Diagnosis of recurrence in Cushing’s disease: American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review

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Abstract

Recurrence of hypercortisolemia after initial treatment of Cushing’s disease (CD) is more common than previously thought, with a third of patients suffering a recurrence over their lifetime. Awareness of this high rate and delayed timeline (sometimes decades) of potential recurrence is critical and patients with CD should be monitored at regular intervals throughout their lives.

In this manuscript, we review the complex evaluation needed for defining CD remission versus persistent disease after surgery, and focus on challenges in diagnosing early recurrent hypercortisolemia. Late night salivary cortisol appears to be an earlier predictor of recurrence when compared with urinary free cortisol excretion. We also review the criteria suggested to define recurrence of hypercortisolemia in patients treated with medical therapy. Further research is needed to determine the optimal way to evaluate a patient with Cushing’s disease recurrence as well as the risk-benefit ratio of treatment in early, mild recurrent disease.

Key words: Cushing disease, remission of Cushing’s, recurrence of Cushing’s, hypercortisolemia, urinary free cortisol, late night salivary cortisol, overnight dexamethasone suppression test
1. Introduction

Cushing’s disease (CD) is the most common cause of endogenous hypercortisolism (1, 2), with a reported prevalence of approximately 40 cases per million. However, it has been suggested that the disease is under-diagnosed, and that the prevalence may be much higher (3). Patients with CD have significant morbidity and increased mortality. Mortality in CD is higher than in non-functioning pituitary adenomas (4) even though patients with CD are much younger. If untreated, the death rate may approach 50% at 5 years (5, 6).

A recent systematic review and meta-analysis of studies that included 766 patients who achieved remission from CD showed a pooled standard mortality ratio (SMR) of 2.5 (95% CI 1.4-4.2). Mortality appears to remain higher in patients with CD even after initial biochemical remission. (7). Hypopituitarism, including persistent adrenal insufficiency after surgery, has also been suggested to enhance the mortality risk (7). In one study, depression increased the risk of death among patients who achieved remission (8). Therefore, CD is associated with significant long-term sequelae that may occur despite biochemical control. A single center study with extensive and long-term follow-up (9) reported that patients with CD in remission have better clinical outcomes than those with persistent CD, and they appear to have a SMR similar to the general population.

Transsphenoidal surgery (TSS) remains first line therapy in most cases, but disease activity may persist after surgery in a significant proportion of patients. Rates of surgical remission depend significantly on tumor size and location, neurosurgeon skill and experience, and on the biochemical criteria used to assess remission (10-12). There are as yet no strict criteria to define remission, and clinical evaluation and biochemical testing to diagnose recurrent disease, especially in early and/or mild phases, remains challenging (13). A meta-analysis conducted in
2016 concluded that the current evidence regarding remission and recurrence rates after surgery is limited due to the non-comparative nature and high heterogeneity of the studies included (14).

The most frequently used biochemical tests to evaluate recurrence of CD include 24-hour urine free-cortisol (UFC), midnight or late night salivary cortisol concentration test (LNSC), low dose dexamethasone suppression test (LDDST), overnight dexamethasone suppression test (ODST), and adrenocorticotropic hormone (ACTH) levels (15, 16). Serum midnight (late-night) cortisol, 2-day low dose dexamethasone suppression/corticotropin-releasing hormone (CRH) test and desmopressin stimulation test have also been employed to assess recurrence. The sensitivity and specificity for each of these tests are variable, complicating the interpretation of the findings (1, 2, 17-19).

When reviewing the results of each test, it is important to remember the physiology underlying their use (20). For example, UFC reflects cortisol secretion that exceeds cortisol-binding globulin capacity; only unbound, or “free,” cortisol will be excreted in urine. Elevated LNSC, which also evaluates “free cortisol”, reflects loss of normal cortisol diurnal variation, which may be the first abnormality in recurrent CD. A dexamethasone suppression test (either overnight or low dose) indicates loss of normal feedback physiology (failure to suppress cortisol after administration of low dose glucocorticoids).

False positive tests are seen in pregnancy, uncontrolled hypertension, alcohol dependence, morbid obesity, depression, and poorly controlled diabetes (1, 15, 16, 21). The assays themselves also have variable accuracy. Furthermore, each test comes with specific precautions and caveats, which need to be taken into account. (Table 1) (15, 16).

2. Assessing remission after pituitary surgery in Cushing’s disease

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Transsphenoidal surgery remains first-line treatment for CD (12). Most patients in remission after surgery will have adrenal insufficiency (AI) due to suppression of normal corticotroph cell production of ACTH in the postoperative period, and it may require months to years for the hypothalamic–pituitary–adrenal axis (HPA) to fully recover. Criteria for disease remission vary significantly from study to study, but include resolution of clinical symptoms related to hypercortisolism (22-24), need for corticosteroid replacement for greater than 6 months after transsphenoidal surgery (TSS) (25), hypocortisolemia/eucortisolemia (26), and presence of clinical and laboratory signs of low serum cortisol and AI (11, 22, 27-39).

Criteria for evaluation of disease remission have been reviewed in systematic reviews that include > 6000 patients (1, 2, 18). Low serum cortisol in the immediate postoperative period (in the absence of perioperative GC administration), and normal UFC and LNSC appear to have a higher sensitivity and specificity for determining remission in comparison to other biochemical markers (11, 23, 26, 39-45) However, no cut-off values seem predictive of which patients will experience recurrence, although lower postoperative serum cortisol levels are associated with a lower risk of recurrence (46). The addition of ACTH to cortisol measurements may increase the accuracy of remission assessments (22, 47) (Box 1). Although an early postoperative plasma ACTH level < 20 pg/mL has been suggested as an additional criteria predicting long-term remission (48), this finding has not been noted in all studies (47).
Box 1

- A postoperative cortisol value of < 2 μg/dl predicts a higher chance of long-term remission after TSS in CD.
- Most patients with postoperative cortisol values of 2-5 μg/dl a few days after TSS will also be in remission; these patients do not require immediate adjuvant treatment for CD.
- A small proportion of patients with cortisol > 5-10 μg/dl will have delayed remission.
- Low early postoperative ACTH levels might predict early hypocortisolemia, but may not accurately predict long-term remission.
- All patients require long-term clinical follow-up (there is no single cortisol or ACTH cutoff value that will exclude all patients with recurrence)

3. HPA recovery lag time after CD remission

Hypocortisolemia in the immediate postoperative period has been suggested to indicate remission and predict recurrence risk in CD. Adrenal insufficiency may persist in these cases for months or even years, usually between 13 and 25 months (49-53). The underlying pathophysiology for a delay or lack of recovery of the HPA axis in some patients is not well understood (37, 43, 45, 49, 51, 54-58). In one large study, the time needed to achieve recovery of the HPA axis was the only significant predictor of recurrence, with patients who had a protracted course of secondary adrenal insufficiency following pituitary surgery being less likely to develop CD recurrence (59).

4. Diagnosis of Recurrence of Cushing’s disease

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The definition of recurrence of CD is not well established and varies significantly among studies. (1, 2, 18). The most frequent criteria used are a combination of new onset of symptoms, clinical features and/or abnormal biochemical markers (12, 37, 43, 45, 49, 51, 54-58).

Historically, the most frequently utilized biochemical tests in studies to detect recurrence have been 24 hour UFC and 1 mg DST. However, measuring LNSC has been shown to be sensitive and is being used more commonly (18, 60-62). A combination of an abnormal LDDST and UFC, regardless of whether serum cortisol and/or clinical parameters were also included in the assessment of recurrence, resulted in an overall recurrence rate of 19.4% at 55.1 months (mean duration) after remission (25, 40, 63-66).

4.1 Twenty-four hours urinary free cortisol

Urinary free cortisol is commonly used to screen for hypercortisolemia, (12, 67), but this test becomes abnormal relatively late in the course of CD recurrence (60). The reliability and reproducibility of UFC are both very important (68).

Newer methods such as liquid chromatography–mass spectrometry (LC-MS) improve the analytical diagnostic performance of UFC compared to immunoassays (69-71). Direct comparative studies of the new and old methods in patients with Cushing’s disease have not been published, but it has been suggested that the new, lower reference ranges for UFC by LC-MS/MS may mandate an adjustment in the cutoff value for the screening UFC test (12, 67).

Intra-patient UFC variability is also a well-known phenomenon; large studies have shown up to 50% intra-patient variability at diagnosis (72), but variability in patients with recurrence is not known.
### 4.2 Late night salivary cortisol

In a large single center study of 164 CD patients who were in biochemical remission following TSS (60), LNSC (measured by enzyme immunoassay) at a cutoff of 7.4 nmol/l (higher than the upper limit of normal (ULN) for that assay; 4.3 nmol/l) was linked to recurrence. Recurrence was established by LNSC (75% sensitivity and 95% specificity) and a 24 hour UFC 1.6 fold above normal (68% sensitivity and 100% specificity), respectively, at a median follow up of 53.5 months. However, LNSC in the first 3 postoperative months did not predict recurrence.

A similar study (73) of 36 patients with CD, followed at a single center, analyzed retrospectively the best marker to detect early recurrence. Only patients diagnosed as being in remission or in early-stage recurrence were included. The mean LNSC concentration from a sequence of multiple salivary cortisol tests was higher in the recurrence group than in the remission group (P < 0.0001). The authors noted, however, that there was major within-patient variability of LNSC from one day to another and that the best screening strategies for recurrence required 3 or 4 samplings. (73) Interestingly, UFC was normal in 61% of patients at the time of proven early-stage recurrence and was only mildly elevated (< 2x ULN) in 39% of these patients. Salivary cortisol measured by immunoassay might be better diagnostically than LC-MS. Liquid chromatography–mass spectrometry is, however, better in identifying samples contaminated with dermal preparations of hydrocortisone, as the presence of markedly elevated salivary cortisol without concomitant increases in cortisone implicates contamination with topical hydrocortisone (74). Age, gender, sampling time, smoking and metabolic syndrome are all known factors that can affect salivary cortisol rhythm (71, 75, 76).
4.3 Overnight or Low Dose Dexamethasone Suppression test

The ODST is performed by administering 1 mg of oral dexamethasone at 11 pm and then obtaining a serum cortisol measurement the following morning between 8 am and 9 am. In the LDDST, 0.5 mg of dexamethasone is taken orally every 6 hours for 48 h, and a serum cortisol is measured in the morning after the last dose; alternatively, a 24-hour UFC is obtained before and after the 48 h dexamethasone administration. The LDDST is frequently used in combination with a CRH stimulation test (see below) (15, 16). The diagnostic accuracy appears to be good for both tests, but the 2 day low dose had slightly less diagnostic accuracy than the overnight test (68).

A serum cortisol < 1.8 mcg/dl (50 nmol/l) is now considered to be a normal response to the ODST; this is a more stringent cut-off than the previous values of 5 µg/dl. False negative and false positive tests are quite common, however (Table 1). The role of salivary cortisol measurements after dexamethasone suppression testing has not been defined.

4.4 CRH stimulation test

It has been suggested that a CRH stimulation test in the post-operative period might help predict recurrence. However, despite the presence of higher average values of CRH-stimulated cortisol and ACTH in patients who recurred compared to those in remission, no basal or stimulated ACTH or cortisol cutoff value predicted all cases of recurrence (77).

4.5 Desmopressin stimulation test

This test is rarely used in the United States (16), but is frequently used in Europe, both to differentiate Cushing’s from pseudo-Cushing’s syndrome and to detect recurrences. Several studies (78-80) demonstrated that a persistent postoperative ACTH and cortisol response to
desmopressin in the first week after surgical treatment increases the probability of CD recurrence.

4.6 Biochemical evaluation that involves combined testing

4.6.1 Coupled dexamethasone desmopressin test (CDDT)

   The CDDT has been also suggested as a predictor of recurrence of CD after surgery (81, 82). In a study of 38 subjects, CDDT was positive in 8/10 patients with recurrence 6-60 months before the appearance of classical markers of CD. Interestingly, six patients with AI in the immediate postoperative period had a recurrence (81). A modified CDDT test administered 18 months after surgical remission in 28 patients also suggested a possible confirmatory role in detecting patients at risk of recurrence (82). Furthermore, Le Marc’hadour et al., (83) found that the combination of a low immediate postsurgical cortisol level and a lack of cortisol and ACTH response to desmopressin during the CDDT in the first 3 years after surgery helped define a subgroup of patients who had a lower risk of late recurrence. However, suppressed immediate postoperative cortisol levels associated with early ‘positive’ CDDT did not predict a 100% risk of recurrence. The additional benefit of this test in diagnostically difficult cases of recurrent CD has not been shown.

4.6.2 The combined low-dose dexamethasone suppression/ corticotropin-releasing hormone test

   This test is performed on an outpatient basis; after LDDST, CRH is administered intravenously 2 hours after the last dexamethasone dose. The existence of multiple corticotroph tumor phenotypes shown in vitro (84) may account for the different responses to physiological and pharmacological modulators in vivo. This test may be useful in ruling-out CD in patients
who present with indeterminate results after screening (16, 85). It has been also studied in few patients to evaluate remission and/or recurrence, but its role in such patients needs to be determined.

5. Rates of recurrence in Cushing’s disease after TSS

In 74 studies (from 1976 to 2014) (2) totaling 6091 CD patients treated with TSS as first line therapy, the recurrence rates ranged from 0-65.5% (mean 13.4% and median 10.6%). Interpretation of this data summary is significantly limited by the heterogeneity of the studies included, definition of recurrence, number of patients in each study (between 6-668) and duration of follow up (1-444 months; median 54.6 months). Of note, the remission rate varied widely in this compilation of the studies, from 25-100% (median 78.2%). As expected, patients in studies with longer follow up had a higher recurrence rate (11, 23, 26, 39-46).

In another large analysis of multiple studies (18), those studies that only used biochemical tests to determine overall recurrence rates reported a relatively similar rate as compared with those that used both clinical and biochemical endpoints to determine rate of recurrence.

One large study reported that patients with delayed remission after TSS (patients who were either hyper- or eucortisolemic postoperatively and whose UFC levels subsequently decreased to normal or low cortisol excretion at subsequent follow-up) had a 43% cumulative rate of recurrence at 4.5 years, much higher than the 14% exhibited by patients with low cortisol after TSS (86).

Macroadenomas have been thought to have higher recurrence rates than microadenomas (37, 87-90), but in a meta-analysis by Petersenn, et al., there was no statistical difference based on tumor size (18). However, tumor invasiveness, especially cavernous sinus invasion, regardless of
tumor size, might be of more significance than size \textit{per se} (34). Standardizing biochemical endpoints, duration of follow up, size of the tumor and Knosp score (classification based on the extent of the tumor cavernous sinus invasion) (91) would further assist in defining recurrence. The timeline of follow-up is an essential criterion for recurrence; for example, it has been shown that in some cases, the disease can recur even two decades after the initial therapy (40, 49, 92). A summary of remission and recurrence rates from 42 larger studies all with at least 40 patients is depicted in Table 2 spanning from publication years 2000 to 2016 (8, 23, 25-29, 32-34, 39-42, 45, 46, 49-51, 54, 55, 62, 64-66, 86, 89, 90, 92-103). In six of the last nine studies published since 2013, the surgical technique has been a fully endoscopic approach (as opposed to a microscopic approach), reflecting this emerging trend in transsphenoidal pituitary adenoma surgery. Notably, the remission and recurrence rates for endoscopic and microscopic approaches are similar across these multiple studies.

6. Sequence and timeline of biochemical testing after TSS

The optimal sequence of tests in detecting recurrence has not been determined. In a large study of patients with CD (101 patients followed for a median of 50.4 months, range 7-99 months) (95), the recurrence rate was 20.8%. Recurrence risk was lower and recurrence occurred later in patients with early AI in the postoperative period. Desmopressin and CRH tests were performed in all subjects in the postoperative period and the presence of positive tests, 85% for desmopressin and 93 %, for CRH respectively, was associated with disease recurrence. Increases in LNSC and/or midnight serum cortisol occurred in a mean time of 38.2 months, while UFC became abnormal more than a year later (at 50.6 months). A positive response to desmopressin or CRH preceded the increase in midnight cortisol or UFC in most patients.
Based on available published data and our personal experience, we suggest the following work-up for recurrent hypercortisolemia (Box 2). The choice of which test to perform first depends on individual patient characteristics and the pitfalls of each test (noted in table 1); most patients require more than one test to confirm recurrence. Salivary cortisol is the preferred initial test and more than 2-3 samples are recommended. The timeline for repeat testing also varies based on clinical circumstances. All patients will need yearly life-long evaluation.

**Box 2: Work-up of recurrent hypercortisolemia in patients in remission after TSS**

<table>
<thead>
<tr>
<th>Clinical suspicion of recurrent Cushing’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• New onset or worsening of preexisting symptoms and comorbidities: diabetes mellitus, hypertension, osteoporosis, weight gain, easy bruising</td>
</tr>
<tr>
<td>• Biochemical evaluation</td>
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<tr>
<td>– Collect LNSC X 2-3; if high normal, additional LNSC are recommended</td>
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<tr>
<td>– Overnight dexamethasone suppression test</td>
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<tr>
<td>– Collect UFC X 2</td>
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<td>o if discordant results, repeat testing</td>
</tr>
<tr>
<td>• Role of additional combined testing remains to be determined</td>
</tr>
<tr>
<td>• New evidence of tumor on MRI or increase in size of previous residual tumor will also require additional biochemical evaluation</td>
</tr>
</tbody>
</table>

7. “Escape” or recurrence in patients with Cushing’s disease on medical therapy
The definition of “control”, either clinical or biochemical, in a patient with CD on medical therapy varies among studies, and remains controversial overall (1, 2). Furthermore, there are very few studies emphasizing escape or disease recurrence in patients on medical therapy for Cushing’s. Significant differences in study design and in mechanism of action of each drug, made a direct comparison rather difficult (104-111).

Adequate preoperative treatment with adrenal steroidogenesis inhibitors (either ketoconazole or metyrapone) in CD has been associated with suppressed postoperative cortisol concentrations and an increased long-term remission rate (111). However, it is important to keep in mind that measuring immediate postoperative cortisol in these patients can be misleading.

7.1 Cortisol: UFC and salivary cortisol

Most clinical studies looking at the effects of medical therapies have measured UFC during treatment; furthermore, new clinical guidelines (12) emphasize that despite some caveats, UFC is a good marker to assess response to therapy. One important exception is treatment with a glucocorticoid receptor blocker, which does not lead to decreases in UFC. Here, monitoring depends entirely on clinical criteria.

Pasireotide was approved for the treatment of CD by the US Federal Drug Administration (FDA) based on a large phase III clinical trial where the end point was a normal mean UFC at 3 months without a dose increase (112). However, many patients achieved significant clinical improvement or tumor shrinkage even if they had persistent elevations in UFC. Several ongoing clinical trials for osilodrostat and levoketoconazole also use normal mean UFC as one of their end points (Clinicaltrials.gov).
However, UFC and the salivary cortisol response to medical therapy can be discordant in some patients. In a small subset of patients with CD who all had elevated LNSC (113) and were treated with subcutaneous pasireotide 600 μg bid, LNSC was reduced in six patients in 15 days. But the decrease in LNSC did not always correlate with the decrease in UFC in a larger Phase III study with this drug (114).

A subsequent analysis (115) of a study where UFC normalized in 88 % of patients with triple combination therapy (pasireotide, cabergoline and ketoconazole) (116) showed that circadian rhythm (CR) was abnormal in just 12 of 17 patients at baseline. Circadian rhythm recovery was achieved in 6 of the 12 patients with abnormal baseline CR (3 mono-, 1 duo- and 2 triple-therapy) (115).

Salivary cortisol might be a more convenient biomarker than 24-hr UFC, but its role in assessing response or escape to medical therapy or predicting long-term response needs further study.

7.2 ACTH

ACTH could be a predictor of disease escape in patients treated with medication. A rise in ACTH could be due to the reduction in cortisol synthesis, but also could be due to disease progression, independent of treatment.

The normal response is a decrease in serum ACTH in patients treated with cabergoline and pasireotide (115) and an increase in ACTH with both adrenal steroidogenesis inhibitors and a glucocorticoid receptor blocker (108). Ketoconazole might also have an independent effect on ACTH secretion (117), but this is still controversial (17).
While the decrease in ACTH does not seem to correlate very well with normalization of UFC in patients treated with cabergoline (118) or pasireotide (112), in a small prospective study, patients who escaped after remission had an increase in ACTH, often to levels higher than those before starting treatment (118).

In a large multicenter retrospective study (119), an increase in ACTH with ketoconazole therapy was associated with escape in 15% of the patients treated for more than 2 years.

Interestingly, plasma ACTH elevation in patients on mitotane is linked to a lower probability of recurrence after it is discontinued (120).

In an investigational study using osilodrostat (LCI 699), none of the patients who had an initial biochemical response at 22 weeks lost biochemical control on treatment, despite an increase in ACTH, but longer-duration treatment data is needed (121).

7.3 Clinical features and co-morbidities

Improvement in clinical features and comorbidities is one of the main goals of treatment (12).

Mifepristone induced improvement in global clinical response (GCR) in 87 % of patients enrolled in the SEISMIC study; 37% of patients had positive GCR by week 10 that persisted through study end, whereas only 6.5% of patients had a positive GCR during the study that was not maintained (122). The latter can be considered a possible “escape from treatment,” suggesting the need for higher doses. Several clinical parameters can be used by clinicians to assess mifepristone response and dosing in Cushing’s syndrome (123).

In the phase III pasireotide study, lower blood pressure was observed in both patients with and without full UFC control and interestingly, was decreased more in patients who did not take
antihypertensive medications. Furthermore, body mass index, weight and waist circumference decreased in patients without full UFC control (112, 124), thus making it difficult to assess remission or escape based on clinical features alone.

In a small prospective study of patients treated with cabergoline, clinical features improved overall during treatment in responders and slightly worsened in the patients who experienced treatment escape (118).

**Conclusion**

A patient with CD, regardless of the type of treatment or the initial outcome after surgery, requires lifelong endocrine follow-up. Hypercortisolism can recur in approximately a third of patients who were initially in remission after TSS. The clinical picture needs to be closely monitored, and new onset or worsening of Cushing’s co-morbidities should prompt further evaluation even if initial testing is negative. We recommend an individualized approach to evaluate recurrence for these patients. Late night salivary cortisol seems to be the best early predictor of recurrence, but the ODST and UFC excretion are also valuable tools that should be used during follow up of patients with CD, though they tend to become abnormal later in the disease course. Notably, discordant results between tests are not uncommon and these patients will need to be closely monitored. Other tests, like the desmopressin test or combined testing with dexamethasone-CRH or dexamethasone-desmopressin, have also been studied, but more data is needed to determine their role in assessing recurrence. Multicenter studies with assessments based on combined standardized biochemical markers and clinical parameters should help in guiding best practice evaluations and appropriate individualized treatments for patients with CD recurrence.

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Table 1 Caveats of tests used to detect remission and/or recurrence in CD

1. Salivary cortisol
   a. importance of proper sample collection (multiple samples) and instructions
   b. interference by exogenous glucocorticoids
   c. avoid smoking, licorice, blood leakage
   d. not reliable in shift workers
   e. age, smoking and metabolic syndrome may increase risk of a false positive test
   f. is preferred in testing for cyclical Cushing’s due to ease of repeat testing

2. Overnight dexamethasone test
   a. variable absorption and metabolism of dexamethasone\(^1\)
      – drugs that accelerate metabolism (by induction of CYP 3A4)
      – drugs that impair metabolism (by inhibition of CYP 3A4)
      – dexamethasone levels show inter-individual variation in healthy individuals
   b. drugs that increase CBG can elevate total cortisol results
   c. can be normal in cyclical Cushing’s

3 Urinary free cortisol
   a. importance of proper sample collection (multiple samples) and instructions
   b. high fluid intake (>5L/day) may increase UFC
   c. can be normal in cyclical Cushing’s

4. Using immediate postoperative morning serum cortisol to determine remission for CD
   a. perioperative use of glucocorticoids can potentially affect and suppress residual
      ACTH-secreting cells
   b. not reliable in patients who have been treated before surgery with adrenal
      steroidogenesis inhibitors or drugs acting at pituitary level
   c. can be normal in cyclical Cushing’s

\(^1\) Dexamethasone is metabolized primarily by hepatic CYP3A4. While many drugs are
deactivated by CYP3A4, there are also some drugs that are activated by this enzyme. Few
substances, such as grapefruit juice and many drugs, interfere with the action of CYP3A4. (15, 16).
Table 2 Rates of remission and recurrence in recent studies of patients with CD

<table>
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<tr>
<th>Author &amp; Year</th>
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<th>No. of patients</th>
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<td>Year Range</td>
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<td>End</td>
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<td>50%</td>
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<td>Yap</td>
<td>1969-1988 (19)</td>
<td>97</td>
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<td>92 (6 348)</td>
<td>Morning SC UFC</td>
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SC serum cortisol, UFC urine free cortisol, LDDST low dose dexamethasone suppression test
References


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