Review

Cardiovascular risk assessment, thromboembolism, and infection prevention in Cushing's syndrome: a practical approach

Elena V Varlamov[1], **Fabienne Langlois**[2], **Greisa Vila**[3] and **Maria Fleseriu**

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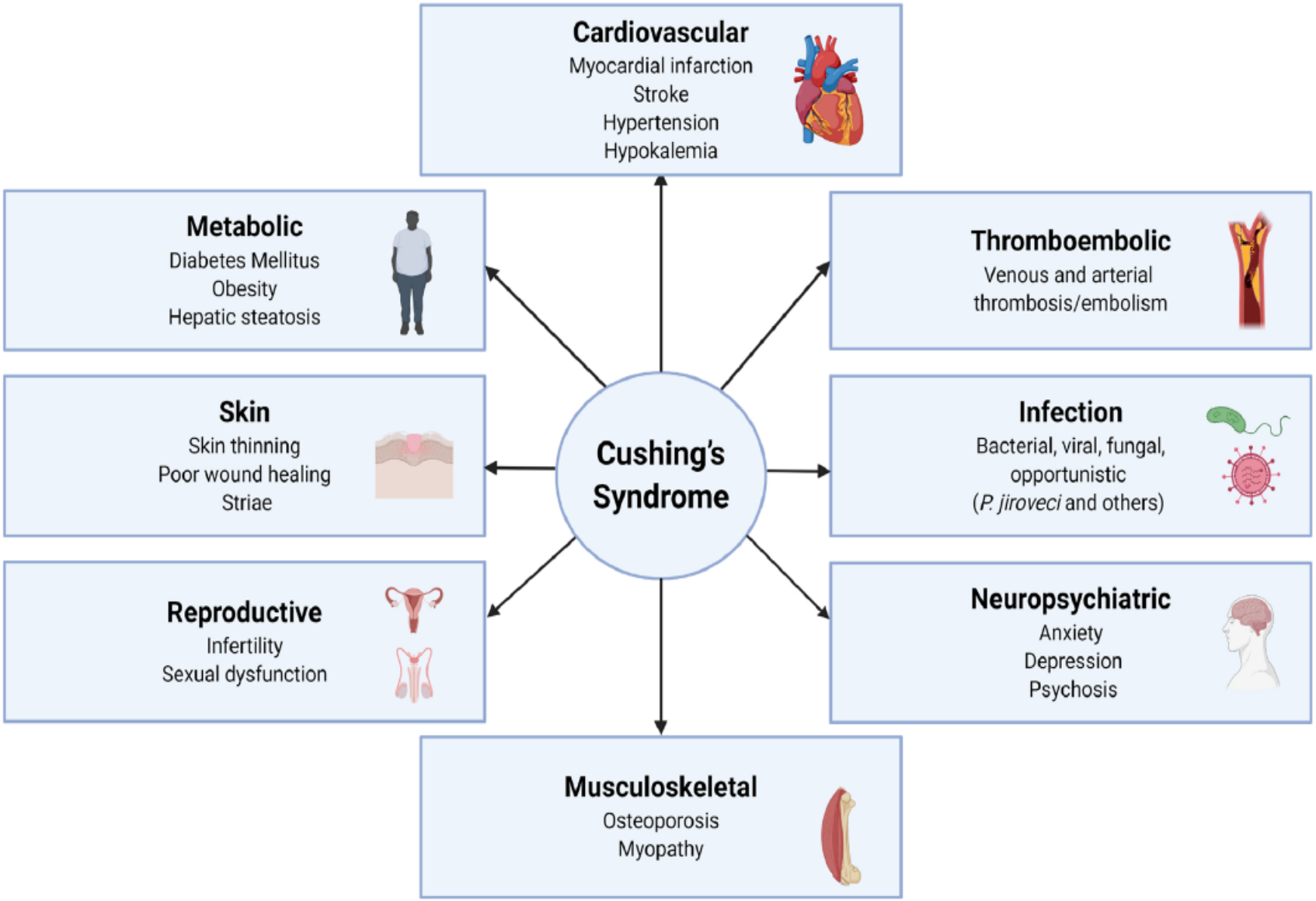
M.Heidarpour.MD

Endocrinologist

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.

Comorbidities



- Some of which can be life-threatening and may even require medical stabilization prior to surgical treatment.

- Thus it is important to diagnose and treat cardiovascular, thromboembolic, and infection complications concomitantly with CS treatment.

- Infections are the leading mortality cause within 90 days of a CS diagnosis.

- CV events are major contributors to increased mortality in patients with active CS and during long-term remission.

Management of CS includes two equally important facets :

- Timely diagnosis and treatment of **hypercortisolism**.

  and

- 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.**

Complications

- ✓ **Cardiovascular**
- ✓ **Thromboembolic**
- ✓ **Infection**

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 ACTH-dependent CS with UFC 4 × the ULN.

MRI shows a 7 mm pituitary adenoma, and ACTH is increased by 200% during CRH test. 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:

- ✓ Visceral obesity
- ✓ Insulin resistance
- ✓ Diabetes(11–47%)
- ✓ Hypertension(25–93%)
- ✓ Hyperlipidemia(12–72%)

MI hazard ratio (HR) is 3.7 and stroke HR is 2.0 in patients with CS, when compared to the general population .

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.**

- Cardiovascular complications have been consistently reported as a leading mortality cause in CS accounting for 47–58% of deaths.

- Both arterial and venous thrombosis contribute to the CV mortality in CS.

Pathophysiology

Glucocorticoids:

Enhance Insulin resistance directly and indirectly by:

- Increasing visceral fat : diabetes and atherosclerosis .
- low-grade inflammation paralleled by an altered immune response:

playing an important role in atherosclerosis, visceral adiposity, and diabetes pathophysiology.

Additional components leading to diabetes are:

- ✓ A strong impairment of insulin secretion
- ✓ Reduced incretin effect
- ✓ Liver glucogenesis

Glucocorticoids:

Induce lipolysis and free fatty acid production resulting in accumulation of lipids in the liver and muscle.

Reduction in glucose uptake, and IR.

Glucocorticoids:

- Microvascular endothelial dysfunction
- Blood vessel fibrosis
- AS coupled with thrombotic diatheses predisposes to MI and stroke.

There are three major players in the pathophysiology of steroid-induced hypertension:

A. Mineralocorticoid receptor (MR) activity
B. RAAS
C. The sympathetic nervous system

These are concomitantly activated by excess GC, thereby disrupting the physiological balance between vasodilators and vasoconstrictors.

Elevated angiotensin levels and GC-mediated MR stimulation:

Suppressed renin and aldosterone levels.

MR stimulation also induces vascular and myocardial remodeling and fibrosis further promoting CV disease.

Cortisol excess enhances reactivity of the vascular wall to vasoconstrictors (catecholamines, angiotensin II and endothelin-1) and inhibits vasodilator release.

GC-induced hypokalemia may contribute to the increased prevalence of CV events, particularly arrhythmias:

- ✓ Cortisol excess and failure of normal cortisol-to-cortisone metabolism by HSD11B2.
- ✓ Side effect of several CS therapies(mifepristone, metyrapone and osilodrostat) .

Increases QT interval and can lead to many cardiac arrhythmias including potentially fatal Torsades de pointes.

Effect of Cushing's syndrome treatment on cardiovascular comorbidities

Appropriate **treatment of comorbidities** from initial CS diagnosis reduces not only perioperative risk, but also long-term morbidity**.**

Preoperative cortisol-lowering therapy :

should be considered in **severe cases** or when **surgery is not immediately available**.

Its benefit on reducing perioperative events related to hypertension, diabetes, thrombosis, infection risk and mortality has not yet been demonstrated in prospective studies.

Disease remission

- Associated with improvement of **most comorbidities.**
- Some may persist, necessitating life-long management.
- Hypertension improves in 30–70%.
- Diabetes prevalence decreases from 20–47% to 10–33% in treated CS .

CV event rates also decline .

- However, risk remains above that of general population:
  HR: 3.6 for MI and HR:1.5 for stroke.

Persisting comorbidities positively correlate with:

✓ Hypercortisolism duration.

✓ **Inversely related to** CS severity (as assessed by UFC).

Possibly reflecting a long diagnosis path in milder CS cases.

Cardiovascular risk assessment and management

- Modifiable factors such as IR, DM, HTN 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.**

Diabetes

- **Cyclic hypercortisolism or therapy-induced cortisol** reduction
- might lead to discrepancies between glucose and HbA1c.

- Lowering of HbA1c to < 7% is desirable if possible, while avoiding hypoglycemia, though cut-off should be individualized based on age, diabetes duration and other factors.

Diabetes

- First-line therapy should include metformin, if not contraindicated.
- Cardiovascular risk-lowering drugs such as SGLT2 inhibitors and GLP1 RA can be considered as a second-line therapy.
- SGLT-2 inhibitors have positive effects in patients with HF 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%).
- 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.

Hypertension

- Hypertension is treated with MRAs, beta-blockers and ACEI or ARB.
- Diuretics: especially if edema and/or HF are present.
- MRAs are effective at hypertension in moderate-to-severe CS.

- 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.

Antiplatelet therapy

Central and peripheral artery disease requires antiplatelet therapy (e.g. aspirin 100 mg daily) .

Systematic reviews for primary prevention of CAD support aspirin for reducing risk of arterial events in **moderate to high-risk patients** (age >50 years with diabetes and additional risk factors).

Risk must be individualized and balanced with GI bleeding risk.

Combined treatment with a PPI seems judicious and this approach could be extrapolated for patients with CS**.**

Hypercortisolism per se is also a CV risk factor

- Preoperative cortisol-lowering therapy may be necessary in patients with existing CV disease, high CV risk and/ or high UFC.

- For acute CV events requiring intervention (MI, pulmonary embolism): Immediate cortisol reduction is needed.

- Steroidogenesis inhibitors :

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.

- Cortisol reduction and cortisol blockade:

  are associated with blood pressure improvement.

Pituitary deficiencies related to pituitary tumor, surgery, radiation increase CV morbidity and mortality.

Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline

Maria Fleseriu (chair), Ibrahim A. Hashim, Niki Karavitaki, Shlomo Melmed, M. Hassan Murad, Roberto Salvatori, and Mary H. Samuels

- Studies have shown a beneficial CV effect of sex hormone replacement in hypogonadal premenopausal women.

- Treatment with estrogens until age 45 years or longer may reduce the risk of cardiovascular disease and mortality.

Testosterone Therapy in Men With Hypogonadism: An Endocrine Society* Clinical Practice Guideline

J Clin Endocrinol Metab, May 2018, 103(5):1715–1744

- There have been no RCTs that were large enough or long enough to determine the effects of T-replacement therapy on major adverse cardiovascular events (MACE).
- Additionally, there is no conclusive evidence that T supplementation is associated with increased cardiovascular risk in hypogonadal men.

Increased CV risk with testosterone replacement in men may exist, although is controversial.

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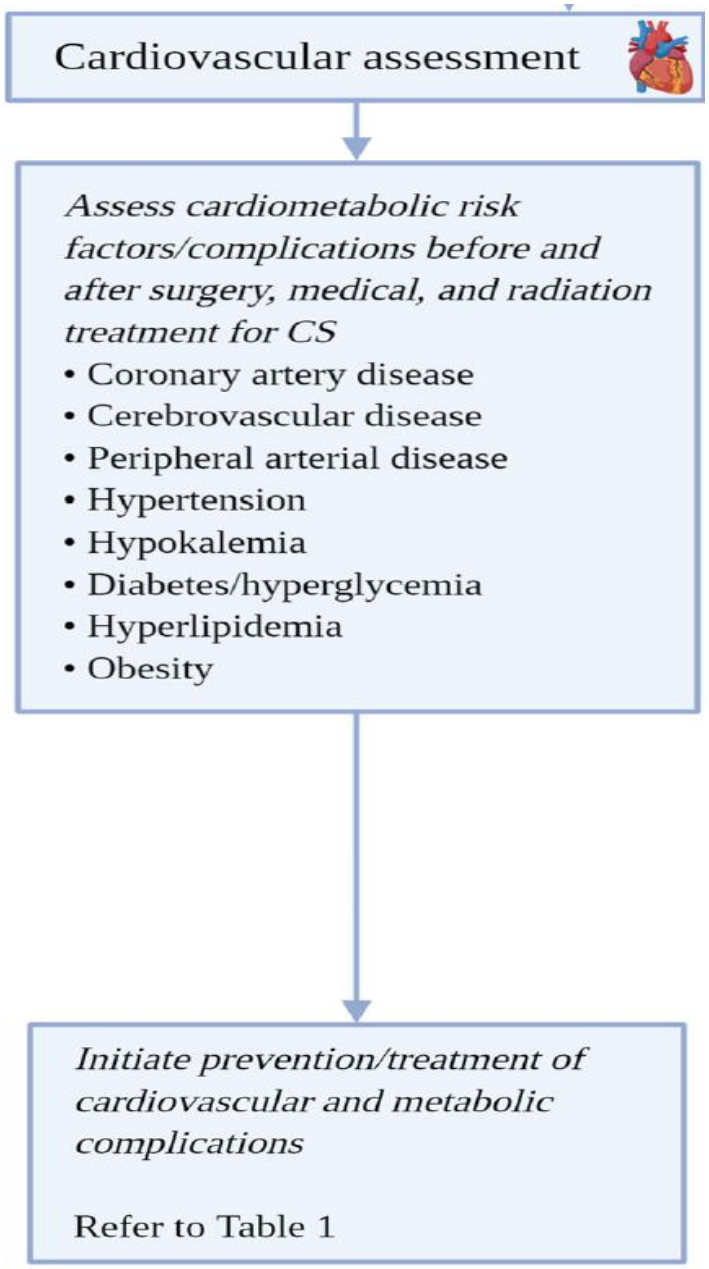


Checklist for the identification and treatment of CV risk factors

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)

Checklist for the identification and treatment of CV risk factors

Cardiovascular risk factors	Assessment	Management	Target
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

Complications

- ✓ Cardiovascular
- ✓ **Thromboembolism**
- ✓ Infection

Clinical case:

A 30-year-old female has persistent CD after unsuccessful TSS.

UFC is 1.5–2 × ULN and BMI is 35 kg/m^2.

She is treated with osilodrostat postoperatively and desires pregnancy; therefore, bilateral adrenalectomy is recommended.

Question:

1. Should one consider thromboprophylaxis in the perioperative management?
2. When should one start and **how long** should treatment continue?

Epidemiology, morbidity and mortality

- Hypercortisolism induces hypercoagulability predisposing to thrombotic and thromboembolic events.

- These can be venous, including DVT, PE, and cerebral venous sinus thrombosis; or arterial, such as MI or stroke, and may affect unusual sites such as **mesenteric artery thrombosis**.

Hypercoagulability and Risk of Venous Thromboembolic Events in Endogenous Cushing's Syndrome: A Systematic Meta-Analysis

frontiers in Endocrinology
January 2019

Jeffrey Wagner[1†], Fabienne Langlois[1,2†], Dawn Shao Ting Lim[1,3], Shirley McCartney[1] and Maria Fleseriu[1]*

Results:

48 studies met inclusion criteria.

There were 7,142 CS patients,average age was 42 years.

Odds ratio of spontaneous VTE in CS is 17.82 (95%CI 15.24–20.85, $p < 0.00001$) when comparing to a healthy population.

- VTE risk in patients with CS was approximately 18-fold that of the general population with rates ranging from 1.9–2.5% pre-operatively to 8.8–20% postoperatively .

Hypercoagulability in Cushing Syndrome, Prevalence of Thrombotic Events: A Large, Single-Center, Retrospective Study

Endocrine Society 2019.

Maria Gabriela Suarez,[1,2] Madeleine Stack,[2] Jose Miguel Hinojosa-Amaya,[2,3,4] Michael D. Mitchell,[5] Elena V. Varlamov,[1,2,3] Chris G. Yedinak,[2,3] Justin S. Cetas,[2,3,6] Brett Sheppard,[7] and Maria Fleseriu,[1,2,3]

Included were 208 patients; and mean age at presentation was 44.

Thirty-nine (18.2%) patients had a TE; extremity DVT (38%), cerebrovascular accident (27%), MI (21%), and PE (14%). Of 56 TEs, 27 (48%) were arterial and 29 (52%) were venous. Patients who underwent bilateral adrenalectomy (BLA) had an odds ratio of 3.74 (95% CI 1.69-8.27) of developing a TE.

Of patients with TE.

40.5% experienced the event within the first 60 days after surgery.

Conclusions: The risk of TEs in patients with CS was approximately 20%. Many patients had more than 1 event, with higher risk 30 to 60 days postoperatively.

- The optimal prophylactic anticoagulation duration is unknown, but most likely needs to continue up to 60 days postoperatively, particularly after BLA.

Venous and arterial events occur with similar frequency, VTE occurring most commonly during the first 2–3 months postoperatively .

VTE accounts for 3.6–11% of all deaths in CS patient however, little guidance is available regarding thromboprophylaxis in this patient population.

Pathophysiology

Four aspects of hemostatic balance are altered in CS:

1. Increase in pro-coagulation factors and shortened activated partial thromboplastin time (aPTT).
2. Impaired fibrinolysis.

3. Increased thrombin, thromboxane A2 and platelets

4. Compensatory increase in anticoagulation factors such as protein C and S.

❖ Coagulation abnormalities persist up to 1 year or longer after remission.

Hypercoagulability and Risk of Venous Thromboembolic Events in Endogenous Cushing's Syndrome: A Systematic Meta-Analysis

48 studies met inclusion criteria.

There were 7,142 CS patients

Odds ratio of spontaneous VTE in CS is 17.82 ($p < 0.00001$) when comparing to a healthy population.

- Coagulation profiles in patients with CS showed statistically significant differences compared to controls, as reflected by:
  - Increases in von Willebrand factor (180.11 vs.112.53 IU/dL, $p < 0.01$)
  - Increases in factor VIII (169 vs. 137 IU/dL, $p < 0.05$).
  - Decreases in activated PTT(26.91 vs. 30.65, $p < 0.001$)

Vascular abnormalities

Vascular abnormalities exist in CS and contribute to the increased thrombotic risk.

- Endothelial dysfunction
- Increased intima-media thickness
- Vascular wall fibrosis and remodeling
- Increased vascular oxidative stress and atherosclerosis

- These may also be related to CS-associated complications such as obesity, hypertension, insulin resistance and diabetes.

Thromboembolism risk factors

- TE risk appears to be similar in pituitary and adrenal CS (HR 2.8 and 2.4, respectively).

- Experts recognize a higher risk of VTE in severe and ectopic CS with a reported PE frequency of up to 14%.

- Patients with cancer-related ectopic CS, as well as those with **adrenal carcinoma** are at even higher thrombotic risk.

- Surgery for CS is a risk factor *per se* for TE related to **immobilization**, **type and extent of surgical procedure.**

- Bilateral adrenalectomy (BLA) increases the odds of TE by **3.74**, 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.

- Limited evidence exists on preoperative medical therapy benefit in reducing thromboembolism risk in this period.

Incidence of Venous Thromboembolism in Patients with Cushing's Syndrome: A Multicenter Cohort Study

- **Results:**
- A total of 473 patients
- The incidence rate for VTE prior to treatment was 12.9 (95% CI 7.5–12.6) per 1000 person-years .
- The risk of postoperative VTE, defined as risk within 3 months after surgery, was **0% for ACTH-independent** and **3.4% for ACTH** dependent CS.
- Most events occurred between 1 wk and 2 months after surgery.

A lower VTE rate in patients pretreated medically prior to pituitary surgery compared to those not pretreated (2.5 vs 7.2%).

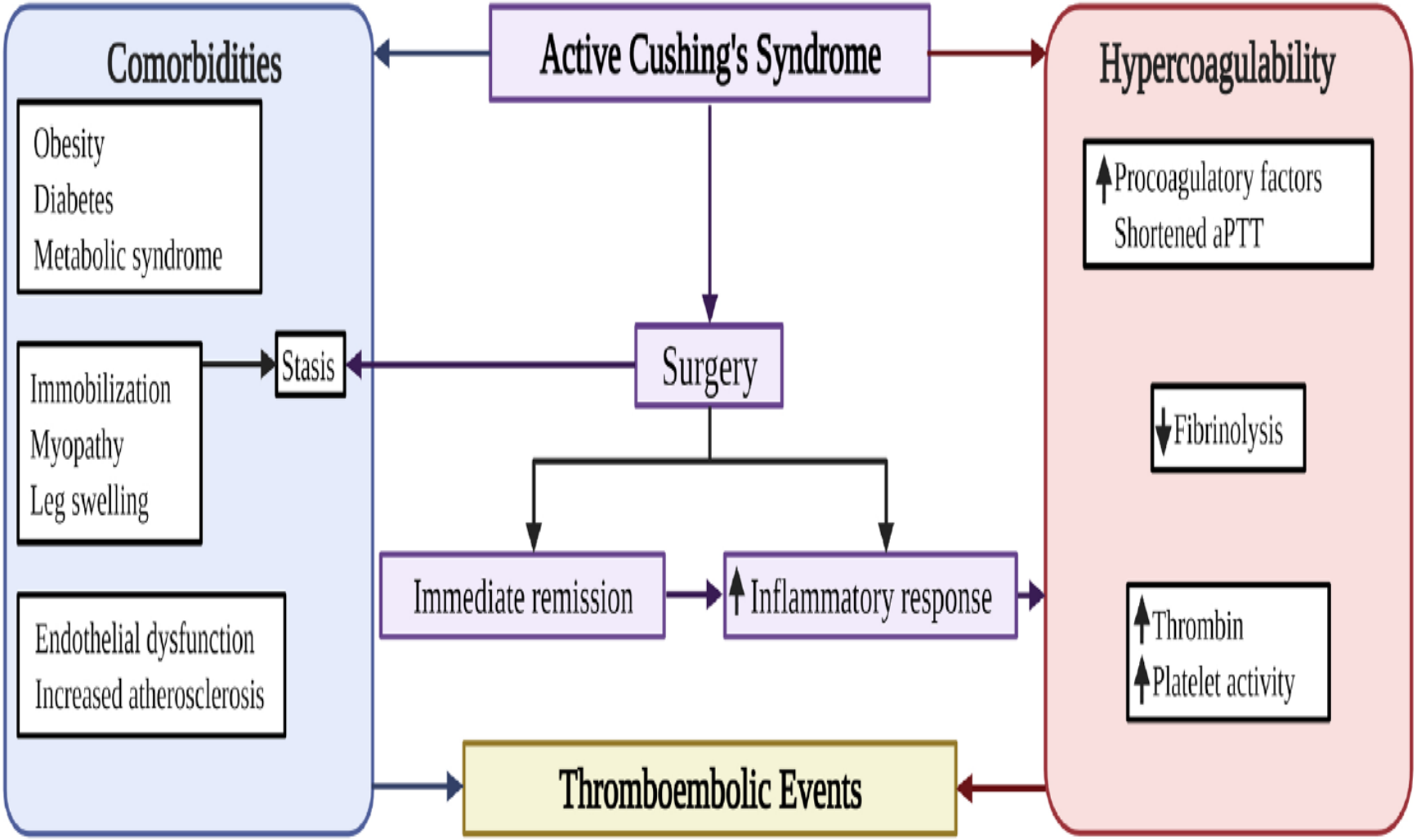
Additional risk factors include:

- Uncontrolled DM
- Hypertension
- Obesity

which carries a two-fold risk of VTE.

- Glucocorticoid-induced myopathy causing muscle weakness and atrophy contributes to poor mobilization and venous stasis.
- As osteoporosis prevalence is higher in this population, limb fractures may occur and also lead to immobilization.

Coagulopathy of Cushing's syndrome



Effects of thromboprophylaxis

There are no RCT studies assessing thromboprophylaxis in patients with CS, But only two retrospective studies.

0013-7227/02/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 87(8):3662–3666

Anticoagulant Prophylaxis Markedly Reduces Thromboembolic Complications in Cushing's Syndrome

- **The hypercoagulable state is related to an increase in plasma clotting factors, especially Factor VIII and von Willebrand factor complex, and to an impairment of fibrinolytic capacity.**

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Anticoagulant Prophylaxis Markedly Reduces Thromboembolic Complications in Cushing's Syndrome

Group 1: 75 patients not receiving anticoagulants.

Group 2 : 232 patients received unfractionated heparin for at least 2 weeks postoperatively, followed by warfarin for at least 4 months.

Incidence of VTE was 3 × less in the treated cohort (6% vs 20%). no bleeding complications were observed.

Perioperative thromboprophylaxis in Cushing's disease: What we did and what we are doing?

***Pituitary* 2015**

Two CD groups:

- Group A (34 patients): received fractionated heparin for a maximum of 14 days after surgery.
- Group B (44 patients): were given no early glucocorticoid replacement therapy, and treated with subcutaneous enoxaparin for 30 days plus graduated elastic stockings until mobilization, and early ambulation.

Three events occurred in the first group (3/34, 9%), there were none in the second group. No hemorrhagic events were reported .

Management

Different strategies are used worldwide, some recommend thromboprophylaxis only in severe/ ectopic CS while others suggest thromboprophylaxis in all patients with CS.

Management

Due to a lack of guidelines, RCT, and bleeding concerns, thromboprophylaxis in CS is not universally implemented.

Indeed, risk of thrombotic complications and thromboprophylaxis benefit should be weighed against bleeding risk.

TSS and adrenalectomy (laparoscopic or laparotomy) are considered interventions with low to moderate thromboembolism risk.

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.

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			

Of note, Caprini score has not been validated in patients with CS.

- 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.

- *Adapted from Gould *et al;*

  *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.

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).

specific regimen recommendations differ depending on the clinical scenario, society recommendations and local practice.

- Zilio *et al.*, proposed a score to stratify VTE risk in patients with active CS.
- Although this study did not focus solely on postoperative events, it may help identify high risk patients.

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%)

Timing of initiation :

- Prophylaxis initiated after 24–48 h post uncomplicated neurosurgery is considered safe.

- 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).

- 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.

Clinical case:

A 30-year-old female has persistent CD after unsuccessful TSS.

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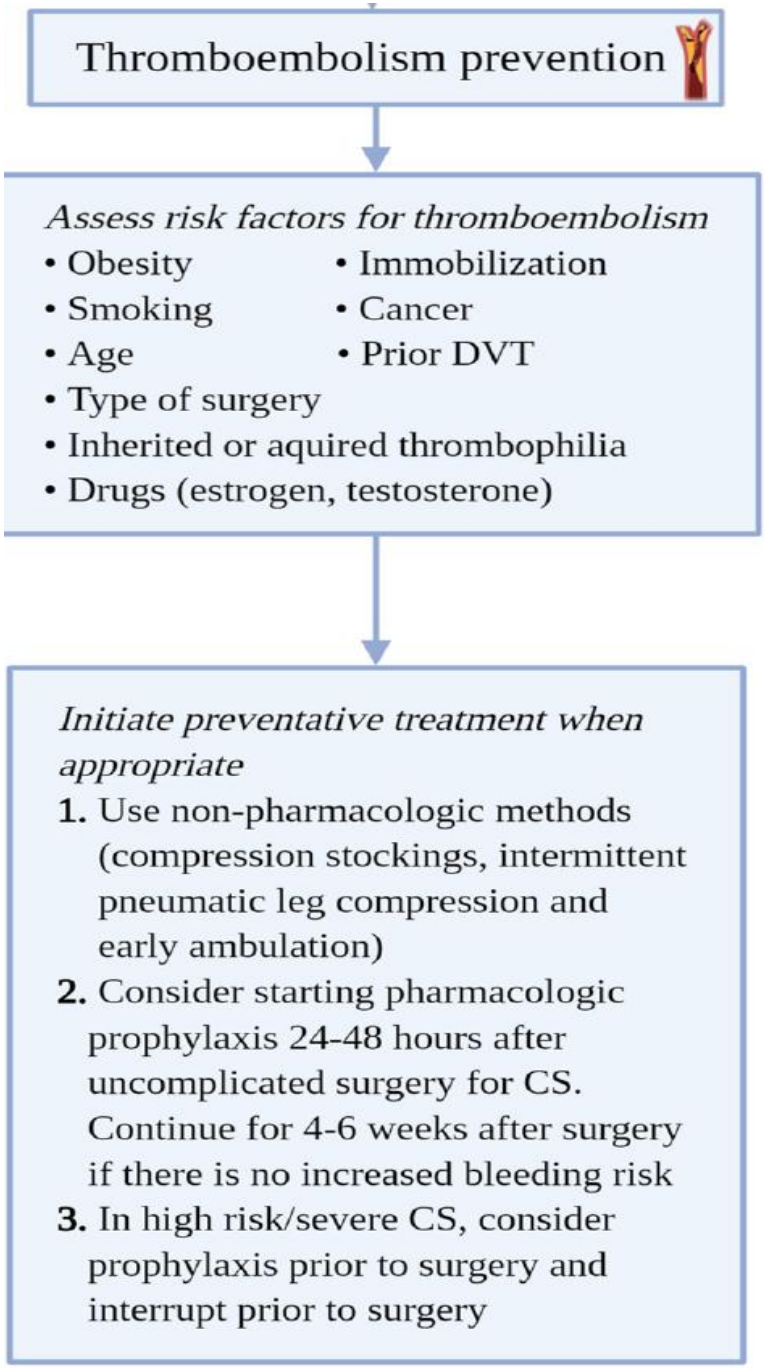

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Complications

- ✓ Cardiovascular
- ✓ Thromboembolism
- ✓ **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 × ULN and ACTH 5 × ULN.

IPSS was consistent with an **ectopic ACTH source.**

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?

Epidemiology

- CS suppresses the immune system and increases patient susceptibility to infections
- Almost five times more likely when compared to matched controls.
- Infection prevalence:

✓ In ectopic CS patients is higher (up to 51%) than in CD (21%) patients.

✓ **Pituitary** and **adrenal** CS patients seem to have a similar infection HR.

Multisystem Morbidity and Mortality in Cushing's Syndrome: a Cohort Study

J Clin Endocrin Metab

343 CS patients and 34,300 controls were included.

Mortality was twice as high in CS patients (HR 2.3, 95%CI 1.8 –2.9) compared with controls.

- Infections: HR 4.9, 95%CI 3.7– 6.4.
- This is particularly evident in the 1-year period after a diagnosis .
  (**HR: 17.8**; range: 10.1– 31.3).
- Reaches a maximum at 3 months after surgery.
  (**HR: 38.2**; range: 16.9–86.1).

Morbidity and Mortality

Infection was the most common cause of death within 90 days after the start of CS treatment in 31% of deaths occur due to infections, surpassing CV and cerebrovascular events as a cause.

High mortality within 90 days of diagnosis in patients with Cushing's syndrome: results from the ERCUSYN registry

European Journal of Endocrinology · September 2019

European Registry on CS (ERCUSYN)

In this cohort study, we analyzed 1564 patients.

49 patients had died .

23 (47%) with **CD**.

18 (37%) with **ectopic** CS.

6 (12%) with **adrenal** CS.

two (4%) with CS due to other causes.

Infection was the most common cause of death within 90 days after the start of CS treatment.

15 (36%) died due to progression of the underlying disease, 13 (31%) due to infections, 7 (17%) due to cardiovascular or cerebrovascular disease and 2 due to pulmonary embolism.

Commonest cause in patients with **CD and adrenal CS** :

infectious diseases (n = 8).

In patients with **ectopic** CS: Progression of the underlying tumor (n = 10).

Infections include :

- Commonly **acquired bacterial infections**:

  Staphylococcus, Streptococcus, Listeria, Nocardia, Legionella, Enterobacteriaceae, Mycobacterium

- **Fungal infections:**

  Pneumocystis jirovecii, *Candida, Aspergillus, Cryptococcus*

- **protozoa**: Toxoplasma

- Prolonged or severe **viral infections** due to herpes simplex, herpes zoster, and CMV.

Pneumocystis jirovecii pneumonia (PJP)

- A life-threatening infection
- Mortality rate as high as 60–65% in patients with CS.

- In comparison, mortality from PJP HIV-infected patients and those with **other** immunodeficiencies is 10–20% and **35–50**%, respectively.

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.

Pneumocystis infection may be misdiagnosed, especially in cases of rapid and fulminant course and/or incomplete workup, and thus could be under reported.

Characteristics and mortality of pneumocystis pneumonia in patients With Cushing's syndrome: a plea for timely initiation of chemoprophylaxis. ***Open Forum Infectious Diseases*** **2017**

Pathophysiology

Persistent hypercortisolism interferes with:

✓ Cellular:

Neutrophil, eosinophil, monocyte, macrophage, NK

✓ Humoral:

Complement and pro-inflammatory cytokines

Pathophysiology

GC excess impairs adaptive immune response by:

- ✓ Inhibiting T- and B-cell maturation
- ✓ Suppresses T helper 1 responses

leading to higher risk of **intracellular and opportunistic** infections

- ❖ **Hyperglycemia** and **vascular damage** also interfere with the immune system.

Clinical manifestations

During the active phase of hypercortisolism:

- May lack classic signs of infection such as **fever** or **localized pain** making it difficult to suspect infection.

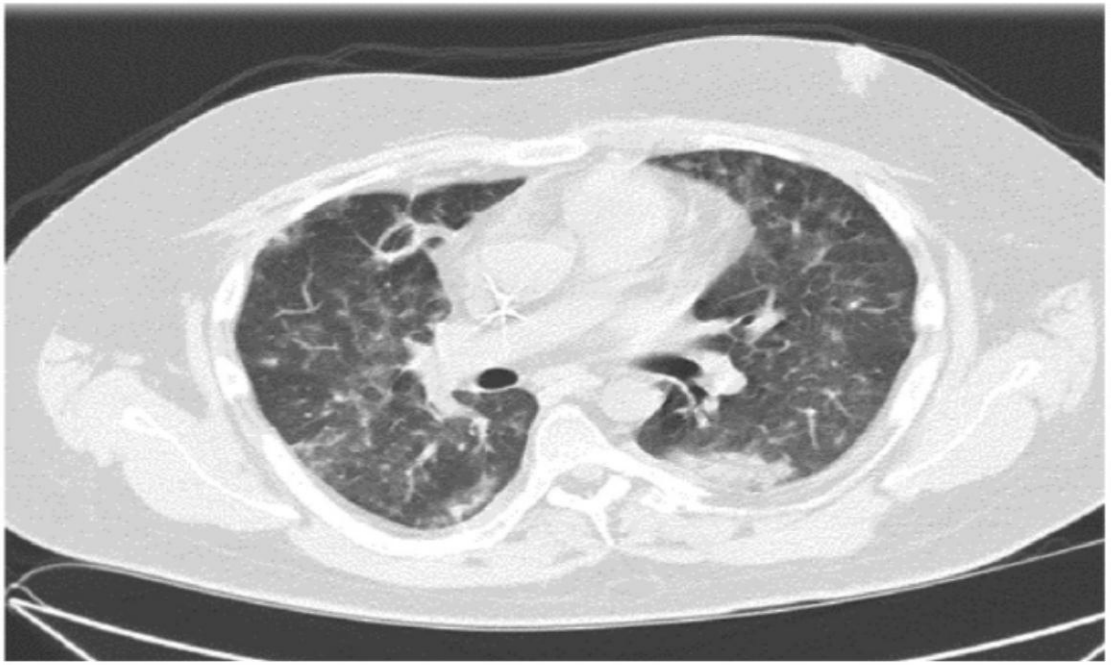
At the onset of CS remission:

Abrupt reversal of immunosuppression can trigger a rigorous and exaggerated response to infections.

This results in unmasking of dormant pathogens such as *P. jiroveci* in the lungs.

P. jirovecii pneumonia manifests with:

fever, hypoxemia, dyspnea, nonproductive cough, bilateral interstitial lung infiltrates on X-ray or CT and increased alveolar-arterial oxygen tension .



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

Diagnosis:

Supported by:

Elevated serum beta-D-glucan.

Confirmed by:

Organism identification in induced sputum or bronchoalveolar lavage.

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**.

Infection risk factors

Severe hypercortisolemia is the main risk factor for serious infection.

Cortisolemic Indices Predict Severe Infections in Cushing Syndrome Due to Ectopic Production of Adrenocorticotropin*

Journal of Clinical Endocrinology & Metabolism

UFC >2000 µg/day (normal < 90 µg/day) had a 62.5% **positive predictive value** for any severe infection.

The predictive value of total WBC count or the presence of an elevated temperature is not sufficient to identify patients with severe, life-threatening infection.

- PJP was mainly described in patients with extreme UFC elevations (> 20 × ULN), it could also manifest with less severe.

Cortisol lowering treatment typically triggers PJP development within a few days.

Though infection may occur before treatment in severe CS.

Effect of *Pneumocystis jirovecii* pneumonia prophylaxis

PJP prophylaxis is routinely used in different immunocompromised states:

- HIV-infected patients
- Transplant patients
- cancer patients
- Patients receiving high-dose GC with an additional cause of immunocompromised.

It effectively prevents infection manifestation and reduces mortality.

A definition of high-dose GC dose is yet to be determined:

prednisone at ≥ 30 mg for >12 weeks

merits PJP prophylaxis.

Management

- PJP prophylaxis has been recommended for patients with high or moderate UFC elevation .

- We consider that PJP prophylaxis should be used:

  For all patients with ectopic or severe cases of CS with UFC >10 × 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 with UFC >20 × ULN but the lowest UFC reported in a patient with PJP was ~5 × ULN,

thus we consider:

Using additional **factors to assess the risks.**

- **Trimethoprim-sulfamethoxazole** (TMP-SMX) is well tolerated and therefore, risk–benefit ratio is low.

- 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).

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 Adjunctive prednisone*	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	Dapsone 100 mg orally once per day **plus** Trimethoprim 5 mg/kg orally three times daily Adjunctive prednisone*	Rash, nausea/vomiting, agranulocytosis, methemoglobinemia, hemolysis (test for glucose-6-phosphate dehydrogenase deficiency prior to use)
Atovaquone	1500 mg orally once daily (with food)	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 $PaO_2 < 70$ mmHg on room air, alveolar-arterial oxygen gradient $\geq$ 35 mmHg, and/or hypoxemia is present.

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.

vaccination

- Age-appropriate vaccinations including those against influenza, herpes zoster, and pneumococcal disease have been also recommended and in an era of COVID-19 are of more importance.

vaccination

- 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 .

vaccination

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.

Clinical case:

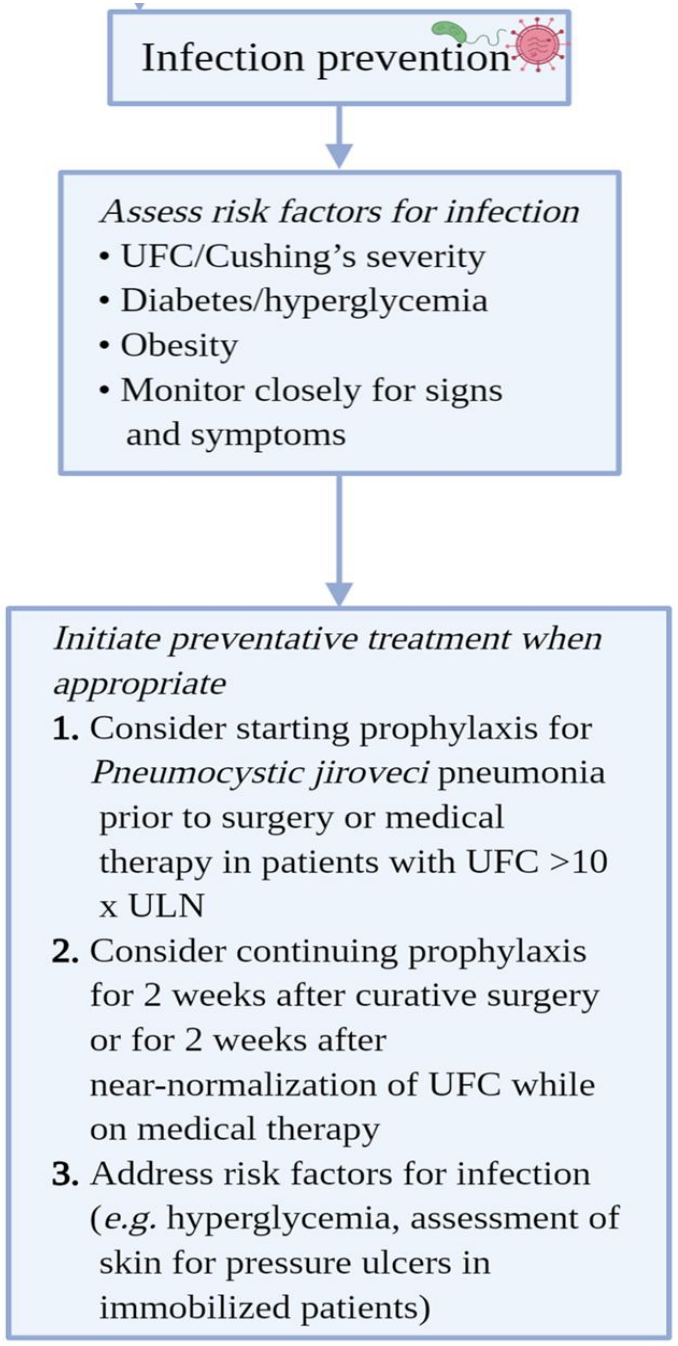
A 70-year-old male was hospitalized with severe CS manifesting with hypertension, diabetes, hypokalemia, and lower extremity edema.

His UFC was >90 × ULN and ACTH 5 × ULN.

Inferior petrosal sinus sampling was consistent with an **ectopic ACTH source**; however, imaging failed to localize a tumor. **Ketoconazole** was initiated to rapidly control hypercortisolemia.

Question:

When should one start and how long should *PJP* prophylaxis continue?



Cushing's Syndrome Diagnosis

Concomitant assessment for comorbidities

Cardiovascular assessment

Assess cardiometabolic risk factors/complications before and after surgery, medical, and radiation treatment for CS

- Coronary artery disease
- Cerebrovascular disease
- Peripheral arterial disease
- Hypertension
- Hypokalemia
- Diabetes/hyperglycemia
- Hyperlipidemia
- Obesity

Initiate prevention/treatment of cardiovascular and metabolic complications

Refer to Table 1

Thromboembolism prevention

Assess risk factors for thromboembolism

- Obesity
- Smoking
- Age
- Type of surgery
- Inherited or aquired thrombophilia
- Drugs (estrogen, testosterone)
- Immobilization
- Cancer
- Prior DVT

Initiate preventative treatment when appropriate

1. Use non-pharmacologic methods (compression stockings, intermittent pneumatic leg compression and early ambulation)
2. Consider starting pharmacologic prophylaxis 24-48 hours after uncomplicated surgery for CS. Continue for 4-6 weeks after surgery if there is no increased bleeding risk
3. In high risk/severe CS, consider prophylaxis prior to surgery and interrupt prior to surgery

Infection prevention

Assess risk factors for infection

- UFC/Cushing's severity
- Diabetes/hyperglycemia
- Obesity
- Monitor closely for signs and symptoms

Initiate preventative treatment when appropriate

1. Consider starting prophylaxis for *Pneumocystic jiroveci* pneumonia prior to surgery or medical therapy in patients with UFC >10 x ULN
2. Consider continuing prophylaxis for 2 weeks after curative surgery or for 2 weeks after near-normalization of UFC while on medical therapy
3. Address risk factors for infection (*e.g.* hyperglycemia, assessment of skin for pressure ulcers in immobilized patients)