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Challenges in post-operative management of Cushing disease

Buddhika P G[1], Wijeyawardena K W S T[1], Punchihewa P G[1], Muthukuda D T[1]

[1] Sri Jayewardenepura General Hospital , Sri Lanka

Abstract

Patients with Cushing disease (CD) undergo transsphenoidal resection of the pituitary tumor as the primary management option. Post operative period is considered as one of the most challenging aspects in the CD management due to the related high morbidity and mortality.

Assessing remission following surgery is done commonly by assessing nadir serum cortisol level, a level < 2 to 5 µg/dL (55-138 nmol/L) during 24 to 74 hours postoperatively is accepted as remission. Values more than 5-10 µg/dL (138-276 nmol/L) considered as non-remission.

If remission is achieved, it is important to treat the adrenal insufficiency (AI) with steroids until the Hypothalamic-Pituitary-Adrenal axis (HPA axis) recovery happens. Other anterior pituitary hormone dysfunctions should be assessed and treated appropriately. If the remission is not achieved by the surgery, secondary management options such as repeat surgery, radiotherapy and medical therapy can be used.

Prevention and management of hypercortisolemia associated complications such as infections, thromboembolic events, cardiovascular and metabolic diseases are also important aspect in the post operative management of CD. It is also challenging to manage surgery related complications such as Syndrome of Inappropriate ADH Secretion (SIADH) and Diabetes Insipidus (DI). Prevention or successful treatment of cortisol withdrawal syndrome is another challenging aspect that a physician needs to focus on.

Keywords: Cushing, post operative management, remission, infection, thromboembolism, cardiovascular disease

Correspondence email: gishanbp@gmail.com

ORCID ID: https://orcid.org/0009-0006-9499-7068

Introduction

Cushing disease (CD) is the most common cause of endogenous Cushing syndrome (CS), which is caused by a pituitary adenoma which secretes adrenocorticotropic hormone (ACTH). Inadequately treated Cushing syndrome will result in high morbidity and mortality [1-4].

Transsphenoidal surgery (TSS) is the recommended first line management option in CD [1, 2]. An experienced neurosurgeon in a specialized unit will achieve an initial cure rate of 80-90 % with microadenomas [3] and 60% with macroadenomas [1]. Clinicians face a number of challenges in the immediate post-operative period which are related to the management of surgical and disease related complications and assessment of remission.

The objective of this review is to provide necessary knowledge to overcome above mentioned challenges faced in the postoperative period.

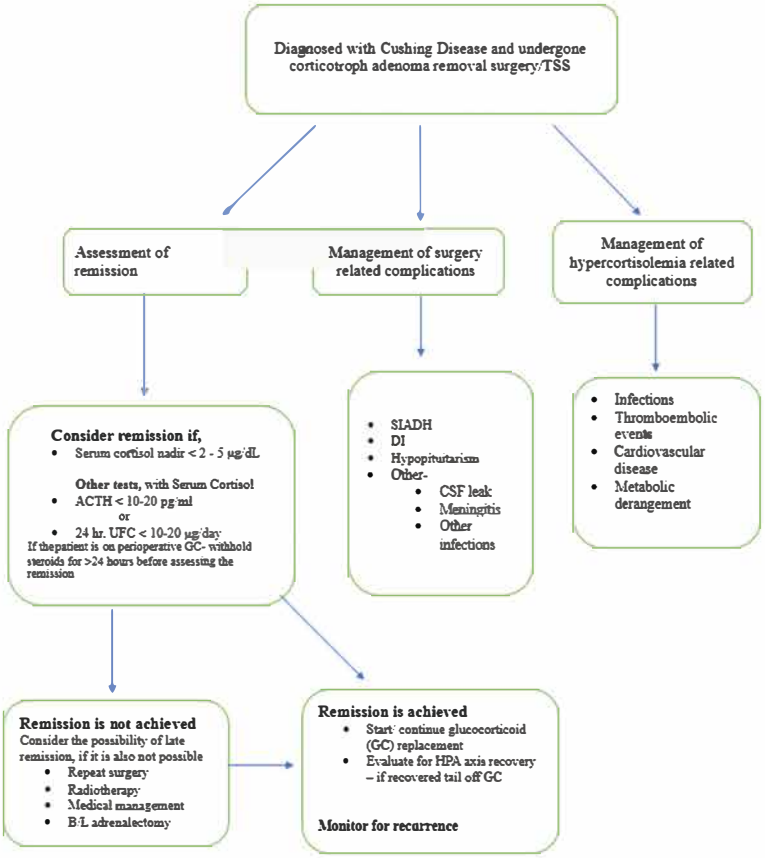

Figure 1: A Summary of challenges in management of postoperative complications of Cushing disease

1.What is remission and how is remission diagnosed?

Post-operative remission of CD is assessed by measuring nadir serum cortisol level [4, 5]. Some studies show that the remission may take days to weeks, showing a significant individual variation.

Morning cortisol level can be measured 48-72 hours (2 -3 days) after surgery up to 7 days if no perioperative glucocorticoids (GC) were administered. Serial morning cortisol levels could be measured. The cortisol level cutoff for establishing disease remission has not yet been standardized, some accept nadir cortisol level <2 µg/dl (< 55 nmol/l) [7-9] as remission but some consider nadir cortisol level <5 µg/dl (138nmol/l) [10] indicative of remission.

Apart from the diagnosis of remission, numerous studies have evaluated the "risk of recurrence" in relation to the nadir serum cortisol values after 2-3 days of surgery. Accordingly, patients with cortisol levels of < 2 µg/dl have low risk of future recurrence and 2 – 5 µg/dl have intermediate risk of recurrence in general [11, 12].

This risk stratification shows that very low cortisol values after surgery are predictive of a favorable short-term outcome in terms of disease recurrence. However, there are studies with long term follow up data reporting recurrence despite initially achieving even undetectable cortisol levels, emphasizing that even undetectable postoperative cortisol values do not eliminate the possibility of a future recurrence [13]. Supporting above, Lindsay et al showed that long term recurrence rates were similar in patients with a serum cortisol level of <2 µg/dL (9.5%) and in those with a serum cortisol level of <5 µg/dL (10.4%) and explained that low postoperative serum cortisol nadir only predicts the short-term remission, but not the long term remission [11].

Normal or high postoperative cortisol levels on post operative day 2-3 is mostly due to the presence of a tumor residual. So, cortisol levels > 5- 10 µg/dl is considered as non-remission and warrants second line treatment [7-10]. However, some patients experience a delayed remission which would initially cause cortisol levels > 5-10 µg/dL [14]. Above levels apply only to patients with active hypercortisolism at the time of surgery. However, eucortisolemic patients who are on medical treatment or with mild or cyclic hypercortisolism may not have a significant suppression of the normal corticotropes, leading to normal cortisol levels after total tumor resection due to the early recovery of hypothalamic-pituitary-adrenal (HPA) axis [15].

Valassi et al suggested that it is important to closely follow up patients until hormonal levels stabilize even if the initial cortisol levels are high which will avoid unnecessary second line interventions [14].

Measurement of **ACTH** is often done within the first 7 days following surgery; however, its role is less clearly defined in diagnosing remission. A postoperative nadir ACTH value lower than 15 to 20 pg/mL (3.3-4.4 pmol/L) can be used as an early marker of disease remission [16, 17]. Some experts recommend a lower ACTH level < 10 pg/ml as the cutoff level to suggest remission [18]. It is also shown that early postoperative ACTH levels show a good correlation with the cortisol levels, ACTH level < 5 had a predictive value of 100% in predicting the remission with a cortisol level < 2 μg/dL [10].

24-hour urinary free cortisol (UFC) has also been used as a predictor of remission, with a low UFC level of less than 10 to 20 μg/d (< 28-56 nmol/d) being suggestive of remission, but it may be difficult to perform an accurate 24-hour UFC in the immediate postoperative period. Hence this is not used often. Current recommendation is to use UFC measurements only when serum cortisol levels are equivocal. Normal UFC levels (range 20–100 mg/24 h) are considered equivocal and elevated values suggest residual tumor [19].

Late-night salivary cortisol has high sensitivity and specificity in detecting surgical failure and recurrence of CD, hence it can be used in patients who had cyclic CS, and who were pretreated medically. Their morning serum cortisol may not fall drastically after TSS as there may not be significant suppression of normal corticotropes [20].
Late-night salivary cortisol is less utilized in the assessment of remission, especially because there are no specified cutoffs agreed to be used after TSS, less availability and high variability in available salivary cortisol assays.

Lack of cortisol suppression with overnight 1 mg dexamethasone (overnight dexamethasone suppression test (**ODST**)) is evidence of persistent disease. ODST is considered less reliable in the assessment of remission especially because cortisol cutoff is not agreed on.

2. What is delayed remission?

Studies have revealed that 5.6% of patients show a gradual decline in cortisol levels after the first week [14].The most possible underlying mechanism to explain this is, the persistence of cortisol secretion due to chronically stimulated adrenal glands and the subsequent post-surgical necrosis of remaining corticotropic tumor cells. Interestingly, Valassi e et al has shown increased long-term recurrence in this group. [14]

3. Post operative glucocorticoid (GC) replacement and how it affects the evaluation of disease remission?

Generally, two steroid replacement strategies are recommended. With one strategy, if the patient is in remission post operatively (serum cortisol < 5 μg/dL), glucocorticoid replacement therapy is started. In these patients routine GC replacement therapy is not given during the immediate postoperative period. Other than biochemical evidence of remission (< 5 μg/dL), glucocorticoid replacement is considered when there is clinical evidence of adrenal insufficiency (AI) such as asthenia, hypoglycemia, nausea, joint and muscle pain, weight loss, low blood pressure and postural hypotension (severe hypotension and hyperkalemia are not common due to the integrity of the renin- angiotensin-aldosterone system) [21-23]. Even though the serum cortisol levels are usually done 2 – 3 days post operatively to evaluate remission [22], some prefer measuring cortisol levels every 6 hours up to 72 hours following the surgery [20, 24].

Patients with a serum cortisol level of 5-10 μg/dl and clinically having AI features, GC replacement is instituted, however, since there is the possibility of delayed remission, GC treatment is considered in these type of marginal cortisol levels even without clinical features of AI [22, 23] to avoid possible AI which can occur with delayed remission.

The second strategy is initiating routine GC replacement therapy during the immediate postoperative period, however, there have been no comparisons of the benefits of one or the other approach. This second approach is mainly considered in patients who were treated medically prior to surgery and in patient who have the potential to develop surgical complications/ AI [21]. On immediate post operative days, replacement is done with intravenous (IV) hydrocortisone 25-50 mg 8 hourly/6 hourly followed by oral hydrocortisone [20, 24]. Some surgeons prefer treating with IV dexamethasone on initial few days before converting to oral hydrocortisone.

Evaluation for remission is a challenge in these patients. GCs are withheld for 24 hours to measure morning or serial serum cortisol levels during the first postoperative week [21].

The dose of hydrocortisone is usually 10 to 12 mg/m^2/day, and in practical terms doses up to 20 mg daily is given in 2 to 3 divided doses. Adjustment of the dose is done according to the clinical assessment. Tapering of the dose is considered after 2-4 weeks [6, 24]. Duration of the GC replacement will vary from patient to patient as time taken for the recovery of the HPA axis is variable and it will depend on the level of suppression of the normal corticotropes and the amount of normal corticotropes remaining [25]. If the complete removal of the pituitary is performed due to the challenging nature of the tumor and/ or surgery, the patient needs to be on lifelong physiological doses of GCs.

4. What are the factors that determine the potential of remission?

A few of the most important factors which increase the remission rates are, performing the surgery at a high volume center by an experienced neurosurgeon and tumour characteristics such as on magnetic resonance imaging (MRI), having a tumor size smaller than 10 mm and noninvasiveness [1, 26, 27].

5. How is a patient treated with preoperative medical treatment managed postoperatively?

Patients who were on medical treatment such as steroidogenesis inhibitors should be stopped several days prior to surgery, to minimize the risk of adrenal crisis (as a result of having low baseline cortisol levels) and to reduce the possible interference with postoperative cortisol assessment for remission [22].

6. What are the management options available following initial surgical failure?

If the biochemical remission is not achieved and the partial resection of the tumor is due to a non-approachable anatomy (e.g.- partial tumor resection due to invasion of the cavernous sinus) repeat surgical options can be considered following pituitary imaging with MRI [28-30]. Some institutes practice early surgery at 3-15 days by an experienced surgeon in a specialized facility if there is a residual tumor with non-remission [31, 32]. Remission rates are lower than with the initial surgery and range from 40-70% [29, 30]. However, early repeat surgery is not practiced in most of the institutes due to the possibility of achieving late remission.

If early surgery is not practiced, generally the repeat MRI is done 3 months after the initial surgery. Other secondary treatment modalities in failure to achieve remission following surgery are radiotherapy and medical therapy [1, 2, 33]. Bilateral adrenalectomy is only practiced as the last resort when all other treatment modalities fail.

7. What are the surgery associated complications and how is sodium related disorders managed?

In general, TSS has a very low perioperative mortality (0–1.5%) and low complication rates (2–1.5%) when performed by experienced neurosurgeons [34]. Myocardial infarction, pneumonia, meningitis, cerebrospinal fluid leak, bleeding or hematomas, epistaxis, venous thromboembolism and sodium disorders are the most commonly seen complications [35].

Transsphenoidal surgery can result in posterior pituitary dysfunction mainly manifesting as hyponatremia due to SIADH [36] or hypernatremia due to DI [37]. Monitoring frequency of serum sodium levels differ. Most monitor sodium levels daily or every second day until post operative day 10. Measurement of serum osmolality daily and monitoring the fluid balance are important in diagnosing and managing both SIADH and DI.

As in any other pituitary surgery, the main cause for the hyponatremia is SIADH and the peak incidence is normally from postop day 5 to 10 [36, 38]. Hyponatremia may be contributed by hypoadrenalism, so inadequate GC replacement may worsen hyponatremia. Mild hyponatremia (125-135 mmol/L) can be managed with fluid restriction, but severe symptomatic hyponatremia might need additional treatment with small boluses of hypertonic saline or slow infusion rates with frequent close monitoring of sodium levels [21].

Transient postoperative DI has been reported in 4% to 30% of patients with sellar lesions, with persisting DI seen in 0.3% to 7.3%. DI usually develops within 24 to 48 hours postoperatively and resolves normally in 3 to 5 days [21]. A combination of high output of hypotonic urine (> 250 -300 mL/h for 2 consecutive hours) and high serum sodium (> 145 mmol/L) are suggestive of DI [37]. DI is treated with desmopressin, starting with 0.5μg (subcutaneously or intravenously) or 50 to 100μg (oral) and repeated as needed [39]. Desmopressin nasal spray is also an alternative mode of administration. Scheduled doses should be avoided to reduce the risk of hyponatremia during the time when SIADH is normally predicted. Treatment duration is to be decided according to the predicted duration of DI, persistent DI need long term treatment.

8. How are other anterior pituitary hormone deficiencies assessed?

Assessment for anterior hypopituitarism is usually performed postoperatively around 4 to 6 weeks, but assessment of free thyroxine levels is done approximately 1 to 2 weeks post operatively (thyroxine half-life is around 1 week). Reevaluation is also recommended 4-6 weekly. If deficiency is diagnosed treatment with thyroxine should be initiated accordingly [40, 41].

In CD normal corticotrophs are suppressed due to the autonomous ACTH production by the tumor cells, following adenoma removal usually there will be in secondary adrenal insufficiency[2, 6].

Recovery of the HPA axis will vary from patient to patient. It might take weeks to years; median is considered around 12 months according to most of the studies [42,43]. Assessment generally starts 1-2 weeks postoperatively and then if needed can be repeated every 4-6 weekly with morning 9 am serum cortisol or dynamic testing (Short Synacthen Test/ Insulin tolerance test) [6]. Hydrocortisone should be stopped 12-24 hours prior to the assessment of the HPA axis. It is important to notice that there are some reported cases of non-recovery of HPA axis as well [42, 43].

Assessment for **growth hormone** is normally delayed until 6 to 12 months postoperatively. **Gonadotropin axis** assessment also done around 4-6 weeks, morning serum testosterone can be measured in males, and in premenopausal women menstrual history and estradiol measurements are used. A low or normal follicle-stimulating hormone (FSH) in a postmenopausal woman is a strong indicator of gonadotrophic dysfunction suggesting hypopituitarism [44].

9. What are the hypercortisolemia related common peri-operative complications?

Untreated CS is associated with significant morbidity and mortality due to complications and the risk is highest from the time of diagnosis until first 90 days post-operatively [45, 46]. Infectious, thromboembolic, cardiovascular, and metabolic complications need to be assessed and managed promptly to reduce the overall morbidity and mortality [2].

10. (A) Infection-related complications

What are the considerations in treating postoperative infections?

Infections are the most common cause of death in patients with CS and the highest mortality is within the first three months of commencement of treatment [45]. Hypercortisolism impairs both the cellular and humoral immune system defenses predisposing to opportunistic infections. Poorly controlled diabetes mellitus and vascular damage further increase the risk of infections [47].

Most frequent infections reported are skin and soft tissue related infections, pneumonias, urinary tract infections and sepsis [48]. P. jirovecii pneumonia (PJP) is one of the devastating infections in patients with CS with high mortality around 60-65% [49, 50]. These patients are also prone for other opportunistic infections such as Listeria, Nocardia, Legionella, Enterobacteriaceae, Mycobacterium, Candida, Aspergillus, Cryptococcus, Herpes simplex, Herpes zoster, Cytomegalovirus and Toxoplasma [3].

How are the at-risk patients identified?

The main risk factor for serious infections is the high circulating level of cortisol. Data of a retrospective study in 2000 by Nicholas J. Sarlis, Stephen J. Chanock et al. strongly suggested that UFC >2000 μg/day has a positive predictive value of 62.5% for severe infection [51]. The UFC for a normal person is < 90 μg/day and this much elevation is > 20 times the upper limit of normal (severe CS). Risk of PJP is highest among patients with severe hypercortisolemia but milder degree of elevation of cortisol (UFC - 5-fold upper limit of normal/ULN) is not a protective factor [49]. Infection risk relatively less in CD compared to ectopic and adrenal CS, but still very high compared to normal population [52]. Poor glycemic control, long standing diabetes and obesity are other associated risk factors for acquiring infections [47].

How do patients present with infections?

The clinical presentation can be diverse in patients with CS with an active infection. Classically patients with severe infection present with high grade fever and elevated inflammatory markers, but these features can be absent in patients with severe CS and often present with full-blown infection. PJP pneumonia is usually manifested as shortness of breath, non-productive cough, hypoxemia, and bilateral interstitial lung infiltrates on imaging. Immune reconstitution syndrome is a trigger for severe infections particularly PJP when treating CS with cortisol lowering medications. A similar phenomenon is observed in patients with retroviral infections with anti-retroviral therapy is initiated.

How are infections prevented in the peri-operative period?

PJP prophylaxis is one of the most important

strategies in patients with CS. There are no consensus guidelines for PJP prophylaxis in CS. PJP prophylaxis should be commenced in all patients with severe CS who have UFC >10 ULN and additional risk factors for immunodeficiency [21, 47]. The available best option is Trimethoprim-Sulfamethoxazole (TMP-SMX). The exact duration of antibiotic prophylaxis is not defined and usually continued 2 weeks following successful surgical therapy. If a patient with suspected PJP who is not responding to conventional antibiotic therapy TMP-SMX therapeutic doses should be initiated. Adjunctive steroids are prescribed if hypoxemia is present with PJP (PaO2 < 70 mmHg on room air or alveolar-arterial oxygen gradient ≥ 35 mmHg) [7]. The available options for PJP are shown in the following table (Table 1) [2, 3].

Table 1: Available prophylactic and treatment regimens for PJP

Drug	Phylactic dose	Therapeutic dose
Trimethoprim-Sulfamethoxazole (TMP-SMX)	A double-strength tablet (160/800 mg) or a single-strength tablet (80/400 mg) per day	15–20 mg/kg/day in 3–4 divided doses
Dapsone	50 mg twice daily or 100 mg daily	Dapsone 100 mg orally once a day + Trimethoprim 5 mg/kg orally 3 times daily

Tight blood sugar control is an important aspect in prevention of infection and is often achieved with insulin therapy.

Prophylactic antibiotics before the TSS of pituitary adenoma is used in patients with CD. Literature suggests the use of prophylactic antibiotics if patients have cerebrospinal fluid leak, comorbidities such as diabetes mellitus or obesity, preexisting sinus disease or having nasal packing after the procedure [53].

Vaccinations against SARS-CoV 2, Pneumococcus, Influenza, and Herpes zoster are recommended in all immunosuppressed patients. However, live vaccines are contraindicated as in patients who are on long term immunosuppressives [54].

10. (B) Thromboembolic complications

Why are the thromboembolic complications common in CS?

Hypercortisolism induces thrombogenicity inside the circulation in both the venous and arterial systems. The risk of venous thromboembolism is highest in the first year after the diagnosis until 2-3 months post-operatively. But it can last for even after remission of the disease because thrombogenic factors last longer [54]. The risk of venous thromboembolism (VTE) is approximately 18-fold compared to normal people [55]. The mechanisms involved in thrombotic complications are shown in the following figure (Figure 2).

Who are at risk of developing thrombotic complications?

Surgical immobilization after the surgery is the major risk factor for VTE in CD. Abrupt cortisol drop is also a well-recognized risk factor which predisposes for thrombosis. Poorly controlled diabetes, hypertension, and obesity along with proximal myopathy are other risk factors [47]

What are the predictive factors of VTE?

Patients with CS fall into moderate to high risk of thromboembolism according to Caprini score which is used for VTE in non-orthopedic surgeries to decide on thromboprophylaxis [58]. This is not validated for CS but still has been used in several studies for prediction of VTE. CD related complications like poorly controlled diabetes, sepsis, high BMI, stoke and history of VTE and post operative immobilization are some of the important risk factors lined up in.

Zilio et al. has also proposed another scoring system to stratify VTE risk based on several risk factors in patients with severe CS [59]. 1 point is given for acute severe infection, previous cardiovascular events, midnight plasma cortisol level > 3.15 ULN and shortened APTT and 2 points are given for elderly patients (age > 69 years) and reduced mobility. Depending on total score the risk is defined as a score of 2 points indicating low risk (10%), 3 points - moderate risk (46%), 4 points - high risk (85%) and

Table 2: Modified Caprini risk assessment and recommended thromboprophylaxis [47]

Risk factor	1 point	2 points	3 points	5 points
Age	41- 60 years	61-74 years	>75 years	
Type of surgery	Minor	Major or laparoscopic		Elective arthroplasty
Medical history	*Inflammatory bowel disease *unexplained/ recurrent abortion *sepsis < 1 month *Diabetes requiring insulin	*Current or past malignancy	*Previous VTE *Family history of VTE *Factor V Leiden, prothrombin 20210A mutation *Lupus anticoagulant *Elevated serum homocysteine *Heparin induced thrombocytopenia; *Other congenital or acquired thrombophilia	*Stroke *Hip, pelvis, or leg fracture *Acute spinal cord injury < 1 month
Physical findings	*Swollen legs *Varicose veins *BMI > 25 kg/m^2			
Other	*Pregnancy or postpartum period *Oral contraceptives or hormone replacement *Bed rest or restricted mobility *Smoking < 1 month			

≥ 5 points - very high risk (100%) for thromboembolism. This study did not focus solely on postoperative events but helps in identifying high risk patients [59].

When do we consider thromboprophylaxis?

There are no consensus guidelines for thromboprophylaxis in patients with CS. Depending on Caprini score of moderate to high risk (score 3 or more), both mechanical and chemical thromboprophylaxis are warranted with low molecular weight heparin, factor Xa inhibitors or vitamin K antagonists [21, 47]. If the bleeding risk is high mechanical thromboprophylaxis with intermittent pneumatic compression needs to be considered.

Timing of the thromboprophylaxis depends on timing of the surgery. Usually, anticoagulants can be restarted 24-48 hours after an uncomplicated TSS. Total duration of treatment after the surgery is 4-6 weeks and may be extended 2-3 months if the risk of VTE persist (history of VTE, immobilization) [47].

10. (C) Cardiovascular complications

What are the considerations related to cardiovascular and metabolic complications?

Hypercortisolemia elevates cardiovascular (CV) risk due to insulin resistance, visceral obesity, hemodynamic changes due to hypertension and activation of renin angiotensin aldosterone system [2]. CV events occur more frequently at the time of diagnosis and in the post-operative period. Most of the comorbidities resolve with remission of CS, but CV risk persist for many years [16].

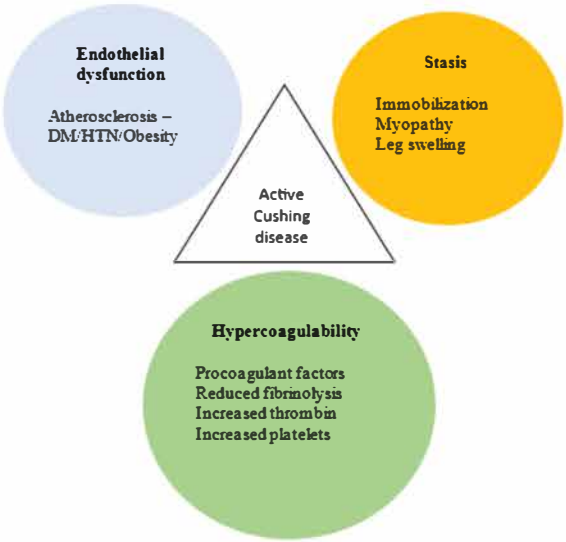

Figure 2: Pathogenesis of thrombotic complications in CS

How are CV events reduced peri - and post-operatively?

The endocrinologists need to be vigilant on development of CV risk factors and manage the risk factors promptly. Proper glycemic control, blood pressure management, lipid control and treatment of hypokalemia are the cornerstones for prevention of CV events. All oral hypoglycemic medications are used as first line therapy. Insulin can be used in poorly controlled diabetes. Selection of the type of oral hypoglycemic agent depends on other compelling indications such as the presence of established CV disease, diabetic nephropathy etc.

Out of the anti-hypertensives, mineralocorticoid receptor antagonists (MRA) are preferred to others as spironolactone or eplerenone effectively block the action of excess cortisol on mineralocorticoid receptors and effectively control elevated blood pressure and hypokalemia. Lipid lowering medications with statins are indicated in patients with diabetes for primary prevention of CV events [47].

11. What is glucocorticoid withdrawal syndrome (GWS)?

GWS is a collection of signs and symptoms which occur because of sudden withdrawal of supraphysiologic exposure to GCs of at least several months duration (either endogenous or exogenous). It is characterized by hypothalamic-pituitary-adrenal (HPA) axis suppression and features of adrenal insufficiency even after the replacement of GCs in physiological doses. Onset of symptoms are usually in 3-10 days of surgery [60].

Typical symptoms are fatigue, myalgias, excessive sleepiness, anorexia, nausea, and abdominal pain. Patients also present with features of psychiatry manifestations like depression and mood swings.

12. Why GWS is challenging to diagnose and manage post-operatively?

It is difficult to differentiate GWS from post operative secondary adrenal insufficiency (SAI) and recurrence of CS. All three conditions are associated with non-specific clinical presentations. Rapid weight loss is more in favor of SAI. Lack of sleep is more common in recurrence of CS while hypersomnia is more common among GWS [60].

It is often difficult to manage even with higher doses of exogenous steroids. But late day steroids should not be entertained as it will delay the recovery of HPA axis. Anti-depressants and short courses of non-steroidal anti-inflammatory drugs (NSAIDs), physical therapy and cognitive behavioral therapy (CBT) has some place in management of these chronic symptoms.

Myopathy is often difficult to treat without targeted treatment. Persistent myopathy after the surgery is associated with chronic fatigue syndrome and a recent study has shown that low IGF-1 is positively corelated with poor muscle function, however pre-operative IGF-1 cannot reliably predict long term muscle dysfunction [61].

Table 3 : Summary of CS related complications - How to prevent and manage.

Complication	Prevention	Management one established
Infections	* PJP prophylaxis for at least 2 weeks after surgery or until UFC is near normal [49] * Tight blood sugar control * Assessment for pressure ulcers -if immobilized * Vaccinations against SARS-CoV-2, Pneumococcus, Infuenza and Herpes zoster * Prophylactic antibiotics prior to TSS – if high risk factors	* PJP pneumonia - treatment dose + steroids
Thromboembolic events	* Early ambulation * Mechanical prophylaxis – compressive stockings, intermittent pneumatic compressions * Pharmacologic prophylaxis started 24-48 hours of TSS and continued for up to 2-6 weeks post-operative period (If high risk – started pre-operatively) [49]	* Therapeutic dose of anti-coagulation Vitamin K antagonists (warfarin), LMWH, Factor Xa inhibitors (Fondaparinaux), Direct oral anticoagulants
CV risk	*Tight blood glucose management * Monitor for hypertension * Correct hypokalemia promptly – predispose to long QT syndrome *Lipid management as indicated	*If established CVD – antiplatelet therapy, high dose statin therapy
GWS		* Steroid replacement – until symptoms resolve dose increment * Mood disturbances – anti-depressants, CBT * Muscle symptoms – NSAIDs, physical therapy

Conclusion

Correct post operative management will reduce the overall morbidity and mortality associated with CD. Following surgery, the challenges faced are related to the assessment of remission, treatment of hypopituitarism and prevention/ treatment of surgery and CD related complications. In this review, we discussed the evidence-based background and available management options, which will be beneficial in overcoming above-mentioned challenges.

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