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Short-term glucocorticoid-related side effects and adverse reactions: a narrative review and practical approach

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Summary

Glucocorticoids are the mainstay treatment of a variety of inflammatory and autoimmune disorders. Unfortunately, metabolic side effects, drug interactions and adverse reactions commonly lead to glucocorticoid-related side effects, thereby compromising their intended anti-inflammatory and immunosuppressive effects. The goal of this review is to help clinicians to monitor the broad spectrum of side effects of short-term systemic glucocorticoid administration, defined as glucocorticoid treatment shorter than 30 days. We review the various systems affected, with a focus on metabolic conditions and hyperglycaemia management.

Introduction

In 1948, cortisone was used for the first time in a patient with rheumatoid arthritis with impressive clinical benefits, and in the following decade synthetic steroids were introduced for anti-inflammatory therapy [1]. Since then, a myriad indications for glucocorticoids have been discovered, including rheumatological, cardiopulmonary, neurological, haematological and multisystem disorders, as well as the treatment of inflammation in some infections and sepsis. However, it soon became clear that undesirable detrimental effects are also pleiotropic, occasionally difficult to distinguish from the underlying disease. Short-term glucocorticoid side effects tend to be overlooked, whereas long-term administration of glucocorticoids is notorious for the occurrence of lipodystrophy, osteoporosis and osteonecrosis, skin thinning, cataract or glaucoma. Nevertheless, even in the modern era of biologicals the use of glucocorticoids is still very common. In a general medicine ward of a tertiary hospital, 11% of the patients received high-dose glucocorticoids for at least 2 days [2]. As a matter of fact, glucocorticoids were the third most common specific cause of adverse drug events in hospitalised patients in the US in 2011, at a rate of 57 per 10,000 discharges [3]. Notwithstanding, the literature addressing the management of glucocorticoid-related adverse events in the hospital setting is scarce. We therefore conducted a review to elucidate in adults the most expected systemic (oral and parenteral) glucocorticoid-related side effects and adverse reactions occurring for a treatment not exceeding 30 days, in order to suggest the most appropriate management.

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Methods

A PubMed search (1990 to January 2020) was conducted using the following keywords: glucocorticoid, corticosteroid, steroid, in combination with hyperglycaemia, diabetes, metabolic, gastrointestinal haemorrhage/bleeding, hypernatraemia, fluid retention, atrial fibrillation/flutter, cardiovascular, hypertension, secondary infection, myopathy, neutrophilia, leucocytosis, (neuro)psychiatric, inpatient, hospitalised, side effects, adverse event/effect, risk/impact, management; we also reviewed the literature citations. The resulting literature about systemic (oral and parenteral) glucocorticoid use in adults (>18 years old) was reviewed to sort information on short-term side effects and adverse reactions, defined as occurring after less than a month of treatment (<30 days); topical and inhaled glucocorticoids were not covered.

Short overview of the mechanism of action of glucocorticoids

Cortisol is a steroid hormone crucial to preparing the metabolism for fight-or-flight responses. This physiological response to stressful stimuli is the result of a well-coordinated sequence of hormonal changes and physiological responses with a potentially deleterious effect in case of overreaction.

Synthetic glucocorticoids mimic the effect of endogenous cortisol. As a nuclear hormone, they diffuse passively across the cell membrane, bind the intracellular glucocorticoid receptor to form the synthetic glucocorticoid-glucocorticoid receptor complex and translocate into the nucleus to regulate the transcription of target genes. The therapeutic effects of glucocorticoids are mediated in three ways: (1) direct transactivation with the binding of the glucocorticoid-glucocorticoid receptor complex on glucocorticoid-responsive elements; (2) direct transrepression (mediated via glucocorticoid-responsive elements); and (3) via

transrepression of other transcriptional factors including nuclear factor "kappa-light-chain-enhancer" of activated B-cells (NFκB), activator protein-1 (AP-1) and signal transducer and activator of transcription 3 (STAT3), well-known mediators of the expected anti-inflammatory effects of synthetic glucocorticoids. The consequences of the supraphysiological transactivation and transrepression of many other genes are responsible for glucocorticoid-related metabolic side effects. Glucocorticoids can also trigger within minutes a non-genomic response through direct physiochemical interaction with the cell membrane [4]. Consequently, intensive research has been conducted to identify synthetic glucocorticoid candidates able to preferentially induce tethered transrepression and be devoid of the other responses.

Synthetic glucocorticoids also bind to the mineralocorticoid receptor, with a higher affinity than to the glucocorticoid receptor. But whereas glucocorticoid receptors are widely expressed in most cell types of the organism, the expression of mineralocorticoid receptors is restricted to epithelial cells in the kidney, colon and salivary glands, and non-epithelial cells in the brain and heart. Table 1 shows the relative glucocorticoid and mineralocorticoid activity of the synthetic glucocorticoids.

The prescription of synthetic glucocorticoids is mostly driven by their potent anti-inflammatory properties, which occur only at supraphysiological levels. Consequently, there is an intrinsic risk of glucocorticoid side effects, which are directly related to treatment duration and dosage, and may not reverse after drug cessation; side effects are defined as all the disorders resulting from the intended use of systemic glucocorticoid preparations responsible for possible toxicity, drug interactions and metabolic effects. It is therefore essential for clinicians to carefully assess all the systems potentially impacted by therapeutic glucocorticoids.

Hypothalamic-pituitary-adrenal axis suppression

The most common cause of adrenal insufficiency is glucocorticoids treatment. The synthetic hormone produces a negative feedback on the hypothalamus and pituitary gland. Short-term therapy may suppress the release of corticotropin-releasing hormone from the paraventricular nucleus of the hypothalamus and adrenocorticotropic hormone from the pituitary gland, which will stimulate the zona reticularis and fasciculata of the adrenal cortex. Prolonged exposure to exogenous glucocorticoids can lead to adrenal cortex atrophy and irreversible adrenal insufficiency, a serious and potentially life threatening adverse effect.

In 2015, a meta-analysis demonstrated that asthmatic patients treated with a glucocorticoid for less than a month (oral or intravenous) showed a percentage of adrenal insufficiency of 1.4% (95% confidence interval [CI] 0.3–7.4%), as opposed to longer treatment, with a rate of 11.9 % for less than a year and 27.4% when more than a year [6]. The risk increased with the dose, with the potency of the glucocorticoid used, and with intravenous administration. Whatever the glucocorticoid duration, adrenal insufficiency should be thoroughly evaluated in the event of nausea, vomiting, abdominal cramps, diarrhoea, fatigue, weakness, dizziness, weight loss and depression [7].

Body composition, adipose tissue and muscle

From the first dose, glucocorticoid increases appetite and craving for highly palatable food (high-caloric, high-fat food). This adaptive mechanism is supposed to help to replace the energy lost in facing a stressful situation [8]. Over time, it can result in weight gain, decrease in insulin sensitivity and a higher risk of glucocorticoid-induced type 2 diabetes.

Glucocorticoid effects on adipose tissue are complex. In the fasting state, endogenous glucocorticoids ensure that adipocytes adapt the lipolysis rate in response to epinephrine and glucagon to fuel the needs of the organism [7–10]. Exposure to synthetic glucocorticoids promotes hydrolysation of triglycerides to glycerol and fatty acids in white adipose tissue, resulting in dyslipidaemia, hepatic steatosis and insulin resistance. For a long time, this phenomenon was considered the permissive effect of glucocorticoids responsible for the transactivation of the genes encoding triglyceride lipase and hormone-sensitive lipase. Recently, it has been shown in rodents, that glucocorticoids exert a direct lipolytic action in a dose- and time- (4–8 h) dependent manner, as well as a permissive effect in response to various hormones [11]. The results are an increase in serum free fatty acids and triglycerides, which accumulate within muscle cells and reduce glucose uptake by interfering with insulin signalling [12]. In the long term, glucocorticoid effects on adipose tissue can lead to lipodystrophy.

In skeletal muscle, glucocorticoids decrease the rate of protein synthesis and increase the rate of protein breakdown, by inhibition of insulin-like growth factor-1, and several other mechanisms. Glucocorticoids have been shown to

Table 1:
Relative potencies and equivalent doses of common glucocorticoids.

Corticosteroid	Relative anti-inflammatory activity	Relative mineralocorticoid activity	Equivalent dose (mg)	Biological half-life (hours)
Cortisone	0.8	0.8	25	8–12
Hydrocortisone (cortisol)	**1.0**	**1.0**	**20**	**8–12**
Prednisone	4.0	0.8	5	12–36
Prednisolone	4.0	0.8	5	12–36
Triamcinolone	5.0	0.0	4.0	12–36
Methylprednisolone	5.0	0.0	4.0	12–36
Betamethasone	25.0	0.0	0.75	36–54
Dexamethasone	25–30	0.0	0.75	36–54
Fludrocortisone	10	125	–	18–36

Adapted from Asare [5]

decrease the size of the muscle fibres, particularly the fast twitch type II fibres, with little effect on the type I fibres [12]. This can lead to a steroid myopathy, which causes weakness and, rarely, myalgia. There is no single diagnostic test for the condition. Muscle enzymes are often normal (but a peak in the acute phase can occur), study of muscle biopsy shows only non-specific atrophy of type II fibres, and electromyography may be either normal or reveal decreased amplitude of muscle action potential. The classic pattern is progressive proximal limb weakness, more commonly symmetric, painless and predominantly affecting pelvic girdle muscles. Chronic myopathy may lead to proximal amyotrophy [13]. However, steroid myopathy can also involve bulbar and respiratory muscles. Steroid myopathy can occur at the beginning of glucocorticoid treatment, or when it is intensified; the symptoms increase with the dose and duration of treatment [14]. Old age, malnutrition, immobilisation, cancer and a prior muscle disease may all increase the risk. It is more frequent with the use of fluorinated glucocorticoid preparations, such as dexamethasone, betamethasone and triamcinolone [13]. It has been well described in the context of critically ill patients requiring ventilator support and receiving high doses of intravenous glucocorticoids , with a relative risk (RR) of 1.21 (95% CI 1.01–1.45) in a recent meta-analysis [15].

Moreover, some cases of acute steroid myopathy with moderate oral doses has also been described, occurring as soon as a few hours after treatment onset [16]. These cases tend to be overlooked, and the weakness attributed to the underlying illness, but are globally rare. Acute steroid myopathy is unpredictable, and should be considered when patients treated with glucocorticoids, regardless of dosage, route of administration or length of treatment, develop muscle weakness at any site. Recovery of muscle strength is variable, and glucocorticoids should be withdrawn rapidly.

Hyperglycaemia

The mechanisms behind glucocorticoid-induced hyperglycaemia are similar to type 2 diabetes. In the skeletal muscle, it interferes with the signalling cascade of the glucose transporter type 4 (GLUT4) [17], which results in a reduction of 30–50% in insulin-stimulated glucose uptake and a 70% reduction in insulin-stimulated glycogen synthesis. Glucose uptake is similarly decreased in adipose tissue. In the liver, glucocorticoids antagonise the metabolic effects of insulin, particularly in the post-prandial state, through the induction of enzymes that promote gluconeogenesis (phosphoenolpyruvate carboxykinase and glucose-6-phosphatase) [18], enhance the effects of counterregulatory hormones such as glucagon and epinephrine, and induce insulin resistance via nuclear peroxisome proliferator-activated receptor-alpha. Finally, it has been shown that glucocorticoids alter the function of pancreatic beta cells through reduction of GLUT2 and glucokinase receptor expression, increased activity of glucose-6-phosphate dehydrogenase, and reduced insulin synthesis and secretion [19]. Notably, impairment in the compensatory increase in insulin secretion has been reported with a combination of glucocorticoids and calcineurin inhibitors [18].

Clinically, doubling the plasma cortisol by an intravenous hydrocortisone infusion is associated with approximately a 50% reduction in insulin sensitivity, mediated by its complex effect on the liver, skeletal muscles and adipose tissue [20], and the effect is greater with a larger dose [21]. Thus, the ability to compensate for this decrease in insulin sensitivity with an increase in insulin secretion determines the extent of the rise in plasma glucose. In healthy subjects, glucose levels can be maintained within the normal range. However, in susceptible populations, such as normoglycaemic individuals with pre-existing reduced insulin sensitivity and a low rate of production, the compensatory increase in insulin may not be sufficient to maintain normoglycaemia. For example, a radiological study found that patients (with and without diabetes) who received oral or intravenous glucocorticoids for preparation before a radiological examination with intravenous contrast had a mean maximum change from baseline glucose of +3.7 mmol/l and +4.6 mmol/l, respectively [22].

Globally, more than 50% of hospitalised patients treated with a high glucocorticoid dosage will show multiple episodes of hyperglycaemia. The predictors are a known diagnosis of diabetes, more comorbid diseases and a longer duration of the glucocorticoid treatment, including glucocorticoid use before hospitalisation [2]. In a study of primary renal disease, the risk factors for developing glucocorticoid-induced diabetes were older age (odds ratio [OR] 1.43, 95% CI 1.07–1.91) and higher body mass index (OR 2.15, 95% CI 1.12–4.13) [23]. Notably, diabetic patients are more often prescribed glucocorticoids than non-diabetic patients [24]. Moreover, acute illness may also result in "stress hyperglycaemia" independent of glucocorticoid administration.

Glucocorticoid-induced hyperglycaemia is mediated by genomic effects and occurs later than the peak concentration of prednisone or prednisolone. When glucocorticoids are given orally, blood glucose will rise after 4 to 8 hours, with a duration of 12 to 16 hours. After intravenous glucocorticoids, the effect is to be expected after 5 hours [20]. In susceptible individuals given prednisone in a single morning dose, blood glucose will rise by late morning, remain high through to the evening and eventually fall back overnight. With dexamethasone, the effect seems to be more prolonged (more than 24 hours with a slight decline during an overnight fast). Blood glucose may return to baseline 24 hours after intravenous glucocorticoids are discontinued. The effect of glucocorticoids is normally transient and reversible. Thus, in the case of a glucocorticoid tapering, glucose levels may decline in a dose-dependent fashion. However, this may not always occur, particularly in those with pre-existing or previously undiagnosed diabetes.

Cardiovascular effects

Hypertension

Glucocorticoids exert their effects on blood pressure regulation at many different levels. Isoforms of the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD), located in steroid-responsive tissues, metabolise endogenously produced glucocorticoids. Thus, 11β-HSD limits steroid access to mineralocorticoid and/or glucocorticoid receptors, resulting in a tissue / cell type relative sensitivity to glucocorticoids. With oral synthetic glucocorticoids, a rise in

blood pressure can be seen within 24 hours, with peak blood pressure at days 4–5 [25]. This effect is not due primarily to sodium and water retention, as previously thought. In fact, synthetic glucocorticoids have a low mineralocorticoid effect (see table 1) and studies with methylprednisolone, dexamethasone and triamcinolone showed an elevation in blood pressure without evidence of plasma volume expansion [26]. Hypertension associated with glucocorticoids is rather associated with increased total peripheral resistance, mainly due to nitric oxide redox imbalance resulting in a state of NO deficiency, and increase of the oxidative stress, which potentiates the response to circulating vasoconstrictors [27]. Moreover, a number of other molecules may also play a role, such as prostanoids, angiotensin II, arginine vasopressin, endothelins, catecholamines, neuropeptide Y, 11β-HSD [28] and atrial natriuretic peptide.

In the kidney, synthetic and endogenous glucocorticoids enhance transepithelial sodium transport in the presence of 11β-HSD inhibition. Proximal tubule reabsorption of sodium can be indirectly increased after chronic exposure to glucocorticoids. Steroids increase the expression of both Na^+/K^+ adenosine triphosphatase along the basolateral membrane and the Na^+/H^+ exchanger along the apical membrane of epithelial cells in the proximal tubule. Glucocorticoids do not directly influence sodium reabsorption in the proximal tubule, but angiotensin II-stimulated sodium transport is significantly greater in proximal tubular cells pre-treated with glucocorticoids. In distal renal segments, the increased transport is more direct, but partly modulated by glucocorticoid cross-over binding to mineralocorticoid receptors [27].

In the context of septic shock, the use of hydrocortisone has been shown to cause hypernatraemia, due to its mineralocorticoid effect [27, 29] (see table 1), showing again that synthetic glucocorticoids can alter both the circulating volume and vascular resistance. Finally, in patients on long-term glucocorticoid treatment, other secondary effects may be involved, such as weight gain and diabetes. Therefore, the full extent of the pathophysiological role of synthetic glucocorticoids on blood pressure should be considered as the integration of extra-renal (cardiovascular and endocrine causes) and renal factors.

Cardiac arrhythmia: atrial fibrillation and flutter, and bradycardia

Atrial fibrillation is the most common cardiac arrhythmia associated with an increased risk of morbidity and mortality. High-dose (pulse) glucocorticoid therapy can induce atrial fibrillation, as demonstrated in several case reports [29, 30] and a Dutch nested case-control study showing a six-fold increased risk with a dose of prednisone ≥7.5 mg (OR 6.07, 95% CI 3.90–9.42) [31]. Furthermore, a large Danish population-based case-control study revealed an almost two-fold increase of atrial fibrillation or flutter and the odds were even four times higher among new users of glucocorticoids (<60 days) compared with never users [32]. In contrast, glucocorticoid use during sepsis decreased the frequency of atrial fibrillation, according to a recent meta-analysis (OR 0.5, CI 0.2–0.9) [33] and glucocorticoid administration decreased the heart rate in healthy subjects [34].

In rare cases, glucocorticoid treatment can also induce bradycardia. The onset of bradycardia may be delayed up to 7 days and is usually self-limiting upon drug discontinuation, but can be fatal if not diagnosed correctly [35].

Future studies may unravel the existence of glucocorticoid-induced hyperglycaemia as an indirect risk factor of heart failure with preserved ejection function [36], as it has been showed for people with diabetes and a high cardiovascular risk.

Gastrointestinal effects

Glucocorticoids have been linked to upper gastrointestinal bleeding, possibly because of impaired tissue healing, increased gastric acid secretion and reduced gastric mucus secretion [36], without causing direct injury to the gastric mucosa. Co-treatment with glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs) has a synergistic effect. A large, multicentre, self-controlled case series demonstrated an increase in the incidence of upper gastrointestinal bleeding of 12.8% (versus an incidence of 4.1% for corticosteroids alone) [37].

Nevertheless, their implication in gastrointestinal bleeding may not be as important as previously thought. In a 2014 meta-analysis, corticosteroids increased the odds of gastrointestinal bleeding or perforation in hospitalised (OR 1.42, 95%CI 1.22–1.66), but not ambulatory patients , when paediatric patients were excluded [38]. In the critically ill setting, a 2019 meta-analysis of double-blind randomised controlled trial found that corticosteroids only slightly increased the incidence of clinically important gastrointestinal bleeding (RR 1.26, 95% CI 1.01–1.57) but not gastrointestinal bleeding of any severity. However, the authors note that uncertainty remains, because the required amount of information had not been met, and because of the overall high risk of bias [39].

Immune system / risk of infection

Glucocorticoids affect the immune system in various ways. The binding of the glucocorticoid-receptor complex to the glucocorticoid receptor may result in either transcription enhancement or suppression of susceptible downstream genes, thereby decreasing the production of almost all known inflammatory cytokines. Glucocorticoids also have effects on post-translational events, altering the stability of the mess enger RNA of various cytokines [40].

Glucocorticoids treatment results in a reduced ability of neutrophils to adhere to vascular endothelium and to exit the circulation, leading to neutrophilia. The impaired entry to sites of infection and tissue injury results in suppression of the inflammatory response. Glucocorticoids only slightly diminish numbers of monocytes and macrophages, but strongly inhibit their phagocytic function. Glucocorticoids suppress dendritic cell maturation, altering their antigen-presenting role [4]. Lymphocytes are redistributed, causing lymphopenia, but B lymphocytes are not much affected. Another important effect of glucocorticoid therapy is eosinophil apoptosis. Overall, these cellular and molecular effects enhance the risk of infection, such as serious bacterial infections, common viral infections (mainly herpes viruses), and fungal infections (mainly *Candida* species), as soon as the first dose of glucocorticoid, and increasing

with time. Opportunistic infections and tuberculosis are more a concern in the case of long-term treatment. However, *Pneumocystis jirovecii* infection can rarely also occur with short-term use of high doses of glucocorticoids [41].

The risk of infection associated with current or recent exposure to glucocorticoids was determined in a French nested case-control study of primary immune thrombocytopenia. Glucocorticoid exposure during the month before the index date increased the odds of 2.5-fold (OR 2.48, 95% CI 1.61–3.83) and increased with the duration of treatment and dose. A dose-effect analysis showed that the risk increased starting from an average daily dose of 5 mg prednisone equivalent [42]. Moreover, a weighted cumulative dose model in rheumatoid arthritis patients showed slightly increased odds of infection (OR 1.03, 95% CI 1.02–1.11) with as little as 7 days of 5 mg prednisone, and a 2-fold increase at 3 months (OR 2.00, 95% CI 1.69–2.26) [43]. The odds also further increase with the dosage, as shown in the same study with 30 mg at 7 days (OR 1.18, 95% CI 1.13–1.86) and at 3 months (OR 4.82, 95% CI 3.12–9.29).

However, the relationship of a short course of glucocorticoids in the acute setting to an increased infection risk was not significant in a meta-analysis evaluating glucocorticoids in the treatment of severe community-acquired pneumonia (OR 1.11, 95% CI 0.14–9.13; p = 0.92) [44] and in a systematic review evaluating glucocorticoids in the context of severe sepsis and septic shock (RR 1.01, 95% CI 0.82–1.25; p = 0.92) [45]. A recent randomised trial on intraoperative use of a single intravenous dose of 8 mg dexamethasone showed no excess surgical site infections and this was true among the 13% of patients with diabetes without a significant increase in hyperglycaemic event [46].

Two recent meta-analysis about the glucocorticoids effects in patients with COVID-19 have been published . They demonstrated a mortality benefit for severely ill COVID-19 patients receiving glucocorticoids [47, 48], but the analysis cannot be extended to less severely ill patients. For this latter group, the heterogeneity of high-dose and low-dose corticosteroid regimens was too high and most studies reported only serious adverse events.

Finally, a systematic review in children (<18 years old) [49] and a large retrospective cohort study in adult outpatients [50] have shown an increase in rates of sepsis after short-term prescription of glucocorticoids . In adults, regardless of dosage, there was a 5.3-fold increase in the incidence rate of sepsis (incident rate ratio [IRR] 5.3, 95% CI 3.8–7.41; p <0.001) as well as fracture (IRR 1.87, 95% CI 1.69–2.07; p <0.001) and venous thrombo-embolism (IRR 3.33, 95% CI 2.78–3.99, p <0.001). The authors of the study also observed that the most experienced sub-specialists in glucocorticoids use were not the more common prescribers and they reported upper respiratory tract infections, spinal conditions and allergies as the most common indications for glucocorticoid prescriptions.

Neuropsychiatric effects

Psychiatric adverse effects of glucocorticoids can be unpredictable and severe. Incidences have ranged from 2% to 60%, reflecting the variability in definitions and the heterogeneity of the reported clinical situations [51]. Most reactions occur early in the course of glucocorticoid treatment (i.e., within days), and are reversible with discontinuation of the medication. Adverse effects tend to occur at higher dosages, but have been reported with doses as low as 2.5 mg prednisone. In neurons, the glucocorticoid-glucocorticoid receptor complex has been shown to translocate to the nucleus and alters neurotransmitter gene transcription, resulting in alterations in the production of dopamine and serotonin, as well as neuropeptides such as somatostatin or beta-endorphin [51].

Mood disorders, and manic and hypomanic episodes are frequent clinical presentations, and can occur as soon as the first dose of glucocorticoid, whereas depressive symptoms are typically seen after the treatment has been discontinued, or in long-term treatment. Delirium can occur at any time of the treatment. The introduction or withdrawal of glucocorticoids can aggravate or precipitate the occurrence of delirium related to other aetiologies, such as neurodegenerative disorders. Psychotic episodes have often been related to glucocorticoid treatment. However, care must be taken to precisely define the symptoms, as psychotic traits may be part of a manic episode or delirium [52].

More subclinical psychiatric effects are frequent with glucocorticoid treatment, and can be distressing to the patient if the are not warned [53]. These include: euphoria (and reduction of dysphoria), depression, mood elevation, irritability, anger, insomnia, excessive talkativeness, temporary mnemonic effects, sensory flooding and increased appetite.

Management of glucocorticoid treatment in the hospital

General considerations

In order to limit glucocorticoid-related side effects and adverse reactions the following points should be checked before prescribing a short course of glucocorticoid treatment in the hospital:

- Use of the lowest dose of glucocorticoid for the shortest period of time needed for a given indication.
- When starting a long-term treatment (>30 days), do not forget to monitor the occurrence of lipodystrophy, osteoporosis and osteonecrosis, skin thinning, cataract or glaucoma, and start preventive treatment if needed.
- Choose the right glucocorticoid for the right indication, according to its anti-inflammatory versus mineralocorticoid effect, its half-life, tissue distribution, and the time of administration (e.g. morning dose versus multiple doses).
- Careful dose adjustment in cases of hepatic or renal failure, and extreme weight.
- Avoid systemic glucocorticoids if a topical route of administration is possible (e.g., inhaled).
- Some indications may also respond to alternate day prescription.
- Review other medications, with special consideration of potential interactions (NSAIDs, anticoagulants) and CYP 3A4 inhibitors/stimulators, which can alter the

metabolism of glucocorticoids and thus increase/decrease their bioavailability (e.g., rifampicin).

– Check for underlying conditions that may increase the risk for adverse reaction (e.g., diabetes mellitus, gastric ulcer). If present, consider the benefit-risk balance of prescribing glucocorticoids
– Close monitoring of the patient's response to glucocorticoid treatment, as well as glucocorticoid side effects, in order to reevaluate the prescription when needed.
– Provide all the relevant information to the patient about the possible side effects.

We consider here the side effects and adverse reactions to be expected with "supraphysiological" doses of glucocorticoids, equivalent to a dose of 5 mg prednisolone or more (see table 1). However, some patients may develop side effects at even lower doses, so clinical vigilance is always recommended (table 2).

Management of hyperglycaemia

Screening and diagnosis

Whether hyperglycaemia occurring in the setting of short-term glucocorticoid treatment is self-limiting will remain a matter of sterile debate. The goal is to keep the glycaemia in the target range.

Indeed, extensive work has shown that hyperglycaemia during hospitalisation increases mortality, complications, length of hospital stay and healthcare costs [59].

First, awareness of the hyperglycaemic effect of glucocorticoids must be raised. In a general medicine ward in Pittsburgh, 24% of the patients with glucocorticoid treatment had not a single blood glucose measurement [2]. At particular risk of hyperglycaemia are patients with a family history or established diagnosis of diabetes, gestational diabetes, previous impaired glucose tolerance, and those who are already on glucocorticoids. It may be useful to obtain a baseline glycated haemoglobin (Hb1AC) level prior to initiating glucocorticoids in these patients.

In the setting of a single morning dose of glucocorticoid, which is the most common, checking only the fasting glucose level may miss the majority of cases of glucocorticoid-induced hyperglycaemia. Glycaemia should be determined after lunch (2 hours post-prandial) once daily in all inpatients on glucocorticoid, a strategy that offers the greatest diagnostic sensitivity [19].

If glycaemia is higher than 10 mmol/l, blood glucose should be checked four times daily. For patients with a pre-existing diabetes, testing should be started directly at four times daily (before meals and before bed). As HbA1c reflects glycaemia of the previous 3 months, it is useful only in long-term glucocorticoid treatment or to screen for pre-existing diabetes. If blood glucose is consistently over 10 mmol/l, i.e., on two occasions during 24 hours, pre-existing antidiabetic treatment should be adapted or a specific treatment initiated. The fact that 40% to 56% of all inpatient endocrinology consultations are asked for new or worsening glucocorticoid-induced diabetes underlines the importance of the issue [17].

Treatment

In line with the usual inpatient glucose targets, the treatment of glucocorticoid-induced hyperglycaemia should aim to keep blood glucose between 4 and 10 mmol/l [20]. When selecting the best treatment, the first consider-

Table 2:
Check-list of reported glucocorticoid short-term side effects and their management.

Effect	Management
Decrease of insulin sensitivity	Check for post-prandial hyperglycaemia
Hyperglycaemia	See table 3, figures 1 and 2
Hypothalamic-pituitary-adrenal axis	Withdrawal according to the disease treated
	Generally no testing needed if treatment for less than 3 weeks [54]
	Inhibition of the HPA axis may however occur [7]. Consider HPA axis testing only in case of clinical suspicion.
Body composition	Follow weight, nutrition counseling
Myopathy	Recommend physical activity, aerobic and resistance exercices
	Look for weakness on physical examination
	If glucocorticoid myopathy suspected, evaluate the pattern of decreased muscle strength and the time-course in relationship with glucocorticoid treatment
	If present, withdrawal of glucocorticoids as soon as possible, or switch to a non-fluorinated glucocorticoid [13]
Fracture	Low threshold for radiological investigations in case of suspicious symptoms [50]
Cardiovascular	Regular blood pressure and pulse rate measurement
	If hypertension, angiotensin receptor antagonists and angiotensin converting-enzyme inhibitors have been shown to be effective in this setting [25, 26].
Gastro-intestinal	A proton-pump inhibitor is not needed for every glucocorticoid prescription
	In the case of co-therapy with NSAIDs, a history of peptic ulcer, clotting impairment or mechanical ventilation for >48 hours, a proton-pump inhibitor should be added [55–57].
Immune system / Risk of infection	Rate of sepsis is increased [50]
	Symptoms and signs of infection may be attenuated, search for mycosis
	Specific prevention of infection not needed for short-term treatment
Neuropsychiatric	Psychiatric comorbidity is not a contraindication [52, 53].
	Prefer administration in the morning
	Warn the patient of potential behavioural changes [58].
	Be careful with cytochrome P450 3A4 inhibitors (such as certain anti-depressants), as glucocorticoids are substrates of CYP 3A4

HPA: hypothalamic-pituitary axis; NSAIDs: non-steroidal anti-inflammatory drugs; CYP: cytochrome P450

ation is whether to use oral anti-diabetic drugs or insulin. Then the molecule and the time of administration should be tailored to treat daytime hyperglycaemia, while avoiding nocturnal and early morning hypoglycaemia.

Oral treatment

Many patients treated with glucocorticoids have significant co-morbidities, such as renal or hepatic insufficiency, which may represent a contraindication to the majority of oral anti-diabetic molecules.

Specific studies on the effect of oral anti-diabetic molecules in the setting of glucocorticoid-induced diabetes are scarce. Sulfonylureas are effective, as they induce insulin release from pancreatic beta-cells [60]. Given once daily in the morning their pharmacokinetics are adequate to manage daytime hyperglycaemia. However, they present several limitations: a narrow therapeutic window, limited titration, and prolonged use increasing the risk of hypoglycaemia. Moreover, in several countries (including Switzerland), only the long-acting form of gliclazide is available, increasing the risk of nocturnal hypoglycaemia. Glinides may be useful in selected patients, their short duration of action decreasing the risk of hypoglycaemia [60].

Metformin may be seen as a good therapeutic option because of its direct effect on improvement of insulin sensitivity. However, there are few data supporting its use. Moreover, it may take some time to be effective, making titration in the hospital setting difficult.

There is currently no sufficient evidence to support the use of glucagon-like peptide (GLP)-1 receptor agonists, dipeptidyl peptidase (DPP)-4 inhibitors [61] or sodium-glucose co-transporter (SGLT)-2 inhibitors for glucocorticoids -induced hyperglycemia, although their mechanism of action suggest that they could be useful [19].

Parenteral treatment

Insulin can be used safely and effectively in patients with glucocorticoid-induced hyperglycaemia.

The timing of the decreased glucose tolerance (with a morning single dose of intermediate acting glucocorticoid such as prednisone) corresponds to the pharmacokinetics of basal human insulin (also called NPH or isophane insulin). The initial dose can be determined according to the glucocorticoid dose and the patient's weight (table 3) [19].

For longer acting glucocorticoids such as dexamethasone, basal analogue insulin (e.g., insulin glargine, detemir and degludec) may be used to match the longer hyperglycaemic effect, although care should be taken to identify and protect against nocturnal hypoglycaemia.

If the glyacemic goals are not achieved with basal insulin, prandial insulin can be added, to treat adequately the postprandial blood glucose rise, starting with 0.05 IU/kg of rapid-acting insulin analogues (aspart, lispro, glulisine,) at each meal. The complexity is related to titration, appropriate diabetes self-management and support in order to sustain adherence to multiple daily injections without leading to threatening hypoglycaemia for the patient.

Multiple daily doses of glucocorticoids will likely result in hyperglycaemia throughout the day and night, and may require multiple insulin injections or a basal-bolus regimen [62] (figures 1 and 2).

Finally, in hospitalised patients receiving high doses of steroids with glucose levels above 25 mmol/l for periods lasting more than 6 hours, an insulin infusion pump is indicated. This is particularly important in patients receiving intravenous steroid pulses in which insulin requirements are difficult to predict.

On hospital discharge, the diabetes treatment plan and a clear strategy in the event of hypo- or hyperglycaemia must be explained to the patient, with close follow-up by the general practitioner or diabetologist.

In the setting of end-of-life care, the glycaemic goals should be larger: 6 to 15 mmol/l, and, chiefly, no symptoms. The treatment is the same as above, but must be undertaken in alignment with the wishes of the patient.

Patient with prior diabetes

If the patient is on antidiabetic drugs such as gliclazide or metformin, those drugs may be up-titrated. Patients on oral treatment may otherwise need temporary addition of basal human insulin, as discussed previously.

For patients already on insulin, the treatment may be switched to morning or increased in the morning, depending on the basic schedule.

For those on a basal-bolus regimen, an increase in lunch and evening meal short-acting boluses may be appropriate. Again, close monitoring should be made in order to avoid night and early morning hypoglycaemia, and to adjust doses (by 10% increments) [20].

In patients with type 1 diabetes, also check daily for ketones if blood glucose is above 15 mmol/l.

For patient with a continuous subcutaneous insulin infusion, some authors have developed closed-loop algorithms that may adequately manage the hyperglycaemic effect of a glucocorticoid [63], but these are still at the experimental level. Hence, those patients should be managed with the local diabetes team.

Treatment cessation

When glucocorticoid treatment is discontinued, or the dosage reduced, a proportional reduction in the anti-diabetic treatment can be anticipated in the next 24 hours.

Thus the blood glucose should continue to be checked, and the treatment down-titrated accordingly. Some patients

Table 3:
Insulin dose according to weight and glucocorticoid dose.

Prednisone equivalent dose (mg/day)	Basal human insulin dose (IU/kg/day)
≥40	0.4
30	0.3
20	0.2
10	0.1

may not return to their baseline treatment, or to the absence of treatment if that was the case before. If the patient is discharged from hospital with blood glucose readings still above the target, capillary blood glucose must be tested at home until normoglycaemia returns or until a definitive test for diabetes is undertaken. It must be remembered that HbA1c can be used as a diagnostic tool only after an interval of 3 months, because of the recent steroid-induced hyperglycaemia [20].

Conclusion

Synthetic glucocorticoids can be prescribed in virtually every specialty of medicine. Patient information and careful clinical attention should be guaranteed straight after glucocorticoids are initiated, and even for a short course. Glucocorticoids can elicit a wide range of side effects too often overlooked in the acute hospital setting [47, 50, 64]. Our review aims at summarising the current literature on the risks to be expected shortly after introducing gluco-

Figure 1: Risk of glucocorticoid-induced hyperglycaemia and treatment algorithm. CBG: capillary blood glucose; BMI: body mass index; pp: post-prandial; * start gliclazide and metformin only if renal clearance > 50 ml/min.

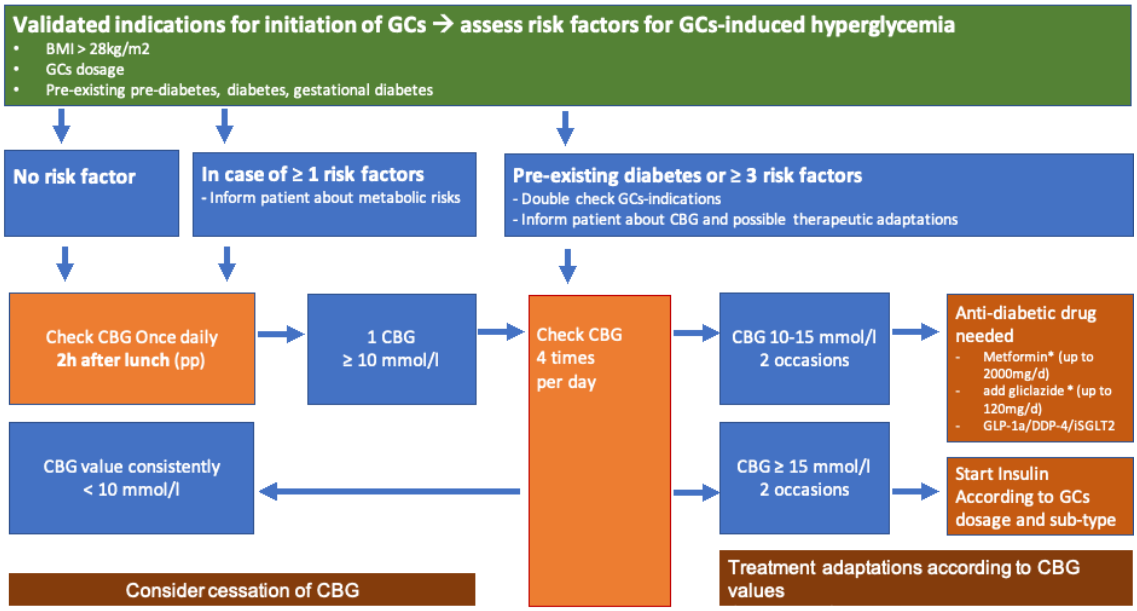
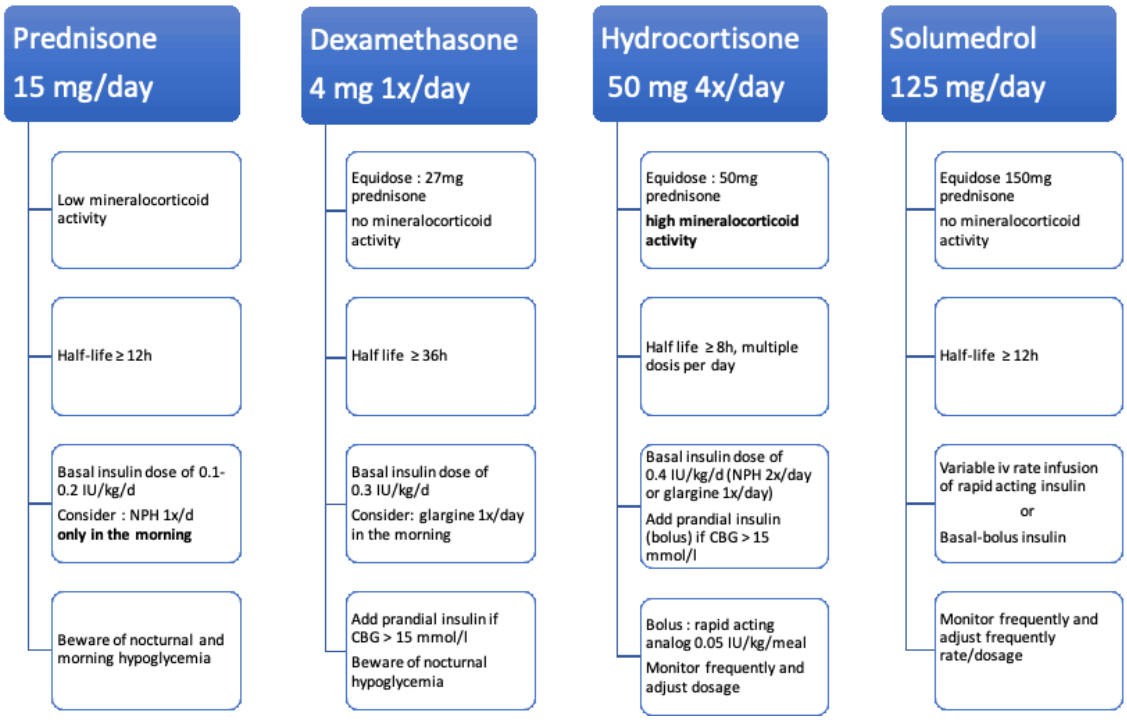


Figure 2: Suggestions for iInsulin initiation according to glucocorticoid dosage and subtype. CBG: capillary blood glucose; NPH: neutral protamin Hagedorn.



corticoid treatment. We also present recommendations for the screening, diagnosis and treatment of hyperglycaemia and other adverse events induced by glucocorticoids. Unfortunately, there are little published data on precise strategies for each problem, and the vast majority of the recommendations are based on a few studies or expert opinion. Therefore, prospective trials are needed to determine the best therapeutic and preventive strategies in the setting of short-term glucocorticoid treatment.

Conflict of interest statement

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. GG receives educational grants from Lilly, NovoNordisk, Sanofi, Medtronic, Dexcom, Roche and Abbott, outside the submitted work. No other potential conflict of interest was disclosed.

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