Treatment Patterns and Unmet Needs in Adults With Classic Congenital Adrenal Hyperplasia: A Modified Delphi Consensus Study

Richard J. Auchus, et al. *Front Endocrinol (Lausanne)*. 2022;13:1005963.

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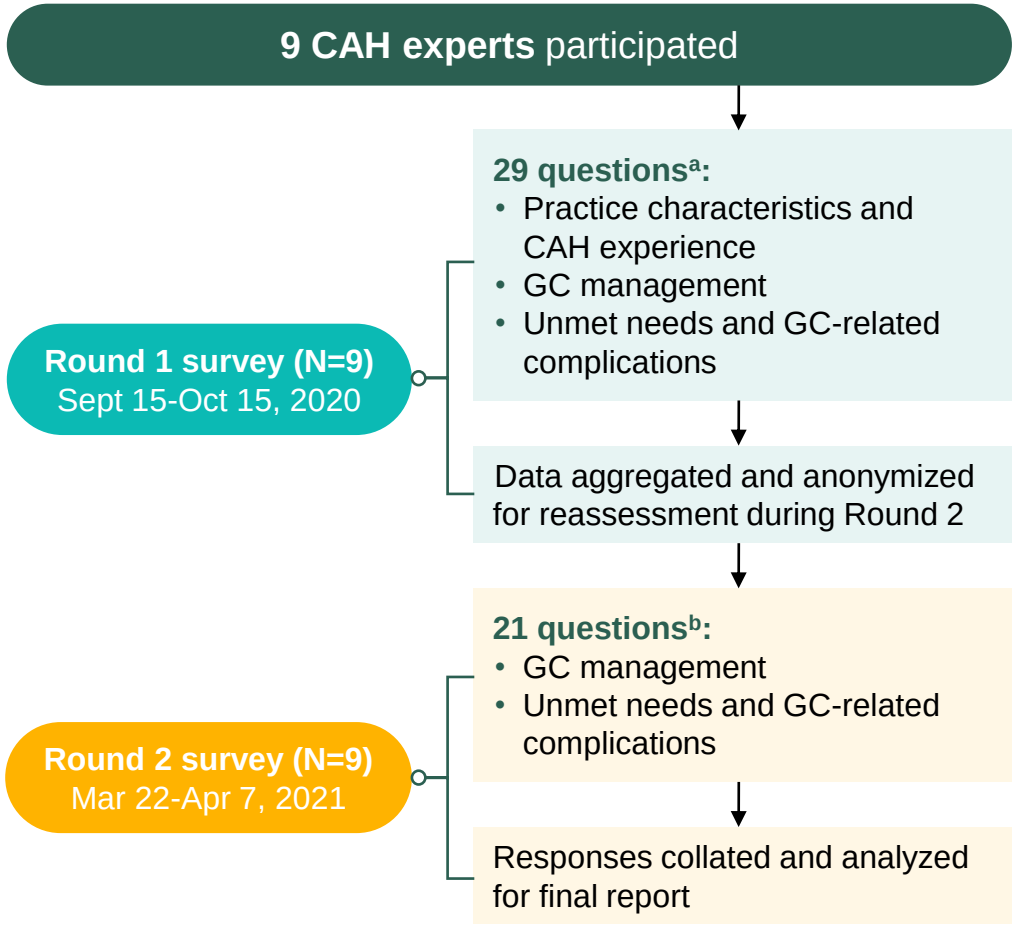
Table of Contents

A Modified Delphi Consensus Study to Assess Treatment Patterns and Unmet Needs in Adults With Classic Congenital Adrenal Hyperplasia (CAH)



Objective: To survey expert opinions on glucocorticoid (GC) treatment practices and unmet needs for adults with classic CAH

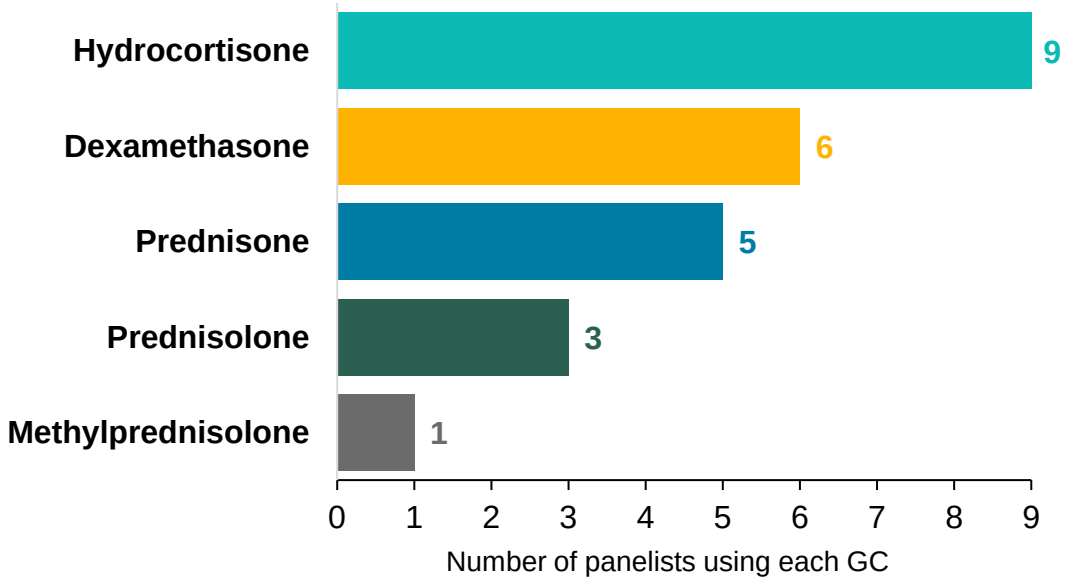
CAH expert recruitment inclusion criteria:

- ✓ Adult endocrinologists from the United States (n=4), France (n=2), Canada (n=1), Sweden (n=1), and the United Kingdom (n=1)
- ✓ Treating 10 to 20 adult patients with classic CAH quarterly
- ✓ Involved in publications on CAH, CAH clinical trials, or development of CAH guidelines

Consensus definitions		
Full consensus 9/9 (100%) ✓	**Near consensus** 7/9 (78%) or 8/9 (89%) ✓	**No consensus** <7/9 (<78%) ✗

[a]Round 1 survey included primarily free-response questions, with some closed-ended and multiple-choice questions.
[b]In the Round 2 survey, panelists were provided anonymized, aggregated Round 1 responses. If agreement was reached in Round 1, panelists were asked if they agreed or disagreed with the conclusion to establish consensus. If no agreement was reached in Round 1, questions were recirculated for another round of input.
CAH, congenital adrenal hyperplasia; GC, glucocorticoid.
Auchus RJ, et al. *Front Endocrinol (Lausanne)*. 2022;13:1005963.

GC Treatment Patterns[1]



	Daily dose (mg/d), mean (SD)	Lower range, mean (SD)	Upper range, mean (SD)	Endocrine Society Recommended daily dose[2] (mg/d)
Hydrocortisone	27.2 (3.6)	14.2 (3.8)	40.8 (10.2)	15-25
Dexamethasone	0.6 (0.3)	0.4 (0.1)	1.5 (0.6)	0.25-0.5
Prednisone	4.9 (1.5)	3.8 (1.8)	7.5 (1.8)	5-7.5
Prednisolone	4.4 (0.9)	3.3 (1.7)	7.1 (2.2)	4-6
Methylprednisolone	5.4 (1.3)	3.8 (2.1)	6.5 (1.9)	4-6

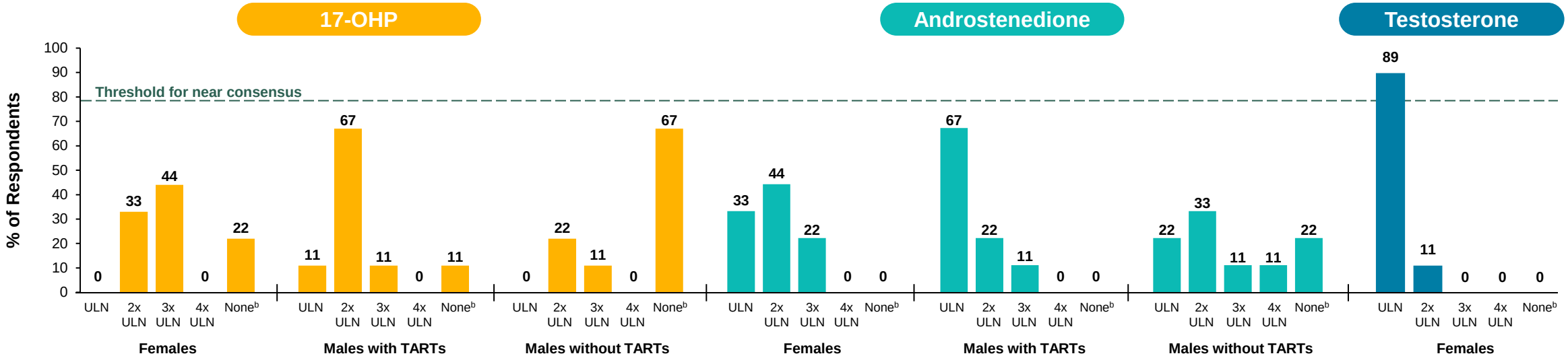
Click to view dosing guidelines

Key findings	Full or near consensus[a]
Hydrocortisone is the most widely used GC globally	8/9 ✓
7/9 panelists preferred **hydrocortisone** for the majority of their patients, but **2/9** preferred **prednisone/prednisolone**	7/9 ✓
The average daily dose of **hydrocortisone** was **27.2 mg/day**, with doses ranging from **14.2 to 40.8 mg/day**	
No consensus was reached on the upper end of a physiologic **hydrocortisone** dose; however, **6/9** panelists agreed that **25 to 30 mg/day** was the upper end of a physiologic dose	6/9 ✗

[a]Consensus was defined as follows: **full consensus, 9/9 (100%)** ✓; **near consensus, 7/9 or 8/9 (78% to <100%)** ✓; **no consensus, <7/9 (<78%)** ✗.
GC, glucocorticoid; SD, standard deviation.

1. Auchus RJ, et al. *Front Endocrinol (Lausanne)*. 2022;13:1005963. 2. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088.

Androgen Laboratory Values and Indicators of Control[1,a]



Click to view Round 1 and Round 2 responses

Key findings	Full or near consensus[c]
There was no consensus on **17-OHP** or **androstenedione** levels indicating good control or on optimal timing for collecting samples for laboratory analysis	✗
89% of panelists agreed that adequate control is best evaluated with a balance of clinical presentation and laboratory values of androgens and precursors	8/9 ✓
Testosterone laboratory values within the ULN indicate good control in female patients	8/9 ✓

Endocrine Society guidelines for the treatment of classic CAH recommend **dose adjustment based on the overall clinical picture** rather than a single laboratory assessment[2]

[a]Round 2 responses. [b]The survey response option for this category was, "I do not have a lab range I treat to."
[c]Consensus was defined as follows: **full consensus, 9/9 (100%)** ✓; **near consensus, 7/9 or 8/9 (78% to <100%)** ✓; **no consensus, <7/9 (<78%)** ✗.
17-OHP, 17-hydroxyprogesterone; CAH, congenital adrenal hyperplasia; TART, testicular adrenal rest tumor; ULN, upper limit of normal.
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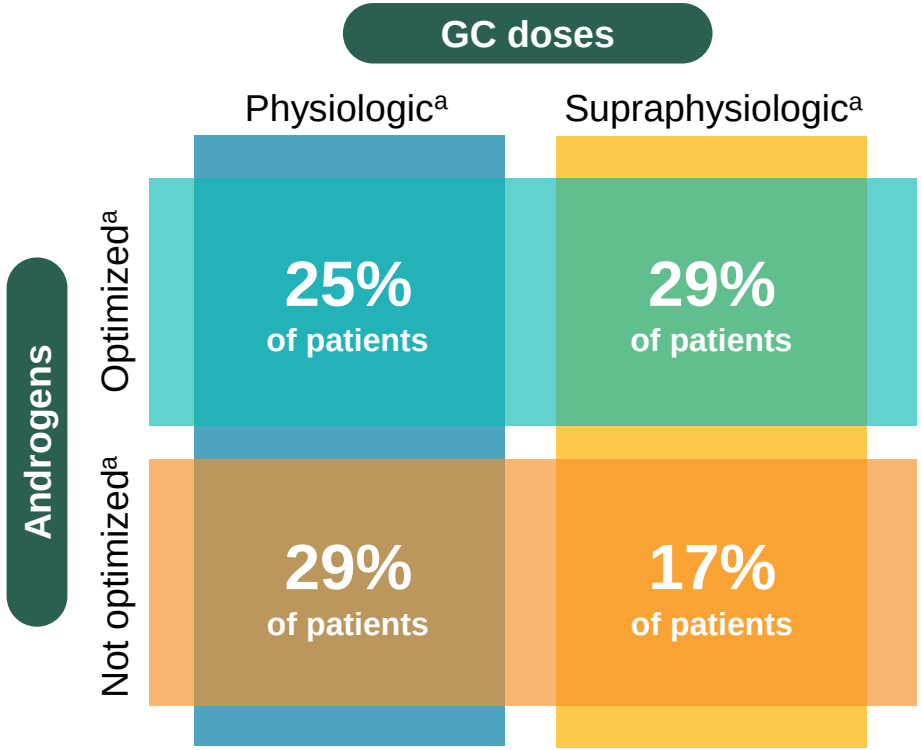
GC Treatment Optimization[1,2]

29% of panelists' patients had optimized androgen levels but were receiving supraphysiologic GC doses



46% of panelists' patients did not have optimized androgen control, regardless of GC dose

Key finding	Full or near consensus[b]
There is an important unmet need for new treatments for adults with classic CAH to achieve androgen optimization	9/9 ✓

[a]The survey questionnaires did not define "optimized" androgen levels or "physiologic" GC doses; therefore, panelists reported percentages of patients in each category based on their own definitions of optimized androgens and physiologic GCs.
[b]Consensus was defined as follows: **full consensus, 9/9 (100%)** ✓; **near consensus, 7/9 or 8/9 (78% to <100%)** ✓; **no consensus, <7/9 (<78%)** ✗.
CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

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Disease- and GC-related Complications

Based on Round 2, the following disease- and GC-related complications were considered **important** or **very important** for adults with classic CAH

Key findings	Full or near consensus[a]
Cardiovascular and metabolic complications, including pre-diabetes (9/9), type 2 diabetes (9/9), hypertension (9/9), obesity (9/9), cardiovascular disease (9/9), and change in body composition[b] (7/9)	✓ ✓
Bone complications, including osteopenia/osteoporosis (9/9) and fragility fracture (9/9)	✓
Female health-related complications, including irregular menses (9/9), hirsutism/acne (9/9), virilization (9/9), and infertility (9/9)	✓
Male health-related complications, including TARTs (9/9) and infertility (9/9)	✓
Psychosocial health issues, including depression (9/9) and decreased sexual satisfaction (9/9)	✓

Click to view supportive data

[a]Consensus was defined as follows: **full consensus, 9/9 (100%) ✓**; **near consensus, 7/9 or 8/9 (78% to <100%) ✓**; **no consensus, <7/9 (<78%) ✗**.
[b]One respondent listed "change in body composition" under "Other" in Round 1.
CAH, congenital adrenal hyperplasia; GC, glucocorticoid; TART, testicular adrenal rest tumor.
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Study Strengths and Limitations[1]

Strengths

- This study captured the opinions of expert endocrinologists with experience treating a substantial number of adults with classic CAH
- Key findings from this study align with previous observational studies of adults with classic CAH[2,3]

Limitations

- The results of this study reflect the opinions of 9 expert panelists from the United States and Europe with experience treating adults with classic CAH
- Due to the limited number of panelists, a few panelists with dissenting opinions could skew results and alter consensus point
- Panelists' responses are likely not reflective of treatment practices and unmet needs for children and adolescents with classic CAH
- Additional surveys of pediatric endocrinologists with experience treating patients with classic CAH are needed to gain consensus on treatment practices and unmet needs for these patients

CAH, congenital adrenal hyperplasia.

1. Auchus RJ, et al. *Front Endocrinol (Lausanne)*. 2022;13:1005963. 2. Arlt W, et al. *J Clin Endocrinol Metab*. 2010;95(11):5110-5121. 3. Finkielstain GP, et al. *J Clin Endocrinol Metab*. 2012;97(12):4429-4438.

Summary

Management of classic CAH in adults remains challenging[1]

- Panel reported that 46% of patients do not have optimized androgen levels, regardless of GC dose[1]

Management of classic CAH **varies widely** across clinicians and patients[1]

However, this study showed full consensus[a] on the **need for new treatments** for classic CAH to achieve **androgen optimization** and **reduce GC-related complications**[1]

Key areas of consensus

- **Importance of disease- and GC-related complications** and the **need for new treatments for adults with classic CAH**[1]
- Patients should be evaluated using a **balance of clinical presentation and androgen/precursor laboratory values**[1]

Key areas lacking consensus

- Optimal GC treatment regimens or timing for collecting samples for androgen testing[1]
- Target values of **17-OHP** or **androstenedione** indicating good control[1]
  - Endocrine Society guidelines for the treatment of classic CAH recommend **dose adjustment based on the overall clinical picture** rather than a single laboratory assessment[2]
- Definition of adult physiologic hydrocortisone dose[1]
  - Endocrine Society guidelines for the treatment of classic CAH recommend hydrocortisone dosing of **15 to 25 mg/day** for adults[2]
  - Typical daily GC doses reported by panelists ranged from hydrocortisone **25 to 40 mg/day**[1]

Click to view treatment and monitoring guidelines

[a]Consensus was defined as follows: **full consensus, 9/9 (100%)** ✓; **near consensus, 7/9 or 8/9 (78% to <100%)** ✓; **no consensus, <7/9 (<78%)** ✗.
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Backup

What Is Classic Congenital Adrenal Hyperplasia (CAH)?

Rare genetic disorder with deficiency of 21-hydroxylase, resulting in[1]:

- Insufficient cortisol and often aldosterone
- Excess adrenocorticotropic hormone (ACTH) and androgen production

Incidence of **~1:15,000 live births worldwide**[1,2]

Complex symptoms affect **multiple organ systems**[1,3]

Clinical characteristics[3]

Infancy

- Salt-wasting adrenal crisis characterized by poor feeding, weight loss, and dehydration
- **Females:** Atypical genitalia

Childhood

- Increased growth velocity
- Advanced bone age
- Premature growth plate closure
- Early puberty
- **Females:** Clitoromegaly

Adolescence and adulthood

- Short stature
- Infertility or subfertility
- Hirsutism
- Acne
- Adrenal myelolipomas
- **Females:** Menstrual irregularities
- **Males:** Testicular adrenal rest tumors (TARTs)

Patients with classic CAH are at risk for potentially fatal adrenal crises, often triggered by infections, throughout their lives[3]

ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; TART, testicular adrenal rest tumor.

1. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088. 2. Pang S, Clark A. *Screening*. 1993;2:105-139. 3. Merke DP, Auchus RJ. *N Engl J Med*. 2020;383(13):1248-1261.

Classic CAH Management

- **GC therapy,** with or without mineralocorticoid treatment, is the current standard of care[1]
- **Supraphysiologic GC doses** are often used to control high ACTH and androgen levels, but chronic exposure to such GC doses can cause complications[2]

Adequate androgen control should be balanced against the risks of GC excess[2]

Androgen excess[3-5]

Abnormal growth and development
- Advanced bone age
- Early puberty
- Short stature

Male health problems
- Testicular adrenal rest tumors (TARTs)
- Infertility

Other problems
- Psychologic impact

Female health problems
- Acne
- Hirsutism
- Oligomenorrhea
- Amenorrhea
- Infertility

GC excess[3-6]

Bone health problems
- Decreased bone density
- Increased fracture risk

Metabolic issues
- Weight gain
- Obesity
- Insulin resistance
- Diabetes

Other problems
- Muscle weakness
- Psychologic impact

Increased cardiovascular risk
- Hypertension

Unmet need: Physician consensus is lacking regarding optimal GC regimens and assessments of androgen control in adults with classic CAH[1]

ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; GC, glucocorticoid; TART, testicular adrenal rest tumor.

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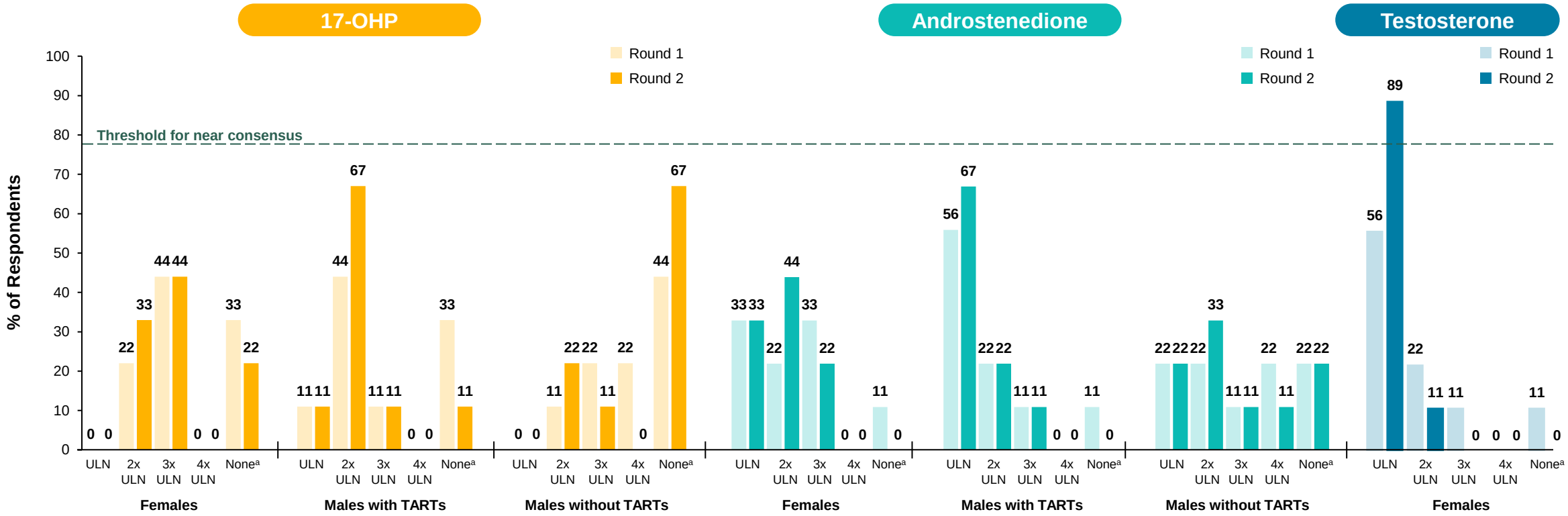
Androgen Laboratory Values and Indicators of Control



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Unmet Needs for Adults With Classic CAH[1,2]

In Round 2, most panelists rated good androgen control and management of supraphysiologic GC doses as **important** or **very important** for most patients

Key findings	Full or near consensus[a]	
Good androgen control is very important for…		
Short-term treatment	7/9	✓
Long-term treatment	7/9	✓
Female patients	7/9	✓
Male patients	6/9	✗
Younger patients[b]	7/9	✓
Patients without optimized androgens	7/9	✓

Key findings	Full or near consensus[a]	
Managing supraphysiologic GC doses is very important for…		
Short-term treatment	9/9	✓
Long-term treatment	9/9	✓
Female patients	9/9	✓
Male patients	8/9	✓
Younger patients[b]	7/9	✓
Older patients[c]	7/9	✓
Patients with supraphysiologic GC doses		
With androgens optimized	8/9	✓
Without androgens optimized	9/9	✓

Click to view supportive data

[a]Consensus was defined as follows: **full consensus, 9/9 (100%)** ✓; **near consensus, 7/9 or 8/9 (78% to <100%)** ✓; **no consensus, <7/9 (<78%)** ✗. [b]Ages 18 to ≤55 years. [c]Ages >55 years.
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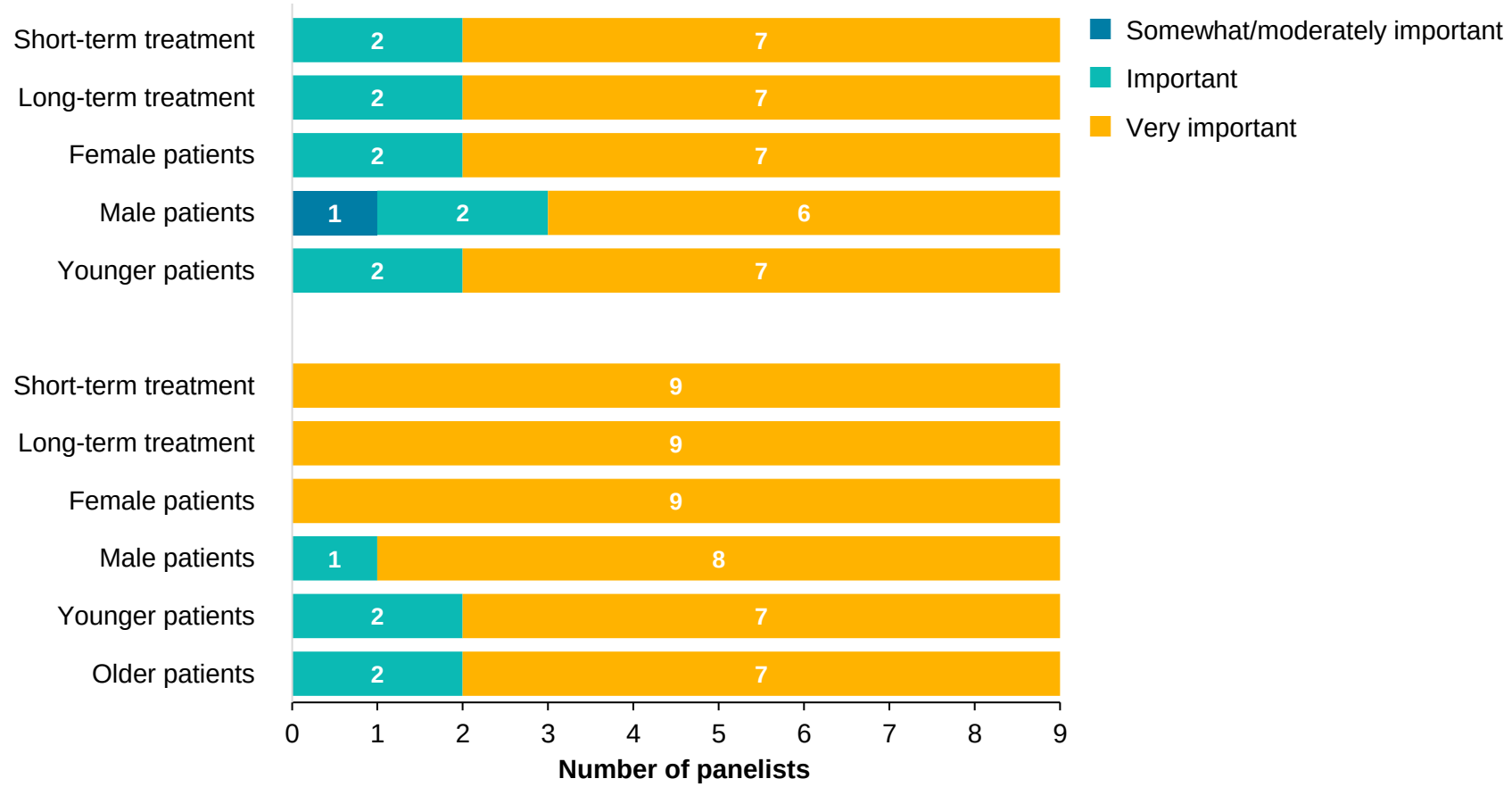
Unmet Needs for Adults With Classic CAH

In Round 2, most panelists rated good androgen control and management of supraphysiologic GC doses as **important** or **very important** for most patients



CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

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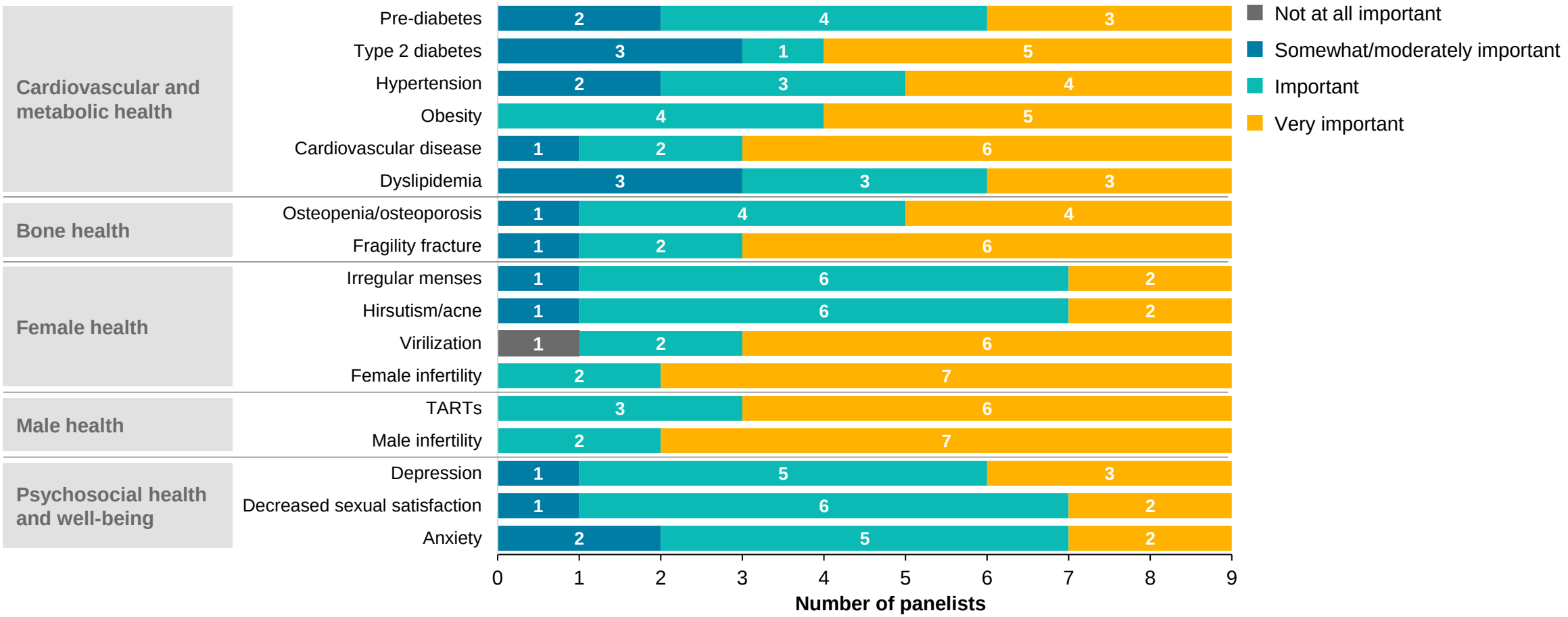
Disease- and GC-related Complications

In Round 1,[a] several disease- and GC-related complications were rated as **important** or **very important** by most panelists



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Treatment and Monitoring Recommendations for Patients With Classic CAH

2018 Endocrine Society clinical practice guidelines for classic CAH

Growth age	Recommended treatment	Monitoring recommendations
Newborn/ early infancy	• Hydrocortisone + fludrocortisone and sodium chloride supplements	• For patients aged ≤18 months, close monitoring during the first 3 months of life and every 3 months thereafter is recommended • After 18 months, evaluation is recommended every 4 months
Growing patients	• Hydrocortisone + fludrocortisone as clinically indicated[a] • Hydrocortisone oral suspension[b] generally not recommended (inconsistent formulation) and chronic use of long-acting potent GCs[c] are generally avoided	• Regular physical examinations; assessments of growth velocity, weight, and BP; and biochemical measurements recommended to assess adequacy of GC/MC therapy • For pediatric patients over the age of 2 years, annual bone age assessments are recommended until near-adult height is attained
Adults	• Hydrocortisone and/or long-acting GCs + fludrocortisone as clinically indicated[a]	• Annual physical examinations, including assessments of BP, BMI, and Cushingoid features, as well as biochemical measurements are recommended • Closely monitor treatment via consistently timed hormone measurements • Complete suppression of endogenous adrenal steroid secretion is not recommended due to the potential for adverse effects
All patients	• Monitoring for signs of GC excess, as well as for signs of inadequate androgen control, to optimize the adrenal steroid treatment profile • Monitoring for signs of MC deficiency or excess • Clinicians should adjust doses in the context of the overall clinical picture and not solely based on a single laboratory measurement • Complete suppression of serum 17-OHP levels is not a treatment goal but instead indicates overtreatment • Acceptably treated patients with classic CAH generally have upper normal to mildly elevated 17-OHP and androstenedione levels when measured in a consistent manner • Guidelines do not provide specific target levels for adrenal steroid measurement because laboratory reference ranges vary, sample timing varies, and one must consider the whole clinical picture	

[a]The need for MCs decreases with age. Most nonhypertensive adults with classic CAH benefit from continued fludrocortisone treatment. The requirement for MC replacement should be reassessed during the transition from pediatric to adult care.
[b]Hydrocortisone cypionate oral suspensions were inadequate to control classic CAH in children due to uneven distribution in liquid form. Good control can be achieved by orally administering crushed, weighed hydrocortisone tablets mixed with a small volume of liquid, if needed, immediately before administration.
[c]During childhood, the preferred GC is hydrocortisone because its short half-life minimizes the adverse side effects typical of longer-acting, more potent GCs (eg, dexamethasone), especially growth suppression.
17-OHP, 17-hydroxyprogesterone; BMI, body mass index; BP, blood pressure; CAH, congenital adrenal hyperplasia; GC, glucocorticoid; MC, mineralocorticoid.
Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088.

Treatment and Dosing Recommendations for Patients With Classic CAH

2018 Endocrine Society clinical practice guidelines for classic CAH: Recommended maintenance therapy[a]				
	Growing patients		Fully grown patients	
Corticosteroid	**Total daily dose**	**Daily dosing frequency**	**Total daily dose (mg/day)**	**Daily dosing frequency**
Hydrocortisone	10-15 mg/m^2	~3	15-25	2-3
Prednisone	–	–	5-7.5	2
Prednisolone[b]	–	–	4-6	2
Methylprednisolone	–	–	4-6	2
Dexamethasone[b]	–	–	0.25-0.5	1
Fludrocortisone	0.05-0.2 mg	1-2	0.05-0.2	1-2
Sodium chloride supplements	1-2 g (17-34 mEq/day) in infancy	Divided into several feedings	–	–

[a]These doses and schedules are meant as examples and should not be construed as a restrictive menu of choices for the individual patient.
[b]Suspension or elixir may permit improved dose titration for these drugs.
CAH, congenital adrenal hyperplasia; mEq, milliequivalent.
Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088.