Congenital Adrenal Hyperplasia and the Second Newborn Screen

Christine L. Chan, MD[1], Kim McFann, PhD[2], Laura Taylor, BA[3], Daniel Wright, BS[3], Philip S. Zeitler, MD, PhD[1], and Jennifer M. Barker, MD[1]

Objective To evaluate the effectiveness of a second newborn screen for congenital adrenal hyperplasia (CAH) in the state of Colorado and report characteristics associated with cases identified on the first versus second screen.
Study design Colorado implemented newborn screening for CAH with 17-hydroxyprogesterone beginning August 2000. The first screening is performed within 72 hours of life and the second between 8 and 14 days of life. We compared infants diagnosed on the basis of the first versus second newborn screen.
Results The first screen identified 29 cases of which 28 represented classical CAH. The incidence of classical CAH on the first screen was 1:24 766. The second screen identified 17 additional cases, of which 11 represented classical CAH. Combined, the incidence of classical CAH was 1:17 789. The sensitivity of the first screen was 71.79%. The false negative rate of the first screen was 28.2%. In the absence of a second screen, 1:47 824 infants would have been missed. Infants diagnosed on the first screen had higher 17-hydroxyprogesterone values compared with those diagnosed on the second screen (P = .0008).
Conclusions The use of a single newborn screen for CAH missed nearly 30% of classical CAH cases in Colorado. Addition of a second screen, therefore, can improve the operating characteristics of the newborn screening program. *(J Pediatr 2013;163:109-13)*.

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Congenital adrenal hyperplasia (CAH) refers to a group of autosomal-recessive disorders of adrenal steroidogenesis. The most common, 21-hydroxylase deficiency, is caused by mutations in the *CYP21A2* gene and accounts for greater than 90% of cases of CAH. The reported incidence of classical CAH ranges from 1:15 000-1:20 000 live births.[1-3] Retrospective studies suggest mortality rates from 4%-11.3%[4,5] in infants with salt-wasting CAH. Because of this high mortality, newborn screening for CAH was instituted in the US, as early recognition and treatment can prevent life-threatening adrenal crisis and assist the evaluation of females with ambiguous genitalia, thus reducing significant morbidity and mortality.

CAH has a spectrum of clinical manifestations attributable to varying degrees of cortisol and aldosterone deficiency. It is generally categorized into 3 forms of severity depending on the initial presentation. They are classical salt-wasting, classical simple-virilizing, and nonclassical CAH. Salt-wasting CAH reflects the most severe deficiency in 21-hydroxylase activity and may manifest as acute adrenal crisis in the first few weeks of life, with poor feeding, vomiting, diarrhea, dehydration, failure to thrive, lethargy, and shock, as well as hyponatremia and hyperkalemia. In contrast, infants with simple-virilizing CAH do not manifest symptoms of acute adrenal crisis, but present with signs of androgen excess leading to virilization in females and rapid skeletal maturation in both sexes. Infants with nonclassical CAH are asymptomatic but may present in childhood with signs of androgen excess and bone age advancement or in adult females with hirsutism, menstrual irregularities, and infertility.

Newborn screening for CAH in Colorado began in August 2000. Presently, Colorado is 1 of only 9 states performing routine second screenings for CAH, although at least 5 others strongly recommend it. The value of a second screen is controversial.[6,7] We report here our experience with CAH and the second newborn screen over the 10-year period from August 1, 2000 through October 31, 2010.

Methods

The legislatively-mandated CAH screening program in Colorado is based on measurement of 17-hydroxyprogesterone (17-OHP) levels from heel-stick blood samples on filter paper. The first screen is obtained within the first 3 days of life and the second screen is obtained on day of life 8-14. The general screening algorithm and recall process is outlined in the **Figure** (available at www.jpeds.com).

17-OHP	17-hydroxyprogesterone
CAH	Congenital adrenal hyperplasia
CDPHE	Colorado Department of Public Health and Environment
PPV	Positive predictive value

From the [1]Children's Hospital Colorado and University of Colorado, Aurora, CO; [2]Colorado School of Public Health, University of Colorado, Aurora, CO; and [3]Colorado Department of Public Health and Environment, Denver, CO

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When a presumptive positive is identified, a pediatric endocrinologist is notified and direct contact between the pediatric endocrinologist and submitting physician occurs. Depending on the clinical situation, this may lead to evaluation of the infant prior to the second screen. When a borderline abnormal 17-OHP is identified, the newborn screening program contacts the original submitter to request a repeat sample. The mandated second screen can serve this purpose. If a second sample is not received, the submitter is called again. If a sample is still not received, a certified letter is sent to the family. Interpretation of cosyntropin stimulated 17-OHP levels is based on the nomogram generated by New from data collected between 1982-1991.[8]

The assay employed for 17-OHP measurements is an automated, time-resolved fluoroimmunoassay (DELFIA, Perkin Elmer Life Sciences – Wallac Oy, Turku, Finland). Colorado uses weight-based cutoff criteria for determination of abnormal values as premature, stressed newborns may have higher levels of 17-OHP than healthy, term babies. Abnormal values are resulted as either borderline or presumptive positive (**Figure**). The Colorado Department of Public Health and Environment (CDPHE) revised the cutoff ranges for the CAH assay in December 2009, due to a reformulation of reagents from the assay kit vendor. To generate the cutoff points used in Colorado, data were pooled from six other Midwestern states and parallel testing was performed on over 26 000 data points, including over 750 data points representing the lowest birth weight tier of ≤1299 grams, and the cutoff points in **Table I** were generated.

During the 10 year time period of study, the following information was collected on all infants with a confirmed diagnosis of CAH: gestational age, birth weight, day of life the screen was obtained, sex, 17-OHP value, and final outcome diagnosis. The final diagnosis (classical vs nonclassical CAH) was provided to the public health department by the consulting pediatric endocrinologist. The CDPHE database contains information regarding false positive results from March 2006 onward. With these data, epidemiological and descriptive statistics were performed to calculate incidence, sensitivity, specificity, positive predictive value (PPV) and negative predictive value of the first and second screens. Second screen data were excluded from analysis if the first screen result led to a positive CAH diagnosis. Characteristics of cases identified by first versus second screen were compared using t-tests or non-parametric rank sum test for continuous variables and Chi square of Fisher Exact for categorical variables. The direct-cost-per-case was identified. Review of these data was approved by the Children's Hospital Colorado Organizational Research Risk and Quality Improvement Panel.

Table I. Weight-based cutoff ranges for diagnosing CAH on newborn screening in the state of Colorado

Weight range (g)	New cutoff (17-OHP ng/mL)	Old cutoff (17-OHP ng/mL)
≥2200	35	55
1700-2199	58	65
1300-1699	75	115
≤1299	125	135

Cutoff values indicate the upper limit of acceptable normal values. Values ≥125 ng/mL (and previously ≥200 ng/mL) are flagged as presumptive positive, and values between the upper limit of normal and presumptive positive are flagged as borderline. Old cutoff ranges were used from August 2000-November 2009. New cutoff ranges have been used since December 2009.

Results

From August 1, 2000 to October 31, 2010, there were a total of 705 444 live births in Colorado. Of those, a total of 693 751 infants were screened on the first screen and a total of 654 588 infants were screened on the second screen; 94.4% of newborns who received their first screen also received the mandated second screen.

On the first screen, 28 infants were identified with classical CAH and 1 with nonclassical CAH. The incidence of classical CAH detected on this first screen was 1:24 766. The second screen identified 11 additional cases of classical CAH and 6 cases of nonclassical CAH. Therefore, the overall incidence of classical CAH detected on both the first and second screenings was 1:17 789. There was 1 false negative case of a female with CAH who had normal first and second newborn screens and was diagnosed subsequently because of ambiguous genitalia, yielding an overall incidence of 1:17 636 for cases of classical CAH.

For the first screen, the sensitivity for detecting classical CAH was 71.8%, the specificity 99%, the PPV 0.4%, and the negative predictive value 99.99%. Following adjustment in cut off ranges due to assay formulation changes in December 2010, PPV (borderline and presumptive positive screens combined) increased to 3.7%. The first and second screens combined resulted in an improvement in PPV to 6.8%, and specificity remained at 99%. In the absence of a second screen, 1 case of classical CAH out of every 47 824 individuals screened would have been missed.

Infants diagnosed on the first screen had higher 17-OHP values compared with those diagnosed on the second screen ($P = .0005$) (**Table II**). There was no significant difference in average birth weight, gestational age, day of life the first screen was obtained, or sex between cases diagnosed on the first versus the second screen. Of the total cases of classical CAH diagnosed, 64.10% were male and 35.9% female, $P = .08$. Birth weight was lower in females at the first screen than males, and 17-OHP was nearly significantly higher at the first screen and significantly higher at the second screen in females versus males (**Table III**).

Outcome analyses were performed on both borderline and presumptive positive abnormal screens (**Table IV**). Overall, PPV for the first screen was 0.4% when both borderline and presumptive positive results were included, but for presumptive positive results only the PPV on the first screen was 15%. The second screen had fewer false positives and had an overall PPV of 8%, including 7.4% for borderline cases and 20% for presumptive positive cases.

Cost analysis was performed based on the cost of reagents and labor estimated at $2.10 per specimen. At this rate, the addition of the second screen increased the direct cost-per-case identified from $52 031 to $72 603.

Table II. Characteristics of cases identified by first versus second screening

	First screen n = 28			Second screen n = 11			
	Mean (SD)	95% CI	Range	Mean (SD)	95% CI	Range	*P* value
17-OHP (ng/mL)	366.5 (326.8)	239.8-493.2	49-1854	118.3 (61.8)	76.7-159.8	41-261	.0005
Day of life first screen obtained	2.6 (1.03)	2.2-3.0	1-5	2.9 (0.70)	2.4-3.4	2-4	.44
Gestational age (wk)	38.7 (1.96)	37.9-39.4	33-41	37.8 (3.16)	35.7-39.9	31-41	.41
Birth weight (g)	3247 (513)	3049-3446	2070-4054	3100 (698)	2631-3569	1864-4451	.47
Sex (% male)	17/28 (60.7%)			8/11 (72.7%)			.71
Nonclassical cases	1/29 (3.4%)			6/17 (35.3%)			.007

Discussion

This analysis aimed to explore the value of the second newborn screen for CAH by examining the screening characteristics of the first screen alone and combined with the mandated second screen. The first screen alone was found to have missed 28% of the total number of classical cases eventually identified. In our program, the sensitivity of the first screen was 71.8%, which is consistent with previous studies that reported sensitivities ranging from 60%-98.9%.[9-12] The addition of the second screen contributed to identification of classical cases missed on the first screen and suggests added value of a second newborn screen for CAH.

A 1998 study from Texas, a 2-screen state, looked at CAH newborn screening results of 1.9 million newborns over 6 years. A total of 175 cases of CAH were identified and of these 121 were classical cases, yielding a total incidence rate of 1:16 008[13] and an incidence rate of 1:18 624 based on the first screen alone (including those identified clinically and based on family history). Overall, 23 classical cases were missed on the first screen in this report, (sensitivity of 81%), although 6 of these were detected clinically, leading the authors to conclude that there is substantial benefit to a second screen. Our analyses support these findings, the only prior report on CAH data from a 2-screen state, and are notable for even higher rates of detection of classical CAH on the second screen.

A recent report of newborns screened over an 11-year period in Minnesota, a state with a single newborn screen, found a false negative rate of 22.4%, where 15 out of 52 patients with classical CAH were missed by newborn screening.[14] Despite the presence of ambiguous genitalia, 3/9 females were not identified until 3 months, 3.4 years, and 6.5 years of age, and males missed by newborn screening were not diagnosed until an average age of 4.2 years (range 2.3-5.5 years). These individuals presented with significant bone age advancement, and 1 missed female was assigned male sex and only diagnosed subsequent to workup for penoscrotal hypospadias. A study from Wisconsin, another state with a single screen, reported sensitivity rates of 60% in females and 80% in males after conducting an analysis of false negative cases missed on newborn screening over a 3-year period.[9] Seven out of the 8 infants missed were female and 4 out of 8 had laboratory evidence of compensated salt-wasting, although the authors noted that none of the infants presented in salt-wasting crisis died, nor were initially assigned the wrong sex. Similarly, all salt-wasting cases from the Texas report were identified either clinically or on the first screen,[13] and a 2005 review of newborn screening cards over 35 years from 5 Middle European countries noted estimated false-negative rates on newborn screening of 30%, all attributable to missed cases of "moderate" CAH.[15] The findings from Texas and Minnesota, in conjunction with our report, suggest that a mandated second newborn screening is helpful in identifying cases of classical CAH that would otherwise be missed or result in significant delays in diagnosis. However, these reports also illustrate an important controversy that exists surrounding the goals of newborn screening for CAH—whether or not the goals of screening are solely to identify and decrease mortality from salt-wasting or to identify all cases along the classical CAH spectrum.

The CDPHE database did not distinguish salt-wasters from simple-virilizers in infants with a diagnosis of classical CAH. Although these 2 diagnoses attempt to characterize infants with varying severities of CAH along the disease spectrum, it is important to note that the distinction between simple-virilizers and salt-wasters is not always apparent. Although the reports from Varness[9] and Votava[15] suggest that most missed cases of CAH tend to fall along the milder

Table III. Sex differences

	First screen			Second screen		
	Boys n = 17	Girls n = 11		Boys n = 8	Girls n = 3	
	Mean (SD)	Mean (SD)	*P* value	Mean (SD)	Mean (SD)	*P* value
17-OHP (ng/mL)	265.5 (155.6)	522.5 (453.3)	.10	90.4 (32.2)	192.7 (63.7)	.01
Day of life first screen obtained	2.5 (0.9)	2.8 (1.2)	.48	3.0 (0.8)	2.7 (0.6)	.51
Gestational age (wk)	39.2 (1.2)	37.8 (2.6)	.11	37.5 (3.7)	38.7 (1.2)	.61
Birth weight (g)	3452 (306)	2931 (615.1)	.02	3150 (791)	2967 (459)	.72

Table IV. Outcomes by first and second screening*

	Outcome positive classical CAH	Outcome negative classical CAH
	n	n
First screen		
Borderline positive	3	2572
Presumptive positive	8	44
Negative	0	320 242
Second screen		
Borderline positive	6	75
Presumptive positive	1	4
Negative	0	299 049

PPV for borderline first screen = 0.12%.
PPV for borderline second screen = 7.4%.
PPV for presumptive positive first screen = 15%.
PPV for presumptive positive second screen = 20%.
*March 2006-October 2010.

end of the salt-wasting spectrum, the argument can be made that distinguishing a salt-waster who may have presented in adrenal crisis from an infant with 'milder,' compensated salt-wasting is difficult when both cases are diagnosed by newborn screening.[13] Because of the diagnostic challenges related to categorization of infants with CAH, definitions among states vary, and individual case definitions are often left to the discretion of the medical provider.[16]

In order to maintain high sensitivity, screening tests for diseases with low incidence rates will have low PPV. Previous data has demonstrated CAH screening to have PPV rates ~1%,[9,10,17] and the PPV for first screens in Colorado was similarly low at 0.4%, though analysis of presumptive positive cases alone yields a PPV of 15% on the first screen. The second screen PPV is better because 17-OHP levels rise within a couple days after birth and fall thereafter into the normal range in infants without CAH, and continue to rise in infants with CAH. Thus, the second screen had fewer false positives and PPV was higher at 7.4% for borderline and 20% for presumptive positive cases. Prior studies have not reported on this difference in PPV between borderline and presumptive positive cutoffs, and this information may give the clinical provider a better understanding of the likelihood of a true positive outcome based on newborn screening results, which is beneficial for counseling and prioritizing follow-up evaluations.

The incidence of CAH detected on the first screen in our population is lower than national incidence rates. The reasons for this discrepancy are unclear. Ethnic differences exist and the highest rates of CAH have been reported in Yupik Eskimos of Alaska (1:280 births) and Brazil (1:7500 births) with lower rates in African American (1:42 000) and Whites (1:15 000)[1,17] The ethnic distribution of Colorado inhabitants is predominantly White (73%) and Hispanic (19%) and does not appear to explain the lower incidence rates reported here. The commercial kit utilized for CAH screening is widely used and the recent assay reformulation occurred due to concerns regarding cross-reactivity in low birth weight infants resulting in high false positive rates in this group. Low sensitivity or assay kit inefficiency is thus unlikely the issue. A relatively smaller population in the state of Colorado and possible under-reporting of positive cases missed on newborn screening to the CDPHE are also plausible explanations. The latter is felt to be unlikely as there are only 2 pediatric endocrine practices in the state, both of which work closely with CDPHE in the newborn screening program.

Whether or not a second screen for CAH is cost-effective is controversial. Currently, only 9 states (Arizona, Colorado, Delaware, Nevada, New Mexico, Oregon, Texas, Utah, Wyoming) perform a mandatory second newborn screen.[6] A comparative cost analysis of the first and second screens for CAH was conducted in Texas[7] and a single screen was found to be effective if the goal of screening was to detect severe salt-wasting cases only. A second screen was found to be less cost-effective than the first, although still necessary if the goals of screening include detection of simple-virilizers. Cost effectiveness analyses of CAH screening are varied and reports on costs per case identified range from $25 000[18,19] to $250 000 with a second screen.[7] Our analysis found direct cost increases from $52 031 to $72 603 for the identification of classical CAH with the addition of a second screen. Indirect costs such as the administrative costs of follow-up, laboratory studies for infants with positive screens, physician visits, and the costs of missed diagnoses, and hospitalization, were not included in this simple analysis. It is also difficult to assess the system-wide cost savings possible when borderline first screen values are followed up with a second screen rather than undergoing clinical evaluation. The second screen also identified a few cases of nonclassical CAH. Detection of these cases is not a goal but rather a by-product of newborn screening.

Second tier screening utilizing tandem mass spectrometry and measurement of steroid ratios[20-22] or molecular analysis have been proposed to improve the PPV of CAH newborn screening.[23] A pilot project assessing tandem mass spectrometry performance is currently underway in Colorado with the goal of validating and implementing these methodologies to reduce the follow-up costs and family anxiety associated with false positives.

17-OHP levels were higher on the first screen in both males and females. Cases missed on the first screen but detected on the second screen had 17-OHP levels in the normal range on the first screen. As 17-OHP levels rise with time in infants with classical CAH, it is possible that those infants detected on the first screen had a more severe enzymatic block than those detected on the second screen. Sex differences were noted in our analysis, with female infants having significantly higher 17-OHP levels than males on the second screen, and a trend toward higher levels on the first screen. One could speculate that the higher 17-OHP values reflect the lower birth weights of females in this cohort. In contrast, the study from Wisconsin also looked at sex differences in 17-OHP levels and found higher levels in males than females and proposed consideration of sex-adjusted thresholds for 17-OHP.[9] Further studies of sex differences are needed to determine if sex-adjusted cutoffs are appropriate. The ratio of males to females detected is 25:14 and the exact reasons for this

difference are unclear, although this may be an artifact of the population sex distribution. The high proportion of males detected, however, many of whom would likely have been missed in the absence of a second screen, highlight the benefits of a second screen.

The false negative rates in this report are dependent on cases of CAH clinically diagnosed and reported as missed cases to the CDPHE. Calculation of combined sensitivity of the 2 screens can only be conducted with false negative cases reported to date. As pediatric endocrinologists notify CDPHE of CAH cases missed by newborn screening, the likelihood of unreported false negative cases is low. However, patients who move out of state or infants who die of an adrenal crisis without a diagnosis could be missed. Continued surveillance is necessary to detect additional cases of CAH that may have been missed on newborn screening yet remain undiagnosed. Additional limitations of this report include the lack of descriptive data available beyond the diagnosis of classical or nonclassical CAH provided by the pediatric endocrinologist. Despite the difficulties noted previously in categorization of CAH infants, this highlights a need for the development of state and regional databases to better characterize positive CAH cases, including documentation of the presence and severity of electrolyte disturbances and presentations in adrenal crisis, presence of genital ambiguity, and any additional diagnostic procedures performed, including molecular testing results.[2] ■

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Reprint requests: Christine L. Chan, MD, Children's Hospital Colorado and University of Colorado, 13123 E. 16th Avenue, B265, Aurora, CO 80045. E-mail: Christinel.chan@childrenscolorado.org

References

1. Pang S, Shook MK. Current status of neonatal screening for congenital adrenal hyperplasia. Curr Opin Pediatr 1997;9:419-23.
2. Therrell BL. Newborn screening for congenital adrenal hyperplasia. Endocrinol Metab Clin North Am 2001;30:15-30.
3. van der Kamp HJ, Wit JM. Neonatal screening for congenital adrenal hyperplasia. Eur J Endocrinol 2004;151(Suppl 3):U71-5.
4. Kovacs J, Votava F, Heinze G, Solyom J, Lebl J, Pribilincova Z, et al. Lessons from 30 years of clinical diagnosis and treatment of congenital adrenal hyperplasia in five middle European countries. J Clin Endocrinol Metab 2001;86:2958-64.
5. Grosse SD, Van Vliet G. How many deaths can be prevented by newborn screening for congenital adrenal hyperplasia? Horm Res 2007;67:284-91.
6. Center NNSaGR. San Antonio: Department of Pediatrics, University of Texas Health Science Center at San Antonio; 2011 Available at: http://genes-r-us.uthscsa.edu/. Accessed May 30, 2011.
7. Brosnan CA, Brosnan P, Therrell BL, Slater CH, Swint JM, Annegers JF, et al. A comparative cost analysis of newborn screening for classic congenital adrenal hyperplasia in Texas. Public Health Rep 1998;113:170-8.
8. Nimkarn S, Lin-Su K, New MI. Steroid 21 hydroxylase deficiency congenital adrenal hyperplasia. Pediatr Clin North Am 2011;58:1281-300. xii.
9. Varness TS, Allen DB, Hoffman GL. Newborn screening for congenital adrenal hyperplasia has reduced sensitivity in girls. J Pediatr 2005;147:493-8.
10. White PC. Neonatal screening for congenital adrenal hyperplasia. Nat Rev Endocrinol 2009;5:490-8.
11. Coulm B, Coste J, Tardy V, Ecosse E, Roussey M, Morel Y, et al. Efficiency of neonatal screening for congenital adrenal hyperplasia due to 21-hydroxylase deficiency in children born in mainland France between 1996 and 2003. Arch Pediatr Adolesc Med 2012;166:113-20.
12. Votava F, Novotna D, Kracmar P, Vinohradska H, Stahlova-Hrabincova E, Vrzalova Z, et al. Lessons learned from 5 years of newborn screening for congenital adrenal hyperplasia in the Czech Republic: 17-hydroxyprogesterone, genotypes, and screening performance. Eur J Pediatr 2012;171:935-40.
13. Therrell BL Jr, Berenbaum SA, Manter-Kapanke V, Simmank J, Korman K, Prentice L, et al. Results of screening 1.9 million Texas newborns for 21-hydroxylase-deficient congenital adrenal hyperplasia. Pediatrics 1998;101(4 Pt 1):583-90.
14. Sarafoglou K, Banks K, Kyllo J, Pittock S, Thomas W. Cases of congenital adrenal hyperplasia missed by newborn screening in Minnesota. JAMA 2012;307:2371-4.
15. Votava F, Torok D, Kovacs J, Moslinger D, Baumgartner-Parzer SM, Solyom J, et al. Estimation of the false-negative rate in newborn screening for congenital adrenal hyperplasia. Eur J Endocrinol 2005;152:869-74.
16. Center TNNSaGR. National Newborn Screening Report – 2000. Austin: Services UDoHaH; 2003.
17. Pass KA, Neto EC. Update: newborn screening for endocrinopathies. Endocrinol Metab Clin North Am 2009;38:827-37.
18. Carroll AE, Downs SM. Comprehensive cost-utility analysis of newborn screening strategies. Pediatrics 2006;117(5 Pt 2):S287-95.
19. Yoo BK, Grosse SD. The cost effectiveness of screening newborns for congenital adrenal hyperplasia. Public Health Genomics 2009;12:67-72.
20. Minutti CZ, Lacey JM, Magera MJ, Hahn SH, McCann M, Schulze A, et al. Steroid profiling by tandem mass spectrometry improves the positive predictive value of newborn screening for congenital adrenal hyperplasia. J Clin Endocrinol Metab 2004;89:3687-93.
21. Janzen N, Peter M, Sander S, Steuerwald U, Terhardt M, Holtkamp U, et al. Newborn screening for congenital adrenal hyperplasia: additional steroid profile using liquid chromatography-tandem mass spectrometry. J Clin Endocrinol Metab 2007;92:2581-9.
22. Trapp CM, Speiser PW, Oberfield SE. Congenital adrenal hyperplasia: an update in children. Curr Opin Endocrinol Diabetes Obes 2011;18:166-70.
23. Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:4133-60.

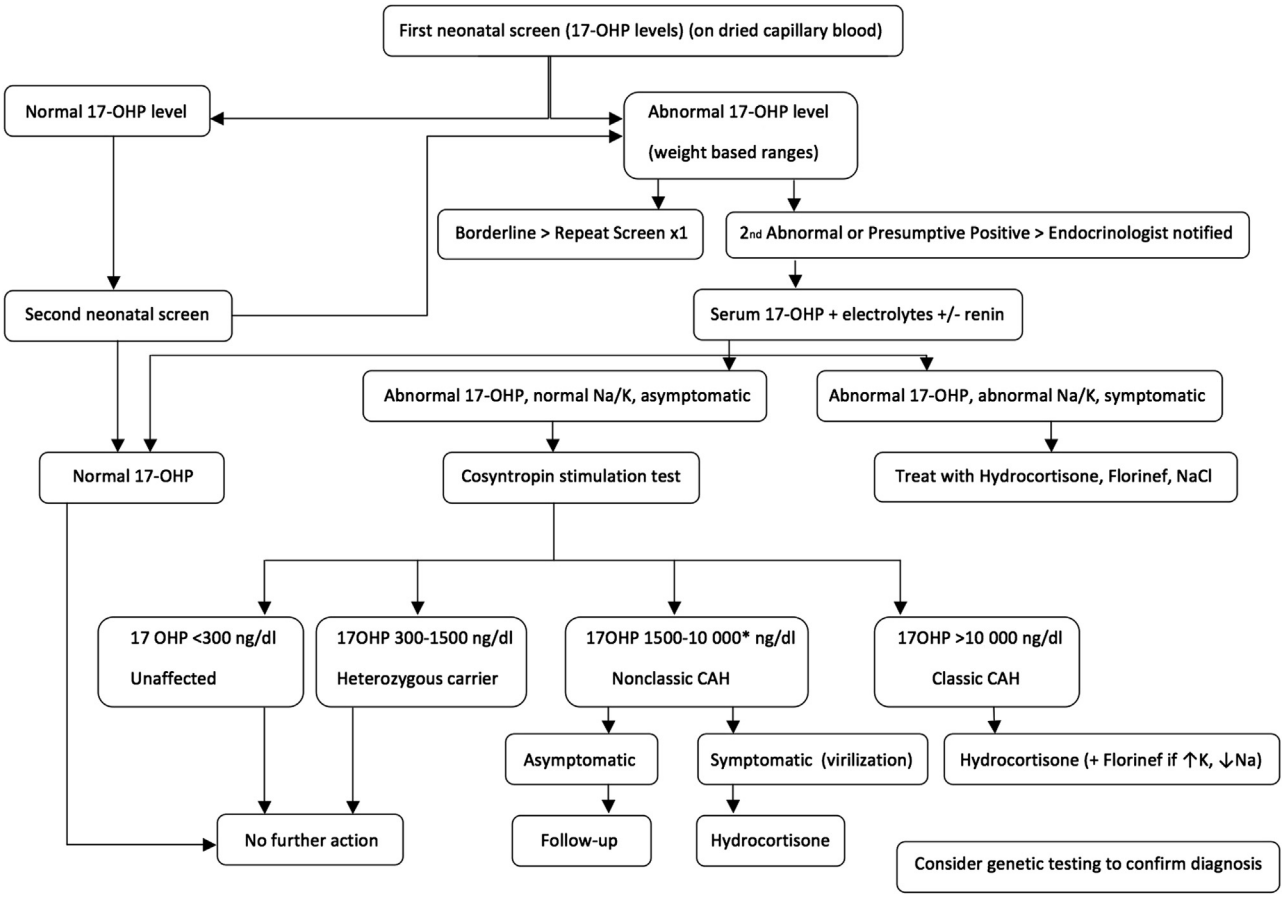

Figure. General screening algorithm for CAH. *CAH represents a spectrum of clinical manifestations and overlap exists between nonclassical CAH and simple virilizing CAH. A final diagnosis should take both laboratory and clinical findings into consideration. *NA*, sodium; *K*, potassium.