Diabetes UK Position Statements

Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care group

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Abstract

Glucocorticoids (steroids) are widely used across many medical specialities for their anti-inflammatory and immunosuppressive properties. However, one of their major side effects is the development of hyperglycaemia. It is well recognized that high glucose levels in people with diabetes in hospital are associated with harm and increased lengths of hospital stay. The use of glucocorticoid (steroid) treatment in people with pre-existing diabetes will undoubtedly result in worsening glucose control, and this may be termed ‘steroid-induced hyperglycaemia’, and will warrant temporary additional, and more active, glycaemic management. A rise in glucose may occur in people without a known diagnosis of diabetes, and this may be termed ‘steroid-induced diabetes’. There is a lack of evidence to guide how people with hyperglycaemia should be managed, and much of the guidance given here is a consensus based on best practice collated from around the United Kingdom. Where evidence is available, this is referenced. These guidelines on the management of people with diabetes treated with steroids has been adapted specifically for Diabetic Medicine. The full version of the guidelines can be found online at: www.diabetes.org.uk/joint-british-diabetes-society or https://abcd.care/joint-british-diabetes-societies-jbds-inpatient-care-group.


Introduction

This guideline aims to help in the management of hyperglycaemia in people given glucocorticoids (hereafter called steroids) in hospital and following discharge.

Recent evidence suggests that the prevalence of steroid use in hospital inpatients may be in excess of 10% [1]. Data from the 2017 National Inpatient Diabetes Audit (NaDIA), showed a diabetes prevalence of up to 30% in people in hospital, with a mean prevalence of 18% [2]. Previous work has shown that 40% of steroid use is for respiratory disease, with most of the rest being for musculoskeletal and cutaneous diseases and conditions requiring immunosuppression. Most steroid use is for < 5 days, but 22% of use is for > 6 months and 4.3% is for > 5 years [3].

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’, and will warrant temporary additional, and more active, glycaemic management.

A rise in glucose may occur in people without a known diagnosis of diabetes; this may be termed ‘steroid-induced diabetes’. This may or may not resolve when the steroids are withdrawn. Steroids may be administered as a single high dose for a defined period, and perhaps titrated down slowly. Steroid treatment can also be used as a maintenance therapy, for a prolonged period, at a high dose, for example, when a malignan tumour is identified or at the end of life and they may be given intravenously.

The management of adrenal suppression due to long-term steroid use is beyond the remit of this guideline and advice on how to do manage this condition should be sought from local endocrine services.

There is a paucity of evidence to guide how people with hyperglycaemia related to steroid use should be managed, and thus much of the guidance given here is a consensus
What’s new?

- This guideline aims to help in the management of hyperglycaemia in people given glucocorticoids as a hospital inpatient, and following discharge.
- The prevalence of steroid use in hospital inpatients may be in excess of 10%.
- There is a lack of evidence to guide how these people should be managed, and the guidance given here is a consensus based on best practice.
- The guideline suggests treatment algorithms and audit standards for benchmarking the management of steroid-related hyperglycaemia.

Table 1: Relative potency and half-life of commonly used steroids

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Potency (dose equivalent)</th>
<th>Duration of action (half-life in h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>25 mg</td>
<td>8</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5 mg</td>
<td>16–36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4 mg</td>
<td>18–40</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75 mg</td>
<td>36–54</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.75 mg</td>
<td>36–54</td>
</tr>
</tbody>
</table>

Glucocorticoid therapy – impact on blood glucose

Glucocorticoids may be administered using various regimens and at variable dosages. A single daily dose of glucocorticoid (e.g. prednisolone) in the morning may be the most common mode of administration. In those who are susceptible, this will result in a rise in blood glucose by late morning that continues through to the evening. Overnight, the blood glucose generally falls back, often to baseline levels by the next morning. Thus, treatment should be tailored to treating the hyperglycaemia, while avoiding nocturnal and early morning hypoglycaemia. In pregnancy, and other situations, a single dose of glucocorticoid may be administered, the effects of which may be temporary or more prolonged.

Whereas most people receive once daily glucocorticoids, for those on more complex regimens, the principles laid out in the guidelines will require adaptation. Multiple daily doses of glucocorticoid, be it intravenous hydrocortisone or oral dexamethasone, may cause a hyperglycaemic effect throughout the 24-h period. Individuals may need to be started on twice-daily pre-mixed or basal bolus insulin regimens 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.

Glucose levels can be expected to rise ~ 4–8 h after the administration of oral glucocorticoids, and ~ 5 h after the administration of intravenous glucocorticoids. Again, capillary blood glucose (CBG) monitoring is paramount to guide appropriate therapeutic interventions. Conversely, glucose levels may improve to pre-glucocorticoid levels 24 h after intravenous glucocorticoids are discontinued. If oral glucocorticoids are weaned down over several weeks, glucose

Table 2: Risk factors for those at risk of hyperglycaemia with steroid therapy

- Pre-existing Type 1 or Type 2 diabetes
- A family history of Type 2 diabetes
- Previous gestational diabetes
- Previous impaired fasting glucose or impaired glucose tolerance
- Polycystic ovarian disease and/or obesity
- Ethnic minority groups
- History of hyperglycaemia with steroid use

trans-repression of pro-inflammatory proteins [4,5]. Glucocorticoid administration also modulates carbohydrate metabolism via complex mechanisms, including effects on β-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 (Table 2). It should be noted, however, that acute illness may result in ‘stress hyperglycaemia’ independent of glucocorticoid administration [6].
levels may decline in a dose-dependent fashion, but this may not always occur, particularly in those with pre-existing or previously undiagnosed diabetes.

Glucose targets

In line with other Joint British Diabetes Societies (JBDS) for Inpatient Care documents, the recommended glucose target level for those in hospital is 6–10 mmol/l, accepting a range of 4–12 mmol/l. However, certain groups do not require such tight control (e.g. those at the end of life) and others who may be severely disabled by a hypoglycaemic event, for example, people with dementia, the confused, the frail older person, people at risk of falling or those with variable appetite and/or dietary intake. Individualized targets and an appropriate care plan should be documented when hyperglycaemia is first identified, mindful of the symptoms associated with uncontrolled hyperglycaemia.

Blood glucose monitoring

At the commencement of steroid therapy, CBG testing should be initiated. The timing and frequency of testing are dependent on the results of initial testing. These are shown in Table 3.

Treatment of steroid-induced diabetes

Once-daily steroid treatments – non-insulin therapies

Algorithm 1 (Doc S1) outlines the treatment regimen for steroid-induced diabetes. Non-insulin therapies such as sulfonylureas, which promote insulin release from the pancreatic β-cell, given once daily in the morning may best manage the glucose excursion associated with a once-daily oral steroid. Intuitively, pioglitazone may seem an appropriate choice for the management of steroid-induced hyperglycaemia. However, the evidence base for the use of pioglitazone above other treatments described within this guideline is weak [7]. Pioglitazone may also take a number of weeks to have a maximal effect. However, once-daily pioglitazone is an option providing there are no contraindications such as heart failure, macular oedema, risk of fractures, bladder cancer or unexplained macroscopic haematuria [8–10]. There is currently no evidence to support the use of glucagon-like peptide (GLP)-1 receptor agonists, dipeptidyl peptidase (DPP)-4 inhibitors or sodium-glucose co-transporter (SGLT)-2 inhibitors in these circumstances.

Insulin therapies

Morning administration of basal human insulin (e.g. Humulin I®, Insuman Basal® or Insulatard®) may closely fit the glucose excursion induced by 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 level, although dose increments of up to 40% have been shown to be required in some individuals [11]. Basal analogue insulin may be appropriate if hyperglycaemia is present throughout the day and into the evening, although care should be taken to identify and protect against hypoglycaemia. However, in hyperglycaemia overnight and in the early morning if these insulin (e.g. insulin glargine, insulin detemir or insulin degludec) are used in this context.

Multiple doses of steroid treatments

Multiple doses of oral or intravenous steroid will likely result in hyperglycaemia throughout the day and night. In these circumstances it is likely that subcutaneous insulin using a multiple daily injection regimen, will be the most appropriate choice to achieve glycaemic control in the event of hyperglycaemia for the majority of people – although the involvement of the local inpatient or community diabetes team is recommended. Consequent titration of the insulin dose will allow maintenance of glucose control in the face of increasing or decreasing steroid dose (see Algorithm 1; Doc S1).

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

**Treatment of steroid-induced hyperglycaemia (Algorithm 2; Doc S1)**

**Type 2 diabetes**

*For non-insulin-treated individuals*

If the person is on gliclazide, the morning dose should be increased in 40 mg increments to a maximum dose of 240 mg, with the total daily dose not exceeding 320 mg. Temporary addition of basal human insulin may be indicated, given in the morning, as discussed previously. Titration of metformin may also be beneficial.

*For insulin-treated individuals*

For those using a basal insulin only, consider switching to morning administration and increase dose in 10% increments every 24–48 h, in line with results of CBG monitoring.

For those using a twice-daily pre-mixed insulin regimen, a 10% increase in the morning insulin dose should be considered every 24–48 h.

For those using a multiple-dose regimen, an increase in lunch and evening meal short-acting boluses may be appropriate.

The person should be monitored closely for early morning hypoglycaemia if a basal analogue insulin is used.

**Type 1 diabetes**

Titration of insulin is indicated to maintain glucose control to target levels. Diabetes inpatient specialist nurses, outpatient diabetes specialist nurses or community diabetes teams should be involved.

For those using a twice-daily pre-mixed insulin regimen, a 10% increase in the morning insulin dose should be considered every 24–48 h.

An increase in lunch and evening meal short-acting bolus insulin dose may be warranted if a basal bolus regimen is utilized (see treatment Algorithm 2; Doc S1).

**Hospital discharge**

After discharge on steroid therapy, a clear strategy for the management of hyperglycaemia or potential hyperglycaemia, and the titration of therapy to address the hyperglycaemia, should be communicated to the community diabetes team, general practitioner (GP) or community diabetes specialist nurses.

Individuals commenced on insulin in hospital and discharged after a short stay with the intention of continuing high-dose steroids should receive education with regard to the risk of hyperglycaemia. The person should be trained in self-monitoring of CBG and test once daily in the late afternoon or evening. If a CBG in excess of 12 mmol/l is recorded, then testing should be increased to four times daily – usually before meals and before bedtime. If two CBG readings exceed 12 mmol/l within a 24-h period, then treatment Algorithms 1 or 2 (Doc S1) should be followed.

On hospital discharge, should the steroid dose remain above 5 mg prednisolone, or equivalent, for a protracted period, and the person with diabetes is treated with insulin, then the CBG should be checked at least once daily and also prior to driving. If the steroid dose is being titrated upwards, the CBG should be tested at least daily, and if a reading exceeds 12 mmol/l, then testing should be increased to four times daily – usually before meals and before bedtime. If two CBG readings exceed 12 mmol/l within a 24-h period, then Algorithms 1 or 2 (Doc S1) should be followed.

If steroids are discontinued prior to discharge, and hyperglycaemia persists, then CBG testing should be continued on discharge until normoglycaemia returns or until a definitive test for diabetes is undertaken (i.e. a fasting glucose or HbA1c) at the appropriate time. As the steroid dose is reduced or withdrawn, CBG testing should continue to monitor for continued hyperglycaemia, and to guide insulin or sulfonylurea dose reduction in order to avoid hypoglycaemia.

If steroid treatment is ceased in hospital and CBG tests are within the normal range, then post-discharge CBG testing is not recommended. A definitive test for diabetes should still be undertaken.

Given the recent hyperglycaemia, the use of HbA1c as a screening tool to diagnose diabetes should be delayed for 3 months following steroid cessation. A fasting glucose, or oral glucose tolerance test (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 diabetes follow-up for the people described in this guideline. This will require tight 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 would be appropriate for all those at risk of hyperglycaemia (as shown Table 2), and those who are expected to remain on steroids for a protracted period to be provided with a glucose meter and instructed on how to check their CBG. (An example of an information leaflet given to people found to have a raised glucose is shown in Appendix 1.)

If glucose readings are persistently > 12 mmol/l, i.e. on two occasions within 24 h, then the person should consult the clinician who commenced the steroid. Alternatively, if agreed locally, the GP should be seen to consider the algorithm for their further management. This potentially
includes the commencement of a sulphonylurea or optimization of existing oral non-insulin or insulin therapies.

**Steroid treatment in pregnancy**

As in other situations, steroid administration in pregnancy may cause transient hyperglycaemia, or result in increased levels of hyperglycaemia in those with gestational diabetes mellitus (GDM) or pre-existent diabetes.

The majority of steroid use in pregnancy will be two single doses administered intramuscularly to promote foetal lung maturity at birth.

This will require CBG monitoring at regular intervals – we suggest four times daily. The duration of this testing will depend on whether the steroid doses are single or multiple.

If the CBG is > 12 mmol/l on consecutive readings treating the hyperglycaemia should be considered.

If the person is already on insulin, the doses may need to be increased significantly by 40% or more at the time of the first steroid injection, for a period of 24–72 h. The diabetes team should always be involved in the management of such people.

**Cessation of steroid or reduction in dose**

When insulin or sulphonylureas have been introduced to manage hyperglycaemia induced by steroids, and the steroid dose is reduced, or withdrawn, there will be a significant risk of hypoglycaemia if the insulin dose or sulphonylurea is not reduced in line with blood glucose monitoring. The advice would therefore be for the person to be educated in regard of the risk of hypoglycaemia, and that the insulin or sulphonylurea doses are titrated according to capillary blood glucose readings which should continue in line with the advice within this guideline as the steroid dose reduces and/or ceases.

**Steroid treatment in end of life care (Algorithm 3; Doc S1)**

People with diabetes at the end stages of life have a unique set of clinical needs and glycaemic targets will be different because treatment will focus on symptomatic relief. Blood glucose targets in end of life differ from those traditionally given. Glucose levels should be targeted at no lower than 6.0 mmol/l and no higher than 15 mmol/l [12]. Steroid therapy is often 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 taken in the morning tends to cause a late afternoon or early evening rise in glucose levels which can be managed by a morning sulphonylurea (e.g. gliclazide) or morning isophane insulin (e.g. Insulatard®, Humulin I® or Insuman Basal®). If steroids are to be given twice daily, for example, splitting higher doses of dexamethasone, it will be necessary to recommend an alternative approach to setting times, for testing glucose levels, and for managing the impact on blood glucose.

Twice-daily gliclazide or isophane insulin 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 (e.g. insulin glargine, insulin detemir or insulin degludec) given in the morning may be a safer, less-complex regimen, especially for those new to insulin. Early discussions with the diabetes specialist team can assist in choosing the most appropriate hypoglycaemic treatment regimens for the steroid utilized.

Short-term courses (< 3 days) of steroids may only require closer 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 latter situation, an insulin regimen (e.g. Humulin I®, Insulatard® or Insuman Basal®) given once daily should be considered. In those without a diagnosis of diabetes prior to the commencement of steroids, then CBG monitoring and education for the person and their carer should be undertaken in alignment with principles outlined within this guideline. Liaison with a community dietitian may assist in meal planning [12].

**Controversial areas**

**Assessment of hyperglycaemia following cessation of steroids**

Steroid treatment may be ceased quickly following a short course, or the dose reduced slowly over days or weeks. Those who have received high dose steroids (i.e. > 5 mg prednisolone or its equivalent – see Table 1) for 2 weeks or longer may be at risk of adrenal suppression and clinicians should be aware of this when assessing such individuals. The management of adrenal suppression due to long-term steroid use is beyond the remit of this guideline and advice on how to do this correctly should be sought from the local endocrine service.

Steroid-induced diabetes should resolve as the steroid dose reduces and stops. However, a proportion of people who were found to be hyperglycaemic on steroid therapy will have had pre-existing Type 2 diabetes. Steroids may reveal a propensity towards Type 2 diabetes, and diabetes may persist following cessation of steroid therapy. A fasting glucose or OGTT 6 weeks after cessation of steroid therapy may indicate the continued presence of diabetes. Utilizing HbA1c in this context will be confounded by the recent hyperglycaemia, thus should an HbA1c be used to confirm the diagnosis of diabetes following an episode of steroid induced diabetes, the test should be undertaken not less than three months following steroid cessation.

**Hospital discharge**

Currently, there is little planning for the discharge of those commenced on steroids with no history of hyperglycaemia.
This guideline sets out a framework which ensures that steroid-induced diabetes is identified, monitored and treated. Although this involves resources to educate patients and carers and the use of monitors and test strips, the benefits of reduced crisis management and potential avoidance of hospital admission and outpatient referral, offsets the initial investment of resources. People with diabetes on steroids who are discharged from hospital require co-ordinated and pragmatic discharge planning and an ongoing care plan. General practices should be informed of the discharge and the care plan communicated.

Where present, the community diabetes team may facilitate the discharge and provide input into ongoing diabetes care. Alternatively, the GP surgery may take responsibility for the person with diabetes and ongoing diabetes care, with support from the hospital or community diabetes team. The person with diabetes and carers should be actively involved in the preparation of the care plan and provided with written instructions and educational material regarding the management of hyperglycaemia, CBG testing and actions in the event of hyperglycaemia. If necessary a ‘hot review’ in a hospital, or community-based diabetes clinic 1–2 weeks following hospital discharge, could be considered.

Newer agents

There is little evidence for the use of GLP-1 receptor agonists or SGLT-2 inhibitors in the management of steroid-related diabetes. DPP-4 inhibitors have been studied in a small number of people in hospital [13], although not specifically for use in people with steroid-induced diabetes. Given the relative lack of evidence to assure the efficacy and safety of the newer pharmacotherapies of those in hospital, we do not recommend their use within this guideline. We welcome emerging evidence that may lead to a change in practice in this area.

Human insulin is recommended within this guideline because its pharmacokinetic profile may be best suited to the profile of hyperglycaemia associated with once-daily steroid administration. However, if steroids are administered in multiple doses then hyperglycaemia may persist throughout the day and basal analogue insulin may be most appropriate. Changes in insulin should be discussed with the diabetes inpatient specialist nurse, diabetes specialist nurse or diabetes inpatient team.

Collaborators

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Competing interests

None declared.

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References


Supporting Information

Additional Supporting Information may be found in the online version of this article:


Appendix

Audit standards

People treated with steroids appropriately screened for hyperglycaemia with capillary blood glucose (CBG) – 90%.

- People with steroid-induced hyperglycaemia with adequate glucose control (CBG not > 12 mmol/l on two consecutive occasions) – 75%.
- People discharged from hospital with an appropriate diabetes discharge plan – 100%.
- People with steroid-induced diabetes, appropriately screened for diabetes – 75%.
- People at end of life managed appropriately on end-of-life steroid-induced diabetes pathway – 75%.

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