

Waterloo Wellington Diabetes

Managing Steroids & Hyperglycemia:

A Guide for Health Care Professionals



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Medical knowledge and treatment is constantly changing. As new information and treatments become available, changes in care may be necessary. The authors have reviewed the current literature extensively; however, health care professionals and readers are advised to confirm that the information, especially related to medication usage and adjustment, complies with the latest legislation and standards of practice.

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A Guideline for Managing Steroids & Hyperglycemia

Introduction

This guidance document was developed to alert healthcare providers to the risks of hyperglycemia in people with pre-existing diabetes and new onset diabetes in those undergoing steroid treatment, and to support our regional Diabetes Education Programs and primary care providers with guidance they require to optimize care. It is based on current published literature and international guidelines, notably those published in the UK¹.

Steroid treatment is used to treat a variety of conditions including auto-immune disease (Lupus, rheumatoid arthritis), inflammatory bowel disease, post-transplant, COPD, chemotherapy protocols, sarcoidosis and neurological disease. Treatment regimes are varied, ranging from acute/short-term high dose situations to those that are more chronic, and low dose in nature. While steroids are prescribed for their therapeutic anti-inflammatory and immunosuppressive effects, they are associated with significant, less desirable side effects including hyperglycemia.

Hyperglycemia affects 20-50% of people treated with steroids who previously had no history of Diabetes (DM).^{2,3} Those with pre-existing DM or risk factors for DM, are particularly susceptible to experiencing escalations in blood glucose (BG) and adverse outcomes, therefore this requires a temporary intensification of BG management. Individuals with A1c ≥ 7 experience worse outcomes including:

- higher risks of infection, hospitalization
- chemo discontinuation or dose reductions
- higher mortality
- lower quality of life (QOL) with increased pain intensity
- risk of hyperosmolar hyperglycemic non-ketotic syndrome (HHS)⁴
- increased BG variability which is associated with increased risk of cardiovascular (CV) mortality⁵ and fatigue⁶

Steroid-induced hyperglycemia needs to be addressed in the clinical setting to optimize outcomes for patients and reduce glucose-related emergencies. This should include screening, pharmacological treatment and patient education to manage blood sugar.

Hyperglycemia induced from glucocorticoid (GCs) steroid therapy largely occurs post-prandially and varies depending on the steroid used. GCs typically cause hyperglycemia within 4-8 hours after ingestion and peak between the mid-day meal and supper meal (steroids are often dosed every morning to avoid insomnia, a common side effect).^{3,7} It is also often transient and reversible upon end of treatment; however, this is not always the case and ongoing surveillance of patients is prudent. In most patients receiving steroid treatment, measuring only an isolated fasting blood sugar is likely to underestimate the incidence of SIH, particularly with intermediate acting agents with once daily morning dosing. Two-hour

post-prandial lunch BG is the best indicator of diagnostic sensitivity, however, pre-dinner BG, while less sensitive, may be easier to implement with patients and is preferred to a fasting blood glucose (FBG) or random blood glucose (RBG) when screening for SIH⁸.

Screening Suggestions

There are currently no standardized guidelines for screening in Canada, however there is broad consensus and international guidelines that people receiving steroid therapy regardless of DM status be screened **baseline** (prior to treatment), and **periodically over the course of therapy** as SIH often presents beyond the first 2 weeks of administration.^{1,5}

Monitoring Parameters:

- In patients, especially those with any risk factors, starting steroid treatment if not done in previous 3 months, measure:
 - A1c,
 - eGFR,
 - FBG
- Capillary Blood Glucose 1-2x/week post prandial lunch or ac dinner (less reliable than pc lunch) after steroid administration, particularly in patients at high risk of SIH/SID (requires provision and teaching of BG meter)

Aims:

1. Surveillance for pre-existing hyperglycemia, undiagnosed Pre DM/DM
2. Surveillance for steroid induced hyperglycemia
3. Achieve acceptable glycemic control (pre-meal 4-7 mmol/L & 2hr post-meal BG 5-11mmol/L)
4. Avoid emergency room visits and admittances for hyperglycemia
5. Maintain quality of life and minimize risk to patient.

BG Requiring Urgent Action & Referral to Endocrinology and Diabetes Education Centre:

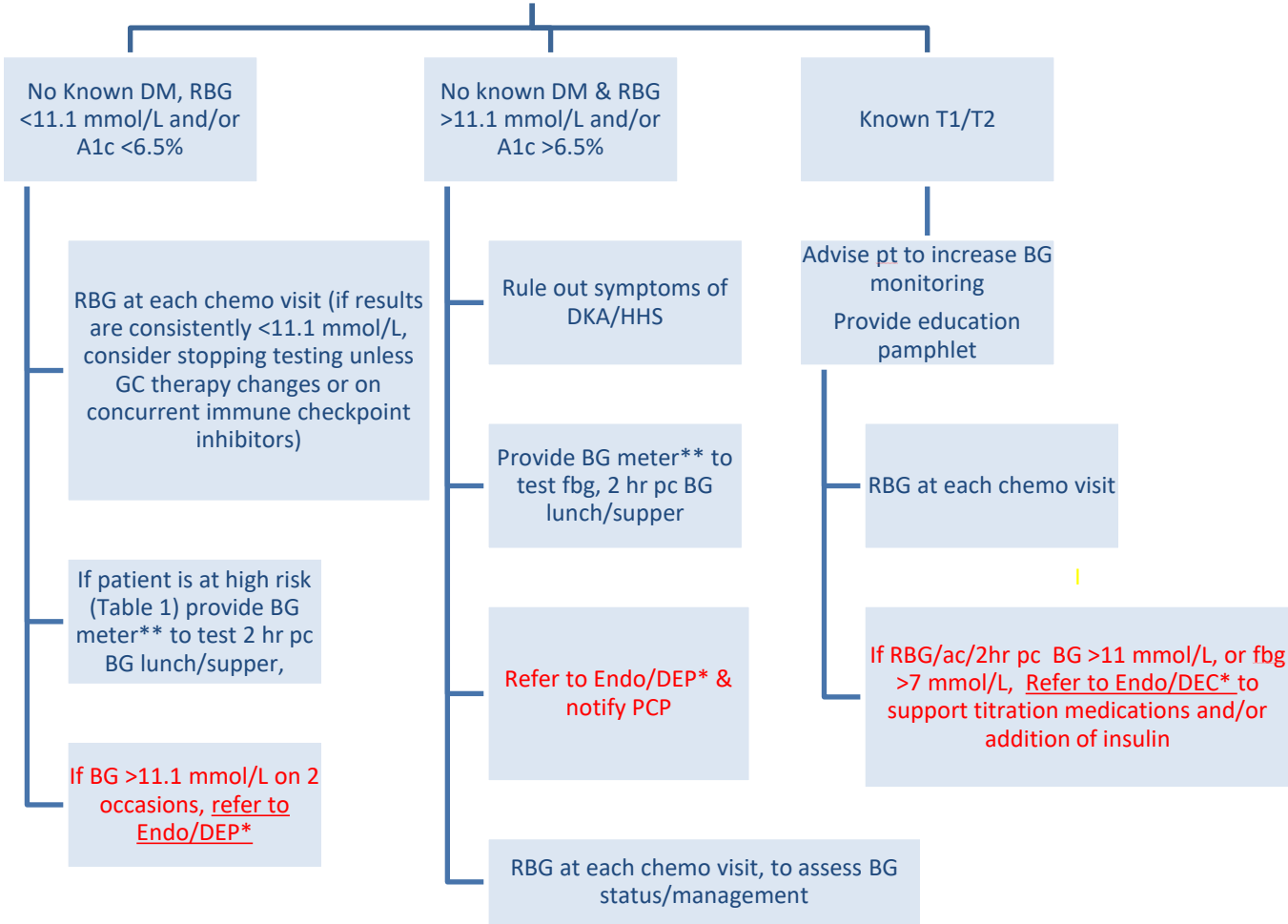
1. BG >18 who is unwell, especially if vomiting or unable to drink water
2. BG >25 or "Hi"
3. BG <5 who is taking glucose lowering medication/insulin requires consideration of a dose reduction of the causative medication
4. Recurring BG <4.0 requires hypoglycemia treatment and dose adjustments of causative medication.

Suggested Screening Algorithm

(Recommended to be done in oncology centers)

**Provide patient with prescriptions for BG monitoring device (flash glucose monitoring preferred)

All patients beginning steroid treatment:
 1. Advise patient of risk of hyperglycemia/symptoms
 2. Check baseline A1c & RBG prior to treatment
 3. Provide hyperglycemia awareness pamphlet



*Refer to Endo/DM Education (use Central Intake Referral Form for Waterloo-Wellington Diabetes)
 **Provide patient with prescriptions for BG monitoring device (flash glucose monitoring preferred)

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICPs), often used in conjunction with GCs, can result in pancreatic toxicity and very rarely can cause diabetes (<1%).⁹ The insulin deficiency brought on by ICPs may present as a new-onset T1DM or sudden worsening of T2DM. It can present more rapidly than a typical new onset T1 situation, and is associated with symptoms of DKA, as the underlying physiology is insulin deficiency¹⁰. Management of this situation is beyond the scope of this document. If this is suspected, an urgent referral to endocrinology and DEP/DEC and/or an emergency department is warranted. Insulin is most often required to manage this situation.

Risk Factors for GC Related Hyperglycemia

Table 1: Risk Factors for Glucocorticoid-Induced Hyperglycemia ^{1,4}

Risk Factors for SIH
Higher Dose Treatment (prednisolone >20 mg, hydrocortisone >50mg, dexamethasone >4mg)
Longer Duration of Treatment
Concurrent cytotoxic therapy known to cause hyperglycemia
Previous glucocorticoid hyperglycemia
Advanced Age
High BMI
Pre DM (IFG, IGT), A1c \geq 6.0
GDM history
Polycystic Ovarian Syndrome
Family History of DM
African, Asian, Indigenous ancestry

Understanding Different Steroids

Our bodies naturally generate steroidal hormones, producing mineralocorticoids (e.g., aldosterone), glucocorticoids and androgens. Cortisol is the primary glucocorticoid produced and supports many physiological functions, including gluconeogenesis. This cortisol production follows a diurnal pattern and has several physiological effects on the body. Highest levels appear in the morning hours and then decline throughout the day, cycling again overnight. 10-20 mg/day cortisol is the accepted normal daily amount produced but this is altered by stress, trauma, hypoglycemia and other situations where there is demand for increased production.¹¹ When GC doses, above physiological levels, are administered there is an exaggerated, pharmacological effect, namely anti-inflammatory, but they also contribute to negative feedback loops that result in the problematic side effects that are associated with their use, including the potential for hyperglycemia. The expected hyperglycemic effect of GCs are related to the dose, half-life, the individual's degree of pre-existing insulin resistance or insulin deficiency amongst other factors. The following summary points and Tables 2, 3 & 4 may help in your understanding of the impact steroid treatment may have on your patients:

- GCs can have a direct hyperglycemic effect within 4-8 hrs of ingestion
- GC doses over 5mg prednisone equivalents is considered 'supra' physiologic
- Post prandial hyperglycemia is often more pronounced than fasting hyperglycemia and this hyperglycemia may not resolve with steroid discontinuation

Table 2 : Physiological and Pharmacological Effects of Glucocorticoids¹¹

Glucocorticoid Effects	
Physiological	Pharmacological
Moderate immune and inflammatory processes	Anti inflammatory/immunosuppression
Gluconeogenesis	Hyperglycemia
Potentiate catecholamines	Hypertension
Increase RBCs	Erythrocytosis
Mild Na ⁺ /water retention	Edema/puffiness

Table 3: Mechanisms of Glucocorticoid-Induced Hyperglycemia⁴

Mechanisms by which GCs induce hyperglycemia:
Reduced Peripheral insulin sensitivity
Promotion of hepatic gluconeogenesis
Destruction of pancreatic cells, β -cell injury/dysfunction
Impairs insulin release
Inhibition of glyceroneogenesis
Increase of Fatty Acid production

Table 4: Relative Steroid Potency Equivalents and Duration of Action^{12,13,14}

Steroid	Potency* (Equivalent Doses, mg)	Duration of Action (anti-inflammatory)	Relative Anti-inflammatory Activity*	Hyperglycemic Effects (hours)		
				Onset	Peak	Resolution
Short Acting						
Hydrocortisone (cortisol)	20	8-12	1	1	3	6
Cortisone acetate	25	8-12	0.8	n/a	n/a	n/a
Intermediate Acting						
Prednisone	5	12-36	4	n/a	n/a	n/a
Prednisolone	5	12-36	4	4	8	12-16
Methylprednisolone	4	12-36	5	4	8	12-16
Long Acting						
Dexamethasone	0.75	36-72	30	8	variable	24-36
Betamethasone	0.6	36-72	30	12	variable	Up to 72

*N.B. steroid doses are often expressed as prednisone equivalent doses & potency relates to anti-inflammatory action, relative to hydrocortisone, which may not equate to hyperglycemic effect

Management of Steroid Induced Hyperglycemia

General international recommendations, including Diabetes Canada, support the use of insulin to manage steroid-induced DM. It offers greatest flexibility (to manage changes in dosing, food intake, etc.), predictability, and targeted intervention. It does require active patient/family members' education and support. Initiate treatment if patient experiences BG>11.1 on 2 or more occasions within a 24-hour period.

Insulin remains the treatment of choice (as it can deal with the rapid onset of hyperglycemia and can be titrated easily as GC doses change, immediate onset, unlimited hypoglycemic power, easily titrated and safe in situations where other agents may be contraindicated), however there may be patients and/or situations that require other options over the course of treatment. Patient education and competence to manage injection, dosing/titrations, hypoglycemia is essential.

Agents other than insulin could be considered in patients with no previous history of DM/hyperglycemia, in those who may experience mild-moderate hyperglycemia or patients who refuse insulin therapy, though this is not the preferred or ideal treatment.

The choice of BG, management will be dictated by the GC in use, its frequency of administration and the BG profiles that patients experience. Generally:

- Prednisone once daily: responds well using NPH, due to its peak hyperglycemia occurring 4-8 hours after ingestion (similar to peak of NPH) or glargine U100.
- Prednisone dosed BID: NPH BID, basal/bolus, or premixed BID may be appropriate.
- If a longer acting GC is used, such as dexamethasone: glargine U100, U300, degludec or NPH, dosed BID, would be preferred options.

Insulin is most often required to manage the hyperglycemia caused by GCs, however, if only mild hyperglycemia (10 - <15 mmol/L) is experienced by your patient some oral agents could be considered (metformin, pioglitazone, gliclazide/MR, DPP-4i, GLP-1a) and are discussed further on. Once again, consider the profile of action of GC when selecting an OHA (shorter acting sulphonylureas: glyburide, gliclazide, repaglinide better suited to once daily prednisone use vs agents with longer half-lives such as gliclazide MR, glimepiride may be more suitable for patients' using dexamethasone or shorter acting GCs dosed more than once daily).¹⁵

Titration and Tapering Management

In those identified as experiencing steroid-induced hyperglycemia (whether new onset or pre-existing DM), BGs need to be monitored more frequently as courses of GC treatment begin to assess a patient's response and the degree of added pharmacology that is required to optimize BGs. Timely dose increases of up to 20%/day are not uncommon as a treatment cycle begins. As tapering or discontinuation of GCs occur, concomitant reduction in BG lowering medications must occur to avoid hypoglycemia. There is no standard algorithm that encompasses the art & science of this process. It depends upon individual responses to the titration schedule, type and dose of steroid, and extent of the duration of steroid

treatment. Have patients monitor BG 4x/day during periods of titration (up or down) and use results to inform your advice for titrating DM medications for subsequent GC courses of therapy. A sample algorithm is provided further on from a pilot study.

Patients on agents that can cause hypoglycemia should be counselled to check their BG more frequently than usual during tapering periods for 1-3 days after a reduction in GC dose, (as it can take this much time for the glycemic effect of GCs to diminish), to be able to make appropriate adjustments to diabetes medications.⁴

Some patients will not return to baseline pharmacologic medication doses and may require higher doses to maintain normal BGs than they did prior to GC treatment.

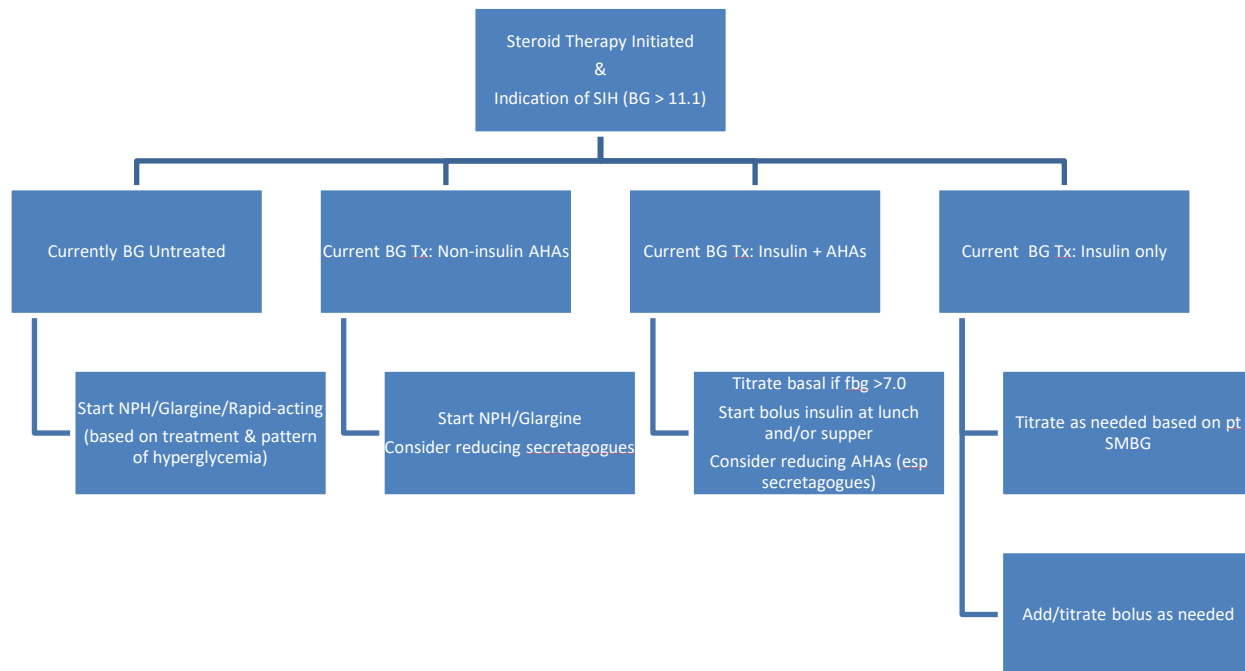
Considerations of Treatment

1. Degree of pre-existing dysglycemia, current level of hyperglycemia, and patient's clinical condition.
2. Type/dose/frequency of administration of corticosteroid formulation:
 - a. **Once Daily Steroid Dose**
 - b. **Multiple Daily Steroid Doses**
 - c. **Long-term Continuous Low Dose**
3. Understand pharmacokinetics/dynamics and mechanisms of action of various hypoglycemic agents
4. Anticipated duration of treatment: short-term vs indefinite/long-term

Blood Glucose Targets

In most patients continuing to aim for targets of A1c $\leq 7\%$, fbg 4-7 is desirable, however, in practice, targeting BGs of 6.0-10.0, and permitting a range of 6.0 -12.0 mmol/L is reasonable and end of life targets may be liberalized maintaining an A1c of $<8.5\%$, and BG 6.0-15.0 mmol/L while preventing symptomatic hypo/hyperglycemia.^{2,16}

SID Management Algorithm: Start/Titrate Insulin (Preferred Treatment)



Generally pharmacological intervention is indicated when 2 or more BGs are above target (>11.1 mmol/L) within a 24-48 hr period. Dosing of insulin to manage GC induced hyperglycemia is highly variable and can be based on a variety of factors, and clinical experience. Weight based dosing, units/kg, or based on BMI are common, and the type and dose of steroid must be considered as well. Generally, pre-existing insulin resistance and hyperglycemia that may be present (and potentially undiagnosed) generates the need for larger doses of insulin, early in treatment.³ Prandial dosing may be based on weight, carbohydrate content of meals eaten, food patterns, degrees of delayed gastric emptying, etc.

Table 5: Weight Based Dosing of Insulin in Glucocorticoid- Induced Hyperglycemia, according to the Type and Dose of Glucocorticoids for SIH in People with No Previous DM. ^{4,17}

(Note: this is a guideline and individual cases can vary widely in their degree of dysglycemia regardless of dose)

Prednisone Dose mg/day (use NPH)	Dexamethasone dose mg/day (use Detemir/Glargine)	Insulin - U/kg/day
≥ 40	≥ 8	0.4
30	6	0.3
20	4	0.2
10	2	0.1

Management in People with No Previous History of DM

Insulin naïve patients, basal insulin can be calculated at 0.2-0.4 u/kg for a 24 hr period and bolus insulin at 0.1U/kg at lunch and/or dinner but will be dependent on whether both FBG and pc BG are elevated or there is isolated post prandial hyperglycemia, as well as type/frequency of the steroid intervention. If only pc BG are elevated and GC administration is 1/day, then addition of NPH at same time as steroid administration will best mirror the glucose rise. This is preferred as it may avoid the need for MDI. Rapid

analogues could be added to mealtimes if FBG remains controlled but post-prandial levels remain elevated.

New Insulin Start: Suggested starting dose: 0.2-0.4 U/kg Body Weight & titrate to BG targets fbg <7.0, ac meals 4-7, 2 hr pc meals 5-10.

Review and Adjust Insulin Daily:

- Titrate daily NPH/Glargine x up to 20% (or more using clinical judgement) if BG continue to be >11, 2 hr pc lunch or ac/pc supper, or fbg >7.0 on Glargine
- When the 4-5 day steroid course is complete:
 - Reduce by 50% or D/C insulin on 1st day w/o steroids (depending on type of GC used and expected duration of glycemic impact)
 - Have pts continue to monitor BG until they return to target to assess modifications to tapering
 - If after 3 days BG remain elevated, have pt call in to review, adjust tapering schedule for next course

For the Next 4–5-day steroid course:

- Day 1- Start insulin dose at ½ to full dose required by the end of the previous course (depending on the onset of action of GC)¹⁸ Eg:
 - If individual is on 20mg cycles of Prednisolone and required 20U added insulin to achieve BG control, then start with same added 20U when next steroid course commences (assuming same dose/type of GC)
 - If on Dexamethasone and required 20U added insulin: start with 10U added insulin when next course commences and titrate more slowly back to 20U as steroid onset of action occurs, assess effectiveness, and adjust if necessary for next GC course
- Day 2- Increase insulin to full dose required on previous course, (if not started on full dose) and adjust as necessary¹⁸

Management in people with pre-existing DM

In people managing with lifestyle (LS) interventions alone, additional pharmacological support is usually warranted, and the above insulin protocol could be implemented. Dose titrations of 10%, up to 40% in some patients may be necessary⁴. In those on AHAs, dose titration could be initiated but if BG persists > 11.1 mmol/L, adding insulin therapy is warranted. Choose a long-acting insulin, best suited to the steroid being administered (NPH more suited for Prednisone, Glargine/Detemir for Dexamethasone) If sulphonylureas are onboard, they should be reduced to avoid risk of hypoglycemia when a decision is made to start insulin.

In patients:

- **Previously treated with insulin:** the usual schedule should be modified. The increment in the usual daily insulin dose will be estimated considering the patient's body weight, the preparation, the particular glucocorticoid, and the degree of hyperglycemia being experienced by the individual. The calculated dose increment is added to the patient's usual total dose, distributing it over the usual insulin schedule and based on the glucocorticoid schedule⁵.
- **On MDI:** added bolus insulin will be required.
- **On a pre-mix insulin:** it may be prudent to consider switching to basal/bolus routine to address specific times of hyperglycemia.

- **On basal only:** prandial doses of rapid acting insulins may be added to lunch and/or supper meals as needed as hyperglycemia is usually experienced late afternoon (if once daily steroid administration)⁵.

Dose Adjustments/Monitoring

Insulin doses must be adjusted frequently depending on the GC regime, titration, and tapering schedules. Dose adjustments of up to 20% are common and correspond to changes in GC dose changes. One rule of thumb is that insulin adjustments correspond to half the per centage of GC change, for example:

- if steroid dose is reduced by 50%, then insulin dose should be reduced by 25% respectively to keep BG within target ranges.³

However, there are no fixed 'rules' for this and individual patients will have unique responses and requirements. Checking in with patients every 1-3 days is crucial to achieve optimal BG control and mitigate hypoglycemia risk and individuals should be encouraged to check their BG more often than normal, 1-3 days after receiving GC treatment, preferably 2 hrs pc meals, as adjustments to their DM medications will likely be required. Insulin needs to be adjusted as steroids are titrated or tapered, and in the 3-4 days after administration ends as the hyperglycemic effect diminishes, in cyclical courses of steroid treatment, as per above guidelines (same guidelines as for those without pre-existing DM). Those with longer standing T2DM or DM, characterized by insulin resistance, may experience higher baseline insulin needs upon completion of GC treatment.

It should be ensured that all individuals with diabetes, who are at high-risk for SIH, have access to blood glucose monitoring equipment, to prevent the development of hyperglycemic emergencies.

The appropriate follow-up of patients with previously unknown diabetes, who develop SID, includes an HbA1c test 12 weeks following completion of glucocorticoid therapy to re-assess their diabetes.

T1DM Considerations

There can be great heterogeneity in the effect of GC on those with T1DM and thus, advising patients to increase their typical frequency of testing, if there is no access to continuous BG sensors, is advised when GC therapy is initiated, as a deterioration in BG control is expected. People with T1DM on GCs are more prone to hypoglycemia and DKA, than those with T2DM, hence, initial dose adjustments should be made carefully and iteratively based on BG data, with increases in total daily dose (both basal/bolus according to the GC being used) and close follow-up is advised¹².

Adjustments for insulin when using short acting GCs (e.g., hydrocortisone)¹²:

- In situations of short acting GCs: increases in bolus insulin may be sufficient.

Adjustments for insulin when using intermediate acting GCs (e.g., prednisone)¹²:

- Increases in bolus dose at the time of GC administration may be appropriate to achieve optimal BG control by noon
- If on NPH bid or detemir BID, a dose increase at the time of GC administration (usually morning) is recommended
- If on ultra-long acting basal (glargine U100/U300 or degludec), increasing the bolus dose with breakfast for short-term, cyclical GC regimes may be best. If the GC treatment is expected to be

longer term (>3mos) then individuals may benefit from switching to NPH BID, increasing the dose associated with the GC administration.

Adjustments for insulin with use of Long-acting GCs (dexamethasone)¹²

- Longer acting GCs cause continuous and long-lasting elevations in BG over 24 hrs and may respond best to increases in basal dosing as discussed above.

Pump Therapy¹²:

- Patients self-managing their CSII devices may continue to manage BG via use of adjustable basal rates, programming different basal rates over a 24hr period, using temporary % increase/decreases in infusion rates and/or using added bolus dosing to administer correctional insulin when required. Supporting patients for matching pump setting changes to mirror the GC response seen in BG sensor data is critical.

Diabetes in Pregnancy & Glucocorticoids

Steroid use in pregnancy is usually, 2 single doses of betamethasone, to promote lung maturity in women who may be expecting to deliver prematurely. Transient hyperglycemia can present, particularly in women with pre-existing DM or GDM. Diabetes Canada does provide guidance for titration and tapering of insulin for women with T1DM on insulin, to prevent severe hyperglycemia, DKA and hypoglycemia in this population.

Table 6: Management of pregnant women with DM on insulin receiving betamethasone²

Following the first dose of betamethasone:	
Day 1	Increase the night insulin dose by 25%
Days 2 and 3	Increase all insulin doses by 40%
Day 4	Increase all insulin doses by 20%
Day 5	Increase all insulin doses by 10% to 20%
Days 6 and 7	Gradually taper insulin doses to pre-betamethasone doses

Non-insulin Treatment Options to manage SIH (excluding people with T1DM)

While **insulin remains the treatment of choice** (it best manages the rapid onset of hyperglycemia and can be easily titrated as GC doses change, has immediate onset, unlimited hypoglycemic power, and is safe in situations where other agents may be contraindicated) there may be patients and/or situations that require other options over the course of treatment. **Non-insulin AHAs are unlikely to be as effective in controlling the hyperglycemia that results from high dose, short-term and/or cyclical courses of GC therapy** where significant titrations in insulin doses may be required to normalize steroid induced hyperglycemia.

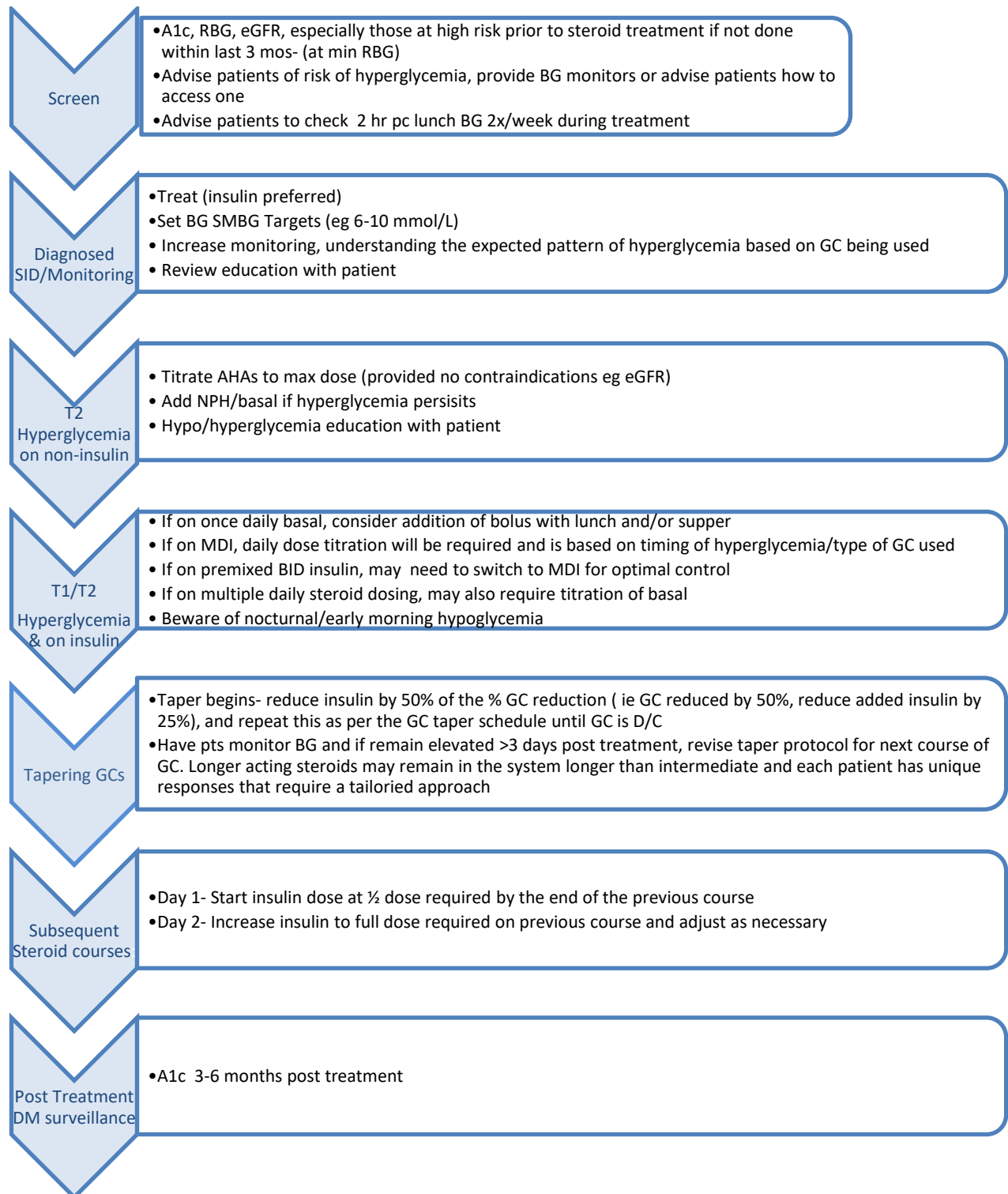
Secretagogues: second generation secretagogues (gliclazide, repaglinide) have a rapid onset of action, a lower risk of hypoglycemia and can be dosed at midday meal to target the post prandial rises in BG usually associated with once daily prednisone. This may be more suitable in people with no prior history of hyperglycemia, and/or short-term use and if effective (based on CBG monitoring by patient).

Incretin Mimetics (GLP-1ra & DPP4i): may be good choices as they act quickly and act on post-prandial glycemia, and have low risk of hypoglycemia, however they are unlikely to manage the hyperglycemia experienced from steroid treatment, and their GI side effects may exacerbate other untoward symptoms patients are experiencing. (Weight loss, nausea, etc)

SGLT2i: trials are underway in this population (vs NPH) and may be a good alternative particularly in those who decline insulin. Like other oral agents these can be administered with once/day dosing. Start with lower dose and titrate to higher does if hyperglycemia persists. Clients should have an eGFR >60 ml/min/1.73 m² as the glucose lowering effect is impaired with lower eGFRs¹⁹

Insulin Sensitizers: (metformin, TZDs) may have a place in long-term, low dose situations, but do not serve the acute transient hyperglycemia often associated with chemotherapy treatment due to their slow onset of action and limited ability to manage highly elevated BG.

Summary



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