Chapter 5: Endocrinology

Diabetes in children

Definition

A complex metabolic disorder characterised by chronic hyperglycaemia resulting from defects in insulin secretion, action, or both which leads to abnormalities of carbohydrate, fat and protein metabolism
The most common type in children is type 1 DM, usually diagnosed from age 6 months to 36 years

Risk/causes factors

- Genetics - family history in parent or sibling of type 1 DM
- Age- Type 1 DM can appear at any age, but it appears at two noticeable peaks. The first peak occurs in children between 4 and 7 years old. The second is in children between 10 and 14 years old
- Environmental factors
    - The environmental triggers include infections, nutritional factors, changes in the microbiome and chemicals.
    - Infections include Enterovirus infection (during pregnancy, infancy, childhood, and adulthood), congenital rubella syndrome, Cytomegalovirus (CMV), mumps, influenza, rotavirus, and H1N1, possibly SARS-CoV
- Idiopathic and sporadic

Prevention/promotion

- Early diagnosis
- Health education and advocacy

Signs and symptoms

• Polyuria • Polydipsia • Nocturia • Changing enuresis • Weight loss • Polyphagia • Fatigue • Frequent Urinary Tract Infections • (UTIs) • Frequent fungal and bacterial • infections	• Abdominal pain (pseudo-appendicitis diabetica) • Behavioural disturbance, including reduced school performance, and blurred vision • Impairment of growth and susceptibility to perineal • candidiasis • In its most severe form, Diabetic Keto Acidosis (DKA) or (rarer) non-ketotic hyperosmolar syndrome may develop and lead to stupor, coma and in the absence of effective treatment, death

Criteria for the diagnosis of type 1 diabetes mellitus

- Classic symptoms of diabetes or hyperglycaemic crisis with plasma glucose concentration
  ≥11.1 mmol/L (200 mg/dL), **or**
- Fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL). Fasting is defined as no caloric intake for at least 8 hrs, **or**
- Two-hour post-prandial glucose ≥11.1 mmol/L (≥200 mg/dl) during an oral glucose tolerance test (OGTT). The OGTT should be performed using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g, **or**
- HbA1c ≥6.5% (important indicator of glycaemic control)

Investigations

- Random blood glucose
- Fasting blood sugar
- Oral glucose tolerance test
- HbA1c
- Serum electrolytes
- Urine dipstick (ketones)
- Insulin & C-peptide levels
- Antibodies- Islet cell cytoplasmic autoantibodies (ICA); Glutamic acid decarboxylase (GADA); Insulinoma-associate-2 autoantibodies (IA-2A); Insulin autoantibodies (IAA)

Differential diagnosis

- Type 2 diabetes mellitus
- Maturity onset diabetes of the young (MODY-DM)
- Psychogenic polydipsia
- Diabetes insipidus
- Stress hyperglycaemia
- Long-standing steroid therapy
- Renal tubular acidosis type 1
- Glucagonoma
- Cushing's syndrome
- Hypothyroidism

Management

- Management follows a multidisciplinary approach, involving dietitians, nutritionists, psychologists, nurses, doctors and endocrinologists
- Diabetes education is a cornerstone

Primary level

- Relevant history and physical exam
- Investigations
  - Random blood sugar
  - Fasting blood sugar
  - Urine dipstick (ketones)
- Treatment (stabilise the patient)
  - Check hydration status and manage as per protocol
- Refer for secondary level

Secondary level

- Relevant history and physical examination
- Investigations
  - Random blood sugar
  - Fasting blood sugar
  - Urine dipstick
- Treatment
  - Rehydrate the patient
  - Screen for and treat for DKA. Refer to DKA section of guideline
  - Prepubertal and pubertal children usually require 0.5 to 1.0 IU/kg/day of insulin. The daily dose is divided and administered as demonstrated below using the glucose and meal- adjusted injection regimen

Type of Insulin and dosing ratio	AM	Noon	PM
Soluble • 1/3 of total daily insulin dose • Administered before main meals	1/3 of total daily dose of soluble insulin	1/3 of total daily dose of soluble insulin	1/3 of total daily dose of soluble insulin
NPH • 2/3 of total daily insulin dose	2/3 of total daily dose of NPH		1/3 of total daily dose of NPH

- Glycaemic targets:
  - Achieving target glucose levels, assessed through HbA1c and/or self-monitoring of blood glucose (SMBG) reduces risks of acute and chronic complications of diabetes This minimizes the detrimental effects of hypoglycaemia and hyperglycaemia on brain development, cognitive function, mood and quality of life
  - Finger capillary glucose should be assessed at least 3 times a day for a person with diabetes taking insulin

Recommended target glucose values for finger capillary testing values are between 4 and 10 mmol (70–180 mg/dL), with a narrower fasting target range of 4–8 mmol/L (70–144 mg/ dL)

Tertiary level

- Relevant history and physical exam
- Investigations
  - Random blood sugar
  - Fasting blood sugar
  - Urine dipstick
  - HbA1c every 3 months
  - Antibody tests (gold standard for type 1 diabetes diagnosis) – in newly diagnosed cases
  - Screen for other autoimmune diseases
    - Thyroid disease and coeliac disease
- Treatment
  - Rehydrate patient
  - Screen for and treat DKA or Honk
  - Prepubertal children usually require 0.5 to 1.0 IU/kg/day and during

puberty. The daily dose is divided and administered as demonstrated in the table above using the glucose- and meal-adjusted injection regimen.
- Glycaemic targets as above
- Adherence to insulin treatment even during sick days. Do not stop insulin on sick days. Instead, adjust up by 10 to 20% of total dose and taper after recovery to previous dosage before illness

Follow up

Short term follow up

- In patients with a new diagnosis of type 1 DM, schedule a 2-weekly visit in which checking of glucose diary and health education are reinforced
- Thereafter, monthly follow-up clinics can be scheduled.

Long term follow up

- Dietary education on every visit
- 3-monthly HbA1c
- Screen for every visit peripheral neuropathy (3-5years after diagnosis or from age of 9-11 years)
- Screen for diabetic nephropathy at every visit annually (starting 3-5 years after diagnosis or from age 9-11 years)
- Screen for diabetic retinopathy annually (starting 3-5 years after diagnosis or from age 9-11 years)

Diabetic Ketoacidosis (DKA)

Definition

A state of absolute or relative insulin deficiency resulting in hyperglycaemia, dehydration and metabolic acidosis. It is the leading cause of morbidity and mortality in children with type 1 DM (T1DM) but can also occur in patients with type 2 DM.

Risk factors

- New onset T1DM, especially due to missed diagnosis
- Omission of insulin or inadequate administration in a known patient with T1DM
- Infection
- Trauma, surgery or emotional stress
- Being a young child and/or adolescent

Prevention

- Early diagnosis
- Diagnose and treat underlying infections/triggers early
- Adherence to insulin treatment even on sick days
    - Do not stop insulin even on sick days.
    - Adjust up by 10 to 20% of the total dose and taper back to the previous dosage after recovery
- Regular reviews in the diabetic clinic
    - Assess for signs of puberty
    - Review insulin dosages
    - Intensify diabetes education (e.g. drug storage, drug administration/injection technique, injection site care, nutrition and diet, identifying complications)
- Ongoing psychosocial counselling

Promotion and advocacy

- Health education and advocacy
- Screening of patients at risk
- Advocate for consistent availability of insulin

Causes

- Missing insulin doses
- New diagnosis of T1DM
- Stress secondary to acute illness, e.g. infection or surgery

Signs and symptoms

- Any patient with T1DM who presents with abdominal pain, nausea, fatigue and/or dyspnea should be evaluated for diabetic ketoacidosis (DKA)

Symptoms of hyperglycaemia	Symptoms of acidosis	Signs of dehydration
Polyuria, polydipsia, fatigue, nocturia in a previously continent child	Abdominal pain, vomiting, nausea, rapid or deep respiration (Kussmaul's), confusion, coma, muscle pains, cramps, fruity smelling breath	Poor skin turgor, dry mucous membrane, sunken eyes, tachycardia

Investigations

- Random blood glucose
- Urine dipstick
- Full blood count (FBC) with differential
- Serum electrolytes (including calculation of the anion gap), blood urea nitrogen (BUN), and plasma creatinine
- Arterial blood gas
- Plasma osmolality
- Serum beta-hydroxybutyrate
- Electrocardiogram – to look for signs of hypokalaemia/ hyperkalaemia

Differential diagnosis

- Gastroenteritis
- Sepsis
- Pneumonia
- Encephalitis
- Acute abdomen
- Metabolic acidosis
- Severe malaria
- Meningitis

Management

Principles of DKA management

- Correct dehydration
- Correct acidosis and reverse ketosis (bicarbonate is contraindicated)
- Normalise blood glucose
- Minimize DKA complications
- Provide diabetes education for DM

Primary level

- DKA is an emergency, follow the ABC approach in managing patient
- Obtain relevant history and conduct physical examination
- Collect relevant investigations: Random blood sugar (RBS) and urine dipstick
- Assess airway and breathing status and provide support accordingly
- Assess circulation: Assess level of dehydration status and start fluid replacement based on the dehydration status
    - **Estimate 5% dehydration for mild/moderate dehydration and 7% in severe dehydration**
    - Two peripheral intravenous (IV) cannula should be inserted
        - If unable to give IV rehydration place a nasogastric tube (NGT) and use oral rehydration solution (ORS) for rehydration (if not vomiting)
        - For severely dehydrated patients, consider intraosseous fluid replacement if available
    - Start fluid replacement prior to insulin therapy
    - **Every patient with DKA is always dehydrated and should get an initial fluid resuscitation volume of 0.9% normal saline/RL 10mL/kg over 1 hour**
        - If the patient is in shock, give 20ml/kg of 0.9% normal saline/RL IV infused over 20 to 30 mins to restore peripheral perfusion
        - Start maintenance fluid with 0.9% normal saline and refer
- Do not transfer the patient while on insulin infusion
- Insulin therapy should only be initiated at the secondary level facility
- Refer to the next level of care once a patient has stable vital signs, refer whilst on fluid rehydration

Clearly document amount of fluids given

Secondary level

See the tertiary-level guidance below

Tertiary level

- As above
- If in shock or severely dehydrated, expand volume using boluses 20 ml/kg of 0.9% normal saline or RL infused over 20–30 min to restore peripheral circulation. **Reassess after every bolus.** If the patient is not responding after 2 boluses, consult paediatrician
- After initial bolus, calculate the subsequent rate of fluid administration which should include maintenance and fluid deficit **(Use 5% deficit for dehydration fluid calculation)**. Deficit should be given over 48 hours.

See example of fluid calculation (Box below).

- If needing more fluid replacement, discuss with a paediatrician.
- Monitor for signs of fluid overload.
- Assess disability
  - GCS, pupillary exam
  - Draw samples: blood glucose, beta-hydroxybutyrate, blood or urine ketones, serum electrolytes and blood gases.

Manage the child in an HDU or a designated area where close monitoring can take place.

- Monitor electrolytes/arterial blood gas every 6 to 8 hours. Correct accordingly
- Continue with fluid replacement and assess for signs of fluid overload every hour
- Catheterize and monitor urine output
- Hourly glucose check
- Insulin therapy:
  - Begin with 0.05 U/kg at least 1 hour after starting fluid replacement therapy
  - Check blood sugars hourly after initiation of insulin
  - RBS should drop by 88 – 100mg/dL every hour
  - If the RBS consistently declines by less than 88mg/dL/hr over the 1st 4 - 5 hours, consult paediatrician for dose adjustment
  - If there is rapid drop of RBS by > 100mg/dl/hr reduce dose of insulin by 10-20% and **consult** paediatrician
- Potassium: All children with DKA have a relative hypokalaemia. Start Potassium therapy after confirming urine void. Begin with 40 mmol potassium added in 1 L of fluid (0.9% NS/RL)
- 6 hourly ketones check
- Treat the underlying cause of DKA
- Keep the patient nil per os during DKA management
- Manage other complications
  - Cerebral oedema is the most common cause of mortality among children with DKA and symptoms include:
    - Onset of headache or vomiting after beginning treatment or progressively worsening or severe headache
    - Slowing of heart rate not related to sleep or improved intravascular

volume
    - Change in neurological status (irritability, lethargy, confusion, incontinence)
    - Specific neurological signs (e.g. Cranial nerve palsies)
    - Decreased oxygen saturation
  - Risk factors for developing cerebral oedema are:
    - Elevated blood urea nitrogen (BUN) concentration (>20 mg/dL)
    - Severe acidosis (ph < 7.1)
    - Severe hypocapnia (PCO2 < 21 mmhg)
    - Age < 5 years)
  - If neurologic status deteriorates acutely, hyperosmolar therapy with mannitol or hypertonic saline should be given immediately
  - If signs of cerebral oedema refer, to the management guideline of cerebral oedema
  - If there is rapid drop of RBS by > 100mg/dl/hr reduce dose of insulin by 10-20% and **consult** paediatrician
- Potassium: All children with DKA have a relative hypokalaemia. Start Potassium therapy after confirming urine void. Begin with 40 mmol potassium added in 1 L of fluid (0.9% NS/RL)
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Example of fluid calculation
A child weighing 20kg on admission in shock:
20 kg x 20ml/kg bolus needed to correct shock = 400ml Maintenance = 1500ml/day (1.5L)
Deficit = 20 kg x 5% = 1L
Requirement (over 48 hours) = Maintenance (1.5L + 1.5L) + Deficit (1L) = 4 litres/48 hours = 83ml/hour

How to select the type of fluid to use

For management of shock use plain Normal Saline or Ringers Lactate

Once the child is no longer shocked **and** is passing urine, add 40 mmol Potassium (KCL) in 1 L of fluid (0.9% NS/RL)

Fluid calculation in DKA

Formulae for fluid deficit calculation

- Weight in kg x % dehydration

(Percentage dehydration is 5% for mild dehydration and 7.5% for moderate/severe dehydration and shock)

- Total fluid for patients in DKA: Maintenance fluid + Fluid deficit

Note that, in DKA fluid calculation, the maintenance volume needs to be doubled as correction occurs over 48 hours

How to prepare and administer insulin

- Mix insulin and fluids in a 1:1 ratio, e.g. 20 units insulin in 20ml normal saline/ringer's lactate
  - This gives a concentration of 1 unit insulin/ml

- Start insulin infusion (via infusion pump) at a rate of 0.05 units/kg/hour
  e.g. for a 20kg child 20kg x 0.05 units/kg = 1ml/hour

If infusion pump is not available, use a burette and calculate drop rate depending on the giving set available.

How to manage glucose levels in a patient on insulin infusion

- Check blood sugars hourly after initiation of insulin.
- RBS should drop by 88 – 100mg/dL every hour.
- After insulin infusion has been started, monitor blood glucose hourly and adjust the IV fluids accordingly:
  - If RBS greater than 270mg/dl give N/S with 40mmoL of Potassium (KCL).
  - If RBS less than 270mg/dl give N/S with 40mmol of Potassium and 5% dextrose
  - If RBS less than 144mg/dl give N/S with 40mmol of Potassium and 10% dextrose

If RBS still dropping despite adjusting the fluids, reduce dose of insulin by 10-20% and CONSULT paediatrician.

If there is rapid drop of RBS by > 100mg/dl/hr reduce dose of insulin by 10-20% and CONSULT paediatrician.

Remember don't stop insulin unless instructed by the paediatrician!

If the RBS consistently declines by less than 88mg/dL/hour over the 1st 4 - 5 hours, consult paediatrician for dose adjustment

Transitioning to fixed dosing of insulin:

- Clearing of beta-hydroxybutyrate (blood ketones) is the gold standard for resolution of DKA.
- Urine ketones take longer to clear and therefore should not be the only measure used to determine resolution of DKA
- Switch to long term, subcutaneous insulin when the patient is improving
- The patient is fully alert and can tolerate oral fluids without vomiting

  and
- The blood glucose has dropped below 270mg/dl
- Aim to switch to maintenance doses during morning hours
- Once DKA has resolved, the patient is ready to transition to subcutaneous insulin. Give the child the subcutaneous insulin dose, then feed the child. Continue IV insulin for 30 minutes after administering subcutaneous insulin then stop.

Thyroid disorders

Congenital Hypothyroidism

Definition

Congenital hypothyroidism (CH) is caused by inadequate thyroid hormone production in newborn infants, resulting from an absent or under-developed thyroid gland (agenesis/dysgenesis) (80-85% of cases) or one that has developed but cannot produce thyroid hormone because of a 'production line' problem (dyshormonogenesis) (10-15% of cases).

Risk factors/causes

- Maternal perinatal factors such as advanced maternal age, gestational complications, maternal iodine deficiency, mother on antithyroid drugs, presence of antithyroid antibodies or excess iodine exposure
- Neonatal perinatal factors such as female sex, preterm birth, post-term birth, low birth weight, presence of other birth defects, and multiple gestation
- Down's syndrome
- Predominantly sporadic
- 2% genetic or familial

Prevention/promotion

- Newborn screening Thyroid Stimulating Hormone (TSH): blood (heel prick or cord blood) is collected from full-term infants, usually one to two days after birth
- Advocate for neonatal screening to prevent intellectual and physical disability
- Health education

Signs and symptoms

- Can be asymptomatic.
- Symptoms usually develop over the first few months of life: lethargy, hoarse cry, feeding problems (often needing to be awakened to nurse), constipation, puffy (myxedematous) and/or coarse facies, macroglossia, umbilical hernia, large fontanels, hypotonia, dry skin, hypothermia, and prolonged jaundice (primarily unconjugated hyperbilirubinaemia)
- Later problems: profound intellectual disability, growth retardation.
- 3-7% have other birth defects (e.g. ASD, VSD, micropenis, undescended testes, hearing loss)

Investigations

- T4 and TSH assays

Primary hypothyroidism	High TSH, low free T4
Subclinical hypothyroidism	High TSH, normal free T4 or total T4
Central hypothyroidism	Low or normal TSH, low free T4

- Cardiac echo and audiology screening
- Additional testing (may be helpful for selected infants):
  - Thyroid imaging
    - Thyroid ultrasonography and colour flow Doppler
    - Thyroid radionuclide uptake and scan
  - Thyroid autoantibodies
  - Serum thyroglobulin concentration
  - Urinary iodine concentration
  - Genetic testing
  - Imaging of left lower extremities: absent distal left femoral epiphysis in 54% of patients

Differential diagnosis

- Spinal muscular atrophy
- Muscular dystrophies
- TORCH infections
- Hirschsprung's disease
- Panhypopituitarism
- Beckwith-Wiedemann syndrome

Management

Primary level
- Identify key diagnostic features (refer to signs and symptoms above)
- Manage acute illnesses like hypoglycaemia as per ETAT protocol
- Refer patient to tertiary level of care

Secondary level
- Proceed as at primary level of care
- Refer patient to tertiary level of care

Tertiary level
- Identify key diagnostic features as highlighted above

- Carry out baseline tests:
  - T4 and TSH assays
  - Random blood sugar
  - Serum electrolytes and liver function tests
  - Manage symptoms of acute illness such as hypoglycaemia as per ETAT protocol

Treatment

- Plot growth chart for length, weight and head circumference. Follow growth charts on every visit.
- 0-3 months of age: Levothyroxine dose of 10 to 15 µg/kg/day.
  - Administration: The tablet should be crushed and mixed with 5-10mL of breastmilk, formula (except soy protein formula), or water and fed to the infant.
  - Give immediately, do not store
- Avoid administration with Soy formula supplements with iron or calcium and antacids (aluminum hydroxide) or infant "colic" drops (simethicone) may reduce absorption
- Treatment goals — Ensure normal growth and neurodevelopmental outcomes. This is achieved by restoring serum fT4 (or T4) and TSH concentrations to the normal range as rapidly as possible, followed by dose adjustment to maintain clinical and biochemical euthyroidism.
  - Target is serum T4 concentration in the upper one-half of the reference range for age.
  - Target for serum TSH should be in the lower end of the reference range
  - For infants with congenital central hypothyroidism, serum free T4 should be used to guide treatment because measurement of serum TSH is not helpful
- Monitoring schedule – For infants with congenital primary hypothyroidism, monitor serum T4 and TSH at the following intervals:
  - Two weeks and four weeks after the initiation of levothyroxine treatment
  - Every one to two months during the first 6 months of life
  - Every three to six months between six months and three years of age
  - Every six to 12 months thereafter until growth is complete
  - Four weeks after any change of dose

Once diagnosis is confirmed and treatment is started refer patient to an endocrinologist

Acquired hypothyroidism in childhood and adolescence

Definition

Abnormally low activity 0of the thyroid gland, resulting in slowing of growth, mental development and metabolic changes in children.

Risk factors/causes

- Chromosomal disorders such as Down syndrome, William's syndrome, or Turner syndrome.
- An autoimmune disorder such as type 1 diabetes or coeliac disease
- Too little or too much iodine intake
- Injury to the thyroid gland
- Radiation to the head and neck
- Nutritional:
    - Iodine Deficiency
    - Excess iodine exposure (e.g. herbal supplements, drugs such as amiodarone, expectorants)
- Drugs:
    - Antithyroid drugs (e.g. methimazole, propylthiouracil)
    - Antiseizure medications (e.g. phenytoin, phenobarbital, valproate)

Promotion

- Health education

Signs and symptoms

- Initial symptoms: constipation, sluggishness, lethargy, cold intolerance, dry skin, brittle hair, facial puffiness, muscle aches and pains
- Declining school performance
- Delayed pubertal development
- Declining growth velocity/short stature
- Encephalopathy
- Hypothalamic or pituitary disease may cause headaches, visual symptoms, or manifestations of other pituitary hormone deficiencies.

Investigations

- T4 and TSH assays

Primary hypothyroidism	High TSH, low free T4
Subclinical hypothyroidism	High TSH, normal free T4 or total T4
Central hypothyroidism	Low or normal TSH, low free T4

- Additional testing (may be helpful for selected patients)
  - Thyroid imaging - thyroid ultrasonography and colour flow doppler
  - Serum thyroglobulin concentration
  - Thyroid autoantibodies - antithyroid peroxidase antibodies (TPO-Ab) and antithyroglobulin antibodies (TrAb)
  - Urinary iodine concentration
  - Genetic testing

Differential diagnosis

- Autoimmune thyroid disease
- Iodine deficiency/malnutrition
- Constipation
- Growth hormone deficiency

Management

Primary level

- Identify key diagnostic indicators:
  - Check random blood glucose
  - Asses signs and symptoms as stated above
  - Manage acute illnesses as per protocol
- Refer patient to the next level of care

Secondary level

- Identify key diagnostic factors as highlighted above
- Carry out baseline tests, including random blood glucose
- Serum electrolytes and liver function tests
- Stabilise patient and manage acute illness as per protocol
- Refer patient to next level of care

Tertiary level

- Take a history and physical exam as outlined.
- Perform baseline investigations
- T4 and TSH.
- Treatment

  Levothyroxine dose — Initial treatment is started with levothyroxine at the following doses, orally, once daily administered in the morning 30 minutes before food and adapt as necessary:
  - Age 1 to 3 years: 4 to 6 µg/kg body weight
  - Age 3 to 10 years: 3 to 5 µg/kg
  - Age 10 to 16 years: 2 to 4 µg/kg
- Monitoring and dose adjustment —
  - Serum TSH and free T4 should be checked six to eight weeks after initiation of treatment, then every 6 to 12 months.
  - Thyroid function tests should be obtained six to eight weeks after any dose change or if the patient develops any clinical manifestations suspicious for hypo- or hyperthyroidism.
  - Adjust levothyroxine dose to maintain TSH and free T4 in the normal reference range for age.
- Once diagnosis is confirmed and treatment is started, refer patient to an endocrinologist.

Follow up

- Review medication use and monitor for potential side effects
- Monitor growth and developmental progress

Hyperthyroidism

Definition

Hyperthyroidism is defined as an inappropriately high production of thyroid hormones from the thyroid gland, leading to various systemic clinical manifestations.

Risk factors/causes

- Drugs (levothyroxine, lithium)
- Having personal or family history of autoimmune disease
- Viral infections (e.g. mumps, influenza)
- Autoimmune dysfunction (e.g. Graves' disease)
- Tumours (thyroid carcinoma)
- Excess iodine intake

Prevention/promotion

- Early diagnosis in patients at risk
- Health education and advocacy

Signs and symptoms

	Symptoms	Signs
Constitutional	Weight loss despite increased appetite; heat-related symptoms (heat intolerance, sweating)	Weight loss
Neuromuscular	Tremor, nervousness, anxiety, fatigue, weakness, disturbed sleep, poor concentration	Tremor of the extremities, hyperactivity, hyperreflexia, pelvic and girdle muscle weakness
Cardiovascular	Palpitations	Tachycardia, systolic hypertension, irregular heartbeat (atrial fibrillation)
Pulmonary	Dyspnoea, shortness of breath	Tachypnoea
Gastrointestinal	Diarrhoea, nausea, vomiting	Abdominal tenderness
Skin	Increased perspiration	Warm and moist skin

Reproductive	Menstrual disturbances	
Ocular (Graves' disease)	Diplopia, sense of irritation in the eyes, eyelid swelling, retro-orbital pain or discomfort	Proptosis, eyelid retraction and lag; periorbital oedema, conjunctival injection and chemosis, ophthalmoplegia

Investigations

- Full blood count
- Serum thyroid function tests (T4, TSH)
- Serum thyroid antibody tests (TPOs and TRAb)
- Ultrasound
- Radionuclide uptake and scan

Differential diagnosis

- Graves' disease
- Subacute thyroiditis
- Hashimoto toxicosis
- Autonomously functioning thyroid nodule
- Factitious hyperthyroidism (intake of exogenous hormone)
- TSH-secreting pituitary tumour (rare)
- Pituitary resistance to thyroid hormone

Management

Primary level

- Identify key diagnostic indicators
- Signs and symptoms as stated above
- Manage acute illnesses as per protocol
- Refer patient to the next level of care

Secondary level

- Identify key diagnostic factors as highlighted above
- Carry out baseline tests
- Random blood sugar
- Serum electrolytes and Liver function tests
- Stabilize patient: manage acute illness as per protocol
- Manage hypertension (see section on Hypertension)
- Refer patient to the next level of care

Tertiary level

- Conduct history and physical exam as outlined above.
- Perform baseline investigations
- T4 and TSH assays
- Initiate treatment with antithyroid drugs:
  - Carbimazole 15mg daily as starting dose
- Once diagnosis is confirmed and treatment has started refer patient to an endocrinologist.

Follow up

- FBC-look for evidence of bone marrow suppression
- Blood pressure monitoring
- Assess nutrition and monitor growth

Approach to disorders of sex development (Ambiguous Genitalia)

Definition

Patients born with genitalia that do not appear typically male or female, or that have an appearance discordant with the chromosomal sex, are classified as having a difference (or disorder) of sex development (DSD).

Risk factors/causes

- Autosomal recessive and X-linked inheritance
- Caused by mutations of genes associated with sex determination

Prevention/promotion

- Genetic counselling of family members
- Advocacy
- Reducing stigma associated with DSD
- Health education for health staff and affected families

Signs and symptoms

- General symptoms
- Overt genital ambiguity

Discordance between genital appearance and (pre-/postnatal) karyotype	
Newborns and infants	
Apparent Male	Apparent female
Largely male appearance of the external genitalia and any of the following: • Bilaterally nonpalpable gonads • Severe hypospadias • Any degree of hypospadias accompanied by unilateral or bilateral cryptorchidism and/or micropenis • Genital appearance discordant with sex chromosomes	Largely female appearance of the external genitalia and any of the following: • Clitoromegaly • Posterior labial fusion • Gonads palpable in the labioscrotal folds or • inguinal region • Genital appearance discordant with sex chromosomes
Children and adolescents	
Male	Female

Largely male appearance of the external genitalia and any of the following: • Bilaterally nonpalpable gonads • Severe hypospadias • Any degree of hypospadias accompanied by unilateral or bilateral cryptorchidism and/or micropenis • Breast development • Genital appearance discordant with sex chromosomes	Largely female appearance of the external genitalia and any of the following: • Clitoromegaly • Posterior labial fusion • Gonads palpable in the labioscrotal folds or • inguinal region • Absent or delayed breast development • Genital appearance discordant with sex chromosomes • Absence of menarche

Investigations

- Biochemistry
  - Urea and electrolytes (sodium and potassium)
  - Blood glucose
  - Hormonal levels, i.e. cortisol, testosterone, estradiol, progesterone, 17-hydroxy-progesterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and Anti-Müllerian Hormone (AMH)
- Abdominal and pelvic ultrasound (USS)
- Karyotyping
- Laparoscopy and gonadal biopsy

Differential diagnosis

- Hypospadias
- Congenital adrenal hyperplasia (CAH)
- Androgen insensitivity
- Ovotesticular DSD (true hermaphroditism)

Management

Do not assign sex before full evaluation at tertiary level and encourage parents to give unisex name.

Primary level
- History - pregnancy and birth + family history of consanguinity
- Conduct physical examination
- Management - Supportive care, correct dehydration and hypoglycaemia

- Referral to higher-level care

Secondary level

- History and examination as above
- Investigations
  - Electrolytes
  - Abdominal and pelvic USS (if available)
- Management - Supportive care, correct dehydration and hypoglycaemia
- Referral to tertiary care

Tertiary Level

- History and examination, as outlined above
- Thorough investigations (see investigation section)
- Management
  - Supportive care, correct dehydration and hypoglycaemia
  - Specific treatment according to underlying disease
- Refer to endocrinologist
- Management requires multidisciplinary team that includes: paediatric endocrinologist, paediatrician, geneticist, urologist, gynaecologist, psychologist, nurses and social worker

Follow up

- Medication review and monitoring for side effects
- Ongoing social counselling

Congenital adrenal hyperplasia (CAH)

Definition

Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders caused by defects in adrenal steroidogenesis. These result from mutations in one or more enzyme-encoding genes, leading to dysfunctional cortisol and aldosterone production and excessive levels of androgens.
The most common form is 21-alpha-hydroxylase deficiency (21-OHD).

Risk factors/causes

Factors that increase the risk of having CAH include:
- Both parents who are known to be heterozygous for one of the severe mutations
- Both parents who have CAH
- Having an affected sibling

Prevention/early diagnosis

- Neonatal screening for elevated 17-hydroxy-progesterone (where screening facilities are available in patients with the above risk factors)
- Genetic testing of other family members
- Early detection and management to prevent complications

Promotion

- Advocacy
- Health education

Signs and symptoms

- Symptoms depend on:
    - Severity of enzyme deficiency
    - Type of enzyme deficiency
    - Age

Infants	
Atypical genitalia/ ambiguous genitalia	Females • Clitoral enlargement • Labial fusion • Formation of a urogenital sinus caused by the effects of in-utero androgen excess on the development of the external genitalia • Virilization may be so profound that genital atypia is unrecognized, and male sex assignment (with undescended testes) is made at birth in a 46XX patient
	Males • Normal-appearing genitalia at birth, but may have subtle findings such as hyperpigmentation of the scrotum or an enlarged phallus • In some rare enzyme defects, ambiguous genitalia may be present due to impaired androgen production
Adrenal crisis	• Vomiting, diarrhoea, hypotension, and hypovolaemic shock can occur, typically between 10 to 20 days of age • Laboratory findings suggesting adrenal crisis include: hyperkalaemia with or without hyponatraemia, metabolic acidosis, and hypoglycaemia
Children and adolescents	
	• Pubic hair appears early, acne may be excessive, and the voice may deepen • Excessive pigmentation may develop • Signs of virilization in girls, early growth of penis and testicles in boys • Isosexual central precocious puberty may occur and bone age is significantly advanced if patient is not adequately treated • Final adult height is often compromised

Differential Diagnosis

- Other forms of DSD
- Metabolic diseases of the newborn
- Addison's Disease
- Sepsis

Management

Primary level

- Identify key diagnostic indicators (signs and symptoms)
- Manage acute illnesses like dehydration and hypoglycaemia as per protocol
- Refer patient to the next level of care

Secondary level

- Identify key diagnostic indicators
- Carry out baseline tests and the following:
  - Random blood sugar
  - Serum electrolytes
  - Abdominal and pelvic ultrasound scan
- Stabilize patient, manage dehydration and hypoglycaemia
- Refer patient to the next level of care

Tertiary level

- History and physical exam as above.
- Stabilise patient, manage dehydration and hypoglycaemia as per protocol.
- Baseline investigations (ordered under guidance from an Endocrinologist)
  - Random blood sugar (hypoglycaemia)
  - Serum electrolytes (hyperkalaemia, hyponatraemia)
  - Serum 17-hydroxyprogesterone (elevated in CAH)
  - Cortisol at a minimum (decreased)
  - Abdominal and pelvic ultrasound scan
- Other tests
  - ACTH stimulation test
  - Genetic testing
- Medical management
  - Supportive management
    - Treat adrenal crisis (refer to adrenal crisis management)
    - Correct dehydration and manage hypoglycaemia
  - Specific management

Newborns:

- Glucocorticoid therapy should be initiated in newborns with:
- Confirmed CAH – Initiate treatment with hydrocortisone, fludrocortisone and sodium supplements indefinitely.
- Suspected CAH (e.g. infant presenting with a positive newborn screen or atypical genitalia) need treatment with hydrocortisone, fludrocortisone and sodium chloride supplements at standard starting doses. Continue this treatment until the diagnosis of CAH is either confirmed or excluded.
- Initial dosing for newborns — In the absence of adrenal crisis, a typical starting regimen for an infant includes:
  - Hydrocortisone 20 to 30 mg/m^2/day, divided three times daily (e.g. 2.5 mg three times a day), with rapid dose reduction when target hormone levels are reached.
  - Fludrocortisone 100 µg (0.1 mg) once or twice daily
  - Sodium chloride, 1 to 2 g or 17 to 34 mEq/day (2 to 4 mEq/kg/day), divided in several feedings.

Infants and children

- Hydrocortisone (cortisol): 10 to 15 mg/m^2/day, divided into three doses.
- Hydrocortisone should be increased 3-5 fold in severe infection, high fever and surgery.

Consult an endocrinologist.

Follow up

- Medication review and side effects
- Patients/guardians should be educated on sick day management

Puberty disorders

Precocious puberty

Definition

Onset of secondary sexual characteristics before the age of 8 in girls and 9 years in boys. It is more common in girls than in boys.

Other forms of premature sexual maturation

- **Premature thelarche** - Premature breast development (as early as first year of life) that can be unilateral or bilateral and is self-limiting usually by the age of 4 years.
- **Adrenarche** - Premature development of pubic hair and axillary hair. If isolated, it is not a sign of puberty in either sex.
- **Precocious pseudo puberty** - When signs of sexual maturation occur due to sex steroid secretion which has a different mechanism from normal puberty. Usually recognised by abnormal sequence of events of sexual maturation.

Risk factors

- Females
- Obesity
- Sex hormone exposure (oestrogen or testosterone cream or ointment, or other substances that contain these hormones such as medication or dietary supplements)
- Other medical conditions (McCune-Albright syndrome or congenital adrenal hyperplasia, hypothyroidism and neural tube defects).
- Radiation therapy of the central nervous system.
- Pituitary hamartomas
- Pituitary adenomas

Causes

Idiopathic

- CNS irradiation
  - Primary hypothyroidism
  - Adrenal pathology
- Females
  - Ovarian cysts
  - Ovarian tumours
- Males

- Leydig cell tumours
- Human chorionic gonadotropin secreting germ cell tumours

Prevention/promotion

- Early diagnosis and treatment
- Health education and advocacy

Signs and symptoms

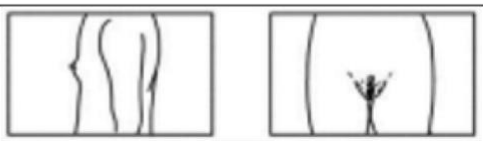
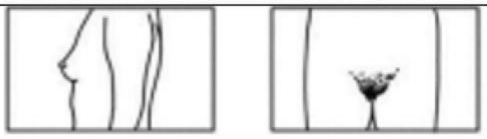
Male

- Testicular enlargement (=/> 4mL)
- Growth of testes correlates well with growth of penis and pubic hair
- Size of penis (if obese, retract the pubic fat pad to obtain an accurate estimation of size). Use penile growth chart.
- Presence of anatomical variants of the penis e.g. hypospadias
- Easy foreskin retractability
- Scrotal pain or swelling

Female

- Breast development
- Colour and size of the area around the nipples
- Presence of pubic hair
- Presence of anatomical variants, labial adhesions, vulvar ulcers.
- Vaginal discharge/bleeding (early menarche)

Tanner staging for sexual development

Tannger stage	Boys	Girls
1		
2		
3		
4		
5		

Investigations

- Medical history
- Physical examination
- Plot height, weight, BMI and bone age on growth chart
- Imaging
  - Bone age (X-ray of the left hand)
    - Abdominal USS and pelvis USS (rule out cryptorchidism)
  - CT/MRI of the brain
- Hormones
  - Testosterone and oestrogen
  - Luteinising hormone (LH) and follicle-stimulating hormone (FSH)
  - LH:FSH ratio

Differential diagnosis

- Premature adrenarche
- Premature thelarche
- Exogenous androgens
- Testicular mass

Management

Primary level

See the secondary-level guidance

Secondary level

- Identify signs and symptoms
- Refer to tertiary care

Tertiary level

- History, physical exam and investigations as above.
- Treatment
  - Psychosocial support to the family
  - Treat the underlying cause.
  - Medical Management
  - Gonadotropin analogues
  - Leuprorelin acetate
- Refer to endocrinologist

Follow up

- Medication review and monitoring for side effects

- Monitor growth and development

Delayed puberty

Definition

Absence of secondary sexual characteristics by 13 years in girls and 14 years in boys. Pubertal arrest is also considered as delayed puberty.

Risk factors

- Male sex
- History of delayed puberty
- Excessive exercise
- Chronic disease
- Radiation
- Radiation exposure
- Eating disorders (e.g. anorexia nervosa)
- Pituitary surgery
- Pheochromocytoma
- Chemotherapy

Causes

- Chronic disease
- Poor nutrition
- Psychosocial deprivation
- Steroid therapy
- Tumours adjacent to the hypothalamus e.g. craniopharyngioma
- Congenital anomalies
- CNS irradiation or trauma
- Testicular torsion/trauma
- Cryptorchidism
- Mumps
- Female DSDs
- Polycystic Ovarian Syndrome (PCOS)
- Gonadal dysgenesis, e.g. Turner syndrome, Klinefelter syndrome
- Chemotherapy

Prevention/promotion

- Early diagnosis
- Health education and advocacy

Signs and symptoms

Girls

- No breast development and/or pubic hair by age 14 OR
- No Menstruation by age 16 OR
- First signs of puberty appeared > 5 years before menarche

Boys

- No enlargement of penis or testes by age 15 years OR
- No pubic hair by age 15 years

Investigations

- Medical history including family history of delayed puberty
- Physical examination - Plot height, weight, BMI and bone age on the growth chart
- Imaging studies
  - Bone age
  - Abdominal USS and pelvic USS
  - CT/MRI of the brain
- Hormones
  - LH, FSH
  - LH:FSH ratio

Differential diagnosis

- Constitutional delay of growth and puberty
- (Congenital) hypergonadotropic hypogonadism
- (Congenital) hypogonadotropic hypogonadism

Management

Primary level Refer to management guidelines at Secondary Level
Secondary level • Identify delayed puberty through history and examination • Refer to tertiary care
Tertiary level • Provide psychosocial support to the family • Investigate and treat the underlying cause • Medical management

  - Male - Testosterone therapy
  - Female - Oestrogen and progestin
- Refer to endocrinologist

Follow up

- 3-monthly follow up in the endocrinology clinic
- Medication review and monitor side effects
- Monitor growth and development

Overweight and obesity

Definition

Overweight and obesity refers to excess of body fat.

- Overweight – BMI between >85th and 95th percentile for age and sex.
- Obesity – BMI ≥95th percentile for age and sex.
- Severe obesity – Severe (class II or greater) obesity is defined as BMI ≥120 percent of the 95th percentile values or a BMI ≥35 kg/m^2 (whichever is lower).

Risk factors/causes

Environmental factors

- Glycaemic index of foods
- Sugar-containing beverages
- Large portion sizes of prepared foods
- Fast food consumption
- Decreased family meals
- Reduced structured physical activity
- Shortened sleep duration
- Changes in elements of the built environment (e.g. availability of sidewalks and playgrounds)
- Excessive screen time
- Medications (e.g. certain psychoactive drugs, steroids)
    - Other Factors
        - Genetic predisposition
        - Endocrine causes e.g. hypothyroidism, Cushing's syndrome

Prevention/promotion

- Lifestyle modification
- Health education and advocacy

Signs and symptoms

- Striae distensae
- Acanthosis nigricans (darkening of the neck, armpits and groin)
- Sleep apnoea
- Joint pains
- Fatigue
- Infections in skin folds
- Shortness of breath
- Heat intolerance

- Excessive sweating
- Depression

Investigations

- Plot height and weight on a growth chart
- Calculate and plot BMI
- Assess for dysmorphic features
- Neurodevelopmental assessment
- Blood pressure
- Random blood glucose
- Urea and electrolytes
- Liver function tests (LFTs)
- Lipid profile – including LDL and HDL

Management

Primary level

- Take relevant history, perform physical examination and anthropometric measurements as above
- Check random blood sugar (RBS)
- Management
  - Lifestyle modification
  - Exercise
  - Reduce consumption of high glycaemic index foods
  - Screen for and manage diabetes and hypertension accordingly
- Refer to next level of care

Secondary level

- Relevant history, physical exam and anthropometric measurements as above
- Measure blood pressure
- RBS, U&Es, LFTs
- Management
  - Lifestyle modification
  - Exercise
  - Reduction of intake of food with high glycaemic index
  - Screen for diabetes and hypertension and manage accordingly
- Refer to next level of care

Tertiary level

- Relevant history, physical exam and anthropometric measurements as above.
- Measure blood pressure
- RBS, U&Es, LFTs, LDL, HDL
- Management
  - Lifestyle modification
  - Exercise
  - Reduction of intake of food with high glycaemic index
  - Screen for diabetes and hypertension and manage accordingly
- Psychosocial counselling
  - Refer to an endocrinologist.
- Multidisciplinary involvement including nurses, dieticians, nutritionists, paediatricians, psychosocial counsellors.

Follow up

- Monthly follow up in the endocrinology clinic
- Medication review for side effects
- Monitor growth and development
- Provide ongoing education/counselling

Growth disorders

Short stature

Definition

Short stature is a term applied to a child whose height is 2 standard deviations (SD) or more below the mean for children of the same sex and chronologic age (and ideally from the same racial-ethnic group).

Risk factors/causes

- Chronic disease
- Chronic malnutrition
- Psychosocial deprivation
- Family history of short stature
- Delayed growth and puberty
- Chronic steroid use
- Genetic syndromes (e.g. Down's syndrome, Turner syndrome)

Prevention/promotion

- Early detection and treatment of underlying causes
- Health education

Signs and symptoms

- Shorter than peers of same age and sex
- May have dysmorphic features
- Signs of underlying disease

Investigations

- Bone age
- Full Blood Count (FBC)
- Erythrocyte Sedimentation Rate (ESR)
- Urea and electrolytes
- Thyroid-Stimulating Hormone (TSH), free thyroxine (T4)
- If available: IGF-1, IGFBP-3, Transglutaminase IgA

Differential diagnosis

- Familial short stature
- Constitutional delay of growth and puberty

- Undernutrition
- Gastrointestinal disease (especially Crohn disease and coeliac disease)
- Renal disease (CKD, renal tubular acidosis)
- Endocrine causes of growth failure (hypothyroidism, isolated growth hormone deficiency, Cushing's disease)
- Cardiac disease
- Genetic diseases with primary effects on growth e.g. Down's syndrome, Turner syndrome

Management

Primary level
- Take history and perform examination
- Plot height and weight on a growth chart
- Check random blood Glucose (RBS) and perform urine dipstick
- Refer to next level of care

Secondary level
- As outlined above
- RBS, FBC, erythrocyte sedimentation rate (ESR)
- Refer to next level of care

Tertiary level
- History and physical examination
- Calculate height velocity
- Plot parents' height and calculate mid-parental height

Investigations
  - Bone age
  - FBC
  - ESR
  - Electrolytes, creatinine
  - Thyroid-stimulating hormone (TSH), free thyroxine (T4)
  - If available and appropriate: IgF-1, IgFBP-3, IgA, Tissue Transglutaminase IgA
- Refer to paediatric endocrinologist

Follow up
- 3-monthly follow up in the endocrinology clinic
- Monitor growth and development
- Ongoing education/counselling

Tall stature

Definition

Tall stature is a term applied to a child whose height is 2 standard deviations (SD) or more above the mean for children of the same sex and chronologic age (and ideally of the same racial-ethnic group).

Risk factors/causes

- Growth hormone excess
- Hyperthyroidism
- Family history of tall stature
- Overweight/obesity
- Accelerated growth and puberty
- Genetic syndromes (e.g. Marfan syndrome, Klinefelter syndrome)

Prevention/promotion

- Early detection
- Health education and advocacy

Signs and symptoms

- Taller than peers of same age and sex.
- May have dysmorphic features

Investigations

- Bone age
- Complete Blood Count (CBC)
- Erythrocyte Sedimentation Rate (ESR)
- Urea and electrolytes
- Thyroid-Stimulating Hormone (TSH), free thyroxine (T4)
- If available and appropriate: IgF-1, IgFBP-3

Differential diagnosis

- Familial tall stature
- Hyperthyroidism
- GH-secreting tumours
- Precocious puberty (temporary tall stature)
- Genetic diseases with primary effects on growth e.g. Klinefelter syndrome

Management

Primary level

See the secondary-level guidance below

Secondary level

- History and physical examination
- Plot height and weight on growth chart

Refer to next level of care

Tertiary level

- History and physical examination
  - Calculate height velocity
  - Plot parents' height and calculate mid-parental height
- Investigations
  - Bone age
  - Thyroid-stimulating hormone (TSH), free thyroxine (T4)
  - If available and appropriate: IgF-1, IgFBP-3

Refer to paediatric endocrinologist

Follow up

- 3-monthly follow up in the endocrinology clinic
- Monitor growth and development
- Ongoing education/counselling

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