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Consensus on Diagnosis and Management of Cushing's Disease:

A Guideline Update

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ABSTRACT

~~Objective:~~ Cushing's disease (CD) requires accurate diagnosis, careful treatment selection, and long-term management ~~of the disease and its associated comorbidities~~ to optimize patient outcomes. The Pituitary Society convened a Consensus Workshop comprising more than 50 academic researchers and clinical experts to discuss ~~recent evidence and its~~the application of recent evidence to clinical practice.

~~Participants:~~ ~~More than fifty academic researchers and clinical experts in pituitary pathophysiology, neurosurgery, endocrinology, and radiation oncology participated. The meeting was supported by unrestricted educational grants to the Pituitary Society.~~

~~Evidence:~~ ~~Speakers critically summarized key~~ In advance of the virtual meeting, recent data on ~~28 discrete topics across areas of~~ screening and diagnosis; ~~optimal use of and outcomes from~~ surgery, medical ~~therapy,~~ and radiation therapy; and ~~identification and management of~~ disease- and treatment-related complications~~.~~ of CD were critically summarized in recorded l~~L~~ectures ~~were recorded approximately one month prior to the meeting, and all experts were invited to watch the lectures and offer comments~~that were reviewed by all participants.

~~Workshop Process:~~ During the ~~virtual~~ meeting, ~~speakers provided highlight summaries of their assigned topics, which were discussed by all participants in~~concise summaries of the recorded lectures were presented, followed by small group breakout ~~sessions~~discussions. ~~Summaries and conclusions from group discussions~~Consensus opinions from each group were collated ~~and an evidence-based~~into a draft document ~~was sent to all participants for accuracy review, additional feedback, and approval~~, which was reviewed and approved by all participants.

~~Conclusions:~~ Recommendations ~~and key considerations for~~regarding use of laboratory tests, imaging, and ~~medical therapy~~treatment options are presented, along with algorithms for diagnosis of Cushing's syndrome~~, monitoring,~~ and management of CD. Topics considered ~~that were rated the~~ most important to address in future research ~~to further improve patient outcomes were~~are also identified.

INTRODUCTION

Cushing's disease (CD), the most common cause of endogenous Cushing's syndrome (CS), is caused by an adrenocorticotropin (ACTH)-secreting pituitary tumor.[1] Optimal patient outcomes require accurate diagnosis, careful treatment selection, and assessment and management of the disease and its associated comorbidities to optimize patient outcomes.[2] Notably, in comparison to patients with adrenal causes of CS, long-term quality of life (QoL) is worse for patients with CD.[3] Since clinical guidelines published in 2003,[4] 2008,[5,6] and 2015,[7] novel screening and diagnostic modalities have been identified and new treatments have been approved for use. These new developments highlight the need for updates to clinical guidelines on this challenging disorder.

The Pituitary Society convened a 2-day virtual workshop in October 2020 to discuss management of CD, with a goal of critically reviewing the current literature and providing recommendations for screening and diagnosis; optimal use of and monitoring outcomes from surgery, medical therapy, and radiation therapy; and identification and management of disease- and treatment-related complications. The focus was on pituitary, rather than adrenal or ectopic CS, and overlapping topics that had been recently covered in other consensus statements/reviews were not included.

We briefly review recent evidence and recommendations for clinical practice, grading the quality of the evidence supporting the recommendations and the strength of the consensus recommendations. ~~A summary of consensus recommendations, k~~Key considerations for use of different laboratory tests and medical ~~therapy~~therapies are presented in Tables 1 and 2.~~,~~ Consensus recommendations for management of CD complications and use of medical therapy for CD are presented in Panels 1 and 2. ~~and e~~Evidence/recommendations grading schema[8,9] are

presented in ~~Tables 1-5~~Panel 3. Algorithms for diagnosis~~, monitoring,~~ of CS and management of CD are presented in Figures 1 and 2. Topics that were rated the most important to address in future research to further improve patient outcomes are listed in ~~Table 6~~Panel 4.

Recommendations for adults with CD are presented here for use in clinical practice but should be considered alongside patient- and disease-specific factors for personalized care. A brief section regarding unique considerations in pediatric CD is presented at the end of the manuscript.

METHODS

Workshop co-chairs and steering committee members identified 28 discrete topics related to CD diagnosis, complications, and treatment to be addressed, and invited experts to summarize key data on their assigned topics in 15-minute, fully referenced slide-lecture~~s~~ presentations recorded approximately one month prior to the meeting. Speakers critically reviewed literature indexed in PubMed and published in English before October 2021. Search terms included "cushing's disease," "ectopic Cushing's," and terms associated with each topic: "diagnosis," "urinary free cortisol," "salivary cortisol," "screening tests," "confirmatory testing," "differential diagnosis," "localization testing," "genetics," "surgery," "radiation therapy," "medical therapy," "biochemical treatment goals," "tumor shrinkage," "clinical outcomes," "adrenal steroidogenesis inhibitors," "glucocorticoid receptor blockers," "somatostatin receptor ligands," "dopamine agonists," "mortality," "comorbidities," "quality of life," "preoperative treatment," "combination therapy," and "guidelines." All ~~experts~~ participants were invited to watch the lectures and offer comments in advance of the meeting. More than 50 academic researchers and clinical experts from 13 countries across 5 continents participated in the Workshop.

During the 2-day meeting, speakers provided 5-minute highlight summaries of their assigned topics. Participants were then divided into 4 small groups for extended discussions of each topic during 6 breakout sessions. ~~Group~~ Session moderators were provided with a set of key questions to prompt discussion. ~~Brief written reports on the discussion and consensus reached, along with lecture material and one-page summary précis from each speaker, were collated and edited to develop the recommendations.~~ One person in each group was designated in advance to take notes and assist in recording key discussion comments and consensus statements based on majority opinion.

After the meeting, speakers prepared detailed précis and literature reviews on their assigned topics. The fully referenced slide-lecture presentations, précis, and literature reviews were collated to prepare a draft manuscript, along with more recent data identified in a second literature review using the same keywords performed by the first and senior author in April 2021. Consensus recommendations for managing CD complications and use of medical therapy shown in Panels 1 and 2 were based on written reports from breakout sessions.

Speakers were asked to verify for accuracy manuscript sections related to their assigned topics, and the draft manuscript and consensus recommendations was circulated to all Workshop participants for review.

Speakers were also asked to suggest topics for future research that they consider most important. The full list of suggestions was sent to all participants, who were ~~invited~~ asked to vote for ~~those they considered most essential; the most highly ranked topics are listed in Table 6~~ their top 5 choices. The senior author tabulated responses; topics with more than 10 votes are shown in Panel 4. ~~Speakers confirmed the accuracy of the evidence summaries and all authors reviewed~~

~~and approved the final version of the manuscript.~~ After incorporating edits and comments, the final manuscript was again circulated for review and approval.

~~**Role of the Funding Source**~~

~~Supporters were invited to observe the highlight summaries, but did not observe the small group discussions, had no role in the development of consensus recommendations or topics for future research, and did not review the manuscript prior to publication.~~

DIAGNOSIS OF CS: SCREENING, CONFIRMATORY, AND LOCALIZATION MODALITIES

Laboratory Tests (Table 1)

Background

Diagnosis of CS is often delayed for years, at least in part due to lack of awareness of the insidious, progessive disease process and the complexity of testing.[10] Screening and diagnostic tests for CS assess cortisol secretory status: abnormal circadian rhythm with late night salivary cortisol (LNSC), impaired glucocorticoid feedback with overnight 1-mg dexamethasone suppression test (DST) or low dose 2-day dexamethasone tes (LDDT), and increased bioavailable cortisol with 24-hour urinary free cortisol (UFC).[5,6,11,12] In this setting, the sensitivity of all tests is above 90%, with the highest rates seen with DST and LNSC and the lowest with UFC; specificity rates are somewhat lower, LNSC being the most specific and DST and UFC the least specific.[12,13]

LNSC

The diagnostic utility of LNSC is based on the assumption that patients with CS lose the normal circadian nadir of cortisol secretion;[14,15] at least two or three LNSC tests are recommended.[5,16] Patients with mild CS may have LNSC results just above the upper limit of normal (ULN). Sampling saliva at usual bedtime rather than at midnight could decrease false positive results,[17] as cortisol nadir is tightly entrained to the onset of sleep. Although mass spectrometry can detect both cortisol and cortisone and therefore avoids potential contamination from topical hydrocortisone preparations, sensitivity is better than with immunoassay, but at the

220 expense of reduced specificity.[18] Multiple, periodic, sequential LNSC are particularly useful for
221 the longitudinal surveillance needed in distinguishing patients with cyclic CS who exhibit weeks
222 to months of normal cortisol secretion interspersed with episodes of cortisol excess.[19] By
223 contrast, this test should not be performed in patients with disruption of the normal day/night
224 cycle, such as night-shift workers.[14,15]
225
226 *Overnight 1-mg DST*
227 In healthy individuals, a supraphysiologic dose of dexamethasone inhibits vasopressin and
228 ACTH secretion, thereby decreasing cortisol levels. Thus, a serum cortisol value < 1.8 µg/dL (50
229 nmol/L) at 0800 h in the morning after oral administration of 1 mg dexamethasone between 2300
230 h and midnight is considered a normal response.[5] Sensitivity at this cut-off is higher than
231 specificity, and a negative result strongly predicts absence of CS. At higher cutoff points, e.g., 5
232 µg/dL (138 nmol/L), DST sensitivity is reduced.[12] When cortisol values are less than the lower
233 cut-off of 1.8 µg/dL, this excludes dysregulated cortisol production from an adrenal
234 incidentaloma;[20] in this setting, values over 5 µg/dL generally identifies patients with
235 dysregulated cortisol secretion from an incidentaloma who have overt CS. False positive results
236 may be seen with rapid absorption/malabsorbtion of dexamethasone, such as in patients with
237 increased gut transit time, chronic diarrhea, or celiac disease; concomitant treatment with
238 CYP3A4 inducers such as phenobarbital, carbamazepine, and St. John's wort (*Hypericum*
239 *perforatum*); and increased corticosteroid binding globulin (CBG) levels resulting from oral
240 estrogens, pregnancy, or chronic active hepatitis, as this may increase total cortisol levels.[21-23]
241 Measuring dexamethasone concomitantly with cortisol, using laboratory-specific ranges of
242 expected values, can confirm a suppressive concentration and reduce the risk for false-positive

results.[24,25] False negative results are less common, and may result from inhibition of dexamethasone metabolism by concomitant medications, such as fluoxetine, cimetidine, or diltiazem, which leads to a higher biologically available dose. Decreased CBG and albumin levels, such as in patients with concurrent nephrotic syndrome, also might produce a falsely low value.[26] Normative data with modern assays are also needed.

UFC

At least two or three 24-hour urine collections are advised to measure UFC to account for intra-patient variability.[5,27] One advantage with UFC over DST is that overall cortisol production is independent of changes in CBG, and is not dependent on dexamethasone compliance. However, although calculating the mean of several collections aids in correct interpretation, random variability can be as high as 50% between collections.[28] As with LNSC, UFC relies on accurate collection by the patient.

Sex, body mass index (BMI), age, very high or low urinary volume, and sodium intake can all influence UFC levels and should be taken into account for correct interpretation.[29-33] As urine volume and glomerular filtration rate strongly predict UFC, other screening tests such as LNSC may be preferred for patients with renal impairment (CrCl <60mL/min) or significant polyuria (>5 L/24 h).[34,35]

Testing for non-neoplastic hypercortisolism (pseudo-CS)

Psychiatric disorders, alcohol use disorder, polycystic ovary syndrome, and obesity may activate the hypothalamic-pituitary-adrenal (HPA) axis.[36,37] Such patients also may have concomitant features of CS that are common in the general population (e.g., weight gain) that

lead to biochemical screening. DST, LNSC, and UFC may all show positive (abnormal) results in these patients with non-neoplastic clinical hypercortisolism, or so-called pseudo-CS.[38] Furthermore, concomitant medications could result in steroid cross-reactivity or otherwise interfere with laboratory test results. However, these abnormal results tend to be mildly elevated; for example, UFC is almost always within 3-fold of normal. The combined LDDT-CRH (Dex-CRH) test, LDDT, or the desmopressin test may be able to distinguish between ACTH-dependent CS and pseudo-CS.[39-41] Utility of the Dex-CRH test in this setting is based on the assumption that only patients with ACTH-dependent CS will show a cortisol response to CRH after dexamethasone suppression.[42] However, test reliability may differ due to different protocols, use of various ovine or human CRH doses, characteristics of cortisol and ACTH assays, and patient characteristics (e.g., degree of hypercortisolism, adrenal versus pituitary CS, and underlying conditions). Use of the desmopressin test is based on the finding that ACTH-secreting adenomas express vasopressin V1b (V3) receptors, producing a rise in plasma ACTH after desmopressin injection.[43] The desmopressin test has a high specificity for CD[44] and is less complex and expensive than the Dex-CRH test, but both have shown good diagnostic performance in distinguishing CS from pseudo-CS in some studies; when both tests are done, they showed excellent agreement.[45,46]

Clinical Considerations and Recommendations

Screening and confirmatory testing for CS

There is no single preferred diagnostic test for CS, nor is there consensus on how to decide whether and when to test, although there have been attempts to develop a score for ease of diagnosis.[47] Clinical judgment and index of suspicion for CS are very important[48] and underscore

the need to individualize decisions about timing and selection for diagnostic testing based on the clinical scenario (HQ, SR).

If CS is suspected, any of the diagnostic tests may be useful. We recommend starting with DST, UFC, and/or LNSC (HQ, SR) depending on local availability, with the recognition that multiple LNSCs may be easier for the patient to complete (HQ, SR). If an adrenal tumor is suspected, we recommend starting with DST (MQ, SR) and only using LNSC if cortisone levels can be also reported[16,18] (MQ, SR).

DST may be the preferred test for shift workers and patients with disrupted circadian rhythm due to uneven sleep schedules, but may not be reliable in women treated with oral estrogen (HQ, SR). Measuring dexamethasone level may be useful if a false-positive DST is suspected due to the clinical scenario (MQ, SR). If UFC is used, two or three collections should be obtained to evaluate variability (HQ, SR). If LNSC is used, we recommend at least two or three tests (HQ, SR). Although there were initial concerns about increased risk for infection from SARS-CoV-2 with LNSC,[49] it remains safe for testing for lab personnel when used with proper precautions.[50] Bilateral inferior petrosal sinus sampling (IPSS) should not be used to diagnose hypercortisolism because the central-to-peripheral ACTH gradient in healthy controls and pseudo-CS overlaps that seen in patients with CD[51] (HQ, SR). In cyclic CD, dynamic testing and localization testing, including IPSS, should be preceded by a confirmatory LNSC, DST, or UFC to document that the patients are in the active phase.[52]

At this time, there is no preference for mass spectrometry over immunoassay in measuring cortisol level for diagnosis to ensure that patients with mild hypercortisolism are not excluded.[18,27] However, there remains a need for normative data with modern assays.

Ruling out pseudo-CS

Because the etiology of pseudo-CS can vary, there is no single approach to rule it out.[53] We recommend considering the patient's clinical history, particularly the duration of symptoms, and repeating testing to avoid implementing inappropriate treatment if CS is not present (LQ, DR). In most cases, patients have mild hypercortisolism and can be monitored for 3-6 months to see whether symptoms resolve; treatment of the underlying condition (such as depression) can restore normal HPA axis function and cortisol levels (LQ, DR). Standard diagnostic testing is unreliable in this population. LDDT or serial LNSCs over time correlate with the clinical picture (LQ, DR). Desmopressin is easy to use and easily administered in an outpatient setting. Dex-CRH in this setting could be valuable, but published diagnostic accuracy results have varied; use at an expert center with measurement of dexamethasone levels is advised (MQ, SR),[54] as is cortisol cut-off adjustments in very obese patients. Note that ovine CRH is not presently available in the United States, Canada, Brazil, Argentina, Mexico and some other countries.

Imaging and Tumor Localization

Background

MRI is the imaging method of choice for detecting ACTH-secreting pituitary adenomas. However, as most lesions are very small, using standard 1.5T MRI, only approximately 50% of microadenomas can be clearly depicted.[55]

Technical refinements including spoiled gradient–recalled (SPGR) acquisition echo with 1 mm slice intervals, fluid attenuation inversion recovery (FLAIR)[56] and constructive interference in the steady state (CISS), may enhance detection, while variants of T1-weighted turbo spin echo (TSE) sequences and use of ultra high field 3T and 7T magnets allow improved localization of

335 microadenomas.[57-60] Nevertheless, approximately one-third of scans in patients with CD still
336 remain negative,[61] and higher resolution with 3T or 7T magnets can increase the risk of detecting
337 incidentalomas that may be unrelated to the disorder.
338 Importantly, tumor size does not necessarily correlate with degree of hypercortisolism in CD.
339 In fact, patients with larger adenomas frequently present with milder hypercortisolism.[62]
340 Positron emission tomography (PET) has been explored as an alternative to, or in
341 combination with, MRI for localization of corticotroph adenomas. ^{18}F-fluoro-deoxy-glucose
342 (^{18}F-FDG) PET/CT was shown to be largely comparable to standard fast spin echo MRI in
343 detecting pituitary lesions in one series,[63] while a separate study found both standard spin echo
344 MRI and high resolution ^{18}F-FDG PET were inferior to SPGR MRI.[64] Prior stimulation with
345 ovine CRH can increase ^{18}F-FDG uptake and thus increase detection.[65] PET coregistration with
346 volumetric MRI (PET/MRCR) combines functional and anatomical imaging. ^{11}C-methionine
347 used in this setting may permit more accurate localization of sites of radiotracer uptake.[66] In one
348 series, this technique correctly localized corticotroph adenomas in patients with *de novo* disease
349 and persistent/recurrent hypercortisolism following primary surgery, most of whom had negative
350 or equivocal standard spin echo MRI.[67] However, this approach is not available or approved in
351 most countries. Alternative strategies (e.g., targeting CRH-R1 expression on corticotroph
352 tumors) have also recently been proposed, but require further study.[68]
353
354 ***Clinical Considerations and Recommendations***
355 MRI remains the imaging modality of choice for ACTH-secreting pituitary adenomas (HQ,
356 SR). We suggest 3T over 1.5T MRI where available (LQ, DR). 7T MRI is not widely available

and there is currently no justification for re-imaging on 7T MRI if no tumor is detected on 1.5T/3T MRI.

It is likely that functional imaging will ultimately prove a better approach than MRI alone. However, more data are needed to define use of different ligands in various clinical settings. Although advanced imaging technologies may be available in some centers of excellence, the benefit of referring all patients for further imaging beyond 3T MRI remains unknown.

Distinguishing Between CD and Ectopic ACTH-dependent CS

Background

In patients with CD, glucocorticoid (GC) receptors typically retain the ability to inhibit ACTH secretion in the presence of high doses of dexamethasone, and V2 and V1b (V3R), along with CRH receptor are all overexpressed. By contrast, most (but not all) ectopic ACTH-secreting do not express these receptors. Accordingly, desmopressin and CRH stimulation testing have proven useful in distinguishing between pituitary and ectopic tumors.[69-71] Increased plasma ACTH and increased cortisol following CRH or desmopressin administration usually indicates CD.[72-76] Using more than one dynamic test might further improve accuracy.[77] Nevertheless, well-differentiated neuroendocrine tumors (NETs) may also express any or all of these receptors, potentially leading to a false positive result. High-dose DST, although it has low accuracy overall, is still used in some countries. None of the diagnostic tests reach 100% specificity and results may be discordant in up to one-third of patients;[5,6] differences in type of ectopic tumor, as well as patient age, sex, and severity of hypercortisolism can all influence outcomes.

IPSS, which measures ACTH in pituitary vs peripheral venous drainage, has long been the gold standard to reliably exclude ectopic ACTH production.[78,79] and should preferably be

performed in a specialized center due to the potential risks. A central-to-peripheral ACTH gradient <2 before or <3 after stimulation suggests an ectopic tumor; however, both false negatives and false positives have been reported. Prolactin measurement may improve diagnostic accuracy in such cases and it is essential that patient is hypercortisolemic at the time of IPSS.[80]

A non-invasive approach using a combination of three or four tests, specifically CRH and desmopressin stimulation plus MRI, followed by whole-body CT if diagnosis is equivocal, correctly diagnosed CD in approximately half of patients in one series, potentially eliminating the need for IPSS.[81] Interestingly, a positive CT scan despite negative CRH/desmopressin stimulation and MRI had a negative predictive value of 100%. Currently, this combination of laboratory and imaging testing as a noninvasive approach to distinguish between pituitary and ectopic ACTH-secreting tumors is likely limited to specialized centers.[82]

^{68}Ga-DOTATATE is a modified (Tyr3)-octreotide molecule covalently linked to 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetra-acetic acid (DOTA) combined with the radioactive ^{68}Ga isotope. The radiopharmaceutical, with a half-life of approximately 1 hour, binds to somatostatin receptors with an affinity similar to octreotide and can be used as a tracer in PET imaging of ectopic ACTH-secreting NETs.[83] ^{68}Ga-DOTATATE localizes about 65% of these tumors,[84] including those not seen or not definitively identified on cross-sectional imaging, and images are sharper than with single photon ^{111}In-DTPA-pentetreotide, with greater sensitivity for small tumors.[85,86] False positives can occur due to chronic inflammation, and a positive scan does not definitively prove that the NET is the source of ACTH, but ^{68}Ga-DOTATATE imaging can be useful in guiding clinical management.[87]

The ^{68}Ga isotope is typically derived from decaying ^{68}Ge and the worldwide supply of ^{68}Ge is being exhausted. The ^{68}Ga isotope, if it can be generated locally via a cyclotron, or ^{64}Cu,

403 which has a longer 12.7-hour half-life and can be centrally produced, may be used as alternative
404 DOTATATE, DOTATOC, or DOTANOC conjugates.[88]
405
406 ***Clinical Considerations and Recommendations***
407 No single laboratory test or combination of tests can absolutely differentiate between
408 pituitary and ectopic ACTH-secreting tumors (HQ, SR). We recommend using both the clinical
409 context and test results to guide management (HQ, SR). ~~For example, in a patient with features~~
410 ~~strongly suggesting an ectopic ACTH syndrome,~~When prompt access to brain MRI is not
411 available, neck-to-pelvis thin-slice CT scan ~~may be performed prior to pituitary MRI~~is useful if
412 suspicion is high for ectopic ACTH syndrome, such as in a male with very high UFC and/or
413 profound hypokalemia[81] (LQ, DR).
414 If a pituitary tumor ≥10 mm is detected on MRI and dynamic testing results are consistent
415 with CD, IPSS is not necessary to confirm the diagnosis (MQ, SR). As it is possible that a
416 pituitary lesion seen on MRI is an incidental nonfunctioning adenoma or other sellar mass and
417 the ACTH source is ectopic, clinical presentation should always be considered. Some studies
418 suggest this is true for lesions >6 mm, but not all expert centers use this lower cutoff. There was
419 consensus that all patients with lesions <6 mm should have IPSS and those with lesions of ≥10
420 mm do not need IPSS (MQ, SR). Expert opinions differ regarding tumors 6-9 mm, but the
421 majority recommended IPSS to confirm the diagnosis in this circumstance (MQ, DR). Notably,
422 some of the differences between centers and countries are based on interventional radiology
423 availability. Prolactin measurement can be useful in ruling out a false negative IPSS (MQ, DR).
424 While IPSS has high diagnostic accuracy for localization to the pituitary gland, it is not
425 sufficiently reliable for tumor lateralization to the right or left side of the gland (MQ, SR).

A noninvasive alternative using high-dose DST and CRH stimulation test could predict CD if both tests are positive.[89] However, if tests are discordant, IPSS is necessary (LQ, DR). Emerging data suggest that CRH/desmopressin testing with pituitary MRI followed by whole-body CT scan might be a reliable alternative, if assessed by an experienced multidisciplinary team (VLQ, DR).

COMPLICATIONS OF CD (~~Table 2~~Panel 1)

Strategies for CD management should consider how comorbidities and complications associated with CD may compromise patient health and QoL. Comorbidities should be addressed in many cases concomitant with or even before CD-specific treatments to restore normal cortisol levels.

Hypercoagulability

Background

Hypercoagulability in CS resulting in an increased risk of thromboembolic events (TE) is paradoxically coupled with an increased bleeding tendency due to skin atrophy and capillary fragility.[90,91] Most patients show an activated coagulation cascade, including shortened activated partial thromboplastin time and increased concentrations of fibrinogen, von Willebrand factor, and factor VIII, as well as impaired fibrinolysis mediated by elevated levels of plasminogen activator inhibitor-1 and antiplasmin. Increased thrombin, thromboxane 2, and platelets, with a compensatory increase in anti-coagulation factors such as protein C and S, have also been implicated.[92,93]

The incidence of venous thromboembolic events (VTE) in patients with endogenous CS is more than 10-fold higher versus those with nonfunctioning adenomas undergoing surgery[94] and the odds-ratio is 18-fold higher compared with the healthy population.[92] VTE risk persists in the first few months after CD surgery, indicating that hypercoagulability is not immediately reversible with cortisol normalization.[92,95,96] At 30 days, VTE risk post adrenalectomy was 3.4 to 4.75%,[96] and the odds ratio for TE after bilateral adrenalectomy (BLA) in a longer-term study was 3.74 (95% CI: 1.69-8.27).[95] In a series of 17 patients, biochemical remission following

short-term medical therapy (pasireotide ± cabergoline ± ketoconazole) also did not seem to reverse the risk, as it was not accompanied by changes in pro-anticoagulation factors, and pulmonary embolism occurred in two patients with a marked UFC decrease.[90,97]

Data from retrospective studies[98,99] indicate that thromboprophylaxis can decrease the incidence of postoperative VTE, particularly when extended to 30 days. Surveys indicate increased awareness of the need for thromboprophylaxis as well as increased anticoagulation use in clinical practice,[100] but strategies to identify patients most likely to benefit are still being developed.[101]

Clinical Considerations and Recommendations

There is currently no standard practice for preoperative or postoperative thromboprophylaxis in patients with CD. Some experts hold estrogen therapy in women who are awaiting surgery, but care should be taken if it was being used as contraception, because pregnancy also is associated with increased risk of thrombosis (LQ, DR). In the absence of contraindications, we recommend prophylactic anticoagulation be considered for all patients at increased VTE risk, including: a history of embolism or abnormal coagulation testing; severe preoperative hypercortisolism (e.g., UFC >5 × ULN); current use of estrogen or oral contraceptives; poor mobility; von Willibrand factor polymorphism; extended preoperative or postoperative hospital stay; and high postoperative cortisol levels or GC over-replacement for adrenal insufficiency (MQ, SR). For all patients, early postoperative ambulation and use of compression stockings should be encouraged[102] (HQ, SR).

In cases where perioperative anticoagulant thromboprophylaxis is administered, there was strong consensus for preference of low molecular weight heparin over oral anticoagulants given

477 the long half life of the latter and the lack of therapy to reverse their effect, which may be
478 especially concerning in the preoperative setting (LQ, DR).

479 There is also no standard practice for the duration of anticoagulation if administered. Among
480 meeting participants, recommended treatment duration ranged in the preoperative setting from 2-
481 4 days to 1-2 weeks, and in the postoperative setting from 1-2 days of the hospital stay up to 2-4
482 weeks or even longer to 2-3 months (LQ, DR). Anticoagulants may be stopped before surgery
483 and restarted after surgery to minimize intraoperative bleeding risk, but there was no consensus
484 on the timing of when to stop and restart prophylaxis.

485

486 **Cardiovascular Disease**

487 ***Background***

488 Patients with CD show an adverse cardiovascular disease risk profile that may persist even
489 after successful treatment.[103-106] Visceral, subcutaneous, and total fat may decrease after
490 remission, although most patients remain overweight or obese.[107] Type 2 diabetes mellitus
491 (T2DM) is present in up to 30% of patients, and dyslipidemia, with low high-density lipoprotein
492 (HDL), high low-density lipoprotein (LDL), and high triglycerides, has been reported in 16-64%
493 of cases at diagnosis. In many patients, but not all, T2DM resolves after remission.[108] Structural
494 cardiovascular changes improve, including left ventricular hypertrophy, concentric remodelling,
495 dilated cardiomyopathy, increased intima media thickness, and increased formation of
496 atherosclerotic plaques, as well as their clinical manifestations, including hypertension and heart
497 failure, but may not fully resolve despite remission of hypercortisolism.[109]

498 Myocardial infarction, stroke,[110,111] and other vascular events are a primary cause of
499 increased standardized mortality ratio (SMR; 4.1 to 16) in patients with active/persistent CD.[112]

Most studies show these rates do not entirely normalize,[111,113] yet some show rates are lowered upon remission and one study showed that patients in remission after a single pituitary surgery have normal SMR at 10 years.[114] Screening and risk assessment for cardiovascular risk factors before and after surgery is therefore essential.[102]

Clinical Considerations and Recommendations

We recommend patients with CD be evaluated, monitored, and treated according to accepted guidelines for patients at high risk for cardiovascular disease (HQ, SR). The management approach should be individualized (HQ, SR) based on the complications present, such as hypertension or hyperlipidemia. Care should be coordinated with the primary care physician and cardiology consultant, as needed (VLQ, DR).

Bone Disease

Background

Skeletal fragility is a frequent and early complication of hypercortisolism, and fractures may be the first clinical manifestation of the disease. Vertebral fractures occur in 30-50% of patients, largely correlating with the severity of hypercortisolism.[115] Suppression of the growth hormone (GH)/insulin-like growth factor (IGF)-I and hypothalamic-pituitary-gonadal axes as well as altered parathyroid hormone pulsatility lead to decreased osteoblast number and function, as evidenced by decreased serum levels of bone formation markers including osteocalcin and alkaline phosphatase.[116] Dual X-ray absorptiometry (DXA) of the lumbar spine may show low bone mineral density (BMD), but fractures may occur even in patients with BMD in the normal or osteopenic range.[117] Although BMD increases were reported after hypercortisolism resolution,

some patients show persistently high fracture risk, with men at higher risk compared with women. Conventional osteoporosis treatments, e.g., bisphosphonates, as well as supportive treatment with vitamin D and calcium may induce a more rapid improvement in BMD than cortisol normalization alone, and could be useful in patients with persistent postsurgical hypercortisolism to prevent further bone loss.[118] Data on the role of specific bone treatments for patients with osteopenia who are in remission after CD treatment are lacking.

Clinical Considerations and Recommendations

We recommend that all patients undergo risk assessment for bone loss and fracture (HQ, SR). Given the risk for fracture even in patients without osteoporosis, standard DXA alone may not be sufficiently informative; bone quality assessment (microscanner or trabecular bone score) is recommended where available (HQ, SR). Morphometric vertebral assessment on x-rays or vertebral fracture assessments on DXA can be useful in detecting subclinical fractures (HQ, SR) but might not be practical for all patients. The FRAX tool to assess fracture risk is not validated for CD.

We recommend monitoring and follow-up for all patients with CS who are at high-risk for osteoporosis and fractures (HQ, SR). Conventional treatment for osteoporosis should be considered for all patients with persistent CD even in the absence of osteoporosis on BMD because of the increased fracture risk due to cortisol excess (HQ, SR).

Growth Hormone Deficiency

Background

GCs, both endogenous and exogenous, inhibit GH secretion, thereby decreasing IGF-I production by the liver in patients with CS.[119,120] Although GH production can be fully restored in most patients after successful therapy and recovery of HPA axis, even years after remission,[121] persistence of GH deficiency (GHD) can potentially worsen hypercortisolism complications such as bone loss, myopathy, and memory deficits.[122] Using the insulin tolerance or glucagon stimulation test, GHD prevalence in adults varies with timing of the diagnosis, ranging from 50-60% when testing was performed within 2 years after surgery to 8-13% when done more than 2 years after surgery.[121,123] A GHD rate of 65% was observed with the GHRH-arginine test after a median remission time of 3 years post-surgery,[124] while 36% of patients were diagnosed with GHD at 99 months after remission post-radiotherapy.[123] Prevalence using the newly approved macimorelin stimulation test is not known.[120] Notably, IGF-I is an insensitive screening test for diagnosing GHD in adults.[124]

Compared with other GHD etiologies, GHD in patients with CS is more common in women and younger patients; generally, these patients exhibit higher rates of T2DM, hypertension, low bone mass, fractures, and worse QoL.[125-127] Myopathy may be partially related to GHD among patients in remission. While preoperative IGF-I levels during active CS did not predict long-term myopathy risk, lower 6-month postoperative IGF-I levels strongly predicted more severe long-term muscle atrophy and weakness after CS remission.[128]

GH replacement ameliorates a number of complications associated with metabolic syndrome and risk for cardiovascular and cerebrovascular disease. Studies show decreased body weight, waist circumference, and total and LDL-cholesterol, as well as improvement of QoL and BMD. Conversely, in patients with pre-existing glucose intolerance, it may lead to worsening of glucose metabolism.[125-127,129-131] GH treatment has not yet been shown in randomized,

prospective trials to reverse increased risk for metabolic syndrome and cardiovascular or cerebrovascular complications.[126]

Clinical Considerations and Recommendations

There is currently no standard practice for whether, when, and how to test for GHD in adults with CD. As postoperative HPA axis recovery is often delayed, we recommend waiting at least 6-12 months after surgery before considering GHD assessment (MQ, SR). Patients with macroadenomas and more aggressive surgical resection are at higher risk for hypopituitarism. Patients with 3 or more pituitary hormone deficiencies are more likely to have GHD and do not need dynamic testing (HQ, SR). Serum IGF-I level alone is not likely to be a reliable indicator, as levels can be in the lower half of the normal range in patients with GHD on dynamic tests. Accessibility of GH replacement may be an important factor in determining testing and treatment considerations. If GH replacement is implemented earlier than 2 years after pituitary surgery, we recommend retesting periodically to determine whether GH secretion has normalized upon HPA axis recovery (MQ, SR) .

As CS-associated myopathy does not spontaneously resolve during remission,[132] physical rehabilitation is recommended for all patients (HQ, SR).

Other Complications

Increased risk for infection,[102] dysfunction of one or more pituitary axes such as central hypothyroidism,[133] gonadal function impairment, infertility, and other complications may be seen in patients with CD. Physical and psychological morbidity commonly affects QoL, even after successful treatment in some patients. Persistence of several features associated with prior

591 hypercortisolism, including affective disorders, cognitive dysfunction, and negative illness
592 perception can have a sustained impact on well-being.[134] Proximal myopathy, with impaired stair
593 climbing and straightening up, are characteristic of CS myopathy. The pathology is
594 multifactorial, including protein degradation through the forkhead box O3 (FOXO3) pathway as
595 well as accumulation of intramuscular fat and inactivity-associated muscle atrophy.[135]
596 Furthermore, hypercortisolism remission can induce exacerbation of pre-existing autoimmune
597 disorders.

598 As these complications have been the subject of recent guidelines[136] and reviews,[102,134] they
599 were not specifically addressed at the Workshop.

INITIAL TREATMENT OF CD AND MONITORING FOR RECURRENCE

Pituitary Surgery

Background

Transsphenoidal surgery (TSS) is recommended as first-line therapy for patients with CD.[6,7] Remission following surgery, typically defined as postoperative serum cortisol <55 nmol/L (<2 μg/dL), is seen in approximately 80% of patients with microadenomas and 60% with macroadenomas if the procedure is performed by an experienced surgeon.[137-140] Patients in remission require GC replacement until the HPA axis recovers.[7,136] Some patients may have a delayed remission; monitoring until cortisol nadir has been reached postoperatively can usually identify such cases.[141,142] Occasional patients with mild hypercortisolism, cyclic CD, or those treated medically prior to surgery may achieve remission without demonstrating marked postoperative hypocortisolism. Treatment at a high-volume center by an experienced surgeon and tumor characteristics such as detection on MRI, noninvasiveness, and size <1 cm appear to correlate with higher remission rates;[138,143] whether there is a potential incremental benefit with an endoscopic approach for macroadenomas remains unclear.[144,145] Overall, complication rates are low, with more experienced surgeons having even lower rates.[146,147] New-onset pituitary insufficiency, seen in approximately 10% of patients, as well as permanent diabetes insipidus (DI), cerebrospinal fluid (CSF) leak, and VTE seen in <5% of patients, are the most common complications; peri-operative mortality is <1%.[143,144]

How to measure surgical expertise for CD remains unclear. Hospitals that limit the number of neurosurgeons performing TSS show better outcomes and reduced complication rates, shorter postoperative length of stay, and lower costs, and survey data demonstrate that neurosurgeons

623 who have performed more than 200 TSS in their careers have the lowest complication rates.[148-
624 151] It has been suggested that regionalized neurosurgery teams of 4-5 experts per 2.5-5 million
625 inhabitants could allow for optimal outcomes, reduced costs, and increased quality of care
626 overall.[149,152]
627
628 ***Clinical Considerations and Recommendations***
629 We recommend patients with CD undergo surgery in specialized Pituitary Tumor Centers of
630 Excellence (PTCOE) wherever possible (HQ, SR).[152] Surgery should be performed by an
631 experienced pituitary neurosurgeon and follow-up conducted by a multidisciplinary team that
632 includes a pituitary endocrinologist (HQ, SR). Outcomes of pituitary surgery and cost
633 effectiveness (LQ, DR) should be reported and be made available in the public domain.
634
635 **Monitoring for Recurrence (Table 1)**
636 ***Background***
637 Recurrence after successful pituitary surgery is characterized as the reappearance of clinical
638 and biochemical features of hypercortisolism following initial remission. Low or undetectable
639 cortisol in the immediate postoperative period is a defining criterion of remission, but does not
640 necessarily predict lack of recurrence;[153] some patients who show early remission with very low
641 postoperative cortisol levels may experience later recurrence.[154] Published recurrence rates vary
642 between 5% and 35%, with half appearing within the first 5 years after surgery and half after up
643 to 10 years or more.[137,155-157]
644 Lifelong monitoring for recurrence is required.[158] In patients who responded preoperatively
645 to desmopressin, early postoperative loss of response to desmopressin with/without

dexamethasone or CRH may offer a more precise prediction of recurrence risk,[70,159-165] but is not consistently used or recommended by most experts.

Compared to their use in the initial diagnosis of CS, LNSC, 1-mg DST, UFC, and desmopressin tests have a lower sensitivity for recurrence, but specificity is high, up to 95% or more.[158] LNSC can detect postoperative elevated cortisol levels earlier than 1-mg DST, while UFC is usually the last test to become abnormal in patients who recur.[166,167] Thus, LNSC may allow for earlier intervention, but serial tests are advised due to wide variability in results.[167-170]

Evaluation for recurrence should begin when the HPA axis recovers, and then annually or sooner if clinical suspicion.[171,172] In practice, however, clinical manifestations and biomarkers may be discordant. Moreover, diagnosis of early recurrence presents the additional challenge about when and how to intervene with treatment in these patients.[171,172]

Clinical Considerations and Recommendations

We recommend lifelong monitoring for recurrence of CD (MQ, SR). Postoperative dynamic testing can potentially predict recurrence (LQ, DR), but its utility in clinical practice remains to be established as some patients with low predicted likelihood of recurrence may recur many years later.

Among the tests available, LNSC is the most sensitive for detecting recurrence and should be done annually after the HPA axis has recovered postoperatively (MQ, SR). LNSC usually becomes abnormal before DST and UFC, although monitoring for recurrence should also take into consideration which specific tests were abnormal for an individual patient at initial diagnosis (MQ, SR). If only slight biochemical abnormalities are seen without clinical features of

668 hypercortisolism, close monitoring with repeat testing and treatment of comorbidities rather than
669 treatment of the underlying disorder per se can be considered (LQ, DR).
670
671 **Repeat Pituitary Surgery**
672 ***Background***
673 Repeat TSS can be considered in patients with biochemical evidence of recurrent CD if
674 tumor is evident on MRI.[139,173-176] At select expert centers where successful reoperation has been
675 reported despite a lack of detectable adenoma on MRI, either ACTH-staining adenoma on
676 pathology or a central ACTH gradient on IPSS at initial operation was often present.[174,175]
677 Tumor factors including size and presence of extra-sellar extension should be considered in
678 determining eligibility for reoperation, and neurosurgeon experience likely plays a role in
679 achieving good results.[155,156,177] Remission rates after reoperation vary widely in the literature,
680 ranging from a low of 37% to a high of 88%, at least in part due to different remission criteria
681 and durations of follow-up.[174] Although some have reported a significantly higher incidence of
682 both surgical complications (e.g., CSF leak, meningitis) and endocrinological complications
683 (e.g., DI and hypopituitarism) with repeat than with initial surgery, significant deterioration of
684 pituitary function or serious morbidity is less likely in experienced hands.[155,156]
685
686 ***Clinical Considerations and Recommendations***
687 If there are no contraindications for surgery, we suggest repeat TSS in patients with
688 biochemical evidence of recurrent CD if tumor is evident on MRI, especially if the first surgery
689 was not done in a PTCOE (LQ, DR). If MRI does not show tumor presence, reoperation may be

690 appropriate if an experienced surgeon at a high-volume center considers it feasible and positive
691 pathology or a central gradient on IPSS was seen before initial operation (LQ, DR).

MEDICAL THERAPY FOR CD

Drugs used for treatment of CD target adrenal steroidogenesis, somatostatin and dopamine receptors in the pituitary, and GC receptors.[6,7,178] They may be used to treat hypercortisolism in patients with persistent or recurrent CD and those who are not candidates or refuse surgery, and to control cortisol levels in patients undergoing radiation therapy (RT).[139,179,180] Available medications and investigational drugs that reported phase 3 trial results are described in **Table 23**.

Medical Therapy: Targeting Adrenal Steroidogenesis

Background

Adrenal steroidogenesis inhibitors that have been available for many years, including ketoconazole, metyrapone, mitotane, and etomidate, as well as the recently approved osilodrostat, block one or more adrenal enzymes, decreasing GC synthesis and/or adrenal androgen production and secretion.[181] They are effective in controlling cortisol excess, but do not directly target the pituitary ACTH-secreting adenoma, nor restore HPA axis circadian rhythm.[182]

When treatment is dose-titrated to achieve cortisol normalization, there is a risk of adrenal insufficiency (AI) with overtreatment. Alternatively, for patients treated with a block-and-replace regimen, there is a risk of inappropriate GC over-replacement if complete blockade is not achieved.[180] Some adverse events (AEs) relate to the increase in ACTH seen in CD patients. Buildup of adrenal hormones proximal to the blockade with mineralocorticoid or androgenic activity may result in edema, alkalosis, and hypokalemia, or hyperandrogenic symptoms such as acne and hirsutism in women. Potential AEs related to drug-drug interactions are a key factor in treatment selection and use.[183]

Ketoconazole

Ketoconazole blocks multiple adrenal enzymes, including those involved early in the steroid biosynthetic pathway. This avoids excess circulation of androgen and mineralocorticoid precursors, but it may also decrease gonadal steroid synthesis; men may experience hypogonadism and gynecomastia, which can limit prolonged treatment.[184] Review of 310 CS patients treated in 5 studies with a mean dose of 673.9 mg/d and followed for a mean of 12.6 months showed UFC normalization in 64.3% (median 50%; range 44.7-92.9%), but up to 23% of initially responsive patients lost biochemical control and escaped.[179] Similarly, data derived from the largest retrospective study of 200 patients with CD who took ketoconazole showed that 64.7% of 51 patients treated for more than 24 months with a mean dose of 600 mg/d normalized UFC levels, but 15.4% escaped.[185] Improvement in clinical features of CS has also been seen, including decreased body weight and blood pressure, improved glucose metabolism, and decreased muscle weakness.[179]

Hepatotoxicity, seen in 10-20% of patients, is mostly asymptomatic with mild or moderate increases in liver enzymes ($\leq 5 \times$ ULN)[186] and typically appears within the first 6 months of treatment initiation; these seem not to be dose-dependent and are reversible within 2-12 weeks after dose decrease or discontinuation. However, as serious hepatotoxicity has been reported, in patients with no obvious risk factors, the United States Food and Drug Administration (FDA) introduced a black-box warning and recommends weekly monitoring of liver function tests (LFTs) in patients with fungal infections treated with ketoconazole. Of note, the use of ketonazole for CS is off-label in the US. Gastrointestinal disturbances and AI are also common, seen in 5-20% of patients, and skin rash is observed in approximately 5%.[179] It is important to

738 note that there are a number of drug-drug interactions with ketoconazole; careful review of the
739 patient's medication list for potentially problematic interactions is essential.
740
741 *Metyrapone*
742 Review of treatment experience with the 11β-hydroxylase inhibitor metyrapone in 120 CS
743 patients in 5 studies with a mean dose of 2127.5 mg/d and followed for a mean of 8.7 months
744 showed normalization of UFC in 71% (median 75.5%; range 45.4-100%), with up to 18%
745 escaping after initial response.[179] A subsequent retrospective multicenter study of 164 CS
746 patients reported that 43% of patients achieved biochemical control with monotherapy given for
747 a mean duration of 8 months at a mean starting dose of 1040 mg/d and escalating to 1425
748 mg/d.[187] An observational study of 31 CS patients, including 20 with CD, demonstrated that
749 treatment with metyrapone at a median dose of 1000 mg/d for 9 months induced a rapid decrease
750 in both UFC and LNSC after the first month of treatment (–67 and –57%, respectively, from
751 baseline), with sustained normalization at the last visit in 70% and 37% of patients,
752 respectively.[188] Three patients exhibited loss of control at the 9-month visit despite normal UFC
753 levels at 6 months and 2 patients also showed normal LNSC. Notably, 11-deoxycortisol may
754 produce clinically relevant cross-reactivity with cortisol in both blood and urine
755 immunoassays.[189] A recently presented multicenter prospective study of 50 patients with CS
756 showed 47% had UFC normalization at 12 weeks; median metyrapone dose was 1500 mg/day
757 (250; 5750) and AI was reported in 12% of patients.[190]
758 Patients treated with metyrapone typically show a general improvement in clinical features of
759 CS (66% in the prospective study), such as blood pressure, glucose metabolism, psychiatric
760 disturbances, and muscle weakness.[179]

761 Hirsutism, dizziness, arthralgia, fatigue, hypokalemia, and nausea are the most commonly
762 reported AEs with metyrapone; AI, abdominal pain, and atopic dermatitis are less frequently
763 reported.[179] AEs secondary to hyperandrogenism can limit prolonged treatment, especially in
764 females.
765
766 *Osilodrostat*
767 Proof-of-concept and phase 2 prospective studies showed that osilodrostat, an 11β-
768 hydroxylase and aldosterone synthase inhibitor, was effective in reducing cortisol and was well-
769 tolerated.[191-193] This was further evaluated in 137 CD patients enrolled in a phase 3, prospective,
770 multicenter, double-blind randomized withdrawal study.[194] After 12 weeks of open-label dose-
771 titrated treatment and another 12 weeks of open-label dose-optimized treatment, 72 patients
772 (53%) had maintained normal UFC and were eligible for randomization. By week 34, at the end
773 of the randomized treatment period, 86% of those randomized to osilodrostat maintained normal
774 UFC versus 29% of those randomized to placebo (OR 13.7 [95% CI: 3.7, 53.4]; $p<0.0001$).
775 Treatment with osilodrostat also yielded clinical improvements. By week 48, patients
776 demonstrated significant decreases in body weight, blood pressure, and total and LDL
777 cholesterol, as well as decreased fasting serum glucose and HbA1c levels. QoL and depression
778 scores also improved.[194]
779 Nausea, anemia, and headache were reported in 8-11% of patients, while AEs related to
780 hypocortisolism were reported in about half of patients, mostly during the open-label dose-
781 titration period. These were generally manageable with dose reductions or interruptions,
782 although GC replacement was required in 25 of 70 (36%) patients with one or more
783 hypocortisolism-related AE. In addition, 42% of treated patients in the phase 3 study showed

784 effects from increased levels of adrenal steroid precursors, including hypokalemia and
785 hypertension; 11% of women reported hirsutism.[194] In another large prospective phase 3 study, a
786 significantly greater proportion of patients receiving osilodrostat (77.1%) achieved mean UFC ≤
787 ULN after 12 weeks of treatment versus placebo (8.0%), with improvements seen in clinical
788 features, cardiovascular disease markers, and QoL. Interestingly, hypocortisolism-related AEs
789 occurred in 27.4% of patients, far fewer than in the prior study.[195]
790
791 *Mitotane*
792 Mitotane inhibits several steroidogenic enzymes and has a long-lasting adrenolytic action in
793 steroid-secreting adrenocortical cells. It suppresses hypercortisolism in 80% of cases, but with a
794 slow onset of action and highly variable bioavailability.[180] Induction of CYP3A4-mediated rapid
795 inactivation of cortisol leads to a requirement for a 2- to 3-fold increased GC replacement dose
796 when treatment of AI is needed or with a block-and-replace strategy.[196] It is rarely used for
797 CD;[179] in the largest study, a mean dose of 2.6 g/d controlled hypercortisolism in 71.6% of
798 patients after a median of 6.7 months.[197]
799 Gastrointestinal disturbances are common, dose-dependent, and reversible; neurological
800 toxicity, seen in up to half of patients in some studies, can limit long-term use. Increases in liver
801 enzymes are often observed and treatment should be stopped if elevations are > 5 × ULN.
802 Mitotane is teratogenic and an abortifacient. Because of its long terminal half-life, this may
803 limit its use in women who desire future pregnancy. Most participants considered that use of
804 mitotane should be limited to patients with adrenal carcinoma.
805

Etomidate

Originally developed as an anesthetic, etomidate was shown to rapidly normalize cortisol levels in almost all cases, leading to its use in the acute control of severe hypercortisolism in hospitalized patients.[198] Low-dose etomidate (0.04–0.05 mg/kg/h) is used for partial blockade, with a high-dose (0.5–1 mg/kg/h) regimen for complete blockade. In such cases, IV hydrocortisone is required to avoid etomidate-induced AI.[199] Very low doses (0.025 mg/kg/h) may be used in hospitalized patients outside ICU,[200] although this may depend on local practice.

Myoclonus, nausea, vomiting, and dystonic reactions are seen in up to one-third of patients at higher anesthetic doses. Compared with the lipid formulation, the propylene glycol preparation is more frequently associated with thrombophlebitis and pain on injection, and also with additional AEs, such as hemolysis and renal tubular injury, as well as lactic acidosis at high doses.[199]

Medical Therapy: Targeting Pituitary Somatostatin and Dopamine Receptors

Background

Both the dopamine agonist cabergoline and the somatostatin receptor ligand pasireotide are used in CD patients with persistent or recurrent hypercortisolism,[7,139,179] although only pasireotide is approved for use in this population.[7,201,202] Pasireotide and cabergoline normalize UFC in 25-50% of patients and can lead to adenoma shrinkage in some patients with a detectable adenoma. This tumor effect is clinically important for patients with a large residual tumor as well as for patients with corticotroph tumor progression, or Nelson's syndrome.

Pasireotide

In a phase 3 study of 162 CD patients treated with SC pasireotide, UFC normalized at month 6 in 26% of those treated with 900 µg BID and 15% of those treated with 600 µg BID without dose increases. Higher rates of UFC normalization were seen in those with baseline UFC <5 × ULN[201] and signficant clinical improvement was noted in most patients.[202]

A second phase 3 study treated 150 CD patients with 10 mg or 30 mg monthly IM pasireotide LAR. At month 7, 40% of patients in both groups showed normalized UFC regardless of dose titration, with higher response rates in those with baseline UFC <2 × ULN.[203] At month 12, improvements in blood pressure were greater in those with normalized UFC; BMI, weight, waist circumference, and QoL were all improved regardless of UFC control.[204] Long-term extension studies showed that biochemical and clinical improvements could be maintained for up to five years in select patients who continued the study.[205,206] Of note, in real-life settings, limited data are available on long-term treatment compliance, and several studies show a high rate of treatment discontinuation. Treatment with pasireotide LAR also led to a decreased median tumor volume of 17.8% in those treated with the 10 mg dose and 16.3% in those treated with 30 mg dose, with 43% and 47% of patients, respectively, showing ≥20% reduction.[203]

Of note, a separate longitudinal study in CD patients with Nelson's syndrome after BLA showed that pasireotide LAR rapidly suppressed ACTH levels and yielded sustained reductions over 24 weeks.[207]

Between one- and two-thirds of CD tumors harbor a mutation in *USP8*,[208,209] and these mutated tumors may show higher SST5 expression compared with wild-type tumors.[210,211] As pasireotide has a high affinity for this receptor, *USP8* mutational status may prove a useful marker for predicting treatment response.

The risk for hyperglycemia is high with pasireotide.[201,203,212] In the two phase 3 studies, approximately 70% of patients reported hyperglycemia-related AEs, with new antidiabetic medication initiation or dose adjustments required in approximately half of patients.[201,203] The high rates of hyperglycemia are thought to result from inhibition of insulin and incretin secretion combined with a lesser degree of glucagon inhibition.[213] Management with GLP-1 receptor agonists or DDP-4 inhibitors are therefore thought to be particularly useful.[214,215]

Cabergoline

Available data on cabergoline use in patients with CD are derived mostly from small retrospective studies demonstrating biochemical normalization in 25-40% of patients, with loss of control observed in 20-40% of patients initially controlled.[216,217]

A retrospective, multicenter cohort study of 53 patients treated with a median cabergoline dose of 2.3 mg/wk (range, 0.5-6.0) yielded normal UFC levels in 40% of patients during the first year, but only 23% of those showed sustained UFC normalization after a median 32.5 months of follow-up.[218] The lower control rate may be due to under-titration, as a smaller study of 20 patients treated with cabergoline titrated to a maximum of 7 mg/wk (median 3.5 mg/wk) showed normalized UFC in 40% of patients at 24 months.[219] Weight, glycemic control, and hypertension improved in 25-40% of complete responders,[218] and tumor shrinkage was reported in 50%.[219] Patients with Nelson's syndrome may also respond to cabergoline treatment, and both ACTH normalization and tumor shrinkage have been reported.[220] Although not approved in this setting, cabergoline has been used in pregnant patients with prolactinomas and other pituitary adenomas, including CD.

Cabergoline-induced impulse-control disorder is likely under-reported, and can manifest as hypersexuality, pathological gambling, excessive alcohol consumption, overeating, and uncontrolled shopping.[221] This behavior may occur within months of initiating cabergoline therapy, or may manifest later, and improves or resolves on treatment discontinuation.[222,223]

High cumulative doses of ergotamine-derived dopamine agonists used in patients with Parkinson's disease were associated with risk for cardiac valve regurgitation.[224] Although one retrospective review of 50 prolactinoma patients found that moderate tricuspid regurgitation was more frequent in those treated with higher doses,[225] a large multicenter study found no association between the cumulative cabergoline dose and age-corrected prevalence of any valvular abnormality.[226] Furthermore, a meta-analysis showed that it remains an open question whether such echocardiographic findings are clinically significant.[227]

Medical Therapy: Targeting the Peripheral Tissue Glucocorticoid Receptor

Mifepristone

The glucocorticoid receptor blocker mifepristone is effective in controlling some effects of hypercortisolism regardless of etiology. As endogenous cortisol is not decreased, the efficacy of mifepristone can only be evaluated clinically. Close monitoring for AI is required, and the anti-progesterone action in women can cause endometrial hyperplasia and vaginal bleeding.

An open-label study of 50 patients with uncontrolled endogenous CS, including 43 with CD, showed that after 24 weeks of treatment, 60% with a concurrent diagnosis of T2DM or impaired glucose tolerance had a significant reduction of ≥25% from baseline in area under the curve for glucose during an oral glucose tolerance test; 38% of those with hypertension showed a

894 significant reduction of ≥5 mm Hg from baseline in diastolic blood pressure. Insulin resistance,
895 weight, waist circumference, and QoL also improved.[228]
896 Twelve patients showed increased blood pressure, including 9 with hypokalemia who
897 required spironolactone, consistent with activation of the mineralocorticoid receptor.
898 Endometrial hypertrophy and irregular menstrual bleeding were also reported, consistent with the
899 anti-progesterone activity of this medication. Dexamethasone was administered in 7 patients with
900 signs and symptoms of AI, underscoring the need for careful monitoring.[228] Importantly, cortisol
901 levels remain high, and measures of low cortisol typically used to confirm AI due to
902 overtreatment with other medical therapies cannot be used with mifepristone. Rather, only
903 clinical features can be used.[229]
904 Continued mifepristone treatment of 27 patients with CD included in a long-term extension
905 study showed sustained ≥2-fold ACTH elevations, but tumor volume progression, seen in 3
906 patients with macroadenomas up to 25 months from baseline, did not correlate with ACTH
907 increases.[230] Thyroid function should be closely monitored and thyroid hormone replacement
908 adjusted as needed.[231] All medications taken by the patient should be carefully reviewed given
909 the potential for drug-drug interactions with mifepristone.
910
911 **Medical Therapy: Clinical Considerations and Recommendations**
912 We recommend individualizing medical therapy for all patients with CD based on the clinical
913 scenario, including severity of hypercortisolism. Regulatory approvals, treatment availability,
914 and drug costs vary between countries and determine treatment selection. However, where
915 possible, it is important to consider balancing cost of treatment with the cost and significant
916 adverse consequences of ineffective or insufficient treatment. In patients with severe disease, the

primary goal is to treat aggressively to normalize cortisol levels (or cortisol action if using mifepristone). Multiple serial tests of both UFC and LNSC are used to monitor treatment outcomes.[158,232,233]

A brief summary of Workshop discussions about how to best incorporate each of the different treatment options is presented below and in ~~Table 4~~Panel 2.

Initial treatment selection for medical therapy

Adrenal steroidogenesis inhibitors are usually used first given their reliable effectiveness. For patients with mild disease and no visible tumor on MRI, ketoconazole, osilodrostat, or metyrapone are typically preferred. Cabergoline also may be used for mild CD; it is less effective and has a slower onset of action, but requires less frequent dosing. For patients with mild-to-moderate disease and some residual tumor, there may be a preference for cabergoline or pasireotide because of the potential for tumor shrinkage. However, the high rate of hyperglycemia with pasireotide would make patient selection critical.

For patients with severe disease, rapid normalization of cortisol is the most important goal. With osilodrostat and metyrapone, response will typically be seen within hours, and with ketoconazole within a few days. Etomidate also works rapidly and could be used if the patient is hospitalized and cannot take oral medications. For patients with severe hypercortisolism, combinations of steroidogenesis inhibitors may be necessary. However, if hypercortisolism is very severe and not responsive to optimized medical therapy, including combinations, BLA should be considered to avoid worsening outcomes.

Other patient factors can be important for initial treatment selection. For example, cabergoline should not be used in patients with a history of bipolar or impulse control disorder,

but may be a preferred first choice in a young woman desiring pregnancy. Although none of these drugs is specifically approved for use in pregnancy, metyrapone may be also considered with precautions in selected women who are pregnant. In such cases, given the higher normal cortisol levels during pregnancy, a higher cut-off target for cortisol, such as 1.5 × ULN, is used.

Mifepristone improves key clinical features associated with hypercortisolism, specifically hyperglycemia and weight gain. However, it could be challenging to use in standard clinical practice, and often worsens hypokalemia. There are no biochemical markers that can be reliably used to follow to monitor cortisol levels, increasing the risk for AI due to overtreatment, and its long half-life requires several days of stress-dose GC replacement, preferably dexamethasone, if AI ensues. Because cortisol measurements cannot be used for dosing or safety monitoring, this should be used only by clinicians with extensive experience in CD; counseling patients that cortisol levels monitoring is not reliable, especially for adrenal insufficiency, is also important.

There are few rigorous data supporting specific regimens for combination therapy, but several have been described [234-236]. Many experts consider combining ketoconazole with metyrapone to maximize adrenal blockade when monotherapy is not effective or to allow lower doses of both drugs, although a steroidogenesis inhibitor plus a tumor-targeting agent, such as ketoconazole plus cabergoline, is also a rational combination, especially if there is visible tumor present. Other combinations that may be used include triplets of cabergoline, pasireotide, plus ketoconazole, and metyrapone, ketoconazole, plus mitotane. Risk for potentiating adverse effects with combination therapy, such as QTc prolongation, should also be considered.

961 *Selecting an adrenal steroidogenesis inhibitor*

962 The longest clinical experience for adrenal steroidogenesis inhibitors is with ketoconazole
963 and metyrapone. These agents are approved for use in CD in Europe, but not in the United States
964 (where only osilodrostat is approved in this category), and they may not be available in some
965 countries. Ketoconazole may be favored for ease of dose titration, but it is often under-dosed for
966 fear of inducing hepatotoxicity. LFTs should be regularly monitored, but treatment does not
967 necessarily have to be discontinued if LFTs are mildly elevated, yet stable.[237] Osilodrostat and
968 metyrapone can induce rapid control in the majority of patients. They are not limited by
969 monitoring of LFTs and hypogonadism does not occur in men. It is expected that osilodrostat
970 will be increasingly used as it becomes widely available given its high efficacy and twice-daily
971 dosing. It is necessary to monitor for AI and osilodrostat effects on androgens, but whether
972 treatment selection should be based on patient sex in long-term treatment is not yet known.
973 Mitotane, rarely used for patients with CD in most centers, has a slower onset of action.

974 A block-and-replace regimen may be considered for patients with severe disease, cyclical
975 CS, and patients ineligible for surgery. This may be a particularly useful approach if monitoring
976 visits are infrequent due to external factors such as pandemic, lack of transportation or other
977 issues. Caution is needed to avoid GC over-replacement and inducing iatrogenic CS.

978

979 *Monitoring response to medical therapy*

980 For all patients, regular monitoring for treatment efficacy is required, including measures of
981 cortisol and patient symptoms and comorbidities, especially weight, glycemia, and blood
982 pressure. In addition, QoL is important to take into account, preferably through patient-reported
983 outcomes. Cortisol levels are often measured by UFC; notably, this test is not useful when there

are concerns for AI. Morning cortisol and/or LNSC may be used as an alternative, but because of the loss of circadian rhythm, it is unclear whether targeting diurnal secretion alone is meaningful. Nevertheless, morning cortisol values may be especially pertinent in patients taking higher medication doses in the evening than in the morning.[182]

As designs, medication up-titration schemes, comparator arms, inclusion/exclusion criteria, and primary endpoints differ even among prospective studies, it is difficult to directly compare treatment outcomes, either for efficacy or for adverse effects. Furthermore, some drugs have not been prospectively studied for CS. When using UFC normalization as a target, osilodrostat has the highest efficacy based on data from several prospective clinical trials, followed by metyrapone (retrospective and prospective data), ketoconazole (retrospective data), pasireotide (prospective), and cabergoline (retrospective and prospective). As improvement in clinical features of CS and diabetes are used as markers of mifepristone efficacy, it cannot be directly compared for biochemical efficacy with other available treatments. Patients who normalized both UFC and LNSC with pasireotide LAR showed better clinical outcomes than those who normalized UFC alone,[232] and a higher treatment dose at bedtime may help restore circadian rhythm patterns, but there is no rigorous evidence to support the latter approach.

Change in treatment should be considered if cortisol levels are persistently elevated after 2-3 months on maximum tolerated doses. If cortisol does not normalize but is reduced and/or there is some clinical improvement, combination therapy can be considered. If there is clear resistance to treatment, we suggest switching to a different therapy. However, it is important to ensure that insufficient disease control due to under-dosing is not misinterpreted as treatment resistance.

With adrenal-targeting agents, there may be concern for tumor growth due to ACTH-cortisol feedback interruption. However, it can be difficult to determine whether such tumor progression

is due to this loss of feedback or reflects the underlying behavior of aggressive, recurrent disease. We suggest monitoring ACTH levels, as significant elevations may be a sign of new tumor growth and a need for MRI, with the important caveats that ACTH has a short half-life and levels fluctuate and do not necessarily reflect tumor growth. If progressive increase in tumor size is seen,[238] treatment should be suspended and the management plan reassessed. MRI is typically done 6-12 months after initiating treatment and repeated every few years depending on the clinical scenario.

With combination therapies, it is also important to monitor for potential overlapping toxicities, particularly QTc prolongation, as well as drug-drug interactions.

Primary and Preoperative Medical Therapy for *De Novo* CD

Primary medical therapy is used when successful resection of an adenoma is unlikely due to unfavorable localization, significant invasiveness, or lack of visualization on MRI. Recent double-blind randomized phase 3 studies evaluating the efficacy of several novel drugs included only a small percentage of patients with *de novo* CD, ranging from 0% to 28%.[196] Further studies are needed to demonstrate utility of the different medical therapies in this setting, either as monotherapy or in combination, while also taking into account the potential effects of such treatment on adenoma size.

Published evidence supporting the role of preoperative medical therapy in patients with CD is sparse, and it is not used in the majority of patients, although there are regional variations. A meta-analysis showed no differences in cortisol normalization rate between those who received cortisol-lowering medications in the preoperative setting versus use as adjuvant treatment.[239] It may be an option in severely ill patients for whom surgery is contraindicated or if waiting time

for surgery is long[139] or in patients with life-threatening complications of hypercortisolism requiring rapid control of cortisol excess.[230,240] Physician surveys show that preoperative therapy, mostly with ketoconazole and/or metyrapone, is used in up to 20% of CD patients, especially those with more severe clinical features or nonvisible adenoma.[241]

Retrospective studies show preoperative steroidogenesis inhibitor therapy for a mean of 4 months yields cortisol normalization rates of 50% to 72%, although subjective symptom improvement was observed in only one-third of cases.[185,187] Lower rates of postoperative hypoadrenalism from preoperative medical therapy could, in theory, protect against the occurrence of a proinflammatory and procoagulant state,[94,241] but the prevalence of postsurgical complications, including VTE, are similar regardless of its use.[241] If the HPA axis recovers during preoperative treatment, AI may not be seen postoperatively, so it may be more difficult to determine whether remission is present.

Preoperative cabergoline likely has limited value, as a significant decrease in cortisol was seen in only one-fourth of patients in a cohort treated prospectively for 6 weeks.[242]

Clinical Considerations and Recommendations

There are no rigorous data supporting use of primary or preoperative medical therapy. Most experts would consider such an approach with adrenal steroidogenesis inhibitors if surgery is delayed, either because of scheduling or due to outside factors such as a pandemic (VLQ, DR).

Patients with severe CD who have potentially life-threatening metabolic, psychiatric, infectious, or cardiovascular/thromboembolic complications also may benefit from preoperative medical therapy in select cases (LQ, DR). Although this has not been clearly confirmed, some experts consider it may have a potentially favorable effect on glucose, cardiovascular, and

coagulation parameters (VLQ, DR). Few use it to decrease the extent of postoperative cortisol withdrawal manifestations.

Monitoring and follow-up of patients treated with preoperative therapy can be challenging as postoperative cortisol assessments for surgical cure are not reliable. The patient's perspective regarding this approach would be valuable to incorporate into future research studies (VLQ, DR).

RADIATION THERAPY

Background

RT is primarily used as adjuvant therapy for patients with persistent or recurrent disease after TSS [7,243] or in the setting of aggressive tumor growth. Approximately two-thirds of patients achieve biochemical remission during the years after treatment with conventional external-beam RT, typically 45-50 Gy administered in <2 Gy fractions, or stereotactic radiosurgery (SRS), which is administered as single dose or a few fractions of approximately 20 Gy.[244] However, more recent series with SRS, including whole sellar RT,[245] show higher biochemical remission rates. In a multicenter study of GammaKnife SRS in 278 subjects followed for a mean of 5.6 years, biochemical control was attained in 80% and durable control of hypercortisolism was maintained in 57%.[246] Tumor control rates are typically higher, with approximately 95% of patients treated with SRS showing decreased or stable tumor volume on MRI.[244] A small single-center study of proton beam RT showed complete response (either cortisol or ACTH normalization) in patients with persistent corticotroph adenomas due to CD or Nelson's syndrome, with low morbidity after a median follow-up of 62 months.[247]

SRS may also be used as primary therapy in patients with high surgical risk or who refuse surgery. In this setting, endocrine remission was attained in 81% of 46 patients at 5 years of follow-up.[248] Long-term follow-up is needed as reccurence and tumor growth have been described post-RT.

Given the latency until remission is achieved with RT, adjuvant medical therapy is needed to control hypercortisolism, and periodic withdrawal of medication to allow measurement of cortisol secretion is performed to assess treatment effect.[7] Although data are mixed on whether

ketoconazole[246,249] or cabergoline[250] treatment at the time of SRS limits efficacy, these medications are often withheld temporarily at the time of RT.

Hypopituitarism is the most common side effect of both conventional RT and SRS, seen in 25-50% of patients, and generally increases over time. Risk of secondary malignancy, cranial nerve damage, and stroke are low with SRS.[251] In patients treated with SRS, distance of at least 3-5 mm between the tumor and the optic chiasm and a chiasm dose <8 Gy is recommended to limit treatment damage.[251] Longer term data will help address whether use of different SRS modalities (GammaKnife, LINAC, proton beam) confers lower rates of stroke and hypopituitarism compared with conventional RT.

Clinical Considerations and Recommendations

RT is most commonly used in cases of persistent hypercortisolism after incomplete corticotroph tumor resection, particularly if the tumor is aggressive or invasive and/or considered unresectable (HQ, SR). SRS is likely more convenient as few treatment sessions are required, but avoiding optic chiasm exposure is critical (HQ, SR). Lifelong monitoring for pituitary hormone deficiencies and reccurence is required in all patients undergoing RT (HQ, SR). Imaging for secondary neoplasia in the radiation field also should be considered (HQ, SR).

ADRENALECTOMY

Background

BLA offers immediate control of cortisol excess in patients with persistent or recurrent CD not responsive to medical therapy,[7,139,252] but is only considered for select patients due to the resultant AI and need for life-long GC and mineralocorticoid replacement therapy.[253] Laparascopic BLA using either a transperitoneal or posterior retroperitoneal approach is associated with a complication rate between 10% and 18% in the largest series, and a mortality rate of <1%.[254,255] Long-term clinical relapse of hypercortisolism due to adrenal rest stimulation by high ACTH is uncommon (<10%), while clinical improvement in BMI, T2DM, hypertension, and muscle weakness is reported in more than 80%.[256]

Corticotroph tumor progression after BLA is a long-term concern in 25% to 40% of patients after 5 to 10 years.[256-258] Most cases can be managed with surgery, RT, or medical therapy. However, as a subset of patients with aggressive tumors will show clinical consequences from the tumor mass despite treatment, long-term monitoring is required. A European consensus focused on management of these patients was recently published.[259]

Corticotroph tumor progression after BLA does not seem to be influenced by pregnancy.[260] This may make BLA a preferred option in female patients with an immediate pregnancy plan. In most cases, however, BLA is rarely performed as the first-line treatment after failure of initial pituitary surgery, and duration of disease before adrenal surgery is typically 3 to 4 years or more.[255] Whether and how this might impact long-term treatment outcomes remains unknown.

Clinical Considerations and Recommendations

In patients with CD, BLA is often considered a treatment of last resort in most centers after all other options have failed (MQ, SR). However, BLA may be warranted earlier in patients with severe hypercortisolism in whom a rapid, definitive effect on cortisol is needed to avoid prolonged systemic effects of uncontrolled disease (MQ, SR). Many expert centers recommend BLA earlier in the course of the disease for females with CD desiring pregnancy (MQ, SR).

After BLA, plasma ACTH and serial imaging of the pituitary gland are used for monitoring at intervals dictated by the clinical scenario, usually starting 6 months after surgery (HQ, SR). More frequent evaluation may be necessary if there is a clinical suspicion of corticotroph tumor progression (HQ, SR).

~~Unilateral adrenalectomy has been suggested for patients with primary bilateral macronodular adrenal hyperplasia with mild-to-moderate hypercortisolism and/or overt CS with asymmetric glands; in such cases, the larger adrenal gland is usually removed (LQ, DR). Importantly, if hypercortisolism persists or recurs, BLA and/or medical therapy is required. Unilateral adrenalectomy is not recommended for patients with very severe bilateral hyperplasia and symmetrical glands (HQ, SR).~~

ADDITIONAL CONSIDERATIONS

Genetics of CD

Corticotroph adenomas are predominantly of sporadic origin, based on a monoclonal expansion of a singular mutated cell.[261] These adenomas abundantly express EGFR, which signals to induce ACTH production.[262] Somatic activating driver mutations in *USP8* are present in 36-60% of corticotroph adenomas.[209] These mutations lead to persistent overexpression of EGFR, thereby perpetuating the hyper-synthesis of ACTH. Rarely, mutations in the glucocorticoid receptor *NR3C1*, the *BRAF* oncogene, the deubiquitinase *USP48*, and *TP53* are encountered.[261] Patients with familial tumor syndromes, such as *MEN1, FIPA,* and *DICER1* rarely develop corticotroph adenomas. It has been proposed that corticotroph tumors may be sub-classified based on *USP8* driver mutations and clinical behavior.[263] As *USP8* mutational status may predict recurrence after TSS,[264] such genomic classifications may open new avenues for more targeted, personalized treatment modalities in the future.

Diagnosis and Management of CS in Children

Endogenous CS is extraordinarily rare before age 18. Germline mutations in *MEN1, RET, AIP, PRKAR1A, CDKN1B, DICER1, SDHx,* and *CABLES1* may all predispose children to CD, although screening is usually reserved for cases in which there is either family history or other signs suggestive of a genetic syndrome.[265]

Lack of height gain concomitant with weight gain is the most common presentation of CS in children, making the disorder somewhat easier to detect in children than in post-pubertal adolescents or adults. Using the insulin tolerance test or the glucagon stimulation test, the

estimated prevalence of severe GHD (< 9 mU/L) and partial GHD (< 30 mU/L) is 31% and 54%, respectively.[266]

Documentation of hypercortisolism with 24-hour UFC, LNSC, or overnight 1 mg DST are all used to confirm diagnosis. The diagnostic approach and test performances are slightly different from adults, as recently extensively reviewed.[267] The Dex-CRH test is not useful in children. In children over age 6, CD is the most common cause of CS; in children under age 6, adrenal causes are more common. Algorithms for testing to distinguish ACTH-dependent disease from ACTH-independent syndromes are available. Notably IPSS role in children is more limited compared with adults.[268]

As in adults, surgical resection of the ACTH-secreting tumor is the first-line treatment intervention. However, unlike in adults, thromboprophylaxis should not be routinely used due to bleeding risk, but reserved for selected pediatric patients. With successful treatment, adrenal function typically recovers within approximately 12 months.[269] Evaluation for GHD should be done by 3-6 months after surgery and immediate GH replacement given if needed to ensure proper growth. Use of GH replacement is associated with adequate final height, but obesity is not fully reversible.[270] For those who require medical therapy, ketoconazole or metyrapone is typically used and morning cortisol is used to monitor response. Pasireotide is not recommended and clinical trials of osilodrostat in children are underway. Block-and-replace regimens with metyrapone also may be considered.

Early diagnosis and expert management is critical given the potential for long-term adverse health outcomes from prolonged hypercortisolism as well as from morbidity associated with TSS or RT. Children with CS should be referred to multidisciplinary centers of excellence with pediatric endocrinologists expert in managing disorders of the pituitary, and with specialized

neurosurgery units. If an underlying genetic syndrome is present, genetic counseling for the child and family members as well as investigations into other disorders associated with the syndrome are necessary.[267,271,272]

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed.

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NB has served on the Board or as an advisor for European Neuroendocrine Association and the European Reference Network on Rare Endocrine Conditions.

CLB has received grants and personal honoraria for lectures from Novartis and served on the Board or as an advisor for Sociedade Brasileira de Endocrinologia e Metabologia, Endocrine Society, and European Society Of Endocrinology.

MDB has nothing to declare.

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FFC has served on the Board for Pituitary Society.

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MCZ has served as a Board member for European Neuroendocrine Association.

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Contributions

MF, BMKB, AG, and SM initiated/conceived the consensus meeting. MF and BMKB serving as co-chairs and project administrators/supervisors, as well as JN-P, NK, MG, AT, SP, LN, PM, AG, and SM serving as steering committee members, developed the workshop topics, identified expert speakers, participants, and breakout group assignments and moderators, and developed the first draft of the manuscript based on speaker slide-lecture presentations and précis, and participant breakout discussion comments. MF, BMKB, EVV, GV, and SM contributed to development of the tables, figures, and panels. MF, BMKB, AG, SM, JN-P, NK, MG, AT, SP, LN, PM, EVV, GV, RA, IB, AB, JB, NK, CB, MDB, MB, JDC, FFC, FC, PC, JF, EGB, AG, MG, KH, AGI, UKB, LK, DFK, AL, AM, MM, AMP, RP, HR, MR, RS, CS, IS,CS, BS, AT, YT, MT, ST, EV, JW, SMW, and MCZ reviewed the entire manuscript, approved the final version, and made the decision to submit.

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~~Table 2~~Panel 1. Complications of CD: Summary of Recommendations

Hypercoagulation
• Prophylactic anticoagulation should be considered for patients at risk for VTE, including history of embolism or abnormal coagulation testing; severe preoperative hypercortisolism; current use of estrogen or oral contraceptives; poor mobility; extended preoperative or postoperative hospital stay; and high postoperative cortisol levels or cortisol over-replacement in patients with AI (MQ, SR) • Early postoperative ambulation and use of compression stockings should be encouraged for all patients (HQ, SR) • If thromboprophylaxis is administered, low-molecular weight heparin is preferred over oral anticoagulants (LQ, DR) • Anticoagulants may be discontinued before surgery to minimize intraoperative bleeding risk, but the timing of when to stop and when to reinitiate after surgery is unclear (LQ, DR) • Optimal duration of anticoagulation after surgey is still unclear (LQ, DR) • Thromboprophylaxis should not be routinely used in pediatric patients due to bleeding risk but reserved for selected patients
Cardiovascular Disease
• Evaluate, monitor, and treat according to current guidelines for patients at high risk for cardiovascular disease (HQ, SR) • Management approach should be individualized (HQ, SR) based on the complications present and care should be coordinated with primary care and cardiology physicians as needed (VLQ, DR)
Bone Disease
• Risk assessment for bone loss and fracture recommended in all patients (HQ, SR) • Standard DXA alone may not be sufficiently informative; bone quality (microscanner or trabecular bone score) or morphometric assessment is recommended where available (HQ, SR) • Monitor and follow-up as for all adults high-risk populations (HQ, SR) • Consider conventional osteoporosis treatments, e.g., bisphosphonates, for patients with persistent CD even if BMD is normal because of increased fracture risk due to cortisol excess (HQ, SR)
GH Deficiency
• In adults, wait at least 6-12 months after surgery to allow HPA axis recovery before considering GHD assessment (MQ, SR) • If GH is replaced earlier than 2 years after surgical remission, retest periodically off treatment as the axis may recover (MQ, SR) • In children, evaluate for GHD 3-6 months after surgery and immediately initiate GH replacement if needed to ensure proper growth

Abbreviations: AI, adrenal insufficiency; BMD, bone mineral density; CD, Cushing's disease; DXA, dual x-ray absorptiometry; GHD, growth hormone deficiency; HPA, hypothalamus-pituitary-adrenal; VTE, venous thromboembolism.

~~Table 4~~Panel 2. **Medical Therapy for CD: Summary of Recommendations**

Which factors are helpful in selection of a medical therapy?
• If there is a need for rapid normalization of cortisol, we recommend an adrenal steroidogenesis inhibitor; osilodrostat and metyrapone have the fastest action and are orally available, while etomidate can be used intravenously in very severe cases (HQ, SR) • In mild disease, if residual tumor is present and there is a potential for tumor shrinkage, consider pasireotide or cabergoline (MQ, SR) • If there is a history of bipolar or impulse control disorder, consider avoiding cabergoline (MQ, SR) • If an expert pituitary endocrinologist is not available to monitor treatment response, use mifepristone cautiously (LQ, DR); we recommend counseling patients that cortisol cannot be used to monitor treatment response or AI (SQ, SR). Drug-drug interactions must be considered when this medication is used. • In pregnant women or those desiring pregnancy, consider cabergoline or metyrapone, although no CD medications are approved for use in pregnancy (LQ, DR) • Drug intolerance or side effects as well as concomitant comorbidities such as T2DM and hypertension should further guide type of medication used (MQ, SR) • Consider cost and estimated therapy duration, especially if definitive treatment (i.e., pituitary and adrenal surgery) is planned or while awaiting effects of radiotherapy (LQ, DR)
Which factors are used in selecting an adrenal steroidogenesis inhibitor?
• Rapidity of action, tolerability, ease-of-use, degree of likely biochemical normalization, and specific clinical improvement as well as local availability and cost of each drug should be considered at therapy start (MQ, SR) • Ketoconazole may be favored for ease of dose titration; concern about inducing hepatotoxicity and the need to monitor liver enzymes may lead to under-dosing (MQ, SR). Drug-drug interactions must be considered and hypogonadism may occur in men • Osilodrostat achieves high rates of cortisol normalization. Dosing schedule may be more convenient for patients compared with metyrapone, but neither metyrapone nor osilodrostat is limited by hypogonadism in men (HQ, SR) • Mitotane is rarely used as monotherapy in CD in most centers (LQ, DR)
How is tumor growth monitored when using an adrenal steroidogenesis inhibitor or glucocorticoid receptor blocker?
• MRI is typically obtained 6-12 months after initiating treatment and repeated every few years depending on the clincal scenario (MQ, SR) • It can be difficult to determine whether tumor progression is due to loss of cortisol feedback or reflects the underlying behavior of aggressive, recurrent disease (LQ, DR) • We suggest monitoring ACTH levels, as progressive elevations in ACTH may be a sign of tumor growth and a need for MRI, although the half-life of ACTH is short, levels fluctuate and do not necessarily reflect tumor growth (LQ, DR) • If progressive tumor growth is seen, medical treatment should be suspended and the management plan reassessed (MQ, SR)

When is preoperative medical therapy used?
• There are no rigorous data supporting use of preoperative medical therapy (MQ, SR) • Most experts would consider use of adrenal steroidogenesis inhibitors if surgery is delayed, either because of scheduling or due to external factors (LQ, DR) • Patients with severe CD who have potentially life-threatening metabolic, psychiatric, infectious, or cardiovascular/thromboembolic complications may benefit in select cases (LQ, DR)
How is treatment response monitored? Which factors are considered in deciding whether to use combination therapy or to switch to another therapy?
• Response should be defined based on a combination of clinical (improved phenotype, weight, hypertension, glucose metabolism, QoL) and biochemical endpoints or only clinical endpoints when glucocorticoid receptor blockers are used (MQ, SR) • Cortisol levels are often measured by UFC (except when using mifepristone); UFC is not useful if AI is a concern (HQ, SR) • Because of the loss of biologic circadian rhythm, it is unclear whether targeting diurnal secretion alone with morning cortisol and/or LNSC is meaningful (LQ, DR) • Change in treatment should be considered if cortisol levels are persistently elevated after 2-3 months on maximum tolerated doses (MQ, SR) • If cortisol does not normalize but is reduced and/or there is some clinical improvement, combination therapy can be considered (LQ, DR) • If there is clear resistance to treatment despite dose escalation, we suggest switching to a different therapy (LQ, DR)
Which agents are used for optimal combination therapy?
• There are few rigorous data supporting specific regimens for combination therapy (HQ, SR) • Many experts consider combining ketoconazole with metyrapone or potentially ketoconazole with osilodrostat to maximize adrenal blockade when monotherapy is not effective or to allow lower doses of both drugs (LQ, DR) • Ketoconazole plus cabergoline or pasireotide, and pasireotide plus cabergoline may be rational combinations if there is visible tumor present (LQ, DR) • Other combinations that may be used include triplets of cabergoline, pasireotide, plus ketoconazole, and ketoconazole, metyrapone, plus mitotane (LQ, DR)

Abbreviations: ACTH, adrenocorticotropin; AI, adrenal insufficiency; CD, Cushing's disease; LNSC, late-night salivary cortisol; MRI, magnetic resonance imaging; QoL, quality of life; UFC, urinary free cortisol.

~~Table 5~~Panel 3. **Grading of Evidence and Recommendations**

Evidence	• Very low quality (VLQ): expert opinion supported by one or few small uncontrolled studies • Low quality (LQ): supported by large series of small uncontrolled studies • Moderate quality (MQ): supported by one or few large uncontrolled studies or meta-analyses • High quality (HQ): supported by controlled studies or large series of large uncontrolled studies with sufficiently long follow-up
Recommendations	• Discretionary recommendation (DR): based on VLQ or LQ evidence • Strong recommendation (SR): based on MQ or HQ evidence

Based on Guyatt et al *BMJ* 2008 and Giustina et al *Nat Rev Endocrinol* 2014.

~~Table 6~~Panel 4. ~~Topics for~~ Future Research Topics Ranked of Highest Importanvce

Screening and diagnosis of CS
• Optimize pituitary MR and PET imaging using improved data acquisition and processing to improve microadenoma detection • Compare diagnostic algorithms for the differential diagnosis using invasive versus non-invasive strategies • Identify additional corticotroph adenoma mutations and development of a comprehensive panel of genomic/proteomic tests for CD diagnosis
Complications of CD
• Define use of anticoagulant prophylaxis and therapy in different populations and settings • Optimize the approach in managing long-term complications
Treatment of CD
• Determine clinical benefit of restoring the circadian rhythm, potentially with a higher nighttime medication dose • Identify better markers of disease activity and control • Develop new, better tolerated, more effective medical therapies • Define populations that might benefit from preoperative medical treatment

Abbreviations: CD, Cushing's disease; CS, Cushing's syndrome; MR, magnetica resonance; PET, positron emission tomography.

Figure Legends

Figure 1. Algorithm for diagnosis of Cushing's syndrome

Abbreviations: ACTH, adrenocorticotropin; CBG, corticosteroid binding globulin; CD, Cushing's disease; CRH, corticotropin stimulating hormone; CS, Cushing's syndrome; CT, computed tomography; Dex, dexamethasone; DM, diabetes mellitus; DST, dexamethasone suppression test; GC, glucocorticoid; IPSS, inferior petrosal sinus sampling; MRI, magnetic resonance imaging; PCOS, polycystic ovary syndrome; UFC, urinary free cortisol.

Figure 2. Algorithm for management of Cushing's disease.

Abbreviations: ACTH, adrenocorticotropin; DST, dexamethasone suppression test; IPSS, inferior petrosal sinus sampling.