MANAGEMENT OF ENDOCRINE DISEASE

**Cardiovascular risk assessment,
thromboembolism, and infection prevention
in Cushing's syndrome: a practical approach****Elena V Varlamov¹, Fabienne Langlois², Greisa Vila³ and Maria Fleseriu^{ID}¹**

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Abstract

Cushing's syndrome (CS) is associated with increased mortality that is driven by cardiovascular, thromboembolic, and infection complications. Although these events are expected to decrease during disease remission, incidence often transiently increases postoperatively and is not completely normalized in the long-term. It is important to diagnose and treat cardiovascular, thromboembolic, and infection complications concomitantly with CS treatment. Management of hyperglycemia/diabetes, hypertension, hypokalemia, hyperlipidemia, and other cardiovascular risk factors is generally undertaken in accordance with clinical care standards. Medical therapy for CS may be needed even prior to surgery in severe and/or prolonged hypercortisolism, and treatment adjustments can be made based on disease pathophysiology and drug-drug interactions. Thromboprophylaxis should be considered for CS patients with severe hypercortisolism and/or postoperatively, based on individual risk factors of thromboembolism and bleeding. *Pneumocystis jiroveci* pneumonia prophylaxis should be considered for patients with high urinary free cortisol at the initiation of hypercortisolism treatment.

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Introduction

A high mortality rate in untreated hypercortisolism patients drives a need for rapid diagnosis and treatment (1, 2). Patients with Cushing's syndrome (CS) have a

considerably high risk of cardiovascular, thromboembolic, and infectious complications, some of which can be life-threatening and may even require medical stabilization

Invited Author's profile

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prior to surgical treatment (3, 4, 5). Infections are the leading mortality cause within 90 days of a CS diagnosis, and cardiovascular (CV) events are major contributors to increased mortality in patients with active CS and during long-term remission (6, 7). Standardized mortality ratio is 1.6–3.5 (up to 10.0) in patients in remission and 4.1–6.9 (up to 16.0) in patients not in remission (8).

Management of CS patients includes two equally important facets, (i) timely diagnosis and treatment of hypercortisolism, and (ii) concurrent assessment and treatment of comorbidities. This approach should be considered in all CS patients, not only in severe cases, because the clinical phenotype and complications related to active CS may not correlate with the degree of cortisol elevation (9, 10, 11, 12). Coexistence of certain risk factors or complications may impact decision patterns for hypercortisolism treatment.

Here we summarize a practical approach for evaluating risks and management of high-mortality complications; CV, thromboembolic, and infections. Recognition and prevention of these complications are particularly important in the era of COVID-19 when delays in diagnosis and treatment can be anticipated

(13, 14). Other comorbidities are beyond the scope of this manuscript (Fig. 1).

Cardiovascular complications

Clinical case: A 56-year-old female is hospitalized with severe pneumonia. She has hypertension, obesity, osteoporosis with vertebral fractures and Cushing's stigmata on clinical exam. Evaluation reveals adrenocorticotrophic hormone (ACTH)-dependent CS with urinary free cortisol (UFC) 4 × the upper limit of normal (ULN). MRI shows a 7 mm pituitary adenoma, and ACTH is increased by 200% during corticotropin-releasing hormone (CRH) test. Transsphenoidal surgery (TSS) is recommended by a multidisciplinary team.

Question: How does one screen for and treat CV risk factors and comorbidities?

Epidemiology, morbidity and mortality

Chronic hypercortisolism increases CV morbidity and mortality by heightening several CV risk factors, such as

Figure 1

Complications of Cushing's syndrome. Created with BioRender.com.

visceral obesity, insulin resistance, diabetes, hypertension and hyperlipidemia compared to the general population (3, 4, 8, 10, 15, 16). Hypertension is reported in 25–93% of patients, diabetes in 11–47% and dyslipidemia in 12–72% (17). Myocardial infarction (MI) hazard ratio (HR) is 3.7 and stroke HR is 2.0 in patients with CS, when compared to the general population (3). Incidence of CV complications seems to be particularly high at the time of diagnosis, increases further postoperatively, and remains elevated during long-term follow-up (2, 3).

Cardiovascular complications have been consistently reported as a leading mortality cause in CS (17) accounting for 47–58% of deaths in long-term cohort studies (4, 8). Both arterial and venous thrombosis contribute to the CV mortality in CS (7, 17).

Pathophysiology

Glucocorticoids (GC) enhance insulin resistance directly and indirectly by increasing visceral fat, thereby contributing to the development of both diabetes and atherosclerosis (18, 19). Chronic hypercortisolism leads to low-grade inflammation paralleled by an altered immune response, thus playing an important role in atherosclerosis, visceral adiposity, and diabetes pathophysiology (20). Additional components leading to diabetes are a strong impairment of insulin secretion, reduced incretin effect, and liver glucogenesis (21). Glucocorticoids induce lipolysis and free fatty acid production resulting in accumulation of lipids in the liver and muscle, reduction in glucose uptake, and insulin resistance (22). Microvascular endothelial dysfunction, blood vessel fibrosis, and atherosclerosis coupled with thrombotic diatheses predisposes to MI and stroke (23, 24, 25).

There are three major players in the pathophysiology of steroid-induced hypertension; (i) mineralocorticoid receptor (MR) activity, (ii) the renin-angiotensin-aldosterone system (RAAS), and (iii) the sympathetic nervous system (26). These are concomitantly activated by excess GC, thereby disrupting the physiological balance between vasodilators and vasoconstrictors (26). Studies on the RAAS in CS have illustrated heterogeneous results, some showing low renin and aldosterone levels, while others normal or elevated levels (27). Suppressed renin and aldosterone levels may be due to elevated angiotensin levels and GC-mediated MR stimulation (27). Mineralocorticoid receptor stimulation also induces vascular and myocardial remodeling and fibrosis,

further promoting CV disease development in CS (28). Additionally, cortisol excess enhances reactivity of the vascular wall to vasoconstrictors (catecholamines, angiotensin II and endothelin-1) and inhibits vasodilator release (29).

Lastly, GC-induced hypokalemia may contribute to the increased prevalence of CV events, particularly arrhythmias. Hypokalemia is due to MR activation by cortisol excess and failure of normal cortisol-to-cortisone metabolism by renal 11-beta-hydroxysteroid dehydrogenase type 2 (HSD11B2). Defective HSD11B2 function may be due to saturation of its enzymatic capacity by cortisol, product inhibition or other mechanism (30). Hypokalemia is also a side effect of several CS therapies, such as mifepristone, metyrapone and osilodrostat (31, 32, 33, 34). Hypokalemia increases QT interval and can lead to many cardiac arrhythmias including potentially fatal Torsades de pointes (35).

Effect of Cushing's syndrome treatment on cardiovascular comorbidities

Glucose intolerance/diabetes, hypertension, dyslipidemia, and obesity must be assessed and treated prior to and after surgery or medical therapy. Appropriate treatment of comorbidities from initial CS diagnosis reduces not only perioperative risk, but also long-term morbidity (36).

Severe and/or prolonged hypercortisolism prior to surgery may necessitate cortisol-lowering therapy. Indeed, CS-specific therapy was used in 20% of the European Registry on Cushing's Syndrome (ERCUSYN) cohort, mainly in patients with worse clinical phenotype and more severe biochemical hypercortisolism (37). To date, preoperative cortisol-lowering therapy should be considered in severe cases or when surgery is not immediately available, but its benefit on reducing perioperative events related to hypertension, diabetes, thrombosis, infection risk and mortality has not yet been demonstrated in prospective studies (37).

Disease remission is associated with improvement of most comorbidities; however, some may persist, necessitating life-long management. Hypertension improves in 30–70% of patients in remission, diabetes prevalence decreases from 20–47% to 10–33% in treated CS patients, and CV event rates also decline. However, risk remains above that of general population: HR 3.6 for MI and HR 1.5 for stroke (3, 38). Persisting comorbidities positively correlate with hypercortisolism duration, and are inversely related to CS severity (as assessed by UFC), possibly reflecting a long diagnosis path in milder CS

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cases (10). Data assessing CV events when comorbidities were normalized or eliminated is lacking (36).

Cardiovascular risk assessment and management

Cardiovascular risk factors include not only CS-related cardio-metabolic changes and pre-existing CV disease, but also age, family history, and lifestyle which should be also considered for evaluating overall CV risk (Table 1). Modifiable factors such as insulin resistance, diabetes, hypertension and hyperlipidemia should be immediately treated to reduce perioperative risk. Hypercortisolism-

induced obesity is not expected to respond to lifestyle measures, nevertheless a healthy diet is recommended (39). A checklist for the identification and treatment of CV risk factors is provided in Table 1.

Diabetes treatment is dependent upon severity, which in turn is linked to genetic predisposition (40). Cyclic hypercortisolism or therapy-induced cortisol reduction might lead to discrepancies between glucose and HbA1c. Lowering of HbA1c to < 7% (53 mmol/mol) is desirable if possible, while avoiding hypoglycemia, though cut-off should be individualized based on age, diabetes duration and other factors (41). First-line therapy should

Table 1 Assessment and management of different aspects of cardiovascular health in Cushing's syndrome. Choice of test, procedure, and management should be individualized based on history, clinical presentation, comorbidities, tolerability and other factors.

Cardiovascular risk factors	Assessment	Management	Target
Not modifiable			
Age	—	—	—
Genetic predisposition	Family history of premature CVD (at age < 55 years in males or/ and at age < 65 years in females)	—	—
Modifiable			
Obesity	BMI, WC	Weight reduction; healthy diet; GLP-1 receptor agonists	BMI < 25 kg/m ² ; WC < 94 cm (male) and < 80 cm (female)
Smoking	Medical history	Cessation	Cessation
Hypertension	Single or 24–48 h ambulatory blood pressure monitoring	Spironolactone; beta blockers; ACE inhibitors/ ARBs; Other diuretics	Blood pressure < 140/90 mmHg, < 130/80 in patients with diabetes
Diabetes	Random glucose; fasting glucose; postprandial glucose/OGTT; HbA1c	Metformin, DPP4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, insulin, antithrombotic therapy	Fasting glucose: < 125 mg/dL (7 mmol/L); HbA1c: < 6.5–7% (or individualized goal); for both parameters, the lower the better without risking hypoglycemia
Hyperlipidemia	Total cholesterol; LDL cholesterol; HDL cholesterol; triglycerides	Statins, ezetimibe, PCSK9 inhibitors, fibrates	LDL cholesterol: < 2.6 mmol/L (< 100 mg/dL); LDL cholesterol in the presence of diabetes or hypertension: < 1.8 mmol/L (70 mg/dL); triglycerides: < 1.7 mmol/L (< 150 mg/dL)
Coronary artery disease, heart failure, arrhythmias, peripheral arterial disease, cerebrovascular disease	Electrocardiogram, echocardiography, cardiac CT, myocardial perfusion scan/ stress test, BNP/NT-proBNP, cardiac enzymes, carotid artery duplex, ankle-brachial index	Antithrombotic therapy, angioplasty, ACE inhibitors/ARBs, beta blockers, spironolactone, antiarrhythmics, in AF: anticoagulation	Heart rate 60–100 bpm; LVEF > 60%; normal coronary perfusion; normal BNP/ NT-proBNP; prevention of thromboembolic events
Hypercortisolism	24-h UFC, baseline cortisol, ACTH, midnight salivary cortisol, dexamethasone suppression test	Preoperative medical therapy if needed; surgery; postoperative medical therapy	Normal 24-h UFC; normal midnight salivary cortisol; normal morning cortisol/ ACTH; cortisol: < 1.8 µg/dL after overnight 1 mg dexamethasone

ACE, angiotensin-converting enzyme; ACTH, adrenocorticotrophic hormone; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; BNP, brain natriuretic peptide; CVD, cardiovascular disease; GLP-1, glucagon-like peptide -1; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro b-type natriuretic peptide; OGTT, oral glucose tolerance test; PCSK9, proprotein convertase subtilisin/kexin type 9; SGLT2, sodium-glucose cotransporter 2; UFC, urinary free cortisol; WC, waist circumference.

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include metformin, if not contraindicated, as an insulin-sensitizing agent (42, 43). Additional therapy should be started immediately if HbA1c is > 9% and within a few days at lower HbA1c levels if glucose targets are not achieved. Cardiovascular risk-lowering drugs such as sodium glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP1) receptor agonists can be considered as a second-line therapy (44). SGLT-2 inhibitors have positive effects in patients with heart failure and impaired renal function. Nevertheless, risk for genitourinary infections might be even higher in CS than that observed in other patients with diabetes. Sulfonylureas may have poorer response rate in CS (<25%) (21, 43). Thiazolidinediones (TZDs) may add risks of water retention, heart failure and fractures and may not be ideal choices in patients with CS. Insulin therapy can further predispose to weight gain, but may be required when targets are not achieved with other agents (45). A mixed basal/prandial insulin regimen allows adjustments for increased infection risk and changing degrees of hypercortisolism (e.g. during the initiation of specific medical therapy, in cyclic CS, and post-surgery). Per the American Diabetes Association guidelines, patients with diabetes and high CV risk should be also considered for antithrombotic therapy (e.g. aspirin 75–162 mg daily) (46).

Hypertension is treated with mineralocorticoid receptor antagonists (MRAs), beta-blockers and angiotensin-converting-enzyme-inhibitors or angiotensin 2 receptor blockers (36). Additionally, other drugs such as diuretics might be required, especially if edema and/or heart failure are present; MRAs (spironolactone, eplerenone) are effective at hypertension treatment in moderate-to-severe CS. Hypertension may occur in patients treated with mifepristone due to unopposed mineralocorticoid receptor activation by cortisol (32, 33, 36, 47), and less frequently with metyrapone and osilodrostat due to accumulation of cortisol/aldosterone precursors (32, 33, 36). MRAs can be used to counteract these effects (17, 32). Hypertension generally improves in remitted CS, however, may persist long-term. Close monitoring immediately postoperatively is necessary; pro-active reduction or even withdrawal of antihypertensive medications is needed in patients with adrenal insufficiency (AI) (36).

Structural heart disease diagnosed by echocardiography and other modalities (Table 1) should be treated appropriately. Central and peripheral artery disease requires antiplatelet therapy (e.g. aspirin 100 mg daily) (48, 49, 50, 51). Systematic reviews for primary prevention of coronary artery disease (CAD) support aspirin for reducing risk of arterial events in moderate

to high-risk patients (e.g. age >50 years with diabetes and additional risk factors) (52, 53), but risk must be individualized and balanced with gastrointestinal (GI) bleeding risk (46). Combined treatment with a proton-pump inhibitor seems judicious (53) and this approach could be extrapolated for patients with CS.

Hypokalemia predisposes to cardiac arrhythmias and increases perioperative risk, therefore should be treated promptly. Potassium replacement and administration of MRAs is often necessary, especially in patients treated with mifepristone, osilodrostat and metyrapone (32, 36).

Hypercortisolism *per se* is also a CV risk factor, and preoperative cortisol-lowering therapy may be necessary in patients with existing CV disease, high CV risk and/or high UFC (6, 54, 55). For acute cardiovascular events requiring intervention (e.g. MI, pulmonary embolism; PE), immediate cortisol reduction is needed. Steroidogenesis inhibitors are the pharmacotherapy of choice due to their rapid action; block and replace regimens are preferable in severe cases. In intubated patients with active CS, etomidate provides both sedation and decreases cortisol (54, 55). While cortisol reduction and cortisol blockade are associated with blood pressure improvement, patients treated with metyrapone, osilodrostat and mifepristone should be monitored for worsening hypertension as discussed earlier (33, 56). Improvement in blood sugar following cortisol reduction or due to GC blocker may require adjustment of the diabetes medications (32, 33).

Additionally, pituitary deficiencies related to pituitary tumor, surgery, radiation increase CV morbidity and mortality (57, 58, 59, 60, 61). Increased CV risk with testosterone replacement in men may exist, although is controversial, and few studies have shown a beneficial CV effect of sex hormone replacement in hypogonadal premenopausal women (57, 62). Other CS comorbidities such as depression, are known to increase CV risk in the general population, however, there are no conclusive results that illustrate a CV risk benefit from depression treatment (63).

Future perspectives

There is a need for comprehensive risk factors evaluation, establishment of screening algorithms and appropriate multidisciplinary (neuroendocrinologists, diabetologists, cardiologists) management after an initial CS diagnosis. Studies assessing the impact of early screening and intervention on CV risk reduction peri-operatively and the long-term are needed.

Thromboembolism in Cushing's syndrome

Clinical case: A 30-year-old female has persistent Cushing's disease (CD) after unsuccessful TSS. UFC is $1.5\text{--}2 \times \text{ULN}$ and BMI is 35 kg/m^2 . She is treated with osilodrostat postoperatively and desires pregnancy; therefore, bilateral adrenalectomy is recommended.

Question: Should one consider thromboprophylaxis in the perioperative management? When should one start and how long should treatment continue?

Epidemiology, morbidity and mortality

Hypercortisolism induces hypercoagulability predisposing to thrombotic and thromboembolic events (17, 64, 65). These can be venous, including deep venous thrombosis (DVT), PE, and cerebral venous sinus thrombosis; or arterial, such as MI or stroke, and may affect unusual sites such as mesenteric artery thrombosis (3, 64, 65, 66, 67, 68).

A recent meta-analysis showed that venous thromboembolism (VTE) risk in patients with CS was approximately 18-fold that of the general population (69), with rates ranging from 1.9–2.5% pre-operatively to 8.8–20% postoperatively (65). Excess VTE risk appears maximal during the first year after treatment (standardized incidence ratio; SID of 18.3) and persists long-term after remission (SID of 4.9) (2, 3). Venous and arterial events occur with similar frequency, VTE occurring most commonly during the first 2–3 months postoperatively (3, 70). Importantly, VTE accounts for 3.6–11% of all deaths in CS patients (12, 71), however, little guidance is available regarding thromboprophylaxis in this patient population.

Pathophysiology

Four aspects of hemostatic balance are altered in CS; (i) increase in pro-coagulation factors and shortened activated partial thromboplastin time (aPTT), (ii) impaired fibrinolysis, (iii) increased thrombin, thromboxane A₂ and platelets, and (iv) compensatory increase in anticoagulation factors such as protein C and S (72, 73, 74, 75, 76, 77, 78) (Fig. 2). Coagulation abnormalities persist up to 1 year or longer after remission (72, 78). Studies on changes in pro- and anticoagulant factors showed heterogeneous results; for instance, some demonstrated elevated Von Willebrand factor in active CS (75, 79, 80) while others did not (73, 78). Interestingly, a subset of CS patients has been found to have no changes in

coagulation parameters (81). Additionally, most (69), but not all studies (80) show no linear relationship between coagulation parameters and thrombotic events or degree of UFC elevation. Thus, there is not a definite coagulation profile linked to a higher thrombotic risk, and no evidence currently supports use of blood coagulation parameters to stratify individual patient's risk.

Additionally, vascular abnormalities exist in CS and contribute to the increased thrombotic risk. These include endothelial dysfunction (82, 83), increased intima-media thickness, vascular wall fibrosis and remodeling, increased vascular oxidative stress and atherosclerosis (24, 25, 84); these may also be related to CS-associated complications such as obesity, hypertension, insulin resistance and diabetes (85, 86, 87, 88).

Thromboembolism risk factors

Thromboembolism risk appears to be similar in pituitary and adrenal CS (HR 2.8 and 2.4, respectively) (3). However, experts recognize a higher risk of VTE in severe and ectopic CS/with a reported PE frequency of up to 14% (5, 35, 79). Patients with cancer-related ectopic CS, as well as those with adrenal carcinoma are at even higher thrombotic risk (89, 90, 91).

Surgery for CS is a risk factor *per se* for thromboembolism related to immobilization, type and extent of surgical procedure. Bilateral adrenalectomy (BLA) increases the odds of thromboembolism by 3.74 (70), however, this might be due to the underlying CS etiology or to CS severity.

Postoperatively, abrupt cortisol drop activates inflammation and increases coagulation parameters, further enhancing thrombosis risk (72, 78). However, limited evidence exists on preoperative medical therapy benefit in reducing thromboembolism risk in this period. Stuijver *et al.* found in a retrospective study a lower VTE rate in patients pretreated medically prior to pituitary surgery compared to those not pretreated (2.5 vs 7.2%) (92) though other studies did not find a benefit (37). A 12-month treatment with pasireotide did not improve the coagulation profile of patients with CS (15).

Additional risk factors include uncontrolled diabetes, hypertension and obesity, which carries a two-fold risk of VTE (93, 94). Glucocorticoid-induced myopathy causing muscle weakness and atrophy contributes to poor mobilization and venous stasis (95). As osteoporosis prevalence is higher in this population (96), limb fractures may occur and also lead to immobilization. Smoking, estrogen, and testosterone replacement could

Figure 2

Coagulopathy of Cushing's syndrome. Created with BioRender.com.

be additive risk factors for thromboembolism (97, 98), though not shown to affect VTE rates in CS in a recent meta-analysis (69).

Effects of thromboprophylaxis

There are no randomized placebo-controlled studies assessing thromboprophylaxis in patients with CS, and only two retrospective studies (79, 99). Boscaro *et al.*, studied two consecutive cohorts, one managed without thromboprophylaxis and one with unfractionated heparin for at least 2 weeks postoperatively, followed by warfarin for at least 4 months (79). Incidence of VTE was 3 × less in the treated cohort (6% vs 20%). However, improved surgical technique and non-pharmacologic prophylaxis could have contributed to improved outcomes in the second group. Barbot *et al.*, described two CD groups; one received postoperative enoxaparin for 14 days and perioperative glucocorticoid (GC) coverage and the other received enoxaparin for 30 days plus compression stockings and early mobilization. Three events occurred in the first group (3/34, 9%), there were none in the second group (99). Longer thromboprophylaxis, non-pharmacological

treatment or increased clinician's awareness possibly contributed to the observed difference. Interestingly, no bleeding complications were observed in either study in any of the treatment groups. In another retrospective study, only 1/50 anticoagulated patients developed a bleeding complication after receiving combined warfarin and enoxaparin regimen for bilateral DVT (70).

Smith and colleagues described their experience with a 6-week postoperative DVT prophylaxis using aspirin at 81 mg in 82 patients with CD and silent corticotroph adenomas; no symptomatic DVT was detected and 2 patients developed epistaxis (100).

Management

Different strategies are used worldwide, some recommend thromboprophylaxis only in severe/ectopic CS while others suggest thromboprophylaxis in all patients with CS (5, 35, 69, 79, 99). Due to a lack of guidelines, randomized controlled trials, and bleeding concerns, thromboprophylaxis in CS is not universally implemented. Indeed, risk of thrombotic complications and thromboprophylaxis benefit should be weighed

against bleeding risk. Though TSS and adrenalectomy (laparoscopic or laparotomy) are considered interventions with low to moderate thromboembolism risk (101), patients with CS fall into the moderate to high risk category based on Caprini score (not validated specifically for CS) and should be at least considered for anticoagulation (101, 102) (Tables 2 and 3). Zilio *et al.*, proposed a score to stratify VTE risk in patients with active CS (103) (Table 4); although this study did not focus solely on postoperative events, it may help identify high risk patients.

Common thromboprophylaxis regimens are presented in Table 5, however, specific regimen recommendations differ depending on the clinical scenario, society recommendations and local practice (101, 104, 105, 106, 107, 108, 109, 110). Timing of initiation should be coordinated with the surgeon (111, 112, 113). Prophylaxis initiated after 24–48 h post uncomplicated neurosurgery is considered safe (114, 115, 116), and may be extrapolated to patients undergoing TSS. In cases of clinically severe CS, thromboprophylaxis initiation could be considered while awaiting pituitary or adrenal surgery and held prior to surgery (timing adjusted based on anticoagulation regimen).

Given a higher VTE risk early postoperatively, it seems reasonable to continue thromboprophylaxis for 4–6 weeks (provided low risk of bleeding) and consider extending

up to 2–3 months in select patients with persistent thrombotic risk (e.g. immobilization, previous VTE). Additionally, elastic compression stockings, intermittent pneumatic leg compression and early ambulation should be incorporated in the prophylactic regimen of all patients (Fig. 3).

Future perspectives

There is an urgent need to develop guidelines for selecting patients for anticoagulation, duration and type of thromboprophylaxis in patients with CS patients. Prospective controlled studies would help answer these questions and provide a higher level of evidence. Additionally, studies investigating thromboembolism risk during medical therapy and the effect of preoperative medical therapy on VTE postoperatively are needed.

Infection

Clinical case: A 70-year-old male was hospitalized with severe CS manifesting with hypertension, diabetes, hypokalemia, and lower extremity edema. His UFC was $>90 \times \text{ULN}$ and ACTH $5 \times \text{ULN}$. Inferior petrosal sinus sampling was consistent with an ectopic ACTH source;

Table 2 Modified Caprini risk assessment and recommended thromboprophylaxis.

Risk factor	1 point	2 points	3 points	5 points
Age (years)	41–60	61–74	75	
Type of surgery	Minor surgery	Laparoscopic or major open surgery > 45 min		Elective arthroplasty
Medical history	Inflammatory bowel disease; unexplained/recurrent abortion; sepsis <1 month; COPD or pneumonia <1 month; acute myocardial infarction; congestive heart failure < 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 signs	Swollen legs; varicose veins; BMI > 25 kg/m ²			
Other	Pregnancy or postpartum; oral contraceptives or hormone replacement; bed rest or restricted mobility; smoking < 1 month			

This model is used frequently for assessment of VTE risk in non-orthopedic surgery. Thromboprophylaxis is warranted for moderate/high risk. Patients with CS often will score > 4 (based on age 40–60 years, swollen legs, obesity, low mobilization) and thus would be considered at least moderate risk. Of note, Caprini score has not been validated in patients with CS.

*Adapted from Gould *et al.* (101). *One might consider Cushing's coagulopathy similar to inherited coagulopathy. For comparison, levels of factor VIII >150 IU/dL reported in CS patients are similar to levels found in hereditary factor VIII elevation (149).

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Table 3 Recommended thromboprophylaxis based on calculated risk of venous thromboembolism in Caprini model.

	Postoperative VTE risk	Recommendation for most patients	If a high bleeding risk
Caprini Score			
0	Very low	No specific thromboprophylaxis	
1–2	Low risk	Mechanical prophylaxis*	
3–4	Moderate risk	LMWH or LDUH; mechanical prophylaxis	Mechanical prophylaxis
5+	High risk	LMWH or LDUH; mechanical prophylaxis	Mechanical prophylaxis (IPC > ES); initiate prophylaxis when bleeding risk diminishes
	High risk + cancer surgery, consider in all CS	Same as above + 4 weeks prophylaxis with LMWH post discharge	Mechanical prophylaxis (IPC > ES); initiate prophylaxis when bleeding risk diminishes
	High risk and contraindication to LMWH or LDUH	Fondaparinux or ASA 160mg daily; mechanical prophylaxis (IPC > ES)	Mechanical prophylaxis (IPC > ES); initiate prophylaxis when bleeding risk diminishes

*Mechanical prophylaxis, ideally with intermittent pneumatic leg compression (IPC) or elastic stockings (ES).

however, imaging failed to localize a tumor. Ketoconazole was initiated to rapidly control hypercortisolemia.

Question: When should one start and how long should *Pneumocystis jiroveci* pneumonia prophylaxis continue?

Cushing's epidemiology, morbidity and mortality

Cushing's syndrome suppresses the immune system and increases patient susceptibility to infections (17), which are almost five times more likely when compared to matched controls (3). This is particularly evident in the 1-year period after a diagnosis (HR: 17.8; range: 10.1–31.3) and reaches a maximum at 3 months after surgery (HR: 38.2; range: 16.9–86.1) (3). Infection prevalence in ectopic CS patients is higher (up to 51%) than in CD

(21%) patients (117, 118, 119, 120); pituitary and adrenal CS patients seem to have a similar infection HR (3).

As mentioned before, infection was the most common cause of death within 90 days after the start of CS treatment in the ERCUSYN registry study (6); 31% of deaths occur due to infections, surpassing CV and cerebrovascular events as a cause (6).

Infections include opportunistic and commonly acquired bacterial infections (*Staphylococcus*, *Streptococcus*, *Listeria*, *Nocardia*, *Legionella*, *Enterobacteriaceae*, *Mycobacterium*) as well as fungal infections (*Pneumocystis jirovecii*, *Candida*, *Aspergillus*, and *Cryptococcus*) and protozoa (*Toxoplasma*) (121, 122). Prolonged or severe viral infections due to herpes simplex, herpes zoster, and cytomegalovirus also occur (17, 118). To date, few case reports of COVID-19 infection in CS patients have been described in the literature (123, 124). Detailed expert opinions on management of such patients have been published (13, 14), but future studies will highlight the outcomes and management challenges in these patients.

P. jirovecii pneumonia (PJP) is a life-threatening infection with a mortality rate as high as 60–65% in patients with CS (though overestimation due to publication bias is possible) (17, 125). In comparison, mortality from PJP in human immunodeficiency virus (HIV)-infected patients and those with other immunodeficiencies is 10–20% and 35–50%, respectively (126, 127, 128, 129, 130). The incidence of PJP in CS is not well known, however, in one case-series, PJP occurred in 2% of pituitary and 57% of ectopic CS cases (125). Furthermore, *pneumocystis* infection may be misdiagnosed as other types of pneumonia due to unawareness, especially in cases of rapid and fulminant course and/or incomplete workup, and thus could be under reported.

Table 4 Venous thromboembolism risk evaluation in Cushing's syndrome proposed by Zilio *et al.*

	Risk factor
Evaluation	
1 point	Acute severe infection Previous cardiovascular events Midnight plasma cortisol level > 3.15 × the upper limit of normal shortened APTT
2 points	Age > 69 years Reduced mobility
Interpretation	
2 points	Low risk (10%)
3 points	Moderate risk (46%)
4 points	High risk (85%)
≥ 5 points	Very high risk (100%)

Based on retrospective analysis of data in 176 CS patients (103).

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Table 5 Examples of pharmacologic thromboprophylaxis regimens.

Regimen type	Consideration
Low-molecular weight heparin (LMWH) Enoxaparin 40 mg S.C. daily Dalteparin 5000 U S.C. daily Tinzaparin 4500 U S.C. daily Unfractionated (UF) heparin 5000 U twice S.C. daily or 7500 U twice S.C. daily (in higher risk patients) Factor Xa inhibitor Fondaparinux 2.5 mg SC daily Direct oral anticoagulants*** Apixaban 5 mg twice daily for 12 days (knee replacement) or 35 days (hip replacement) Rivaroxaban 10 mg daily for 12 days (knee replacement) or 35 days (hip replacement) or up to 31–39 days (acutely ill medical patients) Dabigatran 110 mg on day 1 and 220 mg daily for 28–35 days (hip replacement)	LMWH should be adjusted; if CrCl < 20–30 mL/min or if weight is over 100 kg. Alternative to LMWH in renal insufficiency; usually available only in hospital setting Alternative option to UF heparin or LMWH (e.g. in heparin-induced thrombocytopenia); avoid if CrCl < 30 mL/min Benefit/risk ratio similar to LMWH; convenient oral administration; No antidote; avoid if CrCl < 15 mL/min

Choice of the regimen depends on the clinical scenario (e.g. hospitalized acutely ill patient, orthopedic and non-orthopedic surgical patients), country, local practice and availability of the drug. Aspirin and warfarin are rarely used for thromboprophylaxis and are not included in the table. Listed regimens have not been prospectively studied in CS patients.

***Agents approved in the United States and some other countries for DVT prophylaxis after orthopedic surgery; Rivaroxaban is approved by FDA for VTE prevention in acutely ill medical patients who are at risk for thromboembolic complications not at high risk of bleeding.

COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; GI, gastrointestinal; LDUH, low dose unfractionated heparin; S.C., subcutaneously.

Pathophysiology and clinical manifestations

Persistent hypercortisolism interferes with cellular (neutrophil, eosinophil, monocyte, macrophage and natural killer) and humoral (complement and pro-inflammatory cytokines) immune system defense mechanisms (17, 20). Glucocorticoid excess impairs adaptive immune response by inhibiting T- and B-cell maturation and suppresses T helper 1 responses leading to higher risk of intracellular and opportunistic infections (17). Hyperglycemia and vascular damage also interfere with the immune system (17).

During the active phase of hypercortisolism, patients may lack classic signs of infection such as fever or localized pain making it difficult to suspect infection (122). At the onset of CS remission, abrupt reversal of immunosuppression can trigger a rigorous and exaggerated response to infections, similar to immune reconstitution inflammatory syndrome in HIV patients (125). This results in unmasking of dormant pathogens such as *P. jirovecii* in the lungs. *P. jirovecii* pneumonia manifests with fever, hypoxemia, dyspnea, nonproductive cough, bilateral interstitial lung infiltrates on X-ray or CT (Fig. 4) and increased alveolar-arterial oxygen tension

gradient (Table 6) (131, 132). Diagnosis is supported by elevated serum beta-D-glucan and confirmed by organism identification in induced sputum or bronchoalveolar lavage (133). Opportunistic and fungal infections should be suspected early in the course of any infection in CS patients, particularly in cases of no response to broad-spectrum antibiotics (17).

Infection risk factors

Severe hypercortisolemia is the main risk factor for serious infection. In a retrospective study, UFC >2000 µg/day (normal < 90 µg/day) had a 62.5% positive predictive value for any severe infection (118). Although, PJP was mainly described in patients with extreme UFC elevations (> 20 × ULN), it could also manifest with less severe hypercortisolemia (125). Cortisol lowering treatment typically triggers PJP development within a few days (134, 135, 136), though infection may occur before treatment in severe CS (137, 138). For comparison, in patients on GC treatment, median time to immune reconstitution after end of GC therapy is 8 days for fungal and 21–42 days for viral infection (139). Similarly, PJP due to immune

Figure 3

Proposed approach to prevention of cardiovascular, thromboembolic and infectious complications. Created with BioRender.com.

reconstitution syndrome in HIV-infected patients develops at median 15 days after antiretroviral therapy initiation (140).

Effect of *Pneumocystis jirovecii* pneumonia prophylaxis

P. jirovecii pneumonia prophylaxis is routinely used in different immunocompromised states (HIV-infected patients, transplant patients, cancer patients, and patients receiving high-dose GC with an additional cause of immunocompromise) and it effectively prevents infection manifestation and reduces mortality (141, 142).

A definition of high-dose GC dose is yet to be determined, though prednisone at ≥ 30 mg for >12 weeks merits PJP prophylaxis (143, 144).

Management

P. jirovecii pneumonia prophylaxis has been recommended for patients with high or moderate UFC elevation (5, 125). We consider that PJP prophylaxis should be used for all patients with ectopic or severe cases of CS with UFC >10 x ULN and patients with other risk factors for immunodeficiency. The chosen cut-off is, of course, somewhat arbitrary as risk of PJP seems to be the highest

Figure 4

CT showing bilateral ground glass opacities in a patient with Cushing's syndrome who developed *Pneumocystis jirovecii* pneumonia after initiation of ketoconazole.

with UFC $>20 \times$ ULN but the lowest UFC reported in a patient with PJP was $\sim 5 \times$ ULN (125), thus we consider using additional factors to assess the risks, as mentioned above. Trimethoprim-sulfamethoxazole (TMP-SMX) is well tolerated and therefore, risk-benefit ratio is low (125). However, physicians should be aware of potential interactions with ketoconazole and other medications due to risk of hepatotoxicity and QT prolongation. Prophylaxis should be initiated before CS therapy (either surgery or

medical therapy), however, can be initiated concomitantly in severe cases when emergent cortisol lowering is indicated.

Duration of PJP prophylaxis is not well-defined, but should be continued until infection reactivation and immunosuppression concerns are alleviated. It seems reasonable to continue for at least 2 weeks after curative surgery or near-normalization of cortisol with medication.

When PJP pneumonia is highly suspected or confirmed, treatment doses of TMP-SMX are needed typically along with adjunctive GC (starting with 40 mg prednisone twice daily with a subsequent taper). Prophylactic and treatment regimens for PJP are outlined in Table 5 (131, 132). Patients with AI following curative surgery and those receiving block-and-replace regimens should receive GC in stress-dose for illness. For patients with active CS and elevated cortisol levels, GC administration should be assessed on a case-by-case basis.

Other infection prevention

As hyperglycemia and DM are associated with infectious complications, we advise that patients with CS have strict glucose control, particularly postoperatively. Continuous insulin infusion with frequent glucose monitoring is often necessary peri-operatively and in seriously ill patients with CS (35).

Age-appropriate vaccinations including those against influenza, herpes zoster, and pneumococcal disease have been also recommended (5) and in an era of

Table 6 Common prophylactic and treatment regimens for *Pneumocystis jirovecii* Pneumonia.

Drug	Prophylactic dose	Treatment dose	Side effects and considerations
Trimethoprim-sulfamethoxazole	One double strength (160/800 mg) tablet daily or One single strength (80/400 mg) tablet daily	15–20 mg/kg/day in 3–4 divided doses	Fever, rash, agranulocytosis, nausea/vomiting, elevated transaminases Use with caution concurrently with ketoconazole (risk of QT prolongation and hepatotoxicity)
Dapsone	50 mg twice daily or 100 mg daily	Adjunctive prednisone* Dapsone 100 mg orally once per day plus Trimethoprim 5 mg/kg orally three times daily	Rash, nausea/vomiting, agranulocytosis, methemoglobinemia, hemolysis (test for glucose-6-phosphate dehydrogenase deficiency prior to use)
Atovaquone	1500 mg orally once daily (with food)	Adjunctive prednisone* 750 mg orally twice daily (with food) Adjunctive prednisone*	Nausea, diarrhea, rash, elevated transaminases

Alternative prophylactic regimens using pyrimethamine, leucovorin, and treatment regimens using primaquine, clindamycin, pentamidine are also available (131, 132).

*Adjunctive prednisone (40 mg twice daily for 5 days, then 40 mg once daily for 5 days, then 20 mg once daily for 11 days) is administered if $\text{PaO}_2 < 70$ mmHg on room air, alveolar-arterial oxygen gradient ≥ 35 mmHg, and/or hypoxemia is present.

COVID-19 are of more importance (13, 14). Live vaccines (such as varicella, herpes zoster, measles/mumps/rubella) are generally avoided in highly immunocompromised individuals and in those receiving immunosuppressive GC doses due to risk of disease caused by viral strains in the vaccine (145, 146). Since it is hard to assess the degree of immunosuppression in CS patients, we consider that live vaccine may be administered after CS has been in remission or controlled for a sufficient time and patient is no longer considered immunocompromised. Novel mRNA vaccine against SARS-CoV-2 is not contraindicated in CS patients; rare individual contraindications related to severe allergies exist (147, 148).

Future perspectives

Prospective randomized controlled studies in severe CS afflicted patients are likely not possible. Prospective or retrospective data collection into registries (institutional, national, international) may help better understand the incidence of PJP and other severe infections in CS. Guidelines should include recommendation on PJP prophylaxis and treatment in CS.

Conclusion

Recognition and treatment of cardiovascular, thromboembolic and infection complications are paramount in every CS patient, and should start at the time of diagnosis and continue through long-term follow up. A multidisciplinary approach, implementation of screening and management protocols will likely help reduce CS patient mortality.

Declaration of interest

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