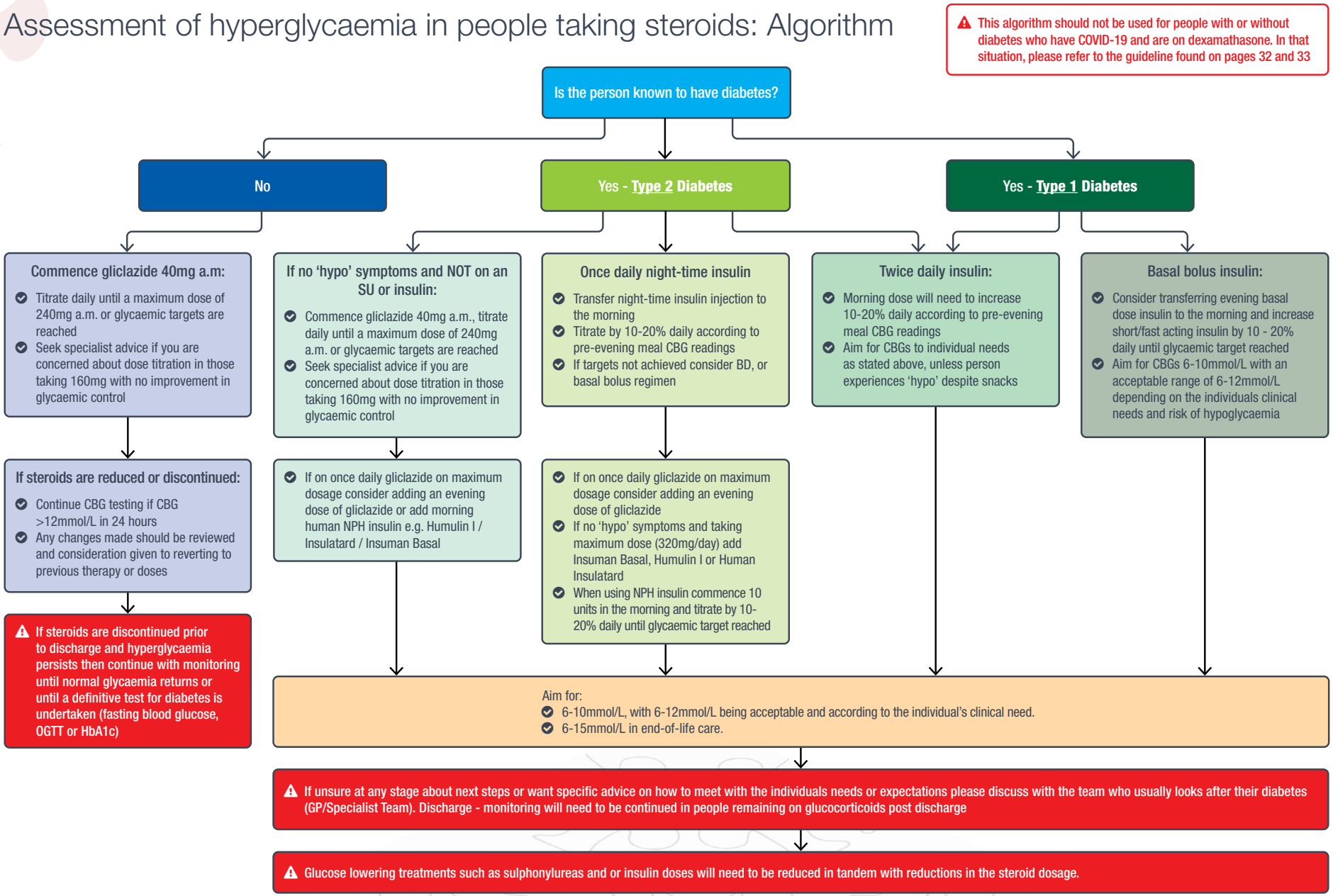
End of Life care

- Discuss changing the approach to diabetes management with the individual, and family or carer, if not already done.
- If the individual remains on insulin therapy, ensure the diabetes specialist team are involved and the management plan is agreed.
- Aim for CBGs 6-15mmol/L and symptom relief.

If steroids are reduced or discontinued:

- **Blood glucose monitoring may need to be continued in inpatients and, individuals discharged, assessed by their GP.**
- **Any changes made should be reviewed and consideration given to reverting to previous therapy or doses.**
- **If unsure at any stage about next steps or want specific advice on how to meet with the individual's clinical needs or expectations please discuss with the team who usually looks after their diabetes (GP/Specialist Team).**
- **Glucose lowering treatments such as sulphonylureas and or insulin doses will need to be reduced in tanden with reductions in the steroid dosage.**

Figure 1- Assessment of hyperglycaemia: algorithm



Mechanism of Action

Synthetic glucocorticoids mimic the effect of the endogenous steroids, nuclear hormones that cross the cell membrane to bind to specific glucocorticoid receptors in the cytoplasm of target cells to form glucocorticoid-receptor (GR) complexes. The activated GR complex is translocated to the cell nucleus and modulates DNA transcription. This results in activation of anti-inflammatory proteins and repression of pro-inflammatory proteins (11). Steroid administration also modulates carbohydrate metabolism via complex mechanisms, including effects on beta cell function as well as inducing insulin resistance by effects on insulin receptors in liver, muscle and adipose tissue. These effects promote hyperglycaemia in "at risk individuals".

Predisposing factors leading to increased risk of hyperglycaemia with steroid therapy include:

- Pre-existing type 1 or type 2 diabetes
- People at increased risk of diabetes (e.g. obesity, family history of diabetes, previous gestational diabetes, ethnic minorities, polycystic ovarian syndrome)
- Impaired fasting glucose or impaired glucose tolerance, HbA1c 42-47mmol/mol
- People previously hyperglycaemic with steroid therapy
- Those identified to be at risk utilising an appropriate diabetes risk calculator e.g. University of Leicester/Diabetes UK (www.riskscore.diabetes.org.uk – last accessed 1st January 2021)

Impact on glycaemia

Steroids may be administered by various regimes and in variable doses. A single or short course of steroid, for example, prednisolone given in the morning may be the commonest mode of administration. In susceptible patients, this will often result in a rise in blood glucose by late morning that continues into the evening. Overnight the blood glucose generally falls back, often to baseline levels the next morning. Treatment should therefore be tailored to treating the hyperglycaemia, whilst avoiding nocturnal and early morning hypoglycaemia.

In pregnancy and other situations, a single dose or short course of steroid may be administered. Many hospital inpatients will receive multiple daily doses of steroids. Glucose concentrations in most individuals can be predicted to rise approximately 4 to 8 hours following the administration of oral steroids and sooner following the administration of intravenous steroids. Capillary blood glucose (CBG) monitoring is paramount to guiding appropriate therapeutic intervention. Conversely, glucose concentrations may improve to pre-steroid levels 24 hours after intravenous steroids are discontinued.

If oral steroids are weaned down over several weeks the glucose levels may decline in a dose-dependent fashion. This may not always occur, particularly in those with pre-existing undiagnosed diabetes.

The duration of action depends on the specific drug used (Table 1)

Table 2. Duration of action

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	0.75 mg	36.54
Betamethasone	0.75 mg	26-54

N.B. Potency relates to anti-inflammatory action, which may not equate to hyperglycaemic effect

Glucose targets and monitoring

Glucose targets differ depending on the clinical needs of the individual along with other factors and person-centred characteristics. The recommended target level for glucose in hospital inpatients is 6.0-10.0mmol/L, accepting a range of 6.0-12.0mmol/L. However, certain patient groups may not require such tight control, such as those who may be severely disabled by a hypoglycaemic event or in:

- People with dementia
- Individuals who are confused
- Frail individuals
- People with recent brain injury
- People at risk of falling
- Dialysis patients
- People with renal impairment
- Individuals with variable appetite and dietary intake
- End of life care

In others, for example, who are diet controlled, or on insulin pumps, glucose concentrations may go safely lower than 6.0mmol/L. However, staff and the person with diabetes should act if the glucose is <5.0mmol/L to prevent the glucose falling to <4.0mmol/L. An exception is those people who are diet controlled. Individualised targets and an appropriate care plan should be documented when hyperglycaemia is first identified, mindful of the symptoms associated with uncontrolled hyperglycaemia.

Table 3. Glycaemic targets

Inpatient blood glucose targets	6-10mmol/L recommended but 6-12mmol/L is acceptable (8)
People with COVID-19	< 10mmol/L (12)
Frailty	6.7–11.1mmol/L throughout the day (13)
Care home residents	7-12mmol/L
End of life care	6-15mmol/L (14)

An HbA1c prior to the commencement of steroids in inpatients perceived to be at high risk of steroid induced diabetes and in those with known diabetes may be informative (15). At the commencement of corticosteroid therapy in people considered at risk of steroid induced diabetes, capillary blood glucose (CBG) testing should be initiated once daily. This should be prior to or following lunch or evening meal when the hyperglycaemic effects of morning steroid dosing is likely to be greatest.

Table 4. Blood glucose monitoring

In people without a pre-existing diagnosis of diabetes	In people with a pre-existing diagnosis of diabetes
Monitor blood glucose at least once daily – preferably prior to lunch or evening meal, or alternatively 1-2 hours post lunch or evening meal. If the initial blood glucose is less than 12.0mmol/L continue to test once prior to or following lunch or evening meal	Test four times a day, before or after meals, and before bed, irrespective of background diabetes control after 2 hours
If a subsequent capillary blood glucose is found to be greater than 12.0mmol/L, then increase the frequency of testing to four times daily (before meals and before bed)	If the capillary glucose is found to be consistently greater than 12.0mmol/L i.e. on two consecutive readings in 48 hours refer to the treatment algorithm
If the capillary glucose is found to be consistently greater than 12.0mmol/L i.e., on two occasions during 24 hours, refer to the treatment algorithm	

Diabetes management in people taking oral steroids

All those experiencing hyperglycaemia should receive appropriate education from trained individuals including:

- Diabetes management
- Healthy lifestyle choices
- The risk of hypoglycaemia with non-insulin and insulin therapies

Medication options for people taking *once daily* steroid therapy

These include:

- Metformin
- Pioglitazone
- DPP-4s
- SGLT2 Inhibitors
- GLP-1RAs
- Sulphonylureas and meglitinides
- Insulin

Metformin

Metformin decreases gluconeogenesis and increases peripheral utilisation of glucose. Early indications are that metformin may reduce long term side effects from steroid use (16) but evidence of benefit in acute steroid induced hyperglycaemia is lacking.

Sulphonylureas and Meglitinides

These agents promote insulin release from the pancreatic beta cell. By consensus, a short acting sulphonylurea, such as gliclazide, taken once daily may best manage the glucose excursion associated with a once daily oral steroid treatment. Whilst monitoring for hypoglycaemia the gliclazide may be titrated to a maximum of 240mg in the morning. An evening dose of gliclazide may also be initiated to achieve a maximum daily dose of 320mg.

Pioglitazone

This drug may seem an appropriate choice for the management of steroid induced hyperglycaemia. Pioglitazone may also take a number of weeks to achieve maximal effect. The evidence-base for the use of pioglitazone above other treatments described within this guideline however is weak (17; 18).

DPP-IV inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors

There is currently no evidence to support the use of DPP-IV inhibitors, GLP-1, or SGLT-2 inhibitors in the management of steroid induced diabetes/hyperglycaemia (19).

Insulin

Morning administration of basal human insulin (Humulin I, Insuman Basal, Human Insulatard) may closely fit the glucose excursion induced by a single dose of oral steroid in the morning. We advocate the commencement of 10 units of basal human insulin

with a daily dose increase of between 10% and 20%, titrated to the blood glucose concentration, although dose increments of up to 40% and more have been shown to be required in some individuals (20). Basal analogue insulin may be appropriate if hyperglycaemia is present throughout the day and into the evening. In this context, basal insulin may best be administered in the morning. The American Diabetes Association (ADA) suggests that as NPH action peaks at 4–6 h after administration, it is best to give it concomitantly with steroids (21). For long-acting glucocorticoids such as dexamethasone and multi-dose or continuous glucocorticoid use, long-acting insulin may be required to control fasting blood glucose (22). For higher doses of glucocorticoids, increasing doses of prandial and correctional insulin, sometimes in extraordinary amounts, are often needed in addition to basal insulin. Care should be taken to identify and protect against nocturnal and early morning hypoglycaemia if insulin glargine, insulin detemir or insulin degludec are used in this context. Inpatients should be offered a bedtime snack to reduce the risk of nocturnal hypoglycaemia.

Medication options for people taking *multiple daily* doses of steroid

Multiple daily doses of steroid such as intravenous hydrocortisone or oral dexamethasone can cause hyperglycaemic effects throughout the 24-hour period. Administration of oral non-insulin therapies is unlikely to be effective in controlling the resultant hyperglycaemia. A trial of gliclazide 40mg twice daily (BD) may be indicated and titrated daily to a maximum of 160mg BD. Metformin and pioglitazone are unlikely to be of significant, swift benefit and likewise there is no firm evidence to support the use of GLP-1RAs, DPP-4 inhibitors, or SGLT-2 inhibitors in these circumstances.

Subcutaneous insulin using a basal or multiple daily injection regimen will be the most appropriate choice of treatment to achieve glycaemic control for the majority of individuals, although it is recommended that the local inpatient or community diabetes team be involved. It may be that a twice daily premixed, basal bolus, or more complex insulin regimen will be required if oral medication, or once daily insulin proves insufficient to control hyperglycaemia. Close attention will need to be paid to blood glucose monitoring and early intervention may be necessary to prevent prolonged symptomatic hyperglycaemia. Consequent titration of the insulin dose will allow maintenance of glucose control in the face of increasing or decreasing steroid dose.

In acutely unwell inpatients with significant hyperglycaemia, oral non-insulin therapies are unlikely to achieve glucose control. In this situation, temporary use of a variable rate intravenous insulin infusion (VRIII) with urgent review by the diabetes inpatient team would be appropriate.

Similar care will need to be taken when steroid doses are reduced and withdrawn to prevent iatrogenic hypoglycaemia.

Treatment of steroid induced hyperglycaemia in people who have type 1 or type 2 diabetes

If treated with gliclazide, increase the morning dose in 40mg increments to a maximum of 240mg, with a total daily dose not exceeding 320mg. Titration of metformin may also be beneficial. There is little good evidence to suggest benefit of DPP-4 inhibitors, GLP-1 receptor agonist or SGLT-2 inhibitors in this situation so temporary addition of basal human insulin may be indicated.

Table 5. Treatment of steroid induced hyperglycaemia in people who have type 1 or 2 diabetes

Type 2 diabetes	Type 1 diabetes
1. Set target for capillary blood glucose (CBG) e.g. 6.0-10.0mmol/L 2. Consider increasing monitoring to 4 times daily 3. Refresh diabetes education with person with diabetes	Insulin doses can be titrated in at least 2 unit increments every 24-48 hours, to achieve target glucose concentrations, though evidence suggests that significant increases in the insulin dose of up to 40% may be required to normalise the steroid induced hyperglycaemia (20)
If hyperglycaemia on non-insulin therapies - Gliclazide – titrate to maximum of 320mg daily, with maximum 240mg in the morning - Metformin – titrate to maximum of 1g BD	Diabetes Specialist Nurses (DSN) or community diabetes teams should be involved
If hyperglycaemia on insulin therapies - If on evening once daily human insulin consider switch to morning dosing - If uncontrolled hyperglycaemia or multiple daily dosing of steroid consider switch to basal analogue insulin (or alternative regimen) and involve diabetes team in hospital or community - Beware of nocturnal and early morning hypoglycaemia	An increase in lunch and evening meal short-acting bolus insulin dose may be warranted if a basal bolus regimen is utilised. Alternatively, a switch of insulin regimen may be required, for example from twice daily premixed insulin to a basal-bolus regimen. Transferring the evening dose of NPH to morning may also prove effective

Discharge Planning

Hospital discharge in inpatients without a previous diagnosis of diabetes

When an inpatient is discharged from hospital on steroid therapy a clear strategy for the management of hyperglycaemia or potential hyperglycaemia should be in place. The titration of therapy to address the hyperglycaemia should be communicated to the GP or community DSNs in the discharge letter. Similarly, the risk of hypoglycaemia and the appropriate de-escalation of therapy when steroid doses are reduced or withdrawn should also be part of the communication strategy.

Individuals commenced on steroids as an inpatient and discharged after a short stay, with the intention of continuing high dose steroids, should receive standard education including:

- Diabetes management
- Lifestyle advice
- Risks associated with hyperglycaemia and hypoglycaemia
- Blood glucose monitoring and the need to test once daily in the late afternoon or evening
- If a reading is in excess of 12.0mmol/L, then testing should be increased to four times daily
- If two consecutive readings in 48 hours exceed 12.0mmol/L, refer to the treatment algorithm

Post hospital discharge:

- If the steroid dose remains above 5mg prednisolone or equivalent, for a protracted period, and the patient is insulin treated then the blood glucose should be checked at least once daily and prior to driving
- If the steroid dose is being titrated upwards, then test at least once daily
- If a reading exceeds 12.0mmol/L increase testing to four times daily, including post prandially
- If two readings exceed 12.0mmol/L in a 24-hour period then follow the algorithm in Appendix 1
- As the steroid dose decreases, the treatment of hyperglycaemia will similarly need to be titrated down e.g., a weekly 5mg reduction of prednisolone from 20mg may require a 20-25% reduction in insulin dose, or a 40mg reduction in gliclazide
- If steroids were discontinued prior to discharge and hyperglycaemia persists, then blood glucose monitoring should be continued post discharge until normoglycaemia returns or until a definitive test for diabetes is undertaken such as an HbA1c
- If steroid treatment is ceased in hospital and blood glucose tests are in the normal range, then post-discharge blood glucose testing is not recommended. A definitive test for diabetes should still be undertaken

Screening post discharge

- After stopping steroid therapy in people without pre-existing diabetes who experienced steroid induced hyperglycaemia there should be screening for a diagnosis of diabetes. Given the recent hyperglycaemia the use of HbA1c as a screening tool should be delayed until 3 months following steroid cessation
- A fasting glucose or OGTT may be advantageous if a diagnosis of diabetes is clinically suspected prior to 3 months elapsing. Where present, practitioners should adhere to local guidelines for diabetes screening

It is anticipated that general practices will provide the majority of follow up of diabetes for the individuals described in this guideline. This will require robust lines of communication between hospital and community settings and the local diabetes team.

Outpatient management and high dose steroid therapy

Outpatient departments and general practices may commence a course of steroids for use in the community setting. It is advised that people treated in this context be screened for the potential emergence of steroid induced diabetes or hyperglycaemia.

It is advised that those who are expected to remain on steroids for a protracted period, and who are "at risk" of hyperglycaemia with steroid therapy should be provided with a glucose meter and instructed on how to check their CBG. Initially it is recommended that these individuals:

- Check their CBG once daily prior to or 1-2 hours following lunch or evening meal. If a CBG is recorded greater than 12.0mmol/L, then blood glucose monitoring should be increased to a maximum of four times daily
- If two consecutive readings in 48 hours exceed 12.0mmol/L, refer to the clinician who commenced the steroid therapy, or if agreed locally, the general practitioner. The clinician should then consider the algorithm for the management of hyperglycaemia with steroid use, and potentially commence a sulphonylurea or optimise existing non-insulin or insulin therapy

Hospital discharge of inpatients with steroid induced hyperglycaemia

These individuals should continue to blood glucose test and reduce their sulphonylurea and or insulin doses in tandem with reductions in the steroid dosage. If blood glucose readings remain raised and are out of target, they should seek advice from the local diabetes community team or their GP.

Special populations:

Diabetes and pregnancy

Steroid administration in pregnancy may cause transient hyperglycaemia or result in increased levels of hyperglycaemia in those with gestational diabetes mellitus or pre-existent diabetes. If blood glucose readings remain high this can have adverse outcomes for the mother and foetus and this is true for women with pre-existing diabetes and in gestational diabetes (23). The majority of steroid use in pregnancy will be two single doses of betamethasone administered intramuscularly to promote foetal lung maturity at birth. Various strategies have been used to manage significantly raised blood glucose in women given betamethasone and these include the use of a variable rate intravenous insulin infusion, continual insulin systems (CSII) or titration of existing insulin regimens. There is no clear evidence as to which method is the most effective.

The following options are recommended in women on oral treatment and/or single or multiple daily insulin:

Variable rate intravenous insulin infusions (VRIII)

- VRIII - Urea and electrolytes (U&Es) should be checked prior to starting a VRIII and repeated daily to monitor fluid balance and electrolyte abnormalities
- VRIII [50 units human soluble (Humulin S) insulin or Actrapid insulin made up to 50 ml with 0.9% NaCl] should be started with the first dose of steroids
- The VRIII may be needed for up to 24 h after the administration of the last dose of steroids
- Basal insulin should be continued as usual. Pre-meal boluses insulin can be stopped even if the woman is eating and drinking, if it is preferable to keep the insulin regimen simple. Many women and diabetes pregnancy specialists prefer to continue to use both pre-meal and basal insulin, particularly in a Type 1 diabetes pregnancy
- Capillary blood glucose should be checked hourly, aiming to keep it within the target range of 4.0–7.8 mmol/L
- Prescribe 0.9% NaCl with 5% glucose and 0.15% KCl (20 mmol/l) or 0.3% KCl (40 mmol/l) as the substrate fluid to run alongside the VRIII to avoid hypoglycaemia, hyponatraemia and hypokalaemia
- The rate of substrate infusion should take into account the volume status (typically 50 ml/h). Fluids, particularly those containing dextrose, may have to be restricted in women with or at risk of hyponatraemia. In some cases, VRIII without substrate fluids may have to be used (difficult I.V. access, fluid overload states, pre-eclampsia). Additional I.V. fluids may be needed if the woman is not eating or drinking adequately. Senior medical/obstetric staff should be consulted as needed

Women using CSII during steroid treatment

- Women on CSII may be able to safely maintain glycaemic control following steroid administration by use of correction boluses and temporary basal rate increases
- In general, an increase in total daily insulin doses of ~ 40–50% is needed
- If optimal glycaemic control cannot be achieved (e.g. two consecutive blood glucose readings >7.8 mmol/L), VRIII can be considered
- The specialist antenatal diabetes team should always be involved (23)

Use in people undergoing chemotherapy

Individuals with pre-exiting diabetes are at increased risk for developing several cancers, possibly due to shared risk factors (24). It is estimated that 20% of cancer patients have concurrent diabetes (25). People with cancer are also at an increased risk of developing new onset diabetes or hyperglycaemia, independent of an underlying diagnosis of diabetes, as well as worsening control of their pre-existing diabetes (26).

Steroids are commonly used in advanced cancer as they help control symptoms in palliative care, and also have an antiemetic effect when used as part of a chemotherapy regimen (27). It is recommended that individuals under the care of oncology teams have their baseline HbA1c and venous plasma glucose when starting steroid therapy. Glucose targets for this population are in line with JBDS existing clinical inpatient targets, allowing for a range of 6-12mmol/L as is the management of hyperglycaemia.

If blood glucose readings remain suboptimal despite diabetes treatment, a referral should be made to the diabetes specialist team or GP depending on where care is delivered.

Various chemotherapy regimens are used in this population depending on the type of cancer and the individual's specific clinical needs. It is important that people undergoing treatments and associated courses of steroids are taught how to manage hyperglycaemia at these times.

Dexamethasone and COVID-19

In March 2020, the World Health Organisation (2020) declared that COVID-19 was a pandemic infection (28). Many studies were done to try to see which, if any, drugs could help people with the infection. The Recovery Trial in 2020 brought new hope of an effective steroid treatment in those inpatients with 'severe COVID-19' (5). The severity of COVID-19 was defined as shown in Table 6.

Table 6. Severity of severity of COVID-19

Critical COVID-19	Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock or other conditions that would normally require the provision of life-sustaining therapies, such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy
Severe COVID-19	Defined by any of: • oxygen saturation < 90% on room air • respiratory rate > 30 breaths per minute in adults and children > 5 years old; ≥ 60 in children less than 2 months; ≥ 50 in children 2–11 months; and ≥ 40 in children 1–5 years old. • signs of severe respiratory distress (i.e., accessory muscle use, inability to complete full sentences; and in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs
Non-severe COVID-19	Defined as absence of any signs of severe or critical COVID-19

Dexamethasone 6mg administered once daily, either orally of intravenously, for up to 10 days compared with usual care significantly reduced 28-day mortality. The dose of 6mg of dexamethasone is equivalent to 40mg of prednisolone.

At the time of publication of this guideline, the proportion on inpatient with pre-existing diabetes or the number who may have subsequently developed steroid induced diabetes had not been reported.

The management of hyperglycaemia

In November 2020, The Association of British Clinical Diabetologists published specific information on how to manage inpatients with COVID-19; this included the discontinuation of metformin due to the risk of lactic acidosis, as well as discontinuing the use of SGLT2 inhibitors due to an increased risk of diabetic ketoacidosis (DKA) (12). It is acknowledged that COVID-19 increases insulin resistance and impairs insulin production, which can result in hyperglycaemia and life threating DKA in people with diabetes and even in people not known to have diabetes. Conversely, steroid therapy impairs glucose metabolism and is the commonest cause of life threatening inpatient Hyperosmolar Hyperglycaemic State (HHS). Glucose concentrations above **10.0 mmol/L** have been linked to increased mortality in people with COVID-19. Sulphonylureas are **NOT** recommended in this context as beta cell function may be impaired and insulin resistance is likely to be severe. Other information is included on glucose management using various insulin regimens (12).

Discharge planning in COVID-19 inpatients

Specific advice is issued around discharge planning and this states that:

- Once steroids are discontinued insulin resistance and consequently insulin requirements usually fall gradually requiring a gradual reduction in insulin requirements. However, in people with COVID-19 a faster and a more aggressive reduction in insulin dose may be necessary
- From the first day, the total insulin dose may need to be reduced by as much as 50% guided by 'pre-steroid' insulin requirements. Subsequent insulin dose changes should be guided by 6 hourly glucose monitoring and input from the diabetes specialist team

Follow up

- Diabetes precipitated by COVID-19 infection and dexamethasone treatment - normoglycaemia may occur after discontinuing dexamethasone without the need for ongoing diabetes therapy
- Up to a third of people may later develop diabetes so annual screening for diabetes using HbA1c needs to be in place
- People with known diabetes - these individuals will need close support and surveillance following discharge. The discharge guidelines and patient information leaflet produced by Diabetes UK and ABCD are available for download (29)

End of life care

People with diabetes at the end stages of life have a unique set of clinical needs (14). Steroid therapy is frequently used in palliative care for symptom control, usually as dexamethasone or prednisolone. Regardless of the indication, the impact of steroids on glucose control can cause additional hyperglycaemic symptoms.

Once daily steroid therapy

This can be managed by morning administration of a sulphonylurea, (e.g. gliclazide) or morning isophane insulin (e.g. Insulatard, Humulin I or Insuman Basal).

Twice daily steroid therapy

This may include splitting higher doses of dexamethasone. If so, seek advice from the diabetes specialist team as it is likely that hyperglycaemia is likely to be persistent throughout the day and that more intensive insulin regimens will be required such as a basal bolus regimen.

Twice daily gliclazide or isophane insulin

This can be effective but there is a risk of early morning hypoglycaemia and care must be taken in adjusting doses with that risk in mind. If hypoglycaemia is a concern, once daily insulin glargine, insulin degludec, or insulin detemir given in the morning may be a safer, less complex regimen - in particular for those new to insulin. Early discussions with the diabetes specialist team can assist in choosing the most appropriate diabetes treatment regimens for the steroid used.

Short-term courses (less than 3 days) of steroids

This may only require closer blood glucose monitoring but longer courses will require a review of glucose-lowering therapy and may result in a switch from oral agents to insulin. In this situation, it may be necessary to use frequently (3-4 times per day) injections of fast or short acting analogue insulin. Discuss a plan with the local diabetes specialist team so that individual clinical needs can be taken into account.

In those without a pre-existing diagnosis of diabetes prior to the commencement of steroids, blood glucose monitoring, and person-centred and carer education should be undertaken in alignment with principles outlined within this document. Liaison with a community dietitian may assist in meal planning. Blood glucose targets at the end of life may differ from those traditionally given. Glucose concentrations should be targeted between 6mmol/L and 15mmol/L, though targets should be individualised, and the individual's wishes considered.

Summary

The use of glucocorticoid steroids is becoming more widespread. Use of these medications can impact adversely on glycaemic management in those individuals living with diabetes and others without a previous diagnosis of diabetes. Surveillance is required in both populations to mitigate against the harmful effects of hyperglycaemia. Glycaemic targets differ in certain populations and healthcare professionals are required to consider this when treating these individuals. Following a hospital admission care must be taken to ensure the safety of individuals when steroid doses are lowered to reduce the risk of hypoglycaemia in those treated with sulphonylureas, meglitinides or insulin. Screening needs to be in place in the community setting for people treated for hyperglycaemia but not previously known to have diabetes.

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