NEWSLETTER
SEP-OCT 2024
Volume 28 - Issue 4

CAPE News

Newsletter of
The Indian Society for Pediatric and Adolescent Endocrinology (ISPAE)

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EDITOR'S MESSAGE

Dear Readers,

We present this issue of CAPE News on Adrenal disorders and DSD. This issue is being released as September-October issue to accommodate the successful APPES-ISPAE joint meeting at New Delhi in October 2024. We have included learning points from serially conducted meetings, most of which covered adrenal disorders. This issue also presents glimpses of the APPES-ISPAE meeting which briefly describe the academic feast that we witnessed. The award section proudly mentions a few laurels that our members have duly earned.

The last few months have kept most of us occupied with additional professional commitments. The tragic incident at RG Kar Medical College in August 2024 united the voices of resident doctors, senior professionals and the public across India. We strive to stay united and keep working to the best of our abilities till justice is served.

The next issue will be on **Water and Electrolyte disturbances** that will also be the last issue of the present editorial team.

November is Diabetes Awareness month. We look forward to accommodate inspiring activities on World Diabetes Day by our enthusiastic hardworking members in the last issue.

Keep learning and shining!

Best wishes,

Aashima Dabas

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MESSAGE FROM THE ISPAE PRESIDENT

Dear Friends,

It is a pleasure to write this message after the successful completion of the APPES-ISPAE Joint Meeting 2024 at New Delhi. The enormous effort of Dr Rajesh Khadgawat, Dr Anju Seth, Dr Rakesh Kumar, Dr Ravindra Kumar and Dr Jaivinder Yadav, and the Local Organizing Committee bore fruition in the success of the meeting. The Executive Council of ISPAE is happy to congratulate the team for the grand success of the APPES-ISPAE Joint Meeting 2024.

The Council is pleased to announce the release of educational modules on type 1 diabetes mellitus (T1DM), growth and thyroid. The T1DM module was prepared by the team guided by Dr Aspi Irani along with Dr Rakesh Kumar, Dr Zalak Upadyay and Dr Akanksha Gandhi. The Thyroid module was prepared by the team headed by Dr P Raghupathy along with Dr Mahesh Maheshwari and Dr Amarnath Kulkarni. Dr Vaman Khadilkar has readied the module on growth with Dr Aayush Gupta, Dr Diksha Shirodkar and Dr Anshika Singh. Dr PSN Menon has been kind enough to review the modules. These modules are available at the ISPAE website and can be accessed by all life members of ISPAE to conduct programs for Pediatricians. ISPAE-EC 2023-24 expresses thanks to all the teams for their efforts.

ISPAE-EC 2023-24 feels privileged to announce the establishment of ISPAE Pediatric Diabetes Registry (IPDR). This is an important step in our efforts to consolidate the details of children living with diabetes in our country. The information gained from the registry would be helpful in formulating guidelines and improve the delivery of care to children with T1DM.

The first batch of ISPAE Fellows graduated and students were duly awarded at the recent ISPAE AGM at New Delhi. The next ISPAE Pediatric & Adolescent Endocrinology Fellowship Eligibility Entrance Test (FEET) was also conducted recently. ISPAE is looking towards a great future filled with growth!

ISPAE 2025 will happen at Nagpur from 14-16 November and will be preceded by the Fellows School. We look forward to welcoming all our members at this forthcoming meeting.

Happy Diwali!

Drs Ahila Ayyavoo, Rakesh Kumar, Sirisha Kusuma Boddu & ISPAE-EC 2023-24

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WELCOME NEW ISPAE MEMBERS

Honorary Life Member
Dr Wayne Cutfield, Professor of Pediatric Endocrinology, Liggins Institute, University of Auckland, New Zealand

Life members	
• Dr Rajesh Y Borra, Pondicherry • Dr Shweta Choudhary, Delhi • Dr Muragesh Mathapati, Maharashtra • Dr Nitika Mittal, Uttarakhand • Dr Urvee Swaika • Dr Delhi Kumar CG • Dr Anamika Das	• Dr Anusha Reddy, Assam • Dr Manisha Maurya, UP • Dr Kiran Narayan Kudlikar, Maharashtra • Dr Shipra Mandraha, Madhya Pradesh • Dr Saketh Kadiveti • Dr Nikita Agrawal
Associate members	
• Dr Ayushi Singhal, Uttar Pradesh • Dr Anish Kar, West Bengal • Ms Nikki Dahiya, Haryana • Ms Himani, Delhi • Ms Aruna Sharma, Delhi • Ms Roshni Mary, Kerala • Mr Sabari Krishnan, Kerala • Ms Shajini Joseph, Tamil Nadu • Ms Mridula Bhargava, Delhi	• Ms Amrita Rupani, Delhi • Ms Saranya Ann Issac, Kerala • Ms Simran Bhumra, Maharashtra • Ms Samrin Khan, Maharashtra • Ms Riddhi Modi, Maharashtra • Ms Aruna Devi, Karnataka • Ms Sree Dharshini, Tamil Nadu • Ms Ashna Shaji, Kerala • Mr Muhammed Shameer, Kerala

ISPAE Fellows (First Batch 2024)	Institution
Dr Shagun Mahajan	BJ Wadia Children's Hospital, Mumbai
Dr Kavya Raj	BJ Wadia Children's Hospital, Mumbai
Dr Jayashri MN	JJ Medical College, Davangere
Dr Dhvani Raithatha	Regency CDER, Kanpur
Dr Joewin Monterio	SRCC Children's Hospital, Mumbai
Dr Vibha Yadav	Regency CDER, Kanpur

WINNERS - June 2024 Quiz - CONGRATULATIONS!
1) DR RESHMA M -Assistant Professor, Government Medical College, Alappuzha. 2) DR SUKRUTHA SURANDRAN- Fellow in Pediatric Endocrinology, IGICH, Bangalore 3) DR MOUMITA SAHA- Pediatric Endocrinologist, CMC Vellore

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EUROPEAN SOCIETY OF ENDOCRINOLOGY AND ENDOCRINE SOCIETY: JOINT CLINICAL GUIDELINE MAY 2024: DIAGNOSIS AND THERAPY OF GLUCOCORTICOID-INDUCED ADRENAL INSUFFICIENCY

Tejasvi Sheshadri, Consultant Pediatric Endocrinologist, Rainbow Children's Hospitals, Bangalore

Glucocorticoids (GC) remain the cornerstone of therapy in treating a wide array of medical conditions, ranging from autoimmune diseases and inflammatory disorders to severe allergic reactions, and are used through multiple modes of administration (oral, inhaled, intranasal, intra-articular, topical, and intravenous). Suppression of the hypothalamic-pituitary-adrenal (HPA) axis is an inevitable effect of chronic exogenous GC therapy. GC inhibit the production of corticotropin-releasing hormone by the hypothalamus and adrenocorticotropic hormone by the pituitary gland. Detailed education, prompt diagnosis and management of GC-induced adrenal insufficiency (AI) is recommended.

RECOMMENDATIONS

1) Clinicians who initiate treatment with GC need to educate patients about various endocrine aspects of GC therapy as good clinical practice.
2) In patients on short-term GC therapy of less than 3-4 weeks, tapering of GC is not required, irrespective of the dose: they can be stopped without testing, due to the low possibilityof HPA axis suppression.
3) For patients on long-term GC therapy, tapering should only be attempted if the underlying disease for which GC were prescribed is controlled, and they are no longer required. In these cases, GC are tapered tilla level close to the physiologic daily dose equivalent is reached.
4) GC withdrawal syndrome may occur during GC taper. When the withdrawal syndrome is severe, the dose can be temporarily increased to the most recent one that was tolerated, and the duration of taper increased.
5) Routine testing for AI in patients on supraphysiologic doses of GC is not recommended.
6) Patients taking long-acting GC (e.g., dexamethasone or betamethasone) should be switched to shorter-acting GC (e.g., hydrocortisone or prednisone) when long-acting GC are no longer needed.
7) Patients on a physiologic daily dose equivalent and aiming to discontinue GC, should continue to gradually taper the GC dose, while being monitored clinically for signs and symptoms of AI.
8) If confirmation of recovery of the HPA axis is desired, morning serum cortisol is recommended as the first test. The value of morning serum cortisol should be considered as a continuum, with higher values more indicative of HPA axis recovery.
    a. Cortisol >300 nmol/L or 10 µg/dL indicates recovery of the HPA axis:GC can be stopped safely.
    b. Cortisol between 150-300 nmol/L or 5-10µg/dL suggests the physiologic GC dose should be continued, and the test repeated after a few weeks to months.
    c. Cortisol <150 nmol/L or 5 µg/dL suggests the physiologic GC dose should be continued, and the morning cortisol retested after a few months.

9) Routine dynamic testing for diagnosing AI in patients tapering or stopping GC therapy is not recommended.

10) Awareness of possible GC-induced AI is important in patients with
   a. Current or recent use of non-oral GC formulations, presenting with signs and symptoms indicative of AI,
   b. Using multiple GC formulations simultaneously,
   c. Using high-dose inhaled or topical GC,
   d. Using inhaled or topical GC for >1 year,
   e. Received intra-articular GC injections in the previous 2 months, or
   f. Receiving concomitant treatment with strong cytochrome P450 3A4 inhibitors.

11) Patients with current or previous GC treatment presenting with signs and symptoms of exogenous Cushing syndrome are assumed to have GC-induced AI.

12) Fludrocortisone is not recommended in patients with GC-induced AI.

13) Patients with current or recent GC use who have not undergone biochemical testing to rule out GC-induced AI, should receive stress dose coverage when they are exposed to stress.

14) Oral GC should be used in case of minor stress, and when there are no signs of hemodynamic instability or prolonged vomiting or diarrhea.

15) Parenteral GC should be used in case of moderate to major stress, procedures under general or regional anesthesia, procedures requiring prolonged avoidance or inability of oral intake, or when there are signs of hemodynamic instability or prolonged vomiting or diarrhea.

16) Patients with current or recent GC use who have not undergone biochemical testing to rule out GC-induced AI, and present with hemodynamic instability, vomiting, or diarrhea, should be considered to be in a state of adrenal crisis, irrespective of the GC type, mode of administration, and dose. Patients with suspected adrenal crisis should be treated with parenteral GC and fluid resuscitation.

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DISORDERS OF SEXUAL DEVELOPMENT A PEDIATRIC SURGEON'S PERSPECTIVE

Aneesh Shah, Consultant Pediatric Surgeon, Surgikids Hospital, Ahmedabad.

Disorders or differences in sexual development (DSD) pose unique medical, surgical, social and emotional challenges, and require multidisciplinary care involving pediatrician, pediatric endocrinologist, pediatric surgeon, psychologist, geneticist, and gynecologist. It is the responsibility of the pediatric surgeon to counsel the caregivers regarding surgical interventions required through the lifespan of the child and the potential consequences of any such surgery.

Aims of surgery[1]:

1. Restore functional urogenital anatomy to allow good appearance and future penetrative intercourse. Avoid stigmatization related to abnormal anatomy.
2. Facilitate reproduction when possible.
3. Prevent any potential urinary tract consequences/gonadal malignancies.
4. Avoid fluid/blood accumulation in the vagina/uterus.
5. Avoid late virilization at puberty in 46XY individuals raised as girls or breast development in individuals raised as boys.

DSDs are broadly divided into the following 5 groups, with management discussed accordingly[2]:

A. 46,XX DSD

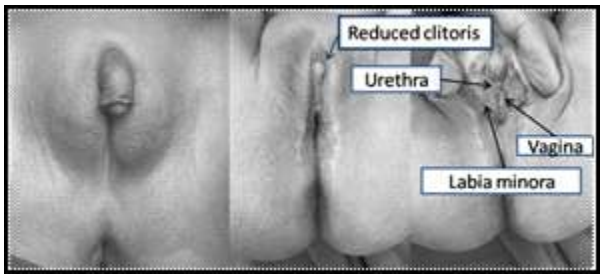
It comprises most commonly of congenital adrenal hyperplasia (CAH) leading to variable degree of virilization in a 46XX fetus. Generally, gender assignment is not a problem, except in cases of severe virilization and/or late presentation.

Genital anatomy:

- Hypertrophy of the genital tubercle (GT) occurs, along with an increased length of the urethra. Urethral opening is situated ventrally.
- Urogenital sinus - the vaginal cavity opens into the posterior wall of the urethra at a variable distance from the bladder neck. It is not higher than where the verumontanum is normally located in the male urethra. The degree of urethro-vaginal confluence is NOT related to the degree of external virilization.
- Labioscrotal folds show variable degrees of fusion, ranging from an almost feminine vulva, to a complete scrotum-like appearance.

46XX CAH raised as a girl:

- Cystogenitoscopy is done to mainly to assess the height of the confluence and understand the genital anatomy.
- Clitoral reduction is restricted to only when the clitoris is significantly enlarged, and only undertaken after adequate hormonal replacement, since suppressing androgens does lead to reduction in size. It consists of reducing the length, while preserving the nerves and vessels leading to the clitoris. Degloving is done and the corpora cavernosa removed; the clitoral head is reattached to the corporeal stumps near the lower edge of the pelvis. It is an irreversible procedure, requiring utmost care in preserving the neurovascular bundle to maintain clitoral sensitivity.



- The timing of vaginoplasty is debated. Vaginoplasty in the same sitting has certain advantages, like avoidance of potential complications of confluence e.g. UTIs, obstruction of menstrual flow, use of excess urogenital sinus tissue to reconstruct the anterior vaginal wall, parental relief, and better healing in younger children. Factors in favor of delaying mainly include unknown gender identity of the child, risk of lifelong complications like vaginal stenosis and loss of clitoral sensitivity, and limited evidence of outcomes. In our practice, after full counseling of the family, vaginoplasty is done in same sitting in Prader III and IV cases. In cases of high confluence, vaginoplasty is usually delayed till puberty, unless the child presents with frequent UTIs.
- The wall of the urogenital sinus is used for creating a mucosa-lined vestibule.
- The skin of the shaft of the clitoris is refashioned as labia minora, and the labia majora are pulled down by YV plasty to create normal looking and functional female genitalia.
- Vaginal dilatations are NOT done until puberty. In a few cases,introitoplasty (cutback procedure) is required at puberty.

B. 46,XY DSD[3]: It is most variable. It includes

Abnormal androgen synthesis (commonly 17βHSD type 3 deficiency, 5α reductase deficiency, CAH with underproduction of testosterone). When gender assignment is male at birth, treatment is similar to severe hypospadias correction. Testosterone is given before the surgery to increase the size of the phallus and preputial skin. Repair is done on the principles of Braka/Byars staged surgery. In the first stage, chordee correction is done and inner preputial graft is placed. Urethroplasty is done in the second stage. Orchiopexy can be done in the same sitting.

In children reared as females, pubertal virilization is common, with diagnosis of DSD at puberty. In such cases, the decision of gonadectomy is extremely delicate, and should be undertaken only after thorough evaluation of the person's gender identity and wish. Risk of gonadal tumor is not high, and is the same as in undescended testes.

Androgen insensitivity: *Complete*: Gender assignment is female, vaginoplasty is sometimes necessary to create a vaginal cavity if vaginal dilatations are not successful. Testes are usually left in the abdomen until puberty, to allow for breast development, since risk of malignancy is low.

Partial: Gender identity is uncertain. Decisions on surgical management may be based on the response of the phallus to testosterone therapy: male gender-of-rearing is appropriate for those who respond to testosterone. The other approach is to delay any surgical correction tillthe child is old enough to understand gender identity and to give consent. Laparoscopic orchiopexy should be early in such cases.

Defects in gonadal development (gonadal dysgenesis (GD)): In complete GD, gender of rearing and genitalia are female. Gonadectomy should be done as soon as the diagnosis is made. In partial GD, the treatment depends on the gender of rearing. The decision to do gonadectomy depends on naked eye exam and biopsy results. Orchiopexy should be done

as soon as possible if neither testis shows dysgenesis. Mullerian structures may be retained if not causing symptoms like dysuria, pain etc., because the vas is in close proximity and it is difficult to separate without causing injury.

Disrupted Mullerian inhibition (Persistent Mullerian Duct syndrome): This is not associated with male gender assignment difficulty; being usually diagnosed during the work-up for undescended testes. The child bears Mullerian remnants; testes may be intraabdominal, or herniating as inguinal hernia. Orchiopexy is done as early as possible, with care to prevent damage to Wolffian duct structures, to maximize the potential of fertility. Mullerian remnant may be retained if there are no symptoms, since the chances of malignancy in Mullerian remnants are very low.

C. **Sex chromosome DSD** (Mixed gonadal dysgenesis(MGD) 45,X/46XY mosaicism): Most individuals with MGD have male gender identity. Surgical interventions are then directed at preoperative testosterone treatment and hypospadias correction. The 'testis' is usually scrotal or brought down, and the streak gonad is removed. A scrotal gonad needs careful follow-up,with a biopsy done after puberty.

D. **Ovotesticular DSD:** Poses unique challenges,with surgical interventions driven by the assigned gender. Often, surgical intervention on external genitals may be delayed until the child is old enough to understand gender perception.

E. **Non-hormonal/non-chromosomal DSD:** Mainly represented by anomalies of the caudal extremity e.g. cloacal extrophy, extrophy bladder, penile agenesis etc. They require complex surgical procedures and outcome may not be very satisfactory.

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ADRENAL DISORDERS AND HYPERTENSION

Ruchi Shah, Consultant Pediatric Endocrinologist, EndoKids, Ahmedabad

Hypertension (HTN) in children is defined as systolic and/or diastolic blood pressure at or above the 95th percentile, based on the normative distribution by age, sex and height (or ≥130/80 mmHg for age ≥13 years), with 50% due to secondary causes. Endocrine HTN, comprising up to 6%, is most commonly due to adrenal diseases, characterized by overproduction of mineralocorticoids (MC), glucocorticoids (GC) and catecholamines. Non-adrenal endocrine disorders such as excess growth hormone, hypo/hyperthyroidism and hypercalcemia also lead to HTN. In children whom cardiovascular and renal causes of HTN are ruled out, symptoms and signs attributed to HTN and the underlying condition should be assessed in detail, including family history of early HTN. Here is a brief review of adrenal HTN in children. Many of the following conditions present solely with HTN.

Disease	Gene and inheritance	Clinical clues	Diagnostic tools	Management
MC-related HTN				
Primary aldosteronism (PA)[1] – autonomous production of aldosterone [Adrenal adenomas (Conn's syndrome), idiopathic adrenal hyperplasia, ACC]	Somatic KCNJ5 mutations in some	Resistant HTN, polyuria, hypokalemia (not universal), mild hypernatremia	Suppressed PRA (<1 ng/kg/hr), elevated PAC:PRA ratio, dynamic aldosterone suppression tests, CT, AVS as per need	Surgery and/or MC receptor antagonist(MRA) as per the disease, accessibility and patient consent for surgery
Familial Hyperaldosteronism(FH) type I[2] (Glucocorticoid remediable aldosteronism) (GRA)	Chimeric CYP11B1/CYP 11B, AD	Early and severe hyperaldosteronism relieved by treatment with GC; higher risk of cerebral hemorrhage	Genetic testing	Low dose GC enough to suppress ACTH without causing side effects, prednisolone/dexamethasone preferred; alternatively MRA
FH type II	Germline CLCN2, AD	Indistinguishable from PA except for positive family history	Similar to PA + genetic testing	Similar to PA
FH type III	Germline KCNJ5 mutation, AD	Severe early-onset resistant arterial HTN and hypokalemia; massive bilateral adrenal hyperplasia	Similar to PA + genetic testing	Similar to PA
FH type IV	CACNA1H, AD	Early-onset hyperaldosteronism; developmental delay or ADHD in some patients	Genetic testing	Similar to PA
11β-hydroxylase deficiency CAH (11OHD)	CYP11B1, AR	Virilization (female), pseudo-precociouspuberty, sometimes prepubertal gynecomastia (male)	Elevated 17OHP, DOC, 11-deoxycortisol, androgens Germline mutation testing	Physiological replacement of hydrocortisone, MRA if needed
17 β-hydroxylase deficiency CAH(17OHD)	CYP17A1, AR	DSD (male), sexual infantilism, primary amenorrhea (female)	Low/low normal androgens, 17OHP, aldosterone, cortisol; Germline mutation testing	Physiological replacement of hydrocortisone, MRA if needed, induction and maintenance of puberty, fertility concerns
Apparent mineralocorticoid excess (AME) – 11β -hydroxysteroid dehydrogenase type 2 (HSD11B2)	HSD11B2, AR	Severe HTN, Failure to thrive, delayed puberty, polydipsia,polyuria, muscle weakness, nephrocalcinosis, early organ damage	Hypokalemic alkalosis, low renin, low aldosterone; Normal plasma cortisol levels; High urinary cortisol-cortisone ratio	Difficult to treat - MRA with/without K sparing diuretic, Kreplacement, low salt diet

Iatrogenic – fludrocortisone excess	-	Likely given for 21OHD CAH, can lead to severe HTN and end organ damage if not identified	Suppressed renin, aldosterone, hypokalemia	Reduce the offending agent, important to reduce MC dose with age in 21OHD
GC-related HTN				
Cushing syndrome including iatrogenic	--	Weight gain, growth failure, fatigue, round face, proximal myopathy, plethora, hirsutism, buffalo hump, central obesity	Elevated 24-hr urinary free cortisol excretion for 3 days, loss of circadian rhythm of serum cortisol, 1 mg overnight dexamethasone suppression test etc. Imaging as required.	Treat primary pathology, important to provide hydrocortisone cover till recovery of HPA axis
Primary GC resistance[3]	*NR3C1*	Symptoms of GC deficiency with MC excess and hyperandrogenism	Raised cortisol and ACTH, raised PAC:PRA, raised androgens Genetic testing	High doses of MC activity sparing GCs like dexamethasone
Catecholamine-induced HTN				
Pheochromocytoma - catecholamine producing tumor from chromaffin cells of adrenal medulla **Paraganglioma** – from paraganglia of the autonomic nervous system outside of the adrenal medulla. Involving sympathetic nervous system usually secrete catecholamines[4]	RET, VHL, NF1 (mainly pheo) SDHD,SDH, SDHAF2 (mainly paragangliom a) etc	Episodic headache, palpitation, sweating, pallor; Sustained or paroxysmal HTN (60-90%)[3]. Compared with adults, children with catecholamine-secreting tumors have a higher incidence of familial disease, bilateral adrenal tumors, extra-adrenal tumors (paragangliomas), and multiple tumors.	Fractionated plasma or 24-hr urine metanephrines – gold standard. Genetic testing recommended in ALL patients	Surgery – curative. In case of inoperable metastasis/recurrence, chemotherapy may be offered. Preoperative alpha followed by beta adrenergic blockade Post-op volume expansion, SOS ionotropes

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CYCLICAL CUSHING SYNDROME: A REVIEW

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Cyclical Cushing Syndrome (CCS) is a rare variant of Cushing Syndrome (CS) characterized by periodic episodes of hypercortisolism, interspersed with intervals of normal cortisol production. This cyclical pattern can complicate diagnosis and management, often leading to a delay in appropriate treatment.

CS results from prolonged exposure to elevated levels of glucocorticoids, primarily cortisol. This can be due to endogenous overproduction from the adrenal glands, typically driven by a pituitary adenoma (Cushing's disease), ectopic ACTH secretion, or adrenal tumors. In CCS, the fluctuating nature of cortisol levels can be due to episodic secretion of adrenocorticotropic hormone (ACTH) or intermittent adrenal hyperplasia. The exact mechanisms underlying these cyclical patterns are not well understood.

Clinical Presentation: Patients with CCS exhibit classic symptoms of hypercortisolism, including weight gain, central obesity, facial rounding, hypertension, glucose intolerance, and skin changes such as purple striae. However, these symptoms may wax and wane in correlation with the cycles of cortisol secretion. During periods of normal cortisol levels, patients may experience symptom relief, adding to the diagnostic challenge.

Diagnosis: Diagnosing CCS is particularly challenging, due to the intermittent nature of cortisol secretion. Standard diagnostic tests for CS, including 24-hour urinary free cortisol, late-night salivary cortisol, and dexamethasone suppression tests, may yield normal results if conducted during a period of eucortisolism. Thus, repeated testing over an extended period is often necessary. Additional dynamic tests and imaging studies may be required to localize the source of cortisol overproduction.

Management: The management of CCS involves addressing the underlying cause of hypercortisolism. Surgical resection of a pituitary adenoma or ectopic ACTH-secreting tumor is the preferred treatment, when feasible. In cases where surgery is not possible or has failed, medical therapies aimed at controlling cortisol production, such as ketoconazole, metyrapone, or pasireotide, may be employed. Monitoring and managing the cyclic nature of the syndrome is crucial, often requiring long-term follow-up and repeated evaluations.

Prognosis: The prognosis of CCS varies depending on the underlying cause and the effectiveness of treatment. Successful surgical intervention can lead to remission, though recurrence is possible. Long-term outcomes depend on the control of hypercortisolism and the management of associated comorbidities such as diabetes, hypertension, and osteoporosis.

CCS is a rare and complex endocrine disorder that poses significant diagnostic and therapeutic challenges. A high index of suspicion and repeated, thorough testing are crucial for accurate diagnosis. Tailored treatment strategies focusing on the underlying cause and vigilant monitoring are essential for effective management.

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DIAGNOSIS CORNER

GENETIC TESTING IN XY DSD

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Genetic testing is now an important diagnostic tool in DSD. Obtaining a genetic diagnosis is vital for managing the individual case, and predicting the future risk in the family, facilitating discussions about future reproductive risks and enabling genetic counseling. Diagnostic genetic laboratories are shifting from using targeted single analyses to high-throughput sequencing techniques, either through targeted gene panels, or whole genome/exome sequencing, with customized filters to ensure sufficient coverage of relevant genes. It is crucial to understand the advantages and disadvantages of the various techniques employed in the genetic diagnosis of DSD:

Test	Method	Comments
Conventional G-banded Karyotype	Microscopic visualization of condensed metaphase chromosomes additionally stained by trypsin in combination with Giemsa or Leishman stain	Interpreted by chromosomal number, appearance, and banding patterns to identify aneuploidy or mosaicism; relatively large chromosomal abnormalities (larger than 5–10 Mb in size) like translocations, deletions, duplications, and inversions. Turn-round time 7-10 days as cell culture required.
FISH	Specific fluorescently labelled DNA probes that hybridize to complementary target regions at any chromosomal site of interest.	Rapid analysis of numerical and structural abnormalities of sex chromosomes, like aneuploidies or isodicentric Y translocations of SRY gene in individuals with 46,XX testicular or ovotesticular DSD.
QF-PCR	Microsatellite loci on the sex chromosomes are amplified with fluorescent primers and separated by length through electrophoresis.	Allows quick quantification of X and Y chromosomes, detection of structural abnormalities such as isodicentric X, partial Y chromosome translocation on X chromosome. Deletions and amplifications >50 kb can be identified for known chromosomal regions only.
CMA: aCGH and SNP	Hybridizing patient's DNA fragments with fluorescently labeled synthetic nucleotide probes on arrays.	Identifies CNVs between 10 kb and 5 Mb in size. Does not detect SNV or INDELs and balanced translocations.
MLPA	A variation of the polymerase chain reaction (PCR) that uses a single primer pair to amplify multiple targets.	Analysis of the loss or gain of specific exons or whole genes on a predefined panel of probes. eg: duplication/loss of *NR0B1.* can only identify copy number changes, and it can't define the exact break points of a mutation
Sanger sequencing/ single gene sequencing	Single-gene analysis based on random incorporation of chain-terminating dNTPS during DNA replication.	Rapid turnaround time from 3 to 14 days; reduced chance of incidental findings e.g. *AR* and *SRD5A2*

Next generation sequencing of targeted gene panel	Rapidly sequencing large amounts of DNA or RNA of targeted gene panels, spanning protein coding regions of common DSD genes.	Analysis of multiple short DNA target sequences (<300 kb) simultaneously provides a molecular diagnosis for about 50% of patients.
Whole-exome sequencing (WES)	Analysis of all the coding exons in DNA (1-2% of genome), which may show changes in known, putative, or novel DSD associated genes	Can identify novel candidate DSD genes within protein-coding regions of genome, time efficient. Cost effective, strong discovery power; may not detect low-frequency variants due to higher sequencing error rates or poor exome coverage
Whole genome sequencing (WGS)	Comprehensive picture of entire genome including chromosomal and mitochondrial DNA	Displays the broadest diagnostic perspectives due to entire genome coverage to detect SNV, CNV, INDELs, and larger structural variants (ploidy changes, balanced translocations, inversions)

FISH: Fluorescent in-situ Hybridization, QF-PCR: Quantitative Fluorescence PCR, CMA: Chromosomal Microarray technology, aCGH:microarray-based Comparative Genomic Hybridization, SNP: Single Nucleotide Polymorphism arrays, CNV: Copy Number Variations, SNV: Single Nucleotide Variations, INDELs: Insertion-Deletion Variants, MLPA: Multiplex Ligation-dependent Probe Amplification (MLPA), dNTPs: deoxynucleotide triphosphates

ISOLATED ACTH DEFICIENCY

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Isolated ACTH deficiency (IAD) is a rare disorder, characterized by secondary adrenal insufficiency (AI), normal secretion of pituitary hormones other than ACTH, and absence of structural defects of the pituitary gland [1]. First described by Steinberg in 1954, it can be classified into two forms, adult isolated ACTH deficiency (AIAD) and congenital isolated ACTH deficiency (CIAD). AIAD commonly affects middle-aged and elderly individuals and is typicallyassociated with autoimmune conditions, such as lymphocytic hypophysitis or trauma. Conversely, CIAD presents in the neonatal or early childhood period and is commonly attributed to genetic causes, particularly mutations in *TBX19* (encoding for TPIT, a pituitary transcription factor essential for corticotroph development), *POMC* (proopiomelanocortin, a precursor of ACTH and α-MSH), or *PCSK1* (prohormone convertase, enzyme which cleaves POMC) genes. These mutations disrupt normal ACTH production by the pituitary gland[1]. Descriptions of childhood-onset IAD are mostly limited to case reports and series.

The classic triad of clinical features in congenital IAD consists of hypoglycemia, seizures, and prolonged cholestatic jaundice. The exact pathophysiology of cholestasis in IAD is unknown, but it is postulated that cortisol deficiency interferes with bile acid formation and transport[2]. Additional manifestations may include vomiting, anorexia, and poor weight gain. Unlike primary AI, hyperpigmentation is not seen. Children with POMC defects often have early-onset obesity andred hair pigmentation, in addition to ACTH deficiency. As *POMC* and *TPIT* mutations are inherited in an autosomal recessive pattern, a family history of parental consanguinity, or sibling deaths during the neonatal period, are key pointers towards CIAD.

The diagnosis of IAD can be established by demonstration of low ACTH levels, in conjunction with low levels of cortisol at baseline and following synacthen (synthetic ACTH 1-24) stimulation, along

with normal levels of thyroid stimulating hormone, prolactin and insulin-like growth factor-1. Cortisol levels below 5 mcg/dL at baseline and below 18 mcg/dL following stimulation are indicative of AI. Both the high-dose (250 mcg Synacthen) and the low-dose (1 mcg Synacthen) stimulation tests have been proposed as sensitive tests for the diagnosis of secondary AI, though challenges in dilution of the 250 mcg ampoules may pose technical difficulties for the low-dose test[1]. Mineralocorticoid function (ACTH-independent) is preserved, which is evident by the absence of electrolyte abnormalities (hyperkalemia, hyponatremia), along with normal blood pressure and plasma renin activity[3]. Neuroimaging (MRI) of the pituitary gland should be done to rule out structural pituitary abnormalities, which are often absent in IAD.

Genetic testing by NGS (Next generation sequencing) can assist in providing a definite genetic diagnosis is congenital IAD cases. For families at risk, e.g., those with an affected child,identification of TPIT mutations can also aid in prenatal diagnosis insubsequent pregnancies, enabling early initiation of glucocorticoid (GC) therapy to prevent neonatal mortality. Additionally, non-invasive prenatal diagnosis is possible through the measurement of maternal plasma or urinary estriol levels in pregnancy, as decreased levels with no other apparent cause (placental sulfatase deficiency or Smith-Lemli-Opitz syndrome) may suggest fetal adrenal insufficiency secondary to CIAD.

Management of childhood-onset IAD primarily comprises of GCreplacement in standarddoses. The caregivers should be educated about the nature of the disease, need of lifelong hormone replacement, increasing doses during illness or stress, and continued follow-up. There is relative lack of long-term follow-up data for children with CIAD. Failure to recognise symptoms and institute GC therapy early can be life-threatening. Mortality has been reported in 20-25% of neonatal IAD cases, if not treated in time[2]. Recurrent episodes of hypoglycemia and seizures may lead to epilepsy and adverse neuro-developmental outcomes.With appropriate treatment, children with IAD lead normal lives; however, short stature, low bone mineral density, and absent adrenarche have been reported.

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PATIENT CORNER

GENDER ASSIGNMENT IN DSD

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Disorders of sex development (DSD) can often be difficult to manage, particularly in those cases where the sex of rearing is uncertain. Gender assignment of infants with DSD requires an open and direct communication between the doctor and family as gender uncertainty might be stressful for families.

Gender assignment in DSD depends on multiple factors such as diagnosis, gender identity, appearance of external genitalia, need for surgery, need for hormone replacement therapy, the potential for fertility, views of the family, and cultural practices.

Gender dysphoria denotes an individual's dissatisfaction and intense distress with the assigned gender. It occurs more frequently in individuals with DSD than in the general population. Fetal androgen exposure has a significant impact on gender identity and sexual behavior; however, the exact mechanism is unknown.

Do'sand Don'ts of gender assignment

Do's-	**Don'ts-**
1. Should be a multi-disciplinary approach. 2. Open and intense conversation between medical team and family. 3. Complete information must be provided including future prognosis for sexual function and fertility. 4. Should be individualized. 5. Use generalized terminologies to refer to baby until sex is assigned. 6. Speak in simple language. 7. Comprehensive evaluation by psychologist/ psychiatrist to diagnose gender identity/ dysphoria.	1. Do not oversimplify 2. Do not delay sex assignment of child. 3. Sexual orientation should not be confused with gender dissatisfaction. 4. Do not assign sex without complete and expert evaluation. 5. Decision regarding surgical correction to be made by the MDT and parents within legal limits. No irreversible surgeries like gonadectomy should be performed unless indicated due to gonadal tumor risk. 6. Avoid using complex medical terminologies during counselling.

Role of MDT: The multi-disciplinary team should include specialists in endocrinology, surgery, urology, clinical psychology/psychiatry, radiology, neonatology and nursing. Discussions with the family should be led by one professional.

Role of support groups: Support groups can provide ongoing support to parents and the affected individual, help to gather and explore information and build knowledge regarding the diagnosis of DSD. They can work in collaboration with the MDT to help families in seeking appropriate medical care and improve understanding of the condition and treatment.

Gender assignment in CAH- The DSD Consensus Group supports female gender assignment for patients with XX CAH because more than 90% of patients identify themselves as women and the presence of normal female internal genitalia offers the potential for fertility. The incidence of gender dysphoria in women with CAH is around 5%. Male gender assignment was earlier considered for markedly virilised patients (Prader 5 and some Prader 4); though this has now been refuted to accept the gender as per the patient's choice as they grow up.

Gender assignment in PAIS, Androgen biosynthetic defects- In the past, severely under-virilized XY patients were offered feminizing surgery, gonadectomy, and hormonal replacement on the assumption that sex of rearing overrules chromosomal or gonadal sex. Partially virilized XY women demonstrate the highest rates of gender dysphoria among all patients with DSD. In patients with PAIS, androgen biosynthetic defects, and partial gonadal dysgenesis, there is dissatisfaction with the sex of rearing in about 25% of individuals, whether raised male or female.

Available data supports assigning the male gender to XY patients with at least one functional testis and reasonable penile tissue.

Gender assignment in 5α Reductase- Patients with this disorder identify in adulthood as men in over 50% cases. This, along with virilization at puberty, with significant phallus growth and potential for fertility, justifies male assignment unless the phenotype is completely female.

Gender assignment in 17HSD- Almost 50% of patients with 17-hydroxysteroid dehydrogenase (17HSD) deficiency tend to identify as male: this should be considered by the treating team. A combination of a male gender identity in the majority, and the potential for fertility, should be discussed when providing evidence for gender assignment.

Gender assignment in Ovotesticular DSD- Assignment is based on gonadal differentiation and genital development, potential for fertility and surgical outcomes. Assignment should be considered for the gender for which potential for fertility is present, with good cosmetic outcome of external genitalia.

Gender assignment in MGD- Gender assignment decisions are individualized, based on the appearance of the external genitalia, hormonal profile, and response to HCG; and are usually split equally between the male and female gender.

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DRUG CORNER

ISPAD WEBINAR: INSULIN THERMOSTABILITY- A REPORT

Anju Virmani, Director, Pediatric Endocrinology, Max Smart Super Specialty Hospital & Senior Consultant, Endocrinology, Rainbow Children's Hospital, Delhi (Recording of this and other ISPAD webinars is freely available at www.ispad.org)

This important webinar held on 23 July 2024, was moderated by **Dr Graham Ogle**, Life For A Child (LFAC). The speakers were **Dr Sanket Pendsey**, Diabetologist & Trustee, Dream Trust, Nagpur, and **Dr TimothyJ Garrett**, Associate Professor, Dept of Pathology, Immunology & Lab Medicine, Univ of Florida, Gainsville, FL.

Insulin action requires adequate cold chain maintenance at all times. Insulin thermostability is a major issue in large parts of the world, which may not have access to cold storage, either an ongoing situation due to poverty, or during natural disasters and wars. Degradation occurs in 2 primary ways: deamidation and polymerization; interestingly, the deamido product has the same potency of insulin, so both insulin and deamido product must be measured, and compared with a USP reference standard.

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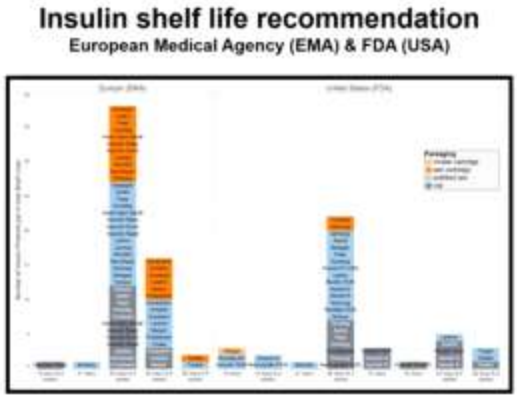
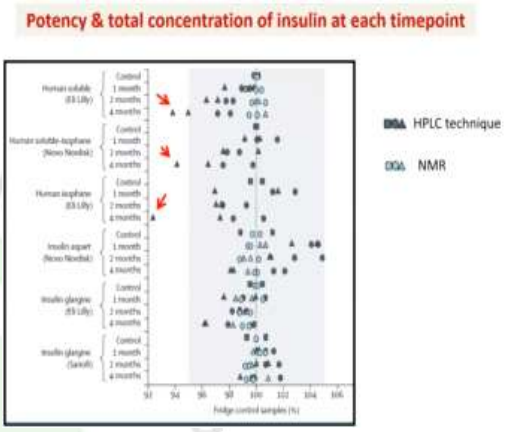
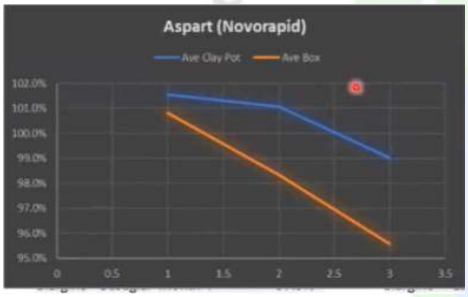


Insulin shelf-life recommendations by the European Medical Agency and the US FDA, are quite variable, ranging from 2-6 weeks, with somewhat uncertain data to support the recommendations. The package insert of one company advises that in-use insulin should be kept below 30°C, away from heat and light, and *thrown away after 28 days*, regardless of how much insulin is wasted in the process. It is usually in situations where storage is a problem, that wastage of insulin leading to higher costs and greater insulin scarcity can be most devastating, increasing poor glycemic control and family anxiety.

A few studies on thermostability were done on animal insulins in the 1960s and 1970s, and did show loss of potency at high temperatures. This led to many groups suggesting the use of traditional cooling devices for insulin storage, including earthen pots of various types and goatskin pouches[1]. The DREAM Trust founded by Dr Sharad Pendsey in Nagpur, which is one of the 10 hottest cities in India, with temperatures rising up to 48-49°C, began advising the use of double clay pots, with insulin in the inner pot and water or wet sand in the outer pot (Pendsey, Diabetes Voice, 2006).





Recent studies on thermostability have been reassuring. Dr Garrett discussed a recent Cochrane review[2] which showed that insulin can be stored for up to 6 months at 25°C and up to 2 months at 37°C. Refrigerated insulin has been shown to retain adequate potency even 9 years later. Dr Pendsey presented a 2021 thermostability study[3] in a real-world setting done by them in Nagpur, when during the 4 months of summer, the highest maximum temperature was 41.1-42.2°C. They collaborated with LFAC (Dr Ogle), University of Gothenburg, Sweden (Dr Gun Forsander), and University of Florida (Dr Garrett) to study Huminsulin R (soluble insulin), Huminsulin N (NPH insulin), Mixtard 30/70 (R+N), Novorapid (aspart), Lantus (glargine), and Basaglar (biosimilar glargine). Insulin stored with T1D families, in an open shelf and in a double clay pot, and fridge as control, was retrieved at 1, 2 and 4 months and analyzed in Sweden and Florida. The mean temperatures in the open boxes were 29.1-32.6°C, while the clay pots achieved 26.3-29.9°C. The potency of the insulin remained with the acceptable range of 95-105% in 98 of the 102 vials; in 4 it dropped to 91-95%. Compared with the refrigerated insulins, the potency differences of the insulin in the clay pots were -2.8% to2%, with those in the boxes was -7.9% to -0.1%. Clay pots were more effective when humidity was low. Thus, unrefrigerated insulin can be quite thermostable for 2, perhaps even 4 months, with clay pots being a safeguard, especially in places with dry heat.

These results concurred with a study by Kaufman et al[4] comparing NPH, rapid acting and mixed insulins, replicating in the lab the cyclical temperatures recorded in summer in northern Kenya, which found potency was maintained up to 12 weeks.

Dr Garrett presented the lab aspects of the Nagpur study, the Cochrane review mentioned above, data from Novo Nordisk, and also a study done by his center[5] collaborating with 4 other regions in the USA (Southeast, Northeast, Midwest, West and Southwest): Gainsville, Seattle, Ann Arbor, Houston, Boston; in each of 4 seasons (summer, spring, fall, winter). 200 samples of vial or cartridge packaging of Aphidra, Humulin R, Novolin R, Humulin N, Novolin N, Lantus, Basaglar, Humulin 30/70, Humalog, Novorapid (total 800 samples), which found insulin was stable in extremes of temperatures.

Standard teaching is that insulin should be purchased from reliable stores, transported with adequate cooling, kept in the fridge till used, and kept in a cool part of the house when in use. All this data shows that ***even if a fridge is not available, insulin may safely be used for 2-4 months*** by keeping in the coolest environment possible, e.g. a clay pot.

The dilemma of throwing away unused insulin at 2-6 weeks as per manufacturers' advice, arises when doses are small - young children, or the honeymoon phase - the same situations whereintensive blood glucose monitoring (BGM) by 4-7 finger prick tests daily or continuous glucose monitoring (CGM) is critically needed (expensive), andrapid-acting analog insulins (also expensive) may be preferable to reduce the risks of hypoglycemia. In resource-limited settings, we have therefore long been advising that in-use insulin should continue to be stored in the fridgeor perhaps a thermos with 1-2 cubes of ice; and used till it is over, adjusting the insulin doses according on the BG patterns. Parents are taught and reminded to be careful to avoid possible hypoglycemia when a new vial or cartridge is started. The money saved by not wasting this expensive insulin can help in enabling frequent BGM/ CGM.This data vindicates this stand.

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CRINECERFONT- Holding out Hope

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Crinecerfont is a corticotropin releasing factor(CRF) type 1 receptor antagonist that has received approval for use in CAH in adolescents. The deficiency of cortisol in CAH leads to build-up of androgens and lack of feedback inhibition of ACTH production. Glucocorticoid (GC) replacement is needed for the cortisol deficiency and to suppress ACTH. Control often requires GC use in supraphysiologic doses that may have long term complications, including suppression of growth and metabolic complications (weight gain, dyslipidemia and hypertension). ACTH production is

driven by CRF acting on the CRF receptor; thus, an agent antagonizing the receptor would be successful in limiting ACTH rise. Use of Crinecerfont in adults with 21-hydroxylase deficiency has been successful in suppressing excess ACTH and androgen. Its oral use offers ease of administration. It has been found to be safe and efficacious in a recently conducted phase 2 study on eight adolescents (14-16 years)[1]. More than 50% participants achieved more than 50% reduction in levels of ACTH and 17OHP after receiving Crinecerfont in doses of 50 mg twice daily for 14 days. Headache and dizziness were the minor side effects reported.

A recently concluded phase 3 trial in 103 children 2-17 years old reported promising results[2]. Crinecerfont (n=69) was compared with placebo (n=34) in classical CAH with trial period of 28 weeks. After 4 weeks of continuous use, GC doses were reduced while androstenedione levels were maintained within the reference range. At the end of 28 weeks, GC doses were reduced by 18%, while theyincreased by 5.6% in the placebo group. Headache, pyrexia and vomiting were reported in less than 25%.

Crinecerfont may thus bring forth a new era of management of CAH.

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PEDENDOSCAN

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Babu R, Shah U. Gender identity disorder (GID) in adolescents and adults with differences of sex development (DSD): A systematic review and meta-analysis. J Pediatr Urol 2021 Feb;17(1):39-47.

Gender assignment in infants born with a difference in sexual development (DSD) is one of the many difficult decisions faced by the multi-disciplinary team managing them, as some of them develop GID or gender dysphoria (strong feeling of dissatisfaction about oneself as male or female) in adolescence or adulthood. This prevalence in DSD patients older than 12 years of age was reviewed, aiming to help physicians with appropriate sex assignment to reduce development of GID in later life, with a meta-analysis of articles published between 2005 and 2020 of congenital adrenal hyperplasia (CAH); complete androgen insensitivity syndrome (CAIS); partial androgen insensitivity syndrome (PAIS); 5α reductase deficiency (5ARD); 17-hydroxysteroid dehydrogenase deficiency (17HSD); mixed gonadal dysgenesis (MGD) and complete gonadal dysgenesis (CGD). Within each condition, GID percentage was compared between female and male rearing. Statistics for prevalence of GID in DSD showed high heterogeneity with *I2* of 93% (95% CI 90-95%) among the 20 articles included. The overall prevalence of GID was 15% (95% CI 13-17%). CAH reared females had 4% GID and those reared as males had 15% GID (p = 0.0056). All CAIS patients were raised as females,with GID prevalence of 1.7%. In PAIS reared females GID prevalence was 12%,cf. 25% in PAIS raised males (not significant: p = 0.134). GID was significantly high in 5ARD (53%) and 17HSD (53%) reared as females, with half of them virilizing at

puberty, forcing a gender change. Among sex chromosome DSD, 22% of those reared as females had GID, while none in those raised as male with no significant difference. **GID is low in women with CAH, CAIS and CGD, favoring female sex of rearing in these conditions. GID is high in women with 5ARD and 17HSD, favoring male sex of rearing in these conditions. GID is variable in PAIS or MGD,with no recommendations made on sex of rearing. Each DSD patient is unique, warranting multi-disciplinary care and long-term psychosexual support.**

Gunawardana S, Jayarajah U, Ahmed SF, Seneviratne SN. Health-Related Quality of Life in Children and Adolescents With Congenital Adrenal Hyperplasia: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab 2024;109(6):1618-1629.

Health-related (self-reported/parent-reported)quality-of-life (QoL) and associated factors among children/adolescents (≤21 years)with CAH were reviewed in studies up to March 2022. There was moderate to considerable heterogeneity. Parent-reported psychosocial QoL in school, emotional and social domains, and self-reported school domain QoL,were lower in children/adolescents with CAH, while parent-reported and self-reported physical QoL were similar to controls. Factors associated with lower QoL among children/ adolescents with CAH included poor disease control, poor medication compliance, and complications including hyperpigmentation, virilization, hypertension, hospital admission, and urinary incontinence. **Children/adolescents with CAH had preserved physical QoL but impaired psychosocial QoL, especially in the school domain. Factors associated with lower QoL included poor disease control and disease/treatment-related complications. There is a need for further high-quality research that investigates the relationship between disease control, provision of psychosocial support, and improvement in QoL in children/adolescents with CAH.**

Augsburger P, Liimatta J, Flück CE. Update on Adrenarche-Still a Mystery. J Clin Endocrinol Metab 2024 May 17;109(6):1403-1422.

Authors searched literature of the past 5 years, using search terms adrenarche, pubarche, DHEAS, steroidogenesis, adrenal, and zona reticularis. Numerous studies addressed different topics of adrenarche and premature adrenarche (PA). The exact mechanism leading to adrenarche remains unsolved. A promising marker of adrenarche (11-ketotestosterone) was found in the 11-oxy androgen pathway. By current definition, the prevalence of PA can be 9% to as high as 23% in girls and 2-10% in boys, but only a subset of these children might face related adverse health outcomes. New criteria for defining adrenarche and PA are needed to identify children at risk for later disease and spare children with a normal variation. **Further research is required to understand adrenarche. Prospective, long-term studies should characterize prenatal or early postnatal developmental pathways that modulate trajectories of birth size, early postnatal growth, childhood overweight/obesity, adrenarche and puberty onset, and lead to abnormal sexual maturation, fertility, and other adverse outcomes**.

Sarafoglou K, Kim M, Lodish M, et al. Phase 3 Trial of Crinecerfont in Pediatric Congenital Adrenal Hyperplasia. N Engl J Med2024 Aug 8;391(6):493-503.

Children with classic CAH need long term steroid replacement, but this confers a predisposition to glucocorticoid-related complications. In 2-week phase 2 trials, patients with CAH who received crinecerfont, a new oral corticotropin-releasing factor type 1 receptor antagonist, had decrease in androstenedione levels. In this phase 3, multinational, randomized trial, 103 pediatric participants with CAH, in a 2:1 ratio, received crinecerfont (n=69) or placebo (n=34) for 28 weeks. A stable glucocorticoid (GC) dose was maintained for 4 weeks, aiming to control the androstenedione level

(≤120% of the baseline level or within the reference range). At baseline, the mean glucocorticoid dose was 16.4 mg/m^2/d, and the mean androstenedione level was 431 ng/dL (15.0 nmol/L). At week 4, androstenedione was substantially reduced in the crinecerfont group (-197 ng/dL [-6.9 nmol/L]) but increased in the placebo group (71 ng/dL [2.5 nmol/L]); P<0.001); the observed mean androstenedione value, obtained before the morning glucocorticoid dose, was 208 ng/dL (7.3 nmol/L) in the crinecerfont group, as compared with 545 ng/dL (19.0 nmol/L) in the placebo group. At week 28, the mean glucocorticoid dose had decreased (while androstenedione control was maintained) by 18.0% with crinecerfont but increased by 5.6% with placebo (LSMD, -23.5 percentage points; P<0.001). Headache, pyrexia, and vomiting were the most common adverse events. In this phase 3 trial, **crinecerfont was superior to placebo in reducing elevated androstenedione levels while decreasing GC dose from supraphysiologic to physiologic levels in pediatric participants with CAH.**

Lucas-Herald AK, Kyriakou A, Alimussina M, et al. Serum Anti-Müllerian Hormone in the Prediction of Response to hCG Stimulation in Children With DSD. J Clin Endocrinol Meta 2020 May 1;105(5):1608-1616.

Children who had hCG stimulation tests in one tertiary centre from 2001 to 2018 were included (n = 138). Serum testosterone was measured before (day 1 [D1]) and after 3 days (D4) of hCG stimulation. Sixty-one of these children also had prolonged hCG stimulation for 2 more weeks and serum testosterone measured after 21 days (D22). All children had a serum AMH measured on D1. D4 testosterone was normal in 104 children (75%). AMH was low in 24/138 (17%) children, and 16 (67%) of these had a low D4 testosterone. Median AMH in those who had a normal vs low D4 testosterone was 850 pmol/L (24, 2280) and 54 pmol/L (0.4, 1664), respectively (P < 0.0001). An AMH > 5th centile was associated with a low D4 testosterone in 18/118 (13%; P < 0.0001). Of the 61 children who had prolonged hCG stimulation, D22 testosterone was normal in 39 (64%). AMH was low in 10/61(16%) children and 9 (90%) of these had a low D22 testosterone. Median AMH in children who responded and did not respond by D22 was 639 pmol/L (107, 2280) and 261 pmol/L (15, 1034) (P < 0.001). **A normal AMH may provide valuable information on overall testicular function. However, a low AMH does not necessarily predict a suboptimal testosterone response to hCG stimulation.**

CASE REPORTS

Fe(Male) with Hypertension!!!

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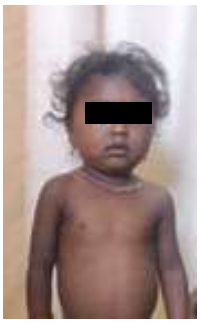
Congenital adrenal hyperplasia (CAH),which may present as DSD,is an autosomal recessive disorder caused by deficiency of steroidogenic enzymes. Although renal and renovascular conditions are the commonest causes of secondary hypertension (HTN) in children, a few forms of CAH can also present with HTN.

We describe a 2.7 year old child reared as female,born at term with second degree consanguinity, with an uneventful birth history, who was referred from Nephrology Department for evaluation of anasarca and HTN. She had complaints of bilateral swelling of lower limbs from 2 weeks, insidious in onset with gradual progression, and a significant past history of repeated episodes of urinary tract infection and HTN. Evaluation for renal, renovascular and cardiac causes of HTN was non-



confirmatory. On examination, anthropometric parameters were normal; with HTN(116/76mm of Hg >above 95th + 12mmHg) in all four limbs; mild periorbital edema and bilateral pitting pedal edema. SMR was B1P1A1 with normal female genitalia.

On investigation, 8am serum cortisol was low (0.41mcg/dL), Plasma Renin Activity low (0.06 microIU/ml/hr), serum aldosterone elevated (75ng/dL), with metabolic alkalosis (pH 7.49, bicarbonate 28mEq/L) and hypokalemia (2.09mEq/L). Ultrasonography and MRI of abdomen and pelvis showed no evidence of uterus, ovaries or testes. Karyotyping confirmed 46XY. Synacthen stimulated steroid panel showed raised progesterone and aldosterone levels, with decreased cortisol, DHEAS and testosterone. Serum AMH levels was low (1.88ng/mL). There was poor testosterone response on HCG stimulation test. Genetics revealed homozygous stop gain variant c.695T>G,p.L232X (chr10:102834094A>C) in the CYP17A1 gene, causing CAH due to 17α hydroxylase deficiency. Cystogenitoscopy showed a 4cm blind ending vaginawith no cervical impression. Diagnostic laproscopy showed bilateral gonads 2cm from the deep inguinal ring, measuring 1.5*1cm, appearing like testis with gonadal vessels and vas-like structure. No mullerian structures were seen. Polar biopsy of bilateral gonads showed testicular tissue with atrophic seminiferous tubules lined only by Sertoli cells. No germ cells or Leydig cells were seen.

The child was started on oral hydrocortisone (15mg/m2/day), with amlodipine (0.6mg/kg/day) and spironolactone (2.5mg/kg/day) for HTN. A multidisciplinary team including child psychiatrist and pediatric surgeons were involved in the assessment. After multiple counselling sessions, the parents decided to continue raising the child as a female. In view of the intra-abdominal location of the gonads, bilateral gonadectomy is planned at the time of puberty, with subsequent hormone replacement therapy.

17α-hydroxylase deficiency (17OHD) represents 1% of cases of CAH, with mutation in the gene coding for cytochrome P450 C17 enzyme, located on chromosome 10q24.3[1]. The hallmark of 17OHD is elevated serum progesterone, 11-deoxycorticosterone, and corticosterone[2]. Subjects with 17OHD usually present at adolescence, with HTN and delayed puberty in girls/undervirilisation in boys. Glucocorticoid replacement reverses the DOC-induced suppression of the RAAS and lowers the BP. Fertility, TART, adrenal myelolipoma, gender dysphoria, and gonadal malignancy are rarely reported in 46XY patients with 17OHD[3].

To conclude,this case highlights the importance of considering endocrine disorders in the differential diagnosis of pediatric HTN. Early recognition and appropriate management of CAH are crucial to prevent complications which can significantly impact long-term outcomes.

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LEARNING PEARLS- APPES-ISPAE 2024

25th APPES FELLOWS SCHOOL

(Report by Biswajit Sahoo, Dept of Pediatrics, Maulana Azad Medical College, New Delhi)

The 25th APPES Fellows school was held from 28 Sep to 02 Oct 2024 at The Royal Plaza, New Delhi, coordinated by the APPES secretariat. A total of 48 fellows from different countries of Asia-Pacific region attended the meeting, including 17 from India. The fellows had an opportunity to be trained under 16 faculty from different parts of the globe, namely, Drs Ben Albert, Reiko Horikawa, Silva Arslanian, Joseph Dung, Sylvia Estrada, Tony Huynh, Raja Padidela, Meng-Che Tsai, Paul Van Trotsenburg, Aram Yang and Margaret Zacharin. Among these, five were national faculty namely Drs Vaman Khadilkar, Sudha Roa, Vandana Jain, Rakesh Kumar and Ravindra Kumar. The sessions discussed cases followed by faculty presentations on different aspects of endocrinology. Three small group discussions were organized on Diabetes technology, dynamic function testing and water balance. A total of 30 cases were presented by the fellows followed by Faculty lectures that guided the learning process. These cases included a case of pituitary macroadenoma who presented as gigantism, two children with severe short stature with *ACAN* mutation and IGF-1 receptor defect, two cases of MODY with mutations in *GCK* and *HFN1B* gene and one case of Renal cysts and diabetes (RCAD) syndrome (MODY 5), ROHHAD (R Rapid onset O Obesity H Hypoventilation H Hypothalamic AD Autonomic Dysregulation)- NET SYNDROME with Hypothyroidism with severe obstructive sleep apnea with hypertension with amblyopia, neonatal severe hyperparathyroidism, tumour-induced osteomalacia, thyroid malignancy, VDDR type 2, isolated hyperandrogenism, and 46, XY gonadal dysgenesis, to name a few. The fellows and faculty had an opportunity for local sight-seeing in Delhi. An insulin pump workshop was organized at the last day that concluded the proceedings at the Fellows school.

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13th APPES ISPAE Joint Meeting 2024

(Organizing Committee- Dr Rajesh Khadgawat, Dr Anju Seth, Dr Rakesh Kumar, Dr Ravindra Kumar, Dr Jaivinder Yadav)

The 13th Biennial Scientific Meeting of the Asia Pacific Paediatric Endocrine Society (APPES), co-organized by APPES and Indian Society for Pediatric and Adolescent Endocrinology commenced on 02 October 2024 at Yashobhoomi, India International Convention & Expo Centre, New Delhi. The program began with APPES council meeting, followed by three Special Interest Group (SIG) meetings. The first was on Phaeochromocytoma and Paraganglionoma chaired by Professor Nalini Shah, with panelists as Prof Steven Waguespack, Prof Roderick Clifton and Prof Vijaya Sarthi. The speakers in this session were Prof Maria Craig, Prof Junfen Wu and Dr Ahila Ayyavoo with Dr Manjiri Karlekar who presented the case. The second was DSD moderated by Professor Paul Hoffman and Rieko Horikawa. Dr Dhivyalakshmi and Dr Shaila presented cases that steered the discussion. The third SIG was on Bone that was conducted in association with the International Society of Children's Bone Health. The session was moderated by Professor Raja Padidela and covered physiology of calcium metabolism followed by interactive case based discussions.

The main conference began with an inaugural function. Professor K N Aggarwal, former Director, Sanjay Gandhi PGI Medical Sciences, Lucknow and ex Director/Dean Institute Medical Sciences, Varanasi was the Chief Guest for the event. The inaugural was followed by a brief cultural dance performance displaying rich cultural diversity of India. The scientific program commenced with the Plenary lecture by Prof Jenny Couper followed by Growth Symposium. The scientific proceedings on the remaining days had plenary lectures by lead eminent researchers from across the globe. Each day had oral paper presentations and poster walk that provided young researchers and clinicians to showcase their work and invite discussion from experts. The Kaichi Kida oral session had five top oral presentations eligible for two awards. Dr Dhvani Raithatha won the Kaichi Kida award and Dr Nimisha Dange won the best paper in other endocrinology/ diabetes section. The awards were presented by Professor Noriyuki Namba, Chair of the scientific committee. Three parallel 'Meet the Experts' sessions provided an opportunity for the attendees to interact and learn from stalwarts. The first session was on Renal tubular acidosis led by Prof Arvind Bagga. The next session was on management of hypogonadotrophic hypogonadism moderated by Prof Nalini Shah and Dr Manjiri Karlekar. The third was on CGM and CGM apps led by Prof Ryan Paul.

The program concluded with welcoming the new APPES council and announcement of APPES 2026 at Brisbane, Australia. The next Biennial meeting of ISPAE was announced at Nagpur from 14-16 November 2025. The meeting successfully concluded on 05 October. The delegates and Faculty appreciated and thanked the organizers for the academic feast and the wonderful hospitality at APPES-ISPAE meeting.

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LEARNING PEARLS

28TH ISPAE ACES MEETING: EARLY LIFE ORIGINS OF LATER HEALTH AND DISEASE

Experts: Prof Wayne Cutfield, Liggins Institute, University of Auckland, New Zealand; & Prof Krishnaveni GV, CSI Holdsworth Memorial Hospital, Mysore, Karnataka. (Compiled by Zalak Upadhyay, Pediatric & Adolescent Endocrinologist, Endocare for Kids, Rajkot)

The 28th ISPAE ACES meeting was conducted on 22 June 2024, on the topic *Early Life Origins of Later Health and Disease*. The term Developmental Origins of Health and Disease (DOHaD) has evolved to Early Life Origins of Later Health and Disease to emphasize the critical impact of early life experiences on long-term health outcomes. *Barker Hypothesis* proposed by British epidemiologist Dr David Barker, postulated there are long-term effects of adverse conditions during early development, particularly in utero. It revolutionized our understanding of how early life events, especially those occurring during critical periods of fetal and early postnatal development, can program the body's susceptibility to diseases; highlighting the importance of maternal health and prenatal care in preventing adult-onset diseases.

Premature small for gestational age (SGA) babies tend to have higher insulin resistance than term SGA babies. This difference arises because prematurity adds another layer of developmental challenge on top of intrauterine growth restriction (IUGR). Post-term babies (born after 42 weeks of gestation) can exhibit features associated with metabolic syndrome (a cluster of conditions which increase the risk of diabetes, cardiovascular disease, and other health issues). Some key metabolic abnormalities seen in post-term babies include insulin resistance, elevated lipids, high leptin and low adiponectin, raised IGF-BP1,increased abdominal fat, and diminished night-time systolic blood pressure dip (an early sign of hypertension).

High carbohydrate intake in the first months of life can have long-term effects on obesity risk. During this critical period of early development, the infant's metabolic system is highly sensitive to dietary inputs, which can influence future health outcomes. Interesting findings are that first-born children are more intelligent, usually taller, more insulin resistant and have higher blood pressure than later children. The metabolic disadvantages of the first-born children could be linked to several factors, including differences in maternal physiology and placental development between first and subsequent pregnancies. During pregnancy, spiral arteries in the uterus undergo remodeling to increase blood flow to the placenta. In the first pregnancy, this remodeling may be less efficient, leading to reduced blood flow and nutrient delivery to the fetus. In subsequent pregnancies, these arteries often undergo more extensive dilation and remodeling, providing the fetus better blood flow and nutrition.

Low birth weight, rapid postnatal growth, and low vitamin B12 are risk factors for higher central adiposity later. Early life is a vulnerable window in which events, including nutrition, contribute to long-term metabolic health. Adversely programmed infants have a greater risk of obesity and metabolic disease when exposed to a later unhealthy diet and lifestyle. Both paternal overnutrition and undernutrition can also influence the metabolic health of offspring. The role of epigenetics in metabolic programming is still being untangled.

The next meeting was held on **14 Sep 2024** on **Mc Cune Albright Syndrome**

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WORKSHOP ON GENDER AFFIRMATIVE CARE FOR CHILDREN AND ADOLESCENTS

(Organized at AIIMS, New Delhi; Compiled by Dr Rajni Sharma with contributions from Dr Anju Virmani, Dr Sukanya and Dr Konpal)

The estimated prevalence of transgender identity in the general population is estimated to be 0.3-0.5% in adults and upto 1-2% in children and adolescents.Families often seek consultation for concern regarding their gender non-conforming child with primary care physicians or pediatricians, whose role is to educate the parents, offer support and guidance to the child and family,providing a non-judgmental environment. A supportive family environment would help prevent many psychological issues developing in the future and ensure a safe space to the child. Pediatricians can also pick up signs of gender incongruence at an early stage and provide necessary support. A child psychologist should be consulted if the child develops features of gender dysphoria (distress related to gender incongruence) or other forms of psychological distress.

Difference Between Gender Non-conformity and Gender Dysphoria: Gender Non-conformity refers to an individual's self-expression and behavior, which may be different from the gender assigned at birth. Some individuals experience extreme distress with their gender. This is defined as gender dysphoria and diagnosed as per the criteria used in the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* (American Psychiatric Association, 2000).

- In most children, gender dysphoria will disappear before or early in puberty. Gender non-conforming behavior or gender dysphoria during childhood persists into adulthood inapproximately 10-20% of children. The persistence of gender dysphoria into adulthood is higher for adolescents.
- In some children, gender dysphoria becomes more distressing as they develop secondary sexual characteristics in puberty. Many gender dysphoric adolescents have a strong wish for gender change, for which they seek treatment.
- Assessment and psychosocial interventions for children and adolescents should be provided by a *multi-disciplinary gender identity specialty service*. If such a service is unavailable, a mental health professional should be consulted and collaborate with a pediatric endocrinologist for assessment, education, and decision-making regarding any physical intervention.
- A qualified and competent mental health professional plays a crucial role in the management of gender dysphoric children and adolescents, and has multiple roles, including assessing and diagnosing gender dysphoria, providing family counselling and supportive psychotherapy, addressing the distress associated with gender dysphoria and other psychosocial issues, treating co-existing mental health concerns, and referring adolescents for additional physical interventions (such as puberty blockers) to alleviate gender dysphoria.
- **Mental health:** Transgender children and adolescents face several prejudices and stigma and have higher rates of depression, anxiety, eating disorders, high risk behavior,substance abuse,self-harm and suicide, for all of which they must be screened timely.
- Clinical evaluation of a transgender adolescent, including detailed history-taking and examination, should be done in an empathetic and respectful manner.

- Importance of immunization withHuman Papilloma Virus (HPV) and Hepatitis B virus (HBV) vaccines before gender affirmative hormonal and surgical therapy should be emphasized.
- Words matter. Use of sensitive terminology when addressing gender-diverse people is important.
- There is need for gender-neutral washrooms in all public places.
- **Modes of therapy for treating individuals with gender dysphoria include:**
  - Non-medical therapy
  - Reversible medical therapy (puberty blockers)
  - Partially reversible therapy (hormonal interventions)
  - Irreversible therapy (genitourinarysurgery: can only be done after the legal age of consent, i.e.> 18 years of age).
- Treatment for gender dysphoria should be individualized: Some trans-individuals only need non-medical therapy to express themselves; some need additional hormonal therapy; while many need both hormonal therapy and surgery.
- ***Non-medical therapy*:** Individual expression of preferred gender identity helps alleviate gender dysphoria. This may include dressing up in the affirmed gender, adopting a preferred hairstyle, tucking the genitals (in trans-males), and banding of breasts (in trans-females). These practices can help transgender youth express their identity and experience living in a trans-role, before or even without medical or surgical interventions.

- **The role of the pediatric endocrinologist includes pubertal assessment, providing puberty blockers/hormone replacement therapy (HRT) where indicated, and monitoring the effects and side effects of medical therapy on follow-up.**
- Prerequisites for initiating puberty blockers (reversible medical therapy):
  - Persistent gender dysphoria has been documented by a trained mental health specialist.
  - The childhas entered puberty (Sexual Maturity Rating/Pubertal stage ≥2).
  - There are no medical contraindications to GnRH agonist intervention.
  - The adolescent and family are informed in detail of the expected effects and side-effects of the intervention.
  - Informed signed assent and parental consent when the adolescent has not reached the age of legal medical consent is mandatory. The consent form should have all the details of the expected effects and side-effects of therapy.
- Prerequisites for initiating HRT (partially reversible medical therapy)
  - Persistentgender dysphoria has been documented by a mental health specialist, withabsence of a major psychiatric condition.
  - Age of majority in a given country and capacity to make a fully informed decision and to consent to treatment (>18 years) has been reached.
  - The patient has been informed in detail of the expected effects and side-effects of intervention, including potential loss of fertility and options to preserve fertility
  - There are no medical contraindications to hormonal intervention.

- Prior to HRT, a complete physical examination including BP and baseline blood tests (full blood count, renal and liver profile, fasting blood glucose levels, lipid profile, thyroid function estradiol, testosterone and prolactin levels), VDRL, and hepatitis and HIV serology has to be done.
- Consider gamete cryopreservation.
- Bone density is more of an issue in male-to-female transition; bone mineral density (BMD) should be monitored at baseline and periodically thereafter.
- There is a need to establish BMD reference ranges for different transgender groups to facilitate screening and monitoring, which is presently difficult due to limited available data.

Female-to-male (FTM) hormonal therapy

In case the individual only wishes for menstrual suppression, high dose progesterone therapy works well. For virilization, testosterone can be administered by the intramuscular (IM), subcutaneous (SC) or transdermal route. The starting dose of testosterone is usually half of the full replacement dose: it is then gradually titrated to full dose over a period of 6 months. Once adequate virilization has been attained, the dose is decreased to 50% of the full replacement dose to maintain masculinizing characteristics. Inj. testosterone enanthate 250 mg given IM every 2 weeksis the method most commonly employed. Alternatively, SC testosterone 25 mg can be given weekly. The target is to keep testosterone levels within the normal male physiological range (3001000 ng/dL).

Complications of testosterone therapy: include polycythemia which can predispose to a cerebrovascular accident and stroke; elevated liver enzymes; and hyperlipidemia. Local testosterone gel 1% (25 mg or half sachet daily for maintenance) is safer with respect to polycythemia, as it leads to more stable blood levels with less spikes. Local application is less effective for induction, and more useful for the maintenance phase.

Absolute contraindications: pregnancy, unstable coronary artery disease, and untreated polycythemia. *Monitoring:* Serum testosterone levels, hematocrit, cardio-metabolic risk factors.Testosterone is not a contraceptive and is teratogenic, so it is essential to ensure contraception during the transition process.

Male-to-female (MTF) hormonal therapy

High dose oral estradiol valerate (2-8 mg) or transdermal patches (not easily available) are used to induce feminization and suppress testosterone. The goal is to keep testosterone levels within the normal female range (30100 ng/dL), while keeping estradiol below supra-physiological levels (<200 pg/mL).

***Complications of estrogen therapy*:** include potential risk of *venous thromboembolism (VTE)* associated with estrogen (less risk with transdermal estrogen); *gallstones, liver dysfunction, and i*ncreased incidence of *breast cancer.*

Contraindications: Previous VTE, history of estrogen-sensitive neoplasm, and chronic liver disease.

Monitoring: Check testosterone, estradiol, prolactin and triglyceride levels at baseline and at follow-up.Monitor serum potassium levels on spironolactone. Screen for breast and prostate

cancer as per recommendations. Monitor BMD by DXA scan at baseline and three yearly if there is risk of osteoporosis.

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PEDIATRIC ONCO-ENDOCRINOLOGY MEETING

(Compiled by Dr Soundaram Karthik, Consultant Pediatric Endocrinologist, Apollo Hospital, Chennai)

- Insulin is the mainstay of therapy for steroid induced diabetes and post-transplant diabetes mellitus (PTDM). Post-transplant hyperglycemia is common (though not labelled as PTDM) and a risk for future PTDM. Good glycemic control of post-transplant hyperglycemia may help avert the risk of PTDM.
- Thyroid disorders post-radiation include hypothyroidism, hyperthyroidism, thyroid nodules and thyroid cancer. Risk factors for thyroid carcinoma post-radiation are age less than 5 yrs, females, increasing post-radiationduration, and radiation dose (risk increases proportionally with radiation dose upto 20Gy).
- There is a possible association between cancer and sodium-transporting proteins, which result in hyponatremia. Cancer cells proliferate more rapidly and exhibit higher motility when cultured in low sodium conditions. Tolvaptan counteracts cancer cell proliferation and invasiveness in vitro.
- **Immune check point inhibitors** cause hypophysitis, primary adrenal insufficiency (AI), thyroid and gonadal disorders, Type 1 diabetes mellitus, worsening of Type 2 diabetes mellitus; rarely they also cause ACTH dependent Cushing disease, diabetes insipidus and hypoparathyroidism. ICI endocrinopathy portends a good prognosis for recovery from cancer, though the endocrinopathy usually persists, necessitating lifelong replacement, except in transient thyroiditis.
- **Hypophysitis** presents nearly 11 weeks after the dose of CTLA4 inhibitors (monoclonal antibodies), with severe hypocortisolemia and normal neuroimaging in most cases. If hypophysitis is suspected, 8 am cortisol, thyroid profile, electrolytes and glucose should be checked before the due dose. The pituitary hormonal work-up should be done if cortisol is low, and pituitary hormone replacement started, before continuing CTLA4I. High dose steroids are required only if there is severe headache and/or visual disturbances. ICI-hypophysitis related secondary AI is generally irreversible.

- **Pheochromocytoma** age-related cut-offs must be usedfor Normetanephrine. Gallium Dotatate PET/CT scan is highly sensitive for diagnosis of primary tumor and metastasis. Pre-operative amlodipine is efficacious in controlling intra-operative HDI.
- **Adrenocortical carcinoma** Mitotane is considered in stage 3 and 4 along with chemotherapy. It should be started at 1.5 g/m^2/day,with gradual dose hike every 3 days to reach 4 g/m^2/day (in 2-3 divided doses with a glass of water and fatty substance). It should be continued for atleast 2 years. Monitor trough levels (12 hrs after the last dose), target level: 14-20 mg/L. The effective serum level is reached in 2-3 months, after which the dose should be decreasedto 1-2 grams/day to avoid toxicity.
- Current evidence does not support an association between GH therapy and primary tumor or cancer recurrence. However, GH replacement should be discontinued when disease relapse or clinically significant tumor progression is confirmed. There is no significant association between GH duration and dose, and the occurrence of meningioma. For solid cancers, the onset of GH replacement can be delayed until patients are in remission for 5 or more years.
- For improving bone health during and post-cancer treatment, nutrition, growth and pubertymust be optimised. Screening BMD with DXA should start 2 years after completion of treatment.
- Ovarian tissue cryopreservation(OTC) is an established oncofertility option in children aged 0-15 years (those not started or completed puberty). Steroidogenic and reproductive function are preserved. OTC is not advisable in cases of systemic diseases such as leukemia, neuroblastoma, and Burkitt's lymphoma. Harvesting ovarian tissue while patients are in complete remission may be safer, especially since neither graft follicle density nor reproductive performanceis significantly affected by chemotherapy administered before OTC.
- Sperm is found in 50% of boys by the age of 14 years and when testicular volume is 8-15 mL. Sperm cryopreservation after masturbation is the most established and effective method of FP in male adolescents. Sperms should be collected before initiation of cancer therapy as sperm quality and DNA integrity may be compromised.

ISPAE- PEP MEETING 31 JULY 2024- CONGENITAL ADRENAL HYPERPLASIA AND DIFFERENCES OF SEX DIFFERENTIATION

Jaivinder Yadav, Amarnath Kulkarni, Prof Raghupathy Palany

A case of congenital adrenal hyperplasia was presented by Dr. Rishab Gupta (PG, LLRM Medical College, Meerut, UP) under the guidance of Prof. Vijay Jaiswal (LLRM Medical College, Meerut, UP). The examiner for this case was Dr. Rajni Sharma (Additional Prof, AIIMS, New Delhi). Dr Rajni Sharma delivered a talk on CAH followed by Prof Sudha Rao (Bai Jerbai Wadia Hospital for Children Parel, Mumbai) who spoke on DSD.

CAH

1. CAH is the most prevalent cause of genital ambiguity in female infants.

2. The salt-wasting classical CAH manifests in the first month of life with genital ambiguity (in females), hyperpigmentation, failure to thrive, and electrolyte imbalance (hyponatremia and hyperkalemia).
3. The simple virilizing form typically presents with precocious puberty. Some rare types of CAH (17 hydroxylase, 11 beta HSD) present with hypertension.
4. 17-OH progesterone levels, basal or stimulated, are diagnostic of the most common (95%) CAH type 21 hydroxylase deficiency. The preferred assay method is LCMS, which can facilitate the diagnosis of other rare forms of CAH.
5. Genetic diagnosis is increasingly utilized to confirm the diagnosis.
6. Hydrocortisone (10-15mg/m2 in three divided doses) and fludrocortisone (100-300ug/day), along with salt supplementation, are used for CAH treatment.
7. The stress dosing and intramuscular hydrocortisone administration should be taught to the family to prevent adrenal crisis.
8. Growth, blood pressure, 17-OHP, serum electrolytes, and testosterone level should be measured in follow-up to make dose adjustments and assess compliance.
9. Newborn screening is recommended for early diagnosis but is not available in most parts of India.

Disorders of Sex Differentiation

1. DSD is a disorder characterized by incongruence in genetic, phenotypic, and gonadal sex. The prevalence of DSD is approximately 1:4500.
2. DSD is considered a social emergency and should be addressed with appropriate care, compassion, and support.
3. The contemporary classification for DSD should be utilized for description, and outdated terms such as ambiguous genitalia, intersex, and hermaphrodite should be avoided.
4. The newborn should be referred to using gender-neutral terms such as "baby" or "child" until gender assignment is completed.
5. A comprehensive clinical examination of the genitalia, along with assessment of any syndromic features, should be conducted. Appropriate scoring systems, such as Prader's Score or External Masculinization Score, should be employed to describe the degree of virilization.
6. Karyotype analysis or Fluorescence In Situ Hybridization (FISH) for SRY is the initial investigation. The gonads and Müllerian structures should be evaluated using clinical and imaging techniques. Subsequent biochemical tests, including 17-OHP, testosterone, dihydrotestosterone, AMH, beta HCG stimulation, gonadal biopsy, and genetic studies, should be guided by clinical examination findings.
7. Irreversible gender assignment surgeries should be avoided during early developmental stages.

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IDEAS -Transforming Diabetes Education in Indian Schools Through Multilingual and Digital Outreach

Anju Virmani, Director, Pediatric Endocrinology, Max Smart Super Specialty Hospital, & Senior Consultant Endocrinologist, Madhukar Rainbow Children's Hospital, New Delhi; Sirisha Kusuma Boddu, Senior Consultant Pediatric Endocrinologist, Rainbow Children's Hospitals, Hyderabad; Preeti Singh, Professor, Dept of Pediatrics, Lady Hardinge Medical College & Kalawati Saran Children's Hospitals, Delhi

IDEAS has highlighted the need for healthcare providers to focus on sensitizing school staff to enable good diabetes care in schools, a vital but neglected aspect of diabetes care. Vital, because school is where a child spends half the waking hours, and which shapes the child's future earning potential as well as social integration.

Using the IDEAL platform, IDEAS is slowly expanding this awareness across India; to ensure accessibility and inclusivity. In the last two years, ISPAE has developed and provided on its website comprehensive school-related material, including a set of slides giving clear information on all aspects of diabetes care in school to teachers and other staff. In its ongoing journey, IDEAS has begun reaching out to schools across the country, to encourage them to utilize these resources. Initially launched with content only in English, the need to provide resources in multiple languages to reach a more diverse audiencewas soon recognized. The live session conducted on the first Sunday of each month was adapted and delivered in Kannada, Hindi, Gujarati, and Telugu, with Tamil and Marathi in the pipeline. The aim was to expand reach and improve comprehension by allowing diabetes education to resonate with teachers, students and parents, in their native languages. However, we have struggled with finding the optimal time to deliver these messages to teachers, who are already overburdened by professional and personal responsibilities. Teachers have also been reluctant to register, as it involves sharing personal information, raising the fear of being spammed. We therefore are altering our strategies to facilitate provision of our messages in the most effective manner. We are preparing video recordings of the power point presentation of diabetes care in school in different Indian languages to make them available on the IDEAS YouTube channel to parents for sharing with teachers at opportune moments. This plan highlights the commitment to delivering accessible educational content in innovative ways.

This initiative was launched on 5th September to mark Teacher's Day, with the release of the first IDEAS recorded module in English. The aim of recorded modules is to provide consistent messages to teachers and staff at a time convenient to them. Parents are encouraged to familiarize themselves with the contents of the module and share it with school staff at the time of diagnosis and at the beginning of each academic year, when the child moves to a new class, or even from primary to secondary to high school. Having the module in their phones would enable teachers to listen to it at their own pace, as needed, and more than once if they

want. This approach makes diabetes education available in any part of India, without constraints of access to time-consuming traditional workshops or in-person sessions. The release has received positive feedback, and we hope it will become a valuable resource for educators nationwide.

October has marked the launch of the Gujarati version on the IDEAS YouTube channel. The Hindi, Tamil, and even Hinglish are in the pipeline. We healthcare professionals, diabetes educators, and community members who recognize the importance of diabetes education are excited. The availability of the modules in multiple languages, on digital platforms like YouTube, will enable reaching beyond metros to tier 2 and 3 cities, and even small and remote areas, where experts are scarce and in-person sessions may not be feasible. Making diabetes education widely, easily and freely accessible to underserved populations, overcoming geographic and language barriers, is the dream we are working towards.

BEST: A Comprehensive Education Series for Type 1 Diabetes Empowerment in India

The Basic Education Series on T1D, a spin-off from IDEAL and drawing from their pool of dedicated and excellent faculty, recently completed its 8th batch in August, with 30 enthusiastic participants. The program has consistently proven to be a valuable platform for individuals to deepen their understanding of Type 1 diabetes. The participants not only gained valuable insights but also shared experiences and built a supportive community. The upcoming batch is scheduled for December 2024-January 2025, with applications invited from individuals living with T1D, caregivers and those who wish to support loved ones in managing the condition, and diabetes educators who see fewer persons with T1D. The program's continued success highlights the growing demand for accessible and practical diabetes education in India, and it remains committed to empowering participants with the knowledge and skills they need to live healthier, more informed lives.

IDEAS at ISPAD

Santhosh Olety, Pediatric Endocrinologist, Karnataka Institute of Endocrinology and Research, Bengaluru

IDEAS (Initiative for Diabetes Education and Awareness in Schools) is a school awareness virtual program initiated in October 2023 to improve awareness on type 1 diabetes among school teachers and various other supporting staff to improve and provide safe environment at school for children to manage their type 1 diabetes. So far 350 teachers from various parts of India have participated in our awareness sessions. Ms Sheryl Salis had an oral presentation, updating the current status and ongoing plans of the IDEAS program at the ISPAD 2024 conference at Lisbon, Portugal. It was well appreciated by the delegates, who evinced much interest in emulating the model to create similar awareness programs in their regions.

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AWARDS

ISPAD HERO AWARD 2024-Lakshminarayana Varimadugu

ISPAD acknowledged **Lakshminarayan V** by awarding him the prestigious ISPAD HERO AWARD 2024. Lakshmi was born with blindness in a poor farmer family and developed Type 1 Diabetes at the age of 17 years, but has overcome both these major handicaps with support from NGOs to complete his education. He is now employed with TCS, is a certified diabetes educator ('IDEALite') and works tirelessly to empower children and youth with T1D, especially in remote villages and among poor families. A huge source of inspiration for everyone he comes in contact with, he and Sweet Souls are currently setting up a Pediatric Diabetes Clinic in RDT Battalapalli Hospital in Anantapuram, a low resource setting where children with T1D will receive insulin, glucostrips and most importantly diabetes education to empower them and families to manage T1D confidently. ISPAE and IDEAL salute Heroes like Lakshmi who prove that nothing is impossible if we learn to work together and never give up!

AWARDS at APPES-ISPAE 2024: **Dr Dhvani Raithatha**, Fellow at Regency CDER, Kanpur, was awarded the **Kaichi Kida Award** for best oral paper on Growth for her paper titled *Development and validation of DSD interpreter, a mobile application based tool for point-of-care evaluation of children with atypical genitalia*. The award was sponsored by Human Growth Foundation and included cash prize of USD 1000, awarded by **Prof Noriyuki Namba**, Chairperson of the Scientific Committee, APPES-ISPAE 2024.

Dr Nimisha Dange, Fellow at Hirabai Cowasji Jehangir Medical Research Institute, Pune won the best oral paper in other Endocrinology and Diabetes for her paper titled *Bone health, body composition and dynamic muscle function in Indian children born small for gestational age- a case-control study*. This award was sponsored by APPES and was presented by **Prof Noriyuki Namba**, Chairperson of the Scientific Committee, APPES-ISPAE 2024.

Dr Swathi Padmanaban, Consultant Pediatric Endocrinologist, Rainbow Children's Hospital, Chennai, was awarded the 2024 International Scholar Award by Pediatric Endocrine Society.She will be hosted by the University of California, San Fransisco (UCSF) for 2 months at their Pediatric Endocrinology and Diabetes clinics. PES awards two scholarships every year, one for applicants from Central America and The Caribbean, and the other for applicants from the rest of the world. The award is designed to allow young pediatric colleagues from foreign countries interested in endocrinology to visit and work in the clinics and laboratories of PES members and to attend the PES Annual Meeting, with the aim of helping young physicians from LMIC. During the visit, the awardee will be shadowing clinicians, be involve in training their trainees, and participate in clinical research.

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BOOK RELEASE

Case based Reviews in Pediatric Endocrinology

Prof Vandana Jain (Pediatric Endocrinology Division, Dept of Pediatrics, All India Institute of medical Sciences, New Delhi) and Prof Ram Menon (Pediatric Endocrinology Division, CS Mott Children's Hospital, University of Michigan, Ann Arbor, USA) have brought out the 2nd edition of the book 'Case based Reviews in Pediatric Endocrinology' (Jaypee Brothers publications, with forewords by Prof P Raghupathy and Prof VK Paul. The first edition of the book, released in 2014, has been very popular among pediatric endocrine Fellows and practitioners. The 2nd edition has been thoroughly revised and updated, and includes several new and relevant case scenarios. It was officially released during the PCNI Workshop on Case-based Approach to Pediatric Endocrine disorders on 23rd September at AIIMS, Delhi. The Chief Guest was Prof VK Paul, Former Head, Dept of Pediatrics, AIIMS, Delhi and Member, NITI Ayog, Govt of India. Senior faculty from the Endocrine fraternity included Prof PSN Menon, Prof Anju Seth,and Prof Ravindra Goswami.

ACTIVITIES by ISPAE MEMBERS

Child and Adolescent Gender Affirmative Care

Rajni Sharma, Additional Professor, Division of Pediatric Endocrinology, Dept of Pediatrics, AIIMS Delhi

A one-day workshop and symposium on Child and Adolescent Gender Affirmative Care was organized by the Dept of Pediatrics, AIIMS, New Delhi, in association with the Association for Transgender Health in India (ATHI) and the Indian Professional Association for Transgender Health (IPATH) on 8th June 2024. Conducted in hybridmode, it was attended by international faculty and participants from all over India. The organizers included Dr Manish Singhal (Burns & Plastic Surgery), Dr Pratap Sharan (Psychiatry), Dr Rajesh Khadgawat (Endocrinology), Dr Rajni Sharma (Pediatric Endocrinology), Air Commander (retd.) Dr Sanjay Sharma (ATHI), Dr Sukanya and Dr Konpal. Esteemed national faculty included Dr Debmalaya Sanyal (President IPATH), Dr Sanjay Kalra (Endocrinologist), Dr Richie Gupta (Plastic Surgeon), Dr Kavita Arora (Mental Health Specialist), Dr Bela Sharma (Medical Specialist), Dr Umang Kothari (Pediatric Surgeon) and Dr Virender Sekhon (Pediatric Urologist). International experts from University of Colorado, USA, including Dr Micol Rothman (Endocrinologist), Dr Natalie Nokoff (Pediatric Endocrinologist), Dr Veronica Alaniz (Gynecologist) and Dr Marissa Nunes-Moreno (Clinical Psychologist) and Dr Jennnifer Solavis (Director, Multi-specialty Transitions Clinic, Oakland, USA) also joined. Dr Zoya Ali Rizvi, Deputy Commissioner at the National Health Mission, Ministry of Health and Family Welfare, Govt of India, delivered an important talk on

interventions planned by the government at the school level on issues of transgender health care in India. The workshop was attended by various stakeholders, including mental health specialists, pediatricians, pediatric and adult endocrinologists, and residents and consultants from various departments of AIIMS, New Delhi.

The importance of gender affirmative care in children and adolescents and various psychological, endocrine, surgical, and medico-legal aspects of adolescent transgender health were discussed. Dr Arora discussed mental health issues in adolescents and youth with transgender identity. This was followed by a panel discussion on mental health issues and ways to support transgender individuals and their families. Dr Solavis led an interesting and important session on non-medical gender affirmative interventions. There were two engaging postgraduate case presentations mentored by Dr Kalra and Dr Sanyal. ATHI routinely conducts workshops and sensitization programs for healthcare professionals on issues related to transgender health. ATHI and IPATH have developed the Indian Standards of Care (ISOC-1), an excellent resource material for health care professionals. Other resources for transgender health include WPATH (World Professional Association for Transgender Health) Guidelines.

Pediatric Onco-Endocrinology Meet (POEM) 2024

Vijayasarathi HA, HOD,Deptof Endocrinology, Vydehi Institute of Medical Sciences, Bengaluru and VSoundaram, Consultant Pediatric Endocrinologist, Apollo Children's Hospital and Apollo Proton Cancer Center, Chennai

The Dept of Pediatric Endocrinology at Apollo Children's Hospital, Chennai, in collaboration with the Chennai Pediatric Endocrinology and Diabetes Foundation, and in association with ISPAE, successfully organized the inaugural Pediatric Onco-Endocrinology Meeting (POEM 2024) on 6-7 July 2024.

This pioneering conference, the first of its kind globally, delved into the unique and complex intersection of pediatric oncology and endocrinology. POEM 2024 brought together 40 distinguished national faculty members who are leading experts in oncology and onco-endocrinology. The agenda was rich with critical topics, including late endocrine effects in cancer survivors, thyroid nodules and carcinoma, parathyroid hormone and phosphatonin excess, adrenal and gonadal tumors, pituitary tumors, and craniopharyngioma.There was robust participation of 140 delegates attending in person and 30 joining virtually. The success of POEM 2024 highlights Chennai's emerging role as a hub for cutting-edge medical conferences and sets a new benchmark in the field of pediatric onco-endocrinology. The event not only fostered valuable academic discourse but also laid the groundwork for future collaborations in this vital and evolving area of medicine.

Pediatric Endocrinology Post-Conference Workshop (Pediatric Conference of North India)

Vandana Jain, Rajni Sharma, Medha Mittal, AIIMS Delhi

A one-day workshop conducted at AIIMS, New Delhi on 23rdSep 2024 as part of PCNI, covered basic endocrinology topics (approach to short stature, DKA, office management of T1D, approach to DSD, precocious and delayed puberty, obesity and rickets) and was

attended by 73 delegates. Dr VK Paul, member NITI Ayog and former HOD, AIIMS, New Delhi was the chief guest. The distinguished faculty included the organizers and Drs PSN Menon, Anju Seth, Bhanu K Bhakhri, Preeti Singh and Aashima Dabas. A post-test in MCQ format was conducted at the end of the scientific sessions.

Nutrition Week Celebration at Karnataka Institute of Endocrinology and Research, Bengaluru

Dietitian and Certified Diabetes "Educator" Deepthi is at KIER, Bangaluru

Nutrition Week, celebrated at KIER, supported by Novo Nordisk, had over 45 kids participating in a series of interactive activities aimed at promoting healthy eating habits.The event also featured an interactive session where the kids learnt about balanced nutrition through a quick talk on MNT, followed by traffic zone concept-based segregation of foods as per their health benefits and frequency of consumption. Additionally, kids enjoyed participating in solving puzzles and answering the quizzes. Ms Deepthi S, Dietitian in KIER, along with Diabetes Educators Ms Syeda Atiba(NN) and Ms Cynthial T, actively engaged kids and conducted the event. The celebration concluded with the distribution of healthy snacks, allowing everyone to sample nutritious snack options. Paper plates printed with a healthy meal plate concept were given as a take away. Trophies were awarded to those who excelled in the activities.

Yog Dhyan Foundation Quarterly Report (July to September 2024)

Anil Vedwal, Chief Functionary, YDF

This third quarter of 2024 was as vibrant as ever, with physical and virtual activities supporting children with Type 1 Diabetes (T1D), and daily counseling and diabetes management sessions at our center in Kailash colony. Some brief highlights:

July: On 7th July, an HbA1c camp was attended by over 450 people, including 200 children with T1D, for blood tests, birthday celebrations for children born in this quarter, and a nutritious lunch sponsored by BIG PICTURE. Our monthly Second Sunday virtual session had Ms Deepika Kamboj as the Hero of the Month; Dr Beena Bansal discussed “Calculating Insulin-to-Carb Ratio and Insulin Correction Factor”, with panelists Ms Chhavi Kohli, Ms Tina Khanna and Dr Anju Virmani.

August: The Second Sunday virtual session honored Dr Priyanka K Bondare as Hero; Dr Archna Sarda (Udaan Foundation) focused on "A Doctor's Role in the Psychosocial Well-Being of People Living with T1D." The panelists were psychologists Prof Jyoti Kakkar and Dr Srishti Puri. On 13th August, YDF participated in a Roundtable Discussion organized by PPHF and DEESHA Foundation in Delhi. Chief Guest Dr L Swasticharan, Additional Dy. Director General (MoHFW), delivered the keynote address. YDF, represented by Dr Vedwal and T1D volunteers, shared insights on improving nationwide T1D care.

September: Two camps, on 1st and 15th, focused on diabetes education and benefits of daily yogic exercises; with distribution of free diabetes supplies (glucometers, glucostrips, insulin, pen needles, syringes). This month we began a four part “Power” series for the monthly virtual sessions. Dr Bhanu Kiran Bhakhri discussed "The Power of *Communication*: bridging the gap

between teaching and understanding", with panelists Dr Shuchy Chugh, Ms Beenu Singh, and Dr Virmani. Ms Dilpreet Kandhari, a businesswoman with T1D, was the Hero. October will have "The Power of *Unity*"; November will combine "The Power of *Diabetes Education*" with World Diabetes Day; and December will have "The Power of *Charity*". We hope you and your families with T1D will join in; else these informative sessions are available on YDF's **YouTube channel**. We were faced with the challenge of providing financial help to the family of a 9mo baby admitted in Rainbow Children's Hospital, Delhi, with severe DKA and multiple complications. Several people from the community donated for his hospital bills and ongoing care and sent valuable help in the form of 0.5 unit pens and insulin syringes. Grateful thanks to Mr Harsh Kohli.

Acknowledgment: YDF extends heartfelt appreciation to its dedicated staff - Ms Amrita Rupani, Ms Himani and Ms Ishika - helping Dr Vedwal and Dr Virmani with organizing and managing events and counselling with tireless enthusiasm.

Patient Safety Week 2024 | Initiative: Swachhata Hi Seva

Deepthi S, Dietitian and Certified Diabetes Educator, Karnataka Institute of Endocrinology and Research, Bengaluru

As part of Patient Safety Week 2024, we, hosted a creative Poster making campaign on Safe Medical Waste Disposal of Diabetes Essentials under the ***Swachhata Hi Seva*** initiative. The campaign aimed to raise awareness about the safe disposal of diabetes-related medical waste, including syringes, needles, insulin vials/cartridges, glucometers, test strips, CGM devices, and insulin pump essentials. Around 30 children with T1D participated in the campaign, creating digital posters that highlighted the importance of proper waste disposal. These posters were shared in a dedicated WhatsApp group with more than 500 kids with T1D to spread awareness among peers and families.

NEWSLETTER
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CAPE News | ISPAE

TRAINEES' SECTION

THE SEARCH FOR ELUSIVE ETIOLOGY!

Tejasvi Sheshadri, Consultant Pediatric and Adolescent Endocrinologist, Rainbow Children's Hospitals, Bengaluru & Aashima Dabas, Professor, Maulana Azad Medical College & Lok Nayak Hospital, New Delhi

Please answer the questions below on Adrenal and DSD. Correct answers and individual quiz scores will be mailed to the respective email address after the quiz closes

https://forms.gle/chYf4KK58Nai5wpM9

"LAST DATE- 31 OCTOBER 2024"

ANNOUNCEMENT- ENPP1 Deficiency

INZ-701 is an ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) enzyme replacement therapy in development for the treatment of ENPP1 deficiency, an ultra-rare genetic disorder with an incidence of 1 in 64,000 pregnancies. ENPP1 deficiency can cause pathological calcification, neointimal proliferation and impaired bone mineralization. The resulting generalised arterial calcification of infancy (GACI) carries a 50% mortality in infants and the associated autosomal recessive hypophosphatemic rickets type 2 (ARHR2) has a lifelong morbidity in those that survive the neonatal period.

The ENERGY 3 Study is a multi-center, randomized in a 2:1 ratio, controlled, open-label Phase 3 study to evaluate the efficacy and safety of INZ-701 in children with ENPP1 Deficiency. Full details of the study can be found at https://www.clinicaltrials.gov/study/NCT06046820?cond=NCT06046820&rank=1

Abbreviated inclusion criteria:

1. A confirmed postnatal molecular genetic diagnosis of ENPP1 Deficiency with biallelic mutations (ie, homozygous or compound heterozygous) performed by a College of American Pathologists/Clinical Laboratory Improvement Amendments (CAP/CLIA) certified laboratory or regional equivalent. If genetic testing cannot be performed locally then please contact the study team to further advise.
2. Age ≥1 year and <13 years
3. Open growth plates of the distal femur and proximal tibia in both legs
4. Radiographic evidence of skeletal abnormalities based on a Rickets Severity Score (RSS) ≥2.

Please contact A/Prof Andrew Biggin at Queensland Children's Hospital (andrew.biggin@health.qld.gov.au) if you have any potential patients and/or questions regarding taking part in the ENERGY 3 Study in Australia. Travel and medical costs will be covered for participants/families.


EARLY BIRD REGISTRATION
NOW OPEN
ISPAE 2025
Nagpur
9th Biennial Meeting of
Indian Society for Pediatric and Adolescent Endocrinology (ISPAE)
14th to 16th November 2025
ISPAE PET Fellows School
11th to 14th November 2025
SCAN TO REGISTER