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Follow-up intervals in patients with Cushing's disease: recommendations from a panel of experienced pituitary clinicians

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Abstract
Purpose Follow-up guidelines are needed to assess quality of care and to ensure best long-term outcomes for patients with Cushing's disease (CD). The purpose of this study was to assess agreement by experts on recommended follow-up intervals for CD patients at different phases in their treatment course.
Methods The RAND/UCLA modified Delphi process was used to assess expert consensus. Eleven clinicians who regularly manage CD patients rated 79 hypothetical patient scenarios before and after ("second round") an in-person panel discussion to clarify definitions. Scenarios described CD patients at various time points after treatment. For each scenario, panelists recommended follow-up intervals in weeks. Panel consensus was assigned as follows: "agreement" if no more than two responses were outside a 2 week window around the median response; "disagreement" if more than two responses were outside a 2 week window around the median response. Recommendations were developed based on second round results.
Results Panel agreement was 65.9% before and 88.6% after the in-person discussion. The panel recommended follow-up within 8 weeks for patients in remission on glucocorticoid replacement and within 1 year of surgery; within 4 weeks for patients with uncontrolled persistent or recurrent disease; within 8–24 weeks in post-radiotherapy patients controlled on medical therapy; and within 24 weeks in asymptomatic patients with stable plasma ACTH concentrations after bilateral adrenalectomy.
Conclusions With a high level of consensus using the Delphi process, panelists recommended regular follow-up in most patient scenarios for this chronic condition. These recommendations may be useful for assessment of CD care both in research and clinical practice.

Keywords Cushing's disease · Expert panel · Consensus statements · Follow-up · Biochemical status · Treatment

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Introduction

Cushing's syndrome (CS) is a rare disorder that results from excessive exposure to glucocorticoids (GCs). Cushing's disease (CD), which is CS caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary tumor, accounts for 70% of CS cases [1–3]. The incidence of this condition is reported to range from 1.2 to 2.4 per million population per year in Europe and up to 8 per million population per year in the US [4–7]. Left untreated, CD leads to significant morbidity and mortality [6, 8, 9]. Overall standardized mortality ratios for patients with CD have been reported to range from 1.7 to 4.8 [6, 8, 9]. Moreover, patients with CD have increased mortality compared with both patients with nonfunctional pituitary macroadenoma and acromegaly [9].

Complications related to CD include cardiovascular sequelae (increased risk of myocardial infarction, congestive heart failure, stroke), psychiatric illness (affective disorders including major depression, anxiety, emotional lability), cognitive deficits, bone loss, muscle weakness, skin changes (striae, hirsutism, ecchymoses, acne, poor wound healing), and fatigue [8–11]. Patients also experience long-term quality of life impairment [10–12]. Surgical removal of the pituitary adenoma via transsphenoidal pituitary surgery is the first-line treatment in patients with CD [13, 14]. Remission rates in patients with microadenomas undergoing initial pituitary surgery range from 48.7 to 100%, while in those with macroadenomas the remission rates range from 30.8 to 100% [14, 15]. Recurrence rates range from 0 to 36.4% in patients with microadenomas and from 0 to 59% in patients with macroadenomas undergoing initial pituitary surgery [14, 15]. If CD persists after first-line pituitary surgery, other treatments may include repeat pituitary surgery, radiotherapy, medical therapy, or bilateral adrenalectomy [13, 14]. Repeat surgery typically results in lower success rate than initial pituitary surgery, while radiotherapy achieves biochemical control in 50–60% of patients within 3–5 years, and bilateral adrenalectomy provides immediate control of cortisol excess [14]. In all cases, long-term follow-up of CD patients is essential for detecting recurrence and to optimally manage this complex condition. This is important because biochemical control of cortisol excess or deficiency can ameliorate associated morbidity and excess mortality. A consensus on appropriate follow-up and monitoring intervals may allow earlier detection of cortisol abnormalities and lead to improved management in patients with a history of CD.

Despite the need for long-term follow-up in CD, there are no consensus- or evidence-based guidelines about the frequency of monitoring patients with CD at different phases of their treatment. The goal of the present study was to assess expert agreement on recommended follow-up intervals for patients with CD for use as a quality tool in assessment of care, and ultimately to ensure the best long term outcomes for patients with CD.

Materials and methods

Delphi panel methodology

Panelists were identified on the basis of having been involved in multi-center clinical trials of treatments for CD. From among those approached and available to participate, a group of 12 who represented a diversity of practice setting, geography, and time in practice were selected. Ultimately, 11 of those 12 were able to participate. The panelists had practiced medicine in the United States for 5–35 years, spent 20–85% of their time seeing patients, and 10–40% of time conducting research. All had academic affiliations (ten were in tertiary clinical settings and one was in private practice). All panelists had extensive experience with CD. Geographic regions represented included the US South, Northeast, and West.

The survey and meeting used the modified RAND/UCLA Delphi panel process to reach consensus, which combines the best judgment of experts with the available scientific literature [16]. According to this process, the authors developed a theoretical framework and a detailed, written questionnaire ("rating form"). Next, each of the 11 physician panelists completed the rating form individually (termed the "first round") before an in-person meeting. At the meeting, which was held in early 2016, the panelists reviewed the results of the initial form to identify areas of agreement and disagreement and discussed definitions of the clinical scenario terminology. At the end of the meeting, the panelists repeated the completion of the rating form ("second round"). These second round results were then scored and interpreted for development of expert consensus statement recommendations for follow-up intervals in patients with CD.

Rating form

The goal of the form was to elicit panelists' opinions about the appropriate follow-up intervals for patients with CD. To do this, the rating form presented a series of patient descriptions, and panelists were asked to indicate the appropriate follow-up interval (in weeks) for each type of patient represented by each cell in the form. The structure of the rating form can be found in Tables 1, 2 and 3, which captures the many possible trajectories of CD. Each table includes factors that influence follow-up intervals for the corresponding patient type, and each cell corresponds to a description of a unique type of CD patient. Tables 1 and 2

Table 1 Follow-up intervals in Cushing's disease patients after pituitary surgery

		In a patient with:	Currently not on steroid replacement and not on drug therapy for Cushing's disease		Currently on exogenous glucocorticoid supplementation		Currently on drug therapy for Cushing's disease[a]	
			Current biochemical hypercortisolism[b]		Current biochemical adrenal status		Current biochemical hypercortisolism[b]	
			a. Absent[c]	b. Present[d]	c. Low[e]	d. Normal[f]	e. Absent[c]	f. Present[d]
Following pituitary surgery	(i) 1–3 months after surgery	A. No symptoms	***4***	***4***	***6***	***4***	***4–6***	***2–4***
		B. Symptoms of adrenal insufficiency currently[g]	***4–6***		***4***	***4***	***4***	
		C. Symptoms of Cushing's Disease currently[h]	***4***	***4***	***6***	***4***	***4–6***	***4***
	(ii) 3–12 months after surgery	A. No symptoms	***12*** *(8–26)*	***4***	***8–10***	***4–6***	***6***	***4***
		B. Symptoms of adrenal insufficiency currently[g]	***4***		***4***	***4***	***4***	
		C. Symptoms of Cushing's Disease currently[h]	***4***	***4***	***6***	***4***	***6–8***	***4***
	(iii) Beyond 12 months after surgery	A. No symptoms	***24***	***4***	***6–8***	***6***	***12***	***3–4***
		B. Symptoms of adrenal insufficiency currently[g]	***4***		***4***	***4***	***4***	
		C. Symptoms of Cushing's Disease currently[h]	***4*** *(4–8)*	***4***	***6***	***4***	***8*** *(8–12)*	***4***

Notes empty solid grey cells indicate deleted scenarios, which the panel decided were implausible

This table refers to patients with Cushing's disease who have had pituitary surgery (white cells indicate agreement; grey cells indicate disagreement). In each cell, the value in bold is the median panel response (i.e., median follow-up recommendation in weeks); values in parenthesis are the range of panel response values

[a]Medical therapy including: (1) steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane, etomidate); (2) somatostatin analog (pasireotide); (3) dopamine receptor agonists (cabergoline); (4) glucocorticoid receptor agonists (mifepristone); frequency of follow-up may vary based on the specific medical therapy

[b]e.g. determined by urinary 24-h free cortisol, midnight salivary cortisol, serum cortisol after 1 mg dexamethasone suppression test (for all medical therapies except mifepristone)

[c]e.g. normal urinary 24-h free cortisol, normal midnight salivary cortisol, suppressed serum cortisol after 1 mg dexamethasone suppression test (for all medical therapies except mifepristone)

[d]e.g. elevated urinary 24-h free cortisol, elevated midnight salivary cortisol, lack of serum cortisol suppression after 1 mg dexamethasone suppression test (for all medical therapies except mifepristone)

[e]May require glucocorticoid dose adjustment

[f]An indicator of adrenal function recovery in patients with CD who are in remission

[g]Symptoms thought to be associated with adrenal insufficiency that are a significant problem for the patient

[h]Symptoms of CD that are a significant problem for the patient

Table 2 Follow-up intervals in Cushing's disease patients after radiation therapy

		In a patient with:	Currently not on steroid replacement and not on drug therapy for Cushing's Disease		Currently on exogenous glucocorticoid supplementation		Currently on drug therapy for Cushing's disease[a]	
			Current biochemical hypercortisolism[b]		Current biochemical adrenal status		Current biochemical hypercortisolism[b]	
			a. Absent[c]	b. Present[d]	c. Low[e]	d. Normal[f]	e. Absent[c]	f. Present[d]
Following radiation	i. 1–6 months after radiation	A. No symptoms		***4***			***12*** *(8–24)*	***4***
		B. Symptoms of adrenal insufficiency currently[g]					***2–4***	
		C. Symptoms of Cushing's disease currently[h]		***4***			***8*** *(8–12)*	***4***
	ii. Beyond 6 months after radiation	A. No symptoms	***24***	***4***	***24***		***12*** *(6–24)*	***4***
		B. Symptoms of adrenal insufficiency currently[g]	***2–4***		***4***		***4***	
		C. Symptoms of Cushing's disease currently[h]	***4***	***4***	***4–6***		***12***	***4***

Notes empty solid grey cells indicate deleted scenarios, which the panel decided were implausible

This table refers to patients with Cushing's disease who have radiation therapy (white cells indicate agreement; grey cells indicate disagreement). In each cell, the value in bold is the median panel response (i.e., median follow-up recommendation in weeks); values in parenthesis are the range of panel response values

[a]Medical therapy including: (1) steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane, etomidate); (2) somatostatin analog (pasireotide); (3) dopamine receptor agonists (cabergoline); (4) glucocorticoid receptor agonists (mifepristone); frequency of follow-up may vary based on the specific medical therapy

[b]e.g. determined by urinary 24-h free cortisol, midnight salivary cortisol, serum cortisol after 1 mg dexamethasone suppression test (for all medical therapies except mifepristone)

[c]e.g. normal urinary 24-h free cortisol, normal midnight salivary cortisol, suppressed serum cortisol after 1 mg dexamethasone suppression test (for all medical therapies except mifepristone)

[d]e.g. elevated urinary 24-h free cortisol, elevated midnight salivary cortisol, lack of serum cortisol suppression after 1 mg dexamethasone suppression test (for all medical therapies except mifepristone)

[e]May require glucocorticoid dose adjustment

[f]An indicator of adrenal function recovery in patients with CD who are in remission

[g]Symptoms thought to be associated with adrenal insufficiency that are a significant problem for the patient

[h]Symptoms of CD that are a significant problem for the patient

describe scenarios of patients with CD who have had pituitary surgery and radiation therapy, respectively. Table 3 refers to scenarios of patients with CD following bilateral adrenalectomy who are on GC replacement. The panel also evaluated scenarios of patients with CD who were not on replacement therapy and were recently discovered to be hypopituitary by biochemical measurement (not shown). For example, in Table 1, the cell 'IiCb' corresponds to a

Table 3 Follow-up intervals in Cushing's disease patients after bilateral adrenalectomy

	Current diagnosis of Nelson's syndrome[a]		No prior diagnosis of Nelson's syndrome[a]	
In a patient:	Current ACTH levels[b]		Current ACTH levels[b]	
	a. Stable[c]	b. Rising[d]	c. Stable[c]	d. Rising[d]
A. Currently with symptoms of adrenal insufficiency	***2***	***2***	***2***	***2***
B. Currently with no symptoms of adrenal insufficiency	***12***	***8***	***24***	***8***

This table refers to patients with Cushing's disease following bilateral adrenalectomy who are on steroid replacement (white cells indicate agreement). In each cell, the value in bold is the median panel response (i.e., median follow-up recommendation in weeks)

[a]Patient with an underlying ACTH-secreting pituitary adenoma that recurred or progressed following bilateral adrenalectomy for the treatment of Cushing's disease

[b]Measured to monitor for recurrence or progression of ACTH-secreting pituitary adenoma following total bilateral adrenalectomy

[c]Biochemical marker of pituitary adenoma tumor control

[d]Biochemical marker of pituitary adenoma tumor progression

CD patient who is between 1 and 3 months after pituitary surgery, currently not on GC replacement and not on drug therapy for CD, and has biochemical hypercortisolism with symptoms of CD.

For each scenario, panelists indicated the appropriate follow-up interval from 0 to 52 (in weeks) for a patient with the characteristics that were represented by that cell. Many of the scenarios represented states that required some action at the current visit. The phrase "follow-up interval" was used to mean the next time the patient should be evaluated, not when (or whether) an action was needed at the current visit. For example, in a patient with adrenal insufficiency who needs immediate medical therapy, the assumption was that cortisol replacement would be initiated at the current visit. A panelist response of "2" for the number of weeks until follow-up meant that the visit to evaluate the response to medication should take place within 2 weeks, not that nothing should be done for the patient except to re-evaluate in 2 weeks. In the context of this study, "follow-up" was defined as *any* patient contact, including an office visit, telephone call, e-mail contact, or biochemical test assessment.

Rating form scoring

Panelists indicated their recommended follow-up interval in weeks for each scenario, and submitted their ratings independently, before and after a face-to-face discussion. The experts' recommended follow-up interval for the given scenario represented the next time the physician thought that tests should be done and/or the patient should be communicated with or seen. Based on Fitch [16], *The Rand/UCLA Appropriateness Method User's Manual*, and panelists' suggestions, each rated scenario was assigned a level of consensus based on the following classification: Agreement was defined as having no more than two responses outside a 2 week window around the median response. Disagreement was listed if more than two responses were outside a 2 week window around the median response. If a particular scenario cell in the form had an even number of responses (i.e., resulting in two medians) then "agreement" was marked for the scenario if at least one of the medians indicated agreement based on the rule above.

Results

Overview

The first round of ratings yielded a high level of consensus (65.9%) on the recommended follow-up intervals in the majority of scenarios, with initial disagreement on follow-up intervals for 29 of 85 patient scenarios (34.1%). During the face-to-face discussion, the experts identified six scenarios that were unlikely to be observed in typical clinical settings and eliminated them from the second round rating form. The overall second round agreement was 88.6% (70 of 79 scenarios), distributed as follows: 91.2% (62/68) agreement for scenarios referring to patients with CD who had pituitary surgery or radiation therapy, and 100% (8/8)

agreement for scenarios referring to patients with CD following bilateral adrenalectomy who were on GC replacement. The recommended follow-up intervals varied for scenarios describing CD patients who were discovered to be hypopituitary while not on replacement therapy. The individual patient scenarios are described in Tables 1 and 2. The values in these tables are scenario-specific medians of panelists' responses, which indicate the follow-up recommendations in weeks for each patient scenario.

Consensus statements

All statements recommend a follow-up interval after appropriate intervention based on the patient's current clinical circumstances. For example, a patient with adrenal insufficiency may need immediate medical therapy, and then should be re-evaluated within 2 weeks. The statements below reflect the interval following the appropriate action until the next evaluation (2 weeks in the above example) not the time to the action itself (immediate in this example). Appropriate follow-up intervals for patients on medical therapy depend on the specific therapy, and so only general guidelines are given.

In the first year following surgery, patients should be re-evaluated within 4–8 weeks of surgery and subsequently at 4–24 week intervals, depending on clinical circumstances (Table 1).

Beyond 12 months after surgery, patients with persistent or recurrent disease and not well-controlled on medical therapy should be re-evaluated within 4 weeks. Patients in remission with hypothalamic–pituitary–adrenal (HPA) suppression (adrenal insufficiency on adequate GC replacement) should be re-evaluated within 8 weeks (Table 1). During the same period, patients with persistent or recurrent disease and well controlled on medical therapy should be re-evaluated within 12 weeks. Patients in remission with a recovered HPA axis (not on GC replacement) should be re-evaluated within 6 months.

In the first 6 months after radiotherapy, patients in biochemical control on medical therapy should be re-evaluated within 8–24 weeks (depending on clinical circumstances) (Table 2). Beyond 6 months after radiotherapy, patients in remission should be re-evaluated within 6 months, while patients with persistent or recurrent disease and well controlled on medical therapy should be re-evaluated within 12 weeks.

The panel recommended follow-up intervals for CD patients presenting at any time after bilateral adrenalectomy. Following bilateral adrenalectomy, patients with symptoms of adrenal insufficiency despite hormone replacement should be re-evaluated within 2 weeks (Table 3). This and other recommendations are for the next follow-up after the appropriate interventions based on the patient's current clinical circumstances have taken place. Patients with no symptoms of adrenal insufficiency on hormone replacement and who have rising ACTH levels should be re-evaluated within 8 weeks. Patients with no symptoms of adrenal insufficiency on hormone replacement and who have stable ACTH levels should be re-evaluated within 12 weeks if they have an expanding pituitary mass. Patients with no symptoms of adrenal insufficiency on hormone replacement and stable MRIs and ACTH levels should be re-evaluated within 24 weeks.

Discussion

CD is a chronic disease requiring life-long surveillance, but no consensus- or evidence-based follow up guidelines exist for these patients. The goal of the present study was to elicit expert agreement on recommended follow-up intervals for patients with CD for use as a tool to assess quality of care, and to improve long term outcomes for patients with CD. Using the RAND/UCLA modified Delphi method, experts achieved a high level of consensus on recommended follow-up intervals for CD patients under most circumstances, but disagreement remained for some scenarios. Agreement substantially increased from 65.9 to 88.6% after in-person discussion during which panelists clarified definitions and shared their thoughts about the various scenarios.

Consensus statements included panel recommendations to follow-up within 8 weeks for patients in remission on GC replacement and within 1 year of pituitary surgery; within 4 weeks for patients with uncontrolled persistent or recurrent disease; within 8–24 weeks for post-radiotherapy patients controlled on medical therapy; and within 24 weeks for asymptomatic patients with stable plasma ACTH concentrations after bilateral adrenalectomy. Key factors that seemed to drive the recommendation for shorter follow up times included scenarios that involved patients with active disease or possible adrenal insufficiency. For example, patients with current biochemical hypercortisolism or symptoms of adrenal insufficiency were recommended to follow up within 2 weeks, whereas patients with CD in remission and no symptoms of adrenal insufficiency were recommended to follow up as long as 26 weeks later.

The RAND/UCLA modified Delphi process is a well-documented and systematic methodology that has been shown to capture group decision making in a valid, reproducible, and reliable way [16–18]. The Delphi process enables elicitation of the collective opinion of experts, resulting in detailed consensus statements that can inform the development of treatment guidelines and may also guide clinicians' medical decision making. The method has been used extensively in a various clinical areas to develop consensus statements on topics such as coronary revascularization,

hysterectomy, glaucoma treatment initiation, stroke prevention, systemic management of neuroendocrine tumors, and nomenclature of menstrual bleeding abnormalities [18–25]. The Delphi process allowed consensus to be elicited from a panel of experts on appropriate follow up intervals for 79 distinct, clinical, treatment scenarios of patients with CD.

Despite the strengths of the Delphi process, the current expert consensus recommendations were not developed based on data from randomized controlled trials of follow-up intervals because such data do not exist. Instead, the panelists relied on their clinical practice experience and published literature on CD remission and recurrence rates, comorbidities, and mortality risk to arrive at their recommendations. A different panel composition may have yielded somewhat different consensus statements. The Delphi panel method has been shown to be reproducible, but is more reproducible the stronger the evidence base. Shekelle et al. [17] conducted six separate panels for coronary revascularization and hysterectomy (three for each procedure). The authors found agreement in the 90% range for coronary revascularization, where much of the evidence was from RCTs, and in the 70–80% range for hysterectomy, which lacked as rigorous a research base. Nonetheless, the method is the only consensus methodology with strong evidence of validity. That is, there is evidence that patients treated in concordance with criteria developed using the method have better outcomes than those who receive discordant care [26]. In addition, a modified Delphi panel's recommendations were developed at a time when only one RCT was available on a topic, compared to six RCTs published over the next 14 years, and none of the panel's recommendations were refuted [27]. Finally, this Delphi panel only included US endocrinologists, so these recommendations may not be generalizable to other countries.

CD requires long-term follow-up, and often involves multiple therapies over time to achieve remission. The risk of late recurrences in particular necessitates ongoing surveillance, and there are many clinical scenarios that may occur in patients with a history of CD. Yet no specific guidelines exist focused on the recommended frequency of monitoring for these patients. The current panel was assembled to provide consensus-based data to inform the long-term care for patients with CD. Delphi expert consensus recommendations on appropriate follow-up intervals may be useful as a quality tool for assessment of care for these patients in future research and clinical practice [18–25].

As the Delphi panel process does not develop new information, observational and/or prospective studies will be useful to further evaluate the appropriateness of the current follow up intervals for different clinical scenarios along the treatment course for patients with CD. It will be valuable for future studies to identify patients at risk for being lost to follow up and investigate the effects of follow up intervals on long term outcomes. Appropriate follow up may lead to prompt identification and treatment of recurrent and persistent disease in CD patients, and reduce the burden of comorbid diseases. With a high level of consensus using the Delphi process, panelists recommended regular follow-up in most patient scenarios for this chronic condition. These recommendations may be useful for assessment of CD care both in research and clinical practice.

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Compliance with ethical standards

Conflict of interest Maureen P. Neary and Qayyim Said are employees of the Novartis Pharmaceuticals Corporation. Michael S. Broder, Dasha Cherepanov, Marianne Eagan, and Jackie Lee are employees of the Partnership for Health Analytic Research, LLC, a health services research company paid by Novartis to conduct this research. Beverly MK Biller has been PI of research grants to Massachusetts General Hospital from Cortendo and Novartis and has served as an occasional consultant to Cortendo, HRA Pharma, Ipsen and Novartis. Eliza B. Geer has been PI of a research grant from Novartis and has served as an occasional consultant to Cortendo, Novartis, IONIS, and Chiasma. Laurence Katznelson has been PI of a research grant from Novartis and is a consultant for Pfizer, Novartis and Chiasma. John Carmichael has been PI of research grants from Novartis and Cortendo, and has served as a consultant to Pfizer, Novartis, Chiasma, and Ionis. Murray B. Gordon has been PI of research grants from Cortendo, Ipsen, Opko, Pfizer, Teva, Novartis, Chiasma, NovoNordisk and Corcept and has served as an occasional consultant to Novartis, Ibsen, Corcept and NovoNordisk. Ismat Shafiq and Ekaterina Manuylova received a research grant from Novartis, and also occasionally consultant for Novartis. The content of the manuscript was discussed in detail by the investigators led by the first author, Dr. Geer, and the first draft was then prepared by authors from Partnership for Health Analytic Research. Subsequently, the investigators provided substantial edits with several revisions being circulated and all authors approved the final, submitted version. Novartis authors reviewed the manuscript but did not write or edit the text.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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