AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE DIAGNOSIS AND TREATMENT OF ACROMEGALY—2011 UPDATE: EXECUTIVE SUMMARY

Complete guidelines are available at http://aace.metapress.com

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American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health care professionals in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

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Abbreviations:
AACE = American Association of Clinical Endocrinologists; **BEL** = "best evidence" level; **CPAP** = continuous positive airway pressure; **CPG** = clinical practice guidelines; **EL** = evidence level; **GH** = growth hormone; **IGF-I** = insulinlike growth factor-I; **LAR** = long-acting release; **LFTs** = liver function tests; **MEN 1** = multiple endocrine neoplasia type 1; **MRI** = magnetic resonance imaging; **OGTT** = oral glucose tolerance test; **R** = recommendation; **RT** = radiation therapy; **SSAs** = somatostatin analogues

1. INTRODUCTION

Acromegaly is a disorder characterized by growth hormone (GH) hypersecretion, multisystem-associated morbidities, and increased mortality. In 2004, the American Association of Clinical Endocrinologists (AACE) published medical guidelines for the clinical management of acromegaly **(1 ["evidence level" or EL 4])**. Those guidelines summarized the then-current literature on the management of acromegaly and have been used for the clinical approach to patients with that disorder. Since publication of those guidelines, a number of studies have addressed further the biochemical diagnostic criteria for acromegaly and the appropriate biochemical assessment for therapeutic monitoring. In addition, the literature regarding medical therapy, in particular the use of combination medical therapy for acromegaly, has expanded. The goals of these guidelines are to update clinicians regarding all aspects in the current management of acromegaly and to use methods of current clinical practice guidelines (CPG) to support the recommendations.

2. GUIDELINES FOR CPG

Current guidelines in clinical medicine emphasize an evidence-based approach rather than simply expert opinion **(2 [EL 4], 3 [EL 4])**. Even though a purely evidence-based approach lacks applicability to all actual clinical scenarios, its incorporation in these CPG provides objectivity.

3. TRANSPARENCY: LEVELS OF SCIENTIFIC SUBSTANTIATION AND RECOMMENDATION GRADES

All clinical data that are incorporated in these CPG have been evaluated in terms of levels of scientific substantiation (evidence levels [EL]; Table 1). This evidence rating system has one minor modification in comparison with the original AACE protocol **(3 [EL 4])** in that level 2 (EL 2) prospective studies now may be randomized or nonrandomized to allow for well-designed cohort studies. This modification was incorporated because it is difficult to perform well-controlled, randomized clinical trials in surgery, unlike what physicians have been accustomed to in pharmaceutical trials. Another point worth mentioning is that when consensus statements are cited, even if based on a synthesis of evidence as in a published "evidence-based report," then an evidence level 4 [EL 4] is assigned. Clinical references have been assigned an evidence rating, which is provided in brackets at the end of the citation in both the Appendix and Reference sections. The "best evidence" level (BEL) corresponds to the best conclusive evidence found. The BEL accompanies the recommendation Grade in the Executive Summary and maps to the text in the Appendix section, where transparency is paramount.

Final recommendation grades incorporate EL ratings (Table 2), and in situations in which there is no clinical evidence, various subjective factors are considered: physician preferences, costs, risks, and regional availability of specific technologies and expertise. Hence, recommendation grades are generally based on strong BEL (Grade A; BEL 1), intermediate BEL (Grade B; BEL 2), weak BEL (Grade C; BEL 3), or subjective factors when there is no clinical evidence, inconclusive clinical evidence, or contradictory clinical evidence (Grade D; BEL 4). All recommendations result from a consensus among the AACE primary writers and influenced by input from reviewers. If subjective factors take priority over the BEL based on the expert opinion of the task force members, then this is described explicitly. Thus, some recommendations may be "upgraded" or "downgraded" according to explicitly stated subjective factors. Furthermore, the correctness of the recommendation Grades and EL is subject to review at several levels. In addition, recommendation Grades are assigned only if a specific action is recommended. The action may be ordering a particular diagnostic test, using a particular drug, performing a particular procedure, or adhering to a particular algorithm.

Shortcomings of this evidence-based method in this CPG are as follows: (*1*) relative paucity of strong (EL 1 and 2) scientific data, leaving the majority of recommendations based on weaker, extant EL 3 data and EL 4 consensus opinion; (*2*) potential subjectivity of the primary writers when weighing positive and negative, or epidemiologic versus experimental, data to arrive at an evidence-based recommendation grade or consensus opinion; (*3*) potential subjectivity of the primary writers when weighing subjective attributes, such as cost-effectiveness and risk-benefit ratios, to arrive at an evidence-based recommendation grade or consensus opinion; (*4*) potentially incomplete review of the literature by the primary writers despite extensive diligence; and (*5*) bias in the available publications, which originate predominantly from experienced

Table 1
Levels of Scientific Substantiation in Evidence-Based Medicine[a]

Level	Description	Comments
1	Prospective, randomized, controlled trials—large	Data are derived from a substantial number of trials, with adequate power involving a substantial number of outcome data subjects Large meta-analyses using raw or pooled data or incorporating quality ratings Well-controlled trial at one or more centers Consistent pattern of findings in the population for which the recommendation is made (generalizable data) Compelling nonexperimental, clinically obvious evidence (for example, use of insulin in diabetic ketoacidosis); "all-or-none" indication
2	Prospective with or without randomization—limited body of outcome data	Few number of trials, small population sizes in trials Well-conducted single-arm prospective cohort study Meta-analyses are limited but are well conducted Inconsistent findings or results not representative for the target population Well-conducted case-controlled study
3	Other experimental outcome data and nonexperimental data	Nonrandomized, controlled trials Uncontrolled or poorly controlled trials Any randomized clinical trial with 1 or more major or 3 or more minor methodologic flaws Retrospective or observational data Case reports or case series Conflicting data with weight of evidence unable to support a final recommendation
4	Expert opinion	Inadequate data for inclusion in above necessitate an expert panel's synthesis of the literature and a consensus Experience-based Theory-driven

[a] Levels 1-3 represent a given level of scientific substantiation or proof. Level 4 represents unproven claims. It is the "best evidence" based on individual ratings of clinical reports that contributes to a final grade recommendation.

pituitary endocrinologists and neurosurgeons and therefore may not reflect the experience at large. These shortcomings have been addressed by the primary writers through an a priori method and multiple levels of review by a large number of experts.

4. EXECUTIVE SUMMARY OF RECOMMENDATIONS

*Each recommendation is labeled "**R**" in this summary.*

The following recommendations are evidence-based (Grades A, B, and C) or based on expert opinion because of a lack of conclusive clinical evidence (Grade D) (see Tables 1 and 2). Details regarding the mapping of clinical evidence ratings to these recommendation grades are provided in the Appendix (Discussion) section.

4.1. Presenting Features and Assessment of Comorbidities

- **R1.** Patients should be queried regarding and examined for typical signs and symptoms of acromegaly, including somatic enlargement, excessive sweating, jaw overgrowth, joint pains, cardiomyopathy, carpal tunnel syndrome, sleep apnea syndrome, osteoarthropathy,

diabetes mellitus, menstrual irregularities in women and sexual dysfunction in men, headache, and visual field loss (attributable to optic chiasmal compression) and diplopia (due to cranial nerve palsy) **(Grade C; "best evidence" level or BEL 3)**.

- **R2.** Headaches and painful osteoarthritis are common in patients with acromegaly, and appropriate analgesic management should be considered. Definitive therapy for acromegaly is the most helpful intervention to diminish or prevent worsening of such comorbidities **(Grade C; BEL 3)**.
- **R3.** The finding of hypercalcemia should prompt an evaluation for primary hyperparathyroidism and, if present, consideration of multiple endocrine neoplasia type 1 (MEN 1). Likewise, the presence of multiple family members with pituitary tumors should prompt investigation into a genetic predisposition to pituitary tumors, including MEN 1, familial acromegaly, or familial isolated pituitary adenomas **(Grade C; BEL 3)**.
- **R4.** Corrective orthopedic or plastic surgical procedures should be postponed until serum concentrations of GH and insulinlike growth factor-I (IGF-I) normalize **(Grade C; BEL 4)**.
- **R5.** Performance of a sleep study for evaluation of sleep apnea syndrome, which is frequently associated with acromegaly, should be considered **(Grade C; BEL 3)**.

Table 2
Grade-Recommendation Protocol
Adopted by the American Association of Clinical Endocrinologists[a]

Grade	Description	Recommendation
A	≥1 conclusive level 1 publications demonstrating benefit >> risk	Action recommended for indications reflected by the published reports Action based on **strong** evidence Action can be used with other conventional therapy or as "**first-line" therapy**
B	No conclusive level 1 publication	Action recommended for indications reflected by the published reports
	≥1 conclusive level 2 publications demonstrating benefit >> risk	*If* the patient refuses or fails to respond to conventional therapy; must monitor for adverse effects, if any Action based on **intermediate** evidence Can be recommended as "**second-line" therapy**
C	No conclusive level 1 or 2 publication	Action recommended for indications reflected by the published reports
	≥1 conclusive level 3 publications demonstrating benefit >> risk	*If* the patient refuses or fails to respond to conventional therapy, provided there are no significant adverse effects; **"no objection" to recommending their use**
	or	*or*
	No risk at all and no benefit at all	**"No objection" to continuing their use** Action based on **weak** evidence
D	No conclusive level 1, 2, or 3 publication demonstrating benefit >> risk	**Not recommended** Patient is advised to **discontinue use**
	Conclusive level 1, 2, or 3 publications demonstrating risk >> benefit	Action not based on any evidence

[a] The final recommendation grades are determined by the primary writers by consensus based on (*1*) "best evidence" ratings and (*2*) subjective factors (see text section 3 on Transparency).

- **R6.** Measurements should be performed for assessment of diabetes mellitus, and appropriate therapy should be administered if diabetes is diagnosed **(Grade A; BEL 3)**.
- **R7.** Blood pressure should be measured, and appropriate therapy should be administered if hypertension is present **(Grade A; BEL 3)**.
- **R8.** Cardiovascular risk status, including measurement of a lipid profile (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), should be assessed **(Grade C; BEL 3)**.
- **R9.** Cardiac evaluation including an electrocardiogram and an echocardiogram may be considered, particularly if the patient has signs or symptoms suggestive of cardiac involvement, such as arrhythmias and shortness of breath **(Grade C; BEL 4)**.
- **R10.** Patients with known cardiac disease should be considered for a formal cardiology consultation before a surgical procedure is performed **(Grade C; BEL 4)**.
- **R11.** Although there is insufficient evidence to state that patients with acromegaly have an increased risk of colon cancer, there is evidence of an increased prevalence of colon polyps. Therefore, colonoscopy is recommended **(Grade C; BEL 4).**

4.2. How Is the Diagnosis Made?

- **R12.** Acromegaly is a clinical syndrome that, depending on its stage of progression, may not manifest with clear diagnostic features. Clinicians should think of this diagnosis in patients with 2 or more of the following comorbidities: new-onset diabetes, diffuse arthralgias, new-onset or difficult-to-control hypertension, cardiac disease including biventricular hypertrophy and diastolic or systolic dysfunction, fatigue, headaches, carpal tunnel syndrome, sleep apnea syndrome, diaphoresis, loss of vision, colon polyps, and progressive jaw malocclusion **(Grade A; BEL 1)**.
- **R13.** A serum IGF-I level, if accompanied by a large number of results from age- and sex-matched normal subjects, is a good tool to assess integrated GH secretion and is excellent for diagnosis, monitoring, and especially screening. A random IGF-I value (a marker of integrated GH secretion) should be measured for diagnosis and for monitoring after a therapeutic intervention **(Grade B; BEL 2)**.
- **R14.** Serum GH assays are not standardized and should not be used interchangeably. Multiple samples, random GH, and GH after glucose administration have considerable variability and are useful, but they must be used in the clinical context **(Grade C; BEL 3)**.
- **R15.** A GH value <1 ng/mL after an oral glucose tolerance test (OGTT) (75 g of glucose orally followed by GH measurements every 30 minutes for 120 minutes) is considered normal **(Grade C; BEL 3)**.
- **R16.** This panel suggests that the serum GH nadir after glucose administration be lowered to 0.4 ng/mL to increase the sensitivity of testing **(Grade D; BEL 4)**.
- **R17.** Currently, there are insufficient data to recommend additional testing with insulinlike growth factor-binding protein-3 measurement or use of a thyrotropin-releasing hormone test (which can lead to a paradoxical increase in GH levels in patients with acromegaly) **(Grade A; BEL 1)**.

4.3. Further Evaluation After Diagnosis of Acromegaly

- **R18.** Once a biochemical diagnosis of acromegaly has been made, a magnetic resonance imaging (MRI) scan of the pituitary gland (the physician should order a dedicated pituitary MRI with and without use of contrast medium) should be performed because a pituitary GH-secreting adenoma is the cause in most cases. A computed tomographic scan of the pituitary offers less anatomic detail and is not suggested, but it may be necessary if the patient has a contraindication for MRI, such as the presence of a cardiac pacemaker **(Grade B; BEL 1)**.
- **R19.** Visual field testing should be performed if there is optic chiasmal compression noted on the MRI or if the patient has complaints of reduced peripheral vision **(Grade A; BEL 1)**.
- **R20.** Further biochemical testing should include a serum prolactin level (to evaluate for hyperprolactinemia) and assessment of anterior and posterior pituitary function (for potential hypopituitarism) **(Grade A; BEL 1)**.
- **R21.** All patients should undergo a comprehensive medical history, physical examination, and appropriate laboratory testing **(Grade C; BEL 4)**.

4.4. What Are the Therapeutic Options?

- **R22.** There should be a thorough discussion with the patient regarding the risks and benefits of surgical, medical, and radiotherapeutic options **(Grade C; BEL 4)**.
- **R23.** The pros and cons of pituitary surgery should be discussed, with emphasis on the value of surgical intervention as the primary therapy in most patients because it is the most effective option for inducing rapid and complete biochemical cure of acromegaly in patients who meet surgical criteria **(Grade C; BEL 3)**.
- **R24.** The pros and cons of primary medical therapy should be discussed, particularly in those patients who have a tumor that cannot be completely removed surgically, who have no compressive tumor effects, who are poor surgical candidates, or who have a preference for medical management **(Grade C; BEL 3)**.
- **R25.** The pros and cons of radiation therapy (RT) should be discussed, with an emphasis on its use as adjuvant

treatment, the potential efficacy, and the long-term side effects **(Grade C; BEL 3)**.
- **R26.** Financial counseling should be provided regarding the various therapeutic options **(Grade C; BEL 4)**.

4.5. What Are the Goals of Therapy?
- **R27.** There should be a thorough discussion with the patient regarding the goals of therapy, which include normalization of biochemical variables, reversal of mass effects of the tumor, improvement in signs, symptoms, and comorbidities of the disease, and minimization of long-term mortality risk **(Grade B; BEL 3)**.
- **R28.** Treatment goals include assessment and management of the comorbidities, such as aggressive control of lipid abnormalities, type 2 diabetes mellitus, obstructive sleep apnea, arthritic complications, and cardiac dysfunction as well as surveillance for colon polyps **(Grade C; BEL 2)**.

4.6. Therapeutic Options
- **R29.** There is sufficient evidence for recommending pituitary surgery as the primary treatment in patients with microadenomas and in patients with macroadenomas that are associated with local mass effects or are enclosed and potentially curable surgically because surgery can lead to durable control of the tumor mass and associated biochemical effects **(Grade B; BEL 2)**.
- **R30.** In most patients, medical therapy is used as adjuvant treatment in the setting of persistent disease despite surgical intervention **(Grade B; BEL 2)**.
- **R31.** A role of primary medical therapy, especially with somatostatin analogues (SSAs), has been suggested in patients with macroadenomas who have no local mass effects and have a minimal chance of surgical cure (because of extrasellar extension of the tumor, especially into the cavernous sinus) or in patients who are poor surgical candidates or who prefer medical treatment **(Grade B; BEL 3)**.
- **R32.** RT is recommended as adjuvant treatment in patients with active disease despite surgery and medical therapy or in patients who prefer RT in light of the cost of long-term medical treatment **(Grade C; BEL 3)**.

4.7. Surgery
- **R33.** There is sufficient evidence linking surgical experience (number of pituitary surgical procedures performed) with surgical cure rate as well as morbidity and mortality **(Grade A; BEL 2)**.
- **R34.** There is sufficient evidence to recommend surgery as the primary therapy for all patients with microadenomas **(Grade A; BEL 2)**.
- **R35.** Surgery is indicated for all patients with a macroadenoma and mass effects, including visual loss **(Grade A; BEL 1)**.
- **R36.** There is sufficient evidence to recommend surgery as the primary therapy for all patients who have macroadenomas with a high predicted chance for cure (that is, no invasion of local structures such as the cavernous sinus) **(Grade A; BEL 2)**.
- **R37.** In the patients with macroadenomas that are not likely to be cured with surgery, and without compressive effects on local structures, surgery may be recommended for debulking to improve the response to subsequent medical therapy or RT. There should be a thorough discussion with the patient regarding the use of primary medical therapy as an alternative in this setting **(Grade B; BEL 3)**.

4.7.1. How Should Patients Be Prepared for Surgery?
- **R38.** The preoperative evaluation must include a comprehensive medical history, physical examination, and appropriate laboratory testing **(Grade C; BEL 4)**.
- **R39.** Laboratory testing should include an evaluation for hypopituitarism, and the hormone axes, particularly adrenal and thyroid, should be replaced as indicated **(Grade C; BEL 4)**.
- **R40.** A role for medical therapy with SSAs preoperatively has been suggested to reduce surgical risk, although further studies are necessary to support general use **(Grade C; BEL 4)**.
- **R41.** A role for presurgical medical therapy with SSAs to improve biochemical outcomes with surgery has been suggested, although further studies are needed to support general use **(Grade B; BEL 2)**.
- **R42.** Consideration should be given to careful perioperative airway management because patients with acromegaly often have a compromised airway **(Grade C; BEL 3)**.
- **R43.** Cardiovascular risk assessment should be performed preoperatively in accordance with standard protocol. Routine echocardiography is not recommended preoperatively, although a role for echocardiography may be suggested, depending on attributable signs and symptoms **(Grade C; BEL 4)**.

4.7.2. Management After Surgery
- **R44.** Postoperative management should include monitoring for electrolyte abnormalities, including diabetes insipidus and syndrome of inappropriate secretion of antidiuretic hormone, for up to 2 weeks **(Grade C; BEL 3)**.
- **R45.** In the postoperative setting, the presence of diuresis may reflect obligate natriuresis after a rapid reduction in GH and IGF-I values **(Grade C; BEL 3)**.
- **R46.** Adrenal function should be monitored and replaced as appropriate **(Grade C; BEL 3)**.

- **R47.** It is recommended that a fasting GH level be measured early postoperatively; a postoperative day 1 GH level less than 2 ng/mL correlates with long-term remission. An OGTT can be performed 1 to 2 weeks after surgery for further diagnostic confirmation, although this procedure is not generally performed at this point **(Grade C; BEL 2)**.
- **R48.** A serum IGF-I level should be remeasured at 12 weeks; a normal IGF-I value is consistent with surgical remission **(Grade C; BEL 2)**.
- **R49.** A repeated OGTT may be performed at 12 weeks; a GH value <1 ng/mL is consistent with surgical remission **(Grade C; BEL 2)**.
- **R50.** This panel suggests that the serum GH nadir after glucose administration be lowered to 0.4 ng/mL to increase the sensitivity of testing **(Grade D; BEL 4)**.
- **R51.** Repeated imaging with an MRI scan should be performed at 12 weeks after surgery to assess for residual tumor and establish a postoperative baseline **(Grade C; BEL 3)**.
- **R52.** Repeated pituitary hormone testing, including the thyroid and gonadal axes, should be performed at 6 to 12 weeks postoperatively in order to assess pituitary function and the need for hormone replacement therapy **(Grade C; BEL 3)**.
- **R53.** If the repeated serum IGF-I value is reduced from baseline but still elevated at 12 weeks, repeated testing in another 9 to 12 weeks should be considered to determine whether there may be delayed biochemical normalization, before proceeding with potential surgical reexploration, medical therapy, or RT **(Grade C; BEL 3)**.
- **R54.** For patients who use a nasal continuous positive airway pressure (CPAP) device for management of sleep apnea syndrome, the CPAP device is generally withheld postoperatively for a temporary period, as recommended by the neurosurgeon and sleep specialist **(Grade C; BEL 4)**.

4.8. Medical Therapy

- **R55.** Medical therapy is appropriate as adjuvant treatment in patients with residual disease after surgery **(Grade A; BEL 2)**.
- **R56.** There are 3 classes of medical therapy: dopamine agonists, SSAs, and a GH receptor antagonist **(Grade A; BEL 1)**.
- **R57.** There should be a thorough discussion with the patient regarding the risks and benefits of each medication. This discussion should include financial counseling, and the physician should be able to provide clinical material for information on the medications as well as their costs **(Grade A; BEL 2)**.

4.8.1. Dopamine Agonists

- **R58.** There are 2 dopamine agonists, cabergoline and bromocriptine, available for patients in the United States **(Grade A; BEL 1)**.
- **R59.** Cabergoline may be more effective and better tolerated than bromocriptine **(Grade C; BEL 3)**.
- **R60.** Dopamine agonists may be considered as first-line medical therapy because these agents are orally administered and relatively inexpensive in comparison with the other medical therapy options **(Grade C; BEL 3)**.
- **R61.** Dopamine agonists may be considered particularly in patients with mild biochemical activity, such as in the setting of modestly elevated serum IGF-I levels in the absence or concomitant presence of SSA therapy **(Grade B; BEL 3)**.
- **R62.** The response of GH to cabergoline is not clearly demonstrated to be related to the presence or absence of hyperprolactinemia **(Grade C; BEL 3)**.
- **R63.** Patients should be counseled about the potential side effects of dopamine agonists, including gastrointestinal upset, orthostatic hypotension, headache, and nasal congestion **(Grade A; BEL 1)**.
- **R64.** Patients should be counseled that cabergoline, when administered in high doses to patients with Parkinson disease, has been associated with echocardiographically evident valve abnormalities. The clinical effect of this finding in patients with acromegaly is unclear **(Grade C; BEL 3)**.
- **R65.** Repeated GH, prolactin, and IGF-I levels should be determined 4 to 6 weeks after each dose change for a dopamine agonist **(Grade B; BEL 3)**.

4.8.2. Somatostatin Analogues

- **R66.** There are 2 long-acting, depot SSAs available: octreotide LAR (long-acting release, administered as an intramuscular injection) and lanreotide Autogel (administered as a deep subcutaneous depot injection) **(Grade A; BEL 1)**.
- **R67.** A 2-week trial of octreotide is recommended before institution of octreotide LAR therapy (based on the US package insert), although this panel feels that a single test dose to rule out a severe reaction is sufficient **(Grade D; BEL 3)**.
- **R68.** SSAs are effective in normalizing IGF-I and GH levels in approximately 55% of patients. The clinical and biochemical responses to SSAs are inversely related to tumor size and degree of GH hypersecretion. Octreotide LAR and lanreotide Autogel have similar efficacy profiles **(Grade B; BEL 2)**.
- **R69.** SSAs reduce pituitary tumor size modestly in approximately 25% to 70% of patients, depending on whether they are used as adjuvant or de novo therapy,

respectively. Patients should be counseled that, although tumor shrinkage can occur, SSAs should not be relied on for decompression of local structures in the presence of mass effects **(Grade B; BEL 3)**.

- **R70.** Patients should be counseled about the potential side effects of SSAs, including gastrointestinal upset, malabsorption, constipation, gallbladder disease, hair loss, and bradycardia. It is not recommended that patients have close radiologic imaging surveillance for symptomatic gallbladder disease, but patients should be queried about potential symptoms during follow-up appointments. Octreotide LAR and lanreotide Autogel have similar side effect profiles **(Grade B; BEL 2)**.
- **R71.** In patients with an inadequate response to SSAs, the addition of cabergoline or pegvisomant may be effective for further lowering of GH or IGF-I levels (or both) **(Grade B; BEL 3)**.
- **R72.** The short-acting subcutaneously administered SSA octreotide is effective and may be used, especially in the setting of financial constraints or the need for rapid onset of action **(Grade C; BEL 3)**.

4.8.3. GH Receptor Antagonist

- **R73.** Pegvisomant is a GH receptor antagonist that competes with endogenous GH for its receptor and prevents functional dimerization and signal transduction by the GH receptor **(Grade A; BEL 2)**.
- **R74.** Pegvisomant is highly effective in normalizing IGF-I values (>90%), including patients who are partially or completely resistant to other medical therapies **(Grade A; BEL 2)**.
- **R75.** Pegvisomant is effective at improving glucose homeostasis in patients with associated diabetes mellitus **(Grade C; BEL 2)**.
- **R76.** Pegvisomant is often used as a medical therapy in patients with inadequate response to or tolerability of SSAs **(Grade A; BEL 2)**.
- **R77.** Patients should be counseled that pegvisomant is administered as a subcutaneous injection daily, although alternative protocols, including twice-a-week or once-a-week administration, have been suggested in specific patients **(Grade B; BEL 3)**.
- **R78.** Patients should be counseled about the side effects of pegvisomant, including flulike illness, allergic reactions, and increase in liver enzymes. Therefore, serial monitoring of results of liver function tests (LFTs) is suggested at monthly intervals for the first 6 months, quarterly for the next 6 months, and then biannually. Patients with elevated baseline results of LFTs need more frequent monitoring **(Grade B; BEL 3)**.
- **R79.** Patients should be counseled that tumor enlargement has been infrequently associated with use of pegvisomant. Therefore, serial monitoring with pituitary MRI scans is suggested **(Grade C; BEL 3)**.
- **R80.** Pegvisomant therapy may be effective regardless of baseline tumor size or degree of GH hypersecretion **(Grade B; BEL 2)**.
- **R81.** Because endogenous GH levels increase with pegvisomant administration and pegvisomant may be cross-measured in GH assays, serum GH levels are not specific and should not be monitored in patients receiving pegvisomant **(Grade A; BEL 2)**.

4.8.4. Combination Therapy

- **R82.** In patients with a partial response to SSA therapy, the addition of cabergoline may be useful for further lowering of GH or IGF-I levels **(Grade C; BEL 3)**.
- **R83.** In patients with a partial response to SSA therapy, the addition of daily, weekly, or twice weekly pegvisomant may be beneficial **(Grade C; BEL 3)**.

4.9. Radiation Therapy

- **R84.** Pituitary RT in acromegaly should be considered an adjunctive treatment in patients not fully responding to surgical or medical treatments (or both) **(Grade C; BEL 4)**.
- **R85.** Because RT may lead to normalization of biochemical indices of acromegaly, this modality may be used in an effort to limit lifelong use of GH and IGF-I suppressive medical therapy **(Grade C; BEL 4)**.
- **R86.** Patients may be counseled about the options of RT, including conventional fractionated RT versus stereotactic radiosurgery, which can be administered by means of Gamma Knife, proton beam, CyberKnife, or a linear accelerator **(Grade C; BEL 4)**.
- **R87.** Because of the technical advances and convenience, stereotactic radiosurgery may be considered the preferred mode of RT over conventional RT in patients with acromegaly, unless the technique is not available, there is substantial residual tumor burden, or the tumor is too close (<5 mm) to the optic chiasm **(Grade C; BEL 4)**.
- **R88.** Patients should be counseled that the benefits of RT on GH hypersecretion may be delayed, up to years, and medical therapy will be needed until the radiation effect is sustained. Intermittent withdrawal of medical therapy will be necessary in order to assess GH secretion **(Grade C; BEL 4)**.
- **R89.** Patients should be counseled that serial pituitary function follow-up is necessary to evaluate for hypopituitarism. This follow-up includes assessment of adrenal, thyroid, and gonadal function, testing that should be performed at least annually **(Grade B; BEL 2)**.

4.10. Acromegaly and Pregnancy

- **R90.** In a pregnant patient with acromegaly, biochemical monitoring with measurement of GH or IGF-I levels is of limited use **(Grade B; BEL 3)**.

- **R91.** Serial visual field monitoring should be performed during pregnancy, at intervals dictated by the tumor size and location before pregnancy **(Grade C; BEL 3)**.
- **R92.** MRI scans should not be routinely performed during pregnancy unless there is evidence of new or worsening visual field compromise. If performed, the MRI scan should be done without administration of a contrast agent **(Grade A; BEL 1)**.
- **R93.** In pregnant patients who have tumor growth with chiasmal compression and visual field compromise, transsphenoidal surgery should be considered **(Grade A; BEL 1)**.
- **R94.** Medical therapy with a long-acting SSA should be discontinued 2 to 3 months before a planned pregnancy, depending on the clinical status of the patient **(Grade D; BEL 3)**.
- **R95.** If the patient conceives while receiving SSA therapy, she should have a discussion with her physician about discontinuing the SSA, with further monitoring as described in **R89 (Grade D; BEL 3)**.
- **R96.** Institution of medical therapy should be considered during pregnancy if there is suggestive evidence of worsening disease **(Grade D; BEL 3)**.

4.11. Approach to Gigantism in Children and Adolescents

- **R97.** Gigantism is a rare clinical syndrome that is associated with dramatic linear growth acceleration **(Grade A; BEL 1)**.
- **R98.** A random serum IGF-I value, normalized for age and sex, should be measured for diagnosis; an elevated IGF-I value is consistent with the diagnosis **(Grade B; BEL 2)**.
- **R99.** Once a biochemical diagnosis of gigantism has been made, an MRI scan of the pituitary gland (the physician should order a dedicated pituitary MRI with and without use of contrast medium) should be performed because a pituitary GH-secreting adenoma is the cause in most cases **(Grade B; BEL 1)**.
- **R100.** Visual field testing should be performed if there is optic chiasmal compression noted on the MRI or the patient has complaints of reduced peripheral vision **(Grade A; BEL 1)**.
- **R101.** The goals of therapy are to control the biochemical variables and reduce tumor volume, as in acromegaly. Another goal of therapy is to control the accelerated linear growth **(Grade A; BEL 1)**.
- **R102.** Transsphenoidal surgery is the primary treatment, where possible **(Grade C; BEL 3)**.
- **R103.** Use of medical therapy as an adjunctive treatment after incomplete surgery is similar to that with adults **(Grade C; BEL 4)**.
- **R104.** In patients with gigantism, RT is often not used **(Grade C; BEL 3)**.

4.12. How Should Medical Comorbidities Be Monitored?

- **R105.** Any corrective surgical procedure, such as maxillofacial correction of dental malocclusion, should be postponed until GH and IGF-I levels normalize for at least 6 months **(Grade D; BEL 4)**.
- **R106.** Patients should be monitored for signs and symptoms of carpal tunnel syndrome, and directed care, including a release procedure, should be considered for persistent or progressive symptoms **(Grade C; BEL 3)**.
- **R107.** Arthropathy should be managed aggressively with physical therapy, systemic or intra-articular anti-inflammatory medications, and consideration of joint replacement, when appropriate **(Grade C; BEL 3)**.
- **R108.** The presence of hypercalcemia should prompt an evaluation for primary hyperparathyroidism and, if present, consideration of MEN 1 **(Grade B; BEL 3)**.
- **R109.** Bone densitometry should be performed in patients with a history of hypogonadism or fracture. If osteoporosis is present and does not improve with correction of hypogonadism, hypercalcemia, GH and IGF-I excess, or any combination of these factors, antiresorptive therapy should be considered **(Grade C; BEL 3)**.
- **R110.** Formal overnight polysomnography or home overnight oximetry (as a screening test for sleep apnea) followed by formal overnight polysomnography should be performed if symptoms are suggestive in patients with either active or biochemically controlled acromegaly **(Grade C; BEL 3)**.
- **R111.** Standard therapy should be used for patients with left ventricular hypertrophy, impaired cardiac systolic and diastolic function, arrhythmias, conduction abnormalities, valvular heart disease, or ischemic heart disease **(Grade C; BEL 4)**.
- **R112.** Routine echocardiography should be considered in patients who have evidence of left ventricular hypertrophy by electrocardiography or who are symptomatic with shortness of breath **(Grade C; BEL 3)**.
- **R113.** Blood pressure should be monitored because hypertension may persist despite biochemical control of acromegaly **(Grade C; BEL 3)**.
- **R114.** All patients should be monitored for evidence of glucose intolerance or overt type 2 diabetes mellitus, and corrective measures should be taken as needed **(Grade C; BEL 3)**.
- **R115.** In patients in whom SSA therapy worsens glucose control, reduction of the SSA dose, addition of or substitution with a GH receptor antagonist, or diabetes management with glucose-lowering agents should be considered **(Grade C; BEL 3)**.
- **R116.** Goals for high-risk cardiac patients should be adopted, including blood pressure less than 130/80 mm Hg and hemoglobin A_{1c} less than 6.5% **(Grade C; BEL 2)**.

- **R117.** Colonoscopy should be performed after diagnosis of acromegaly. Patients with polyps at screening or with persistently elevated IGF-I levels should undergo follow-up colonoscopy. Other patients should undergo follow-up colonoscopy, with a schedule based on current general recommendations **(Grade C; BEL 4)**.
- **R118.** Standard screening guidelines for other cancers should be rigorously followed **(Grade B; BEL 4)**.
- **R119.** In patients with active acromegaly and those in remission, attention to quality-of-life issues is recommended **(Grade C; BEL 4)**.

DISCLOSURE

Chair

Dr. Laurence Katznelson reports that he has received speakers' bureau honoraria from IPSEN and advisory board honoraria and research grant support from Novartis AG.

Task Force Members

Dr. John L. D. Atkinson reports that he does not have any relevant financial relationships with any commercial interests.

Dr. David M. Cook reports that he has received speaker honoraria from Pfizer Inc., research grant support from Indevus Pharmaceuticals, and speaker honoraria and research grant support from Eli Lilly and Company.

Dr. Shereen Z. Ezzat reports that he has received speaker honoraria from Novartis AG.

Dr. Amir H. Hamrahian reports that he has received speaker honoraria from Pfizer Inc. and speaker and consultant honoraria from IPSEN and Novartis AG.

Dr. Karen K. Miller reports that she does not have any relevant financial relationships with any commercial interests.

Reviewers

Dr. William H. Ludlam reports that he has received speaker honoraria from IPSEN, Novartis AG, Pfizer Inc., and Tercica, Inc. and advisory group honoraria from Endo Pharmaceuticals, IPSEN, Novartis AG, and Tercica, Inc.

Dr. Susan L. Samson reports that she has received speaker honoraria from IPSEN and Novartis AG.

Dr. Steven G. Waguespack reports that he does not have any relevant financial relationships with any commercial interests.

REFERENCES

*Note: Reference sources are followed by an evidence level **[EL]** rating of 1, 2, 3, or 4.*

1. **Cook DM, Ezzat S, Katznelson L, et al (AACE Acromegaly Guidelines Task Force).** AACE medical guidelines for clinical practice for the diagnosis and treatment of acromegaly [published corrections appear in *Endocr Pract*. 2005;11:144 and *Endocr Pract*. 2008;14:802-803]. *Endocr Pract*. 2004;10:213-225. **[EL 4]**
2. **Johnson N.** New approaches to the development and use of treatment guidelines. *Formulary*. 1998;33:665-678. **[EL 4]**
3. **Mechanick JI, Bergman DA, Braithwaite SS, Palumbo PJ (American Association of Clinical Endocrinologists Ad Hoc Task Force for Standardized Production of Clinical Practice Guidelines).** American Association of Clinical Endocrinologists protocol for standardized production of clinical practice guidelines [published correction appears in *Endocr Pract*. 2008;14:802-803]. *Endocr Pract*. 2004;10:353-361. **[EL 4]**