Expert Consensus Recommendations for Follow-up Intervals in Patients with Cushing's Disease

SAT 554

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BACKGROUND

- Cushing's disease (CD), excess corticosteroid exposure resulting from an adrenocorticotropin-secreting pituitary tumor, is uncommon.
- Consensus guidelines are available for the diagnosis and treatment of CD, but there are few recommendations on follow-up intervals for patients at different stages of this condition.
- The RAND/UCLA modified Delphi process is a group decision-making method that systematically establishes the appropriateness of a wide variety of medical approaches.

OBJECTIVE

- To achieve expert agreement on recommended follow-up intervals for patients with CD for use as a quality tool in assessment of care in future research.

METHODS

The modified RAND/UCLA Delphi process was used to establish expert consensus, which involved a comprehensive list of clinical patient scenarios, collection of ratings from the expert physicians, statistical summary of panel agreement, and development of consensus statements.

Physician Experts

- Eleven physician experts in management of CD from diverse locations in the US and several practice types participated in the panel.

Development of Clinical Patient Scenarios in CD

- The experts collaborated to develop a list of key variables and used these variables to construct up to 85 unique clinical patient scenarios.

Variable	Range of Values
Months post pituitary surgery	1-3 months (mos); 3-12 mos; beyond 12 mos
Months post radiotherapy	1-6 months; beyond 6 months
Symptoms	No symptoms; symptoms of adrenal insufficiency; symptoms of CD
Medical therapy	No glucocorticoid (GC) replacement or medication to treat CD; on GC replacement; on drug therapy for CD
Biochemical hypercortisolism	Absent; present
Biochemical adrenal status	Low; normal
Current adrenocorticotropin (ACTH) levels	Stable; rising
Hypopituitary by biochemical measurement	Established deficiency in GH, FSH and LH; or, GH, FSH, LH and thyroid hormone (TH); or, GH, FSH, LH, TH, and ACTH

Rating of Clinical Patient Scenarios

- Panelists indicated their recommended follow-up interval in weeks (wks) for each scenario, and submitted their ratings independently, before and after a face-to-face discussion.
- Each scenario was assigned a level of consensus:
  - Agreement: if no more than 2 responses were outside a 2 wk. window around the median
  - Disagreement: >2 responses with >2 wk. window around the median

Assumption During the Rating Process

- The expert's 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.

RESULTS

- The physician panelists had practiced medicine for 5-35 years, spent 20-85% of their time seeing patients and 10-40% of time conducting research.
  - Most were in academic or tertiary clinical settings and one was in private practice.
  - All panelists had seen patients with CD and participated in research for CD
  - Geographic regions represented included South, Northeast, and West.
- The 1st round of ratings yielded a high level of consensus on the recommended length of follow-up in the majority of situations, with initial disagreement on follow-up intervals for 29 of 85 patient scenarios (34.1%).
- During the face-to-face discussion of the 1st round ratings among the panelists, the experts agreed that 6 scenarios were unlikely to be observed in typical clinical settings and eliminated them from the 2nd round rating survey.
- The overall 2nd round agreement was 88.6% (70/79), distributed as follows:
  - 91.2% (62/68) for scenarios referring to patients with CD who have had pituitary surgery or radiation therapy.
  - 100% (8/8) for scenarios referring to patients with CD following bilateral adrenalectomy who are on steroid replacement.
- The recommended follow-up intervals varied for scenarios referring to CD patients not on replacement therapy but who were recently discovered to be hypopituitary by biochemical measurement.

Consensus Statements on Follow-up Intervals for CD Patients

- 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 – the patient should then be reevaluated 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 – only general guidelines are given below.

Consensus Statements: CD Patients who have had Pituitary Surgery

In the period immediately following surgery:

- Patients with hypothalamic–pituitary–adrenal (HPA) axis suppression (adrenal insufficiency on adequate GC replacement) should be re-evaluated within 8 weeks.
- All other patients should be re-evaluated within 4-8 weeks of surgery and subsequently at 4-24 week intervals, depending on clinical circumstances.

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 HPA suppression (adrenal insufficiency on adequate GC replacement) should be re-evaluated within 8 weeks.
- 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.

Consensus Statements: CD Patients who have had Radiation Therapy

In the first 6 months after radiotherapy:

- Patients in control on medications should be re-evaluated within 8-24 weeks (depending on clinical circumstances).
- Patients with uncontrolled persistent or recurrent disease should be re-evaluated within 4 weeks.

Beyond 6 months after radiotherapy:

- Patients in remission should be re-evaluated within 6 months.
- Patients with persistent or recurrent disease and well controlled on medical therapy should be re-evaluated within 12 weeks.
- Patients with persistent or recurrent disease not well controlled on medical therapy should be re-evaluated within 4 weeks.

RESULTS (CONT.)

Consensus Statements: CD Patients post Bilateral Adrenalectomy, on Steroid Replacement

Following bilateral adrenalectomy:

- Patients with no symptoms of adrenal insufficiency on hormone replacement and stable ACTH levels should be re-evaluated within 24 weeks.
- Patients with no symptoms of adrenal insufficiency on hormone replacement and stable ACTH levels should be re-evaluated within 12 weeks if they have Nelson's syndrome.
- Patients with no symptoms of adrenal insufficiency on hormone replacement and rising ACTH levels should be re-evaluated within 8 weeks.
- Patients with symptoms of adrenal insufficiency despite hormone replacement should be re-evaluated within 2 weeks.

LIMITATIONS

- The panelists relied on information from a variety of data sources, including their own clinical practice experience, as there are no randomized controlled trials determining ideal follow up intervals.
- Although the Delphi panel method has been shown to be reproducible, most panelists were from academic settings; a different panel composition may have developed different consensus statements.
- The Delphi panel process does not develop new information; observational and/or prospective studies may also be useful in further evaluating appropriateness of various follow-up intervals given specific clinical patient situations.

CONCLUSIONS

- **Using the RAND/UCLA modified Delphi method, there was a high level of consensus between experts on follow-up intervals for CD patients but disagreement occurred in some scenarios.**
- **Disagreement was substantially decreased from 34.1% to 11.4% after in-person discussion with the panelists.**
- **Further studies should focus on identifying patients at risk for being lost to follow up. Additionally, studies should 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, or to a reduced burden of comorbid disease.**
- **As CD requires long-term follow-up, and often involves multiple therapies over time to achieve remission, 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.**

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