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Original Research

Contemporary global management of 21-hydroxylase deficiency congenital adrenal hyperplasia in early infancy: a multi-national registry study

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Abstract

Objective **Management of 21-hydroxylase deficiency (21-OHD) congenital adrenal hyperplasia (CAH) in early infancy is challenging, with extent of variation in management unclear.**

Design and Methods **Using the I-CAH Registry, we retrospectively reviewed management over the first 90 days of life of 154 infants with 21-OHD born in 2018-2023, across 33 centers in 18 countries.**

Results **Of 154 infants (92 female, 62 male), 136 were diagnosed postnatally, with median (10th centile, 90th centile) presentation age of Day 4 (0, 20.8). At initial hospital discharge, median doses of hydrocortisone (HC), fludrocortisone (FC), and salt were 17 (11.4, 39.6) mg/m^2/day, 100 (50, 200) mcg/day and 3.5 (1.6, 8.7) mmol/kg/day, and at Day 90 (D90) 14.5 (8.7, 24.1) mg/m^2/day, 100 (50, 200) mcg/day, and 2.1 (1.0, 5.2) mmol/kg/day, respectively. Hyponatremia, hyperkalemia, and hypoglycemia were reported in 70.0%, 71.9%, and 13.0% of infants, respectively. At D90, hyponatremia and hyperkalemia were reported in 7.4% and 28.6%, respectively. At D90, BP measurements were recorded in 30.5%, amongst whom 31.9% had hypertension reported. Median total hospitalization duration over 90 days was 9 days (2, 24). Adrenal crises were associated with 40. 6% of hospitalization episodes. Percentages (males:females) of cases seen by a pediatric endocrinologist, psychologist, pediatric endocrine nurse specialist, and surgeon by D90 were 95.9% (58:84), 33.3% (9:35), 42.1% (20:36), and 23.8% (0:35), respectively.**

Conclusions **Contemporary management of CAH in early infancy varies considerably. Hypertension and hyperkalemia are frequently reported. Our data may help inform development of quality indicators for benchmarking CAH care in infancy.**

Keywords congenital adrenal hyperplasia, 21-hydroxylase deficiency, early infancy, treatment variation, quality of care, benchmarking

Significance

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is the commonest genetic cause of adrenal insufficiency. Although guidelines for CAH management exist, their implementation and impact on quality of care remain unclear due to limited standardization in monitoring and benchmarking, particularly in infancy. Using data from the international I-CAH Registry, this study provides the first multi-country analysis of early infancy care. Findings reveal substantial variation in glucocorticoid dosing (often exceeding 10-15 mg/m^2/day), mineralocorticoid use, electrolyte disturbances, and access to multidisciplinary care. The high prevalence of hypertension, persistent hyperkalemia, and adrenal crisis-related hospitalizations underscores key management challenges. These findings highlight the urgent need for standardized early management guidelines and provide a basis for quality indicators and benchmarking to improve CAH care in infancy.

Introduction

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) is the commonest genetic cause of primary adrenal insufficiency, affecting ~1:14,000-18,000 births.[1] Infants typically present with cortisol and aldosterone deficiency and may have life-threatening salt-wasting crises, alongside physical manifestations of androgen excess in females. These pose complex management challenges requiring a multi-disciplinary approach especially in the early months following diagnosis.[2,3]

Although CAH management guidelines exist,[3-6] their real-world implementation and impact on care quality are unclear, partly due to limited monitoring and benchmarking of care.[7] Disease registries provide insights into practice variations across healthcare providers and assess alignment with care standards, facilitating quality improvement.[8] Over the past decade, the I-CAH Registry, part of the SDMregistries platform (https://sdmregistries.org/), has

collected large-scale patient data, identifying variation in diagnosis, treatment, acute adrenal insufficiency-related adverse events, surgical approaches, and long-term monitoring.[9-14]

However, no studies have focused exclusively on early infancy, a critical period when diagnosis is typically made and hence variability in management is likely greatest. Furthermore, Bonfig et al. reported a high prevalence of hypertension at 12-24 months in infants with CAH treated early with glucocorticoids and mineralocorticoids.[15] Similarly, Neumann et al. found that young children with CAH had increased weight gain and high hypertension rates until 3 years of age.[16] These findings suggest that adverse effects of therapy may begin in infancy, underscoring the need for focused research to guide early management and improve both short and longer-term outcomes in this vulnerable population.

We therefore studied contemporary care of infants over the first 90 days of life and assessed alignment with international clinical guidelines,[4] aiming to inform future benchmarking standards.

Materials and methods

Infants born between January 2018 and March 2023 and diagnosed with 21-OHD CAH within the first 90 days of life were identified from the I-CAH Registry. The I-CAH Registry, part of the SDMregistries platform, is an international research database that contains pseudonymized information on patients with CAH, collected as part of routine clinical care, and is approved by the National Research Ethics Service in the UK (NRES UK) (24/WS/0059). Data within this registry are deposited by clinical centers following informed consent from patients or guardians. These centers have obtained their own local institutional approval for participating in SDMregistries. Access to registry data by investigators is reviewed by the SDMregistries Data Access Committee (DAC). Following approval of the data access request by the DAC, centers with eligible cases are approached by SDMregistries to seek approval for sharing their center's data with the investigators. Information sharing between all users adheres to principles of the UK Data Protection Act (2018), EU General Data Protection Regulation (GDPR) (2018), UK GDPR (2021) and the "Conditions of Ethical Approval" as stipulated by NRES UK. Further details are available at https://sdmregistries.org/. Centers with eligible cases were invited to participate between November 2022 and October 2023. The study was conducted in accordance with the Declaration of Helsinki.

Data were obtained at defined timepoints to assess changes in key variables, including weight at birth and Day 90, biochemistry at point of diagnosis (pre-treatment) and Day 90, medication at initial hospital discharge (post-treatment initiation) and Day 90, and blood pressure (BP) at Day 90. For Day 90 measurements, measurements from Day 60-120 were accepted (closest to Day 90 selected if multiple measurements). Other data collected included existence of a newborn screening (NBS) program, clinical presentation, hospitalization, and multi-disciplinary involvement. Weight standard deviation scores (SDS) were based on WHO or country-specific growth standards. Where multiple presenting features existed, the first prompting diagnostic work-up was considered the primary mode of presentation. Hyponatremia and hyperkalemia were defined relative to local laboratory reference ranges. Hypoglycemia was defined as low blood glucose necessitating medical treatment. Equivalent dose (ED) for glucocorticoid (GC) and mineralocorticoid (MC) action was calculated as:[17] ED-hydrocortisone (HC) (GC equivalent dose) = HC (mg) + (fludrocortisone (FC) (mcg) × 0.0125), and ED-FC (MC equivalent dose) = FC (mcg) + (HC (mg) × 5), assuming GC potency of fludrocortisone of 12.5 and MC potency of hydrocortisone of 0.005. Symptomatic adrenal insufficiency (AI) was defined as clinical unwellness (eg, lassitude, poor feeding, weight loss) without adrenal crisis. Adrenal crisis was defined as an acute deterioration with hemodynamic disturbance, or marked hyponatremia, hyperkalemia, and/or hypoglycemia not attributable to another illness, improving significantly following parenteral glucocorticoids.[18] Hospitalization duration was calculated from point of first suspicion of CAH.

Statistical analyses were performed using Social Science Statistics (https://www.socscistatistics.com/). Continuous variables were presented as medians with 10th and 90th centiles. Mann–Whitney *U* test compared continuous variables, Pearson's correlation assessed associations, and Fisher's exact test compared proportions. Statistical tests were 2-tailed, with $P < .05$ considered significant. Countries were categorized by World Bank classification: low, lower-middle, upper-middle, or high-income countries (LIC, LMIC, UMIC, or HIC, respectively).[19]

Results

A total of 154 infants from 33 centers across 18 countries were included: 13 HICs (113 infants), 3 UMICs (18), and 2 LMICs (23). No LICs were represented. Final sex assignment was female in 92 (59.7%) and male in 62 (40.3%) infants, all with 46,XX and 46,XY karyotypes, respectively. Amongst the 92 final sex-assigned females, 3 infants were initially assigned male at birth, all of whom were subsequently re-assigned female. Median (10th, 90th centiles) number of infants per center was 3 (1, 12.6). Median gestational age at birth in completed weeks was 39 (37, 41) weeks, birthweight 3395 (2,632, 3876) grams, and birthweight SDS 0 (−1.36, 1.20). No deaths occurred within 90 days.

Mode of presentation

Primary presentation modes and median ages at presentation were: prenatal diagnosis (18/154, 11.7%), targeted postnatal investigations due to family history (3/154, 1.9%) at Day 0 (0, 0), atypical genitalia (55/154, 35.7%) at Day 0 (0, 0), positive NBS result (56/154, 36.3%) at Day 7 (6, 9) (age at result notification), and AI (22/154, 14.2%) at Day 16.5 (6.3, 47.8). Overall median postnatal presentation age was Day 4 (0, 20.8). Of 136 postnatally diagnosed cases, 53 (39.0%) had genetic confirmation by Day 90. Figure 1 shows primary presentation modes by final sex assignment.

Of the 22/92 females diagnosed through NBS or AI presentation, genitalia appearance was documented in 16: "normal female" 3/16, Prader (virilization stage) I 4/16, Prader II 5/16, and Prader III 4/16; of the remaining 6 without documented staging, 2 were initially sex-assigned male.

Glucocorticoid, mineralocorticoid, and salt administration (Table 1)

There was no difference in age at glucocorticoid versus mineralocorticoid commencement (median Day 7 [2, 25.5] vs 8 [1.6, 20.8],

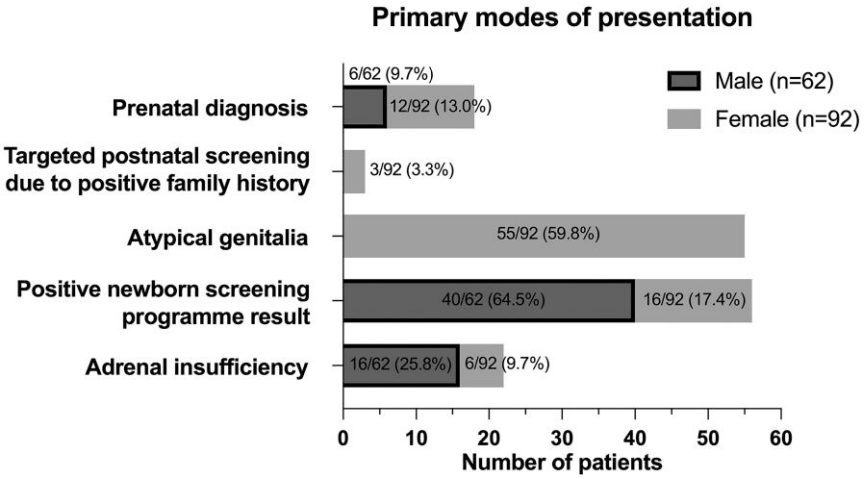

Figure 1 Primary modes of CAH presentation categorized according to sex. Fractions and percentages are calculated based on either the male ($n = 62$) or female ($n = 92$) cohorts.

Table 1 Medication doses and regimes at initial hospital discharge and at Day 90. *P* values are calculated by comparison of medication doses between both timepoints. BSA, body surface area; HC, hydrocortisone; FC, fludrocortisone.

Medication	Initial discharge Median (10th, 90th centile)	At Day 90 Median (10th, 90th centile)	*P* value
Relative hydrocortisone dose (dose per BSA)	17 mg/m^2/day (11.4, 39.6) [$n = 151$]	14.5 mg/m^2/day (8.7, 24.1) [$n = 143$]	$P < .001$
Hydrocortisone absolute dose	3.8 mg/day (2.5, 9) [$n = 148$]	4.5 mg/day (3, 7.5) [$n = 140$]	$P = .21$
Relative fludrocortisone dose (dose per BSA)	473.5 mcg/m^2/day (217.3, 833.3) [$n = 140$]	361.67 mcg/m^2/day (182.4, 704.3) [$n = 134$]	$P = .01$
Fludrocortisone absolute dose	100 mcg/day (50, 200) [$n = 143$]	100 mcg/day (50, 200) [$n = 138$]	$P = .02$
Salt	3.5 mmol/kg/day (1.6, 8.7) [$n = 129$]	2.1 mmol/kg/day (1.0, 5.2) [$n = 109$]	$P < .001$
Equivalent dose-HC	22.5 mg/m^2/day (15.9, 41.8) [$n = 148$]	19.3 mg/m^2/day (13.4, 29.3) [$n = 153$]	$P < .001$
Equivalent dose-FC	120 mcg/day (65.3, 229.5) [$n = 148$]	131.3 mcg/day (75.2, 234.8) [$n = 140$]	$P = .01$
Hydrocortisone			
<10 mg/m^2/day	1.3% (2/151)	22.4% (32/143)	
10-15 mg/m^2/day	43.0% (65/151)	30.8% (44/143)	
>15-30 mg/m^2/day	35.8% (54/151)	45.5% (65/143)	
>30-50 mg/m^2/day > 50 mg/m^2/day	18.5% (28/151)	1.4% (2/143)	
	1.3% (2/151)	0%	
Unknown	*3/154*	*11/154*	
Fludrocortisone			
Not started fludrocortisone	5.3% (8/151)	4.1% (6/145)	
<50 mcg/day	2.6% (4/151)	1.4% (2/145)	
50-200 mcg/day	87.4% (132/151)	86.9% (126/145)	
50-100 mcg/day	*62.3% (94/151)*		
>100-150 mcg/day	*14.6% (22/151)*		
>150-200 mcg/day	*10.6% (16/151)*		
>200 mcg/day	4.6% (7/151)	6.9% (10/145)	
Stopped fludrocortisone	0% (0/151)	0.7% (1/145)	
Unknown	*3/154*	*9/154*	

(*continued*)

Table 1 Continued

Medication	Initial discharge Median (10th, 90th centile)	At Day 90 Median (10th, 90th centile)	*P* value
Salt			
Not started salt	11.8% (18/152)	11.7% (17/145)	
On salt	88.2% (134/152)	85.5% (124/145)	
Stopped salt	0% (0/152)	2.8% (4/145)	
Unknown	*2/154*	*9/154*	
Hydrocortisone doses per day			
Once daily	2.6% (4/151)	2.8% (4/141)	
Twice daily	12.6% (19/151)	7.1% (10/141)	
Three times daily	70.9% (107/151)	75.2% (106/141)	
Four times daily	13.9% (21/151)	14.9% (21/141)	
Unknown	*3/154*	*13/154*	
Hydrocortisone dose weighting			
Circadian rhythm	12.1% (18/149)	22.9% (32/140)	
Reverse circadian rhythm	0.7% (1/149)	5.7% (8/140)	
Highest doses in morning and night	2.0% (3/149)	5.0% (7/140)	
Equal doses	83.2% (124/149)	63.6% (89/140)	
Once at 03:00	2.0% (3/149)	2.9% (4/140)	
Unknown	*5/154*	*14/154*	
Fludrocortisone doses per day			
Once daily	47.7% (72/151)	43.4% (63/145)	
Twice daily	39.7% (60/151)	42.8% (62/145)	
Three times daily	6.6% (10/151)	9.0% (13/145)	
Four times daily	0.7% (1/151)	0% (0/145)	
Not on fludrocortisone	5.3% (8/151)	4.8% (7/145)	
Unknown	*3/154*	*9/154*	

$P = .42$). Salt was commenced at Day 9 (3, 26.6), similar to mineralocorticoid ($P = .08$) but later than glucocorticoid ($P = .01$).

Hydrocortisone was used in 153/154 (99.4%) and prednisolone in 1/154 (0.01%) cases. At presentation, 35/149 (23.3%) infants received hydrocortisone doses per BSA of ≥50 mg/m^2/day, amongst whom 23/35 had biochemical and/or clinical evidence of AI (including adrenal crisis). In these 23 patients, doses at initial discharge following diagnosis were >30-50 mg/m^2/day in 6, >15-30 mg/m^2/day in 8, and 10-15 mg/m^2/day (international recommended range)[4] in 9. In the 12 without AI, 4 were in each dose category.

At initial discharge following diagnosis at a median age of Day 14 (4, 33.6), median absolute hydrocortisone dose was 3.8 (2.5, 9) mg/day, relative hydrocortisone dose 17 (11.4, 39.6) mg/m^2/day, and ED-HC dose 22.5 (15.9, 41.8) mg/m^2/day. At Day 90, versus initial discharge, relative hydrocortisone and ED-HC doses were lower with median doses of 14.5 (8.7, 24.1) mg/m^2/day ($P < .001$) and 19.3 (13.4, 29.3) mg/m^2/day ($P < .001$), respectively, while absolute doses were similar at a median dose of 4.5 (3, 7.5) mg/day ($P = .21$). The commonest dose range was >15-30 mg/m^2/day at both initial discharge and Day 90. At both timepoints, hydrocortisone was most commonly given thrice daily then 4 times daily, and the commonest regimen was equal dose distribution then circadian rhythm dosing.

At initial discharge, median absolute fludrocortisone dose was 100 (50, 200) mcg/day, relative fludrocortisone dose 473 (217.3, 833.3) mcg/m^2/day, and ED-FC dose 120 (65.3, 229.5) mcg/day. At Day 90, absolute fludrocortisone and ED-FC doses rose to 100 (50, 200) mcg/day ($P = .017$) and 131.3 (75.2, 234.8) mcg/day ($P = .01$), respectively, but relative fludrocortisone doses fell to 361.7 (182.4, 704.3) mcg/m^2/day ($P = .01$).

The commonest fludrocortisone dose was between 50 and 200 mcg/day (international recommended range) at both timepoints. At initial discharge, 8/151 (5.3%) infants were not prescribed fludrocortisone, and at Day 90 7/145 (4.8%). At both timepoints, dosing was most frequently once daily then twice daily. Infants not on fludrocortisone at initial discharge did not have a higher proportion with post-treatment adrenal crises, versus infants on fludrocortisone (1/8 vs 16/143, $P = 1$).

At initial discharge, median salt dose was 3.5 (1.6, 8.7) mmol/kg/day, falling to 2.1 (1.0, 5.2) mmol/kg/day ($P < .001$) at Day 90. Salt was given to 134/152 (88.2%) infants at initial discharge, and 124/145 (85.5%) at Day 90.

Biochemical surveillance

Hyponatremia, hyperkalemia, and hypoglycemia occurred in 103/147 (70.0%), 105/146 (71.9%), and 20/145 (13.0%) infants, with peak severity at median ages of Day 12 (6, 37) at 129.3 (117, 134) mmol/L, Day 13 (5, 31) at 6.9 (5.5, 8.7) mmol/L, and Day 1 (0, 35.8) at 1.9 (0.6, 2.8) mmol/L, respectively. Hemolysis-related artifactual hyperkalemia could not be determined. All reported hypoglycemia episodes corresponded to blood glucose levels <3.0 mmol/L. Pre-treatment hyponatremia, hyperkalemia, and hypoglycemia occurred in 86/151 (57.0%), 92/154 (59.7%), and 20/145 (13.8%) infants, respectively. At Day 90, hyponatremia was

Table 2 Comparison of infants diagnosed through newborn screening programme (Group A) versus through identification of atypical genitalia (Group B) and presentation with adrenal insufficiency (Group C). *P* values are calculated by comparing against Group A. NBS, newborn screening.

Group A ($n = 56$) Positive NBS	Group B ($n = 55$) Atypical genitalia	Group C ($n = 22$) Adrenal insufficiency	Groups A + B + C ($N = 133$)
Age at presentation			
Day 7 (4, 9)	Day 0 (0, 0) $P < .001$	Day 16.5 (10, 40) $P < .001$	Day 3 (0, 9) $P = .01$
Age at treatment start			
Day 9 (6.25, 11)	Day 6 (4, 9) $P = .01$	Day 15 (10, 33) $P < .001$	Day 8 (5, 12) $P = .50$
Pre-treatment adrenal crisis			
8/56	4/55 $P = .36$	20/22 $P < .001$	32/133 $P = .17$
Post-treatment adrenal crisis			
5/56	7/55 $P = .56$	4/22 $P = .26$	16/133 $P = .62$
Total inpatient hospitalization duration in 90 days			
8 days (0, 21.6)	12 days (2.1, 24) $P = .049$	14 days (2.8, 27.4) $P = .05$	10 days (0.2, 24) $P = .14$
Pre-treatment hyponatremia			
36/56	25/53 (*Unknown—2)* $P = .09$	20/21 (*Unknown—1)* $P = .01$	81/130 (*Unknown—3)* $P = .87$
Pre-treatment hyperkalemia			
36/54 (*Unknown—2)*	30/55 $P = .24$	20/21 (*Unknown—2)* $P = .02$	86/130 (*Unknown—2)* $P = 1$
Pre-treatment hypoglycemia			
6/53 (*Unknown—3)*	7/52 (*Unknown—3)* $P = .78$	4/20 (*Unknown—2)* $P = .45$	17/125 (*Unknown—2)* $P = .81$
Hyponatremia at Day 90			
3/42 (*Unknown—5, not done—9)*	4/35 *(Unknown—11, not done—9)* $P = .70$	1/15 (*Unknown—4, not done—3)* $P = 1$	8/92 (*Unknown—20, not done—21)* $P = 1$
Hyperkalemia at Day 90			
11/38 (*Unknown—9, not done—9)*	8/31 (*Unknown—15, not done—9)* $P = .79$	4/15 (*Unknown—4, not done—3)* $P = 1$	23/84 (*Unknown—28, not done—21)* $P = 1$

reported in 8/108 (7.4%) infants, and hyperkalemia in 28/99 (28.6%) infants amongst whom 6/28 had concomitant hyponatremia.

Infants with Day 90 hyponatremia (vs infants without) had higher fludrocortisone doses at Day 90 (median 175 [100, 200] vs 100 mcg/day [50, 200], $P = .01$) but not at initial discharge ($P = .23$). They also had higher salt doses at initial discharge (median 6.9 [3, 13.6] vs 3 mmol/kg/day [1.5, 6.7], $P < .01$) and Day 90 (median 3.9 [2.7, 5.9] vs 2 mmol/kg/day [0.6, 4.6], $P < .01$). Comparing both groups, there were no significant differences in initial discharge and Day 90 relative hydrocortisone ($P = .65$ and $P = .90$, respectively), ED-HC ($P = .99$ and $P = .54$, respectively), and ED-FC ($P = .18$ and $P = .07$, respectively) doses.

Infants with Day 90 hyperkalemia (vs infants without) had lower initial discharge relative hydrocortisone (median 14.3 [11.0, 34.1] vs 20.8 mg/m^2/day [12, 45.5], $P = .01$) and ED-HC (median 21.5 [17.5, 38.4] vs 27.1 mg/m^2/day [16.2, 51.6], $P = .03$) doses, and lower Day 90 relative hydrocortisone doses (median 12.5 [7.6, 24.1] vs 16.6 mg/m^2/day [9.5, 24.2], $P = .02$). Comparing both groups, there were no significant differences in Day 90 ED-HC doses ($P = .17$), and initial discharge and Day 90 absolute fludrocortisone ($P = .22$ and $P = .19$, respectively) and ED-FC ($P = .93$ and $P = .44$, respectively) doses.

Blood pressure (BP) monitoring

Day 90 BP was not reported in 107/154 (69.5%) infants. Amongst 47/154 (30.5%) infants with reported measurements, 15 (31.9%) had systolic and/or diastolic BP >95th centile for age and sex.[20] Day 90 systolic BP correlated positively with Day 90 absolute fludrocortisone ($r = 0.23$, $P = .02$) and ED-FC ($r = 0.32$, $P = .03$) doses but not with relative hydrocortisone ($P = .42$), ED-HC ($P = .72$), and salt ($P = .18$).

Weight at day 90

At Day 90, median weight was 5845 (4,544, 7136) grams, and weight SDS was −0.2 (−1.9, 1.8) with no significant difference

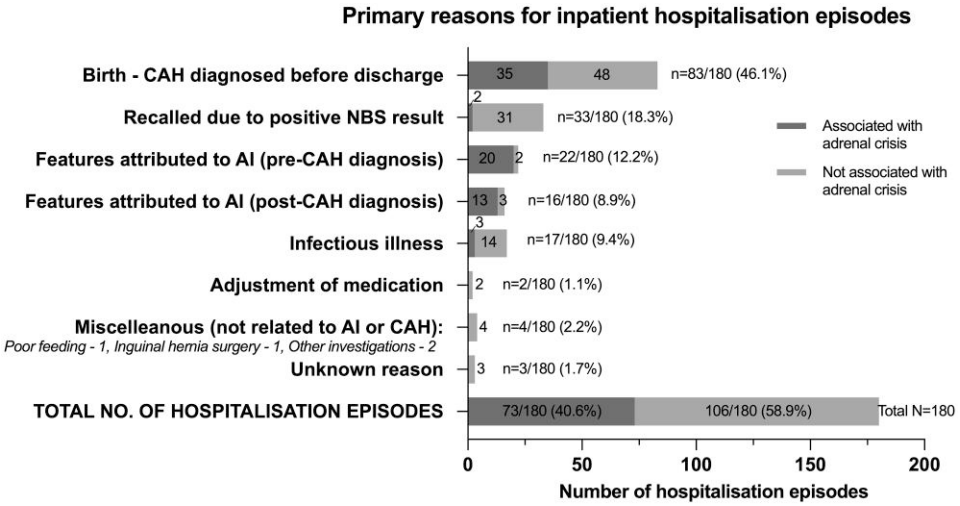

Figure 2 Primary reasons for inpatient hospitalization episodes. There were a total of 180 unique hospitalization episodes over the first 90 days of life in 154 infants. The proportion of these hospitalization episodes due to each primary hospitalization reason, are reported. For each primary hospitalization reason, the proportion of hospitalization episodes associated with adrenal crises are shown.

from birthweight SDS ($P = .80$). No differences were observed in delta weight SDS (difference between birthweight and Day 90 weight SDS) and Day 90 weight SDS, between infants with and without Day 90 hyperkalemia ($P = .05$ and $P = .24$, respectively) and also between infants with and without Day 90 hyponatremia ($P = .91$ and $P = .45$, respectively).

Initial discharge and Day 90 doses of hydrocortisone, ED-HC, fludrocortisone and ED-FC, did not correlate with delta weight SDS or Day 90 weight SDS. There was however, weak negative correlations of salt doses at initial discharge ($r = -0.20$, $P = .04$) and Day 90 ($r = -0.36$, $P < .001$) with delta weight SDS, and of Day 90 salt doses with Day 90 weight SDS ($r = -0.24$, $P = .01$).

Newborn screening program (NBS)

Of 33 centers, 24 (72.7%) participated in a regional or national CAH NBS program. Of 99 infants (48 male, 51 female) from these centers, 56 (56.6%) were diagnosed through NBS (remaining diagnosed before result notification). A larger proportion of males than females were diagnosed through NBS (40/48 vs 16/51, $P < .001$). In all NBS-screened infants, median ages at sampling and result notification were Day 2.5 (2, 6) and Day 7 (3, 14), respectively, with turnaround time of 4 days (1, 10.4). Median age at formal biochemical confirmation was Day 7 (2,30).

We compared infants whose primary mode of presentation was positive NBS (Group A), versus atypical genitalia (Group B) and AI (Group C) (Table 2). Group A presented and started treatment later than Group B ($P < .001$ and $P = .01$, respectively) but earlier than Group C ($P < .001$ and $P = .00032$, respectively). Group A had a similar proportion of pre-treatment adrenal crisis at presentation to Group B, but lower than Group C ($P < .001$); however, post-treatment adrenal crisis rates were similar across groups.

Group A had shorter total hospitalization duration in the first 90 days than Group B ($P = .049$), and similar to Group C. Group A had similar proportions of patients with pre-treatment hyponatremia and hyperkalemia to Group B but lower than Group C ($P = .01$ and $P = .02$, respectively). There were no differences for hypoglycemia. At Day 90, there were no significant differences in proportions of patients with hyponatremia and hyperkalemia in Group A vs Group B and Group C.

Hospitalization (Figures 2 and 3)

There were 180 inpatient hospitalization episodes (median 1 [0.5, 2] episode/patient), with 73 (40.6%) associated with adrenal crises. Median cumulative hospitalization duration was 9 days (2, 24). Of 33 episodes due to positive NBS recalls, 2 involved adrenal crisis, vs 20/22 episodes due to pre-treatment AI ($P < .001$).

Multi-disciplinary team (MDT) involvement (Figure 4, Table 3 and Figures 5A & 5B)

By Day 90, 142/148 (95.9%) cases had medical team contact with a pediatric endocrinologist. Median age at first contact was Day 8 (1.2, 29). Median time taken from presentation to contact was 2 (0, 19.2) days, and from diagnosis to contact 0 (−2, 8) days.

By Day 90, 44/132 (33.3%) cases had contact with a psychologist. Median age at first contact was Day 8.5 (0.5, 51.5). Median time taken from diagnosis to contact was 2 (−2.7, 42.4) days. Psychologist contact was more frequent in females than males (35/79 vs 9/53, $P = .0013$), and similar time was taken from diagnosis to contact between both sexes (median 2 [−2.6, 42.2] vs 5 [−6, 55] days, $P = .98$).

By Day 90, 56/133 cases (42.1%) had contact with a pediatric endocrine nursing specialist (PENS). Median age at first contact was Day 9 (2.7, 42.5) and time taken from diagnosis to contact was 1 (−2, 24) day. There was no significant difference in proportion of patients with post-treatment adrenal crises between those with and without PENS contact by Day 90 (5/56 vs 6/77, $P = 1$).

By Day 90, 35/147 cases (23.8%) had contact with a surgeon, all of whom were female. Median age at first consultation was Day

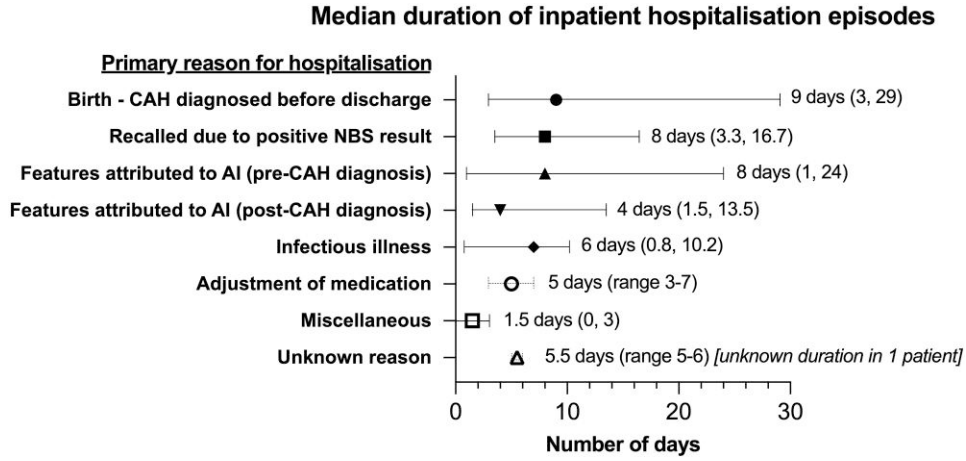

Figure 3 Median hospitalization duration over the 90 days period according to each primary hospitalization reason. Median values (represented by the small shapes) are provided with 10th and 90th centiles (unless otherwise stated).

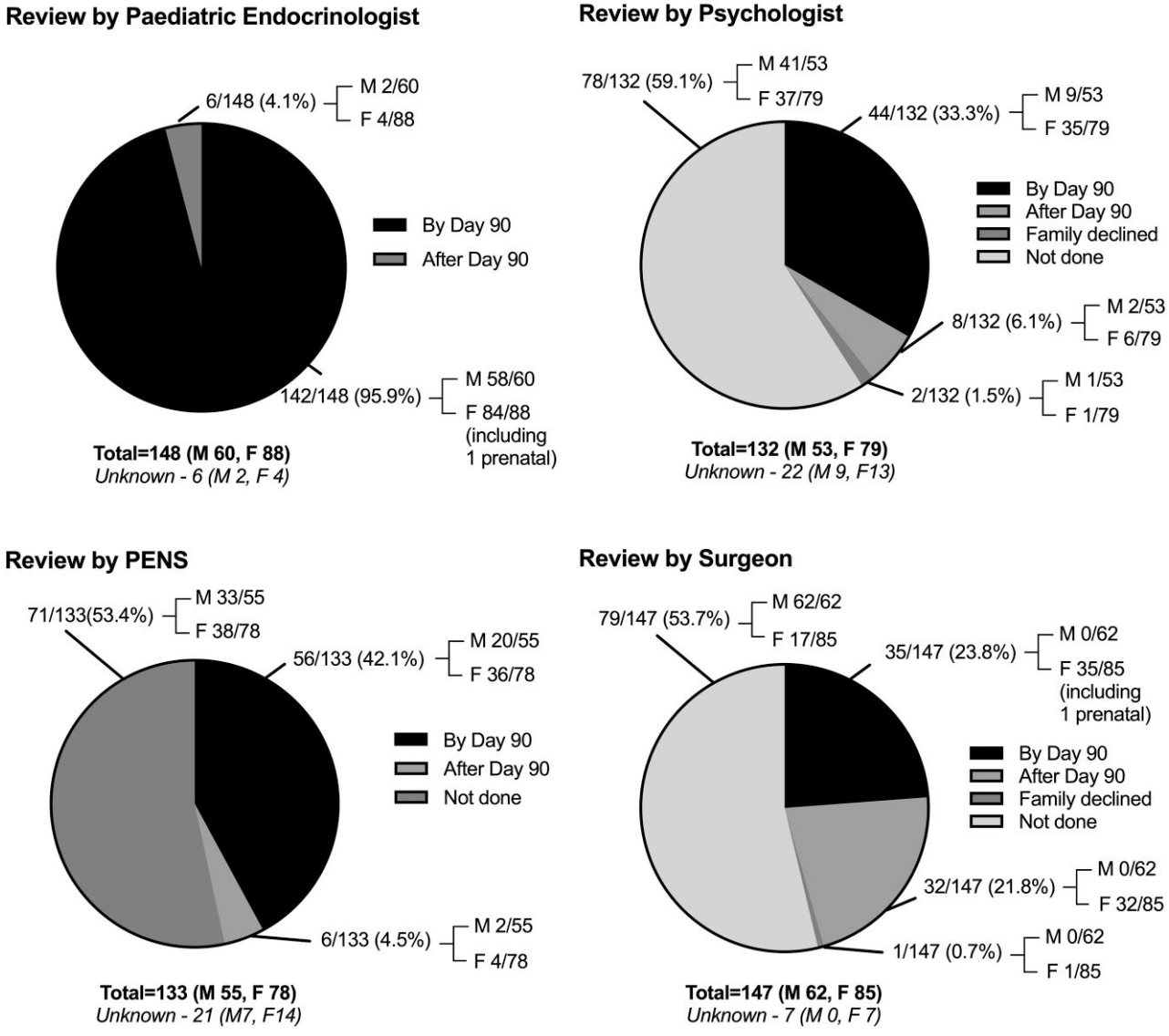

Figure 4 MDT involvement according to each MDT professional.

Table 3 Timings of MDT contact in patients with contact by Day 90 of life. Age at first contact, time taken from presentation to contact, and time taken from diagnosis of CAH to contact, are given. *P* values (in italics) are calculated by comparing data in males versus females. Median values are provided with 10th and 90th percentiles. MDT, multidisciplinary team; M, male; F, female; PENS, pediatric endocrine nurse specialist.

Review by MDT member	In patients with MDT contact by Day 90									
	Median age at first contact (Day of life, D)			Median time taken from presentation to contact (days, d)			Median time taken from diagnosis to contact (days, d)			
	M & F	M	F	M & F	M	F	M & F	M	F	
Pediatric Endocrinologist	D8 (1.2, 29) *P* < .01	D9 (3.9, 39.1)	D6 (1, 28.6)	2d (0, 19.2) *P* < .001	1d (0, 11.2)	3d (0, 28)	0d (−2, 9.2) *P* = .42	0d (−2.4, 7.4)	0d (−2, 10.2)
Psychologist	D8.5 (0.5, 51.5) *P* = .63	D6 (0, 61)	D9 (1, 51.2)		n/a		2d (−2.7, 42.4) *P* = .98	5d (−6, 55)	2d (−2.6, 42.2)
PENS	D9 (2.7, 42.5) *P* = .27	D15.5 (1.3, 52.7)	D9 (2.8, 46.2)		n/a		1d (−2, 24) *P* = .72	1d (−3.9, 27.4)	1.5d (−0.3, 24)
Surgeon	D11 (0.5, 83)	n/a	D11 (0.5, 83)		n/a		8d (−2.4, 78.9)	n/a	8d (−2.4, 78.9)

11 (0.5, 83), and time taken from diagnosis to contact was 8 (−2.4, 78.9) days. These cases constituted 35/85 (41.2%) females in our cohort; in the remaining 50 females (32 had surgical contact after Day 90, 18 had no contact by study date), distribution of genital virilization was "normal female" 4/50, Prader I 5/50, Prader II 9/50, Prader III 15/50, Prader IV 10/50, and Prader V 5/50 (unknown 2/50).

Figure 4 and Table 3 show the breakdown of MDT contact by patient sex. Figures 5A and 5B shows timings of MDT contact.

Geographical setting

Compared to UMIC and LMIC, infants from HIC had higher proportions with postnatal genetic confirmation by Day 90 (53/97 vs 0/39, $P < .001$) and access to a national or regional NBS program (87/113 vs 12/41, $P < .001$), and lower proportions with adrenal crisis in the first 90 days (27/113 vs 20/41, $P = .01$) and pre-treatment adrenal crisis (19/113 vs 15/41, $P = .02$). They also had lower proportions of pre-treatment hyperkalemia (59/107 vs 33/39, $P < .01$), Day 90 hyponatremia (3/82 vs 5/26, $P = .02$), and Day 90 hyperkalemia (13/83 vs 13/26, $P < .01$). They had higher delta weight SDS (median 0 (−1.1, 1.4) vs −0.7 (−3.1, 0.9), $P < .01$) and Day 90 weight SDS (median 0.19 (−1.7, 1.8) vs −0.8 (−3.4, 0.9), $P < .001$). They had more frequent contact by Day 90 with a surgeon (16/32 vs 2/20, $P = .01$), PENS (51/93 vs 5/41, $P < .001$), and psychologist (39/89 vs 5/41, $P < .001$).

Additionally, HIC infants at initial discharge and Day 90 had higher relative hydrocortisone ($P < .001$ and $P < .001$, respectively) and ED-HC ($P < .001$ and $P < .01$, respectively) doses, but lower salt doses ($P < .001$ and $P < .001$, respectively). They also had a higher proportion with Day 90 hypertension ($P = .01$).

Discussion

This is the first international multi-center study describing real-world early infancy management of 21-OHD CAH.

We observed wide variation in treatment doses and regimens. Although relative hydrocortisone doses decreased from discharge to Day 90, absolute doses remained similar, suggesting weight-based dose adjustments were uncommon. Most infants received >15 mg/m^2/day, exceeding the recommended 10-15 mg/m^2/day,[4] possibly reflecting clinicians' prioritization of achieving rapid biochemical stability and/or avoiding adrenal crises in the initial post-diagnosis period, and limited availability of low-dose (<5 mg) formulations. Although high doses in infancy are associated with impaired growth,[16, 21] we found no clear relationship between dose and weight gain over the first 90 days (linear growth not assessed). Given the common practice of higher dosing in early infancy, existing guidelines may require tailoring for this period.

Aligning with recommendations,[4] glucocorticoid replacement was predominantly administered as hydrocortisone, given 3 or 4 times daily, and in equal doses. This reflects the understanding that diurnal variation of cortisol only develops from 2-3 months old, possibly also explaining increased use of circadian rhythm regimens at Day 90. Reverse circadian dosing was uncommon. The optimal dosing strategy is unclear,[22, 23] although higher

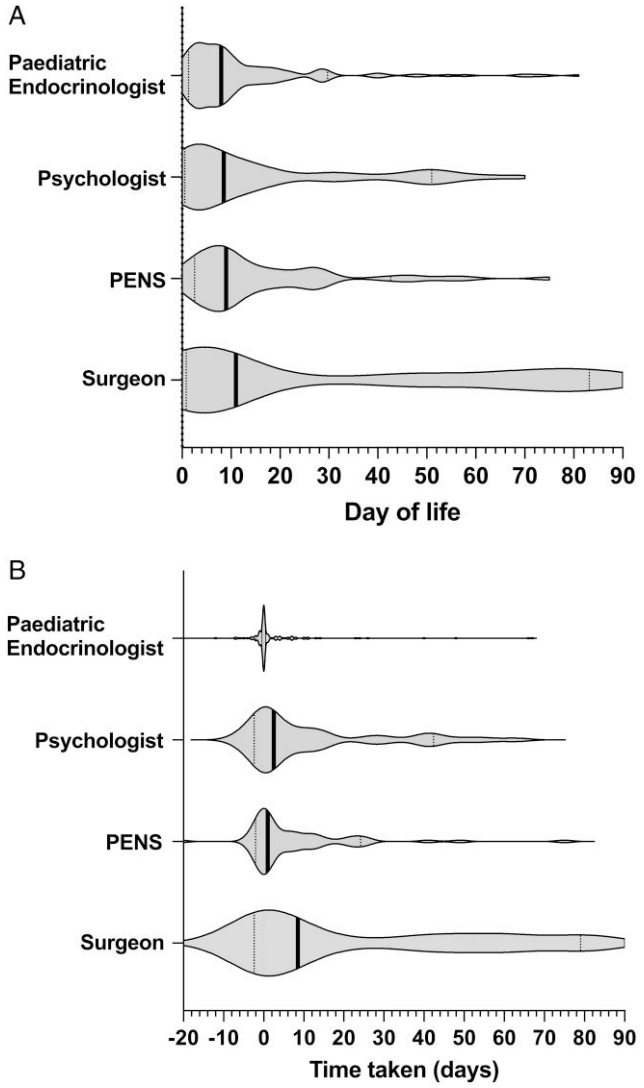

Figure 5 A: Violin plot showing distribution of patient age at MDT professional contact in the first 90 days of life. B: Violin plot showing distribution of time taken from CAH diagnosis to contact by MDT professional in the first 90 days of life. For Figures 5A and 5B, both male and female subjects are combined for calculation. Median values are represented as solid bold lines, and 10th and 90th centiles are represented as faint dotted lines.

evening plasma cortisol levels are associated with metabolic disturbances in older patients.[22]

Fludrocortisone was typically prescribed at 50-200 mcg/day, once or twice daily, consistent with recommendations.[4] However, 4.6% of infants received >200 mcg/day at discharge. We found a weak but significant positive correlation of fludrocortisone doses (and particularly ED-FC) with systolic BP at Day 90, highlighting potential hypertensive effects even in infancy. Yet, only one-third of infants had BP measurements recorded at Day 90, suggesting surveillance gaps. However, we acknowledge that measuring BP in non-compliant infants may be unreliable, potentially contributing to under-recording. Given that sensitivity to fludrocortisone increases rapidly during infancy, and the recognized association of early childhood hypertension from high mineralocorticoid doses in 21-OHD,[15, 16] improved BP monitoring is warranted to guide dosing.

- Medical team contact with Paediatric Endocrinologist: By 2 days from presentation and same day of diagnosis
- Family contact with Psychologist: By 2 days from diagnosis
- Family contact with PENS: By 1 day from diagnosis

Figure 6 Suggested benchmark standards for MDT involvement in 21-OHD CAH, including timing of review. These are derived from the median of data submitted (as illustrated in Figures 5A and 5B).

Salt supplementation practices varied, echoing previous studies.[16, 24] At discharge, 87.0% of infants were salt-supplemented, dropping to 80.5% at Day 90, reflecting variable salt-wasting severity or institutional practices. Whilst supplementation may reduce hydrocortisone and fludrocortisone needs,[16] benefits on early growth remain unclear.

Biochemical abnormalities were frequent, generally within the first 2 weeks postnatally and pre-treatment. At Day 90, hyperkalemia remained common (28.6%). Medication non-compliance or hemolysis-related artefactual elevation (from difficult venipuncture) could be contributory. Nonetheless, clinicians may possibly "tolerate" mild hyperkalemia when normonatremia is maintained. These findings underscore the importance of biochemical surveillance to tailor dosing.

NBS was associated with favorable outcomes: fewer pre-treatment adrenal crises, earlier diagnosis and treatment, and lesser pre-treatment hyponatremia and hyperkalemia, versus infants presenting with AI. While previous studies reported shorter hospitalizations,[25, 26] we found no difference, possibly due to differing definitions of hospitalization stay. Although males would logically benefit most from NBS, a substantial proportion of females (16/92) were also diagnosed through NBS, likely due to mild and/or unrecognized virilization.[27] This finding is supported by Dutch data showing 38% of females with salt-wasting CAH were only detected through NBS.[28] Some cases may also represent non-classical CAH. Regardless, our findings support NBS use in both sexes to avoid delayed diagnosis with potentially life-threatening AI.

Median age at positive NBS result notification was over a week earlier than AI presentation (Day 7 vs 16.5). Even the 90th centile age at positive NBS result notification (Day 9) preceded the 10th centile age at AI presentation (Day 10), underscoring NBS utility in early CAH identification. These findings advocate for maintaining/improving NBS turnaround times, with our proposed benchmark of positive notification before Day 10.

Infants were hospitalized more than once on average, and adrenal crises remained common even post-treatment. While low admission thresholds during infancy may be justified, resource targeting (eg, family education, steroid emergency cards) may help reduce adrenal crises and hospitalization,[29] easing pressures on healthcare systems.

A multi-disciplinary approach in CAH management improves patient outcomes.[4, 30] We therefore propose benchmark standards for MDT involvement derived from median data values across centers (Figure 6), as benchmarking promotes quality improvement through identifying best practices and standardizing processes.[31] Nonetheless, access to complete MDTs may vary, particularly in resource-limited settings, and care must be balanced with local resources and feasibility.[32] In such contexts, practical strategies may

help maximize available care, including enhanced healthcare provider training in the recognition of atypical genitalia to facilitate timely diagnosis, and use of telemedicine to allow local teams to collaborate with specialist teams. Improving medication compliance, for example through culturally tailored caregiver education, may further optimize CAH management, even where resources are limited.[33]

Psychology input was more frequent in females, possibly reflecting perceptions that 46,XY CAH lacks psychological impact given the absence of atypical genitalia. This assumption is increasingly challenged as families may still experience daily routine disruption from intensive medication regimes, and worry about CAH affecting their child's future.[34] When psychology input occurred, timing was similar across sexes, suggesting clinicians' referral urgency was not sex-dependent.

While early feminizing surgery in CAH is controversial,[35] timely but non-urgent surgical consultation allows shared decision-making and time for medical treatment effects on the genitalia. Crucially, surgery should only be performed in centers with specialist expertise.[36]

Infants from HIC had earlier genetic confirmation, better access to NBS programs, earlier surgical, psychological and PENS input, and fewer Day 90 electrolyte abnormalities, likely reflecting better healthcare access. Despite fewer pre-treatment adrenal crises, post-treatment rates were similar to UMIC and LMIC infants, suggesting comparable effectiveness in illness management. This echoes previous findings showing no income-based differences in adrenal crisis rates in children.[11]

Limitations

This study has several limitations. The definition of "adrenal crisis" may be subjective, risking under-/over-reporting. Data on medication formulations (eg, liquid, tablets), which may affect treatment accessibility and dosing, were not collected. Initial discharge doses may not always reflect maintenance doses, particularly in centers where high stress doses are prescribed initially and then reduced after discharge. Hormonal markers (eg, renin, 17-hydroxyprogesterone) were excluded from analysis due to incomplete data and assay variability, although these may have clarified treatment adequacy. Healthcare systems differences may influence use of outpatient care, potentially reducing hospitalization. The relatively small number of UMIC and LMIC limits full socioeconomic representation. Retrospective data collection risks potential bias due to incomplete or missing data. These limitations highlight the need for prospective studies and expanded global participation to better capture CAH care variations and outcomes.

Conclusions and recommendations

Overall, our study offers several novel insights. Analysis of real-world I-CAH Registry data reveals wide variation in early infancy CAH management. Hydrocortisone and fludrocortisone doses frequently exceeded current, non-age-specific international recommendations for pediatric patients.[4] Our findings support refining of age-tailored guidance reflecting realities of clinical practice, including dose ranges, dosing schedules, BP surveillance, and MDT provision. Higher hydrocortisone doses may not immediately translate to excessive weight gain (although clinicians should remain mindful of long-term effects on growth and metabolism), hence short-term weight changes may be an unreliable marker of over-treatment in early infancy. Additionally, relying solely on absolute fludrocortisone doses may risk overtreatment; instead, relative fludrocortisone doses (in mcg/m^2) could guide dose adjustment (although BSA calculations in infancy may lack precision).[10] As hypertension and hyperkalemia were frequently reported, careful BP and biochemical surveillance is required, alongside regular medication dose review.

Our findings reinforce support for including CAH in NBS programs, and highlight persistent disparities between high- and low-/middle-income countries, underscoring the need for more equitable care. Finally, we demonstrate the I-CAH Registry's role not only for research, but also in developing clinical benchmarks to inform quality improvement and standardization of care for infants with CAH worldwide.

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Authors' contributions

David BN Lim (Conceptualization [equal], Data curation [lead], Formal analysis [lead], Investigation [equal], Methodology [lead], Project administration [lead], Writing—original draft [lead], Writing—review & editing [equal]), Jillian Bryce (Data curation [supporting], Project administration [supporting], Resources [supporting]), Salma Ali (Project administration [supporting], Writing—review & editing [equal]), Xanthippi Tseretopoulou (Investigation [equal], Writing—review & editing [equal]), Niels BirkebC3A6k (Investigation [equal], Writing—review & editing [equal]), Sabine E. Hannema (Investigation [equal], Writing—review & editing [equal]), Ariadna Campos-Martorell (Investigation [equal], Writing—review & editing [equal]), Maria Clemente (Investigation [equal], Writing—review & editing [equal]), Uta Neumann (Investigation [equal], Writing—review & editing [equal]), Christa Flueck (Investigation [equal], Writing—review & editing [equal]), Sara Metzger (Investigation [equal], Writing—review & editing [equal]), Ruth Krone (Investigation [equal], Writing—review & editing [equal]), Alina German (Investigation [equal], Writing—review & editing [equal]), Federico Baronio (Investigation [equal], Writing—review & editing [equal]), pascal barat (Investigation [equal], Writing—review & editing [equal]), Marine Delagrange (Investigation [equal], Writing—review & editing [equal]), Vanessa Vautier (Investigation [equal], Writing—review & editing [equal]), Ana Vieites (Investigation [equal], Writing—review & editing [equal]), Rodolfo Rey (Investigation [equal], Writing—review & editing [equal]), Heba Elsedfy (Investigation [equal], Writing—review & editing [equal]), Navoda Atapattu (Investigation [equal], Supervision [supporting], Writing—review & editing [equal]), Sumudu *N* Seneviratne (Investigation [equal], Writing—review & editing [equal]), Martine Cools (Investigation [equal], Writing—review & editing [equal]), Tülay Gran (Investigation [equal], Writing—review & editing [equal]), Zehra Yavas Abalı (Investigation [equal], Writing—review & editing [equal]), Antony Fu (Investigation [equal], Writing—review & editing [equal]), Dominika Janus (Investigation [equal], Writing—review

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Conflict of interest

The authors declare no relevant competing interests.

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Data availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available, but may be available from the corresponding author on reasonable request.

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