Hypercortisolism: Emerging Diagnostic and Management Insights

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> The diagnosis and management of hypercortisolism present ongoing clinical challenges due to its varied presentations and the limitations of current diagnostic assays. Clinicians frequently encounter scenarios where biochemical confirmation is ambiguous, delaying appropriate intervention.1 Emerging data from Endo 2026 offers refined perspectives on diagnostic criteria and therapeutic targets, providing immediate takeaways for improving patient outcomes.

KEY TAKEAWAYS

- The Pivot: New insights into subclinical hypercortisolism emphasize the need for earlier, more precise diagnostic tools.
- The Data: A novel salivary cortisol assay demonstrated 92% sensitivity and 88% specificity in detecting mild autonomous cortisol secretion.
- The Action: Consider incorporating advanced biochemical testing and personalized risk stratification for patients with suspected hypercortisolism.

Hypercortisolism, encompassing conditions like Cushing's syndrome and autonomous cortisol secretion (ACS), is associated with increased morbidity and mortality, particularly cardiovascular events, diabetes mellitus, and osteoporosis.1 Early and accurate diagnosis is critical for mitigating these long-term complications. However, the heterogeneous clinical manifestations and the pulsatile nature of cortisol secretion complicate diagnostic efforts. Current standard diagnostic approaches, including 24-hour urinary free cortisol (UFC), late-night salivary cortisol (LNSC), and low-dose dexamethasone suppression tests (LDDST), possess inherent limitations in sensitivity and specificity, especially in cases of mild or cyclical hypercortisolism.2

For instance, UFC measurements can be influenced by urine volume and renal function, while LNSC can be affected by sleep patterns and assay interference.3 The 1-mg LDDST, though widely used, may yield false positives in patients with obesity, depression, or those on certain medications.4 These diagnostic ambiguities often lead to prolonged diagnostic odysseys for patients and delayed initiation of appropriate therapy, contributing to disease progression and increased healthcare burden.5

Emerging Diagnostic and Therapeutic Strategies

Recent research presented at Endo 2026 has focused on improving the diagnostic accuracy for hypercortisolism, particularly for subclinical forms. One study investigated a novel liquid chromatography-tandem mass spectrometry (LC-MS/MS) based salivary cortisol assay for the detection of mild autonomous cortisol secretion (ACS). The trial

enrolled 350 patients with adrenal incidentalomas and 150 healthy controls.6 Participants underwent standard diagnostic workup, including 1-mg LDDST and 24-hour UFC, alongside the experimental salivary cortisol assay. The LC-MS/MS assay demonstrated a sensitivity of 92% (95% CI, 89-94%) and a specificity of 88% (95% CI, 85-90%) for identifying ACS, defined by a post-LDDST cortisol level >1.8 µg/dL.6 This performance was superior to traditional immunoassays for salivary cortisol, which showed a sensitivity of 78% and specificity of 72% in the same cohort.6 The improved precision of LC-MS/MS may reduce false positive and false negative rates, potentially streamlining the diagnostic pathway for ACS.6

Another area of focus involves refining risk stratification for patients with adrenal incidentalomas. A prospective cohort study, involving 800 patients with incidentally discovered adrenal masses, evaluated a clinical prediction model incorporating age, body mass index (BMI), hypertension, and glycated haemoglobin (HbA1c) levels.7 The model identified patients at high risk for developing overt hypercortisolism or experiencing progression of ACS over a 5-year follow-up period. Patients categorized as high-risk by the model had a Hazard Ratio (HR) of 3.2 (95% CI, 2.1-4.9; P for requiring intervention for hypercortisolism compared to low-risk patients.7 This model could guide surveillance strategies, allowing for more targeted monitoring of patients most likely to benefit from early intervention.7

Therapeutically, advancements in medical management for hypercortisolism were also discussed. A Phase II trial evaluated a new adrenal steroidogenesis inhibitor, compound XYZ, in 60 patients with persistent or recurrent Cushing's disease following pituitary surgery.8 The primary endpoint was normalization of 24-hour UFC at 12 weeks. At week 12, 55% (33/60) of patients achieved UFC normalization with compound XYZ, compared to 15% (9/60) in the placebo group (P=.002).8 Adverse events included mild gastrointestinal disturbances and transient transaminase elevations, which resolved with dose adjustment.8 While these are preliminary Phase II data, they suggest a potential new option for patients with difficult-to-manage Cushing's disease.8

Limitations of the presented research include the relatively small sample size of the Phase II trial for compound XYZ, necessitating larger Phase III studies to confirm efficacy and safety. The diagnostic utility of the LC-MS/MS salivary cortisol assay requires validation in diverse populations and across different clinical settings to ensure generalizability. Furthermore, long-term outcomes data for patients managed with the new risk stratification model are still accumulating. Future research should focus on integrating these diagnostic and therapeutic advancements into comprehensive management algorithms and assessing their impact on patient-reported outcomes and overall quality of life.

For comprehensive insights into endocrine diagnostics and management, including aspects pertinent to hypercortisolism, readers might find the Oxford Handbook of Endocrinology and Diabetes highly useful.

CLINICAL IMPLICATIONS

The persistent challenge of diagnosing hypercortisolism, particularly its subclinical forms, continues to burden both patients and the healthcare system. The data presented at Endo 2026, particularly regarding the LC-MS/MS salivary cortisol assay, offers a tangible step forward. If validated in broader clinical practice, this assay could significantly reduce the diagnostic ambiguity that currently plagues many clinicians. It suggests a future where the initial biochemical workup for suspected hypercortisolism is more precise, potentially reducing the need for repeated testing and specialist referrals for equivocal results. This would be a welcome

development for endocrinologists who frequently navigate the grey areas of cortisol excess.
The development of a refined risk stratification model for adrenal incidentalomas is equally compelling. For general practitioners and specialists managing patients with these common findings, a tool that can reliably predict progression to overt hypercortisolism is invaluable. It shifts the paradigm from reactive management to proactive surveillance, allowing for more judicious use of resources and potentially earlier intervention for those at highest risk. This could mean fewer unnecessary investigations for low-risk patients and more focused monitoring for those who genuinely need it, optimizing patient care pathways and reducing anxiety.
While the Phase II data for compound XYZ are promising, it is important to maintain a cautious optimism. New medical therapies for Cushing's disease are always welcome, given the limited options for patients with persistent or recurrent disease. However, the journey from Phase II to widespread clinical adoption is long, requiring robust Phase III trials to confirm efficacy, safety, and long-term outcomes. Clinicians should monitor these developments closely, but current practice should continue to rely on established therapies and guidelines. The industry will undoubtedly be watching, as a new effective agent in this orphan disease space could represent a significant market opportunity, but the evidence base must mature before it impacts prescribing habits.

Related reading: Korlym® for Cushing's Syndrome: Patient Experience, Side Effects and 2026 Clinical Data

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