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មគ្គទ្ទេសក៍ព្យាបាលគ្លីនិក
CLINICAL PRACTICE GUIDELINES

ផ្នែក
FOR

វេជ្ជសាស្ត្រកុមារ
PEDIATRICS

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នាយកដ្ឋានសេវាសុខភាព
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Kingdom of Cambodia
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CLINICAL PRACTICE GUIDELINES

FOR

PEDIATRICS

Part 2

Department of Health Services

December 2025

Ministry of Health

CLINICAL PRACTICE GUIDELINES FOR PEDIATRICS

Part 2

December 2025

Contents

Chapter IV: Endocrinal diseases

DAIBETES MELLITUS IN CHILDREN

(Insulin Dependent Diabetes Mellitus, Juvenile Diabetes)

IV Malene, BAN Manet

I. Key Facts

- T1DM remains the most common type of diabetes in children, despite the increasing rate of type 2 diabetes mellitus (T2DM). (1)
- Diabetes is found in every population in the world and in all regions, including rural parts of low- and middle-income countries. The number of people with diabetes is steadily rising, with WHO estimating there were 422 million adults with diabetes worldwide in 2014. In addition, the International Diabetes Federation (IDF) estimated that 1.1 million children and adolescent age 14-19 years old have type 1 diabetes mellitus (T1DM). (2)
- The incidence of childhood T1DM varies worldwide, ranging from 0.1 to 65 per 100,000 children < 15 years old. The age of presentation has a bimodal distribution, with peaks between 4 to 6 years old and 10 to 14 years old. (3)
- The differentiation between T1DM, T2DM, monogenic, and other forms of diabetes have important implications for both treatment and education. (4)

II. Overview

1. Definition:

Type 1 diabetes mellitus (T1DM), one of the most common chronic diseases in childhood, is defined by insulin deficiency following the destruction of the insulin-producing pancreatic beta cells. (5)

2. Pathophysiology:

T1DM is the result of the auto-immune destruction of insulin producing β cell of the pancreas islet.

3. Etiology:

The exact etiology is complex and currently unknown. It is believed that it triggers by unknown environmental factors such as viral infection (coxsackie virus, cytomegalovirus, mumps, rubella), cow's milk feeding at an early age, vitamin D deficiency, and perinatal factors in the genetic predisposition individual (HLA DR3/DR4).

III. Symptoms (6,7)

When 80-90% of the β cell mass has been destroyed, the remaining β cell mass is insufficient to maintain euglycemia and clinical manifestations of diabetes result.

More common	Less common	Severe presentation (DKA)
- Weight loss - Polyuria (bed wetting) - Excessive thirst, tiredness	- Excessive hunger - Blurred vision - Mood changes -Skin infections - Oral or vaginal thrush - Abdominal pain	- Frequent vomiting - Acute abdominal pain - Flushed cheeks - Acetone smell of breath - Dehydration with continuing polyuria - Decrease level of consciousness - Kussmaul respiration (deep, rapid, sighing) - Coma - Shock.

IV. Diagnosis

- Criteria for the diagnosis of diabetes mellitus:
  - Classic symptoms of diabetes or hyperglycemic crisis with plasma glucose concentration

≥200 mg/dl (11.1 mmol/L)
  - Fasting plasma glucose ≥ 126 mg/dl (≥7.0 mmol/L)
  - Abnormal oral glucose tolerance test (OGTT) with a 2-hour postprandial serum glucose concentration ≥200 mg/dl.
  - Hba1c ≥6.5%.
- In the present of symptoms: Urine testing: glycosuria, ± Ketonuria
- Inform the patient and their family and refer them to specialized centre if they meet any of the above criteria.

V. Treatment

1. Aims of Diabetes Management

- Optimal glycemic control.
- Normal growth and development (Under-insulinization leading to growth failure and pubertal delay).
- Reduce the risk of long-term complications.

2. Insulin therapy:

a. Type of Insulin:

Human Insulin	Analogue Insulin
Short acting (Actrapid…), Intermediate (Insulatard…) and Premix (Mixtard…)	Rapid acting (Novorapid…) and long acting (Levemir…)

Currently, there is no evidence illustrated that using analogue is better than human insulin in term of improving hba1c level.

b. Subcutaneous injection:

The two most used regimens are:

Conventional regimen (2 injections daily)	Basal Bolus regimen (Multiple daily injection, usually 4 injections)
- Short-acting insulin (Actrapid®) + Intermediate-acting insulin (Insulatard®) given 20-30 minutes before breakfast and dinner (See algorithm). - 2/3 of total daily insulin in the morning and 1/3 in the evening (1/3 of the insulin dose is short-acting and 2/3 is intermediate Acting).	- 3 injections of rapid acting with main meal (bolus) + 1 injection of long or intermediate action (Basal) at bedtime. - If using rapid acting and long acting (analogue insulin): • 50-70% of total daily dose as rapid acting insulin • 30-50% is given as long-acting insulin - If using short-acting (regular) and intermediate-acting (human insulin): • 70% of the total daily dose as short-acting insulin (divided into 3 pre-meal boluses) • 30% of the total daily dose as a single injection of intermediate-acting insulin before bedtime.

Insulin requirement/dosage:

Pre-pubertal children (outside the partial remission phase)	During puberty
Usually require 0.7-1.0 IU/kg/day	Requirements may rise substantially above 1 and even up to 2 U/kg/day

The ''optimal'' dose of insulin is that which achieves the best attainable glycemic control for an individual child or adolescent, without causing obvious hypoglycemia, and resulting in normal growth and development.

c. Injection *site: 4 recommended sites:* [8]

d. Intravenous insulin: Use in case of DKA, IV Infusion of regular insulin (Actrapid®), *See Algorithm.*

e. Insulin pump: Can also use, but this is very expensive and requires expert education to initiate and monitor therapy.

f. Monitoring:

- Blood Glucose testing: usually two to four times per day
- Urine testing: should be tested for ketonuria.
- The hba1c test: Target <7%. This test should be done two to four times per year.

g. Nutritional management:

- The diet for children and adolescent with diabetes is no different. They can eat a normal food plan as recommended for the general population without the need for special foods.
- Children with diabetes need a healthy diet with food in amounts and proportions appropriate to the age and stage of growth.
- The patient or care takers shouldn't restrict excessively the intake of carbohydrate to lower blood glucose levels.
- Sugary soft drinks or foods with high levels of saturated fat should be avoided.
- The overweight or obese should be encouraged to lose weight by a combination of changes in food intake and physical activity.

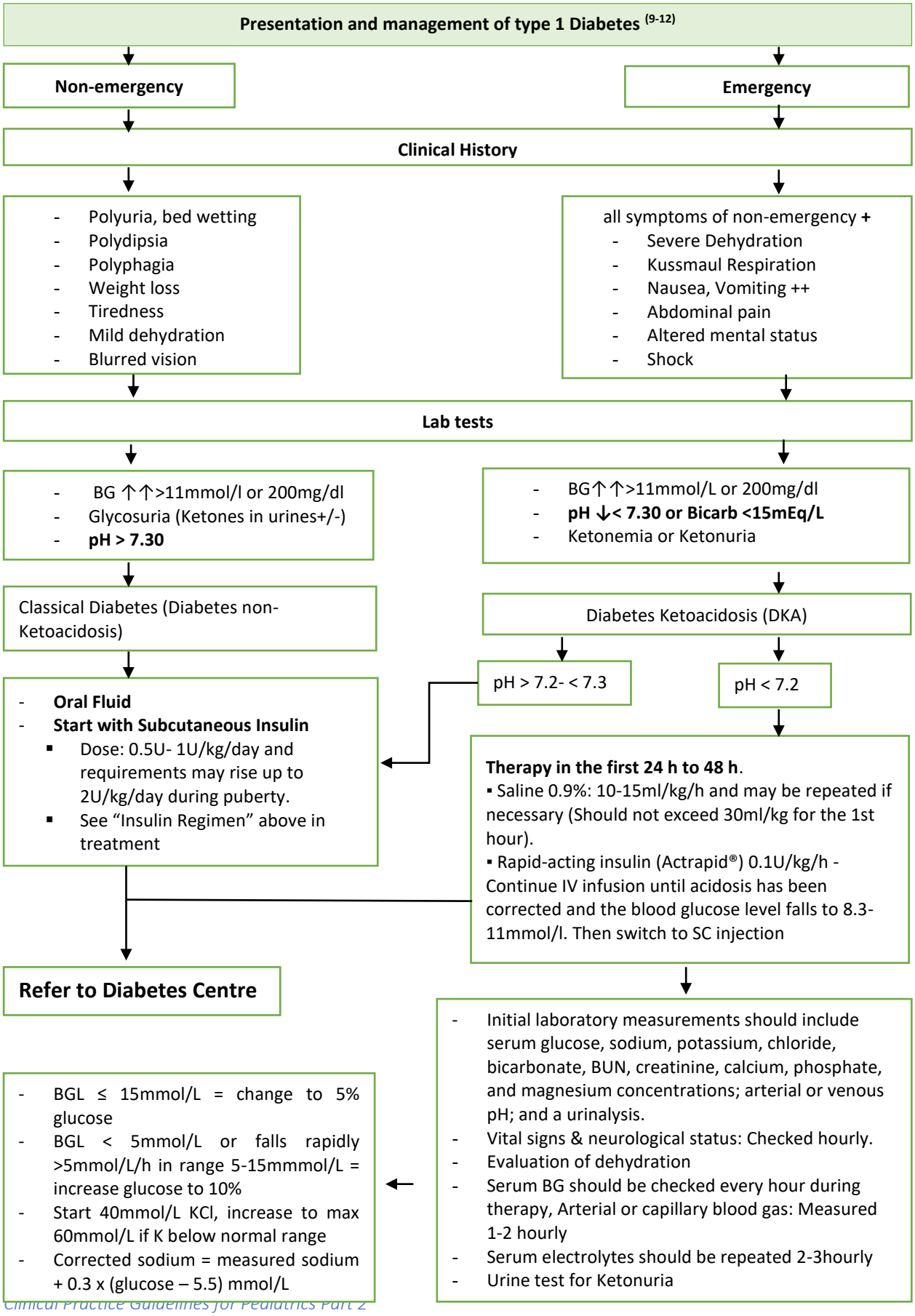
h. Physical activity:

- Any physical activity including exercise is very beneficial and should be encouraged.
- Diabetes should not be a barrier to participating in exercise.
- Exercise increases insulin absorption, again predominantly related to increased subcutaneous blood flow.
- A major complication of exercise in diabetic patients is the presence of a hypoglycemic reaction during or within hours after exercise.

i. Education

- Education is the keystone of diabetes care. (9)
- Empower them and their families to take control of their diabetes.
- All patients and family need careful training for life with insulin. This is best achieved outside hospital.
- Diabetic lesson and other educational materials are given to patients in hard copies, Facebook page and also website expecting that the patient and care givers understand more about diabetic management.

Algorithm


Presentation and management of type 1 Diabetes (9-12)
Non-emergency
Emergency
Clinical History
- Polyuria, bed wetting
- Polydipsia
- Polyphagia
- Weight loss
- Tiredness
- Mild dehydration
- Blurred vision
all symptoms of non-emergency +
- Severe Dehydration
- Kussmaul Respiration
- Nausea, Vomiting ++
- Abdominal pain
- Altered mental status
- Shock
Lab tests
- BG ↑↑>11mmol/l or 200mg/dl
- Glycosuria (Ketones in urines+/-)
- pH > 7.30
- BG↑↑>11mmol/L or 200mg/dl
- pH ↓< 7.30 or Bicarb <15mEq/L
- Ketonemia or Ketonuria
Classical Diabetes (Diabetes non-Ketoacidosis)
Diabetes Ketoacidosis (DKA)
pH > 7.2- < 7.3
pH < 7.2
- Oral Fluid
- Start with Subcutaneous Insulin
▪ Dose: 0.5U- 1U/kg/day and requirements may rise up to 2U/kg/day during puberty.
▪ See "Insulin Regimen" above in treatment
Therapy in the first 24 h to 48 h.
▪ Saline 0.9%: 10-15ml/kg/h and may be repeated if necessary (Should not exceed 30ml/kg for the 1st hour).
▪ Rapid-acting insulin (Actrapid®) 0.1U/kg/h - Continue IV infusion until acidosis has been corrected and the blood glucose level falls to 8.3-11mmol/l. Then switch to SC injection
Refer to Diabetes Centre
- Initial laboratory measurements should include serum glucose, sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, phosphate, and magnesium concentrations; arterial or venous pH; and a urinalysis.
- Vital signs & neurological status: Checked hourly.
- Evaluation of dehydration
- Serum BG should be checked every hour during therapy, Arterial or capillary blood gas: Measured 1-2 hourly
- Serum electrolytes should be repeated 2-3hourly
- Urine test for Ketonuria
- BGL ≤ 15mmol/L = change to 5% glucose
- BGL < 5mmol/L or falls rapidly >5mmol/L/h in range 5-15mmmol/L = increase glucose to 10%
- Start 40mmol/L KCl, increase to max 60mmol/L if K below normal range
- Corrected sodium = measured sodium + 0.3 x (glucose – 5.5) mmol/L

- ❖ *IV regular insulin is very short acting, give first subcutaneous dose 20 min before stopping infusion.* [10]
- ❖ Severity of DKA [11]

Assessment based on the severity of these parameter	Venous pH	Bicarbonate (mmol/L)
Mild	< 7.3	< 15
Moderate	< 7.2	< 10
Severe	< 7.1	< 5

VI. Complications

Acute Complications	Chronic complications	
Hypoglycemia Diabetic keto-acidosis (DKA) - DKA is a life-threatening and the most common cause of deaths, require immediate hospitalization. - Often as a result of inadequate insulin therapy during intercurrent illness and insulin omission. - Cerebral edema occurs 1-5% of cases of DKA.	*Macrovascular complications* - Circulatory: e.g. Stroke - Cardiovascular events: e.g. Myocardial infarction, vascular disease with limb loss.	*Microvascular complications* - Retinopathy - Nephropathy - Neuropathy

VII. Recommendation

- Every child with type 1 diabetes, including those from rural and remote areas after suspecting or confirm diagnosis should transfer to the specialized center to get proper treatment.
- Do not delay the treatment after diagnosis.
- Self-blood glucose monitoring (SBGM) is essential in the long-term management of diabetes.
- In general, postprandial blood glucose should be less than 10 mmol/l (180 mg /dl) and fasting blood glucose should vary between 5 to 7 mmol/l (90-126 mg/dl) to avoid acute and long-term complications.

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DIABETES INSIPIDUS

IV Malene, KIM Dara, SAM-AN Kamnhanroth

I. Key facts

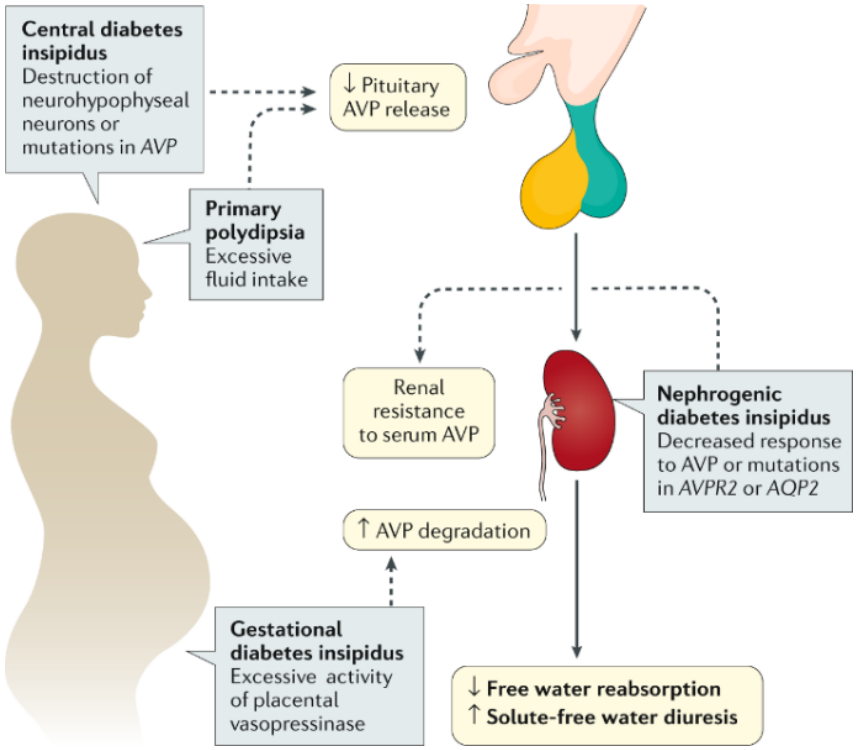
- Diabetes insipidus (DI) is an uncommon endocrine disorder affecting nearly 1 in 25,000 people or about 0.004% of the global population.
- On epidemiological review, DI does not show a predilection for males or females.
- It may develop at any age, with hereditary forms developing earlier in life.
- Untreated DI negatively impacts the quality of life of the patient. [2]

II. Overview

1. Definition

- Diabetes insipidus (DI) is an uncommon condition with either reduced or absent secretion of anti-diuretic hormone (ADH) from the hypothalamus, or insensitivity to ADH within the kidney. This leads to an inability to concentrate urine causing polyuria with compensatory polydipsia and potentially fluid and electrolyte imbalance. [5]
- DI is dangerous when a child is unable to access water freely (eg. Very young child, altered conscious state, nil by mouth or too unwell) or has an impaired thirst response (eg. Complex midline CNS defect, hypothalamic trauma or malignancy). [5]

2. Physiopathology [10]



3. Etiology [5,9,10]

Central Diabetes Insipidus (ADH deficiency)	Nephrogenic Diabetes Insipidus (ADH resistance)
- Primary: idiopathic -Secondary: brain lesions or injury, e.g. Tumour, hypoxic injury, surgery	- Hereditary: ADH receptor mutation - Acquired: ○ Medications, e.g. Lithium, demeclocycline ○ Electrolyte disturbances, e.g. Hypercalcemia, hypokalaemia - Renal disease - Pregnancy

III. Signs and Symptoms [11]

Predominant manifestations	In infants	In children
- Polyuria - Polydipsia - Nocturia	- Crying - Irritability - Growth retardation - Hyperthermia - Weight loss	- Enuresis - Anorexia - Linear growth defects - Fatigability - Constipation - Neurological symptoms: headaches, vomiting, altered sensation, weakness

IV. Diagnosis [5]

Laboratory investigations:

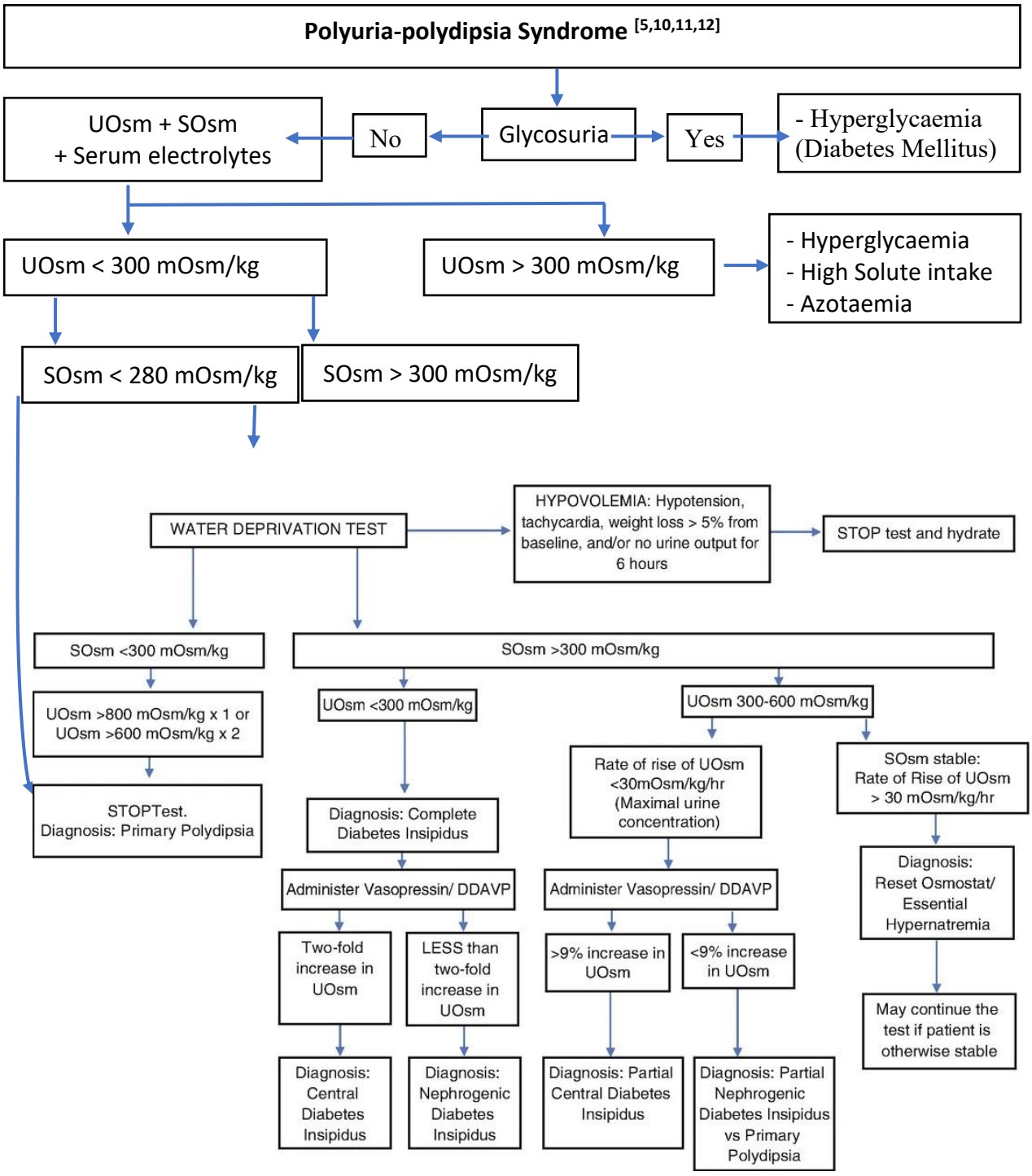
- Urgent Blood glucose level (to exclude Diabetes mellitus)
- Serum electrolyte concentrations and glucose level
- Urine dipstick: check specific gravity, glucose
- Early morning urine and serum osmolality (See table below)
- A 24-hour urine collection for determination of urine volume

Results which may indicate particular diagnoses:

Diagnostic	Urine volume (ml/kg/h)	Serum sodium meq/l	Serum osmolality mosm/kg	Urine specific gravity	Urine osmolality Mosm/kg
Normal	1- 4	135-145	280	1.010-1.030	50-1400
Central DI	>4	>145	>300	<1.010	<300 (<700*)
Nephrogenic DI	>4	>170	>300	<1.005	<300 (<700*)
Primary polydipsia	May be >4	135-145	<280	<1.020	<300

- A water deprivation test (see algorithm and annex) will distinguish central DI from nephrogenic DI and primary polydipsia. This test should only be performed under specialist guidance, and may not be appropriate for infants <12 months due to safety
- Consider renal ultrasound particularly if nephrogenic DI suspected.
- If concern for central DI: MRI brain and pituitary, screen other anterior pituitary hormones

Algorithm 1.



❖ **Differential diagnosis** [11]

- Medications (ex: diuretics)
- Psychogenic polydipsia
- Abnormal thirst mechanism (dipsogenic DI)
- Hypernatremia dehydration
- Diabetes mellitus
- Polyuria's renal Failure (e.g. Renal tubulopathy)
- Hypercalcemia

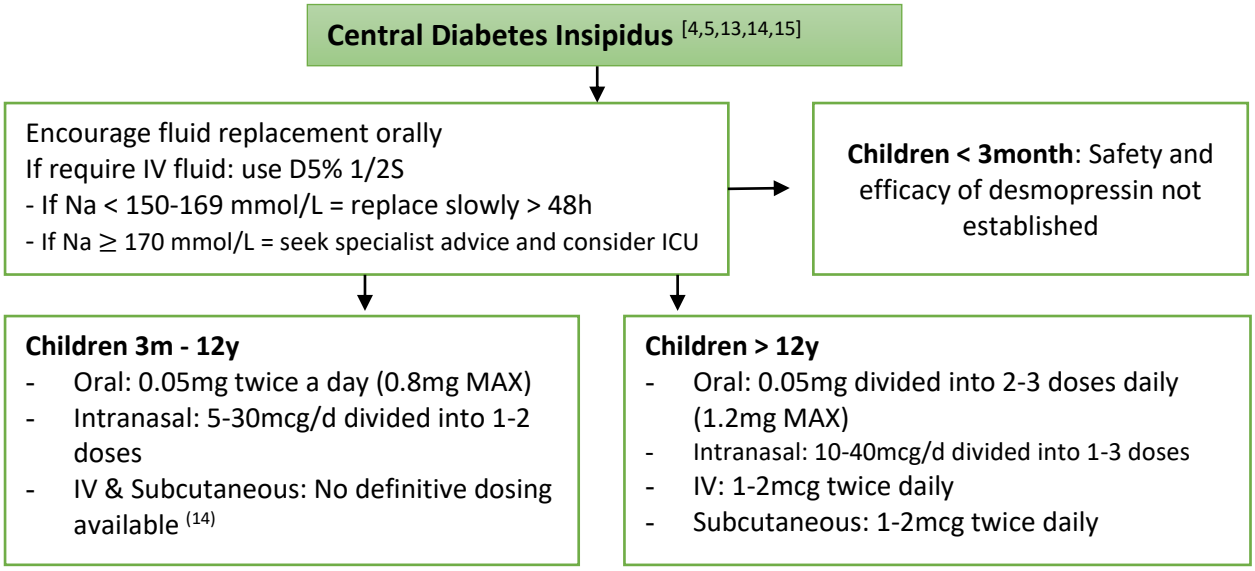
- Adrenal insufficiency
- Cerebral salt wasting.

V. Management

The therapeutic goals are primarily to reduce polyuria and decrease the thirst so that the child is able to grow adequately and maintain a normal lifestyle.

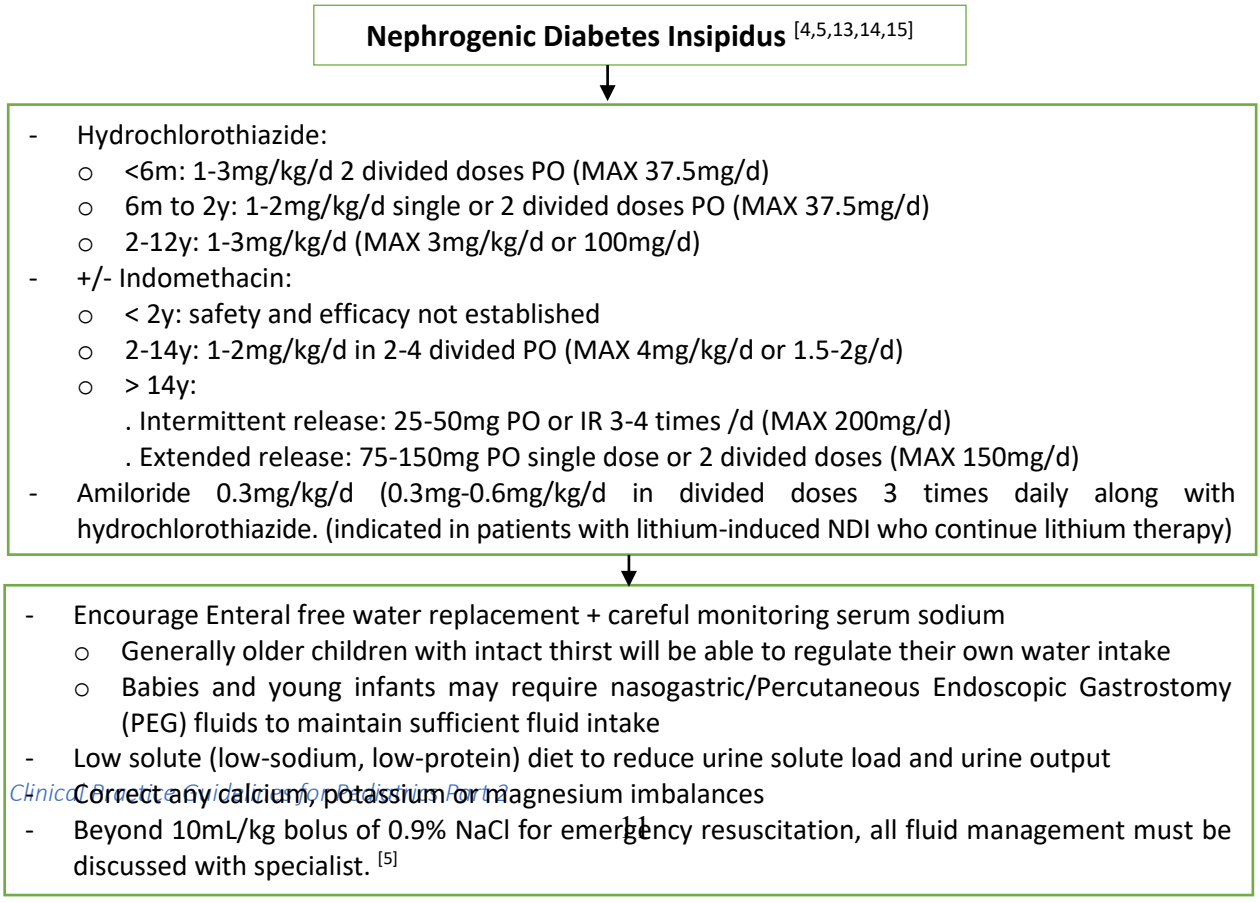
1. **Central diabetes insipidus**:
   - Treat the underlying cause, if applicable
   - Immediately after neurosurgery, a triphasic response (immediate DI followed by a variable period of Syndrome of inappropriate antidiuretic hormone (SIADH) and subsequent permanent DI) may occur. During this period, fluid and electrolyte balance will require very close monitoring by neurosurgery and endocrinology. Desmopressin treatment is generally given as needed rather than regularly until risk of SIADH and sudden hyponatremia has passed. [5]

Algorithm 2.



2. **Nephrogenic diabetes insipidus:**

Algorithm 3. *Treat the underlying cause, if applicable*



VI. Complications

- Growth Failure
- Nocturia and enuresis
- Hypernatremia dehydration
- Seizures
- Mental retardation.

VII. Prognosis

Central diabetes insipidus can be a temporary or a permanent condition, depending on what's causing it. If the condition is permanent, it's typically easily treated with medication. Almost all children with central diabetes insipidus lead full, healthy lives.

Children with nephrogenic diabetes insipidus can also lead relatively normal lives with proper medical care and management.

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ANNEXE

- Desmopressin administration practice points:
  - Ensure serum sodium result is ≥135 mmol/L (or higher threshold as directed) within 1-2 hours prior to administration of desmopressin dose
  - Check urine specific gravity and document (dilute <1.005) prior to every dose
  - 1-2 hours of diuresis is required prior to further doses to allow free water clearance
  - If urine output >4 ml/kg/h for 2 consecutive hours, may need repeat serum sodium and consideration of higher or repeat desmopressin dosing
  - If desmopressin due and there has been no urine output for previous 12 hours, may need to reduce or withhold the dose. [5]
- A recommended protocol (water deprivation test) includes the following steps: [1]
  - The test is performed after breakfast. It is started after the child voids or, in infants, after the first spontaneous void after the morning feed. Body weight and plasma sodium and osmolality are measured after the patient voids. No further fluid is given until the test is terminated.
  - Record each urine void and measure the urine volume, specific gravity, and osmolality.
  - Weight and vital signs are obtained every two hours for the first four hours and then hourly. The plasma sodium and osmolality are measured at four hours and then every two hours until the conclusion of the test.
  - The test is terminated when one of the following end points are attained:
  - Urine specific gravity ≥1.020
  - Urine osmolality is ≥600 mosmol/kg
  - Plasma osmolality exceeds 295 or 300 mosmol/kg or plasma sodium is 145 meq/L or higher
  - The patient has lost 5% of body weight or exhibits signs of volume depletion
  - If the period of water restriction reaches six hours in infants less than 6month of age, eight hours in children from 6month to 2year of age, or 12 hours in children over 2year of age.

  At the end of the test, weight, vital signs, plasma sodium, plasma and urine osmolality, and urine specific gravity should be measured. A specimen should also be obtained for measurement of plasma ADH, which is always elevated during short dehydration tests in patients with hereditary nephrogenic DI.

  Children who continue to have impaired urinary concentration despite reaching a plasma osmolality of 295 mosmol/kg or a plasma sodium of 150 meq/L can be given desmopressin (5 to 10 microg by nasal insufflation or 2 to 4 µg intravenously or subcutaneously). The urine volume and osmolality are measured to detect any antidiuretic response. We no longer use aqueous vasopressin which, due to its vasoconstrictive effect mediated by the V1a receptor, produces sudden and noticeable pallor that raises concerns with the mother.

  Interpretation:
  - Accurate interpretation of the water restriction test usually requires that desmopressin not be given before the urine osmolality has stabilized or the plasma osmolality has reached 295 mosmol/kg. Below this level, maximum endogenous ADH effect may not be present and an antidiuretic response to desmopressin is of no diagnostic benefit, since it will raise the urine osmolality even in normal subjects.
  - At the end of the test, weight, vital signs, plasma sodium, plasma and urine osmolality, and urine specific gravity should be measured. A specimen should also be obtained for measurement of plasma ADH, which is always elevated during short dehydration tests in

Patients with hereditary nephrogenic DI. [1]

PEDIATRIC HYPOGLYCEMIA

SUON Pisey, AN Monychanbo, IV Malene

I. Key facts (1)

- Glucose is the major source of energy for the body and it is essential for cerebral energy metabolism.
- Cerebral glucose uptake occurs through a glucose transporter.
- Cerebral transport of glucose is a carrier-mediated, facilitated diffusion process that is dependent on blood glucose concentration.
- Deficiency of brain glucose transporters can result in seizures because of a low concentration (hypoglycorrhachia) despite normal blood glucose levels. (eg: glucose transporter type I deficiency)
- Glucose regulatory system has evolved to maintain the blood glucose concentration and prevent it from falling precipitously to levels that impair brain function.

II. Overview

1. Definition:

- Hypoglycemia is defined by a blood glucose level (BGL) below 3.3 - 3.9 mmol/L (60-70mg/dl) even in the absence of obvious signs and symptoms.
- In neonates, there is not always an obvious correlation between blood glucose concentration and the classic clinical manifestations of hypoglycemia. Thus BGL < 2.6 mmol/l need immediate intervention.
- Prolonged or recurrent hypoglycemia, especially with clinical features, can cause long term neurological damage or death.

2. Etiology

Age at presentation suggests diagnostic categories (5)

Age	Causes of Hypoglycaemia include
Neonate < 48-72 hrs	Premature, intra-uterine growth retardation, perinatal asphyxia, hypothermia, sepsis, respiratory distress, diabetic mother, macrosomia, syndrome (eg. Beckwith-Wiedemann), pancreatic dysfunction
Neonate – 2yrs	Congenital hyperinsulinism (most common cause of persistent hypoglycaemia < 2 years), inborn errors of metabolism, congenital hormone deficiencies (eg. Growth hormone deficiency)
Child	Accelerated starvation (previously known as “ketotic hypoglycaemia”), hypopituitarism, growth hormone deficiency
Adolescent	Insulinoma, adrenal insufficiency, eating disorder
All ages	Complication associated with type 1 diabetes mellitus, other illness (eg sepsis, congenital heart disease, tumour, adrenal insufficiency)

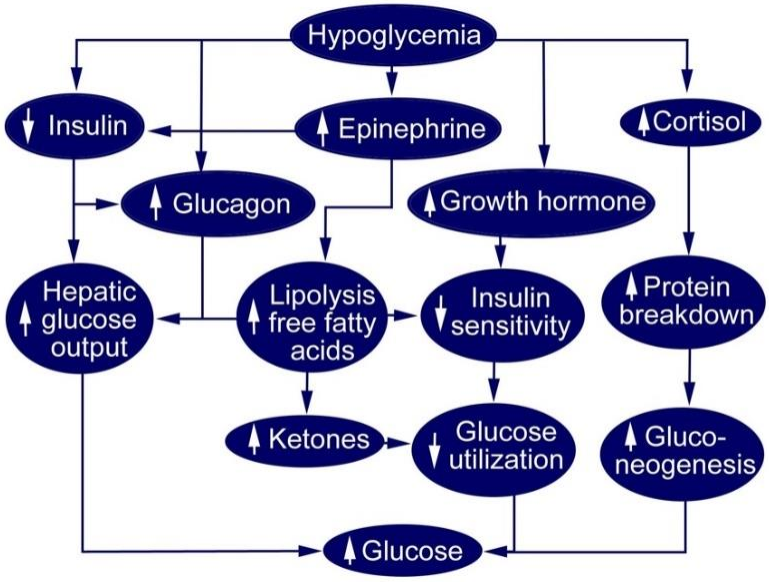
Other causes	- Delays or nutritional deficiencies: deficiencies in certain nutrients, such as biotin and zinc, can also cause hypoglycemia. - Medications: Some medications can cause hypoglycemia such as beta-blockers and sulfonylureas. - Unscheduled exercise - Genetics: o Almost all inborn errors of metabolism causing hypoglycemia are autosomal recessive. One form of hyperinsulinism is autosomal dominant.

The absence of symptoms does not indicate that glucose concentration is normal and has not fallen to less than some optimal levels for maintaining brain metabolism.

There is evidence that hypoxemia and ischemia may potentiate the role of hypoglycemia in causing permanent brain damage.

3. Pathophysiology

The counter regulatory hormones glucagon, cortisol, growth hormone and epinephrine are the predominant hormones secretes in the fasting state. These hormones control glycogenolyses, gluconeogenesis, lipolysis and ketogenesis.



III. Symptoms and diagnosis

Neurogenic (Mild or moderate)	Neuroglycopenia (Severe hypoglycemia)
- Neurogenic (autonomic) symptoms are caused by the sympathetic nervous system's response to hypoglycemia and appear when the plasma glucose is less than 55 to 60 mg/dl. - Manifestations are sweating, tremor, palpitations, and hunger, headache, dizzy, pale, weakness, nausea, vomiting…	- Neuroglycopenic symptoms result from insufficient supply of glucose to the brain, leading to brain dysfunction. They include sleepy, lethargy, confusion, irritability, loss of consciousness, and seizure. - Neuroglycopenic symptoms typically occur when the plasma glucose falls below 50 mg/dl. - In Neonate < 48 hours - Apnea, hypotonia, jitteriness, poor feeding, high pitched cry.

Hypoglycemia has often been described as mild, moderate, or severe. However, there are no clinically important reasons to distinguish between mild and moderate hypoglycemia. Symptoms of hypoglycemia can be divided into neurogenic and neuroglycopenia symptoms:

❖ Investigations

- Venous blood test or glucose rapid test
- Urinary analysis: ketone, glycosuria ….
- Other tests depend on etiology: dosage growth hormone…

IV. Complications

Pediatric hypoglycemia can lead to several complication if not treated promptly and effectively. These complications can range from mild to severe and can have long-term consequences for a child's development and health.

Seizures	Severe hypoglycemia can lead to seizures. Seizures can cause muscle contractions, loss of consciousness, and even brain damage.
Brain Damage	Prolonged or recurrent hypoglycemia can damage brain cells, leading to learning difficulties, behavioral problems, and even cognitive impairment.
Coma	In extreme cases, sever hypoglycemia can lead to coma.
Long-term complications	Impaired Growth and Development: chronic hypoglycemia can interfere with a child's growth and development, both physically and mentally. Children with recurrent hypoglycemia may experience delays in motor skills, language development and cognitive function.

V. Management

1. Management: See Algorithm [3,4,6]

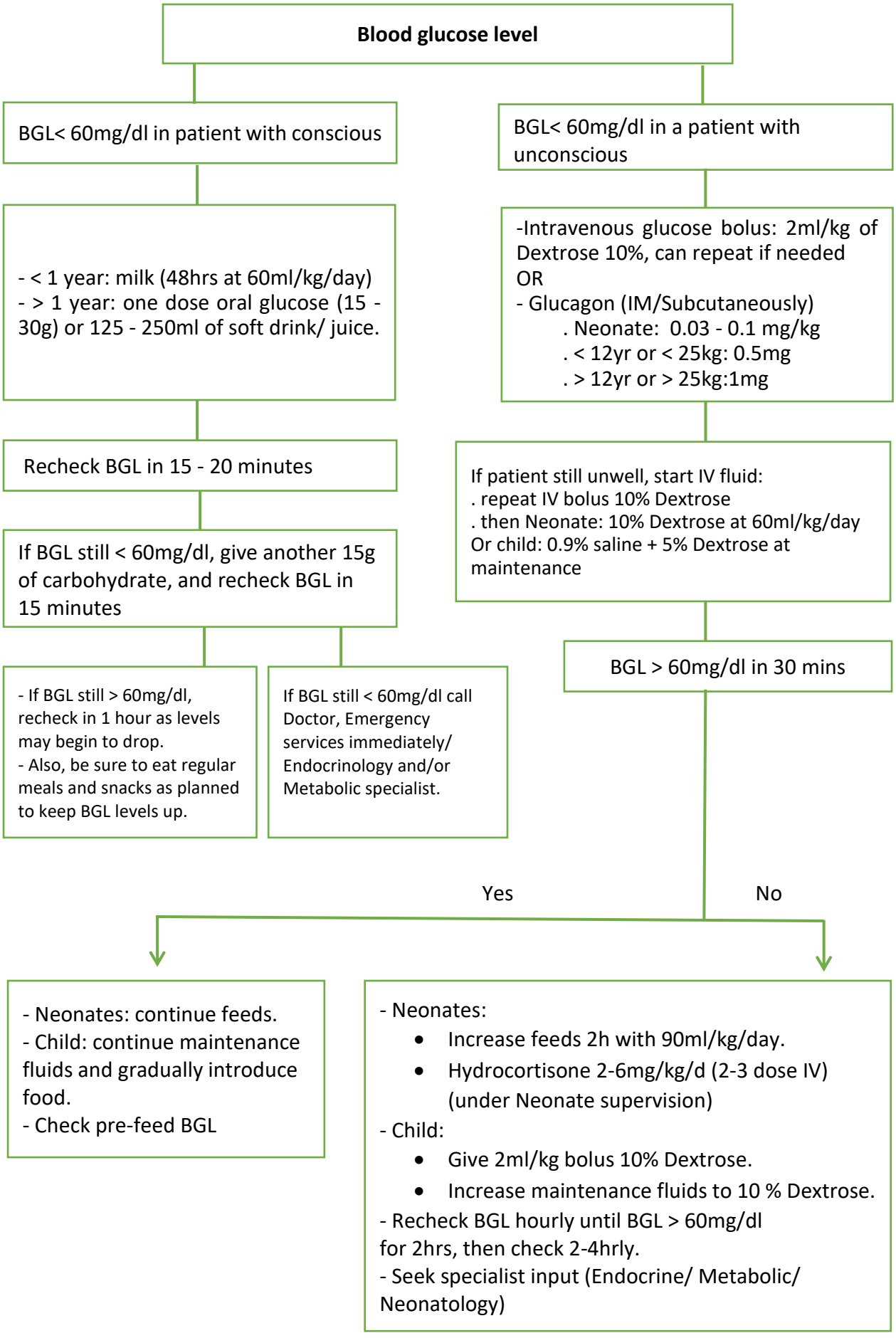
2. Monitoring

The plasma glucose should be monitored every 15 to 20 minutes until it is > 70 mg/dl (3.9 mmol/L). Thereafter, it can be checked hourly to ensure stability, and then subsequent checks can be further spaced to every three to four hours.

After initial hypoglycemia is reversed, provide additional glucose and treatment based upon suspected etiology:

Patients with type 1 diabetes mellitus	Give a normal diet; initiate IV dextrose-containing fluids if intake is inadequate.
Patients with an underlying hypoglycemic disorder or with an unknown cause of hypoglycemia	Continue an intravenous infusion of dextrose 10%.

Algorithm [3,4,6]



VI. Prevention

The best way to prevent pediatric hypoglycemia is to identify and treat the underlying cause.

However, there are also somethings that parents can do to help prevent hypoglycemia in their children such as feeding or eating regular meals and snacks to maintain their blood glucose levels.

VII. Prognosis

Pediatric hypoglycemia is a serious medical condition that can have serious consequences if not promptly treated. However, with proper treatment and prevention, the children can be treated without sequala.

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GOITRE

SUON Pisey, BAN Manet, IV Malene

I. Key facts

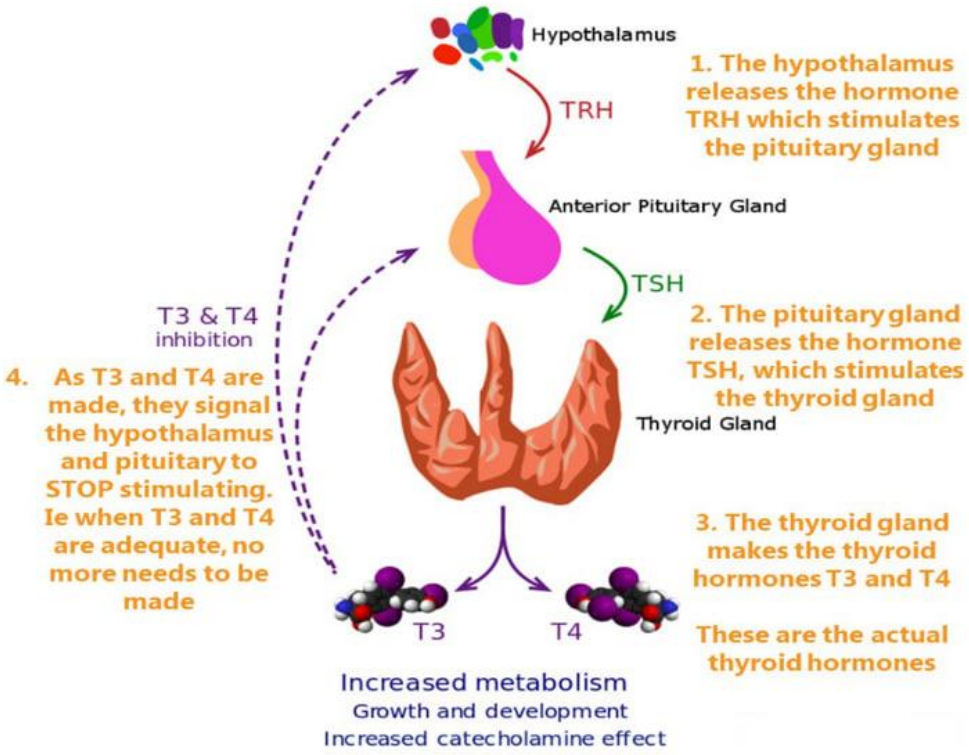
- Acquired goitre can present at any age. Most children and adolescents with goitre have normal thyroid function, but some are hypothyroid or hyperthyroid, depending on the cause and stage of the disorder.
- In iodine-sufficient areas of the world, the most common causes of acquired goitre in children and adolescents are chronic autoimmune (Hashimoto) thyroiditis and colloid goitre.
- Worldwide, iodine-deficiency goitre is far more common. Once a goitre is detected, the diagnostic evaluation is aimed at identifying the underlying cause and assessing thyroid function. Both of these factors will determine management. (4)
- Incidence: Hyperthyroidism occurs in approximately 1 per 5000 children and adolescents, and Grave's disease accounts for the vast majority of these cases, predominant female (5:1). Grave's disease rises sharply during puberty, so that approximately 80 percent of pediatric cases occur after 11 years of age. (2)

II. Overview

1. Definition [1]

Goitre is an enlarged thyroid gland. Children with thyroid disorders usually present goitre with or without symptoms of thyroid hormone deficiency or excess.

2. Physiological effects of Thyroid hormones [16]



3. Pathophysiology [12]

The pathophysiology of goitre divided into 3 domains: stimulation, inflammation and infiltration.

- Stimulation: includes increase TSH (hypothyroid) or activated TSH receptors by antibodies (grave's disease).
- Inflammatory: included acute and subacute thyroiditis that can be infectious or non-infectious.
- Infiltration: malignancy, histiocytosis, thyroiditis lymphocytic and tuberculosis.

4. Etiology [4]

Presentation:	Etiology
- Euthyroid	- Colloid goitre - Thyroid neoplasm (benign adenoma, carcinoma) - Acute suppurative thyroiditis.
- Hypothyroid	- Autoimmune thyroiditis (Hashimoto thyroiditis) - Central hypothyroidism - Ingestion other goitrogen drugs (anti-seizure medication like phenobarbital, valproate, lithium, interferon-alpha…) - Iodine deficiency or excess exposure (supplement food or drug: amiodarone) - Thyroid infiltrative disease (histiocytosis, cystinosis) - Subacute granulomatous thyroiditis (de Quervain disease).
- Hyperthyroid	- Grave disease - Toxic multinodular goitre - Subacute granulomatous thyroiditis (de Quervain disease) - TSH- producing pituitary adenoma - Pituitary resistance to thyroid hormone - Thyrotoxic phase of Hashimoto

III. Signs and Symptoms

1. History [12] [13]

- History of diet goitrogen and medication.
- History of head, neck, or chest irradiation is associated with increased risk of carcinoma
- Family history of thyroid disease, consanguinity, geographical area of residence.
- For neonate: history of maternal exposure to iodine or antithyroid drugs.

Signs of hypothyroidism	Signs of hyperthyroidism
- Symptoms related to decreased metabolic rate: bradycardia, fatigue, cold intolerance, weight gain, poor appetite, hair loss, cold and dry skin, constipation, myopathy, stiffness, cramps, delayed deep tendon reflex relaxation. - Symptoms from generalized myxedema: myxedematous heart disease, puffy appearance, hoarse voice with difficulty articulating words, pretibial and periorbital edema	- General: heat intolerance, weight loss, increased appetite, increased sweating, fatigue - Eyes: lid lag, lid retraction, graves ophthalmopathy - Cardiovascular: tachycardia, palpitations, hypertension, chest pain, abnormal heart rhythms. - Musculoskeletal function: fine tremors of the outstretched fingers, osteoporosis.

- Symptoms of hyperprolactinemia: amenorrhea or menorrhagia, galactorrhea, infertility in men, - Congenital hypothyroidism: umbilical hernia, hypotonia, prolonged neonatal jaundice, poor feeding, absence of thirst (adipsia), decreased activity, pot-belly, puffy-face, protuberant tongue, poor brain development.	- Neuropsychiatric system: anxiety, depression, emotional instability, insomnia

2. Physical Examination [(1)]

- Inspect, palpate, and auscultate the neck:
- Neck extension aids inspection.
- Have patient drink water during inspection of gland.
- Palpation is best performed standing behind the child.
  - Determine if the thyroid is diffusely enlarged or asymmetric, evaluate gland firmness, and assess for any nodularity.
  - Check for cervical lymphadenopathy
  - Pain on palpation suggests acute inflammation.
- Auscultate with the stethoscope (while patient holds his or her breath) for a bruit, which indicates the hyperthyroidism-associated hypervascularity.
- Careful examination for signs of hypothyroidism or hyperthyroidism:
  - Pulse
  - Linear growth and weight pattern
  - Sexual development
  - Deep tendon reflexes
  - Skin

❖ *World Health Organization Classification of Goitre* [(11)]

Grade	Characteristics
0	No visible or palpable goitre
1	Goitre is palpable but not visible in chin-neutral position
2	Goitre is visible and palpable in chin-neutral position

3. Investigation

a. Laboratory

- Thyroid function tests: Total T4/ Free T4, T3 and TSH.
- In case of suspected Grave disease: Thyroid-stimulating immunoglobulins (or TSH-receptor antibodies) and thyroid receptor antibody (trab).
- Antibodies against thyroperoxidase (anti-TPO) and thyroglobulin (anti-TG) is recommended as thyroid autoimmunity may coexist with goitre.
- Urinary iodine (UI) concentration is the best measure of the adequacy of iodine intake.
- Fine-needle aspiration biopsy (nodule >1cm) in children should be considered only for evaluation of low risk or purely cystic thyroid nodules. (A higher percentage of solitary thyroid nodules are malignant in children compared with adults).

b. Imaging

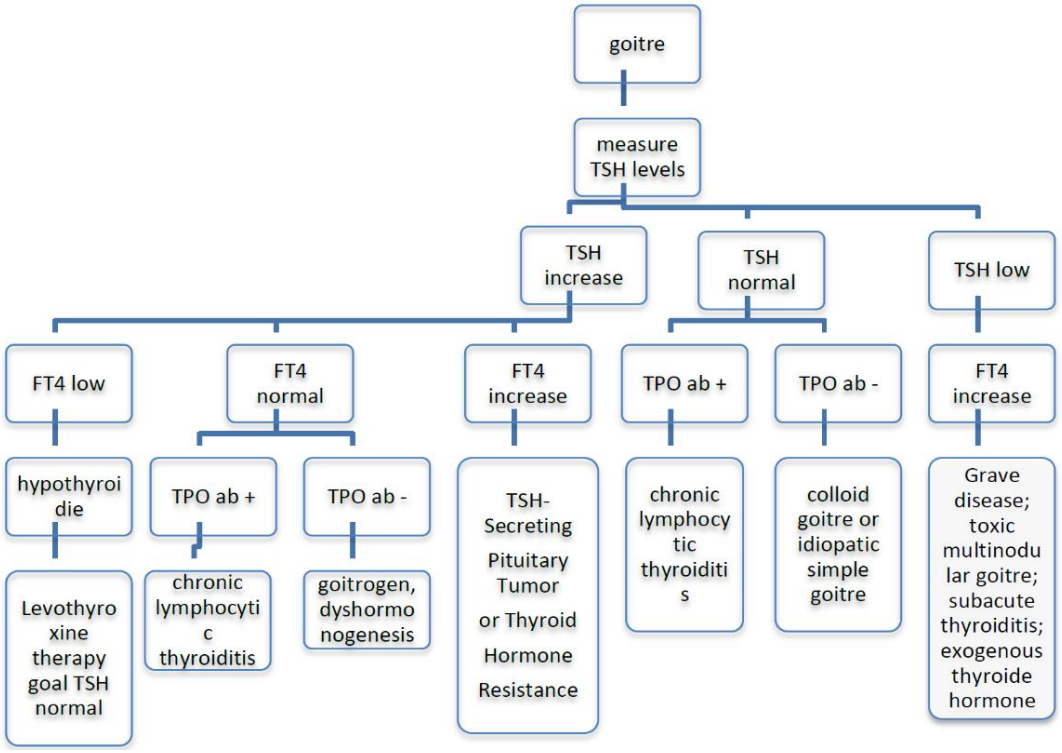
- Ultrasound to determine the number, size, and nature (cystic, solid, or mixed) of nodules.

- Some authors recommend regular sonographic follow-up, although the growth rate does not seem useful in distinguishing malignant from benign nodules.

Benign [1]	Malignant [1]
- Normal echogenicity or hyper echogenicity - Coarse calcifications - Thin, well-defined halo - Regular margin - No regional lymphadenopathy - Low intra nodular flow by Doppler	- Hypo echogenicity - Microcalcifications - Thick, irregular, or absent halo - Irregular margin - Regional lymphadenopathy - High intra nodular flow by Doppler

- Barium swallow studies can reveal a fistulous tract between the left piriform sinus and the left thyroid lobe in children with recurrent acute suppurative thyroiditis. Such fistulas are amenable to surgical resection.
- Radionuclide uptake and scan: if the inborn error of thyroid hormone production (dyshormonogenesis) is suspected.
- Computed tomography (CT): in case of significant compressive symptoms or tracheal compression.

GOITRE ALGORITHM



IV. Differential diagnosis

- Thyroglossal duct cysts
- Nonthyroidal neoplasms: lymphoma, teratoma, hygroma, ganglioneuroma
- Fat neck: adipose tissue, large sternocleidomastoid muscles.

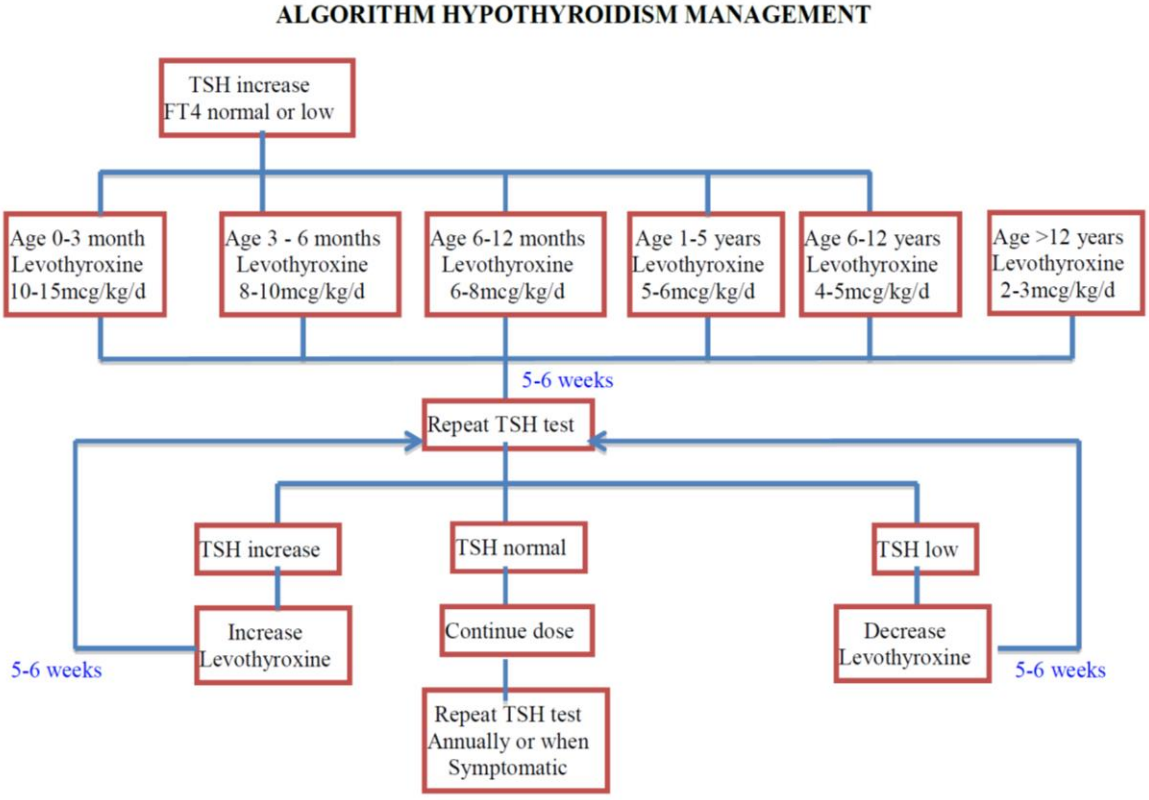
V. Management

The goal of treatment is to maintain clinical and biochemical euthyroid and to ensure normal linear growth and development throughout childhood and adolescent.

1. **General measures (Diet)**
   - Depends on the cause of the goitre
   - Incidence of iodine deficiency (endemic) goitre has greatly declined since the addition of potassium iodide to table salt.
2. **Pharmacotherapy**
   a. Goitre with hypothyroidism

- The drug of choice is Levothyroxine, given by mouth, once daily in the morning before food: see algorithm 1. (1)
- The goal is to keep the serum FT4 concentration at the mid-normal range and the TSH concentration in the normal range. Once the patient is euthyroid, many of the symptoms disappear.
  Course: Once Levothyroxine therapy is started, it probably is best to continue treatment until growth and pubertal development are complete.

❖ *Algorithm 1*



b. Goitre with hyperthyroidism (Grave's disease): Current treatment includes anti-thyroid medication, Radioactive 131I and thyroidectomy.
   B1. Anti-thyroid medication:
   The European Thyroid Association (ETA) released their guidelines for management of pediatric Grave's disease in January 2022 [9]

- Carbimazole (CBZ) (initial dose: 0.25 to0.75 mg/kg daily) or
- Its active metabolite Methimazole (MMI) (initial dose: 0.15 to 0.5 mg/kg daily).
- See algorithm 2

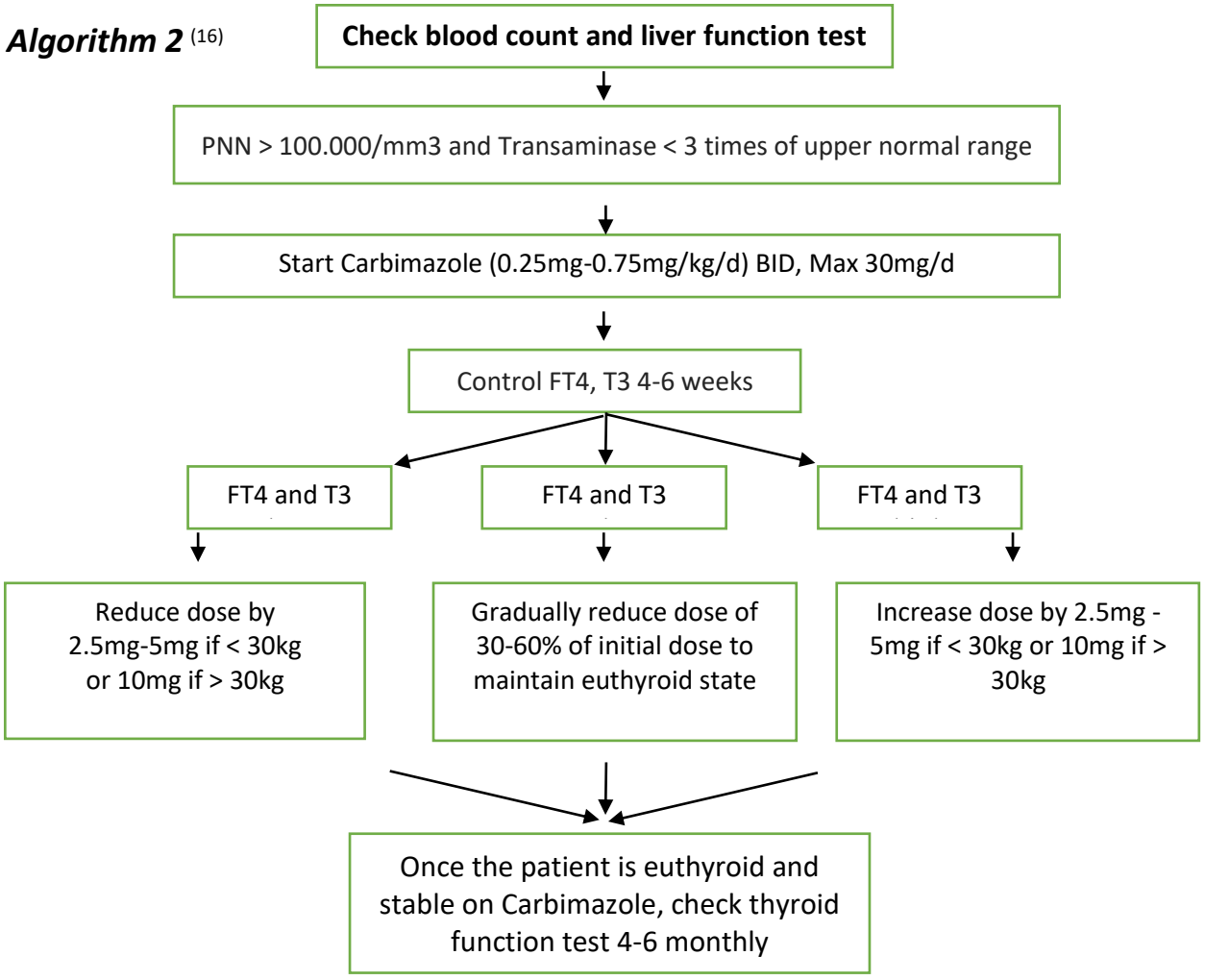
❖ Note: Propylthiouracil is no longer used in pediatric patient due to the risk of fulminant hepatitis.

- Monitoring – If a patient develops a febrile illness or pharyngitis, antithyroid drug treatment (usually MMI) should be stopped immediately and check WBC and its differential. Agranulocytosis (<500/mm3) is a contraindication to future antithyroid drug

treatment. Routine monitoring of WBC is not recommended, because of the rarity of agranulocytosis and its sudden onset, which is generally associated with symptoms.

- The course is shorter in some patients, while others continue treatment for as long as 8 to 10 years. This practice is supported by several reports demonstrating that remission rates improve with long-term treatment.
- Duration: the medication should be continued for approximately 12-18 months, then discontinued of the TSH and trab levels are normal. (15)
- Measurement of trab levels prior to stop ATD therapy is suggested because it aids in predicting which patients can be weaned from the medication, with normal levels trab indicating greater chance for remission.
- Remission: euthyroid for at least 12 months after discontinuation of antithyroid drug therapy, varies from 25 to 65 percent in different series.
  - Adjunctive early therapy: beta adrenergic blockers
    - Propranolol: 0.5 to 2.0 mg/kg daily, is divided into three or four doses daily.
    - Or Atenolol: 1 to 2 mg/kg once daily (cardio selective, suitable for asthma patient).
  - Graves Ophthalmopathy (GO)
  - Assessment of GO includes assessment of activity and severity using standardized criteria. Graves ophthalmopathy is categorized as active or inactive; mild, moderate, severe or sight threatening.
  - Euthyroidism should be restored as soon as possible in patients with GO.
  - Oral prednisolone prophylaxis of 0.4–0.5 mg/kg/day for a total of 3 months is recommended in patients with mild-to–moderate GO who are undergoing radioiodine therapy.

Algorithm 2 (16)



3. Treatments' choice of Grave's hyperthyroidism [4]

Therapy	Advantages	Disadvantages
Thionamides	-Chance of permanent remission -Some patients avoid permanent hypothyroidism -Lower initial cost	-Minor side effects – Rash, hives, arthralgias, transient granulocytopenia, Gastrointestinal symptoms -Major side effects – Agranulocytosis, vasculitis (lupus-like syndrome), hepatitis -Risk of fetal goitre, hypothyroidism, and congenital anomalies if pregnant -Requires more frequent monitoring
Radioiodine	-Permanent resolution of hyperthyroidism	-Permanent hypothyroidism -Patient must take radiation precautions for several days after treatment, Avoiding contact with young children and pregnant women -Development or worsening of Grave's ophthalmopathy -Rare radiation thyroiditis -Patient concerns about long-term oncogenic effects of radiation
Surgery	-Rapid, permanent cure of hyperthyroidism	Permanent hypothyroidism Risks for iatrogenic hypoparathyroidism and recurrent laryngeal nerve damage Risks associated with general anaesthesia High cost

Selection criteria of definitive treatment of graves [12]

Radioiodine ablation	Total thyroidectomy
. Age > 10yr . Goitre < 3-4 times enlarged . No thyroid nodule . No access to a high – volume pediatric thyroid surgeon (< 30 thyroidectomies/ yr) . Minimal or no eyes disease . Patient/ family choice: 1-3m window to achieve hypothyroid state, desire to not have scar.	. Age > 10yr . Goitre >3-4 times enlarged . Thyroid nodule . Access to a high – volume pediatric thyroid surgeon . Significant proptosis with active eyes disease . Patient/ family choice: desire for rapid achievement of hypothyroidism, no concern over having scar.

VI. Complications [18]

- Hypothyroidism as a consequence of Grave's disease or its treatment.
- Treatment with levothyroxine is generally well tolerated and has minimal adverse effects.

  Considerations are:
  - Patients with longstanding hypothyroidism are at risk for developing pseudotumor cerebri
  - Both undertreatment (hypothyroidism) and overtreatment can affect bone mineral density
  - Children with more chronic (or severe) hypothyroidism also are at higher risk of temporary poorer school achievement and hyperactivity at initiation of treatment.

VII. Prognosis

Children whose hypothyroidism is diagnosed and promptly treated prior to puberty typically have good catch-up growth and normal adult height outcomes.

The vast majority of pediatric patient with hyperthyroidism has an excellent prognosis. However, they might have lower quality of life than their healthy peers. The strongest predictor of remission was trab normalization timing. Patients who normalized trab levels in the first year has a 70% remission rate and 50% for who normalized in the second year of therapy.

VIII. Prevention and Education

Children and adolescents with graves hyperthyroidism, lifelong monitoring of thyroid function is necessary especially during puberty and pregnant. There is a risk of neonatal Grave's disease in their offspring because of persistent stimulatory antibodies to the TSH receptor (trab) that cross the placenta.

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ADRENOCORTICAL INSUFFICIENCY

LY Vireak, SUN Sovutha, PHAY Narith, KEO Vanna

I. Key facts

Each year, approximately 6% to 8% of patients with adrenal insufficiency (AI)

Manifest an episode of adrenal crisis (AC) slightly more frequently in patients with primary adrenal insufficiency (PAI) than in those with secondary adrenal insufficiency (SIA), probably due to the concomitant absence of mineralocorticoid secretion, while they are uncommon in a patient with tertiary adrenal insufficiency due to long term glucocorticoid therapy, despite a variable degree of adrenal suppression. The incidence of PAI is relatively constant through ages 1 to 15 years, and 1 out of 10,000 children are diagnosed with PAI before the age of 15 years. [1, 7]

II. Overview

1. Definition

PAI is defined as the impaired synthesis and release of adrenocortical hormones on account of disease intrinsic to the adrenal cortex.

Inadequate production of glucocorticoid and mineralocorticoid by the adrenal gland due to a problem at the level of the adrenal gland (Primary), pituitary (secondary) or hypothalamus (tertiary). [3, 4, 10, 12]

2. Causes

PAI is caused by genetic defects or acquired diseases that affect

Adrenal function by the following processes.

- Steroidogenic disorders- The most common cause of PAI in children is congenital
- Adrenal hyperplasia (CAH) 70% of PAI (due to 21-hydroxylase)
- Adrenal damage-Isolated autoimmune adrenalitis (Addison disease, 15% of cases)
- Peroxisomal disorders- Including adrenoleukodystrophy, which is seen in boys.
- Genetic causes of adrenal hypoplasia- Including adrenal hypoplasia congenita.
- Inherited adrenal unresponsiveness to ACTH- Including familial glucocorticoid deficiency and triple A syndrome.
- Drugs- Including Ketoconazole. (10)

III. Signs and symptoms

In general, clinical findings of children with untreated PAI are often non-specific and include fatigue, nausea, and vomiting. Additional symptoms depend upon the specific hormones affected.

Specific hormones	Symptoms
Glucocorticoid Deficiency	- Weight loss, weakness and fatigue, headache, particularly in the morning - Nausea and vomiting, abdominal pain - Skin hyperpigmentation - Fasting hypoglycemia due to diminished counter-regulation, which leads to increase insulin sensitivity.
Mineralocorticoid deficiency	- Dizziness, headache, lethargy - Dehydration, salt craving, nausea and vomiting - Hypotension
Adrenal androgen	- Androgen excess: + In females: Acne, excessive hair growth, and irregular or absent periods. + In males: Weight gain, decreased testicle size, erectile dysfunction, gynecomastia.

	- Androgen efficiency: Post-pubertal individuals can be subtle, including decreased or absent axillary and pubic hair and decreased libido in females. In pubertal and adult males their androgen production occurs in the testes. Prepubertal children with adrenal androgen deficiency is asymptomatic.

- Adrenal crisis, adrenal crisis results from acute adrenal insufficiency.
- Many patients with adrenal crisis due to primary adrenal insufficiency have features of both glucocorticoid deficiency and mineralocorticoid deficiency.
- In older children with Addison's disease, symptoms include muscle weakness, malaise, anorexia, vomiting, weight loss, and orthostatic hypotension. [3, 10]

IV. Diagnosis

1. Laboratory finding

	PAI	CAH	Adrenal crisis	Addison's disease
Early AM Cortisol	Low	Low	Low (Random cortisol)	<18 µg/dl
ACTH	High		High	High
Glycemia	Low	Low	Low	
Natrimia	Low	Low	Low	
Kalemia	High	High	High	
PRA	High		High	High
Aldosterone	Low	Low or normal		
17 -OHP		High		
ACTH stimulation		(*)		
Testosterone		High		
Genotype		(**)		

❖ Notice:

(*) ACTH stimulation test

(**) Genotype was suggested only when the result of the adrenocortical profile after an ACTH stimulation test is equivocal, or cannot be accurately performed (i.e., a patient Receiving Glucocorticoid), or for purposes of genetic counselling. [3, 5, 8, 10, 13]

2. Imagery services

Normal or reduced adrenal gland volume on computed tomography (CT) and magnetic resonance imaging (MRI) and the absence of calcification on abdominal X-rays or CT. [12]

3. Differential diagnosis

- Addison's disease often needs to be distinguished from more acute illnesses such as gastroenteritis with dehydration or sepsis.
- When CAH is suspected, the serum level of cortisol precursors
- (17-hydroxyprogesterone) should be measured along with cortisol in an ACTH stimulation test.
- Adrenal crises include infants with obstructive uropathy, pyelonephritis, or crisis, presenting with vomiting, hyponatremia, and hyperkalemia. [10]
- Determine whether the AI is primary or central AI
  - PAI is indicated by low early AM Cortisol, high ACTH concentration, and possible hypoglycemia. In addition to glucocorticoid deficiency, these patients are at risk for mineralocorticoid deficiency, which is indicated by hyponatremia, hyperkalemia, elevated plasma renin activity (PRA), and low levels of aldosterone. [10]
  - Central adrenal insufficiency is indicated by low ACTH levels and low early AM Cortisol. These patients have glucocorticoid deficiency but not mineralocorticoid deficiency, so patients have normal results for serum Potassium, PRA, and Aldosterone. Many of these patients have deficiencies in one or more of the other

pituitary hormones (ie. Growth hormone, thyroid-stimulating hormone, luteinizing hormone, and follicle-stimulating hormones).

V. Treatment

1. Primary adrenal insufficiency (PAI)

Treatment of PAI must be immediate and vigorous. If the patient's condition permits, an ACTH stimulation test can be performed while initial fluid resuscitation is underway. [12]

- Adrenal hormone replacement is required in all forms of adrenal insufficiency Hydrocortisone 8-10 mg/m^2/day in 3 divided doses.
  A common recommendation to manage AI sick days is to increase the oral sick day Hydrocortisone to 30 mg/m^2/day divided into 4 doses over the day.
- If Aldosterone deficiency is present, Fludrocortisone (Florinef), a synthetic mineralocorticoid is given orally in doses of 0.05 mg - 0.2 mg/day.
  The mineralocorticoid dose is then adjusted based on PRA. It is not adjusted by age or body surface area.
- Replacement of Dehydroepiandrosterone (DHEA) in prepubertal children do not normally secrete large amounts of DHEA.
- Sodium Chloride supplements: Infants younger than one year with mineralocorticoid deficiency should also be supplemented with Sodium Chloride in addition to mineralocorticoid replacement. The dose is approximately 1 gram (17 meq) daily. [2, 4, 5, 10, 11, 14, 15]
- Restoring functional anatomy by surgery in individuals with CAH. In all pediatric patients with CAH, particularly minimally virilized girls, the parents be informed about surgical options. [13]

2. Adrenal crisis

- Fluid: D5% normal saline 0.9% 10-20 ml/kg, with a repeat bolus if needed. [10] Recognition and prompt therapy of salt-losing. Adrenal crisis is critical to survival. Electrolyte and fluid therapy must be instituted as soon as possible.
- Hypoglycemia: D10% 5ml/kg bolus IV.
- If the hyperkalemia is associated with electrocardiography changes, it may be necessary to use Insulin and Glucose, Kayexalate. [10, 12]
- Steroid replacement Glucocorticoid 4 mg/kg bolus IV, followed by continuous infusion 2 mg/kg/day until stabilization.
  If weight unknown:
  - Consider repeating the IV/IM Hydrocortisone dose if there is a poor response to initial steroid and fluid treatment.
  - When the child is stable, reduce the IV dose, or if tolerating oral medications, switch to triple dose oral hydrocortisone replacement (30-50 mg/m^2/day). [1, 2, 5, 6]

VI. Patient education and emergency precautions

- Screening test for CAH by heel prick should be done for newborn babies between the 3rd and 5th days of life or as soon as possible after 48 hours of age.
- Education of the patient and family is the key to successful therapy of AI and prevention of morbidity and mortality associated with AI. The patient and their caretakers must be instructed about the rationale for replacement therapy, the maintenance medications, and illness stress dosing. All patients should always wear a medical alert identification and carry a medical emergency information card that indicates the diagnosis of "Adrenal Insufficiency" and daily medications. [14]

Age	Initial dose of IM/IV Hydrocortisone	Then Hydrocortisone every 6h
Neonate - 6 weeks	25 mg	5-10 mg
6 weeks - 3 yrs	25 mg	10 mg
3 yrs - 12 yrs	50 mg	- 12.5 mg ages 3 - 6 yrs - 25 mg ages 6 - 12 yrs
≥ 12 yrs	100	25 G

VII. Monitoring

- In infants, the response to therapy should be evaluated monthly in the first three months after starting treatment.
- Every three months in older infants, and every six months thereafter while the child is still growing.
- More frequent monitoring is sometimes clinically indicated. After the completion of growth, annual monitoring may be adequate. [10]

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OBESITY

SUN Sovutha, LY Vireak, PHAY Narith, KEO Vanna

I. Key facts

- Childhood obesity is one of the most serious global public health challenges of the 21st century, affecting every country in the world.
- In 2022, 37 million children under the age of 5 were overweight. Almost half of the children under 5 years who were overweight or living with obesity in 2022 lived in Asia. [5, 6]
- Over 390 million children and adolescents aged 5–19 years were overweight in 2022, including 160 million who were living with obesity. The rise has occurred similarly among both boys and girls: in 2022 19% of girls and 21% of boys were overweight. [5, 6]
- Four percent of children under 5 are overweight in 2021 according to CDHS (Cambodia Demographic and Health Survey) 2021–22. [2, 7]

II. Overview

1. Definition

- Overweight is a condition of excessive fat deposits.
- Obesity is a chronic complex disease defined by excessive fat deposits that can impair health.
- By WHO, Children under 5 years: [5]
- Overweight: weight-for-height is greater than 2 standard deviations.
- Obesity: weight-for-height is greater than 3 standard deviations.
- By WHO, Children between 5-19 years (BMI: kg/m2)
- Overweight: BMI-for-age is greater than 1 standard deviation.
- Obesity : BMI-for-age is greater than 2 standard deviations. See growth chart at Annex.

2. Etiology [3, 8, 9]

- Sedentary lifestyle, imbalance of caloric intake (much consumption of sugar-containing beverages, fast food) and energy expenditure (less physical activity), excessive screentime, shortened sleep duration or irregular sleep schedules
- Medications: glucocorticoids, Sulfonylureas, Tricyclic antidepressants (tcas), Oral contraceptives, Insulin, Thiazolidinediones
- Ghrelin/leptin hormonal pathway dysfunction
- Genetic syndromes:
  - Prader-Willi syndrome
  - Pseudohypoparathyroidism
  - Down syndrome
  - Turner syndrome
- Hormonal disorders:
  - Growth hormone deficiency
  - Growth hormone resistance
  - Hypothyroidism
  - Leptin deficiency or resistance to leptin action
  - Glucocorticoid excess (Cushing syndrome)
  - Precocious puberty
  - Polycystic ovary syndrome (PCOS)
  - Prolactin-secreting tumors

III. Diagnosis [3, 9]

- Weight history
  - Gradual onset: is typical for the most common forms of obesity (genetic predisposition

Combined with excess caloric intake or other environmental contributors).

- Abrupt onset of weight gain: should prompt investigation of a major psychosocial trigger such as a loss or change in the family or new symptoms of anxiety or depression. Other possible causes include medication-induced weight gain and neuroendocrine causes of obesity (eg, Cushing disease, hypothalamic tumor).
- Severe early-onset: is more likely to have a strong genetic component. Some forms of syndromic or monogenic obesity have onset before two years of age, while others (especially Prader-Willi syndrome) tend to have growth failure during infancy followed by rapid weight gain and development of obesity after two years of age.

- Diet: Caregiver involved in feeding, eating patterns, food frequency, food preference and dislike, restaurants and prepared food.
- Growth rate and timing of puberty.
- Activity, screentime, sleep, medications, family history, psychosocial history, comorbidities.
- Calculation of BMI, blood pressure, stature and height velocity.
- Systemic physical examination.
- Laboratory test: fasting plasma glucose, fasting lipid profile, liver function test
- Other laboratory testing and imaging should be guided by history or physical. Examination findings.

IV. Complications [3, 9]

Type 2 diabetes, hypertension, hyperlipidemia, accelerated growth and bone maturation, ovarian hyperandrogenism and gynecomastia, cholecystitis, pancreatitis, and pseudotumor cerebri, fatty liver, cirrhosis, renal diseases, sleep apnea and sleep-disordered breathing, orthopedic disorders, psychologic complications, gout and colorectal cancer.

V. Treatment [1, 9]

1. **5-2-10 rule, everyday**:
   - 5 or more fruits and vegetables
   - 2 hours or less screen time
   - 1 hour or more of physical activity
   - 0 sugary drinks, more water
2. **Traffic Light Diet groups foods** into those that can be consumed without any limitations (Green/low caloric foods), in moderation (Yellow/medium caloric foods), or reserved for infrequent treats (Red/high caloric foods)

FEATURE	Low caloric FOOD	Medium caloric FOODS	High caloric FOODS
Quality	Low-calorie, high-fiber, low-fat, nutrient-dense	Nutrient-dense, but higher in calories and fat	High in calories, sugar, and fat
Types of food	Fruits, vegetables	Lean meats, dairy, starches, grains	Fatty meats, sugar, fried foods
Quantity	Unlimited	Limited	Infrequent or avoided

3. Referrals to dietician, psychologist (screen for possible mental or emotional health concerns) and specialists for other comorbid conditions, including type 2 diabetes, hypertension, nonalcoholic fatty liver disease, and orthopedic disorders.
4. Pharmacotherapy should be considered for adolescents 12 years and older with obesity (≥95th percentile) as an adjunct to diet and physical activity interventions.
   - GLP-receptor agonists (Liraglutide): 12 years and older
   - Orlistat (intraluminal inhibitor of pancreatic and gastric lipase): 12 years and older
   - Metformin: 10 years and older (for T2DM).

VI. Prevention [1, 9]

- Ensure appropriate weight gain during pregnancy;
- Practice exclusive breastfeeding in the first 6 months after birth and continued breastfeeding until 24 months or beyond;
- Limit screen time;
- Limit consumption of sugar sweetened beverages and energy-dense foods and promote other healthy eating behaviors;
- Enjoy a healthy life (healthy diet, physical activity, sleep duration and quality, avoid sedentary behaviors, avoid tobacco and alcohol, emotional self-regulation);
- Limit energy intake from total fats and sugars and increase consumption of fruit and vegetables, as well as legumes, whole grains and nuts.

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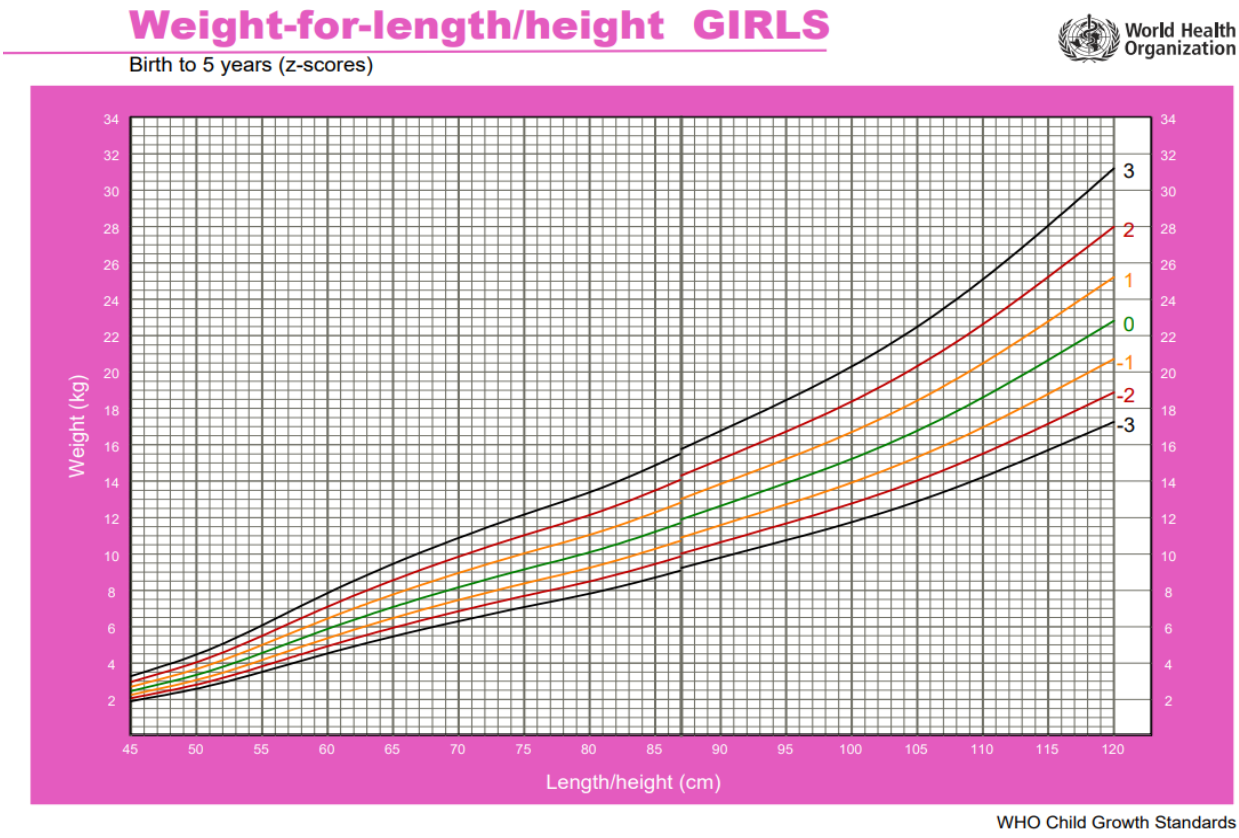
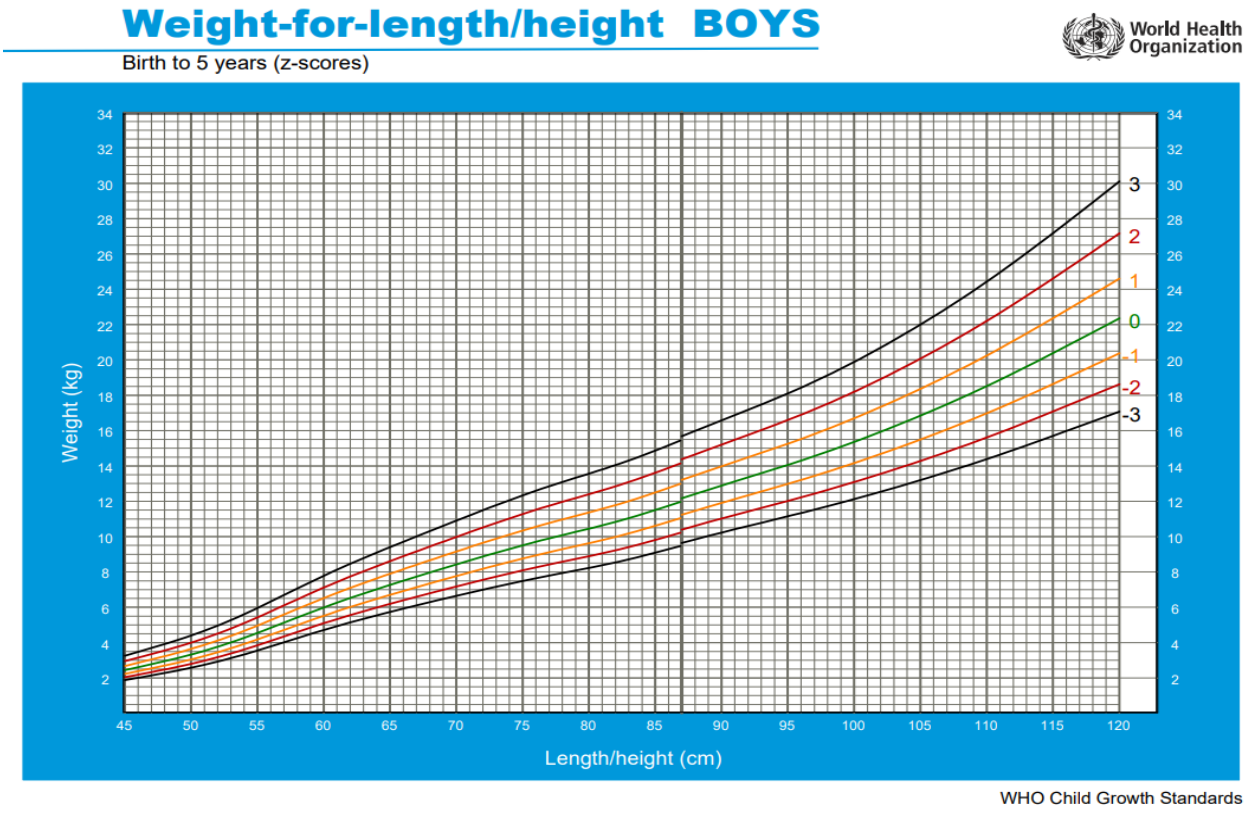
Annexe: **Growth Chart by WHO**

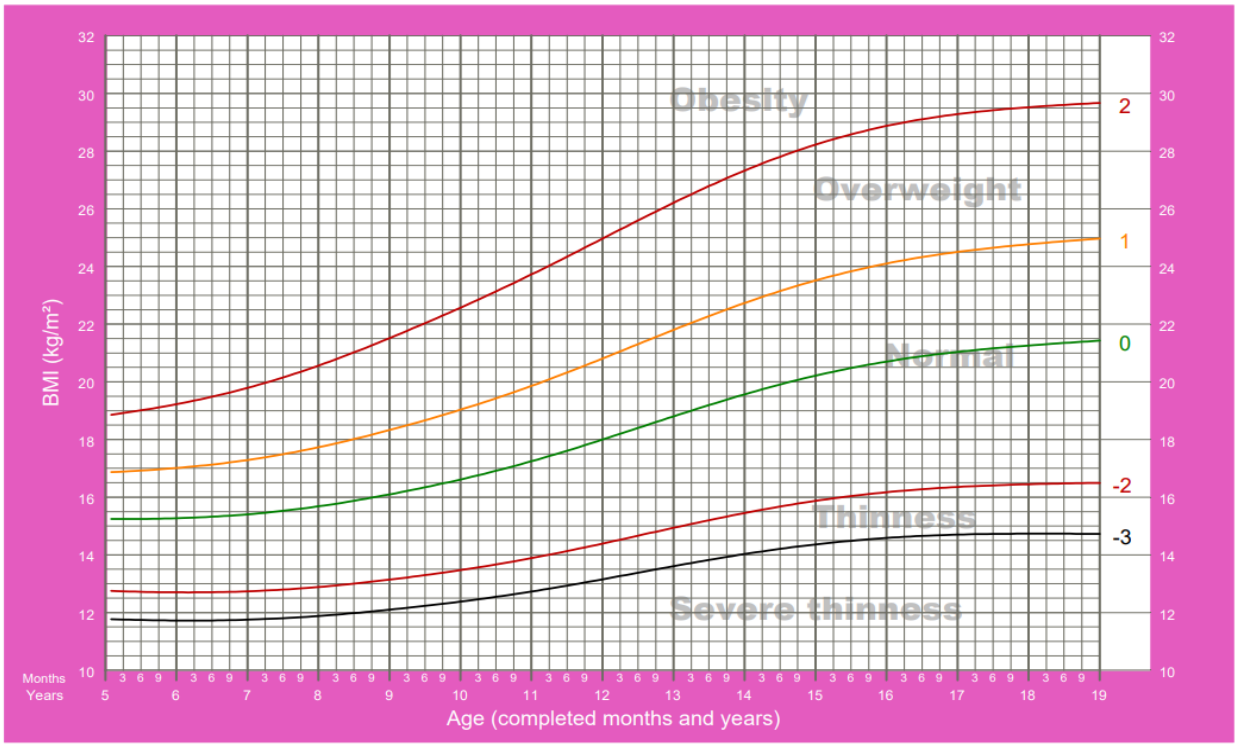




BMI-for-age GIRLS

5 to 19 years (z-scores)

World Health Organization

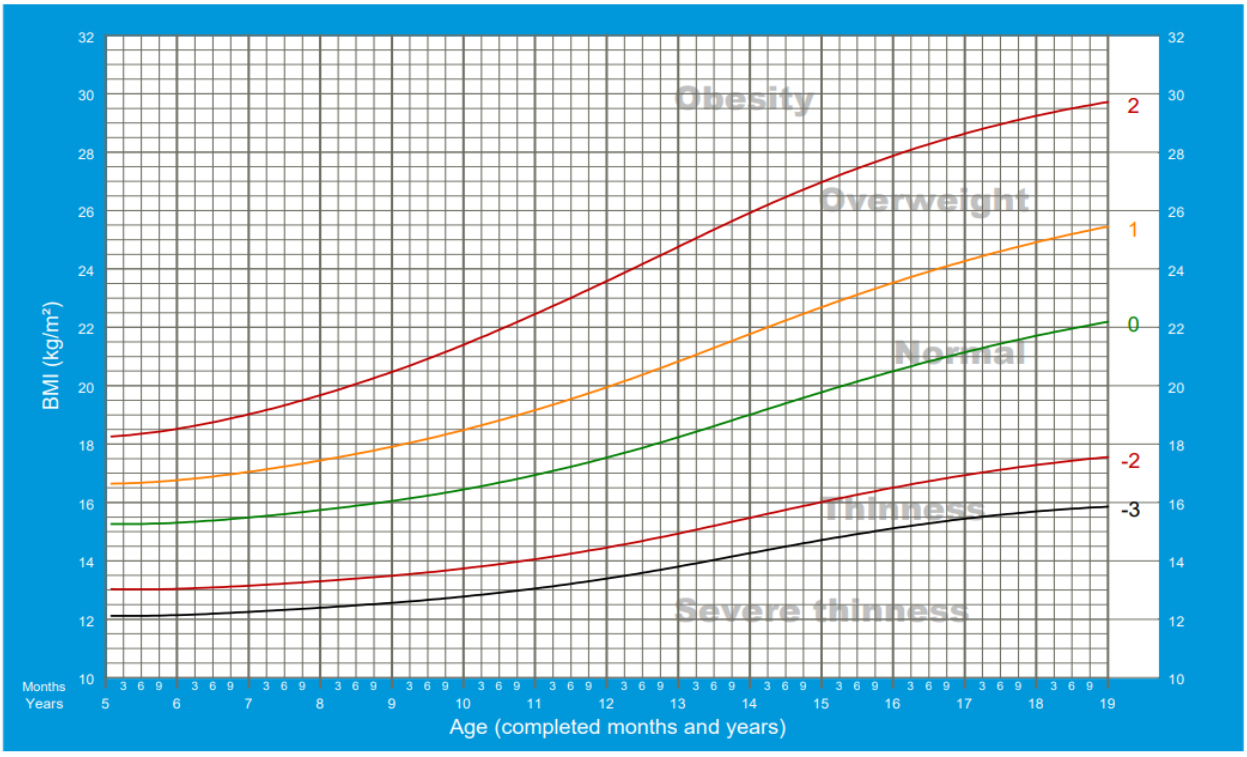


2007 WHO Reference

BMI-for-age BOYS

5 to 19 years (z-scores)

World Health Organization



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Chapter V: GASTRO-ENTEROLOGIC DISEASES

ACUTE GASTROENTERITIS

SING Heng, SOU Thyraroat, NGETH Pises

I. Key Facts

Acute gastroenteritis is a common infectious disease syndrome, causing a combination of nausea, vomiting, diarrhea, and abdominal pain.

The Centers for Disease Control and Prevention (CDC) estimate there are more than 350 million cases of acute gastroenteritis in the United States annually, and 48 million of these cases are caused by foodborne bacteria.

Traveler's diarrhea affects more than half of people traveling from developed countries to developing countries. Prevention can be summarized by the caution, "boil it, cook it, peel it, or forget it."

Except in cases of fever, bloody diarrhea, immunocompromised patients, or patients with significant comorbidities, identifying a specific pathogen is rarely indicated in acute bacterial gastroenteritis because illness is usually self-limited.

Preventing dehydration or providing appropriate rehydration is the primary supportive treatment of acute gastroenteritis.

II. Overview

1. Definition

Gastroenteritis is inflammation of the stomach, small intestine, or large intestine, leading to a combination of abdominal pain, cramping, nausea, vomiting, and diarrhea. Acute gastroenteritis usually lasts fewer than 14 days. This is in contrast to persistent gastroenteritis, which lasts between 14 and 30 days, and chronic gastroenteritis, which lasts more than 30 days. [2]

2. Epidemiology

In the United States, acute gastroenteritis is often viewed as a nuisance rather than the life- threatening illness, it can be in developing countries. Although significant morbidity and mortality have been attributed to acute diarrheal illnesses in the United States, epidemiologic studies in this country have not been as comprehensive as those conducted in developing nations.

The CDC, however, estimate that there are more than 350 million cases of acute diarrheal illnesses in the United States annually. Acute gastroenteritis compares with upper respiratory illnesses as the most common infectious disease syndrome. [4]

Using data from the National Centre for Health Statistics, the CDC recently reported that deaths from all-cause gastroenteritis increased from approximately 7000 to more than 7,000 per year from 1999 to 2007. Adults over 65 years old made up 83% of these deaths and C difficile accounted for two-thirds of these deaths, reflecting that the most significant morbidity and mortality are experienced by the extremes of age. [5]

3. Etiology *(see Appendix 4)*

Infectious etiology: Acute gastroenteritis is caused by many infectious agents as listed in Table 1

None infectious etiology: Medications and toxic ingestions that cause acute diarrhea or gastroenteritis include those listed in *Table 2.*

4. Types of acute gastroenteritis: these are the followings

a. *Traveller acute gastroenteritis/ Traveller's diarrhea* [6]

Travellers to developing countries often present to their primary care providers with Concerns about traveller's diarrhea and how to avoid or treat this problem should it occur;

40% to 60% of travellers to developing countries acquire this problem. It should also be considered if diarrhea develops within 10 days of their return home.

The most common causes are enterotoxigenic E coli (ETEC), followed Campylobacter jejuni, by Salmonella, and Shigella. In 1 study of 322 patients, ETEC caused 12% of bacterial traveller's diarrhea, Salmonella 8%, Campylobacter jejuni 6%, and Shigella less than 1%. In another study of 636 travellers, ETEC caused 30% and enteroaggregative E coli caused 26% of cases. [6] [7]

b. Foodborne gastroenteritis

The acute gastroenteritis is caused by effect of toxin of pathogens or direct invasion to intestinal wall impairment by pathogens.

The pathogenesis of foodborne gastroenteritis can be broken down into 3 mechanisms:

- Pathogens that make a toxin in the food before it is consumed (preformed toxin)
- Pathogens that make a toxin in the gastrointestinal tract, after the food is ingested
- Pathogens that invade the bowel wall and directly break down the epithelial lining, releasing factors that cause an inflammatory diarrhea [8]

c. Antibiotic-associated gastroenteritis

- Antibiotic-associated diarrhea is also called C difficile colitis. The use of multiple antibiotics and duration of antibiotic are associated with an increased risk of C difficile infection. [9]
- Antibiotics most often associated with C difficile infection are fluoroquinolones, clindamycin, cephalosporins, and penicillin. Those least associated with C difficile infection include doxycycline, aminoglycosides, vancomycin, metronidazole [9].
- Transmission occurs by fecal-oral route and colonization occurs because antibiotic use has disturbed the normal flora of the intestinal tract.

5. Risk factors

- New born and infant
- Malnutrition condition

III. Signs and symptoms

1. Functional Signs and Symptoms: *(Table 3 and Box 1 in appendix 4)*

- Asking questions for exploring history of acute gastroenteritis sign and symptoms (box 1)
- Diarrhea; fever; headache; nausea; abdominal pain; self-limiting; vomiting
- These signs and symptoms are varied by cases of illness *(table 3)*
- Questions to consider in the evaluation of patient with signs and symptoms of acute gastroenteritis in *box 1*

2. Physical examination finding

- Abnormal vital signs: fever and/or orthostatic blood pressure, and/or tachycardia, and/or pain.
- Clinical signs of dehydration include the following: dry mucus membranes, decreased skin turgor, absent jugular vein pulsations, mental status changes.

These and other physical examination findings, such as abdominal pain, have poor predictive value but contribute to the diagnosis and help with appropriate management of the illness.

IV. Diagnosis

1. Laboratory [10, 11,12]

Test if symptoms are prolonged or severe or if the patient was recently hospitalized or has fever, bloody stool, systemic illness, recent antibiotic use, or day care center attendance. Assess serum electrolytes, serum urea nitrogen, creatinine to evaluate hydration, and

acid-base status. A complete blood cell count is nonspecific but, if eosinophils are elevated, a parasitic infection should be considered.

These are available tests:

- Fecal leukocytes and occult blood: a bacterial species; white blood cells (70%)
- Fecal lactoferrin: the lactoferrin is a marker for fecal leukocytes, with sensitivity and specificity between 90% and 100%. Test is not readily available.
- Stool cultures
- C difficile assay: if hospitalized or if recent antibiotics or chemotherapy
- Stool ova and parasites
- Specific tests if indication

2. Imaging

- Abdominal ultrasound if indication
- Abdominal x ray if indication
- Abdominal CT scan if indication

3. Differential diagnosis

- Food poisoning
- Food allergy
- Intussusception
- Acute appendicitis
- Bowel obstruction
- FGIDs.

V. Complications

- Dehydration
- Hypovolemic shock
- Electrolyte imbalance
- Hypoglycemia.

VI. Management

1. General treatment

General recommendations Guidelines emphasize hydration or rehydration plus diet changes and bowel rest. Oral rehydration is best, if possible, and is often underutilized in the United States. In diarrheal illnesses that involve the small intestine, oral rehydration is effective because the small bowel can still absorb water but requires sodium-glucose cotransport. To provide the glucose and electrolytes, the World Health Organization recommends rehydration with water containing salt, sodium bicarbonate, and glucose. Gatorade and other sports drinks do not contain sufficient salt *(Box 2 in appendix 4).*

2. Specific treatment: (see appendix 1; 2)

- Dehydration
- Hypovolemic shock
- Electrolyte imbalance
- Bacterial dysentery
- Amoebic dysentery
- Parasitic infection (e.g. Giardia)
- Cholera
- Typhoid fever
- Food poisoning
- Non-GE: intussusception, diarrhea associated to antibiotic use, CMPA, lactose intolerance.

3. Follow up

The condition typically resolves within a few days but can sometimes lead to complications, especially if dehydration occurs.

Here's a brief guide on how acute gastroenteritis might progress and what to consider in its follow-up *(see appendix 5).*

VII. Prognosis

Acute gastroenteritis is a sudden inflammation of the stomach and intestines, commonly Caused by viral, bacterial, or parasitic infections. The condition typically resolves within a few days but can sometimes lead to complications, especially if dehydration occurs.

Here's a brief guide on how acute gastroenteritis might progress and what to consider in its follow-up *(see appendix 6).*

VIII. Prevention and Education

Prevention and education are key components in reducing the incidence and spread of acute gastroenteritis (AGE), especially since it is highly contagious, often transmitted via contaminated food, water, or person-to-person contact. Here are strategies for preventing gastroenteritis and educating individuals on minimizing risks *(see appendix 7).*

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Appendix 1: Classification of hydration status

Classify in the highest group where patient has >/= 2

Sign and Symptom	No dehydration	Mild 3-5%	Moderate, 6-9%	Severe, > 10%
Alert Irritable / agitation Thirsty Eyes sunken Lethargy Unconsciousness Skin turgor	Alert and no other signs and symptoms listed above	Alert and not enough criteria fit	At least two of all Irritable / agitation Thirsty Skin turgor slowly Eyes sunken	At least two of all Lethargic Unconsciousness Eyes sunken Skin turgor very slowly

- If NO dehydration (< 1 any signs): Use Plan A treatment
- If MILD or MODERATE dehydration: Use Plan B treatment
- If SEVERE dehydration: Use Plan C treatment

Appendix 2: Treatment of dehydration (Plan A, Plan B, Plan C)

Plan A: No dehydration

No dehydration

- Give extra fluid (breastfeed, ORS)
- Give Zinc:
  - < 6 months: 10mg PO QD for 10 days
  - >/= 6 months: 20mg PO QD for 10 days
- Continue feeding
- Advise on when to return

Counsel the mother on the 3 rules of home treatment:

- Give extra fluid
- Continue nutritious feeding
- When to return if required

How much fluid to give:

- Children under 2 years of age: 50-100 ml of fluid after vomiting or diarrhea
- Children aged 2 up to 10 years: 100-200 ml
- Older children and adults: as much fluid as they want

Plan B: Treat Mild or Moderate dehydration as outpatient in ORT Corner

Mild or Moderate

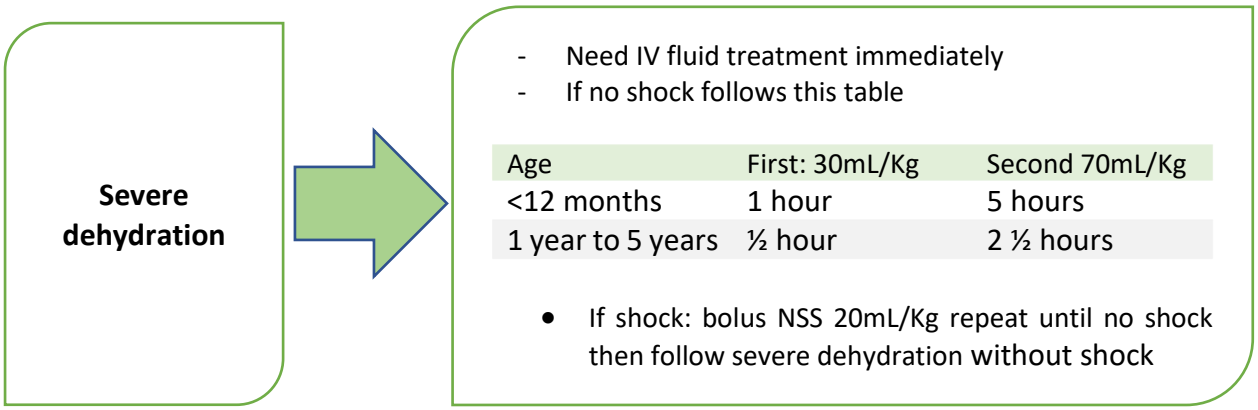
- ORS in the ORT Corner for 4 hours (with ongoing monitoring during this time)
- Reassess and change plan, if necessary, after 4 hours
- More frequent assessments if the child continues to have diarrhea and / or vomiting
- Zinc:
  - < 6 months: 10mg PO QD for 10 days
  - >/= 6 months: 20mg PO QD for 10 days

Amount of ORS to give in first 4 hours

Age	< 4 months	4 to 12 months	1 to 2 years	2 to 5 years
Weight	**<6kg**	**6-<10kg**	**10-<12kg**	**12-19kg**
Amount in ml	200-400	**400-700**	700-900	900-**1000**

- Encourage the mother to continue breastfeeding her child
- Reassess after 4 hours and reclassify patient according to hydration status
- Use the child age ONLY when you don't have the wight
- Appropriate ORS amount (in ml) can be calculated by patient's weight (kg) x 75
- If the patient wants more ORS than shown, give more
- During initial stages of therapy while still dehydration, children drink up to 20 ml/kg/h

Plan C: Treat severe dehydration in hospital



- Bolus repeated if redial pulse is still weak or undetectable
- Best IV fluid solutions: Normal Saline or Lactate Ringer
- Dextrose 5% is NOT effective and is dangerous

Appendix 3: Specific cause of diarrhea

a. Shigella infection

Shigella infection is characterized by high fever, abdominal cramps, and diarrhea. Non-gi manifestations may also occur. The characteristic small-volume, bloody / mucous stools are present in approximately 50% of the children with shigellosis.

The incubation period ranges 1-7 days, with average of 3 days. The diseases typically begin with constitutional symptoms such as fever, anorexia, and malaise. Diarrhea initially is watery, but subsequently may contain blood and mucus. Tenesmus is a common complaint. The child often looks ill.

Treatment

- Supportive care: correct dehydration, electrolytes imbalance orally or intravenous if necessary
- Antibiotics:
  - First choice: Ceftriaxone IV 75mg/kg q24h
  - Alternative: Ciprofloxacin IV 6-10mg/kg/dose q8h
  - 2nd alternative: Azithromycin (PO) 10mg/kg QD
  - Change antibiotic according to culture results as appropriate

- Change to oral antibiotic (Ciprofloxacin 10-15mg/kg/dose BID or Azithromycin 10mg/kg QD) for 5-7 days total as soon as possible.

b. Amoebic dysentery

Clinical amebiasis generally has a subacute onset over 1- 3 weeks. Symptoms range from mild diarrhea to severe dysentery producing diarrhea, bloody stools, and abdominal pain. Weight loss is present in just under 50% of patients. The child generally looks well compared with shigellosis patient.

Treatment:

- Supportive care: correct dehydration, electrolytes imbalance orally or intravenous if necessary
- Metronidazole (PO) 35-50mg/kg/day divided TID for 7-10 days

c. Typhoid fever

Symptoms

Typhoid fever and paratyphoid fever (known as enteric fever) are systemic illnesses characterized by sustained fever and abdominal symptoms.

Classic presentation is often described in characteristic stages:

- First week of illness: rising ('stepwise') fever and bacteremia
- Second week: abdominal pain and rash (rose spots, which are pink colored macules on the trunk and abdomen).
- Third week: hepatosplenomegaly, intestinal bleeding, perforation related to ileocecal lymphatic hyperplasia of the Peyer's patches, may occur and cause sepsis and peritonitis.

Diagnosis:

- Blood culture
- Stool culture
- CBC: leucopenia and anemia
- Widal test is not used any more.

Treatment:

- Admitted: Ceftriaxone IV 75mg/kg Q24h (can be changed to azithromycin before 10 days, but total duration of antibiotics should be at least 10 days)
- Outpatient: Azithromycin PO 10mg/kg QD for 7 days.
- Ciprofloxacin should never be used in Cambodia for empiric treatment due to high resistance rates. If culture results show sensitivity to Cipro, only then can it be used.

d. Cholera

- Cholera differs from acute diarrhea of other causes in three ways:
  - It occurs in large epidemics that involve both children and adults;
  - Voluminous watery diarrhea may occur, leading rapidly to severe dehydration with hypovolemic shock;
  - For cases with severe dehydration, appropriate antibiotics many shorten the illness duration.
- When to suspect cholera:
  - Cholera should be suspected when a child develops severe dehydration from acute watery diarrhea (usually with vomiting), or any patient has acute watery diarrhea when cholera is known to be occurring in the area.
- Dehydration *Treatment:*
  - Initial treatment of dehydration from cholera follows the guidelines given above for patients with some or severe dehydration.
  - For patients with severe dehydration and shock, the initial intravenous infusion should be given very rapidly to restore an adequate blood volume, as evidenced by normal blood pressure and a strong radial pulse.

- With cholera, unusually large amounts of ORS solution may be required to replace large continuing losses of watery stool after dehydration is corrected.
- The amount of stool lost is greatest in the first 24 hours of illness. During this period, the average fluid requirement of such patients is 200ml/kg of body weight, but some need 350ml/kg or more.
- Patients whose ongoing stool losses are in this range or higher usually require IV maintenance therapy using NS or Ringer's Lactate with added KCL. Additional potassium can also be provided by ORS solution as soon as the patient can drink.
- After being rehydrated, patients should be assessed for signs of dehydration at least every 1-2 hours, and more often if there is profuse ongoing diarrhea. If signs dehydration reappear, ORS solution should be given more rapidly.
- If patients become tired, vomit frequently or develop abdominal distension, ORS solution should be stopped and IV rehydration with KCL should be given (50ml/kg in three hours). After this it is usually possible to resume treatment with ORS solution.
- If possible, suspected cholera patients should be treated under observation until diarrhea stops, or is infrequent and of small volume. This is especially important for those who present with severe dehydration.

- Antibiotics *therapy:*
  - Ciprofloxacin 15mg/kg/dose BID for 3 days or
  - Erythromycin 12.5mg/kg QID for 3 days or
  - Azithromycin 20mg/kg Single dose

e. Intussusception:

Intussusception refers to the invagination of a part of the intestine into islet.

- Etiology:
  - 75% of cases of intussusception are considered 'idiopathic', although some of these episodes may be triggered by viral infection.
  - The remain 25% of cases are caused by an underlying disease or condition which creates a pathological lead point for the intussusception, including Meckel diverticulum.
- Clinical presentations:
  - Patients with intussusception typically develop sudden onset of intermittent, severe crampy, progressive abdominal pain; accompanied by inconsolable crying and drawing up of the legs toward the abdomen. These episodes usually occur at 15 to 20 minutes intervals and become more frequent and more severe over time. Vomiting may also occur. Initially emesis is non-bilious, but it may become bilious as the obstruction progresses.
  - Between the painful episodes, the child many behave relatively normal and be free of pain. As a result, initial symptoms can be confused with gastroenteritis. As symptoms progress, increasing lethargy develops, which can be mistaken for meningoencephalitis.
  - A sausage-shaped abdominal mass may be left in the right side of the abdomen. In up to 70% of cases, the stool contains gross or occult blood. The stool many be a mixture of blood and mucous, giving it the appearance of currant jelly.
- Diagnosis: Ultrasound, abdominal plain film
- Treatment:
  - For stable patients, no evidence of bowel perforation, use either hydrostatic or pneumatic enemas.

- Surgical treatment is indicated as a primary intervention for patients with suspected intussusception who are acutely ill or have evidence of perforation.

Appendix 4: Etiology and Symptoms; signs of acute gastroenteritis

Table 1*: Etiology: Infectious*

Viral: 50%–70%	Bacterial: 15%–20%	Parasitic: 10%–15%
Norovirus	Shigella	Giardia
Rotavirus	Salmonella	Amebiasis
Enteric adenovirus types 40 and 41	Campylobacter	Cryptosporidium
Astrovirus	E coli	Isospora
Coronavirus	Vibrio	Cyclospora
Some picornaviruses	Yersinia	Microsporidium
	C difficile	

Table 2: Etiology: Non infectious

Medications	Toxic Ingestions
Antibiotics	Organophosphates
Laxative abuse	Poisonous mushrooms
Sorbitol	Arsenic
Colchicine	Ciguatera or scombroid
Cardiac antidysrhythmics	
Nonsteroidal anti-inflammatory drugs[12]	
Chemotherapeutics	
Antacids	

Table 3: *Evaluation of patients presenting with signs and symptoms of acute gastroenteritis, Etiology unknown,* Onset, duration, and symptoms as caused by specific bacteria

Bacteria	Onset	Duration	Signs
Salmonella	6–48 h	1–7 d	N, V, F, P, ± blood
Campylobacter	1–10 d	5–14 d	F, H, P, N, V ± blood
Vibrio	6 h–4 d	SL (up to 3 d)	N, V, D
Shigella	1–6 d	SL (2–3 d)	F, P, D, ± blood
ETEC	1–3 d	2–3 d	D
C perfringens	8–16 h	Less than 24 h	P, D
EHEC	1–9 d	1 wk	N, P, D + blood
C difficile	4–5 d	Variable	F, N, P, D ± blood

Abbreviations: D: diarrhea; F: fever; H: headache; N: nausea; P: abdominal pain; SL: self-limiting; V: vomiting.

Box 1: *Questions to consider in the evaluation of patient with signs and symptoms of acute Gastroenteritis*

1. Abrupt or gradual onset of symptoms. In cases of foodborne illness, how many hours after

   Eating before symptoms onset?
2. Duration of symptoms
3. Characteristics of stool: watery, bloody, mucus, and color
4. Frequency and quantity of bowel movements.
5. Presence of fever, tenesmus, nausea, vomiting, headache, abdominal pain, malaise
6. Recent hospitalization, recent antibiotic use
7. Recent travel, pets, occupational exposures
8. 8. Food history, specifically consumption of raw milk, cheese, undercooked beef, pork, poultry
9. Immunocompromised
10. Family members, coworkers, or other close contacts with similar symptoms
11. Evidence of dehydration: thirst, tachycardia, decreased urine output, lethargy, orthostasis.

Box 2: *WHO rehydration recommendations*

1. Manufactured 1-L solutions contain

- 3.5 g Sodium chloride
- 2.5 g Sodium bicarbonate
- 1.5 g Potassium chloride
- 20 g Glucose

2. Home 1-L solutions contain

- ½ Teaspoon salt
- ½ Teaspoon baking sod
- 4 Teaspoons sugar.

Appendix 5: Follow up

The condition typically resolves within a few days but can sometimes lead to complications, especially if dehydration occurs.

Here's a brief guide on how acute gastroenteritis might progress and what to consider in its follow-up:

1. Recovery Phase:

- Duration: Most cases resolve in 1–3 days, although symptoms like mild diarrhea may last up to a week.
- Symptoms Improvement: As the infection subsides, symptoms such as vomiting, diarrhea, and abdominal cramps generally decrease. Appetite may gradually return, and energy levels improve.
- Hydration: Focus on rehydration with oral rehydration solutions (ORS) or electrolyte drinks to restore fluids and electrolytes lost due to vomiting and diarrhea.

2. Signs of Complications to Monitor:

- Dehydration: Look for signs such as dark urine, dry mouth, dizziness, and decreased urination, which require immediate attention.

- Persistent Symptoms: If symptoms last longer than expected or worsen (e.g., high fever, blood in stools, severe abdominal pain), it may indicate a bacterial infection or other underlying causes.
- Post-Infection Fatigue: After the acute phase, some people may feel fatigued for a while. This can be due to fluid loss, nutrient depletion, or the body's recovery process.

3. Follow-up Care Recommendations:

- Diet: After symptoms improve, start with bland foods (such as bananas, rice, applesauce, and toast—often referred to as the BRAT diet) and gradually return to a normal diet as tolerated.
- Medications: If prescribed, follow any guidelines for taking medications such as anti-diarrheal agents or antibiotics (if the infection is bacterial).
- Monitoring for Recurrence: In some cases, gastroenteritis can recur, especially if the original infection was viral or due to food contamination. Ensure that proper hygiene and food safety measures are followed.

4. When to Seek Further Medical Attention:

- Severe Dehydration: Persistent vomiting, inability to keep fluids down, or signs of severe dehydration.
- High Fever: A fever that exceeds 102°F (39°C), or fever lasting longer than 2 days.
- Blood in Stool or Vomit: This could be a sign of a more serious bacterial infection or other gastrointestinal issues.
- Chronic Conditions: People with weakened immune systems, chronic health conditions, or young children and elderly individuals should be monitored more closely.

5. Preventing Recurrence:

- Hand Hygiene: Regular handwashing with soap and water, especially after using the bathroom and before eating.
- Safe Food Handling: Practice safe food handling and cooking to avoid foodborne illnesses.
- Vaccination: Vaccines, like the rotavirus vaccine, can reduce the risk of viral gastroenteritis, particularly in children.

  In general, most cases of acute gastroenteritis improve with supportive care (hydration and rest), but if any concerning symptoms persist, it’s important to follow up with a healthcare provider.

Appendix 6: Prognosis

Here's an overview of the prognosis for acute gastroenteritis:

1. In Healthy Individuals:

- Recovery: Acute gastroenteritis typically resolves within a few days, usually 1 to 3 days, depending on the cause (viral infections, like rotavirus or norovirus, tend to improve quickly).
- Mild Complications: The most common complication is mild dehydration, which can be managed with rehydration. With proper hydration and care, the prognosis remains excellent.
- Full Recovery: Most people make a complete recovery without any long-term effects.

2. In Vulnerable Populations (e.g., Infants, Elderly, Immunocompromised Individuals):

- Higher Risk of Complications: These groups are at higher risk for complications such as severe dehydration, electrolyte imbalances, or prolonged illness.
- Severe Dehydration: Dehydration can be life-threatening if not treated promptly, requiring hospitalization for intravenous fluids. This is more common in very young children, the elderly, and those with weakened immune systems.

- Prolonged Illness: In some cases, particularly with bacterial infections like Salmonella, Campylobacter, or Escherichia coli (E. Coli), symptoms may last longer, and recovery can take more time.
- Risk of Post-Infectious Conditions: In rare cases, certain bacterial infections (such as Campylobacter or Shigella) can trigger post-infectious conditions like irritable bowel syndrome (IBS) or reactive arthritis. These complications are uncommon but can occur.

3. In Cases Caused by Specific Pathogens:

- Viral Gastroenteritis (e.g., norovirus, rotavirus):
- Prognosis: Excellent, with recovery occurring within a few days, typically 1–3 days.
- Complications: Rare, but dehydration is a risk if fluids are not adequately replaced.
- Bacterial Gastroenteritis (e.g., Salmonella, E. Coli, Campylobacter):
- Prognosis: Generally good, though it may last longer (up to a week). The need for antibiotics or hospitalization may arise in severe cases.
- Complications: Some bacteria can cause severe illness (e.g., E. Coli O157:H7 can lead to hemolytic uremic syndrome, a kidney failure complication). However, this is rare.
- Parasitic Gastroenteritis (e.g., Giardia):
- Prognosis: Often requires specific treatment like antiparasitic medications, but prognosis is good with treatment. If untreated, some parasitic infections can persist for weeks.

4. Risk of Recurrence:

- Recurrent Episodes: Gastroenteritis can recur if reinfected with the same or different pathogens. Viral infections like norovirus are known for their ability to spread easily, leading to reinfection, especially in communal settings like schools or nursing homes.
- Chronic Gastrointestinal Issues: In some cases, repeated or severe gastroenteritis episodes can lead to chronic gastrointestinal issues, such as irritable bowel syndrome (IBS), though this is not common.

5. Long-Term Effects:

- Minimal in Most Cases: For the vast majority of individuals, acute gastroenteritis does not cause long-term health problems.
- Post-Infectious Complications: As mentioned, rare post-infectious complications like IBS, lactose intolerance, or reactive arthritis may occur in some bacterial infections, but these are exceptions.

❖ Conclusion:

The overall prognosis of acute gastroenteritis is excellent, with the majority of cases resolving without long-term complications. Proper rehydration and supportive care are key to a full recovery. However, the prognosis can be more serious in vulnerable populations (young children, the elderly, immunocompromised individuals), requiring more intensive treatment to prevent dehydration or complications.

Appendix 7: Prevention and Education

1. Hygiene and Handwashing

- Handwashing: Frequent handwashing with soap and water is the most effective way to prevent the spread of viruses and bacteria that cause gastroenteritis. Handwashing should be done:
  - Before eating or preparing food
  - After using the bathroom (or changing diapers)
  - After caring for someone who is ill
  - After handling animals or cleaning up animal waste

- Proper Technique: Hands should be washed for at least 20 seconds, covering all areas (back of hands, between fingers, and under nails). If soap and water are unavailable, alcohol-based hand sanitizers (with at least 60% alcohol) can be used.

2. Food Safety

- Safe Food Handling:
  - Cook foods thoroughly: Ensure that meat, poultry, and seafood are cooked to safe temperatures to kill harmful pathogens.
  - Avoid cross-contamination: Use separate cutting boards for raw meats and ready-to-eat foods like vegetables and fruits.
  - Proper storage: Refrigerate perishable foods promptly and keep cold foods at or below 40°F (4°C). Hot foods should be kept at 140°F (60°C) or hotter.
  - Wash fruits and vegetables thoroughly before eating or cooking.
- Clean Utensils and Surfaces: Sanitize kitchen surfaces, utensils, and cutting boards frequently to prevent contamination.

3. Water Safety

- Drinking Water: Always ensure drinking water is clean and treated. Avoid drinking untreated water from lakes, rivers, or streams, especially while traveling to areas with poor sanitation.
- Hygiene in Public Pools: Avoid swallowing water in pools, and ensure proper chlorination and sanitation of swimming facilities. Do not swim when you have symptoms of gastroenteritis (diarrhea, vomiting).
- Water Treatment: For those traveling to areas with unsafe water, drinking bottled water or boiling water for 1-3 minutes before consumption is recommended.

4. Preventing Person-to-Person Spread

- Isolation of Infected Individuals: People who are sick with gastroenteritis should stay home from work, school, or daycare until they are no longer contagious. For viral gastroenteritis, this often means waiting at least 48 hours after symptoms (vomiting, diarrhea) have stopped.
- Clean and Disinfect: Clean and disinfect contaminated surfaces (like countertops, bathroom surfaces, and door handles) frequently, especially if someone in the household is ill. Use a bleach-based cleaner or another disinfectant proven to kill stomach viruses.
- Avoid Close Contact: Avoid sharing food, drinks, or utensils with others while you are sick.

5. Vaccination

- Rotavirus Vaccine: The rotavirus vaccine is highly effective in preventing rotavirus infections, which are a leading cause of severe gastroenteritis in young children. This vaccine is part of routine childhood immunizations in many countries.
- Vaccination for Travel: Depending on your destination, some vaccines may help reduce the risk of gastroenteritis caused by certain pathogens (e.g., cholera). Travellers should consult with a healthcare provider about recommended vaccines before visiting high-risk areas.

6. Proactive Measures for Vulnerable Groups

- Elderly and Immunocompromised Individuals: Ensure these individuals practice excellent hygiene and receive flu shots, as they are at greater risk for severe complications from gastroenteritis.
- Infants and Young Children: Parents and caregivers should be especially diligent about hand hygiene, food safety, and rehydration. Children should receive the rotavirus vaccine as part of their vaccination schedule.

- Breastfeeding: Exclusive breastfeeding for the first six months of life can help reduce the risk of gastroenteritis in infants by boosting their immune system.

7. Traveller Education

When traveling, particularly to developing countries, take precautions such as:

- Avoid eating food from street vendors.
- Drink bottled or boiled water.
- Wash hands frequently and carry hand sanitizer.
- Be cautious about ice cubes in drinks, as they may be made from contaminated water.

8. Education on Signs and Symptoms

- Recognize Symptoms Early: Educate the public about the common symptoms of gastroenteritis—vomiting, diarrhea, abdominal cramps, fever—and when to seek medical attention (e.g., if symptoms last more than a few days, or if dehydration occurs).
- Hydration: Stress the importance of maintaining proper hydration, especially during diarrhea and vomiting episodes. Oral rehydration solutions (ORS) can help replace lost fluids and electrolytes.

9. General Public Awareness

- Public Health Campaigns: Governments and health organizations can run public health campaigns to raise awareness about gastroenteritis, focusing on prevention methods, the importance of hand hygiene, and proper food safety.
- School and Workplace Education: Schools and workplaces can distribute educational materials and provide resources on how to prevent gastroenteritis, particularly during flu and cold seasons when viral infections are more common.

10. Proper Use of Antibiotics

- Avoid Unnecessary Antibiotics: For viral causes of gastroenteritis (like norovirus or rotavirus), antibiotics are ineffective and should not be used. Misuse of antibiotics can contribute to antibiotic resistance and disrupt gut health.
- Proper Diagnosis and Treatment: In cases of bacterial or parasitic gastroenteritis, seek medical advice for proper treatment, which may involve antibiotics or antiparasitic medications.

Summary of Key Prevention Strategies:

- Practice thorough handwashing, especially before eating and after using the toilet.
- Ensure safe food and water handling, particularly when traveling or preparing food.
- Educate vulnerable populations (e.g., elderly, infants) and caregivers about prevention.
- Get vaccinated (e.g., rotavirus vaccine for children).
- Isolate affected individuals and disinfect surfaces to prevent spread.
- Maintain hydration and recognize signs of complications like dehydration.
- Education and prevention are essential to reducing the impact of gastroenteritis and improving overall public health.

DYSENTERY IN CHILDREN

MILIYA Thyl, SING Heng, MEY Moniborin; NGETH Pises

I. Key facts

- In 2017, 6.2 billion episodes of diarrhea diseases were estimated to have occurred worldwide, including 500,000 incident cases of intestinal/non-invasive /diarrheal non-typhoidal salmonella disease (1)
- Role of antibiotic treatment is not required unless patient present with sepsis or underlying risk factor such as immune compromise (e.g HIV, steroid dependent)

II. Overview

1. **Dysentery is a bloody diarrhea**, often with mucus and associated with tenesmus and/or painful defecation. It can be caused by bacteria or parasites.
2. **Diarrheal diseases** can be acquired through ingestion of food or water contaminated with viral or bacterial pathogens (rarely protozoal or fungal pathogens) or through direct contact with someone carrying the pathogen. Establishment of an enteric infection depends on the capacity of the pathogen to invade the mucosa and overcome the host defences. It is dependent on several factors, including the inoculum, the virulence of the organism and the status of host defences. Production of enterotoxins (i.e. Bacterial proteins that act on the host's intestinal cells) is a frequently encountered mechanism of disease.
3. **Causes / Etiology / Transmission** [2]
   - Dysentery or bloody diarrhea most likely cause are bacteria: Shigella spp., Salmonella spp., Campylobacter spp., Enterotoxigenic Escherichia coli.
   - Parasites are responsible for persistent bloody diarrhoea rather than acute bloody diarrhoea: Entamoeba histolytica, Giardia intestinalis.
4. **Physiopathology**
   - Acute diarrheal diseases can be acquired through ingestion of food or water contaminated with viral or bacterial pathogens (rarely protozoal or fungal pathogens) or through direct contact with someone carrying the pathogen.
   - Establishment of an enteric infection depends on the capacity of the pathogen to invade the mucosa and overcome the host defences. It is dependent on several factors, including the inoculum, the virulence of the organism and the status of host defences. Production of enterotoxins (i.e. Bacterial proteins that act on the host's intestinal cells) is a frequently encountered mechanism of disease.

III. Signs and symptoms

1. **Bacterial dysentery** is characterised by high fever, abdominal cramps, and diarrhoea. Non-GI manifestations may also occur. The characteristic small-volume, bloody, mucus coated stools are present in approximately 50% of the children with bacterial dysentery. The disease typically begins with constitutional symptoms such as fever, anorexia, and malaise. Diarrhoea initially is watery, but subsequently may contain blood and mucus. Tenesmus is a common complaint. The child often looks ill
2. **Amoebiasis generally** has a subacute onset, usually over 1-3 weeks. Symptoms range from mild diarrhea to severe dysentery, with bloody diarrhea and abdominal pain. Weight loss is present in just under 50% of patients. Fever may occur, but the child generally looks well compared with patients with bacterial dysentery.

IV. Diagnosis

- Routine laboratory tests are usually not needed. However, for severe cases, electrolytes should be checked if available

- However, could be consider in certain cases and based on local availability such as stool microscopic, stool culture, antigen testing and nucleic acid amplification test, but only when identifying the causative pathogen may benefit the patient. For example, because specific treatment can be provided or a multidrug-resistant pathogen may be detected

V. Complications

- Rehydration is common in children with gastroenteritis and bloody diarrhea
- Without treatment, amebiasis dysentery may develop into extra-intestinal abscess, such as liver, lung, or rarely the brain. [3]

VI. Treatment

1. The main treatment for acute bloody diarrhea is rehydration. In children treating any diarrhea with oral rehydration therapy using a low-osmolarity oral rehydration solution to prevent dehydration is recommended. [4]
2. Antibiotics usually not needed, including in cases with severe dehydration. Consider antibiotic treatment ONLY if:
   - Significant acute bloody diarrhea AND severely immunocompromised patients
3. Table for antimicrobial empirical treatment of choice [5]

Antibiotic of choice bacterial dysentery			
First line	Medication	Dose and route	Duration
	Ciprofloxacin	15 mg/kg/dose given every 12 hours – Oral	3 days
Second line	Azithromycin	10mg/kg/dose given once a day – Oral	3 days
	Ceftriaxone	80mg/kg/dos given once a day – IV	3 days
Antibiotic of choice amoebic dysentery			
	Metronidazole	10mg/kg/dose given every 8hours - Oral	7 to 10 days

- Metronidazole is active against trophozoites which invade the bowel wall and cause disease. In order to clear a patient's bowel lumen of amoebic cysts and reduce the chances of further complications or recurrent disease, a luminal amoebicidal agent should be given. These are active against amoebic cysts in the gut and ought to be given as part of treatment.
- Diloxanide furoate, paromomycin or iodoquinol are all good options, but it may depend on what is available.

VII. Prevention and education

Key measures to prevent acute diarrheal diseases include

- Access to safe drinking water
- Use of improved sanitation
- Handwashing with soap
- Exclusive breastfeeding for the first 6 months of life
- Good personal and food hygiene
- Health education about how infections spread.

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GASTRITIS

TANG Lenghak, CHRUN Chhunny, EAR Vireak, UN Vallery,
KHUN Leangchhun, YAY Chantana

I. Key facts

- Gastritis, gastropathy, and peptic ulcer diseases (puds) in children are a spectrum of acid-related disorders. [1]
- Gastritis is characterized by the presence of inflammatory cells, whereas gastropathies demonstrate gastric mucosal damage and abnormalities in the absence of inflammatory cells.
- Prior to the discovery of Helicobacter pylori (H. Pylori), primary gastritis was considered disease without an identifiable etiology. With the discovery of H. Pylori, many studies have identified H. Pylori as a primary and the most likely cause of pediatric gastritis.
- In general, the prevalence Helicobacter pyloric infection is high in developing countries and the infection is acquired at a young age. The incidence is 3-10% of the population each year in developing countries compared with 0.5% in developed countries. [2]
- Worldwide, more than 1 billion people are estimated to be infected with H pylori.[3]
- Morbidity/mortality is dependent on the etiology of the gastritis. Generally, most cases of gastritis are treatable once the etiology is determined. The exception to this is phlegmonous gastritis, which has a mortality of 65%, even with treatment. [4]

II. Overview

1. Definition

Gastritis is an inflammation of gastric mucosa layer, it can be:

- Acute: Come up suddenly and last briefly (2 – 10 days).
- Chronic: Come up gradually, long lasting or recurrent.

2. Etiology

Gastritis caused by any of several condition, including: [1,5]

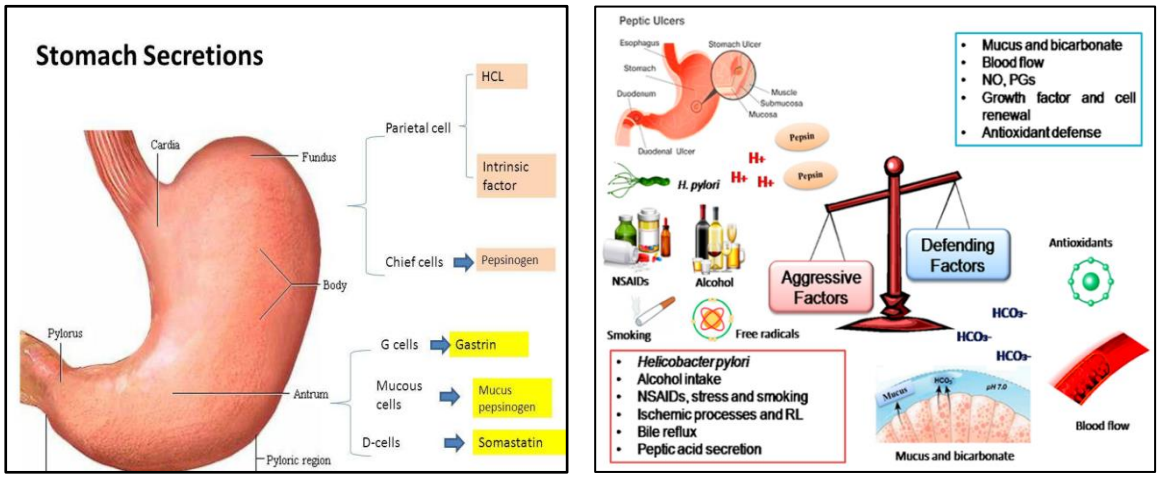
- Infection (Helicobacter pylori, Cytomegalovirus, Candida, Parasites…)
- Drugs induced (NSAID, Corticosteroids, and aspirin)
- Stress
- Celiac disease
- Inflammatory bowel disease (gastritis may be seen in both Cronh's disease and ulcerative colitis)
- Allergic gastritis (Cow's milk allergy, soy milk, egg …)
- Less common causes:
  - Henoch-Schönlein Gastritis (small-vessel iga-mediated vasculitis with systemic involvement)
  - Collagenous Gastritis
  - Radiation Gastritis
  - Smoking
  - Consummation excessive: Alcohol, coffee …

3. Physiopathology

- The gastric mucosa is divided into two levels: the superficial foveolar cells that line the mucosa and the pits and the deeper glandular compartment that contains gastric glands.[1]
- The acidic gastric contents become corrosive when there is an increase in acid production or a disruption of protective factors. Parietal cells of the stomach produce gastric acid via proton pumps (Hþ/Kþ atpase) in response to acetylcholine from vagal efferents, histamine from enterochromaffin cells, and gastrin from G cells.

- There are several mechanisms to protect the gastric mucosa, including a mucus layer, a ph-neutral buffer zone, an epithelial layer, and a rich gastric blood supply. Prostaglandin release mediates mucin secretion from surface foveolar cells and bicarbonate release from epithelial cells. [6]
- Gastritis is formed when the damaging factors overcome the protective mechanisms.

Figure 1. *Mechanism of gastric injury and protection* [7]



III. Signs and symptoms

Symptoms of gastritis vary in children and are often nonspecific. The majority of symptoms include:

- Irritability
- Generalized abdominal pain or poor localized abdominal pain
- Epigastric abdominal pain
- Dyspepsia
- Vomiting
- Gastroesophageal reflux

❖ Alarm sign: [1]

- Persistent vomiting
- Hematemesis or Melena
- Involuntary weight loss
- Poor appetite
- Nocturnal awakening secondary to abdominal pain
- Anemia.

IV. Diagnosis

The diagnosis of gastritis is usually based on the patient's history and symptoms, but sometimes they need to be confirmed by upper gastrointestinal (GI) endoscopy, especially when the alarm signs are present.

1. Laboratory

- CBC for anemia with other signs of chronic blood loss (e.g., microcytosis, low reticulocyte count)
- Electrolyte panel
- Helicobacter pylori identification: [8]
  - Non-invasive *tests:*
    - Serologic tests (saliva/urine/blood): the percentage of false-positive results with serologic assays has increased significantly, making these tests too unreliable in most countries and regions.

- Urea breath tests: use an oral dose of 13C- or 14C-labeled urea. In an infected patient, the organism metabolizes the urea and liberates labelled CO2, which is exhaled and can be quantified in breath samples taken 20 to 30 minutes after ingestion of the urea (sensitivity and specificity are > 95%).
- Stool antigen assays: have a sensitivity and specificity similar to that of urea breath tests.

- Invasive tests: Endoscopy is used to obtain mucosal biopsy sample for a rapid urease test (RUT) or histologic staining.

2. **Imagery finding**

Upper GI Endoscopy: visualize the gastric mucosa for abnormalities and obtain tissue biopsies.

- Possible finding:
- Thickened hyperemic mucosa
- Atrophic mucosa
- Antral micronodules (represent lymphoid follicles) commonly seen in children with Helicobacter pylori infection
- Antral and prepyloric edema with retained gastric secretions

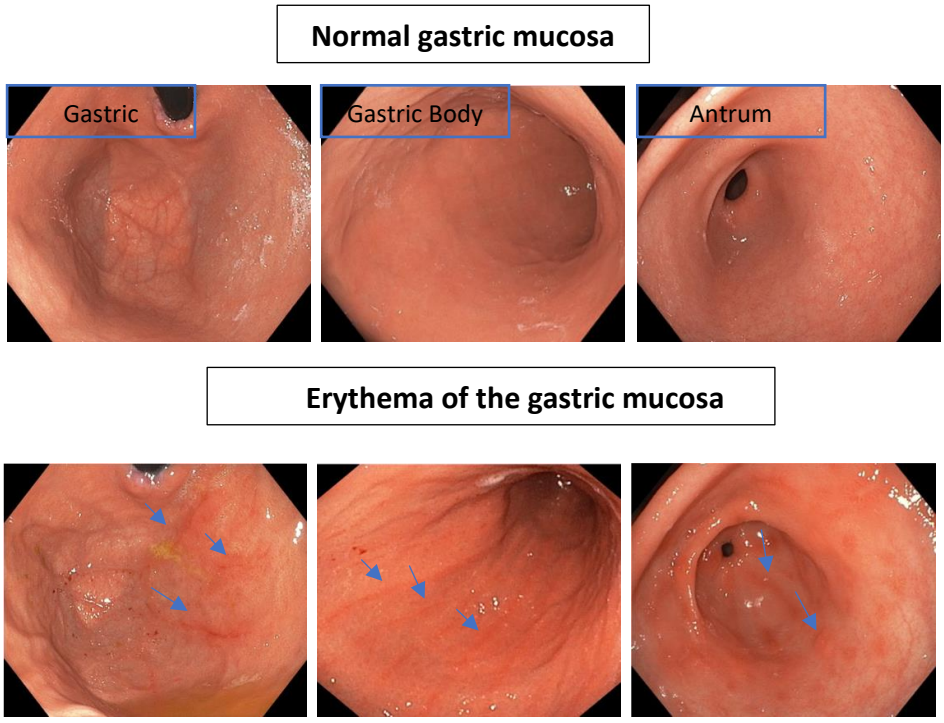


Fig 2. *Gastritis on endoscopic view (Images from Jayavarman 7 hospital)*

3. **Differential diagnosis**

- Functional abdominal pain: chronic or recurrent abdominal pain with the absence of structural or biochemical abnormalities.
- Gastroesophageal reflux with esophagitis: the typical presentation of GERD includes esophageal symptoms such as heartburn, acid dyspepsia, regurgitation, and chest pain
- Peptic ulcer disease: epigastric pain that occurs after meals classically, shortly after meals with gastric ulcers and 2-3 hours afterward with duodenal ulcers.
- Cholelithiasis: pain that is localized to the epigastrium or right upper quadrant, sometimes radiating to the right scapular tip, begins postprandially, described as intense and dull, typically lasts 1-5 hours.

- Cholecystitis: pain in the right upper quadrant, usually with rebound and guarding, positive Murphy sign, frequent presence of fever.
- Pancreatitis: abdominal pain located in the upper abdomen and may radiate directly through to the back, usually sudden in onset and gradually becoming more severe until reaching a constant ache.
- Renal stones: Intense pain that suddenly occurs in the back and radiates downward and centrally toward the lower abdomen or groin.
- Non-ulcer dyspepsia: dyspeptic symptoms (such as indigestion, early satiety, postprandial fullness, gnawing, or burning) in a patient who has no abnormalities on physical examination and upper gastrointestinal (GI) endoscopy.

V. Complications

- Peptic ulcer disease
- Gastrointestinal bleeding
- Gastric outlet obstruction due to edema limiting an adequate transfer of food from the stomach to the small intestine.

VI. Treatment

There are several treatment medications and modalities for gastritis: [1]

- The underlying etiology must be addressed and treated.
- Even with treatment of the underlying disease, acid suppression is usually involved. Other modalities include acid-neutralizing antacid medications.
- In severe, complicated gastritis, more invasive treatment methods with therapeutic endoscopy are required (hemostatic clip, epinephrine injection therapy, hemospray, thermal therapy etc.).

1. Acid Suppression

- Histamine 2 (H2) receptor antagonists
  - Cimetidine: 10-20 mg/kg/day IV/PO divided 12hr. (Frequently used anti H2 receptor)
  - Ranitidine: 4-8 mg/kg PO q12hr; not to exceed 300 mg/day, 2-4 mg/kg/day IV divided q6-8hr; not to exceed 50 mg/dose or 200 mg/day.
  - Famotidine: 0.25 mg/kg IV q12hr or 0.5 mg/kg PO at bedtime; may increase to 1 mg/kg daily for up to 8 weeks; not to exceed 40 mg/day.
  - Proton pump inhibitor (PPI):
  - Omeprazole: 5-10 kg: 5 mg PO qday, 10-20 kg: 10 mg PO qday, >20 kg: 20 mg PO qday. (Frequently used PPI)
  - Lansoprazole: <30 kg: 15 mg PO qday, >30 kg: 30 mg PO qday.
  - Pantoprazole: >5 years => 15 kg to <40 kg: 20 mg PO qday, >40 kg: 40 mg PO qday.
  - Esomeprazole: 1-12 years: 10-20 mg PO qday, >12 years: 20-40 mg PO qday.
- The acid-suppression medications (anti H2 receptors or PPI) should be administered for 2 to 4 weeks.

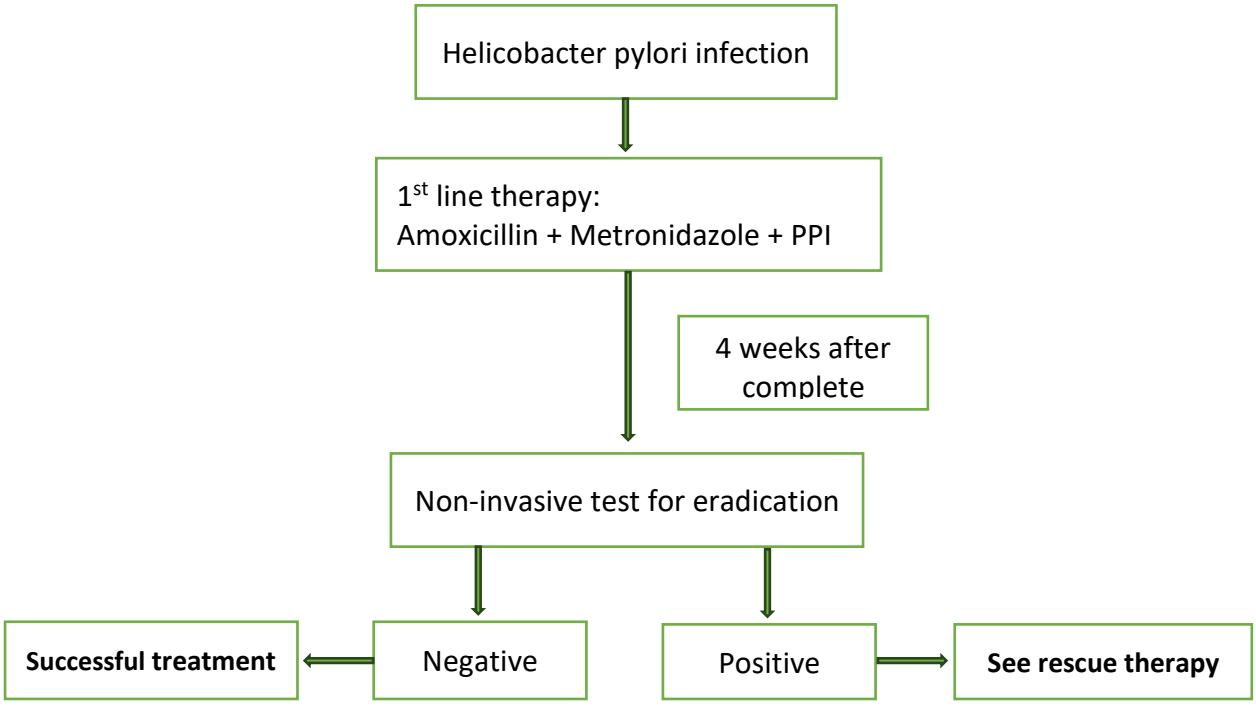
2. Recommended Eradication Therapies for H. Pylori-associated Disease in Children [9]

Medications	**Dose**		**Duration of treatment**
Proton pump inhibitor	1mg/kg/dose twice a day		1 month
Antibiotic	**Weight**	**Dose**	**Duration of treatment**
Amoxicillin	15-24 kg 25-34 kg >35 kg	500 mg twice a day 750 mg twice a day 1000 mg twice a day	14 days

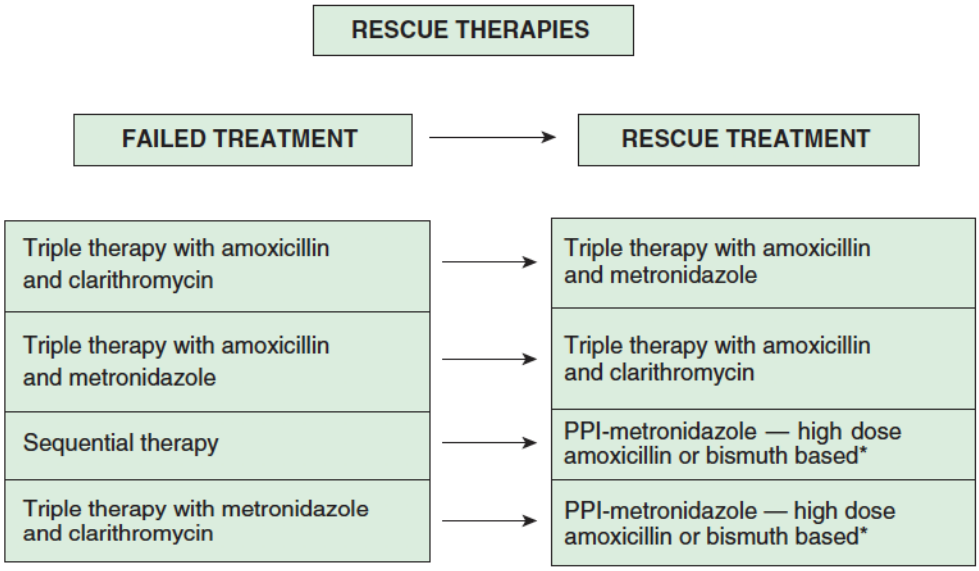
Clarithromycin	15-24 kg 25-34 kg >35 kg	250 mg twice a day 500 mg in AM, 250mg in PM 500 mg twice a day	14 days
Metronidazole	15-24 kg 25-34 kg >35 kg	250 mg twice a day 500 mg in AM, 250mg in PM 500 mg twice a day	14 days

- Recommended combinations for triple therapy are:
  - Amoxicillin + Metronidazole + PPI or
  - Amoxicillin + Clarithromycin + PPI or
  - Clarithromycin + Metronidazole + PPI
- A reliable non-invasive test for eradication is recommended at least 4 weeks following completion of therapy.
- If treatment has failed, rescue therapy should be targeted to antibiotic susceptibility, the age of the individual child, and antimicrobial options.

Figure 4. *Rescue therapy for failed eradication of H. Pylori*



- Bismuth-based therapy with tetracycline instead of amoxicillin if patients >8 yr.
- Bismuth dose is:
  - 262 mg four times a day for patients 8–10 years old
  - 524 mg four times a day for those >10 years old
- High-dose amoxicillin ranges from:
  - 750 mg twice a day for body weight 15–24 kg
  - 1000 mg twice a day for 25–34 kg
  - 1500 mg twice a day for >35 kg.



VII. Patient education

- Gastritis is inflammation of the stomach lining, can be caused by many factors, including infection, stress resulting from severe illness, injury, use of nonsteroidal anti-inflammatory drugs (nsaids), steroid, alcohol, and disorders of the immune system.
- Symptoms of gastritis include abdominal pain or discomfort, and sometimes nausea or vomiting.
- The diagnosis is based on the person's symptoms, but sometimes they need to examine the stomach with a flexible viewing tube (upper GI endoscopy).
- Avoiding unnecessary NSAID use and improving hygiene may prevent gastritis.
- Gastritis's symptoms may be reduced by avoiding beverages that may irritate the stomach lining or increase acid production including coffee, alcohol, and carbonated beverages.

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PEPTIC ULCER DISEASE IN CHILDREN

TANG Lenghak, CHRUN Chhunny, EAR Vireak, UN Vallery,
KHUN Leangchhun, YAY Chantana

I. Key facts

- Peptic ulcer diseases (PUD) in children are a spectrum of acid-related disorders that can affect the stomach and duodenum. The common causes of peptic ulcers include Helicobacter pylori infection, medication use, and stress-related gastric injury.
- Epigastric pain is the most common symptom of both gastric and duodenal ulcers.[1]
- PUD is rare in children, the incidence of PUD in children is lower than that in adult. [2,3]
- Incidence of PUD in children ranging from 0.5 to 4.4 per 100,000 individuals.[4]
- The prevalence is similar between both sexes, with the incidence of PUD increasing after age 10 years.
- In general, the prevalence Helicobacter pylori infection is high in developing countries and the infection is acquired at a young age. The incidence is 3-10% of the population each year in developing countries compared with 0.5% in developed countries.[5]
- The mortality rate for PUD is approximately 1 death per 100.000 cases. [6]

II. Overview

1. Definition

Peptic ulcer disease (PUD) results from a disruption in the mucosal lining of the stomach or duodenum, allowing penetration through the muscularis mucosa.

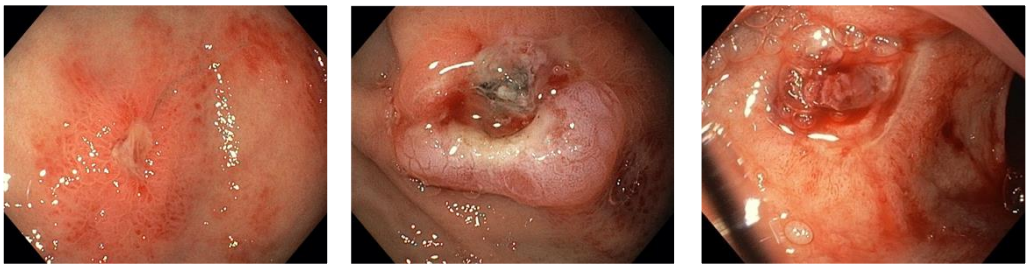

Figure 1. *Gastric and duodenal ulcer aspect on endoscopy*
(Images from Jayavarman 7 Hospital and Kantha Bopha Hospital)

2. Etiology

- The common causes of peptic ulcers include: [3,7]
  - Helicobacter pylori infection
  - Drugs induced (NSAID, corticosteroids, and aspirin)
  - Stress-related gastric injury (usually occurs within 24 hours of the onset of a critical illness in which physiologic stress is present)
  - Idiopathic ulcer (H. Pylori negative peptic ulcers in children who have no history of taking NSAIDS represent 15–20% of pediatric peptic ulcers).
- Less common causes:
  - Ingestion of corrosive substances
  - Hypersecretory states (Zollinger-Ellison syndrome)
  - Inflammatory bowel disease (gastritis may be seen in both Cronh's disease and ulcerative colitis)
  - Other infectious etiology (Cytomegalovirus, Candida, Parasites…)
  - Smoking, consummation excessive: Alcohol, coffee.

3. Physiopathology

- The layers of the stomach consist of the mucosa, submucosa, muscularis propria, and serosa. The gastric mucosa is divided into two levels: the superficial foveolar cells that

line the mucosa and the pits and the deeper glandular compartment that contains gastric glands.[8]

- The acidic gastric contents, which normally aid in digestion, become corrosive when there is an increase in acid production or a disruption of protective factors. Parietal cells of the stomach produce gastric acid via proton pumps (H+/K+ atpase) in response to acetylcholine from vagal efferents, histamine from enterochromaffin cells, and gastrin from G cells. [3]
- There are several mechanisms to protect the gastric mucosa, including a mucus layer, a ph-neutral buffer zone, an epithelial layer, and a rich gastric blood supply. The mucus layer is composed of mucin secreted by surface foveolar cells. This mucus layer acts as a diffusion barrier and overlies a ph-neutral buffer zone composed of bicarbonate secreted by epithelial cells. Prostaglandin release mediates mucin secretion from surface foveolar cells and bicarbonate release from epithelial cells.
- Peptic ulcers are formed when the damaging factors overcome the protective mechanisms.

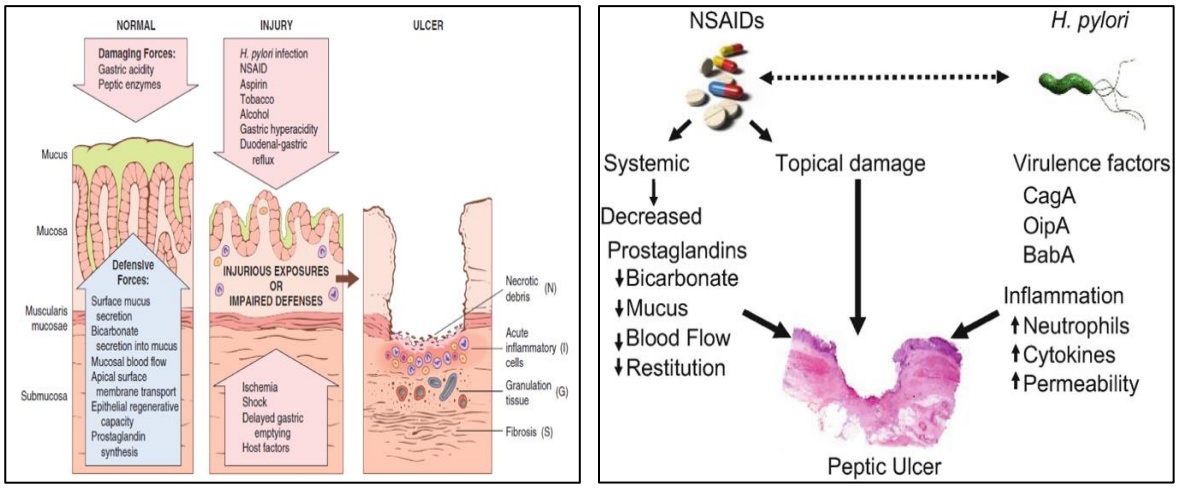

Figure 2. *Mechanisms of gastric injury and protection.*
This diagram illustrates the progression from mild form of injury to ulceration [9]

III. Signs and symptoms

- The presenting symptoms of peptic ulcer disease vary with the age of the patient.
- Hematemesis or melena is reported in up to half of the patients with peptic ulcer disease.
- School-age children and adolescents more commonly present with epigastric pain and nausea, similar to the presentation generally seen in adults.
- Older children usually present with:
  - Dyspepsia
  - Epigastric abdominal pain, and fullness
- Infants and younger children usually present with:
  - Feeding difficulty
  - Vomiting
  - Crying episodes
  - Hematemesis, or melena
- The classic symptom of peptic ulceration, epigastric pain alleviated by the ingestion of food, is present only in a minority of children.
- Many pediatric patients present with poorly localized abdominal pain, which may be periumbilical do not have a peptic ulcer, but rather a functional GI disorder, such as irritable bowel syndrome or non-ulcer (functional) dyspepsia.[7]

- Occasionally, bright red blood per rectum may be seen if the rate of bleeding is brisk and the intestinal transit time is short.[7]

IV. Diagnosis

1. **Diagnosis of peptic ulcer** is suggested by patient history and confirmed by endoscopy.
   - Esophagogastroduodenoscopy is the method of choice to establish the diagnosis of peptic ulcer disease. It can be safely performed in all ages by experienced pediatric gastroenterologists.
   - Endoscopy allows the direct visualization of the oesophagus, stomach, and duodenum, identifying the specific lesions. Biopsy specimens must be obtained from the oesophagus, stomach, and duodenum for histologic assessment as well as to screen for the presence of H. Pylori infection. [7]
   - Laboratory studies:
     - CBC for anemia with other signs of chronic blood loss (e.g., microcytosis, low reticulocyte count)
     - Electrolyte panel
   - Helicobacter pylori identification: [10]
     - Non-invasive tests:
       - *Urea breath tests:* use an oral dose of 13C- or 14C- labelled urea. In an infected patient, the organism metabolizes the urea and liberates labelled CO2, which is exhaled and can be quantified in breath samples taken 20 to 30 minutes after ingestion of the urea (sensitivity and specificity are > 95%).
       - *Stool antigen assays:* have a sensitivity and specificity similar to that of urea breath tests.
       - *Serologic tests (saliva/urine/blood):* the percentage of false-positive results with serologic assays has increased significantly, making these tests too unreliable in most countries and regions.
     - Invasive tests:
       Endoscopy is used to obtain mucosal biopsy samples for a rapid urease test (RUT) or histologic staining.
2. **Classification**
   - Endoscopic evaluation of PUD lesions is classified according to the Forrest Classification:
     - *Forrest I:* Active bleeding (Ia: Arterial, spurting hemorrhage, Ib: Oozing hemorrhage)
     - Forrest II: Stigmata of recent hemorrhage (iia: Visible vessel, iib: Adherent clot, iic: Dark base-hematin-covered lesion)
     - Forrest III: Lesions without active bleeding
   - The American Society for Gastrointestinal Endoscopy (ASGE) and European Society for Gastrointestinal Endoscopy (ESGE) both provide guidelines for the endoscopic management of upper gastrointestinal bleeding. Endoscopic therapy is clearly recommended for Forrest I and Forrest iia lesions.

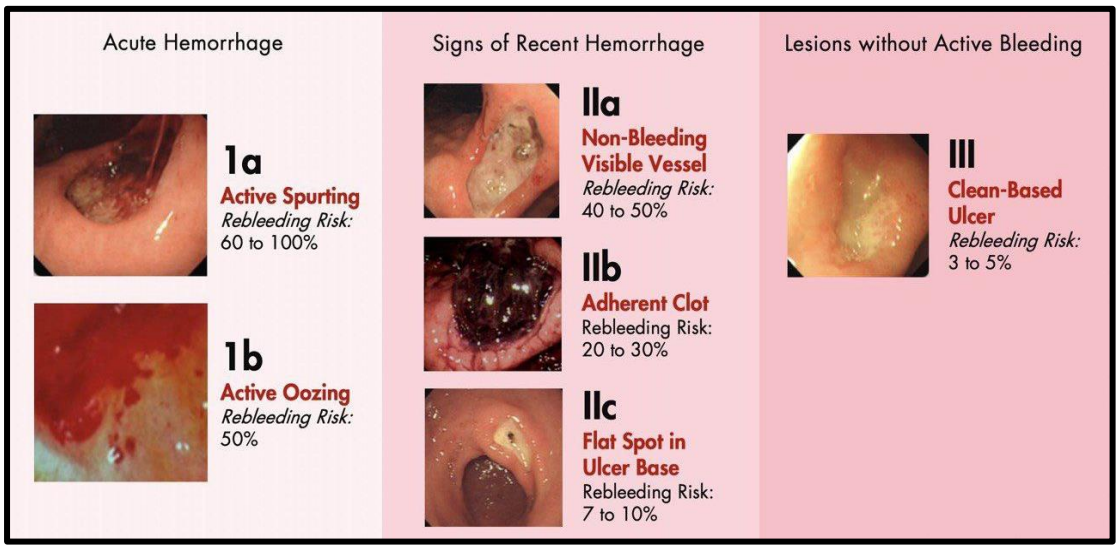

Figure 3. *Forrest classification*

3. **Differential diagnosis**
   - Gastritis: symptoms of gastritis vary in children and are often nonspecific (epigastric pain, poor localized abdominal pain, vomiting, dyspepsia)
   - Functional abdominal pain: chronic or recurrent abdominal pain with the absence of structural or biochemical abnormalities.
   - Gastroesophageal reflux with esophagitis: the typical presentation of GERD includes esophageal symptoms such as heartburn, acid dyspepsia, regurgitation, and chest pain.
   - Cholelithiasis: pain that is localized to the epigastrium or right upper quadrant, sometimes radiating to the right scapular tip, begins postprandially, described as intense and dull, typically lasts 1-5 hours.
   - Cholecystitis: pain in the right upper quadrant, usually with rebound and guarding, positive Murphy sign, frequent presence of fever.
   - Pancreatitis: abdominal pain located in the upper abdomen and may radiate directly through to the back, usually sudden in onset and gradually becoming more severe until reaching a constant ache.
   - Renal stones: Intense pain that suddenly occurs in the back and radiates downward and centrally toward the lower abdomen or groin.
   - Nonulcer dyspepsia: dyspeptic symptoms (such as indigestion, early satiety, postprandial fullness, gnawing, or burning) in a patient who has no abnormalities on physical examination and upper gastrointestinal (GI) endoscopy.

V. Treatment

Initial treatment of peptic ulcer disease includes discontinuation of offending agents and treatment of underlying etiology, acid suppression, and endoscopic management.

1. **Endoscopic management**
   - Endoscopy therapeutic is currently considered the first step in the management of bleeding PUD. [11]
   - Once the patient is hemodynamically stable, endoscopy within 24 hours is indicated to identify the source of bleeding and to treat a potential bleeding site. Methods used to achieve hemostasis include:
     - Mechanical devices (clipping)
     - Injection therapy (diluted epinephrine 1:10,000)
     - Thermal therapy (heater probe)
     - Argon plasma coagulator

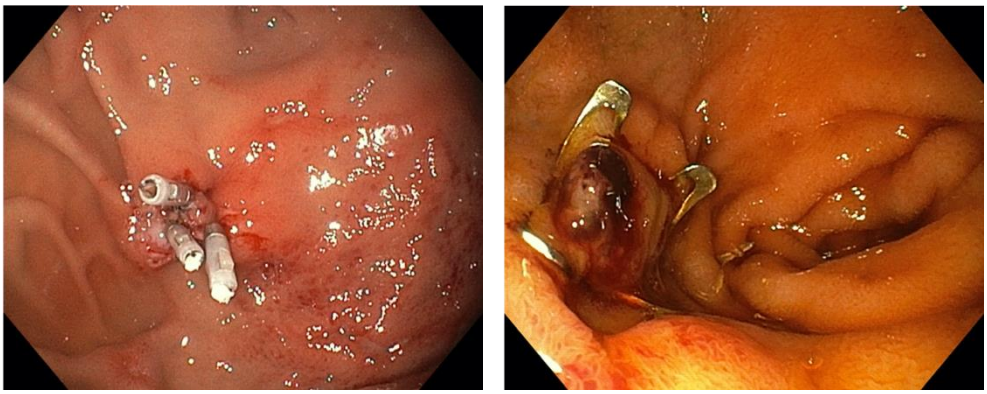

Figure 4. *Bleeding is controlled by the Hemostatic clip and OTSC (Over-The-Scope Clip)*

2. Acid suppression

- Acid suppression is an effective strategy to alleviate symptoms and promote ulcer healing. Available agents on the market include histamine 2 receptor antagonists (h2ras) and proton pump inhibitors (ppis). However, ppis are more potent in ulcer healing. [3]
- Ppis have their greatest effect when given before a meal.

❖ Acid Suppression agents:

- Histamine 2 (H2) receptor antagonists
  - Cimetidine: 10-20 mg/kg/day IV/PO divided q12hr.
  - Ranitidine: 4-8 mg/kg PO q12hr; not to exceed 300 mg/day, 2-4 mg/kg/day IV divided q6-8hr; not to exceed 50 mg/dose or 200 mg/day.
  - Famotidine: 0.25 mg/kg IV q12hr or 0.5 mg/kg PO at bedtime; may increase to 1 mg/kg daily for up to 8 weeks; not to exceed 40 mg/day.
- Proton pump inhibitor (PPI):
  - Omeprazole: 5-10 kg: 5 mg PO qday, 10-20 kg: 10 mg PO qday, >20 kg: 20 mg PO qday.
  - Lansoprazole: <30 kg: 15 mg PO qday, >30 kg: 30 mg PO qday.
  - Pantoprazole: >5 years => 15 kg to <40 kg: 20 mg PO qday, >40 kg: 40 mg PO qday.
  - Esomeprazole: 1-12 years: 10-20 mg PO qday, >12 years: 20-40 mg PO qday.
    - PUD with bleeding signs:
      - Esomeprazole: 1mg/kg IV bolus (Maxi: 40mg), followed by 0.1mg/kg/H for 72H (Maxi: 4mg/H)
      - Then 1-2mg/kg/d
        - ⇨ < 20kg: 10-40mg/d PO
        - ⇨ > 20kg: 20-80mg/d PO in 1 or 2 divided doses for 1-2 months.

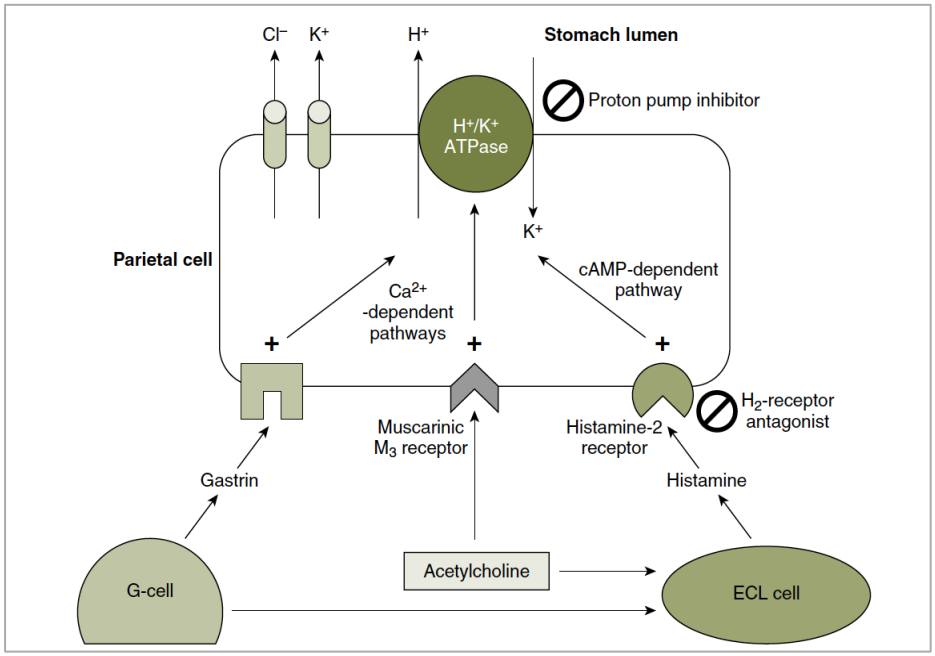

Figure 5. *Schematic of the different pathways leading to acid production from the parietal. Areas of acid suppression from PPI and H2-receptors antagonist are noted. Camp, Cyclic adenosine monophosphate; ECL cell, endochromaffin-like cell.* [8]

3. **Recommended Eradication Therapies** for H.pylori-associated Disease in Children [12]

Medications	**Dose**		**Duration of treatment**
Proton pump inhibitor	1mg/kg/dose twice a day		1 month
Antibiotic	**Weight**	**Dose**	**Duration of treatment**
Amoxicillin	15-24 kg 25-34 kg >35 kg	500 mg twice a day 750 mg twice a day 1000 mg twice a day	14 days
Clarithromycin	15-24 kg 25-34 kg >35 kg	250 mg twice a day 500 mg in AM, 250mg in PM 500 mg twice a day	14 days
Metronidazole	15-24 kg 25-34 kg >35 kg	250 mg twice a day 500 mg in AM, 250mg in PM 500mg twice a day	14 days

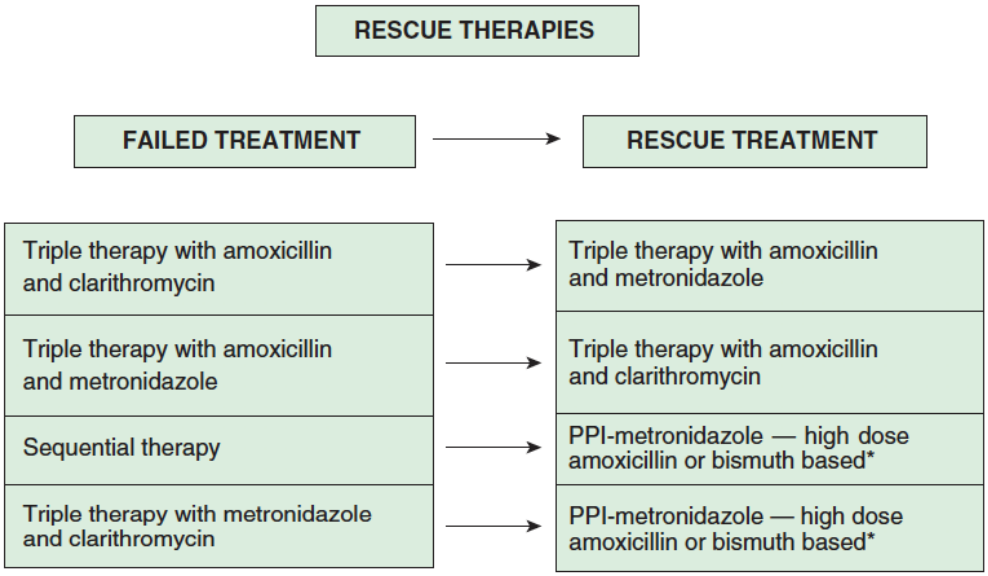

Figure 6. *Rescue therapy for failed eradication of H. Pylori* [7]

a. Recommended combinations for triple therapy are:
- Amoxicillin + Clarithromycin + PPI or
- Amoxicillin + Metronidazole + PPI or
- Clarithromycin + Metronidazole + PPI

b. A reliable non-invasive test for eradication is recommended at least 4 weeks following completion of therapy

c. If treatment has failed, rescue therapy should be targeted to antibiotic susceptibility, the age of the individual child, and antimicrobial options.

- Bismuth-based therapy with tetracycline instead of amoxicillin if patients >8 years old Bismuth dose is:
  - 262 mg four times a day for patients 8–10 years old
  - 524 mg four times a day for those >10 years old
- High-dose amoxicillin ranges from:
  - 750 mg twice a day for body weight 15–24 kg
  - 1000 mg twice a day for 25–34 kg
  - 1500 mg twice a day for >35 kg

VI. Complications

- In the pediatric population, PUD could have rare complications such as:
  - Perforation
  - Hemorrhage
  - Gastric outlet obstruction
- Upper gastrointestinal bleeding is the most common cause of death and the most common indication for endoscopic management and surgery.
- Despite these complications, most patients receiving appropriate treatment will have resolution of gastric and duodenal ulcers within 4 to 8 weeks.[3]

VII. Patient education

- A peptic ulcer is a sore that can form on the lining of the stomach or duodenum.
- Peptic ulcers are much less common among children than adults.
- Children whose parents have peptic ulcers are more likely to have ulcers especially if their parents are infected with Helicobacter pylori.
- Adolescents who drink alcohol or smoke are more likely to develop ulcers.

- PUD can be prevented by avoiding unnecessary NSAID use and improving hygiene.
- There is no specific diet that has been proven to help people with ulcers feel better. But eating plenty of fruits, vegetables, and foods with fiber might help lower the risk of future ulcers.

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GASTROESOPHAGEAL REFLUX DISEASES (GERD)

CHEA Siden, TANG Lenghak, CHRUN Chhunny, EAR Vireak,
KHUN Leangchhun, YAY Chantana.

I. Key facts [1,2,3]

Gastroesophageal reflux (GER) is a normal physiologic process that occurs in healthy infants, children, and adults. It is extremely common in healthy infants, peaks at 4 months, such that physiologic regurgitation decreases in 88% toward the end of the first year of life and is unusual in children older than 18 months old.

In contrast, Gastroesophageal reflux disease (GERD) when GER leads to troublesome symptoms that affect daily functioning and/or leads to clinical complications within the oesophagus or other systems. GERD is the most common esophageal disorder in children of all ages.

A systematic review published in 2019 across a number of prospective studies, demonstrated that the prevalence of GERD in infants in Asia (8.7%) is comparable to both the United States (8.9%) and Europe (8.3%-32.0%).

II. Overview

1. Definition [1,2,5,6]

- *Gastroesophageal Reflux (GER)* is the involuntary passage of gastric contents into the oesophagus (usually < 20 times/day, after eating or feeding).
- *Gastroesophageal Reflux Disease (GERD)* is defined as reflux causing troublesome symptoms and /or complication that may occur when gastric contents reflux into the oesophagus or oropharynx.
- *Regurgitation*, spitting up, posseting, and spilling are synonyms and are defined as the passage of refluxed gastric contents into the pharynx or mouth and sometimes expelled out of the mouth. Regurgitation is generally assigned as effortless and nonprojectile.
- *Vomiting* is the force expulsion of the refluxed gastric contents from the mouth cause by involuntary contraction of diaphragm and abdominal muscles.

2. Etiology and Pathophysiology [3,4,7]

- *The pathogenesis of gastro-esophageal reflux disease is multifactorial, such as:*
  - Increase the rate of transient lower esophageal sphincter relaxations: can be stimulated by increasing intraesophageal pressure as a result of crying, gastric distension, delay gastric empty and respiratory diseases.
  - Impaired the antireflux barrier: the separation of the LES (lower esophageal sphincter) and the crural diaphragm acts to significantly impair the antireflux barrier and contribute to the increase in acid exposure of the oesophagus such as hiatal hernia, Surgical pull up for esophageal …
  - Impaired esophageal clearance: the acid content of any refluxate can be neutralized by both swallowed saliva and esophageal secretions. In infants, volume clearance is less effective due to their mostly recumbent position.
- *When* repeated exposure of the esophageal mucosa to refluxate composed of hydrochloric acid, pepsin, trypsin, and bile leads to tissue injury and chronic inflammation.
  - In extraesophageal manifestation of GERD, such as upper airway diseases or ENT problems, there are many proposed pathways such as GER induced vagally mediated aspiration or insufficiency of upper esophageal sphincter (UES) function.

III. Signs and Symptoms [2,3,4,5]

GER is common in infants and usually is not pathologic. Regurgitation is present in 50 to 70 % of all infants, peaks at age 4 to 6 months, and typically resolves by one year or 18months. In contrast, GERD leading to significant symptoms, signs, and complications. The common symptoms of GERD differ according to age:

- *Infants:*
  - Regurgitation
  - Signs of esophagitis (irritability, arching, chocking, feeding aversion)
  - Failure to thrive
- *Preschool-age children* with GERD may present with
  - Intermittent regurgitation
  - Vomiting
  - Sandifer syndrome, (spasmodic torsional dystonia with arching of the back and pisthotonic posturing, mainly involving the neck and back)
  - Persistent cough/aspiration pneumonia
  - Hoarse voice
  - Asthma
- *School-aged children and adolescents:* The cardinal symptoms of GERD:
  - Heartburn/pyrosis
  - Epigastric pain
  - Dysphagia.

  Physician should recognize the red flags from other serious conditions that may underlie or mimic GERD such as: [10]
    - General: excessive irritability, weight loss, fever, lethargy,
    - Onset of regurgitation at > 6 months of age,
    - Persistent progressive regurgitation at > 1year of age,
    - Vomiting: persistent forceful, nocturnal or bilsious vomiting,
    - Hematemesis, abdominal distension,
    - Neurological: Bulging fontanelle, seizure, neurological abnormality.

IV. Diagnosis [1,3,4,5,8]

For most of the typical GERD presentations, a thorough history and physical examination suffice initially to reach the diagnosis.

1. **Laboratory test:**

   There is no blood test and no gold standard test to diagnosis GERD, most of the esophageal tests are often use to rule out other problem or present red flags signs.

2. **Imaging Studies**:

   - *Upper Endoscopy with biopsy is useful*
     - It is indicated in presence of alarm symptoms or signs, such as hematemesis, dysphagia, or failure to thrive or anemia.
     - To detect complication of GERD, such as erosive esophagitis, strictures, Barrett's oesophagus, and to differential diagnosis such as eosinophilic esophagitis.

     * GERD may exist despite the normal endoscopic appearance of the esophageal mucosa and the absence of histological abnormalities (NERD: Non-erosive reflux disease).
   - *Proton pump inhibitor (PPI)*trail*:*
     - 4-8 weeks trail of ppis is indicated in typical symptoms (heartburn, retrosternal or epigastric pain) in children and adult especially with NERD.

- Studies to support the role of diagnostic trials of PPI in infant are scarce and should not be used as a diagnosis test for GERD in patients presenting with extraesophageal symptoms.

- *Multichannel* intraluminal *impedance (ph-MII) for 24h:*
  - It is indicated when symptoms suggesting reflux but in the absence of esophagitis in upper endoscopy (NERD= non-erosive reflux disease). The detection of acid (ph<4.0), weakly acid (ph 4.0 to 7.0), alkaline reflux (ph>7).
  - Use for diagnosing GERD and for understanding esophageal function such as bolus flow, volume clearance, and (in conjunction with manometry) motor patterns associated with GERD.
- *Extended esophageal ph* monitoring*:*
  - It is indicated for efficacy of acid suppression during treatment and evaluating atypical GERD presentations such as chronic cough, stridor, and asthma.
  - When Intra esophageal ph < 4.0 for confirmed acid reflux.
- *Upper* Gastrointestinal *(GI) barium contrast:*
  - It is indicated in children with vomiting and dysphagia to evaluate for Achalasia, esophageal stricture and stenosis, hiatal hernia and gastric outlet or intestinal obstruction.
  - It has poor sensitivity and specificity in the diagnosis of GERD and the inability to differentiate physiologic GER from GERD.

3. Differential diagnosis:

- *GI obstruction:* Pyloric stenosis, Malrotation with intermittent volvulus...
  - Signs: vomiting, abdominal pain => differentiated by abdominal ultrasound, GI barium, ASP.
- *Other GI disorder:* Achalasia, Peptic ulcer, food allergy, inflammatory bowel disease.
  - Signs: dysphagia, vomiting, abdominal pain => can differentiated by GI endoscopy.
- Neurologic*:* Meningitis, intracranial hemorrhage, intracranial mass…
  - Signs: lethargy, excessive irritability, bulging fontanel, vomiting, anemia => can differentiated Trans fontanelle ultrasound, MRI or CT scan of brain.

V. Complications [1,4,6]

- *Esophageal:* esophagitis, esophageal stricture, Barrett oesophagus an adenocarcinoma.
- *Nutritional:* esophagitis and regurgitation may be severe enough to induce failure to thrive because of caloric deficits
- *Respiratory (*Atypical*) presentation:* Apnea, chronic cough, stridor, recurrence aspiration pneumonia and asthma.
- *Otolaryngologic:* Dental erosion, laryngitis, voice overuse

VI. Management [3,4,8,9]

In GER, non-pharmacological treatments and close follow-up are often sufficient and GERD more therapeutic options are usually needed with careful consideration of treatments that balance optimal symptom resolution with predictable side effects. Treatment of GERD in infants focuses on reassurance and dietary management, and treatment in older children and adolescents focuses on medication, mainly acid-blocking medication.

1. General measure or non-pharmacological treatments:

- Parental *reassurance:* observation of feeding and handling of the child during and after feeding.
- Dietary measures for infants: normalization of any abnormal feeding techniques, volumes, and frequencies, using Anti-reflux formula milk.

- *Positioning measures:* left side position and head elevation during sleep, supine 40 degrees anti-Trendelenburg, avoid abdominal flexion after meals. No *recommendation for prone, right lateral position in infants as it may increase the risk of sudden infant death syndrome.*
-

2. **Pharmacotherapy**:
If GERD symptoms in infants and children are not resolved with non-pharmacological treatment, medication can be considered.

Table 1. *Pharmacotherapy in GERD*: [3,5,6]

Drugs	Dosage + route	Max dosage	Indication	Side effects
Antacid				
Magnesium alginate plus simethicone	- < 5kg :2.5 ml - > 5kg: 5ml x 3t/d, PO		Relief of symptoms by acid neutralization	
Sodium alginate	- < 4.5kg: 1pack/d - > 4.5 kg: 2pack/d, PO		Relief of symptoms by acid neutralization	
Histamine-2 receptor antagonists (H2RA). Duration of treatment: 4 to 8 wks. Effective in healing reflux esophagitis in children of all ages				
Cimetidine	30-40mg/kg/day, PO or IVP	400mg		Headache, confusion,
Proton pump inhibitors (PPI), Duration of treatment: 4 to 8 wks. More effective than (H2RA)				
- Omeprazole	1-4 mg/kg/day, PO	40mg		Diarrhea, flatulence
- Lansoprazole	2 mg/kg/day, PO for infants	30mg		Tarry stool, dark urine
- Esomeprazole	• -< 20kg:10 mg/day • >20kg: 20mg/day • - 1mg/kg/d (IVP/P0)	40mg		
- Pantoprazole	1-2 mg/kg/day (PO)	40mg		
- Prokinetics			Increase LES pressure, some improve gastric emptying or esophageal clearance.	
- Domperidone	0.8-0.9mg/kg/day (PO)	30mg		Prolonged QT
- Ondansetron	0.15mg/kg/dose (IV or PO)	16mg	Blocking the action of serotonin (anti-nausea and vomiting)	Drowsiness, headache, prolonged QT

3. **Surgery treatment**:
Anti-reflux surgery, including fundoplication is indicate in infants and children with

- Life-threatening complications such as apnea or an ALTE = Apparent Life-Threatening Event (apnea associated with bradycardia, pallor, and/or cyanosis) after failure of optimal medical treatment.
- Symptoms refractory to optimal therapy after appropriate evaluation to exclude other underlying diseases.
- Chronic conditions (i.e., neurologic impairment,) with a significant risk of GERD-related complications.
- The need for chronic pharmacotherapy to control signs and/or symptoms of GERD beyond the age of 2 to 3 years.

Table 2. *Schematic Therapeutic Approach* [5]

Phase 1	- Parental reassurance. Observation. Lifestyle changes. Exclude overfeeding.
Phase 2	- Dietary treatment (decrease regurgitation). Thickened formula, thickening agents, extensive hydrolysates or amino acid–based formula in cow's milk allergy.
Positional treatment*	
Phase 3	- For immediate symptom relief: alginates (some efficacy in moderate GERD); antacids only in older children.
Phase 4	- Proton pump inhibitors (drug of choice in severe GERD; more safety data needed). H2 receptor antagonists less effective than PPIs
Phase 5	- Prokinetics (but no one product available on the market has been shown to be effective) and Treat pathophysiologic mechanisms of GERD
Phase 6	- Laparoscopic surgery

VII. Prevention and Education [2,6,9,10]

1. **For baby** is spitting up without discomfort and is gaining weight appropriately, then there is probably no more evaluation or testing that is necessary, 50 to 70 % of all infants, peaks at age 4 to 6 months, and typically resolves by one year or 18moths. Things that you can do at home to help reduce spitting up:
   - Avoid overfeeding:
     - Provide smaller and mor frequent feeding
     - Taking appropriately sized bottles or nursing the appropriate amount of time.
     - Separate feedings by at least 2-2:30 hours from the beginning of one feeding to the next.
     - Don't feed the baby again after spit up - wait until the next feeding.
   - Continue breast feeding, Breast milk cannot be thickened.
   - For formula fed infants, feedings can be thickened using Anti-reflux formula milk or thickening formula with rice cereal.
   - In formula-fed infants, try a hypoallergenic formula (extensive hydrolysates or amino acid–based formula) for 2 weeks if symptoms disappear (cow mild allergy?).
   - Keep infant upright for at least 30 minutes after meals.
   - Avoid car seat positioning in the home.
   - Left side position and head elevation during sleep, supine 40 degrees anti-Trendelenburg.
   - Avoid tight diapers and elastic waistbands.
   - Avoid exposure to tobacco smoke.
2. **For children and teenagers**

Are able to decrease their reflux with lifestyle and diet changes:

- Child eat smaller meals more often.
- Elevate the head of the bed 40 degrees.
- Avoid carbonated drinks, chocolate, caffeine, and foods that are high in fat (French fries and pizza) or contain a lot of acid (citrus, pickles, tomato products) or spicy foods.
- Avoid large meals prior to exercise.
- Help your child lose weight if he or she is overweight.
- Avoid exposure to tobacco smoke.
- Avoid cigarette smoking, drink alcohol.

If symptoms are severe (red flag sings) or persistent then your primary care provider may consider treatment with a medication or referral to a pediatric gastroenterologist:

- General: excessive irritability, weight loss, fever, lethargy,
- Vomiting: persistent forceful, blood or bilious vomiting,
- Persistent Food Refusal: Poor growth or failure to thrive, Difficulty eating.
- Frequent discomfort in the stomach or chest: heartburn
- Swallowing problems: Dysphagia, Odynophagia
- Breathing problems: Wheezing, asthma, chronic cough.

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STOMATITIS IN CHILDREN

LORNTRY Patrich, HENG Sothy

I. Key facts

- Commonly termed canker sores, aphthous ulcers, or aphthous stomatitis, categorized as an idiopathic disease, aphthous ulcers are frequently misdiagnosed, treated incorrectly, or simply ignored. [5]
- Stomatitis is an inflammation of the mucous membranes of the mouth caused by a fungal viral or bacterial infection, a vitamin deficiency, an injury etc. [1,2]
- Recurrent aphthous stomatitis being the most common in children. Recurrent aphthous ulcer (RAU), or recurrent aphthous stomatitis (RAS), represents a chronic inflammatory disease characterized by painful oral ulcers recurring with varying frequency. [5]
- Prolonged, painful stomatitis may contribute to malnutrition or dehydration or dehydration in children: always treat carefully and show the mother how to treat. [5]

II. Overview

1. Type of stomatitis [1,2]

- Aphthous stomatitis
- Nicotine stomatitis
- Herpes simplex stomatitis
- Vincent angina

2. Epidemiology

- Aphthous ulcers (canker sores) are found in all ethnic groups and geographic locations. The prevalence may be increased in affluent countries and socioeconomic classes. [5]
- Aphthous ulcers may be slightly more common in female individuals than in male individuals. [5]
- Recurrent aphthous ulcers begin in childhood or adolescence, with peak onset in persons aged 10-19 years. [5]
- HSV type 1: up to 90% of the adult population has serologic evidence of previous infection. [2]
- Enteroviral infections occur commonly in summer. [2]

3. Cause of stomatitis [4]

- Local factors: local trauma or any injury during mastication or tooth brushing.
- Food hypersensitivity: chocolate, coffee, peanuts, cereal
- Poor dental Hygiene
- Infection: Viral, fungal, bacterial
- Any kind of allergy, esp. Drug NSAID
- Nutrition deficiency associate with anemia (iron, Vitamin B1, B2, B6) are common and poor nutrition.
- The systemic disorder (weakness immune system)
- Hereditary Predisposition: a family history of recurrent aphthous ulcer is common. [5]
- Stress: Psychological and physiologic stress and depression may increase the risk of aphthous ulcers. [5]

4. Pathophysiology

- The pathophysiology of aphthous ulcers remains incompletely understood. The primary disorder appears to be the result of activation of the cell-mediated immune system. Early lesions show a cluster of macrophages and lymphocytes (predominantly

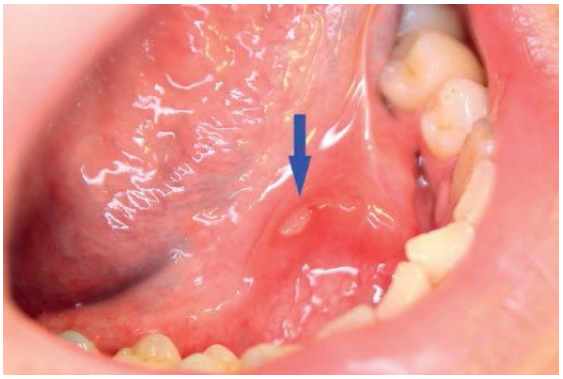
cytotoxic and natural-killer T cells) at the pre-ulcerative base, followed by formation of an ulcer with a neutrophilic base and an erythematous lymphocytic ring. [5]

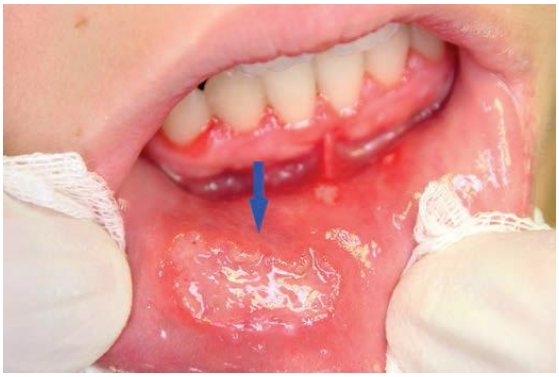
- Patients with recurrent aphthous ulcers have increased numbers of cytotoxic $CD8^+$ cells and decreased numbers of helper $CD4^+$ cells in peripheral blood. [5]
- Invasion of pathogens in the lining of lips or mouth of mucus membranes, lead to redness and inflammation. [4]

III. Diagnosis

1. Common clinical signs

- The diagnosis of aphthous ulcers is primarily clinical. Patients typically describe a prodromal stage of a burning or pricking sensation of the oral mucosa 1-2 days before the ulcer appears. Patients with recurrent aphthous ulcers (raus), or canker sores, often mention precipitating factors, such as local trauma or food hypersensitivity. [5]
- Ask the patient about medication use, chemotherapy, radiation therapy, vitamin supplementation, and recent dietary changes. [5]
- Assess for a family history of the following: [5]
  - Aphthous ulcers
  - Inflammatory bowel disease
  - Gluten-sensitive enteropathy
  - Systemic lupus erythematosus
- During the review of systems, infants and small children should be assessed for decreased feeding, weight, and urine output. Associated symptoms, such as those below, suggest other diagnoses and are not associated with recurrent aphthous ulcers: Fever, Malaise, Myalgias, Arthralgias, Headache, Cough, Nausea, Vomiting, Abdominal pain, Diarrhea, Sore throat, Swollen or painful lymphadenopathy, Rash, Genital or conjunctival lesions. [5]
- In all cases maintain feeding and hydration (use a nasogastric tube for 3 days, only if pain is preventing the patient from eating) and keep the affected areas clean to prevent secondary infections or recurrence. [5]
- Nonspecific symptoms: red mucosa, +/-aphthous ulcers, +/- ulcers, +/-vesiculas, white plaques. [3]





2. Laboratory Studies [5]

The diagnosis of aphthous ulcers is usually based on the history and clinical presentation. No laboratory procedures are available for definitive diagnosis. Note the following:

- In patients with severe recurrent aphthous ulcers (raus), or canker sores, the clinical picture should guide laboratory testing. A complete blood cell (CBC) count, a chemistry panel, and nutritional workup may be necessary.

- Patients with suspected malabsorption or a nutritional deficiency should undergo immediate screening. Consider screening in patients presenting with a history of recurrent aphthous ulcers lasting 6 months or longer.

3. Differential Diagnosis [5]

- Arthritis, Conjunctivitis, Urethritis Syndrome
- Herpesvirus 6 Infection
- Crohn Disease Imaging
- Pediatric Chickenpox
- Pediatric HIV Infection
- Pediatric Herpes Simplex Virus Infection
- Celiac Disease (Sprue) Imaging
- Syphilis
- Systemic Lupus Erythematosus (SLE)
- T-Cell Disorders.

IV. Treatment

The primary goals of medical therapy in patients with aphthous ulcers (canker sores) are pain relief, maintenance of fluid and nutrition intake, early resolution, and prevention of recurrence. Most patients with minor or herpetiform aphthae should be treated empirically before extensive and costly studies are initiated. Treatment of recurrent aphthous ulcers (canker sores) typically includes anti-inflammatory and/or symptomatic therapy, whereas immunomodulators are rarely used, except in severe, refractory cases.

1. Symptomatic therapy [5]

- Paracetamol PO 50-60 mg/kg/day in 4-6 divided
- Lidocaine 2% gel or oral local drop (by prescription only) can also be used, but can also cause toxicity in children.
- Diphenhydramine, the antihistamine used as a swish-and-spit mouth rinse, or applied locally, may provide some pain relief. Diphenhydramine syrup is commonly mixed in a 50:50 dilution with magnesium containing antacid.
- Anti-inflammatory agents include Corticosteroids, Amlexanox and Metalloprotease inhibitors, treat at onset may reduce symptoms or eliminate ulcer development.

2. Treatment according to etiology [3]

a. Candida albicans (thrush):

- Very common in infants on malnourished children, HIV infected patients, long-term antibiothrapy patient.
- Clinical signs: white patches on the tongue may spread to cover the whole mouth
- Management:
  - Clean the mouth with salt water or NSS frequently (every 1-2 hours).
  - Antifungal
    - Gentian violet: local apply to the affected area at 2 times/day for 7 days
    - *Nystatin (*100 000 IU*):* Apply to the affected area between meals in 4 divided doses per day for 7 days. Consider treating for intestinal candidiasis: Nystatin PO: 500.000 IU/day in 4 divided doses for 20 days. Or
    - *Miconazole oral gel: at least 1 week* [6]
      - Babies 6 months to 2 years: 1.25 ml (quarter of the measuring spoon provided) 4 times a day smeared around the inside of their mouth after feeds.
      - Children older than 2 years and adults: 2.5 ml (half of the measuring spoon provided) in their mouth after food 4 times a day.

In patients with extensive forms or with frequent recurrences, consider HIV infection. Do a thorough clinical examination and for treatment.

b. Herpes Simplex infection

Very common in children

- Clinical signs:
  - Primary infection: Very painful lesions, in the form of vesicles, erosions or yellowish ulcerations on the lips and buccal mucosa with general malaise, peripheral lymph swelling and fever.
  - Recurrence: clusters of vesicles in the nasolabial area

Both forms of herpes are contagious. Recurrences may be provoked by an infectious disease such as malaria or pneumonia:

- Management:
  - Clean the affected area with salt water or NSS frequently (every 1-2 hours).
  - Spontaneous resolution usually occurs within 7 to 10 days.

Secondary infections may develop. In patients with extensive forms or with frequent recurrences, consider HIV infection. Do a thorough clinical examination and for treatment.

c. Stomatitis *from vitamin deficiencies*

- Stomatitis *from Scurvy*: Bleeding gums caused by vitamin C deficiency, in infants it is associated with lower limb pain caused by subperiosteal hemorrhage. It is common in contexts of poor food quality or in populations completely dependent on food aid.
  - Clean the mouth and apply gentian violet as for candidiasis
  - Ascorbic *acid (Vitamin C)* PO: 150 to 200 mg/day in 2 divided doses. The treatment is continued until symptoms improve (1 to 2 weeks), then a preventive treatment (25 to 50 mg/day) is given as long as the situation requires.
- Other *stomatitis*
  - Other vitamin deficiencies may provoke mouth lesions: angular stomatitis of the lips and glossitis from Vitamin B2 (Riboflavin) or Vitamin B6 (Pyridoxine) deficiencies.
  - Multivitamins are insufficient to treat true vitamin deficiencies. Give the corresponding vitamins at curative dose.
  - Iron deficiencies may provoke angular stomatitis.

3. Supplementation [5]

Supplementation with vitamins (especially B12 and C), zinc, or iron may prevent recurrence in some individuals. Studies of lysine supplementation are preliminary and equivocal.

4. Surgical Care [5]

Few patients are unresponsive to the local or systemic therapies described above; however, several other invasive and specialized treatments are available for patients with persistent or severe lesions.

5. Refer case [5]

- Consultation may be necessary if an additional disease is strongly suggested or found.
- Patients with severe disease may be referred to a laser specialist for evaluation and treatment.

V. Complications [5]

- Secondary bacterial infection is rare.
- Patients with major recurrent aphthous ulcers can have clinically significant oral scarring.
- Painful lesions can cause interruption in eating and drinking, leading to dehydration and perhaps nutritional deficiencies.

- Patients with acquired immunodeficiency syndrome (AIDS) may have ulcerations that are resistant to topical steroid therapy. However, systemic steroids must be administered only with caution because of the possibility of adverse effects, especially the development of opportunistic infections.

VI. Prognosis [5]

- Herpetiform and minor recurrent aphthous ulcers have a self-limited course and tend to have few or no sequelae.
- Major recurrent aphthous ulcers can cause scarring, dehydration, and malnutrition; however, if recognized early and treated effectively, major recurrent aphthous ulcers can be well controlled, with minimal sequelae.
- Aphthous ulcers are associated with local pain and discomfort. Symptoms usually last 2-10 days with minor and herpetiform ulcers and as long as 30 days with major ulcers. Most cases are self-limited and heal without sequelae in 7-14 days; however, major ulcers heal slowly (10-30 days or longer).

VII. Patient education

- Hand washing can prevent spread of viral infections. [3]
- Contact isolation should be observed for children with viral stomatitis in the hospital setting. [3]
- General therapeutic measures for active ulcers include good oral hygiene, nonirritating gargles, and increased fluid intake. [5]
- Cool bland beverages, such as milkshakes, are well tolerated. Patients should be advised to avoid salty or spicy foods. [5]
- Although efficacy for recurrent aphthous ulcers is unproven, stress control may benefit some patients. [5]

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GASTRO-INTESTINAL BLEEDINGIN CHILDREN

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I. Key facts

- There is a broad clinical spectrum of gastrointestinal bleeding in children.
- Upper gastrointestinal bleeding (UGIB) is an uncommon but potentially serious, life-threatening clinical condition.
- Lower gastro intestinal bleeding (LGIB) is defined as any bleeding that occurs distal to the ligament of Treitz (situated at the duodeno-jejunal junction). Among children the most common causes are infectious colitis and polyps.
- Obtaining an accurate history and conducting a thorough physical examination can provide important clues about the location, severity, and likely etiology of gastrointestinal bleeding.
- Blood tests, radiologic tools, and endoscopic methods are very important to identify a bleeding source.
- Early consultation with a gastroenterologist is recommended, as endoscopy is often required for evaluation and may be needed to control hemorrhage.

II. Overview

1. Definition

Gastrointestinal bleeding (GIB) in children is one of the most serious presenting complaints a pediatric gastroenterologist may need to diagnose and treat. A proper understanding of various etiologies and available treatment modalities is necessary to ensure successful outcome.

- Hematemesis: emission of bright red blood from the mouth, in case of active bleeding, or “coffee- ground” colored material, in case of non-recent bleeding.
- Melena: black and foul-smelling stool emission from the anus. These characteristics are due to the hemoglobin oxidation to hematin by intestinal enzymes and floral bacteria.
- Hematochezia: passage of bright red or dark (due to the presence of clots) blood via rectum, isolated or mixed to stool or mucus.
- Overt bleeding: passage of visible blood whose origin has not been identified by endoscopic or radiological investigations.
- Occult bleeding: passage of not visible blood suggested by laboratory tests (e.g. Iron deficiency anemia) and confirmed by positive fecal occult blood test.
- Massive bleeding: Gastrointestinal bleeding that results in hemodynamic instability, signs of poor perfusion (e.g. Altered mental status, syncope, pallor), need for transfusion of more than 20 ml/kg of packed red blood cells (prbcs) during the initial resuscitation, or blood loss of more than 80 ml/kg in 24 h, more than 40 ml/kg in 3 h or more than 3 ml/kg/min
- Upper gastrointestinal bleeding (UGIB): GI bleeding originating proximal to the ligament of Treitz (esophagus, stomach and duodenum).
- Lower gastrointestinal bleeding (LGIB): GI bleeding originating distal to the ligament of Treitz (small bowel and colon).

2. Epidemiology

GIB is a common condition in children, with a reported incidence of 6.4%. In a study evaluating hospitalized children in the United States, data from greater than 23,000 patients identified a diagnosis of GI bleeding in 0.5% of hospital discharges. Further, a recent analysis of the Nationwide Emergency Department Sample (NEDS) dataset found a 14.3% increase in pediatric emergency department (ED)–associated visits for GI

bleeding from 82.2 to 93.9/100,000 children between 2006 and 2011. After hospital discharge for management of GI bleeding, readmission is not uncommon. A recent study found that within 30 days of discharge for acute GI bleeding, 16% of children returned to the ED and 9% were readmitted to the hospital; children with variceal bleeding were at higher risk than those with nonvariceal bleeding. The same group of authors also reported on mortality in children with GI bleeding admitted to the hospital in a large retrospective review of 19,528 patients, finding death occurred in 0.37% of children with a principal diagnosis of GIB and 2% of children with GIB overall.

3. Etiology

The etiology of upper and lower gastrointestinal bleeding, according to common and rare causes of hematemesis based on age, onset, and bleeding characteristics.

Table 1. *Common and rare causes of upper gastrointestinal bleeding according to the age, Appearing and bleeding entity*

Age	Ill-appearing	Well-appearing		Tropical area
		Severe bleeding	Milder bleeding	
> 5 years	Esophageal varices Hemorrhagic gastritis	Esophageal varices Gastroduodenal ulcer *Rare:* Dieulafoy lesion Arteriovenous malformations Stromal tumors Gastroduodenal duplications Hemobilia	Mallory-Weiss tear Reflux esophagitis Gastritis	Dengue Hemorrhagic Fever Infectious Diseases
2–5 years	Esophageal varices Hemorrhagic gastritis Stress ulcer	Esophageal varices Gastroduodenal ulcer Foreign bodies Ingestion of caustics *Rare:* Dieulafoy lesion Arteriovenous malformations Stromal tumors Gastroduodenal duplications	Mallory-Weiss tear Steroids or nsaids gastritis Reflux esophagitis	
< 2 years	Stress gastritis or ulcer Sepsis *Rare:* Intestinal duplications Vascular anomalies Coagulation disorders		Reflux esophagitis Reactive gastritis Vitamin K deficiency Trauma (nasogastric tube) Rare: Cow's milk protein allergy	

Neonate	Swallowed maternal blood Stress ulcer, Gastritis Necrotizing enterocolitis Gastrointestinal Malformations (duodenal web, antral web, duplications, malrotation) Hemorrhagic disease of newborn Vitamin K deficiency Cow's milk protein allergy Vascular malformation Hemophilia Maternal idiopathic thrombocytopenic purpura Maternal nonsteroidal antiinflammatory drug	

Table 2. ***Common and rare causes of lower gastrointestinal bleeding according to the age, Appearing and bleeding entity***

Age	**Ill-appearing**	**Well-appearing**		**Tropical area**
		Severe bleeding	Milder bleeding	
> 5 years	Infective colitis Ulcerative colitis Henoch-Schönlein purpura Volvulus/intussusception		Infective colitis Ulcerative colitis Juvenile polyp Hemorrhoids Nsaids Rare: Rectal prolapse/ulcer Crohn's disease	Dengue Hemorrhagic Fever Infectious Diseases
2–5 years	Intussusception Volvulus Henoch-Schönlein purpura Uremic-hemolytic syndrome	Meckel diverticulum Esophageal varices Ulcerative colitis Rare: Juvenile polyp Radiation enterocolitis Neutropenia associated colitis Vascular malformation	Infective colitis Juvenile polyp Lymphoid hyperplasia Ulcerative colitis Perianal streptococcal cellulitis *Rare:* Rectal prolapse/ulcer Crohn's disease	
< 2 years	Intussusception Volvulus Infective colitis *Rare:* Necrotizing enterocolitis Hirschsprung enterocolitis Vascular malformation		Anal fissures Allergic proctocolitis Lymphoid hyperplasia Infective colitis	
Neonate	Swallowed maternal blood Dietary protein intolerance Cow's milk protein allergy Infectious colitis			

	Necrotizing enterocolitis Hirschsprung disease and enterocolitis Malrotation with volvulus, Intussusception Duplication cyst, Vascular malformation Hemophilia Maternal idiopathic thrombocytopenic purpura Maternal NSAID Anal fissure	

III. Diagnosis

When assessing a child suspected of having GIB, the foremost priority is to achieve and maintain hemodynamic stability. Subsequently, inquiring into medical history in detail and performing comprehensive physical examination are crucial steps in the evaluation process.

1. **Is it blood?**

It is known that many substances, when mixed to vomit or stools, might be confused for bright red blood (such as food coloring contained in jellies, beverages or candies, tomatoes peel, beets and some antibiotic syrups) or melena (drugs containing bismuth or iron, spinach, blueberries, grape or licorice).

Different tests aiming to identify the presence of blood in stools and vomit are nowadays available. For instance, the Guaiac Test can easily detect blood: it implies the placement of the sample on a guaiac sheet (which contains a phenolic compound, alpha-guaiaconic acid, extracted from Gaiacum trees) and the addition of hydrogen peroxide that, in presence of blood, can oxide guaiac be causing a color change in blue. False positive results can occur in case of dietary interference, e.g. red meat containing myoglobin or certain uncooked vegetables containing specific compounds with peroxidase activities. Similarly, Guaiac Test is also subject to negative interference when testing foods containing vitamin C, such as citrus fruits, as their antioxidant properties can inhibit the color reaction used in the testing process, thus causing false negative results.

Therefore, some immunochemical tests capable of detecting only human blood (largely used amongst adults as a screening test for colon cancer) were proposed in the pediatric population in order to improve sensibility and specificity in detecting blood in stools. Even though these tests are considered as a gold standard to confirm the presence of blood in red or tarry intestinal secretions, their high sensibility might be a limitation in pediatric patients: indeed, in children's fissures and perianal dermatitis are very common and might cause false positive results leading to further unnecessary diagnostic procedures. Therefore, these tests' results should be wisely evaluated.

2. **Is the blood coming from the gastrointestinal tract?**

It is extremely important to investigate the presence of either digestive or non- digestive signs and symptoms, such as abdominal pain, vomiting, cough, odynophagia, and fever. Furthermore, a complete and well-directed anamnesis, inquiring into past medical history, can be diriment. For instance, a medical history revealing recent tonsillectomy, dental procedure, epistaxis, or nasogastric tube placement, may suggest oral/nasal bleeding. Furthermore, in physical examination, the clinician should evaluate for signs of gingival traumas and active bleeding coming from oral, nasal, or genitourinary sites. When gathered, this information can help the clinician to avoid common mistakes, as to confuse hemoptysis with hematemesis, or menstruation with rectal bleeding (particularly in adolescents experiencing menarche).

3. **What is the entity of bleeding?**

The extent of bleeding can be ascertained by assessing the patient's overall appearance

and hemodynamic condition. “Red flags” in signs and symptoms are paleness, diaphoresis, restlessness, lethargy, and abdominal pain.

The association of both hematemesis and melena should raise suspicion of an active severe proximal bleeding. Parameters should always be monitored, and they represent a crucial first step in order to evaluate the patient; thus, children have a major physiological reserve when compared to elderly patients and therefore vital signs could remain normal for a longer time. Indeed, in children, it has been demonstrated that hypotension may not be present until up to 15–30% of the circulating blood volume has been compromised [17]. Hence, the most reliable indicator of significant blood loss is an increase in pulse rate of 20 or more beats per minute (bpm) or a decrease in systolic blood pressure of 10 mmhg or more upon transitioning from a supine to a sitting position.

4. **Which *is the site of bleeding?***

Upper GIB includes hemorrhage originating from the esophagus to the ligament of Treitz, beside the duodenojejunal flexure. Lower GIB bleeding is defined as bleeding that originates from a site distal to the ligament of Treitz. Hematemesis is the classic presentation of upper GIB (proximal to the ligament of Treitz), while lower gastrointestinal bleeding (distal to the ligament of Treitz) often presents as bloody diarrhea or the passage of bright red blood mixed with or coating normal stools. However, melena, hematochezia, and dark/occult bleeding can stem from both upper and lower gastrointestinal sources. In fact, melena that generally indicates an upper GIB (esophagus, stomach, duodenum, and proximal jejunum), in immunocompromised patients with slow intestinal transit may also origin from bleeding within the small bowel or colon. Similarly, hematochezia, commonly suggesting bleeding from the distal small bowel or colon, can also result from severe upper digestive tract bleeding due to a cathartic effect from large blood volumes in the intestinal lumen, hastening intestinal transit.

In doubtful cases, especially in hemodynamically unstable patients experiencing rectal bleeding suspected to stem from significant upper digestive tract hemorrhage, placing a nasogastric (NG) tube and performing a normal saline lavage may help identify the bleeding site, determine the extent of bleeding, assess ongoing bleeding, and mitigate the risk of inhaling gastric contents or developing hepatic encephalopathy in cirrhotic patients. Nonetheless, it is essential to note that the NG tube’s negative predictive value is limited, as it might not detect bleeding from the bulb or duodenum. Moreover, while NG lavage effectively reduces gastric fluid accumulation, it does not halt the bleeding.

5. **Special *considerations in newborn and infants***

In neonates and infants younger than 12 months, unique etiologies of GIB exist. Common causes of GIB in an otherwise healthy infant are anal fissures, eosinophilic proctocolitis or food protein-induced allergic proctocolitis (FPIAP) and ingestion of maternal blood from delivery or fissured nipples during breastfeeding.

To distinguish between fetal and maternal origin of blood, the Apt-Downey test can be performed. It exploits the different denaturing properties of fetal and maternal hemoglobin in the presence of sodium hydroxide. Blood is mixed with a small amount of sterile water to cause hemolysis of red blood cells, producing free hemoglobin. The sample is then centrifuged, and the supernatant mixed with 1% sodium hydroxide (naoh). The fluid color, assessed after 2 min, will remain pink in case of fetal hemoglobin, while it will turn yellow- brown in case of adult hemoglobin because the latter one is less stable and will convert to hematin.

In a newborn, GIB may be one of the presenting symptoms of a cow’s milk protein allergy or an underlying coagulopathy. Bleeding from vitamin K deficiency should be considered in infants with maternal exposure to antiepileptic drugs that affect vitamin K, dysbiosis

from antibiotic exposure, cholestasis, short bowel syndrome, or failure to receive perinatal vitamin K prophylaxis. Vitamin K deficiency is easily corrected by the intramuscular or intravenous administration of vitamin K. Failure to correct bleeding should raise suspicion for congenital bleeding disorders, such as clotting factor deficiencies or von Willebrand's disease.

However, in clinically unstable, premature, or very low birth weight infants, necrotizing enterocolitis should always be suspected. In addition, in this subgroup of infants, severe hematochezia is a late clinical sign in many surgical emergencies, from volvulus to intussusception.

In healthy infants younger than 9 months old straining and crying for at least 10 min before successful or unsuccessful passage of soft stools without blood, infant dyschezia should be suspected and parents should be reassured about the benign nature of this condition.

IV. Paraclinical examination

1. Laboratory tests

Complete blood count and red blood cell indices can shed light on the severity and chronicity of bleeding. A low mean corpuscular volume (MCV) suggests long-duration bleeding even if bleeding has recently arisen. Hemoglobin (Hb) and hematocrit determination are part of the standard procedure, even though initial Hb may be normal. Thrombocytopenia may indicate hypersplenism or, when associated with direct hyperbilirubinemia and increased creatinine levels, uremic-hemolytic syndrome; conversely, thrombocytosis is often associated with inflammatory condition (e.g. Chronic inflammatory bowel disease (IBD), subacute infectious enterocolitis…). In case of severe bleeding, changes in serial blood counts may presage a worsening clinical course and the need for therapeutic interventions.

Liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT)], total and fractionated bilirubin, and albumin are used to assess liver function. The coagulation profile [prothrombin time (PT), partial thromboplastin time (PTT) and international normalized ratio (INR) may indicate pre-existing coagulopathy, chronic hepatopathy, or acute conditions such as sepsis and disseminated intravascular coagulation.

An increase in blood urea nitrogen levels may be related to amino acid catabolism during intestinal digestion of red blood cells, and in children, an azotemia/creatinine

Ratio > or equal to 30 has a sensitivity of 68.8% and specificity of 98% in determining the upper origin of bleeding.

Blood typing and crossmatching should always be required in case the patient needs blood transfusion.

In patients with lower intestinal bleeding associated with symptoms of colitis, in addition to blood tests, stool analysis for infectious agents (Salmonella, Shigella, Clostridium difficile toxin A and B, Yersinia, Campylobacter, Entamoeba histolytica in case of recent travel to a high-risk geographic area, and Escherichia coli O157:H7 in case of impaired renal function) can be performed based on clinical suspicion (e.g. Antibiotic exposure, immunodepression, recent travel).

Additional tests may be pursued according to clinical history, such as inflammatory markers (C-Reactive Protein = CRP) and quantitative fecal calprotectin in suspected IBD. Quantitative fecal calprotectin is a marker for intestinal inflammation with high negative predictive value. Its determination is useful to support the diagnosis of IBD in patients with hematochezia associated with colitis symptoms for more than 2 weeks, but false positive results can be obtained throughout nsaids and proton pump inhibitors therapy.

2. **Imaging studies**
   - Chest and abdominal x-ray: foreign body, constipation, vomiting, dysphagia, odynophagia, drooling, obstruction,
   - Barium enema: suspected stricture, intussusception, Hirschsprung disease (late)
   - Ultrasound (Doppler recommended for liver disease): portal hypertension, intussusception, possible inflammatory bowel disease
   - Meckel's scan: Meckel diverticulum
   - Tagged Red blood cells (RBC) scan: obscure gastrointestinal bleeding
   - MR/CT/direct angiography: obscure gastrointestinal bleeding, suspected arteriovenous malformation

❖ **Gastrointestinal Endoscopy**

- Esophagogastroduodenoscopy (EGD): Bleeding from the upper GI tract can often be readily discovered by NG lavage and further located by endoscopy. NG lavage has good positive predictive value for high-risk endoscopic lesions in patients with acute upper GI bleeding. Ultimately, an esophagogastroduodenoscopy (EGD) is the initial test of choice in the vast majority of cases for the ability to confirm the diagnosis and possibly treat the bleeding lesion. If a patient presents with hematemesis or has blood or heme-positive content found on NG lavage, radiographic testing is rarely indicated unless the EGD is negative. Possible imaging modalities prior to performing EGD include an abdominal x-ray to localize a foreign body, ultrasound with Doppler to evaluate the liver and abdominal vasculature, or CT scan to evaluate organomegaly, masses, or vasculature.
- Ileo-colonoscopy: Hematochezia almost always originates in the colon, except in a very rare case of brisk upper GI bleeding. To evaluate the source of bleeding, and after ruling out infectious causes in the appropriate setting, colonoscopic examination is the best initial diagnostic choice with a reported diagnostic yield ranging 48% to 90%. If the bleeding lesion is not detected during colonoscopic examination, EGD may be needed. If inflammatory bowel disease (IBD) is suspected, both EGD and colonoscopy are recommended to evaluate the full extent of the disease. When polyps are suspected, colonoscopy is the ideal choice due to its diagnostic ability but also to provide definitive treatment.
- Preparation for Procedure: The preparation for EGD mostly consists of adequate NPO time. This may differ depending on institutions' sedation policy but is approximately 3 to 4 hours for clear liquids and 6 hours for solids, depending on the type of fluids ingested and the patient's age. The preparation for colonoscopic examination requires not only the appropriate NPO time but also a bowel purgative, which is of the utmost importance in order to ensure proper mucosal visualization. If the endoscopist attempts to perform a colonoscopy without proper cleansing this will make a thorough exam very difficult and increase the chance of complication. The bowel preparation for colonoscopy may need to be adjusted depending on the type of bleeding encountered and the endoscopist's preference.

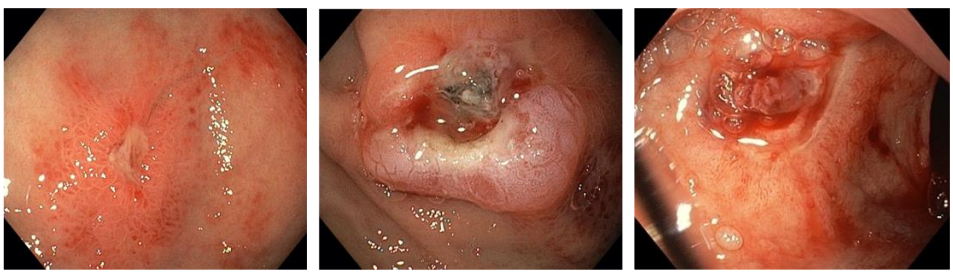


Fig 1. *Gastric and duodenal ulcer aspect on endoscopy*
(Images from Kantha Bopha Hospital and Jayavarman 7 Hospital)

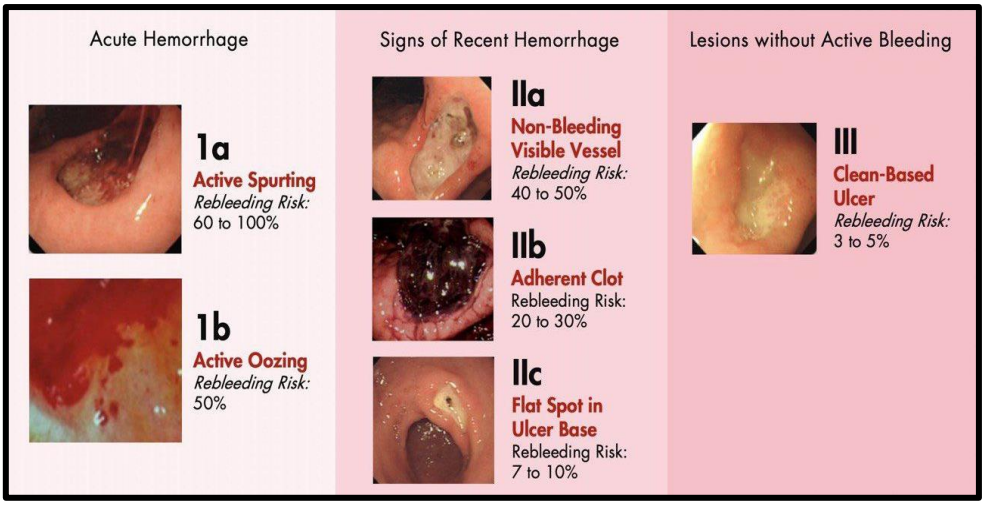


Fig 2. *Forrest classification*

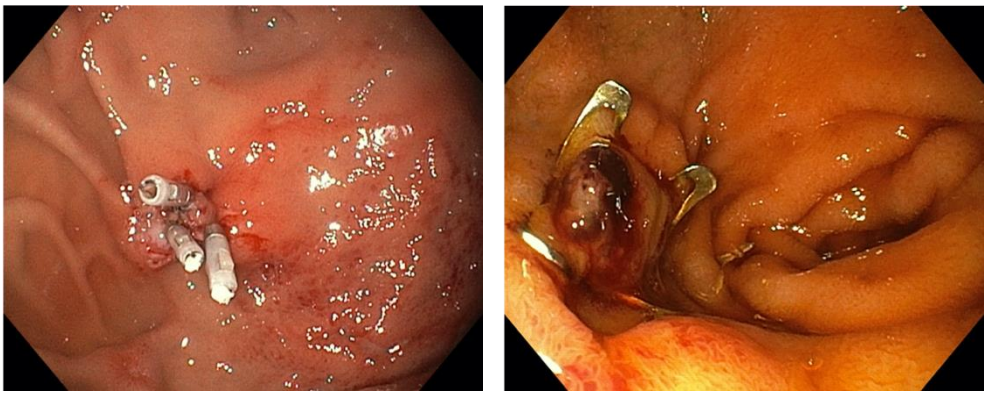


Fig 3. *Ulcer Bleeding is controlled by the Hemostatic clip and OTSC (Over-The-Scope Clip)*
(Images from Kantha Bopha Hospital and Jayavarman 7 Hospital)

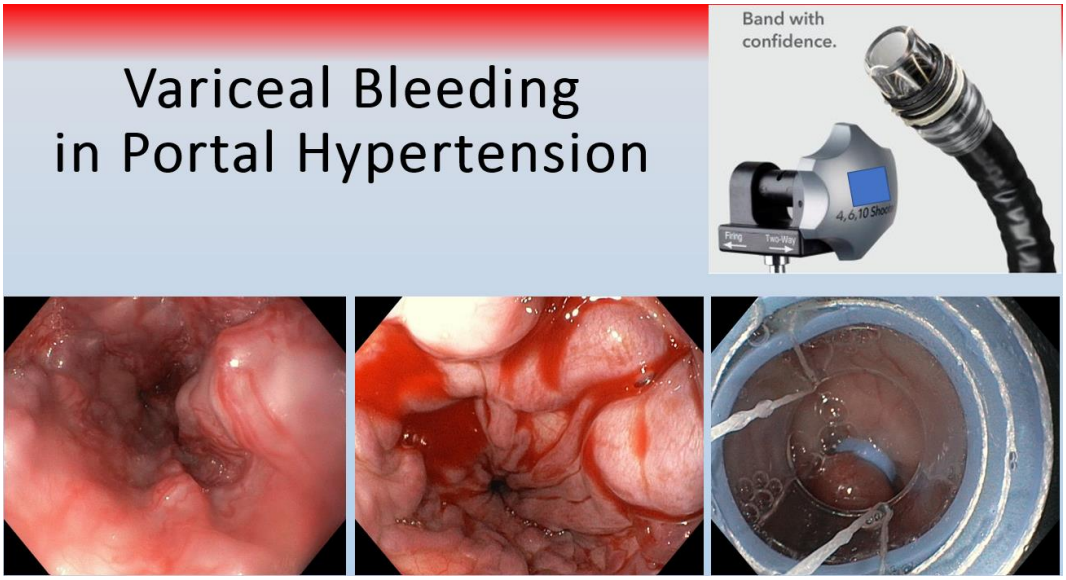


Fig 4. *Esophageal varices bleeding is controlled by band ligations*
(Images from Kantha Bopha's Children Hospital)

V. Management

1. Management of UGIB

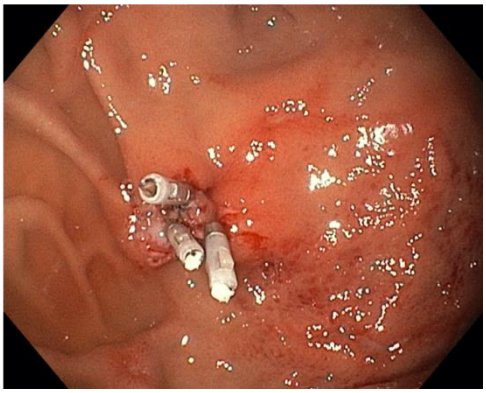
All children with ongoing/significant bleed and those with hemodynamic instability should be admitted in the hospital.

The fundamental clinical principles of management are immediate assessment of severity, determining the possible cause and stabilizing the hemodynamic status. The assessment and management should go hand-in-hand. Vital signs such as heart rate, blood pressure and capillary filling time should be monitored continuously to identify the need for early fluid resuscitation. A clue to the diagnosis may be obtained from a detailed history and physical examination. A history of jaundice and the presence of splenomegaly with or without other features of liver disease suggest variceal bleeding. Similarly, easy bruising and mucocutaneous bleeding may indicate a hematological cause. A history of taking certain medications, such as nsaids, steroids and selective serotonin re-uptake inhibitors (ssris inhibit platelet aggregation) indicate a gastroduodenal erosion/ulcer. Hematemesis preceded by intense retching and vomiting points towards the possibility of a Mallory–Weiss tear. A preceding history of dyspepsia and the presence of epigastric tenderness suggest possible peptic ulcer disease.

Blood should be obtained for a full blood count, coagulation parameters, liver and renal function tests and blood group and cross match. When variceal bleeding is suspected, intravenous octreotide 1 mcg/kg IV bolus (Maxi: 50-80 mcg) followed by 1-2 mcg/kg/H for 72H (Maxi: 50mcg/H) should be administered, and, when non-variceal bleeding is suspected, a PPI such as Nexium 1 mg/kg IV bolus (Maxi: 40 mg) followed by 0.1 mg/kg/H for 72H (Maxi: 4mg/H) should be commenced. Blood transfusion is recommended if there is ongoing bleeding, hemodynamic instability despite colloid infusion and if the hematocrit is persistently <20% (target Hb is 7–9 g/dl as over-transfusion may lead to increased portal pressure which increases the risk of re-bleeding in variceal and non-variceal causes).

Endoscopic Therapy:

- Injection (sclerosant, epinephrine, normal saline, hypertonic saline)
- Coagulation (bipolar, monopolar, heater probe, laser, argon plasma)
- Variceal injection and ligation
- Band ligation
- Polypectomy
- Endoscopic clip
- Endoscopic loop
- Hemospray powder



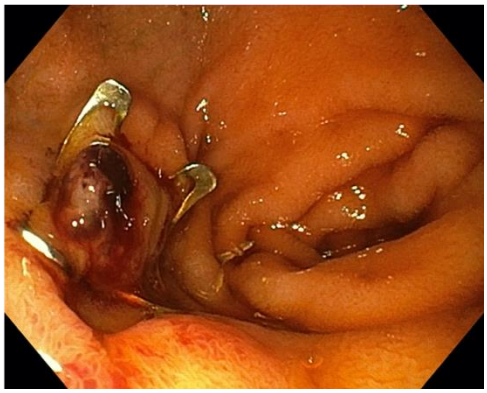
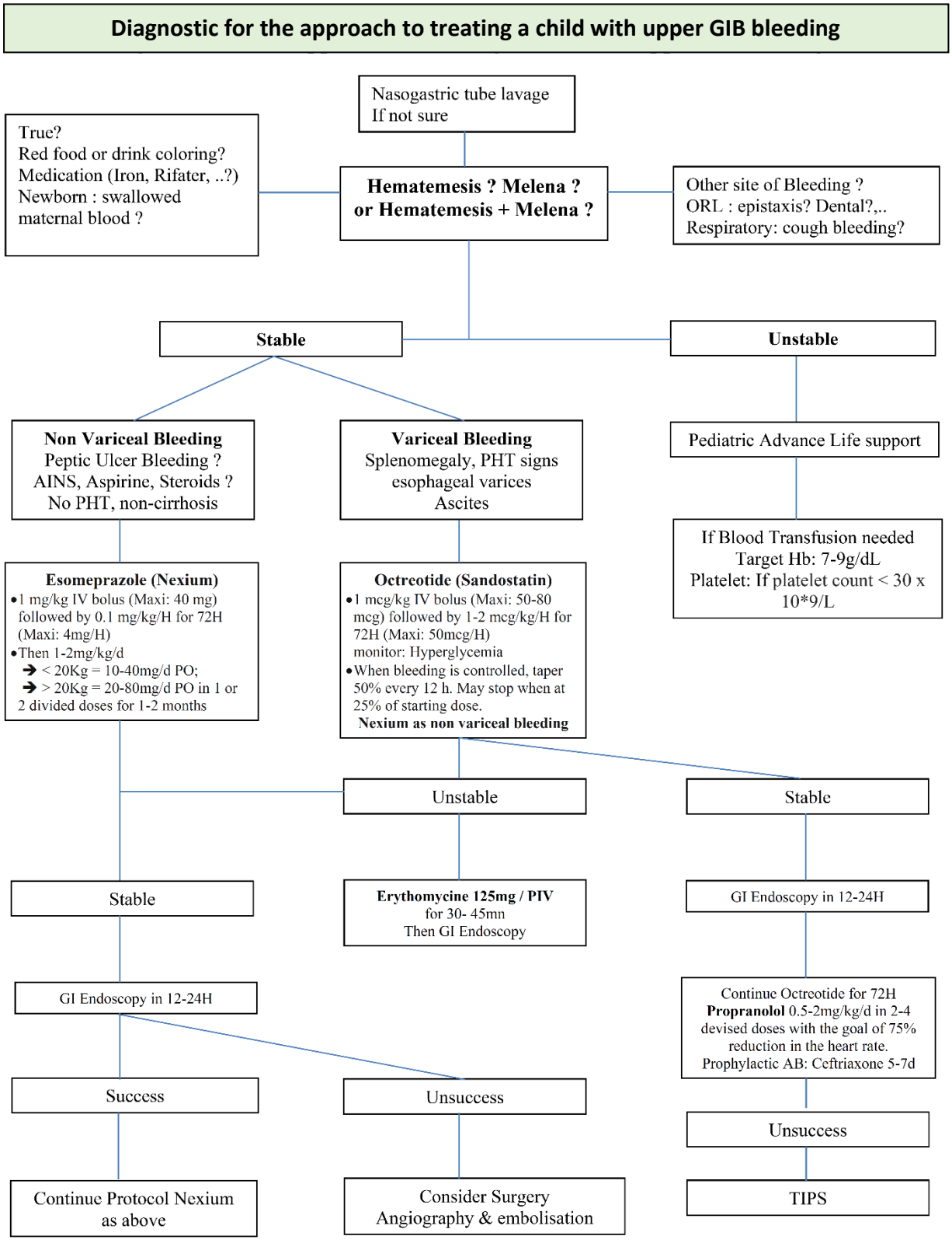


Fig 5. Bleeding is controlled by the Hemostatic clip and OTSC (Over-The-Scope Clip)
(Images from Kantha Bopha Hospital and Jayavarman 7 Hospital)



Team GI endoscopy Kantha Bopha Phnom Penh and Jayavarman 7 Siem Reap

❖ Acid suppression

- Acid suppression is an effective strategy to alleviate symptoms and promote ulcer healing. Available agents on the market include histamine 2 receptor antagonists (h2ras) and proton pump inhibitors (ppis). However, ppis are more potent in ulcer healing. [3]
- Ppis have their greatest effect when given before a meal.

a. Acid Suppression agents:

- Histamine 2 (H2) receptor antagonists
  - Cimetidine: 10-20 mg/kg/day IV/PO divided q12hr.
  - Ranitidine: 4-8 mg/kg PO q12hr; not to exceed 300 mg/day, 2-4 mg/kg/day IV divided q6-8hr; not to exceed 50 mg/dose or 200 mg/day.
  - Famotidine: 0.25 mg/kg IV q12hr or 0.5 mg/kg PO at bedtime; may increase to 1 mg/kg daily for up to 8 weeks; not to exceed 40 mg/day.
- Proton pump inhibitor (PPI):
  - Omeprazole: 5-10 kg: 5 mg PO qday, 10-20 kg: 10 mg PO qday, >20 kg: 20 mg PO qday.
  - Lansoprazole: <30 kg: 15 mg PO qday, >30 kg: 30 mg PO qday.
  - Pantoprazole: >5 years => 15 kg to <40 kg: 20 mg PO qday, >40 kg: 40 mg PO qday.
  - Esomeprazole: 1-12 years: 10-20 mg PO qday, >12 years: 20-40 mg PO qday.

❖ PUD with bleeding signs:

- Esomeprazole: 1mg/kg IV bolus (Maxi: 40mg), followed by 0.1mg/kg/H for 72H (Maxi: 4mg/H)
- Then 1-2mg/kg/d
  - ⇨ < 20kg: 10-40mg/d PO
  - ⇨ > 20kg: 20-80mg/d PO in 1 or 2 divided doses for 1-2 months.

* Note: for dengue patients associated with gastrointestinal bleeding, endoscopic management is rarely indicated. However, with some cases associated with unusual bleeding or suspected of peptic ulcer bleeding, endoscopic management is encouraged.

2. Management of LGIB

All children with ongoing/significant bleed and those with hemodynamic instability should be admitted in the hospital. Those children with colitis symptoms, with stool for pus cell positive can be treated on OPD basis provided they have no signs of dehydration and the oral intake is good.

The most important step in managing a child with LGIB is the continuous monitoring of vital signs and arrangement with blood bank for likely need for blood. In majority of the cases (up to 80%) the bleeding responds to supportive management alone, but episodes of rebleeding can occur.

If clinical deterioration occurs without obvious blood loss, this should be considered as hidden bleed in the bowel lumen. Blood transfusion is required in cases with hemodynamic instability. Transfusion of fresh frozen plasma is required once every 2–3 units of packed red blood cells (PRBC), to correct the ongoing loss of coagulation factors. Platelet transfusion is indicated if the platelet count is <50,000.

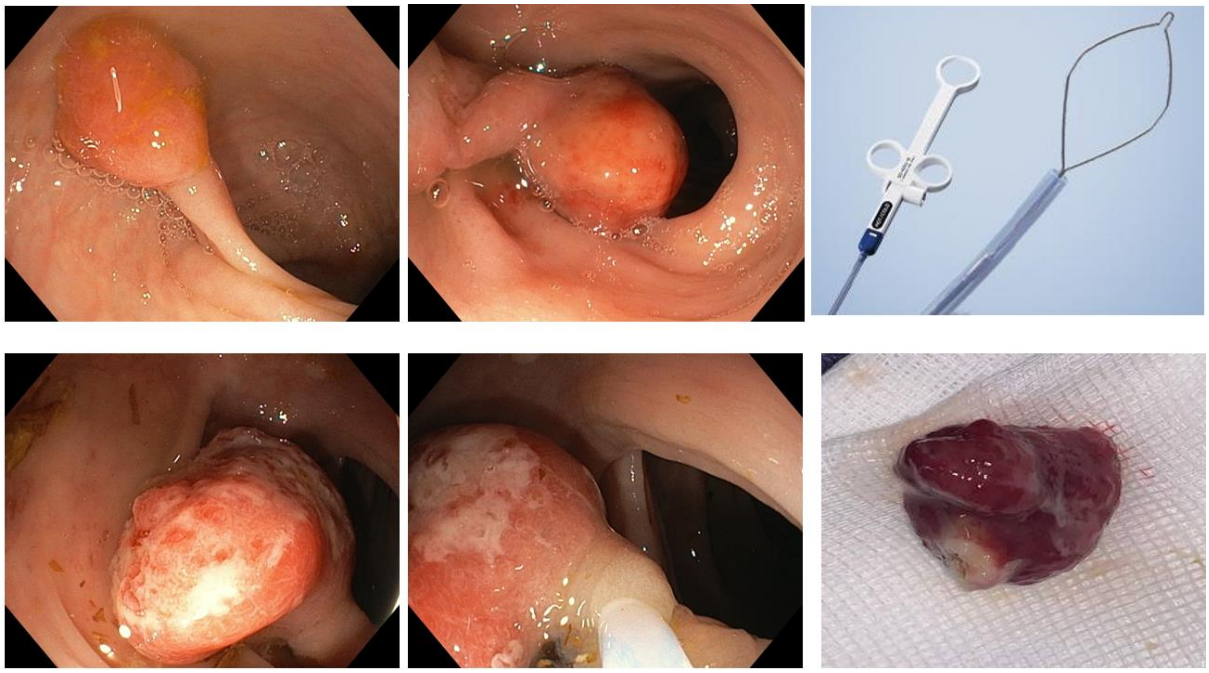
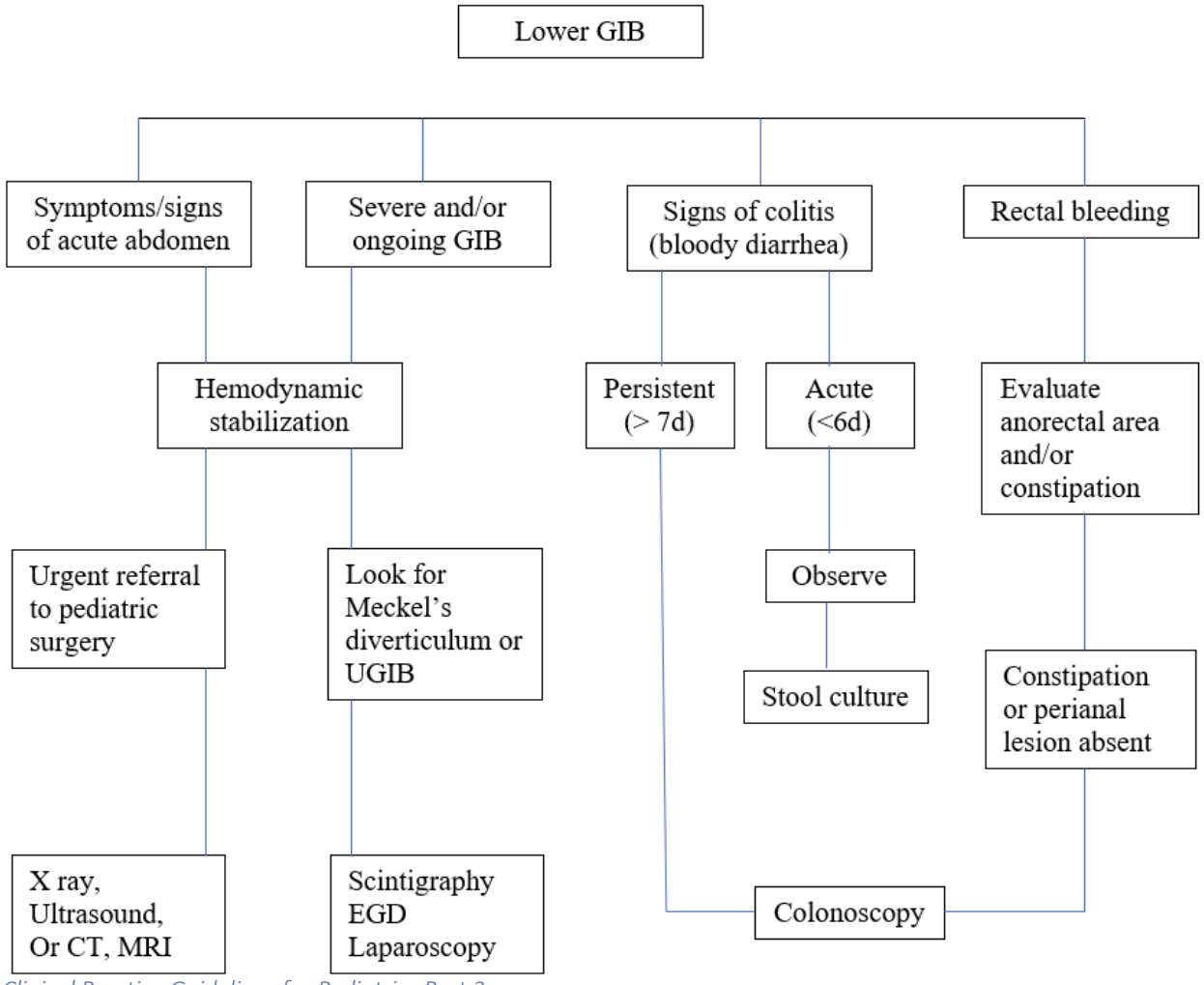


Fig 5. Pedunculated polyp in rectum removed by hot snare
(Images from Kantha Bopha's Children Hospital)

Diagnostic approach of lower GIB in infants and Cheldren



Specific treatment of common conditions causing LGIB

Condition	Treatment
Infectious colitis	
• Campylobactor and Yersinia	Erythromycin, azithromycin
• *E. coli*	Antibiotic treatment of enterohemorrhagic *E.coli* infection—no benefit
• Salmonella	Ampicillin, septran, cefotaxime, ceftriaxone
• Shigella	Ampicillin, Ceftriaxone
• *Clostridium difficile*	Metronidazole, oral vancomycin
• *Giardia lamblia*	Metronidazole
• Amebic dysentery	Metronidazole
Necrotizing enterocolitis	Antibiotics, surgery if needed
Anal fissure	Dietary modification, stool softeners, good toilet training, local anesthetic gels
Hemorrhoids	Banding, sclerosant injection, surgery
Polyps	Polypectomy
Meckel's diverticulum	Surgical excision
Intussusception	Radiological reduction or surgery
Cow's milk allergy	Withdrawal of milk and milk products, substitute with casein hydrolysate formula
Hirschsprung's disease with enterocolitis	Antibiotics and surgery
Henoch Schönlein purpura	Supportive therapy, steroids
Inflammatory bowel disease	Steroids and other immunosuppressants
Nodular lymphoid hyperplasia	Supportive treatment
Arterio venous malformations	Endoscopic/angiographic treatment, surgery

VI. Patient education

- Consider consultation with local pediatric or pediatric gastroenterologist or endoscopist when:
  - Heavy bleeding: large amount of hematemesis or melena or hematochezia
  - Pale skin, fast heartbeat, or low blood pressure
  - Weakness, dizziness, or unusual sleepiness
- Home care after discharge:
  - Giving medications exactly as prescribed
  - Avoiding nsaids or other ulcer-causing drugs unless approved
  - Offering soft, easy-to-digest foods
  - Watching for signs of rebleeding (blood in stool or vomit, fatigue, pale skin)
  - Keeping follow-up appointments and reporting any new symptoms

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Chapter VI: Cardio- Vascularly Diseases

HYPERTENTION IN CHILDREN

YOURK leaksmey, EANG Habsreng; NGETH Pises

I. Key Facts

- Hypertension in children is not so common but becoming more widely recognized as pediatric problem. Blood pressure should be determined at every pediatric visit beginning at age 3 years. (1)
- Primary hypertension is the most common cause hypertension in adolescents and adults. The prevalence of systemic hypertension in children appears to be increasing, especially in view of the growing population of children with obesity (5). The overall estimated prevalence of hypertension in childhood is approximately 2-5%; the prevalence of elevated blood pressure (BP) is 13-18%. (6)
- The worldwide prevalence of hypertension in children is difficult to establish due to regional differences in definition, measurement, and distribution of reference data.
- The incidence of hypertensive crisis in children aged > 1 year 0.021% in retrospective cohort study of pediatric emergency departments in Taiwan.

II. Overview

1. Definition

Hypertension is blood pressure exceeding the 90th percentile for age, height and weight of the patient (Chart 1) (2). Blood pressure in children must be taken when the child is relaxed and an appropriate –size cuff must always be used. The bladder should be wide enough to equal or exceed two thirds of the length of the upper arm and should be completely encircle the arm. Blood pressure should be obtained at least 3 measurements in separate occasion before diagnose as hypertension. (3)

2. Causes

Hypertension can be primary (essential) or secondary. Common secondary causes are (4):

- Renal cause: Acute glomerulonephritis (AGN), Chronic Renal Failure
- Cardiac cause: Coartation of the aorta
- Renovascular: vasculitis, Neurofibromatosis, Renal artery stenosis
- Endocrine: Cushing disease, Pheochromocytoma, neuroblastoma.
- Neurologic: Increased intracranial pressure, Guillain-Barre syndrome
- Drugs: corticosteroids, illicit drugs (cocaine, phencyclidine), oral contraceptive drugs
- Other: Obesity, burns, traction.

3. Risk factors

Risk Factors for Primary Hypertension

- Obesity: Obesity is a common and well-established risk factor for hypertension in children. It is reported to affect 3.8% to 24.8% of children with overweight and obesity.
- A positive family history of hypertension: About 50% of children and adolescents with hypertension have a positive family history of hypertension. And 86% of adolescents with primary hypertension have a positive family history of hypertension.
- Male sex increases the risk of hypertension
- Age also increases the risk of primary hypertension
- Race and ethnicity affect the risk of hypertension.
- Sleep-disordered breathing increases the risk of hypertension
- Shorter sleep duration and poor quality of sleep
- An abnormal birth history
- Rapid weight gain after birth may be associated with hypertension
- Exposure to cigarette smoke may be associated with childhood hypertension

- Health behaviors associated with hypertension
- Dyslipidemia
- Disordered glucose metabolism
- Diabetes, particularly diabetes mellitus type

III. Signs and symptoms

1. History

- Family history: hypertension, heart disease, stroke
- Past medical history: UTI, Umbilical artery line in the newborn
- Medications: Corticosteroids, illicit drugs, Oral contraceptive drugs
- Symptoms: headache, blurry vision, epistaxis, chest pain, weight loss or gain, flushing, rashes
- Trauma: traction.

2. Physical examination [9]

- Blood pressure must be confirmed and pulse should be taken in arm and leg
- Heart rate: tachycardia
- Height and Weight: thin, Obese, growth failure
- Signs of end organ damage
    - Fundoscopy: hypertensive retinopathy
    - Cardiovascular: apical heave, hepatomegaly, oedema
    - Chronic renal failure: palpable kidneys
    - Focal neurology eg. Facial nerve palsies
- Signs of underlying cause
    - General appearance: Cushingoid, proptosis, goitre, webbed neck (Turner syndrome), elfin facies (William syndrome)
    - Skin: Cafe-au-lait spots, neurofibromas, acanthosis nigricans, hirsutism, striae, acne, rash(vasculitis)
    - Cardiovascular: murmurs +/- radiation, apical heave, reduced femoral pulses, oedema, hepatomegaly (CCF)
    - Abdomen: masses, palpable kidneys, flank bruits
    - Genitourinary: ambiguous/virilised genitalia eg. CAH.

IV. Diagnosis

1. Making the diagnosis

- Hypertension in children and adolescents is defined as auscultatory-confirmed average systolic and/or diastolic blood pressure ≥ 95th percentile for gender, age, and height percentile on ≥ 3 occasions (8).
- Primary hypertension is a diagnosis of exclusion.
- Secondary hypertension is diagnosed when an underlying cause can be identified.
- Acute severe hypertension, also called a hypertensive emergency.
- To Assess the severity of hypertension in Children:
- According to American Heart Association and American College of Cardiology state as below for Children (See table 1):
    - Normal Blood Pressure
    - Elevated Blood Pressure
    - Stage 1 hypertension
    - Stage 2 hypertension
    - In Severe Hypertension (see table 2):
    - Hypertensive Urgency: >95th centile + 30mmhg without symptoms/sings of target end organ damage.
    - Hypertensive Emergency: >95th centile + 30mmHg associated with encephalopathy.

Table 1: *Updated Definitions of BP Categories and Stages* [8]

Stage	Children Aged 1-13 Years	Adolescents > 13 years Old
Normal	<90th percentile	<120/<80mmHg
Elevated blood pressure (formerly prehypertension)	- ≥ 120/80 mm Hg to < 95th percentile OR - Systolic and/or diastolic blood pressure from ≥ 90th percentile to < 95th percentile (based on charts for gender, age and height) - Whichever is lower	- Blood pressure 120/< 80 to 129/< 80 mm Hg
Stage 1 hypertension	- 130/80 to 139/89 mm Hg OR - Blood pressure ≥ 95th percentile or 90th to 95th percentile plus 12 mm Hg - Whichever is lower	- Blood pressure 130/80 to 139/89 mm Hg
Stage 2 hypertension	- ≥ 140/90 mm Hg OR - Blood pressure ≥ 95th percentile plus 12 mm Hg - Whichever is lower	- Blood pressure ≥ 140/90 mm Hg

Table 2: Severe Hypertension [9]

Stage	Children Aged 1-13 Years	Adolescents > 13 years Old
Hypertensive Urgency	>95th centile +30 mmHg without Symptoms/signs of target end organs damage (see examination)	>180/120 without Symptoms/signs of target end organs damage (see examination)
Hypertensive Emergency	>95th centile +30 mmHg associated with encephalopathy. eg. Headache, vomiting, vision changes and neurological symptoms (facial nerve palsy, lethargy, seizure, coma) +/ - target end organs damage.	>180/120 associated with encephalopathy. eg. Headache, vomiting, vision changes and neurological symptoms (facial nerve palsy, lethargy, seizure, coma) +/ - target end organs damage.

2. Laboratory test

- CBC and differences, Serum electrolytes, Urea and creatinine, cholesterol, cortisol, fasting glucose
- Urinalysis, urine culture (if indicated)
- Echocardiogram
- ECG
- Renal ultrasound and renal doppler
- Consider LFT, Hb1Ac, fasting lipids particularly in children with obesity

1. Differential diagnosis

- After diagnosis hypertension, the initial objective is to distinguishing primary from the secondary causes. Generally, the younger the child and more elevated the blood pressure measurements are the more likely the cause of hypertension is secondary.
- Causes of false elevation of blood pressure include improper technique, such as using a blood pressure cuff that is too small.
- Common exogenous and physiologic causes of hypertension include:

- Exogenous causes include medications, caffeine, and intoxications.
- Common physiologic causes of hypertension include exercise, anxiety, and pain.

V. Complications

1. **Complications of chronic mild-moderate hypertension in children and adolescents include:**
   - Cardiovascular complications:
     - Children with hypertension may experience accelerated vascular aging including cardiovascular damage.
     - Left ventricular hypertrophy (LVH) is reported in 30%-40% of children with primary hypertension.
     - Other cardiovascular complications:
       - Other cardiovascular complications include intima-media layer thickening of arterial wall, reduced arterial compliance and atherosclerosis, and diastolic dysfunction.
       - Blood pressure rhythmicity may also occur.
   - Neurocognitive complications:
     - Neurocognitive complications include impaired cerebrovascular reactivity and reduced neurocognition and executive function.
   - Ocular complications:
     - Ocular complications: include retinal changes, especially from severe hypertension, and reduced caliber of retinal arterioles.
   - Renal complications:
     - Significant renal complications in children are not common.
     - Renal complications include albuminuria and proteinuria.
2. **Complications of severe hypertension in children and adolescents include:**
   - Seizure
   - Stroke
   - Acute heart failure
   - Acute kidney injury
   - Hypertensive encephalopathy
   - Facial nerve palsy

VI. Prognosis

- Blood pressure control
- Persistence of hypertension into adulthood
- Factors associated with mortality and target organ damage
- Lowering blood pressure may lead to a reduction in left ventricular hypertrophy in children

VII. Management

- According to the AAP guidelines, an optimal BP level to achieve with treatments is <90th percentile or <130/80 mmHg [8].
- Treatments can be differentiated into nonpharmacological and pharmacological, but it is important to remember that pharmacological options should always be accompanied by non-pharmacological treatments.

1. **Nonpharmacologic treatment (Lifestyle modifications)**
   a. ***General recommendations***
      - (1) Physical activity and tailored diet.
      - (2) Encourage parents/family participation.
      - (3) Encourage smoke-free environment.
      - (4) Provide educational support and materials.

- (5) Establish realistic goals.
- (6) Develop a health-promoting reward system.

b. BMI

- (1) If needed, graduate weight-loss program (see also Chapter 6).

c. Physical activity

- (1) At least 60 min of activity per day, at least moderate (jogging, cycling, or swimming).
- (2) More activity = more good health.
- (3) Aerobic mostly, but with resistance components (3 times/week).
- (4) No more than 2-h sedentary behavior per day.
- (5) If stage 2 hypertension, avoid competitive sports.

d. Diet

- (1) Avoid free sugar (≤5% of total calories), soft-sweetened drinks, saturated fat.
- (2) Prefer fruits, vegetables, and grain products (ideally, ≥4-5 servings/day).
- (3) Limit sodium intake (<2300 mg/daily).

2. Pharmacologic therapy:

a. The Consensus Panel agrees that, due to the heterogeneous nature of childhood HTN, drug choice should be based on the following [7]

- (1) Presumed underlying pathophysiology.
- (2) Presence of concurrent disorders.
- (3) Availability of appropriate med formulations.

b. For Stage 1 or/and Stage 2 hypertension who failed nonpharmacologic treatment.

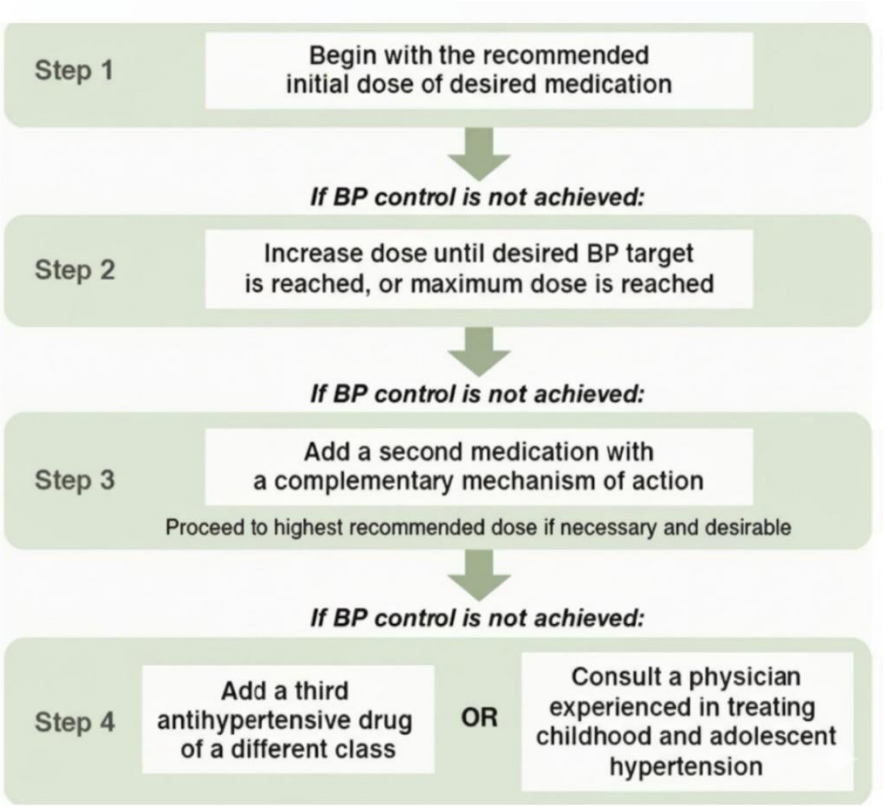
c. Recommended first-line of antihypertensive agents includes: See table 4: Start with single drug. Angiotensin converting enzyme inhibitors (aceis), Or Angiotensin receptor blockers (arbs), Or dihydropyridine calcium channel blockers (ccbs), Beta-adrenergic Blockers or Thiazide Diuretics.

d. If first line does not achieve the target: See Table 5 [10]

Table 4. *Frequently used Antihypertensive Oral Medications for treatment of Chronic pediatric Hypertension.* [7]

Medication Class	Drug	Dose	Interval	Contra Indication
ACEIS	Captopril	0.3–0.5 mg/kg per dose	qd–bid	Pregnancy
	Eralapril	0.08–0.6 mg/kg per day	qd	Angioedema
	Lisinopril	0.08–0.6 mg/kg per day	qd	Hypersensitivity to ACEIS
ARBS	Losartan	0.75–1.44 mg/kg per day	qd	Pregnancy
	Valsartan	2 mg/kg per day	qd	Angioedema
	Candesartan	0.16–0.5 mg/kg per day	qd	Hypersensitivity to ARBS
	Ibesartan	75–150 mg per day	qd	
CCBS	Amlodipine	0.06–0.3 mg/kg per day	qd	Hypersensitivity to CCBS
	Nifedipine	0.25–0.5 mg/kg per day	qd–bid (ER)	
Beta-adrenergic blockers	Propanolol	1 mg/kg per day	qd–bid	Hypersensitivity to Beta-Blocker
	Metoprolol	0.5–1.0 mg/kg per day	qd (ER)	
	Atenolol	0.5–1 mg/kg per day	qd–bid	
Thiazide Diuretics	Furosemide	0.5–2.0 mg/kg per dose	qd–bid	Anuria Hypersensitivity to Thiazides
	HCTZ	0.5–1 mg/kg per day	qd	
	Spironolactone	1 mg/kg per day	qd–bid	

ACEIS: Angiotensin-Converting Enzyme Inhibitor; ARBS: Angiotensin Receptor Blocker; CCBS: Calcium Channel Blocker; HCTZ: Hydrochlorothiazide



3. **Management of sever hypertension:** [10]:
   Should send to pediatric hospital for further investigation and management- Send to PICU and discuss with renal team.
   - Hypertensive urgency
   - If medically stable, consider short acting oral agents while investigating cause
   - Nifedipine
   - Commence 0.25–0.5 mg/kg/day (max 20 mg) and titrate up as required to a maximum of 3 mg/kg/day (max 120 mg)
   - Hypertensive emergency
   - Intravenous therapy; discuss with renal team and retrieval/ICU team
   - Aim to gradually reduce BP to the patient's estimated 95 centile
   - Decrease BP by 25% of the original value every 24 hours till target BP reached. Reduce rate of decrease if patient becomes symptomatic.

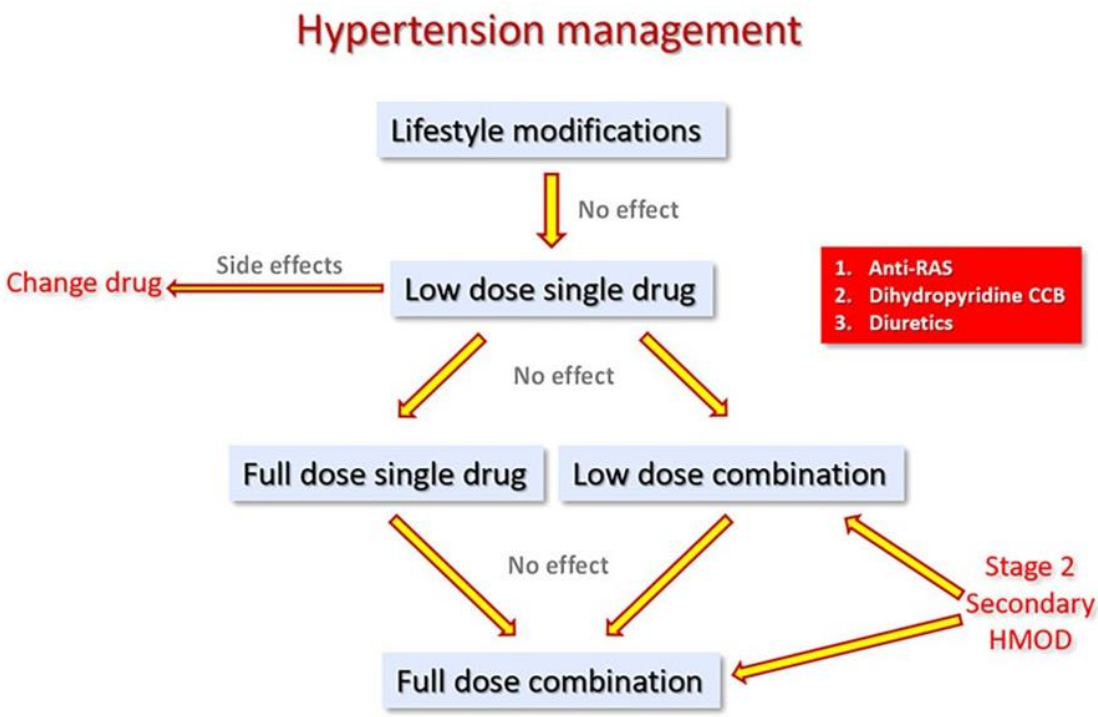
Table 6. *Antihypertensive drugs for management of severe hypertension in children 1–17 years* [10]

Drug	Dose	Indications and Warnings
Beta- and/or adrenergic blockers		
Esmolol	100-500 mcg/kg IV per minute (use constant infusion)	- Use if life-threatening symptoms - May cause profound bradycardia - Avoid with asthma
Labetalol	0.2–1 mg/kg bolus (up to 40 mg/dose) or 0.25–3 mg/kg IV per hour	- Use if life-threatening symptoms - Avoid with asthma and overt heart failure - May cause bradycardia
Direct vasodilators		

Drug	Dose	Indications and Warnings
Hydralazine	0.1–0.2 mg/kg (up to 0.4 mg/kg)	- Use if life-threatening symptoms - Administer with IV (every 4 hours if bolus) or intramuscularly - Causes tachycardia
	0.25 mg/kg (up to 25 mg) orally every 6-8 hours	Use if less significant symptoms
Sodium nitroprusside	0.3 mcg/kg IV per minute (up to 10 mcg/kg IV per minute)	- Use if life-threatening symptoms - With renal failure or use > 72 hours, monitor cyanide levels or use with sodium thiosulfate
Minoxidil	0.1–0.2 mg/kg (up to 10 mg) orally every 8-12 hours	- Use if less significant symptoms - May cause fluid retention
Nitroglycerine	0.1-2 mcg/kg IV per minute	- May cause methemoglobinemia - Limited efficacy in children
Calcium channel blockers		
Nicardipine	30 mcg/kg (up to 2 mg) bolus or 0.5-4 mcg/kg IV per minute	- Use if life-threatening symptoms - May cause reflex tachycardia - Increases tacrolimus and cyclosporine levels
Isradipine	0.05–0.1 mg/kg (up to 5 mg) every 6-8 hours	- Use if less significant symptoms - Higher doses may cause blood pressure drop > 25% - With use of azole antifungal agents, may see exaggerated blood pressure drop
Nifedipine	0.25 mg/kg/dose	May cause reflex tachycardia, unpredictable hypotension
Central agonists		
Clonidine	2-5 mcg/kg (up to 10 mcg/kg) orally every 6-8 hours	- Use if less significant symptoms - May cause drowsiness, dry mouth, and rebound hypertension
Urapidil	- 0.5-4 mg/kg IV per hour (initial dose) - 0.2-2 mg/kg IV per hour (maintenance dose)	May cause nausea, palpitation, and sedation
Dopamine receptor agonists		
Fenoldopam	0.2-0.5 mcg/kg IV per minute (up to 0.8 mcg/kg per minute)	- Use if less significant symptoms - Higher doses increase tachycardia without additional reductions in blood pressure
Angiotensin-converting enzyme inhibitors		
Captopril	0.1-0.2 mg/kg/dose	Avoid if suspected bilateral renal artery stenosis
Enalaprilat	0.005-0.01 mg/kg/dose	Avoid if suspected bilateral renal artery stenosis
Loop diuretic		
Furosemide	0.5-5 mg/kg/dose	- Use if volume hypertension - May cause hypokalemia
Reference - Pediatrics 2017 Sep;140(3): doi:10.1542/peds.2017-1904, J Hypertens 2016 Oct;34(10):1887-920.		

4. Hypertension-mediated organ damage (HMOD)

Algorithm 2. Stepped care approach for management of arterial hypertension in Children and adolescents [7]



VIII. Patient and education

Measure to prevent elevated and high blood pressure include:

- Avoiding excess weight gain and maintaining an appropriate body mass
- Maintaining regular physical activity of 60 minutes/day of moderate-to-vigorous activity
- Restricting sedentary activity
- Eating a healthy diet, including:
  - Consuming a Dietary Approaches to Stop Hypertension (DASH) diet that is high in fruits and vegetables, low-fat dairy, and whole grains and low in sugar and saturated fat
  - Avoiding foods high in sodium
- Avoiding tobacco products
- Establishing normal sleep habits.

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CONGESTIVE HEART FAILURE IN CHILDREN

YOURK Chanleaksmy; ENG Habsreng; NGETH Pises[8]

I. Key facts

Pediatric congestive heart failure or Pediatric Heart Failure (PHF) is a diverse etiology manifesting, a variety of clinical presentations that encompasses a diverse population of patients with congenital heart disease (CHD), cardiomyopathy, infectious and inflammatory diseases, oncologic processes, metabolic syndromes, renal failure, and malnutrition. [1] In all PHF syndromes, whether adult or pediatric, a unifying pathophysiologic mechanism is involved. Chronic or acute CHF progress death if left untreated. Indeed, pediatric congestive heart failure is most common reason presenting in children with heart disease. [2]

II. Overview

1. Definition [3,6]

a. Pediatric Heart Failure (PHF) is the state that heart cannot deliver adequate blood to meet the metabolic needs of the body. In the early stage of PHF, the heart can compensate to maintain normal metabolic function. When the compensate mechanisms become ineffective, severe clinical manifestations present [3]. According to European Society of Cardiology recommendations in 2021, PHF is not a discrete pathological diagnosis but rather a clinical syndrome characterized by a collection of symptoms (e.g., shortness of breath, ankle swelling, fatigue) and occasional comorbid signs (e.g., elevated jugular venous pressure, pulmonary crackles, peripheral edema). [6] PHF classified as Acute Heart Failure and Chronic Heart Failure are summary in Table 1. [6]

b. Acute HF

HF is labeled “acute” when signs and symptoms of mal-perfusion and congestion, such as tachycardia, tachypnea, respiratory distress, and hypotension, appear suddenly (within minutes to hours), usually because of anatomical or functional changes in the heart.

c. Chronic HF

Chronic HF (CHF) is a progressive condition that may have both cardiac and noncardiac causes. Respiratory distress, pedal edema, exercise intolerance, and growth failure are symptoms indicative of underlying neurohormonal, circulatory, and molecular abnormalities.

2. CHF is classified as HF with preserved ejection fraction (hfpef) or HF with reduced ejection fraction (hfref). Hfref, characterized by symptomatic HF with a dilated left ventricle (LV) and an LV ejection fraction (LVEF) <50%, is most often caused by LV systolic dysfunction. Symp-tomatic hfpef, which features normal or near-normal LV systolic function, is usually caused by severe LV diastolic dysfunction and is also known as diastolic HF. *See table 1.*

3. Epidemiology

The overall prevalence and incidence of pediatric heart failure is unknown, generally because of no acceptable universal classification apply to its many forms. The largest PHF burden comes from children born with congenital malformations. It has been estimated that 15% to 25% of children who have structural heart disease develop PHF. Although cardiomyopathy is relatively rare, approximately 40% who experience cardiomyopathy develop heart failure of such severity that it leads to transplantation or death.

4. Etiology [2, 7]

In children, cardiac failure is most often due to chds and cardiomyopathies. The cardiac and noncardiac causes of PHF are summarized in Table 2. At birth, HF is caused by fetal

Table 1. *Classification and causes of heart failure in children*	
Classification	**Examples**
According to the course of the disease	
- Acute HF - Chronic HF	- Arrhythmia - Cardiomyopathies (dilated, hypertrophic, restrictive)
According to the severity	
- Mild or compensated HF - Severe or decompensated HF	- Atrial fibrillation or ventricular tachycardia - Acute myocardial infarction
According to the function impaired	
- Systolic failure - Diastolic failure	- Myocarditis, hypertension - Restrictive cardiomyopathy, cardiac tamponade
According to the location of heart failure	
- Left-sided heart failure - Right-sided heart failure - Biventricular failure	- Cardiomyopathies (dilated, hypertrophic, restrictive) - Acute respiratory distress syndrome, pulmonary embolism - Cardiomyopathies, Acute respiratory distress syndrome, pulmonary embolism (PE)
According to the cardiac output	
- Low-output HF - High-output HF	- Pressure overload, contractility problems, myocarditis - 3As (anemia, arrhythmia, arteriovenous malformation/vein of Galen malformation)
According to the etiology	

- HF due to inherited disorders
  ○ Cardiomyopathy
- HF due to congenital heart disease
  ○ Volume overload
  ○ Pressure overload
  ○ Complex CHD
- HF due to acquired heart disease
  ○ Myocarditis
  ○ Toxic cardiomyopathy
  ○ Arrhythmogenic cardiomyopathy
  ○ Ischemic cardiomyopathy
  ○ Infiltrative cardiomyopathy
  ○ Acquired valvular disease
	
	  ○ Dilated, hypertrophic, restrictive
	
	  ○ Patent ductus arteriosus, ventricular septal defect
	  ○ Critical aortic stenosis, severe pulmonary stenosis, coarctation of aorta
	  ○ Unbalanced atrioventricular canal defects, hypoplastic left heart syndrome
	
	  ○ Viral myocarditis, Kawasaki disease
	  ○ Anthracyclines
	  ○ Tachyarrhythmia induced cardiomyopathy
	  ○ Coronary vasculitis, atherosclerotic disease
	  ○ Iron overload cardiomyopathy
	  ○ Rheumatic heart disease, infective endocarditis

Cardiomyopathies or extracardiac conditions (such as sepsis, hypoglycaemia, and hypocalcaemia). In the 1st week after birth, chds with ductus-dependent systemic circulation (such as severe aortic stenosis/aortic coarctation and hypoplastic left heart syndrome), in which the closure of the ductus arteriosus causes severe reduction of end-organ perfusion, are the main cause. In the 1stmonth of life, frequent causes of PHF are chds with left to right shunt (such as ventricular septal defects, patent ductus arteriosus, and aortopulmonary windows), in which pulmonary blood flow progressively increases

with the fall of pulmonary resistance. Finally, HF in adolescence is rarely secondary to chds, but is more often related to cardiomyopathies or myocarditis.

Table 2. ***Etiology of pediatric heart failure***

Type of diseases	Pathophisiology	Examples
Congenital heart diseases	Left to right shunt (volume overload)	- Ventricular septal defects - Complete atrioventricular canal defects - Patent ductus arteriosus - Aorto-pulmonary windows
	Valvular regurgitation (volume overload)	- Mitral regurgitation - Aortic regurgitation
	Outflow tract obstruction (pressure overload)	- Aortic stenosis - Tunnel type subaortic stenosis - Supravalvular aortic stenosis - Pulmonary stenosis - Pulmonary vein stenosis
	Coronary insufficiency (decreased O2 supply to cardiomyocyte)	- Coronary artery anomalies

Cardiomyopathies (inherited or acquired)	-Systolic dysfunction (low cardiac output)
	-Diastolic dysfunction (elevated pulmonary capillary pressure)
		- Dilated cardiomyopathy
		  ○ Myocarditis
		  ○ Barth syndrome
		  ○ Carnitine deficency
		  ○ Familial dilated cardiomyopathy
		  ○ Neuromuscular disorder (i.e., Becker dystrophy/ duchenne dystrophy)
		- Hypertrophic cardiomyopathy
		  ○ Pompe diseases
		  ○ Noonan syndrome
		  ○ Maternal diabetes
		  ○ Mitochondrial diseases
		  ○ Familial hypertrophic cardiomyopathy
		- Idiopathic restrictive cardiomyopathy

Arrhythmias	Systolic dysfunction (low cardiac output)	- Tachycardia induced cardiomyopathy
		  ○ Atrio-ventricular node re-entry tachycardia
		  ○ Atrio-ventricular re-entry tachycardia
		- Ectopic atrial tachycardia
		- Congenital third degree atrio-ventricular block

Infection	Systolic dysfunction	- Sepsis induced myocardial dysfunction
High output state	Volume overload	- Thyrotoxicosis

		- Systemic arteriovenous fistula - -Severe anemia

III. Signs and Symptoms [3-4]

Due to CHF have many causes, variety of clinical presentations depending on age of the patients and degree of heart failure. There is no single test for specific heart failure; the diagnosis is based on several clinical findings. The assessment of severity of PHF base on Modified Ross heart failure classification in children Table 3.

IV. Diagnostic approach [7]

The first step in diagnostic approach in patients with PHF is based on non-invasive clinical investigations.

1. History

- Infant: poor feeding of recent onset, tachypnea worse during feeding, poor weight gain and cold sweat on the forehead.
- Older children: complaint of shortness of breath, especially with activities, easy fatigability, puffy eyelids, or swelling feet.

2. Physical examination

d. Compensatory sings

- Tachycardia, gallop rhythm and weak and thread pulse are common
- Cardiomegaly
- Growth failure, sweating, and cold, wet skin

e. Signs of left heart failure

- Tachypnea with mild to severe chest retraction
- Dyspnea with grunting (poor feeding in small infants)
- Wheezing and Crackle
- Orthopnea may be seen in older children

f. Signs of right heart failure

- Hepatomegaly
- Puffy eyelids
- Distend neck veins and ankle edema more common in big child and adult.

Table 3. *Severity of pediatric heart failure based on Modified Ross Heart Failure Classification in Children* [5]

Class I	Asymptomatic
Class II	Mild tachypnea or diaphoresis with feeding in infants Dyspnea on exertion in older children
Class III	Marked tachypnea or diaphoresis with feeding in infants Marked dyspnea on exertion Prolonged feeding times with growth failure
Class IV	Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest

3. Investigations

- Chest X-ray: Cardiomegaly, increased pulmonary blood flow or pulmonary edema
- Electrocardiography (ECG): not help to define CHF, sinus tachycardia

- Echocardiography: The most useful, widely available and low cost
  - Confirm an enlargement of chamber
  - Confirm impaired left ventricular function
  - To determine the cause of CHF
  - Effusion (pericardial and pleural)
- Laboratory: summary in Table 4.
- Cardiac magnetic resonance: to look for complex chds and cardiomyopathy
- Cardiac catheterization: Non-invasive diagnostic test indicated for evaluation of pressure gradients in patients with complex valve diseases and evaluation of hemodynamic parameters.
- Endomyocardial biopsy: An invasive procedure performs only for the purpose of confirm the causes of PHF such as myocarditis.

4. Differential diagnosis

- Acute respiratory distress syndrome
- Respiratory failure
- Asthma
- Cardiogenic Shock
- Chronic Bronchitis
- Pneumonia
- Pulmonary edema.

Table 4. *Laboratory test in heart failure*	
Test	**Rational**
Complete blood count	-Useful to assess anemia, which may cause or aggravate heart failure. -Leukocytosis may result from stress or signal an underlying infection.
Electrolytes	-Hyponatremia reflects an expansion of extracellular fluid volume in the setting of a normal total body sodium. -Hypokalemia and hypochloremia can be the result of prolonged administration of diuretics. -Hyperkalemia can be the result of impaired renal perfusion and marked reductions in glomerular filtration rate or from intracellular potassium release due to impaired tissue perfusion.
Renal function tests.	-Elevated BUN and BUN/creatinine ratio are seen in decompensated heart failure.
Liver function tests	-Congestive hepatomegaly is often associated with impaired hepatic function, which is characterized by elevation of AST, ALT, LDH, and other liver enzymes. -Hyperbilirubinemia (both direct and indirect) is related to acute hepatic venous congestion and is common with severe right heart failure. -Elevated ALP, and prolongation of the PTT time can be seen. In children with long-standing heart failure and poor nutritional status, hypoalbuminemia results from hepatic synthesis impairment.
Natriuretic peptides (NT-proBNP/BNP)	-Natriuretic peptides levels correlate closely with the NYHA/Ross classification of heart failure and with ventricular filling pressures.
CPK-MB, troponin I and T	-Useful if the clinical scenario is suggestive of an ischemic process or myocarditis
Lactate	-Elevated lactate is seen in patients with decompensated heart failure as a result of decreased tissue perfusion and/or decreased metabolism due to secondary liver dysfunction and can be a useful serologic marker for monitoring response to therapeutic interventions.
Thyroid function tests	-Both severe hyper or hypothyroidism can cause heart failure
Arterial blood gas	-Usually reveal mild hypoxemia in patients who have mild-to-moderate heart failure. -Severe heart failure often leads to severe hypoxemia, or even hypoxia.

	-Hypocapnia occurs in the early stages of pulmonary edema because of V/Q mismatch, progressing to hypercapnia and respiratory acidosis, related to decreased vital capacity and poor ventilation.

ALT= alanine aminotransferase; AST= aspartate aminotransferase; BNP= B-type natriuretic peptide; BUN= blood urea nitrogen; CPK-MB= creatine phosphokinase; LDH= lactic dehydrogenase; NT-pro BNP= N-terminal proBNP; PTT= prothrombin time; V/Q Z ventilation/perfusion.

V. Complication/Prognosis

- Renal failure: in chronic heart failure
- Pump failure with cardiovascular collapse
- Ventricular tachyarrhythmias or bardyarrhythmias
- Death.

VI. Treatment approach [2,4,5]

The Therapeutic of PHF approach aims to:

A. Eliminate the causes

B. Control the symptoms and disease progression.

1. Eliminate the causes

When possible, the causes of HF must be corrected through different approaches:

- Corrective treatment should be performed in chds.
- Systemic diseases (such as sepsis) or electrolytic imbalance (such as hypocalcemia) must be carefully researched and treated.

2. Control the symptoms and disease progression

a. General measure

- An infant seat or (half sitting position) is used to relieve respiratory distress.
- Humidify O2 (40%-50%) supply, cyanotic chds is not much helpful.
- Sedation with morphine sulfate 0.1-0.2mg/kg/dose IV, IM or SC if needed.
- Daily weight-necessary for hospitalized patients: Infants, caloric intake 150 kcal/kg/d small amount and frequents meals are recommended. Child and adolescent's caloric intake 25-30 kcal/kg/d is reasonable.
- Salt restriction in children(<0.5g/day) and avoid salty food.
- Fluid restriction 2/3 maintenance (D5%1/3NS, D5%1/2NS depend on electrolyte).
- Increased calorie intake.
- In anemia patient-raise hematocrit to ≥35% (See blood transfusion national guideline).

b. Medical treatment

B1)- Medical therapy focuses on 3 mains goals:

- Decrease of pulmonary wedge pressure
- Increase of cardiac output and the improvement of end organ perfusion
- Delay of disease progression.

B2)- Drugs Therapy (Summary Table 5)

- There are 3 major classes of drugs are used in the treatment of CHF in children:
  - Inotropic agents
  - Diuretics (Preload reduction) agents
  - Afterload reduction agents.
- And other drugs: Sympathetic inhibitions.
  - Diuretics Agents (preload reduction)
    - Furosemide 1-2mg/kg/dose PO, IV, IM divided in bid or tid AND/OR
    - Spironolactone 1-3mg/kg/day PO divided in bid or tid OR
    - Hydrochlorothiazide 2-4mg/kg/day PO divided in bid or tid

- Afterload reduction:
  - Captopril 0.5-6mg/kg/day PO divided in qd to qid (for infant) and 12.5mg/dose (for Children) OR
  - Enalapril 0.1mg/kg/dose qd or bid OR
  - Hydralazine 0.1-0.2mg/kg/dose IV q4-6h or 0.75-3mg/kg/day PO bid to qid OR
  - Nitroprusside 0.5-8µg/kg/min IV Infusion OR
  - Metoprolol 0.1-0.9mg/kg/dose PO bid
- Inotropic agents:
  - Epinephrine 0.1-1µg/kg/min IV infusion OR
  - Dobutamine 2-20µg/kg/min IV Infusion OR
  - Dopamine 5-10µg/kg/min IV Infusion OR
  - Milrinone 0.25-1µg/kg/min IV Infusion.
  - Digoxin dose.

Age	Total Digitalizing Dose (TDD)* (µg/kg)	Maintenance Dose** µg/kg/day
Premature	20	5
Newborn	30	8
<2yr	40-50	10-12
>2yr	30-40	8-10

** TDD: divided in 3 doses, 50% first dose then 25% in subsequence 8hours*
*** Maintenance Dose: 25% of TDD divided in 2 doses/day in <10yr and* 1 dose/day in >10yr.

a. Device therapy

Medical therapy has improved the survival and quality of life of children with HF; some patients may need device therapy: There are 2 devices: implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT).

b. Heart transplantation

Heart transplantation is an accepted treatment for patients with refractory HF.

VII. Prevention and Education

- Patient education is the most important. It is necessary to take regular medications to help prevent recurrence heart failure.

- Counsel and educate patients with heart failure following the cause, such as dietary factors or medication noncompliance with regard to the importance of proper diet.

Table 5. *Drugs used in pediatric heart failure*		
Drugs	**Routes of administration**	**Doses**
Furosemide	Oral	1-2 mg/kg q6-q12h
Furosemide	Intermittent IV bolus	0.5-2 mg/kg q6-q12h
Furosemide	Continuous infusion	0.1-0.4 mg/kg/h
Captopril	Oral	0.3-2 mg/kg q8h
Enalapril	Oral	0.05-0.25 mg/kg q12h
Losartan	Oral	0.5-1.5 mg/kg/d
Carvedilol	Oral	0.05 mg/kg/d q12h
Metoprolol	Oral	0.25 mg/kg/d q12h
Spironolactone	Oral	0.5-1.5 mg/kg q12h
Nitroglycerin	Continuous infusion	0.5-10 µg/kg/min
Nitroprusside	Continuous infusion	0.5-4 µg/kg/min
Hydralazine	Intermittent bolus	0.1-0.2 mg/kg q4-6h
Hydralazine	Oral	0.3-1 mg/kg/d q8-12h
Digoxin	Oral	5-10 µg/kg/d
Dobutamine	Continuous infusion	2.5-10 µg/kg/min
Epinephrine	Continuous infusion	0.01-0.1 µg/kg/min
Epinephrine	Intermittent bolus	0.01 µg/kg
Milrinone	Continuous infusion	0.5-1 µg/kg/min
Levosimendan	Continuous infusion	0.05-0.2 µg/kg/min

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STRUCTURAL CONGENITAL HEART DISEASE IN CHILDREN

OUNG Savly, HAV Ratneary, NGUON Yaneth, IV Malene, TEK Lyvannara

I. Key facts

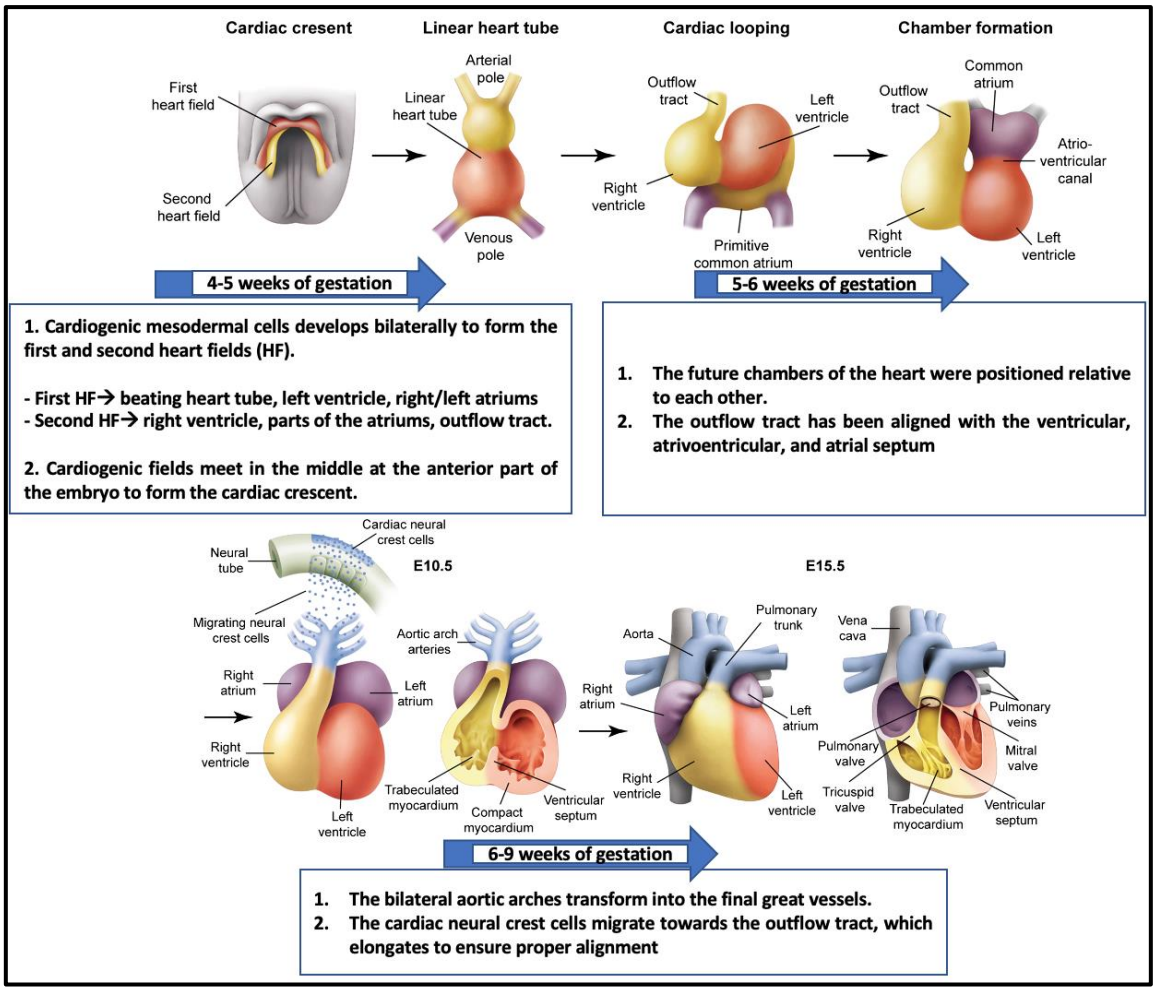
Congenital heart disease (CHD) is the most common birth defect, with an estimated incidence of 8–12 per 1,000 live births. CHD accounts for 28–50% of mortality from congenital anomalies. Advances in fetal echocardiography, neonatal screening, and surgical/interventional techniques have increased survival rates; >85% of CHD patients

now survive into adulthood. Structural chds range from simple lesions (e.g., small vsds) to complex defects requiring staged surgical palliation (e.g., HLHS). Early detection and multidisciplinary management are critical for optimal outcomes.

II. Overview

1. Definition

Structural congenital heart disease refers to malformations of cardiac chambers, septa, valves, or great vessels present at birth, resulting from abnormal cardiogenesis during the 3rd–8th week of gestation.



2. Etiology

- Genetic: Chromosomal abnormalities (Trisomy 21, 18, 13, Turner syndrome), microdeletions (22q11.2), single gene mutations.
- Environmental: Maternal infections (rubella, CMV), teratogens (alcohol, retinoic acid, lithium), uncontrolled diabetes.
- Multifactorial: Combination of genetic predisposition and environmental factors.
- Unknown: Many isolated lesions have unknown etiology.

3. Risk Factors

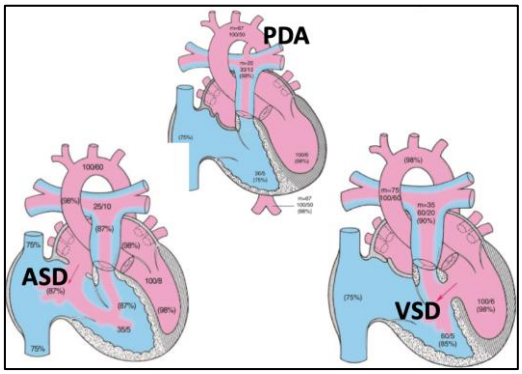
- Positive family history of CHD.
- Maternal conditions: diabetes mellitus, phenylketonuria, connective tissue disease.
- Exposure to teratogens during pregnancy.
- Assisted reproductive technology pregnancies.
- Preterm birth, low birth weight.

4. Pathophysiology

Hemodynamic consequences depend on lesion type, shunt direction, and presence of obstruction/regurgitation.

a. Acyanotic Lesions with Left-to-Right Shunt

Acyanotic congenital heart defects with left-to-right shunting are characterized by the abnormal flow of oxygenated blood from the systemic or left heart circulation into the right heart or pulmonary arterial system. The magnitude of the shunt is determined by defect size and the relative resistances of the systemic and pulmonary circulations. Small defects typically produce minimal hemodynamic effect and remain asymptomatic, whereas large defects result in significant pulmonary overcirculation, left heart volume overload, and, if untreated, may lead to congestive heart failure and progressive pulmonary vascular disease. Common defects include Ventricular Septal Defect (VSD), Atrial Septal Defect (ASD), and Patent Ductus Arteriosus (PDA). Chronic exposure of the pulmonary vasculature to increased flow may induce vascular remodeling and elevated pulmonary pressures, eventually leading to shunt reversal (Eisenmenger physiology).

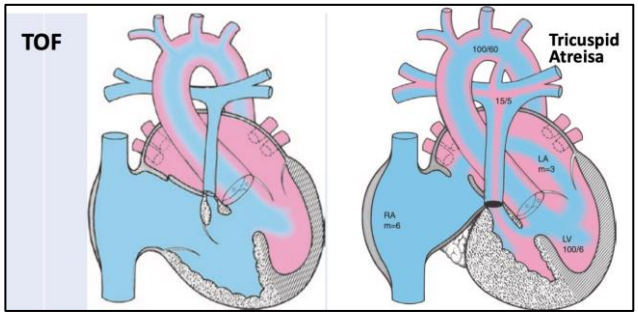


b. Cyanotic Lesions with Right-to-Left Shunt

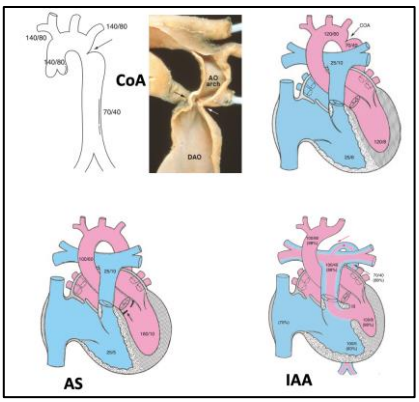
Cyanotic congenital heart defects with right-to-left shunting permit deoxygenated blood from the systemic venous or right heart circulation to bypass the pulmonary circulation and enter the systemic arterial circulation, resulting in systemic hypoxemia and cyanosis. The common cyanotic right-to-left shunt lesions include Tetralogy of Fallot, tricuspid atresia and pulmonary atresia with VSD. The magnitude of the shunt is determined by the relative resistances of the pulmonary and systemic circulations, the presence of anatomical obstructions, and the size and location of the defect. Chronic hypoxemia stimulates compensatory mechanisms including increased cardiac output and erythropoiesis, leading to secondary polycythemia.

c. Obstructive Lesions

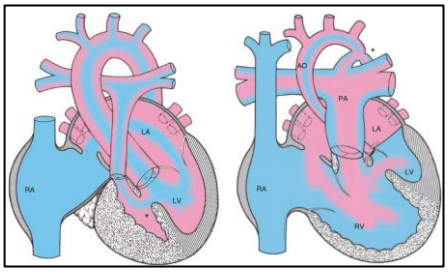
Obstructive congenital heart defects are characterized by anatomic impediments to blood flow within the heart or great vessels, resulting in pressure overload of the proximal cardiac chamber and altered systemic or pulmonary circulation. Common lesions include aortic stenosis, pulmonary stenosis, coarctation of the aorta, and sub or supravalvular obstructions. The degree of obstruction determines the severity of ventricular hypertrophy, diastolic dysfunction, and potential heart failure. Chronic pressure overload may also lead to vascular remodeling, abnormal perfusion, and neurohormonal activation.



d. Complex Lesions

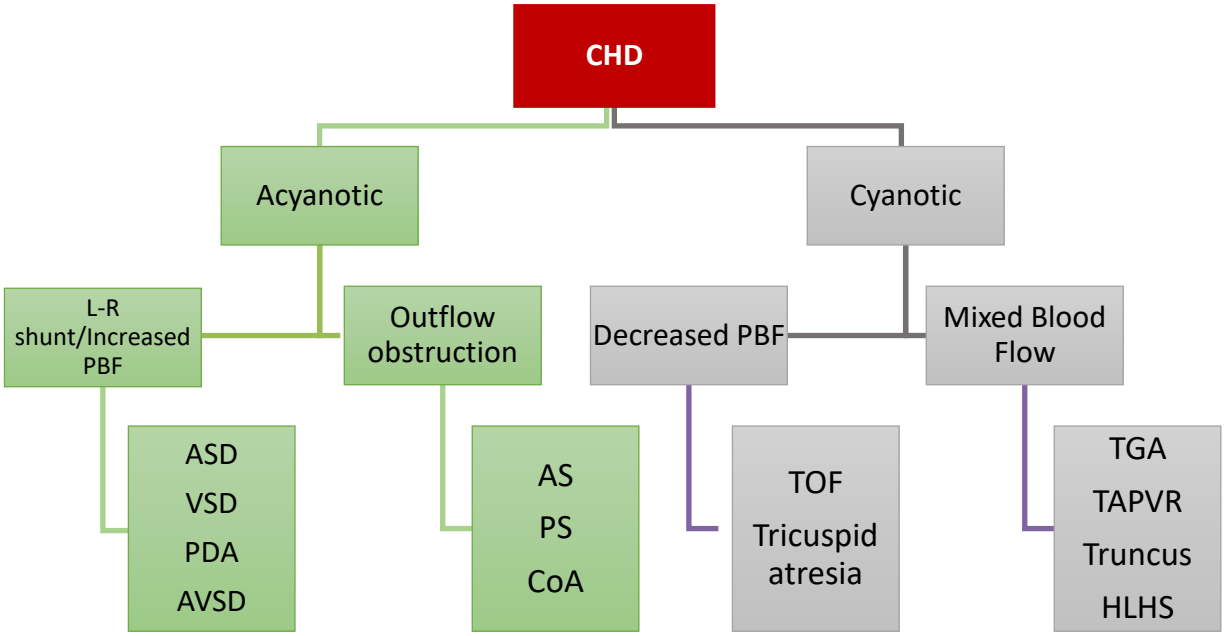


Complex congenital heart lesions, such as single ventricle physiology and heterotaxy syndromes, are characterized by mixed systemic and pulmonary blood flow, chronic volume and/or pressure overload, cyanosis, and progressive ventricular remodeling, leading to heart failure, arrhythmias, and end-organ complications.



5. Classification

Congenital heart disease (CHD) is classified using both anatomic and physiologic systems. The anatomic classification groups defects by structural complexity-simple, moderate, or great complexity, providing a framework for understanding disease severity and the need for specialized care. The physiologic classification complements this by assessing the patient's current functional status, including cyanosis, ventricular function, pulmonary hypertension, arrhythmias, and heart failure symptoms. Together, these approaches offer a comprehensive basis for risk stratification, follow-up, and management. Ultimately, this classification improves communication among healthcare providers, facilitates research, and enhances patient outcomes.



III. Signs and symptoms

1. Neonates

- Cyanosis unresponsive to oxygen (suggestive of cyanotic CHD).
- Shock or collapse after ductal closure in duct-dependent systemic flow lesions (HLHS, COA).
- Severe respiratory distress.

2. Infants

- Poor feeding, diaphoresis during feeds, failure to thrive.
- Recurrent chest infections.

3. Older Children

- Exercise intolerance, easy fatigability.
- Syncope (especially exertional or arrhythmia-related).
- Palpitations.

IV. Diagnostic evaluation

1. **Laboratory Tests**
- CBC: anemia/polycythemia.
- BNP/NT-probnp: assess heart failure severity.
- Arterial blood gases: hypoxemia, metabolic acidosis.

2. **Imaging**
- Chest X-ray: cardiomegaly, pulmonary vascular markings
- ECG: chamber enlargement, conduction disturbances
- Echocardiography: primary diagnostic tool for anatomy, function, and Doppler hemodynamics
- Cardiac MRI/CT: evaluation of complex anatomy or surgical planning
- Cardiac catheterization: diagnostic and interventional purposes

3. **Differential diagnosis**
- Persistent pulmonary hypertension of the newborn
- Respiratory causes of cyanosis
- Sepsis, metabolic disorders.

V. Complications / prognosis

- Heart failure
- Pulmonary arterial hypertension and Eisenmenger syndrome
- Arrhythmias: atrial flutter, ventricular tachycardia
- Endocarditis
- Stroke
- Prognosis depends on lesion complexity, timing of intervention, comorbidities, and access to lifelong follow-up

VI. Treatment

- Medical Therapy: diuretics, ACE inhibitors, beta-blockers, prostaglandin E1 for ductal patency
- Interventional Cardiology: device closures, balloon valvuloplasty, stenting.
- Surgical Repair / Palliation: timing based on anatomy, physiology, and patient stability
- Multidisciplinary Follow-up: growth monitoring, neurodevelopmental support, arrhythmia surveillance

VII. Management for individual common congenital heart defects

1. **Atrial Septal Defects (ASD):**

   An ASD with a left-to-right shunt associated with evidence of right ventricular volume overload (class I). Indications for ASD closure remain the same irrespective of the method of closure. [Figure 3]

2. **Isolated Ventricular Septal Defect (VSD):**

- In patients with VSD, left ventricular volume overload occurs when shunt size leads to significant left-to-right flow, resulting in LV dilation and potential heart failure.
- Aortic valve cusp prolapse may develop, particularly in perimembranous vsds, and can lead to aortic regurgitation. Surgical closure can be performed with low operative mortality (1-2%) and good long-term results.
- Transcatheter closure has become an alternative, particularly in residual vsds, in vsds that are poorly accessible for surgical closure, and in muscular vsds that are located centrally in the interventricular septum. In perimembranous VSD, it has been shown to be feasible. Whether the risk of complete AV block and entrapment of TV tissue leading to TR, or the risk of AR that has been observed in children, is relevant in adults undergoing interventional closure of a perimembranous VSD remains to be seen. [Figure 4]

3. **Patent Ductus Arteriosus (PDA):**

- For small, hemodynamically insignificant pdas with normal LV size and no pulmonary hypertension generally require only follow-up.
- Moderate pdas causing LV volume overload or mild symptoms should be closed, preferably before school age, to prevent progressive dilation.
- Large pdas causing heart failure or significant LV overload require early closure in infancy.
- Closure is also indicated at any age if complications such as endocarditis, progressive pulmonary hypertension, or left heart enlargement occur.[Figure 5]

4. **Native Coarctation of the Aorta (coa)**

- For coa with a gradient ≥20 mmhg, hypertension, or symptoms requires intervention.
- Surgical repair is preferred in neonates and young children, while balloon angioplasty ± stenting is an option in older children or adults.
- Antihypertensive therapy may be used before or after intervention.
- Lifelong follow-up is essential to monitor blood pressure, re-coarctation, and aneurysm formation. [Figure 6]

5. **Right Ventricular Outflow Tract Obstruction (RVOTO)**

- Catheter-based balloon valvotomy is recommended for patients with non-dysplastic valvular PS and with peripheral PS (often with stent implantation).
- Surgery is recommended for patients with subinfundibular or infundibular PS and hypoplastic pulmonary annulus, with dysplastic pulmonary valves, and for patients with associated lesions which need a surgical approach, such as severe pulmonary regurgitation (PR) or severe TR.
- Peripheral PS can rarely be addressed with surgery. Both surgical and catheter interventions should only be performed in centres specialized in CHD.
- In patients with subvalvular, valvular, and supravalvular PS, a markedly dilated pulmonary trunk may be present. Rupture is extremely rare in these low-pressure, highly elastic vessels and these pulmonary aneurysms generally do not require intervention. [Figure 7]

6. **Complete Transposition of the Great Arteries (TGA)**

- Neonates with D-TGA require urgent prostaglandin E1 if oxygen saturation is low, and atrial septostomy may be needed to improve mixing.
- The definitive repair is the arterial switch operation, ideally within the first 2–3 weeks of life.
- Lifelong follow-up is essential to monitor coronary patency, ventricular function, and arrhythmias. [Figure 8]

VIII. Follow-Up and Transition to Adult CHD Care

Structured follow-up according to lesion complexity:

Lesion Complexity	Recommended Follow-up Interval
Simple	Every 2-5 years
Moderate	Every 1-2 years
Complex	At least annually, preferably in a tertiary CHD center

IX. Prevention and education

- Pre-pregnancy genetic counseling for at-risk couples.

- Maternal vaccination (e.g., rubella).
- Avoidance of teratogens and optimal control of maternal comorbidities.
- Universal newborn pulse oximetry screening.
- Education for caregivers on warning signs (cyanosis, tachypnea, feeding difficulty).

X. Newborn Screening for Critical Congenital Heart Disease

Newborn Critical Congenital Heart Disease (CCHD) screening using pulse oximetry plays an important role in the timely identification of children with CCHD, in conjunction with other screening modalities such as prenatal ultrasonography, physical examinations, and genetic testing in high-risk cases. The implementation of CCHD screening using pulse oximetry has been a landmark success in public health. The CCHD screening has proven to decrease infant mortality, to be cost-effective, and to save resources. However, several opportunities remain to improve the implementation and effectiveness of CCHD screening.

Figure1. *Newborn Screening for Critical Congenital Heart Disease*

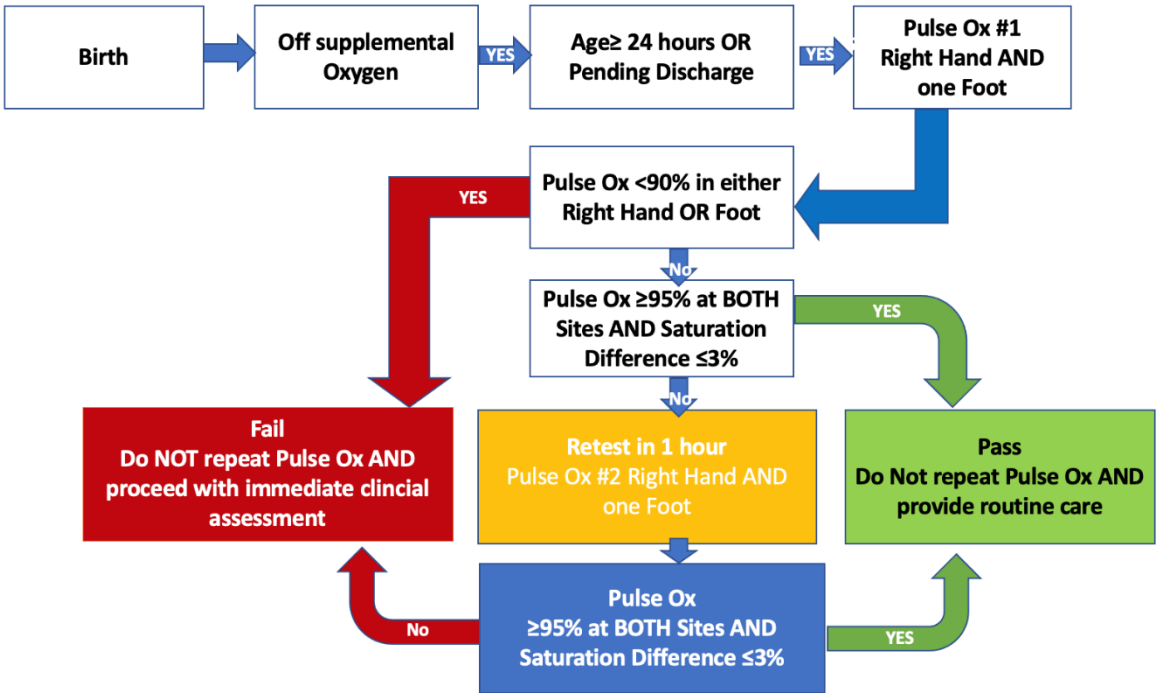


Table 1. ***Classification of Congenital Heart Disease complexity***

MILD	**MODERATE** (Repaired or unrepaired where not specified; alphabetical order)	**SEVERE** (Repaired or unrepaired where not specified; alphabetical order)
- Isolated congenital aortic valve disease and bicuspid aortic disease	- Anomalous pulmonary venous connection (partial or total)	- Any CHD (repaired or unrepaired) associated with pulmonary vascular disease (including Eisenmenger syndrome)
- Isolated congenital mitral valve disease (except parachute valve, cleft leaflet)	- Anomalous coronary artery arising from the PA	- Any cyanotic CHD (unoperated
- Mild isolated pulmonary stenosis (infundibular, valvular, supravalvular)	- Anomalous coronary artery arising from the opposite sinus	- Double-outlet ventricle
- Isolated small ASD, VSD, or PDA	- Aortic stenosis - subvalvular or supravalvular	- Fontan circulation
- Repaired secundum ASD, sinus venosus defect, VSD, or PDA without residuae or sequellae, such as chamber enlargement, ventricular dysfunction	- AVSD, partial or complete, including primum ASD (excluding pulmonary vascular disease)	- Interrupted aortic arch
	- ASD secundum, moderate or large unrepaired (excluding pulmonary vascular disease)	- Pulmonary atresia (all forms)
	- Coarctation of the aorta	- Transposition of the great arteries (except for patients with arterial switch operation)
	- Double chambered right ventricle	- Univentricular heart (including double inlet left/right ventricle, tricuspid/mitral atresia, hypoplastic left heart syndrome, any other anatomic abnormality with a functionally single ventricle)
	- Ebstein anomaly	- Truncus arteriosus
	- Marfan syndrome and related HTAD, Turner Syndrome	- Other complex abnormalities of AV and ventriculoarterial connection (i.e. Crisscross heart, heterotaxy syndromes, ventricular inversion).
	- PDA, moderate or large unrepaired (excluding pulmonary vascular disease)	
	- Peripheral pulmonary stenosis	

MILD	MODERATE (Repaired or unrepaired where not specified; alphabetical order)	SEVERE (Repaired or unrepaired where not specified; alphabetical order)
	- Pulmonary stenosis (infundibular, valvular, supravalvular), moderate or severe	
	- Sinus of Valsalva aneurysm/fistula	
	- Sinus venosus defect	
	- Tetralogy of Fallot À repaired	
	- Transposition of the great arteries after arterial switch operation	
	- VSD with associated abnormalities (excluding pulmonary vascular disease) and/or moderate or greater shunt.	

Figure 2. *Diagnostic Pathway for Suspected Congenital Heart Disease in Neonates*

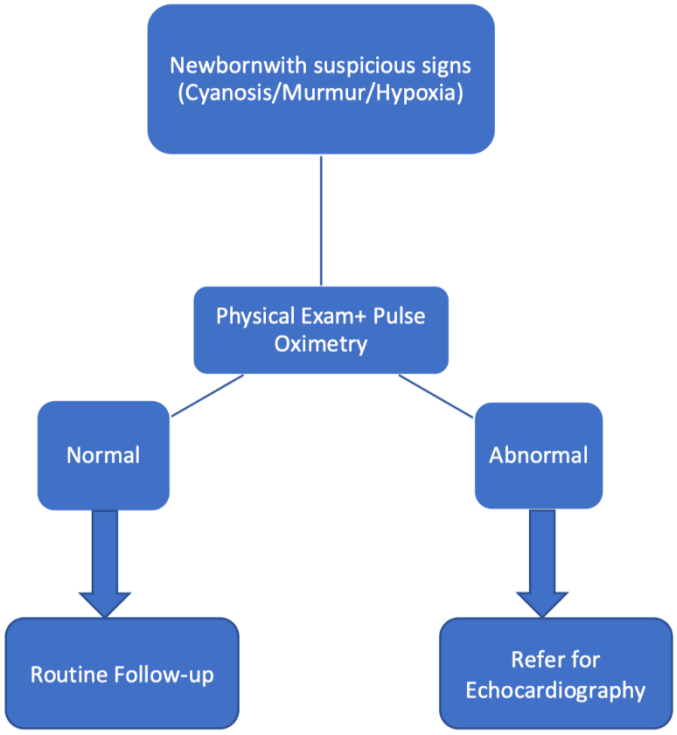


Figure 3. *Management of Atrial Septal Defect.*

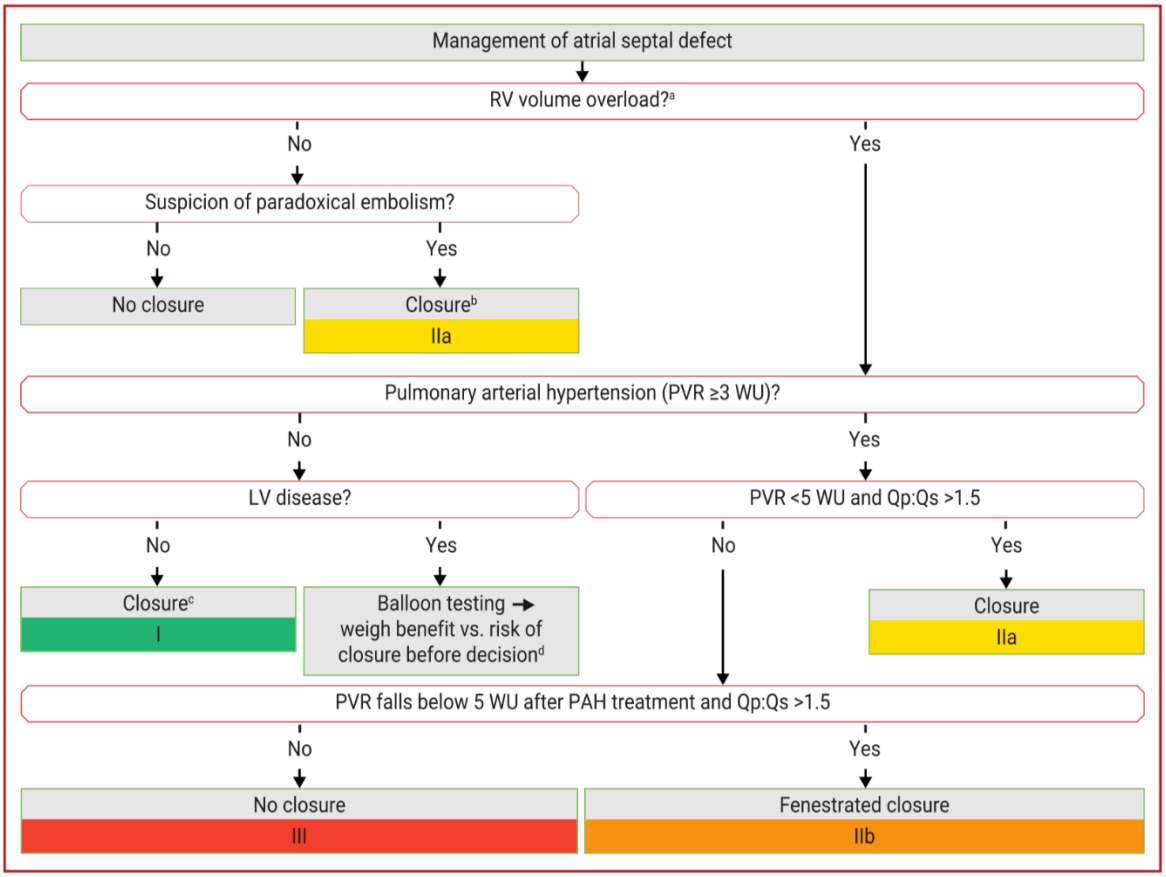


Figure 4. *Management of Ventricular Septal Defect*

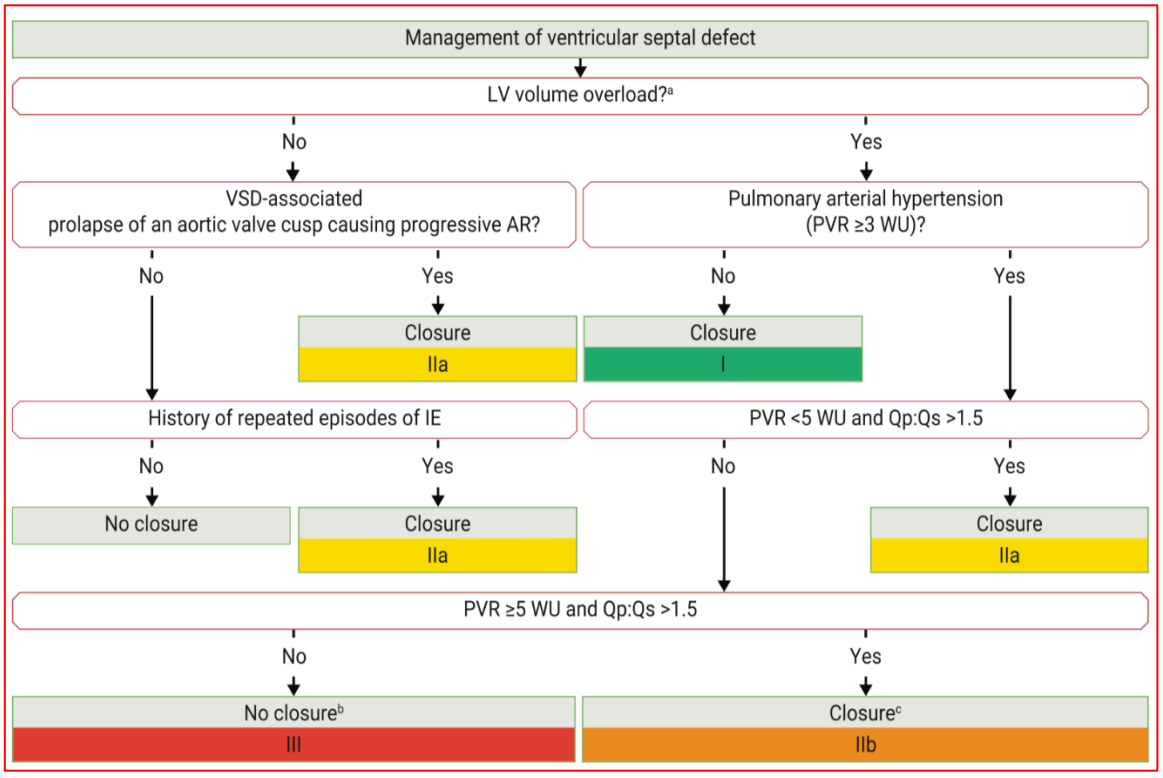
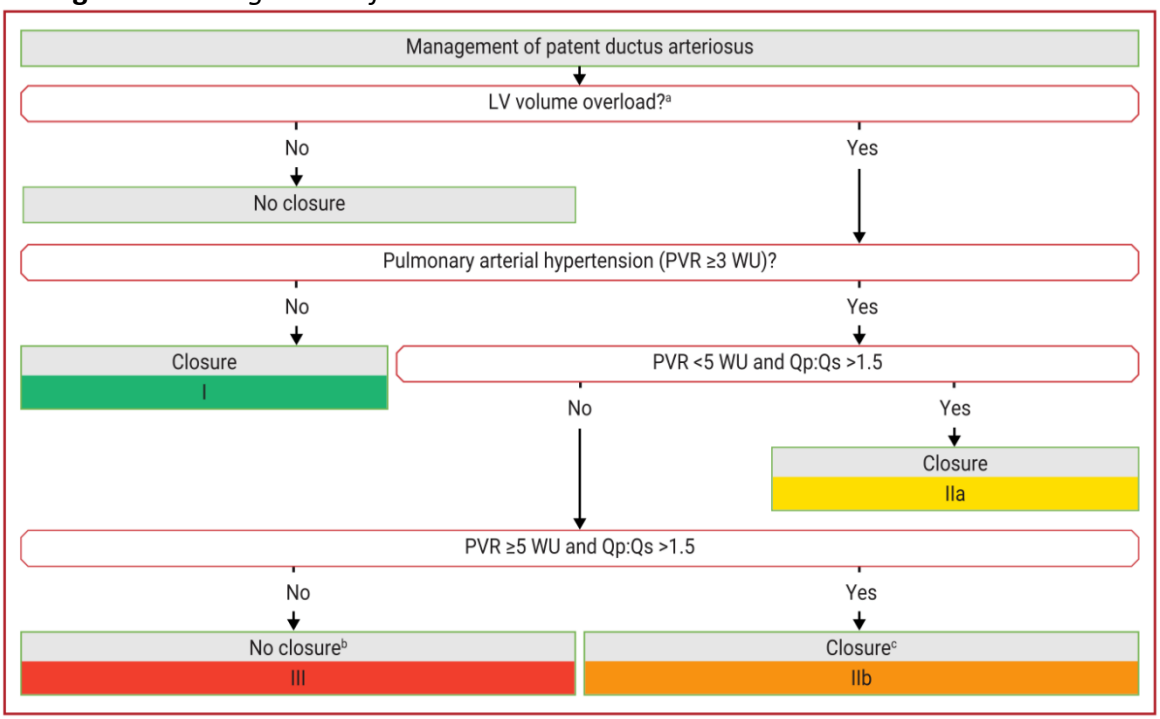


Figure 5. *Management of Patent Ductus Arteriosus*



❖ Abbreviation

ASD = atrial septal defect; AV = atrioventricular; AVSD = atrioventricular septal defect; CHD = congenital heart disease; HTAD = heritable thoracic aortic disease; LV = left ventricle/ventricular; PA = pulmonary artery; PAP = pulmonary artery pressure; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

ASD = atrial septal defect; PS = pulmonary stenosis; R–L = right-to-left; RV = right ventricle/ventricular; RVOTO = right ventricular outflow tract obstruction; RVSP = right ventricular systolic pressure; TR = tricuspid regurgitation; VSD = ventricular septal defect.

[a]In peripheral PS, regardless of symptoms, catheter interventional treatment should be considered if >50% diameter narrowing and RVSP >50 mmHg and/or related reduced lung perfusion is present.

[b]In valvular PS, balloon valvuloplasty is the intervention of choice if anatomically suitable.

Figure 6. *Management of Coarctation of Aorta*

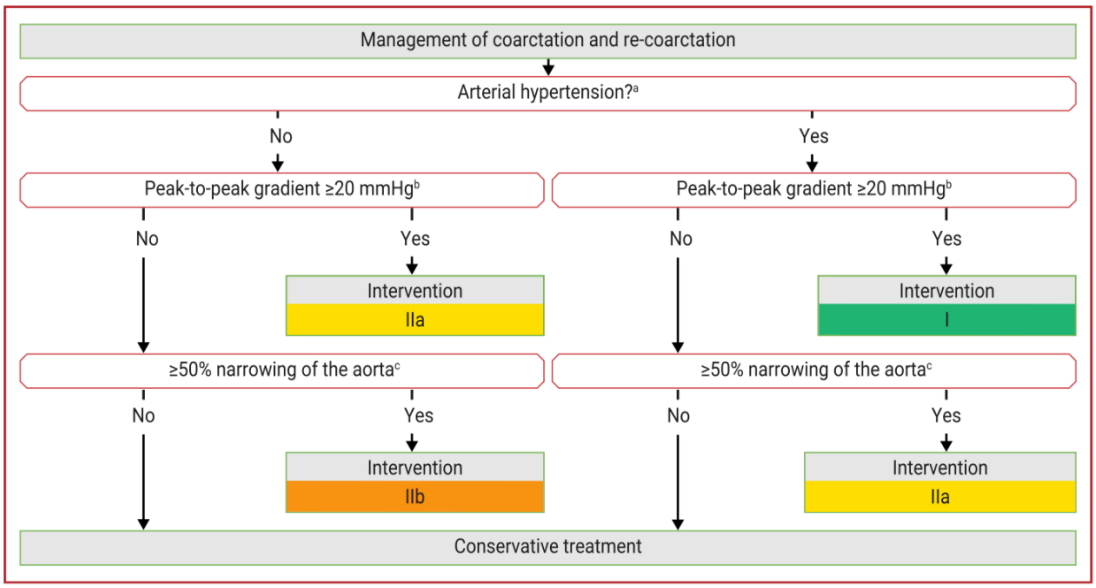


Figure 7: *Management of Right Ventricular Outflow Tract Obstruction*

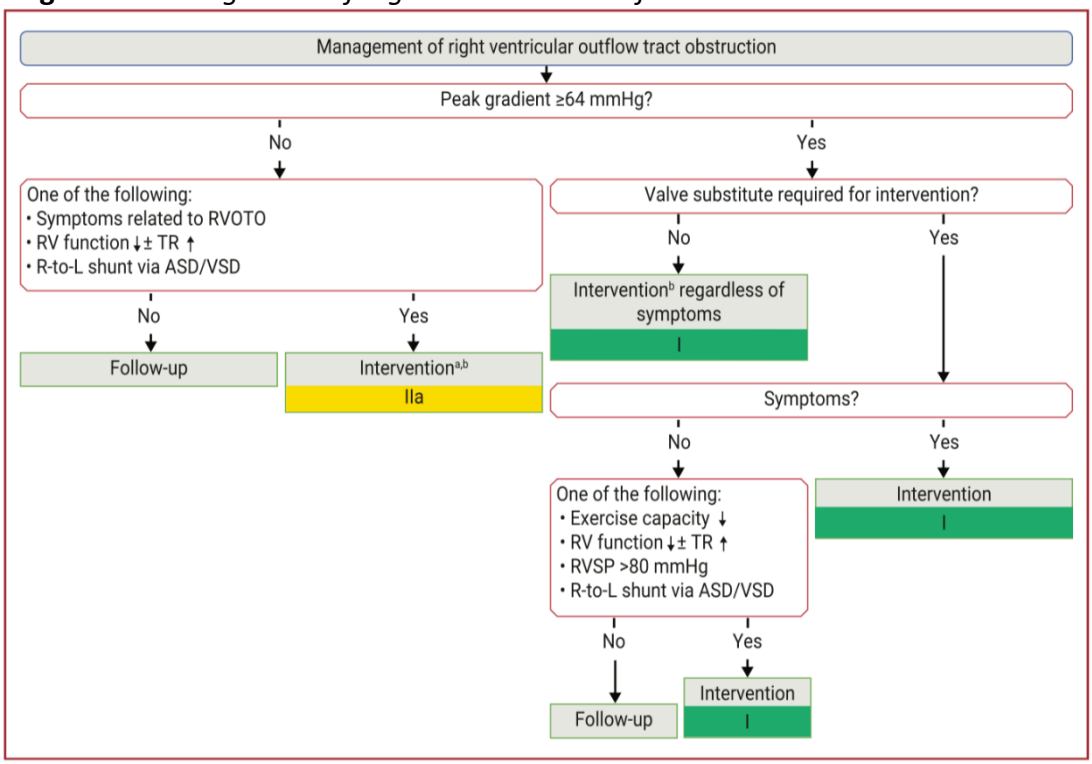
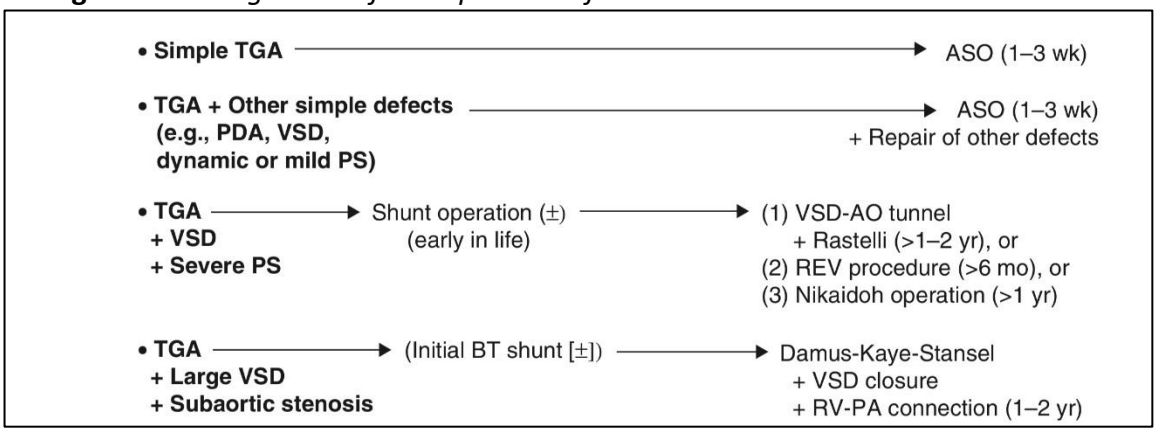


Figure 8. *Management of Transposition of the Great Arteries*



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VALVULAR HEART DISEASES IN CHILDREN

OUNG Savly, HAV Ratneary, NGUON Yaneth, IV Malene, TEK Lyvannara

I. Key Facts

Valvular heart disease (VHD) in children is primarily rheumatic in origin in low- and middle-income countries, while congenital valvular defects are more prevalent in high-income regions. Rheumatic heart disease (RHD) affects nearly 39 million individuals worldwide, causing over 300,000 deaths annually, predominantly among young populations in Asia-Pacific and Africa. The mitral valve is most commonly affected (~75%), followed by the aortic valve (~25%), whereas tricuspid and pulmonary valve involvement is rare. Childhood progression is often gradual, but significant morbidity typically emerges in adolescence and early adulthood.

II. Overview

1. Definition

Structural or functional abnormality of heart valves causing stenosis, regurgitation, or mixed lesions, leading to impaired hemodynamics, ventricular remodeling, and eventual heart failure.

2. Etiology

a. Congenital

- Congenital causes dominate in children from high-income countries; left-sided valves (mitral, aortic) are most commonly affected.
- Isolated valvular malformations (bicuspid aortic valve, parachute mitral valve, dysplastic valves)
- Associated with other chds (VSD, TOF, truncus arteriosus)

b. Acquired

- Acquired causes include rheumatic fever and infective endocarditis; prevalence is higher in low/middle income countries
- Rheumatic heart disease
- Infective endocarditis
- Post-surgical or post-interventional changes

c. Genetic / Connective Tissue Disorders

Genetic / connective tissue disorders (Marfan, Loeys-Dietz, Ehlers-Danlos) are important for progressive valvular regurgitation and multivalvular involvement.

3. Risk Factors

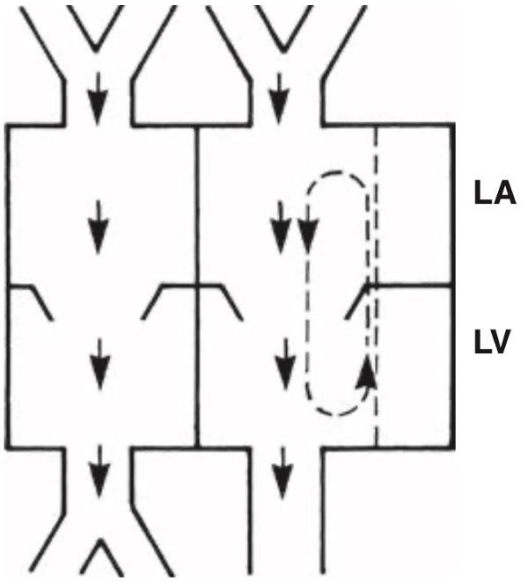
- History of congenital valvular disease
- Maternal rubella, diabetes, lupus, teratogenic drugs
- Recurrent streptococcal pharyngitis (RHD risk)
- Socioeconomic factors affecting access to healthcare.

4. Pathophysiology

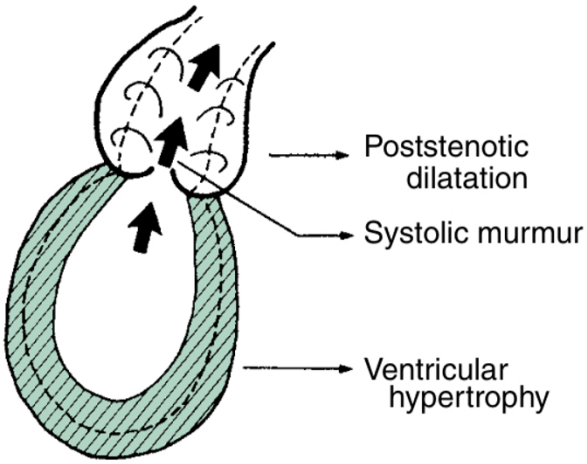
In children, valvular heart disease causes either pressure overload (stenosis) or volume overload (regurgitation), leading to adaptive ventricular remodeling. The pressure overload induces concentric hypertrophy, while volume overload causes eccentric hypertrophy with chamber dilation.

Initially, these adaptations preserve cardiac output, but chronic or severe lesions eventually result in ventricular dysfunction, heart failure, and arrhythmias.

Moreover, the left and right-sided valves differ in hemodynamic impact, but the underlying principle of maladaptive remodeling applies to all.

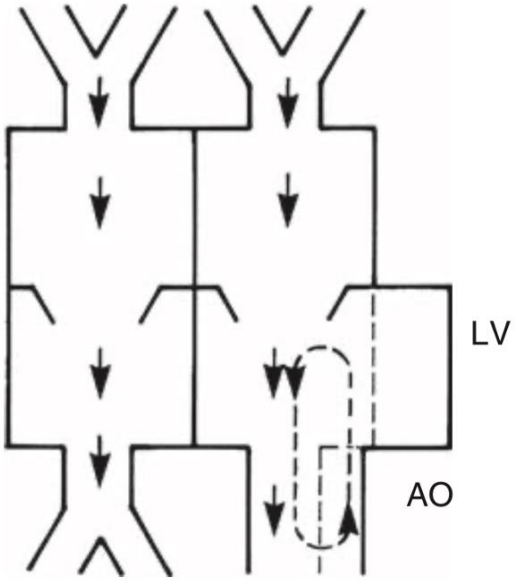


Hemodynamic changes in Mitral Regurgitation

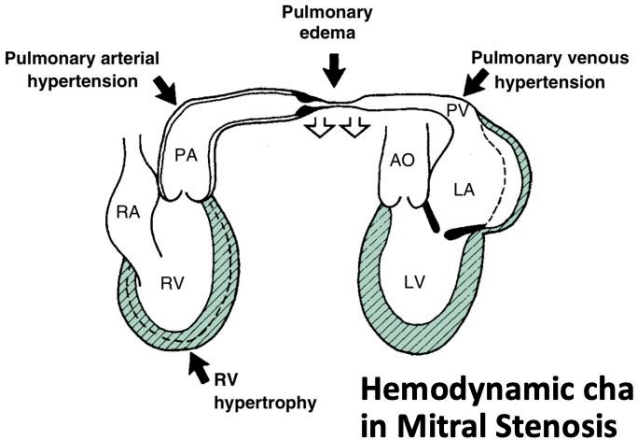


Three secondary changes in Aortic Valve and Pulmonary Valve stenosis:

1. **Hypertrophy of the responsible ventricle**
2. **Poststenotic dilatation of a great artery**
3. **Ejection systolic murmur**



Hemodynamic changes in Aortic Regurgitation



Hemodynamic changes in Mitral Stenosis

III. Signs and Symptoms

Many children with valvular heart disease are asymptomatic, particularly in mild cases. Careful assessment of murmur characteristics, pulse abnormalities, and ventricular impulse is crucial for early detection. Serial clinical evaluation, combined with echocardiography, guides the timing of intervention. The presence of chamber enlargement, exercise intolerance, or heart failure signs indicates moderate-to-severe disease requiring closer monitoring or treatment.

Valve	Lesion	Typical Symptoms	Key Physical Findings / Murmur
Mitral	Stenosis (MS)	- Fatigue, exercise intolerance, growth delay - Children with mild MS are asymptomatic. With significant MS, dyspnea with or without exertion is the most common symptom in older children. - Orthopnea, nocturnal dyspnea, or palpitation is present in more severe cases.	- A loud S1 (apex) and a narrowly split S2 with loud P2 if pulmonary hypertension is present [Fig.1]. - Opening snap and a low frequency mitral diastolic rumble (apex) - A crescendo presystolic murmur may be audible at the apex. - High-frequency diastolic murmur of PR (Graham Steell murmur) is present at the ULSB in patients with pulmonary hypertension.
	Regurgitation (MR)	Most children with mild MR are asymptomatic; some may report fatigue or palpitations with exertion.	- Widely split S2 due to - Shortened LV ejection; loud S3 is frequently present. - Murmur: The hallmark finding is a grade 2–4/6 holosystolic regurgitant murmur at the apex, radiating to the left axilla, best heard in the left lateral decubitus position [Figure 2]. - Additional finding: A short, low-frequency mid-diastolic rumble at the apex may accompany significant MR due to increased diastolic inflow.
Aortic	Stenosis (AS)	- Exertional fatigue, syncope, chest pain - Mild to moderate AS are asymptomatic - Severe AS are exertional chest pain or syncope - Critical AS develops CHF within the first few months of life - Blood pressure is normal in most patients, but a narrow pulse pressure is present in severe AS.	- Systolic thrill → RUSB, suprasternal notch, or carotids. - Ejection click → typical in valvar AS. - Harsh systolic ejection murmur (grade 2–4/6) → best at 2RICS/3LICS, radiating to neck and apex [Fig. 3]. - Early diastolic decrescendo murmur (AR) → may occur in bicuspid valve or

Valve	Lesion	Typical Symptoms	Key Physical Findings / Murmur
			discrete subvalvar stenosis. - Critical neonatal AS → murmur may be faint/absent; pulses weak and thready.
	Regurgitation (AR)	Often asymptomatic; dyspnea or exercise intolerance if severe	- Wide pulse pressure (water hammer), bounding pulses - Laterally displaced, hyperdynamic apex - Early diastolic at LSB; holodiastolic if severe - Austin Flint if mid-late diastolic [Fig. 4]
Tricuspid	Stenosis (TS)	Fatigue, hepatomegaly, peripheral edema	Diastolic murmur at lower left sternal border
	Regurgitation (TR)	- Mild cyanosis (±) - Hepatomegaly with pulsatile liver and neck vein distention when severe	- Regurgitant systolic, grade 2-3/6 - Holosystolic murmur at lower left sternal border
Pulmonary	Stenosis (PS)	- Asymptomatic - Dyspnea on exertion, fatigue - Cyanosis, right to left shunt if critical stenosis	- Harsh systolic ejection murmur at upper left sternal border; thrill often present - Click after S1, split S2 - Soft/absent murmur if critical, dependent on PDA; may require PGE1
	Regurgitation (PR)	- Most children with PR are asymptomatic unless significant RV dilatation develops. - Eexercise intolerance, fatigue, or signs of right heart failure in advanced disease.	- Murmur quality: A low-pitched, decrescendo diastolic murmur best heard along the left sternal border, starting after S2. - Effect of pulmonary hypertension: The murmur becomes high-pitched and closely mimics aortic regurgitation. - Radiation: Unlike AR, the PR murmur radiates toward the right ventricular outflow and pulmonary area, not the apex.

IV. Diagnosis

1. Clinical Assessment

a. History

- Symptom onset, duration, and severity
- Past medical history (rheumatic fever, endocarditis)
- Family history of congenital/genetic syndromes

b. Physical Examination

- Heart sounds & murmurs: timing, intensity, location, radiation
- S2 splitting, S3/S4 for ventricular function assessment
- Peripheral pulses: bounding, weak, delayed
- Signs of congestion or heart failure: hepatomegaly, edema
- Growth and development: weight, height, and developmental milestones
- Careful evaluation of murmur timing, intensity, radiation, pulse quality, and ventricular impulses provides early clues to lesion type and severity.

2. First-line investigations

Transthoracic echocardiography (TTE)

- TTE is the gold standard for defining valve anatomy, lesion severity, associated congenital heart disease, and ventricular remodelling.
- Doppler assessment quantifies pressure gradients in stenotic lesions and regurgitant volume/fraction in insufficiency.
- Serial echocardiography is mandatory to track progression, assess ventricular adaptation, and guide timing for intervention

3. Adjunctive Imaging

- Cardiac MRI (CMR): Provides precise measurement of regurgitant fractions, chamber volumes, and ventricular function, particularly in children with suboptimal echocardiographic windows or complex lesions.
- CT angiography: Reserved for complex anatomy or surgical planning.

4. Additional Investigations

- Electrocardiogram: Detects chamber enlargement, conduction abnormalities, or arrhythmias.
- Chest radiography: Assesses cardiac silhouette, chamber enlargement, or post-stenotic aortic dilation.
- Cardiac catheterization: Indicated only for hemodynamic evaluation, complex lesions, or pre-interventional planning.

5. Laboratory Tests

CBC, ESR/CRP, ASO titer (RHD screening), Blood cultures (suspected endocarditis), BNP/NT-probnp for heart failure evaluation.

❖ ***Severity Classification***

- Severity should be based on echocardiographic parameters and clinical impact
- Stenosis: valve gradient, valve area
- Regurgitation: vena contracta width, regurgitant fraction
- Clinical correlation: symptom presence and ventricular adaptation.

Severity	Key Features
Mild	Minimal hemodynamic impact, asymptomatic, normal ventricular function

Moderate	Hemodynamically significant, mild symptoms, early ventricular adaptation
Severe	Symptomatic, marked ventricular remodelling, high risk of complications

❖ ***Differential diagnosis***

Cardiomyopathy, Pericardial disease, Pulmonary hypertension.

V. Complications

- Heart failure,
- Arrhythmias (AF, VT, complete heart block),
- Infective endocarditis,
- Pulmonary hypertension,
- Sudden cardiac death,
- LV/RV dysfunction,
- Growth retardation.

VI. Management

1. Initial Management at Diagnosis

- Mild lesions: periodic follow-up
- Moderate/severe lesions: referral to pediatric cardiology and/or surgical center
- Supportive care: manage heart failure, arrhythmias, growth failure
- Preventive measures: endocarditis prophylaxis when indicated
- Genetic evaluation: for suspected syndromic or connective tissue disorders.

2. Medical Therapy

- Diuretics for congestion,
- ACE inhibitors/arbs for regurgitation with LV dysfunction,
- B-blockers for symptomatic AS,
- Antibiotic prophylaxis for high-risk patients.

3. Interventional/Surgical Indications

a. Aortic Stenosis (AS)- Class I Recommendations

- Immediate (Class I): Newborns with duct-dependent AS; LV dysfunction from severe AS → balloon/surgery.
- Elective (Class I): Peak >64 mmhg or mean >40 mmhg; symptomatic with invasive gradient ≥40 mmhg.
- Selective (Class iib): Asymptomatic, invasive gradient ≥40 mmhg, wants strenuous sports.
- Avoid (Class III): Preexisting AR > mild.

b. Pulmonic Stenosis (PS)-Class I Recommendations

- Immediate Intervention
  - Newborns with duct-dependent severe PS → balloon/surgery.
  - Any age with RV dysfunction from severe PS, regardless of gradient.
- Elective Balloon Dilation: Symptomatic or asymptomatic PS with peak gradient >64 mmhg.
- Selective Intervention (Class iia):
  - Neonates/infants with PS + hypoxia due to mild RV hypoplasia.
  - Dysplastic valves meeting above criteria.
  - Mode of Intervention:
    - Balloon dilation preferred (Class I).
    - Surgery for subvalvar/supravalvar PS, failed balloon, Noonan syndrome with hypoplastic annulus (Class I).

c. Mitral Stenosis (MS)-Class I:

- Surgery (repair, commissurotomy, or replacement) indicated in severely symptomatic (NYHA III–IV) patients with severe MS (MVA ≤1.5 cm^2, Stage D) who are not candidates for or have failed balloon commissurotomy, and are not high surgical risk.

- MVR preferred if valve thickening, fibrosis, or leaflet tethering present.
- Surgery also favored if concomitant moderate/severe TR requiring repair.
- Timing: delayed until severe limiting symptoms, as LV function usually preserved in MS.

d. Mitral Regurgitation (MR)

- Class I: Symptomatic moderate-to-severe MR with LVEF >30% → surgery.
- Class IIa:
  - Asymptomatic severe MR if:
    - LVEF <60%
    - LV end-systolic dimension Z-score >3 (for MVR) or >2.5 (if repair likelihood >95%)
    - Pulmonary artery systolic pressure >50 mmhg
  - Moderate/severe MR in patients undergoing other cardiac surgery.
- Class IIb: Symptomatic moderate-to-severe MR with LVEF <30% → consider surgery.

e. Aortic Regurgitation (AR)

- 3.5.1 Class I: Valve repair preferred whenever feasible.
- 3.5.2 Class iia: Valve replacement if repair not possible.
  - Ross procedure: young patients with non-rheumatic AR, if surgical expertise available.
  - Bioprosthesis: women planning pregnancy; patients with poor anticoagulation compliance.
  - Mechanical valve: default choice for others.

f. Pulmonary Regurgitation (PR)

- Class I: Symptomatic patients with severe PR and RV volume overload.
- Class iia: (Asymptomatic, if ≥2 criteria present)
  - RV or LV dysfunction (mild–moderate).
  - Severe RV dilatation:
    - RVEDV >160 ml/m² or RVESV >80 ml/m², or
    - RVEDV >2× LVEDV.
  - RV systolic pressure ≥⅔ systemic (due to RVOT obstruction).
  - Progressive decline in exercise capacity.

g. Tricuspid Stenosis (TS) – Class I Recommendations

- During left-sided valve surgery:
  - Surgery recommended for severe TS.
  - Repair preferred; replace if repair not feasible.
  - Higher risk with combined mitral + tricuspid surgery.
- Isolated symptomatic severe TS:
  - Surgery preferred over balloon commissurotomy.
  - Reduces right atrial/systemic venous pressures and symptoms.
  - Outcomes depend on RV function.

h. Tricuspid regurgitation (TR)

- Class I: Severe TR (stage C/D) → surgery at time of left-sided valve surgery.
- Repair preferred, replacement if not feasible.
- Prosthesis choice individualized (mechanical vs tissue).
- Caution: Severe RV dysfunction or irreversible PH → risk of RV failure.

VII. Follow-up and Education

- Mild lesions: yearly echocardiography
- Moderate lesions: every 6–12 months
- Severe lesions or post-intervention: every 3–6 months, individualized

- Educate caregivers on infection prevention, signs of heart failure, growth/activity monitoring
- Transition to adult congenital cardiology for long-term follow-up.

Figure 1. *Cardiac finding of Mitral Stenosis*

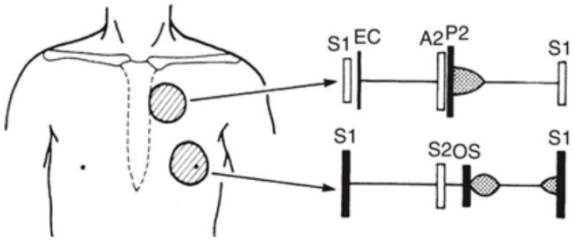


Figure 2. *Clinical finding in Mitral*

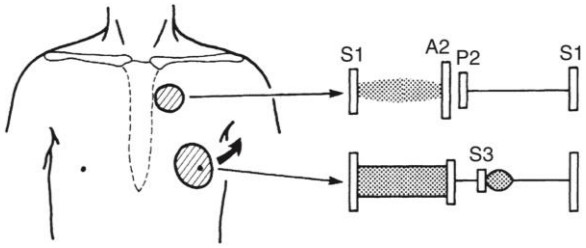


Figure 3. *Clinical finding in Aortic Valve Stenosis Regurgitation*

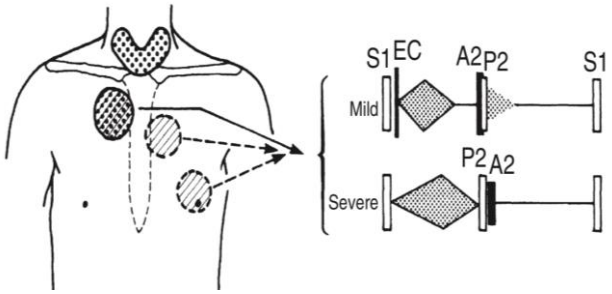
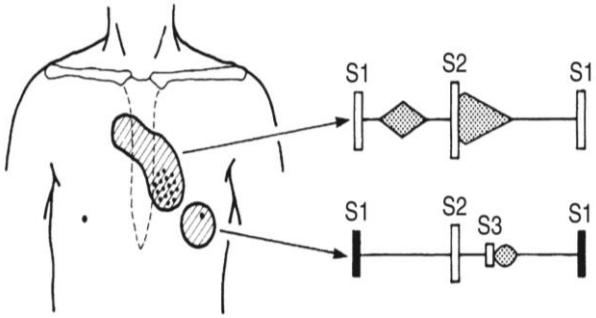


Figure 4. *Clinical finding in Aortic*



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Chapter VII: Renal system diseases

ACUTE POSTSTREPTOCOCCAL GLOMERULONEPHRITIS IN CHILDREN

HIM Sotheara, TEK Lyvannara, NGOUN Yaneth

I. Key Facts

Acute post-streptococcal glomerulonephritis (APSGN) is a major cause of acute glomerulonephritis among children between 3 to 12 years. [2, 7]. The estimated global incidence of APSGN is 472 000 cases per year with 77% of the cases from the low- and middle- income countries. The rate of APSGN has decreased over the last few decades in high-income countries due to the use of antibiotics, improved socio- economic status, and hygiene. The reported estimate annual incidence of APSGN is 9.3cases per 100 000 person in developing countries. [2, 7] The infection occurred during dry and rainy seasons. The clinical presentation of APSGN varies from asymptomatic, microscopic hematuria, proteinuria, edema, hypertension, and acute kidney injury. The prognosis is generally favorable, especially in children, but in some cases, the prognosis is not benign. [3, 7]

II. Overview

1. Definition

APSGN is an autoimmune inflammation of the renal glomerular. APSGN primarily affects children aged between 3 and 12 years. APSGN is uncommon in children less than three years of age. APSGN is more common in males than in females. It follows streptococcal pharyngitis during cold seasons and streptococcal skin infections or pyoderma during hot seasons [1]

2. Etiology and Pathogenesis

APSGN is caused by prior infection of the skin (Impetigo) or throat (pharyngitis) with specific nephritogenic strains of group A beta-hemolytic streptococcus. [1] APSGN is formation by immune complex containing the streptococcal antigen deposit within basal membrane of glomerulus, result in complement activation and subsequent damage to the glomerulus, induce chemoattractant and inflammatory response in the mesangial and endocapillary sites [12,13]. The two leading candidates for nephritogenic antigens are nephritis-associated plasmin receptor (naplr) and streptococcal pyrogenic exotoxin B (spe B). [3]

III. Signs and symptoms

The severity of renal involvement varies from asymptomatic microscopic hematuria with normal renal function to acute renal failure. Depending on the severity of renal involvement, patients may develop various degree of edema, hypertension and oliguria. Patients may develop encephalopathy or heart failure owing to hypertension or hypervolemia [1]. Encephalopathy may also result from the direct toxic effects of the streptococcal bacteria on the central nervous system.

Nonspecific symptoms of APSGN such as malaise, lethargy, abdominal pain and fever. Acute subglottic edema and airway compromise have been reported. The acute phase resolves within 6-8 weeks. Although urinary protein excretion and hypertension normalize by 4- 6 weeks after onset, persistent microscopic hematuria may persist for 1-2 years after the initial presentation. [1, 6]

IV. Diagnosis

APSGN is usually diagnosed based upon clinical findings of acute nephritis and demonstration of a recent group A beta- hemolytic streptococcal (GAS) infection. [3]

- The clinical findings of acute nephritis include: edema, hematuria, proteinuria, oliguria and hypertension. [3,7]
- The evidence of invasive streptococcal by positive throat or skin culture

- Anti-steptolysine O(ASLO) elevated after a pharyngeal infection but rarely increase after skin infection) [1, 4]
- Low C3 level and CH50

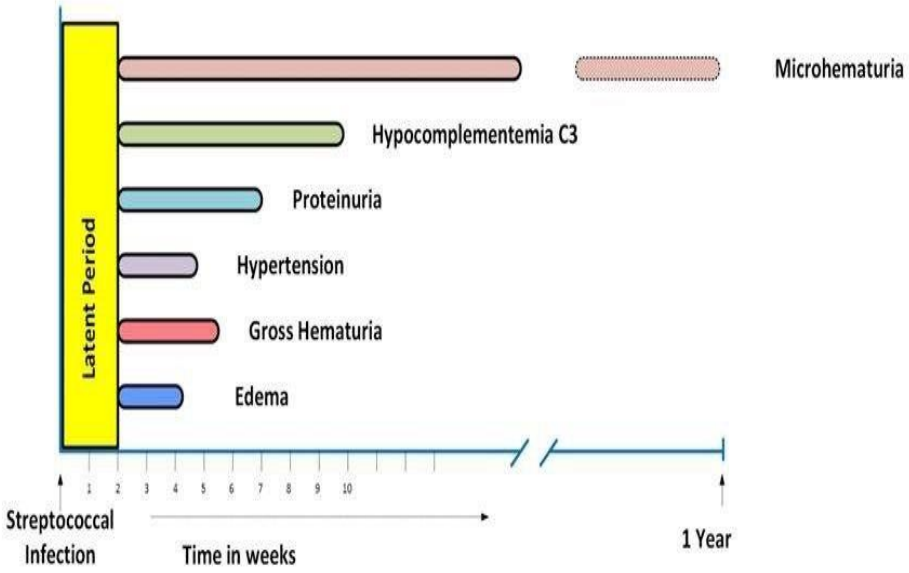

Figure1. *Time course of clinical and laboratory manifestation of Post-streptococcal glomerulonephritis.*

1. Laboratory

- Urine analysis:
  - Macroscopic or microscopic hematuria
  - Proteinuria (varying degree)
  - Red blood cell casts (pathognomonic)
- Blood analysis:
  - Renal function test: Variable BUN, creatinine and electrolytes
  - Protide and lipide are normal
  - Bacteriological: Increase ASLO (> 200IU/ml), Throat swab or skin swab
  - Complement levels: C3 level low, normalize by 6 weeks.
  - C4 normal limits
  - Full blood count: Anemia (mainly dilution). Leukocytosis may be present.

2. Imagery

- Ultrasound of the kidneys: normal or renal enlargement in some case.
- Chest radiology: some time show pleural effusion, pulmonary edema.

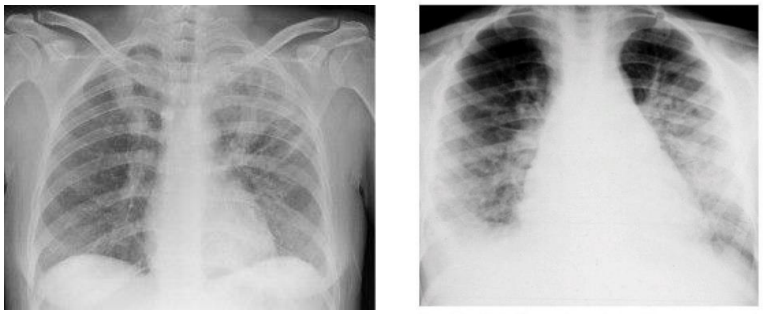

Figure 2. *Chest X-ray of a patient with post- streptococcal Glomerulonephritis showing pulmonary edema.*

3. Differential diagnosis

- Iga Nephropathy: usually occurs after an upper respiratory tract or gastrointestinal infection, but it differs from PSGN in the shorter latency period it takes to appear after the episode of infection. It can also be described as synpharyngitic hematuria and infection coincide.
- Membranoproliferative glomerulonephritis: also presents with a nephritic picture and hypocomplementemia following respiratory tract infection. Complement levels take a longer time to return to normal than in PSGN or persistently low C3 levels.
- Lupus nephritis: sometimes PSGN presents with a picture similar to lupus nephritis. Laboratory testing for antibodies specific to each of the diseases can help in the diagnosis. Positive ANA, ds-DNA, cytopenia, and multi-organ involvement.
- Nephrotic syndrome: 24-hour urine protein excretion is more than 3.5 gram/day along with hypoalbuminemia, edema, hypogammaglobulinemia, and increased risk of thrombosis (due to loss of pro-coagulants).
- Henoch Schonlein purpura (HSP): The typical presentation is palpable purpura, renal failure, gastrointestinal and musculoskeletal manifestations. Have normal complement levels.
- Hemolytic uremic syndrome (HUS): Labs consistent with Hemolysis (schistocytes, LDH, reticulocyte count, indirect bilirubin), bloody diarrhea, thrombocytopenia, stool culture for Escherichia coli O157: H7
- Goodpasture disease: Involves lung and kidneys. Have anti-glomerular basement antibody and normal complement levels.

V. Treatment

1. Monitoring

- Bed rest and immobilization are recommended in the first few days of the disease
- Fluid input and output to control oedema and circulation in acute phase
- All children should be weighed daily.
- All patients should be low salt diet <2g/day
- Fluid restriction: to control oedema and circulatory overload during oliguric phase
    - Day1: debit up to 400ml/m2/day (Do not Intravenous or oral fluid)
    - Day 2: debit still 400ml/m2/day (if patient in overload phase)
    - If patient have diuresis free fluid is allow [1]

2. Management

a. Hypertension

- Management of oedema and volume overload
- Check blood pressure closely
- Treat fluid overload which is the usual cause
    - Furosemide: dose 1-2mg/kg/dose (IV/PO) bid or tid
- Anti- hypertensive: in severe case:
    - Angiotensin-converting enzyme inhibitor (ACEI) :(Risk of hyperkaliemia):
        - Captopril 0.3-0.5mg/kg/dose or tid or qid (PO), adolescent:25mg bid or tid (Max 150mg)
        - Enalapril maleate: child 0.05-0.15mg/kg/dose (PO) qd or bid, adolescent 2.5mg-5mg qd or bid (Max 40mg/d)
    - Calcium channel blocker: Nifedipine (Adalate 0.25mg-0.5mg/kg/dose) (PO) tid or qid: when there was no response
    - Angiotensin receptor blockers (arbs): Use in stable GFR and normal potassium: . Lorsartan 0.75mg/kg/dose qd (PO)
    - Vasodilator: Hydralazine 0.1mg-0.2mg/kg/dose (IM/IV) q4-q6

0,75mg-3mg/kg/day (PO) q6-q12 [14]

- Beta-Blocker: Atenolol 0.5-1mg/kg/day (once daily) when there was no response

b. Pulmonary oedema

- Give oxygen, ventilation if necessary
- Furosemide 1-2mg/kg/dose (Max 40mg)
- Fluid restriction
- Dialysis (to manage acid-base balance, electrolyte abnormality, fluid management)

c. Acute Kidney Failure

- Fluid management
- Electrolyte management: hyperkaliemia, metabolic acidosis, hyperphosphatemia and hypocalcemia
- Hypertension
- Nutrition support
- Drug management.

d. Antibiotics

- Phenoxymethyl Penicillin (Penicillin V): Dose 4 time /d for 10days, (1-5yr 125mg,
- 6-11yr 250mg, 12-17yr 500mg)
- If Penicillin allergic use Clarithromycin: Dose 7,5mg bid for 10days
- Amoxicillin+ clavulanic acid: Oral 25-50mg/kg/day in 2 divided doses for 10 days. [5]

e. Immunosuppressive therapy: no evidence of useful in APSGN. [11]

3. Follow-up:

- For at least 1 year
- Monitor BP at every visit
- Urinary and renal function to evaluate recovery
- Repeat C3 levels 6 weeks later. [1]

VI. Prognosis:

APSGN generally has a favorable prognosis with less than 1% of children progressing to End stage renal failure. Severe systemic complications can occur due to severe renal inflammation and hypervolemia but are rare. A small percentage of patients may have persistent hypertension, persistent hematuria or proteinuria or progressive to chronic kidney disease following the acute episode of APSGN. [2]

VII. Complications

The complications that might occur during acute phase of APSGN include:

- Congestive heart failure
- Pulmonary edema
- Severe hypertension- induced encephalopathy due to hypervolemia
- Retinopathy
- Other potential complications include hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, seizure and uremia. [2, 6, 7]

VIII. Prevention and Education

- Stay hygiene.
- Early systemic antibiotic therapy for streptococcal throat and skin infections does not eliminate the risk of glomerulonephritis.
- Family members of patients with acute glomerulonephritis should be cultured for group A beta-hemolytic streptococci and treated if culture positive. [6]

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IDIOPATHIC NEPHROTIC SYNDROME IN CHILDREN

LY Rada, PRUM Chumneanh, EAR Vireak, TEK Lyvannara, NGOUN Yanet

I. Key facts [2,4]

- 90% of nephrotic syndrome is idiopathic
- Asia more frequent (incidence 16 to 100.000 children), familiar “more frequent” until 3% of the siblings affected 60% relapse
- Atopy: commonly (till 50% of all patients), boy: girl=2:1 (compare also atopy)
- Secondary causes such as Systemic Lupus Erythematosus (SLE) or Henoch Schoenlein Purpura (HSP) should be considered if there are atypical features
- 80-90% of cases of Idiopathic Nephrotic Syndrome (INS) are steroid sensitive and respond to initial therapy, it’s first nephrotic syndrome onset within age 1-6 years (The peak age at onset is at 2 to 3 years)
- Of the children with steroid-sensitive Nephrotic Syndrome 80% will have one or more relapses.

II. Overview

1. Definition [1,2,3]

Nephrotic syndrome (NS) is a clinical syndrome defined by massive proteinuria (greater than 50 mg/kg/day) responsible for hypoalbuminemia (less than 30 g/L), with resulting hyperlipidemia, edema, and various complications.

2. Etiology [5,6,7]

a. Common primary causes of nephrotic syndrome are intrinsic kidney diseases, such as membranous nephropathy, minimal-change nephropathy, and focal glomerulosclerosis. Secondary causes may include systemic diseases, such as lupus erythematosus, diabetes mellitus, and amyloidosis. Congenital/hereditary focal glomerulosclerosis could occur because of genetic mutations in podocyte proteins, such as podocin, nephrin, or the cation channel 6 protein. An episode of infectious diseases, particularly the upper respiratory tract, is a triggering factor in almost half of cases, an allergic reaction in a third of cases, and more rarely, an insect bite or vaccination. Nephrotic syndrome can also result from drugs of abuse, including heroin.

b. Secondary causes of nephrotic syndrome include the following:

- Diabetes mellitus
- Immune: lupus erythematosus, antibody vasculitis, Berger disease, glomeruli acute post-infectious nephritis, antineutrophil cytoplasmic neutrophils (ANCA), Goodpasture syndrome, extra membranous or membranoproliferative glomerulonephritis, thrombotic microangiopathy, alloantibodies from enzyme replacement therapy, or toxicity of nonsteroidal anti-inflammatory drugs (NSAIDs) or gold salts
- Infection: human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C, cytomegalovirus, parvovirus.

3. Physiopathology [2,3,4]

The glomerular capillaries are lined by fenestrated endothelium, which sits on the glomerular basement membrane, covered by glomerular epithelium, or podocytes, which envelop the capillaries with the capillaries' cellular extensions called foot processes. These processes interdigitate with special cell-cell junctions called the slit diaphragm, which together form the glomerular filter. Normally, larger proteins (greater than 69 kD) are excluded from filtration. The destruction of podocytes above a critical mass also leads to irreversible glomerular damage.

In a healthy person, the loss of plasma albumin through the glomerular filtration barrier is less than 0.1%. Filtration of plasma water and solutes occurs extracellularly and through

the filtration slits and endothelial fenestrae. The glomerular changes that may lead to proteinuria are damage to the glomerular basement membrane, the endothelial surface, or the podocytes. Albumin is the main constituent in proteinuria, accounting for 85%. Albumin carries a net negative charge. The loss of glomerular membrane negative charge plays an important role in causing albuminuria. A generalized defect in glomerular permeability is associated with nonselective proteinuria causing a glomerular leakage of various plasma proteins. This phenomenon does not allow a clear-cut separation of causes of proteinuria.

4. Pathogenesis of Edema

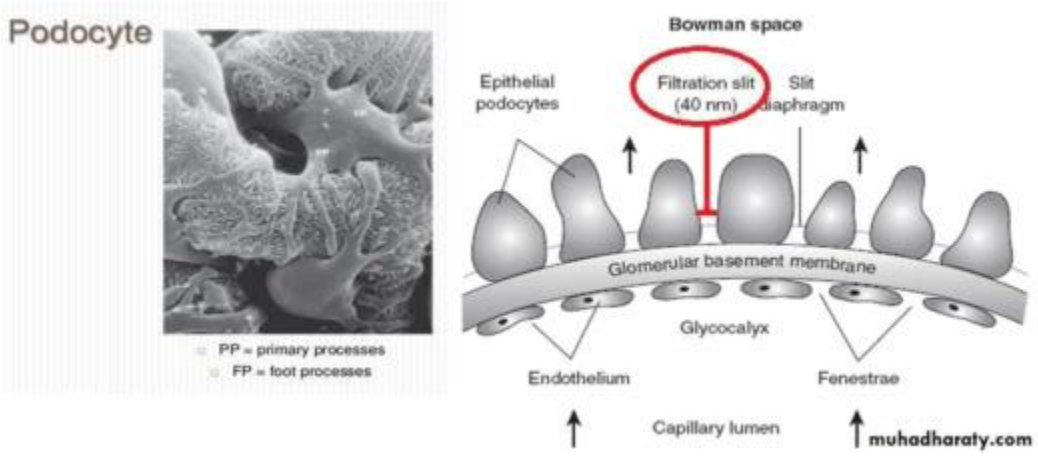
The following are the two hypotheses for the occurrence of edema in nephrotic syndrome:

- Underfill Hypothesis

  Increased glomerular permeability causes albuminuria, eventually leading to hypoalbuminemia. Consequently, hypoalbuminemia results in a decline in plasma colloid osmotic pressure, in turn causing increased transcapillary filtration of water in the body. Subsequently, this process leads to the development of edema. Capillary hydrostatic pressure and oncotic pressure control the fluid movement from the vascular compartment into the interstitium. Protein content mainly determines the oncotic pressure. For edema to occur, the amount of fluid filtered should exceed the maximal lymphatic flow, which happens secondary to a low enough intravascular oncotic pressure and a high enough capillary hydrostatic pressure. In nephrotic syndrome, this results in reduced plasma volume, with a secondary rise in sodium and water retention via the kidneys.

- Overfill Hypothesis

  An alternative hypothesis states that an intrinsic defect in the renal tubules leads to a decline in sodium excretion. This might occur if the intraluminal protein directly causes renal epithelial sodium re-absorption. The following points support this hypothesis:
  - Sodium retention occurs even before the serum albumin level starts to fall
  - Intravascular volume is normal or even raised in many patients with nephrotic syndrome
  - There is an exaggerated peripheral capillary permeability to albumin, as reported in the radio-isotopic technique in studies of 60 patients with nephrotic syndrome. This would lead to increased interstitial oncotic pressure and fluid retention in the peripheral tissues.



III. Signs and symptoms [1,2,5]

1. Clinical signs:

- Generalized edema: Peri-orbital swelling, noticed particularly in the morning ankle and lower limb swelling-pitting edema abdominal swelling and scrotal/vulvar edema.
- Heavy proteinuria (3+/4+ on dipstick) > 50mg/kg/day, Urine protein/creatinine ration >200mg/mmol
- Hypoalbuminemia: serum albumin<30g/l (Hypoprotidemia< 60g/l)
- Hyperlipidemia (Cholesterol).

2. Initial Assessments:

- Initial clinical assessment to include:
    - Height and Weight
    - Calculation of body surface area (4P+7)/(P+90)
    - Blood pressure
    - Capillary refill time.
- Assessment of edema-Lower limb
    - Spine – sacral
    - Ascites
    - Scrotal/Vulvar.
- Assessment of fluid status
    - Hypovolemia (Tachycardia; hypotension; dizziness; cool peripheries; delayed capillary refill time; severe abdominal pain)
    - Fluid overload (Tachycardia; hypertension; warm peripheries; respiratory distress; hepatomegaly).
- Severe or symptomatic edema:
    - Discomfort (genital, abdominal), gross scrotal/vulvar edema
    - Gross limb edema with potential for skin breakdown/cellulitis
    - Increased work of breathing from pleural effusion
    - Ascites.
- Infection (increased risk in nephrotic state):
    - Cellulitis
    - Spontaneous bacterial peritonitis-abdominal pain, fever, nausea/vomiting, rebound tenderness
- Thrombosis (increased risk in nephrotic state)

Features suggesting diagnosis other than idiopathic nephrotic syndrome

- Systemic symptoms of fever, rash, joint pain (SLE, HSP)
- Features of nephritic syndrome (macroscopic hematuria, hypertension and renal impairment).

IV. Diagnosis [4,5,8]

1. Laboratory test:

- Blood test:
    - Full blood counts
    - Electrolytes-including bicarbonate; chloride
    - Calcium; phosphate; serum albumin; cholesterol
    - LFTs (liver function test)
    - Varicella IgG
    - Vitamin D.
- Urine test:

- Urinalysis including glucose-document proteinuria and the presence of any hematuria
- Urinary protein: creatinine ration (PCR)
- Urinary sodium concentration-helpful in aiding fluid status

- Further investigation to be performed in children with atypical features:
  - ASOT- may be elevated in Streptococcal beta haemolytic group A throat or skin infection
  - Anti-DNaseB- may be elevated in Streptococcal beta haemolytic group A skin/throat infection
  - C3/C4- low C3 levels may be seen in post-streptococcal/infectious glomerulonephritis (PIGN), C3 glomerulopathy (previously called MPGN=Membranoproliferative glomerulonephritis types I-III), systemic lupus erythematosus (SLE)
  - Hepatitis B status in children at high risk: family history of hepatitis B infection or history of travel in endemic areas.

2. Imagery services:

- Chest X-ray: showing a diffuse opacity occupying most of the right-side chest obscuring the costophrenic and the cardio-phrenic angle, a tracheal deviation to the left side with absence of air bronchogram, and positive meniscus sign.
- Abdomen ultrasound: fluid in peritoneal cavity with moderate quantities.

3. Differential diagnosis:

The differential diagnosis for nephrotic syndrome includes the following:

- Hepatic: Insufficiency, hepatocellular cirrhosis, Budd-Chiari syndrome
- Digestive: exudative enteropathy, lymphangiectasis, malnutrition
- Cardiac: hereditary angioneurotic edema
- Immune: anaphylaxis
- Renal: chronic glomerulonephritis, diabetic nephropathy, focal segmental glomerulosclerosis, HIV-associated nephropathy, IgA nephropathy, membranous glomerulonephritis, minimal change disease.

I. Complications [9]

- Metabolic consequences of proteinuria of the nephrotic syndrome:
  - Infection
  - Hypocalcemia and bone abnormalities
  - Hyperlipidemia and atherosclerosis
  - Hypercoagulability
  - Hypovolemia
- Acute kidney injury may suggest underlying glomerulonephritis but is more commonly precipitated by hypovolemia or sepsis. Another proposition is that the edema of the kidneys causes a pressure-mediated reduction in the GFR. Additional consequences include the following:
  - Hypertension due to reduced kidney function and fluid retention
  - Edema of the gut could cause defective absorption resulting in malnutrition
  - Ascites and pleural effusion
  - Generalized edema
  - Respiratory distress
  - Sepsis
  - Peritonitis
  - Thromboembolism
  - Failure to thrive

I. Treatment [7,8,10]

1. Specific treatment of nephrotic syndrome

a. Medical Treatment of steroid sensible nephrotic syndrome:

- Prednisone 60mg/m2/day oral dose (morning dose) 4 weeks
- Prednisone 60mg/m2/2days oral dose (morning dose) 8 weeks
- Prednisone 45mg/m2/2days oral dose (morning dose) 2 weeks
- Prednisone 30mg/m2/2days oral dose (morning dose) 2 weeks
- Prednisone 15mg/m^2/2days oral dose (morning dose) 2 weeks
  - then stop.

b. First relapse occurring more than 3 months after finish the treatment:

- Prednisone 60mg/m2/day for 6 days after urine shows no protein
- then 60mg/m2/2days oral dose (morning dose) 4 weeks
- then 45/mg/m2/2days oral dose (morning dose) 4 weeks
- then 30/mg/m2/2days oral dose (morning dose) 4 weeks
- then 15/mg/m2/2days oral dose (morning dose) 4 weeks
- then stop.

c. First relapse occurring less than 3 months after finish the treatment or during the decline of the steroid treatment:

- Prednisone 60mg/m2/day for 6 days after urine shows no protein
- then 60mg/m2/2days oral dose (morning dose) 4 weeks
- then 45/mg/m2/2days oral dose (morning dose) 4 weeks
- then 30/mg/m2/2days oral dose (morning dose) 4 weeks
- then 15/mg/m2/2days oral dose (morning dose) 12-18 months or at a dose slightly higher than the level at which relapse occurred.

d. Treatment of further recurrences or often recurrences:

- Levamisole 2.5mg/kg/2days in one dose during 18-36 months.
- Cyclosporine A 150mg/m2/ in two doses (= every 12 hours) for at least 18-24months Through level 140-200ug/l, check renal function regularly.
- Mycophenolate mofetil 1200 mg per m2 in two doses per day.
- Tacrolimus 0.2mg/kg/day in two doses (morning and evening)
- Rituximab Anti-CD 20 = B-Lymphocytes (low dose 375 mg/m^2 or median dose 750 mg/m^2 IV.).

e. Steroid-resistant nephrotic syndrome:

- ***Definition:*** Persistent proteinuria 4 - 6 weeks although steroids are given consequently, including 3 days of methyl-prednisolone iv. (500 mg per sqm) every 2days (Perfusion with 4-6 hours), and then persistent proteinuria 8 days after perfusion.
- ***Treatment:***
  a. First choice of the treatment: Cyclosporine A 150mg/m^2/day in two doses (=every 12 hours) for at least 18-24 months Through level 140-200ug/l, check renal function regularly.
  b. Second choice of the treatment: **Endoxan** 2mg/kg/day, (10-12weeks). Stop Endoxan: polymorphonuclear cells < 2000/mm3, lymphocyte < 800/mm^3, platelets < 100,000/mm^3.
- ***Renal biopsy:*** should performance and genetical analysis (Podocin, Nephrin, Laminin, WT1, CD2AP …)

  Histology: Minimal change, Patients with focal segmental glomerulosclerosis (FSGS): Cyclosporine A and ACE – inhibitor.

2. Symptomatic treatment

- Plasma perfusion: 10-20ml/kg or albumin20% 0.5g-1g/kg
- Anti-hypertension: Angiotensin-converting enzyme (ACE) Inhibitor: Captopril 0.5-1mg/kg/day oral dose or Calcium channel blocker (Nifedipine=Adalate 1mg/kg/day oral dose)
- Diuretic: Furosemide (1-2mg/kg), Aldactone (0.5-1mg/kg) (in case of nephritic syndrome associated)
- Treatment of thrombosis: rare but fatal (brain, lung…), general measures (mobilization and avoid bed rest, avoid unnecessary infusion.
- Anticoagulant: Aspirin 5mg/kg/day one dose (oral dose)
- Infection: bacterial infection (Prescribe antibiotic therapy only in the event of a declared infection; also oblige to carry out a tuberculosis assessment during basic treatment. Viral infection (Varicella or Herpes zoster virus: Acyclovir 10mg/kg 3 times per day oral dose for 7 days, children>6 age 200mg x 4 times oral dose per day.
- Vaccination*:* Varicella and Pneumococci during steroid treatment on every other day (on every alternate day), but not during Cyclosporine A.
    - ❖ Remission

      If the urine dipstick will show either “trace” or “negative” for protein for three days consecutively in a row, the nephrotic syndrome has gone into remission. The kidneys have stopped leaking protein.
    - ❖ Relapse

      If the urine dipstick shows relapse of proteinuria was defined as 24-h urinary protein of ≥ 1.0 g/day, urinary protein-to-creatinine ratio of ≥ 1.0 g/l either 3+ or 4+ protein for three days in a row, the nephrotic syndrome has relapsed. The kidneys have started leaking protein again.
    - ❖ Recovery

      Recovery is considered if no relapse has occurred for 2 years after stopping any specific treatment. However, this does not exclude a late relapse.

V. Prevention and Education [7,9]

1. Parental teaching

The objective is to allow the patient to fully understand their illness, particularly on certain aspects related to therapeutic care such as:

- The long duration of treatment
- The capital of dietetics treatment
- Treatment (Steroid, immunosuppressants, anticoagulants, diuretics…)
- The risk of nephrotic syndrome complication and treatment related complication.

2. Dietary education during the treatment period

- Very salty foods prohibited: smoked or salted meats and fish, shellfish, all canned goods, bread, various biscuits, store-bought pastries, all canned vegetables, sauces, bacon, etc.
- Food allowed in the low salt diet: all foods (plain) not cooked in an industrial way.

3. Hygienic and dietary measures

The diet should provide any protein ration of 1 to 2 g/kg. It must be low in salt and fluid restriction is only indicated if the corrected serum sodium level is less than< 130mmol/l. The low salt diet (<1mmol/kg/day or 35mg/kg/day) must be maintained until remission and in the event of high dose steroid therapy (0.5mg/kg/every 2 days).

4. Follow up

The patient will need to have medical assessments in the hospital or clinic. It is important that the parents bring the patient to these follow-up appointments even if the patient seem well. Parents will also have the opportunity to ask any questions. Remember to bring the patient's records of the home urine testing.

At these appointments, the patient needs to have:

- their height and weight checked
- a physical examination
- urine tests – to check for protein and other substances in the urine
- blood tests – to check for the amount of protein and other substances in the blood; blood tests may also be used to check the kidneys' function (how well the kidneys are working)
- blood pressure measurements.

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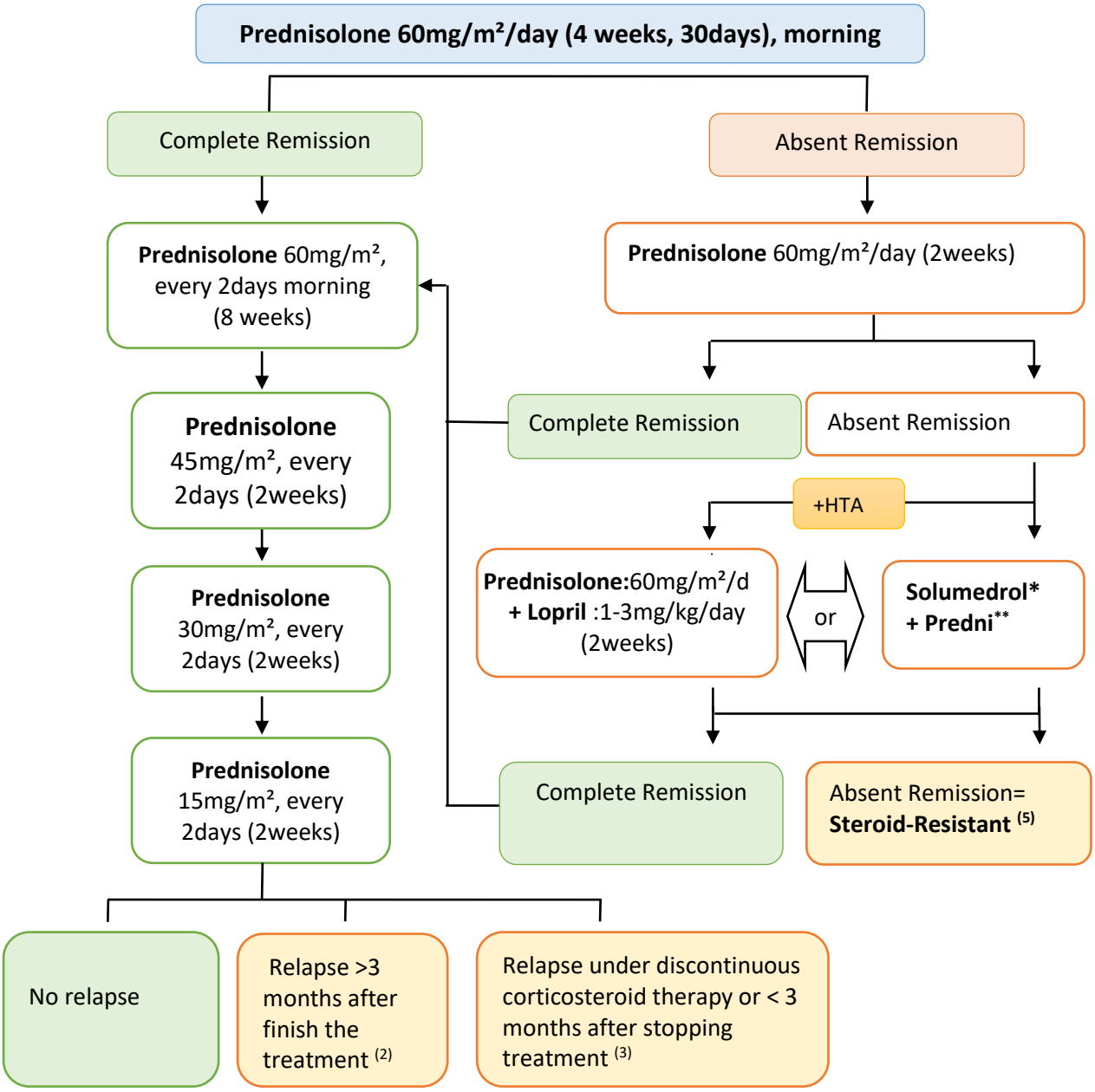
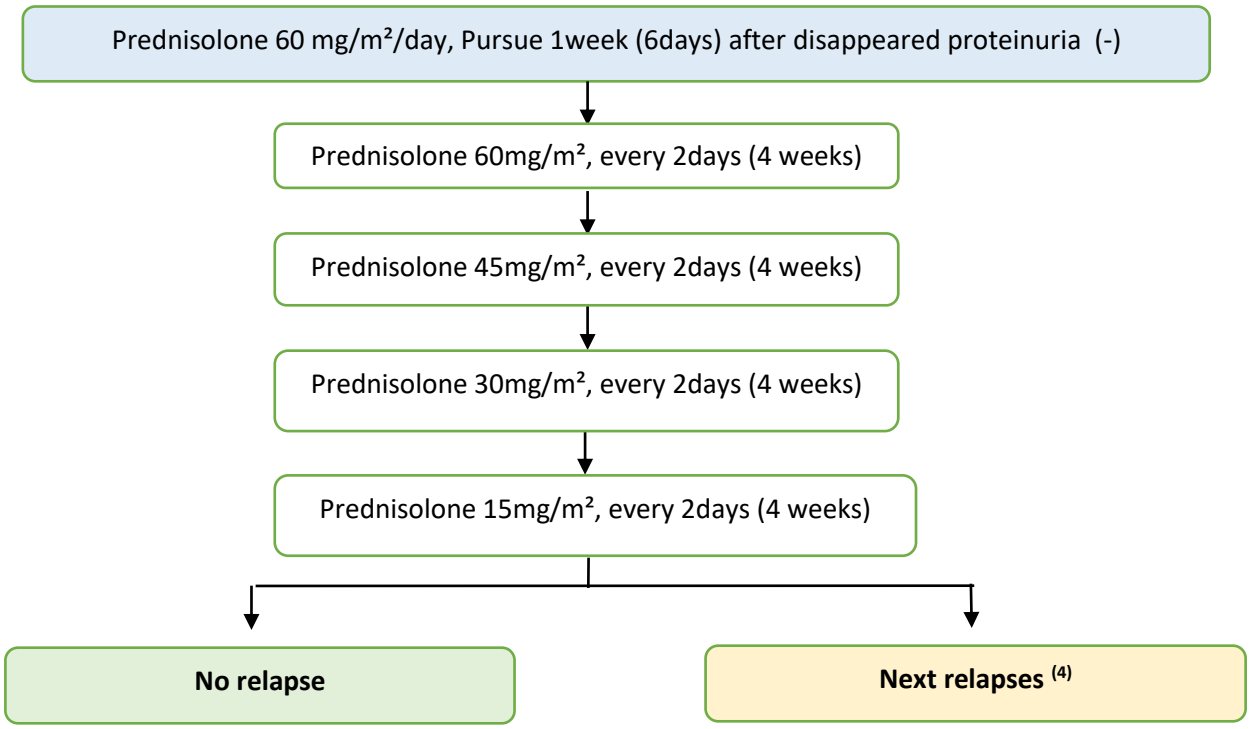
ALGORITHMS OF NEPHROTIC SYNDROME TREATMENT

1. Treatment of initial episode: Prednisolone 60mg/m²/day (Maximum 60mg/day) [11]



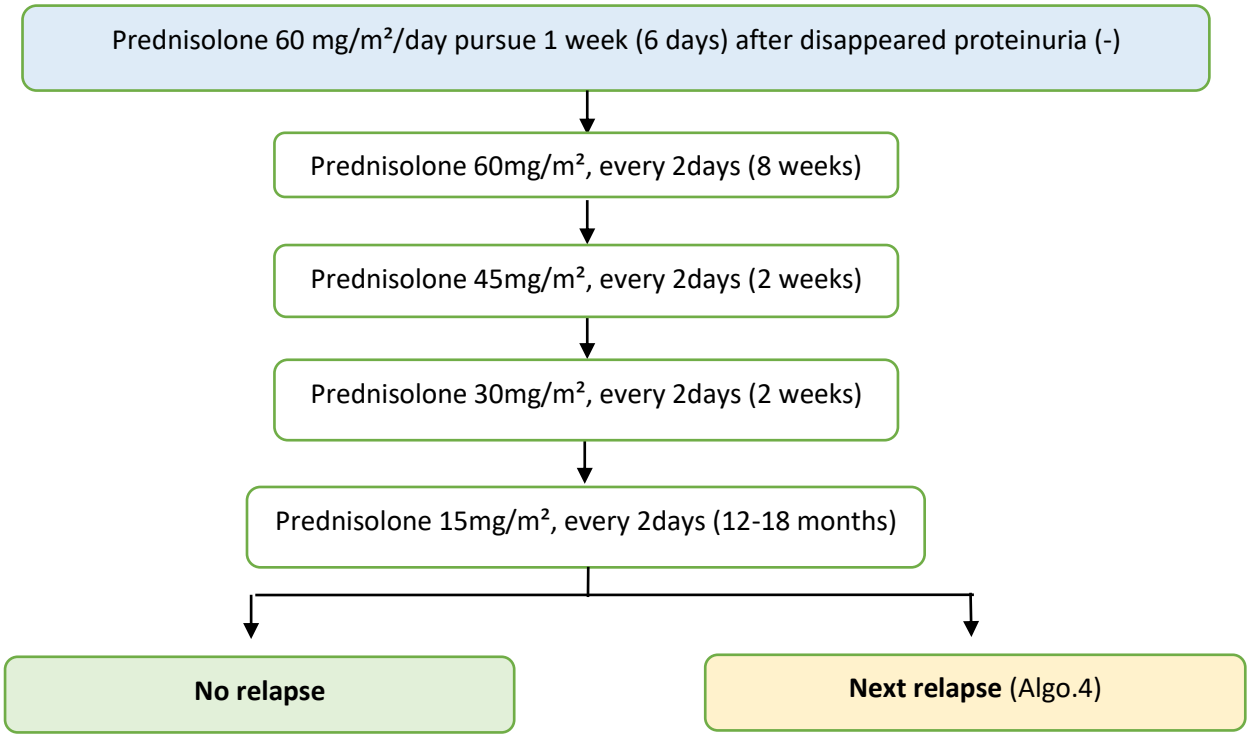
***Solumedrol:** 1g/1.73m², PIV 4-6h, 3 doses 48h apart, Evaluate 8 days after infusions*
***Prednisolone**: interrupt on the day of infusions.*

2. Treatments for relapses occurring apart (>3 months after stopping treatment) [11]

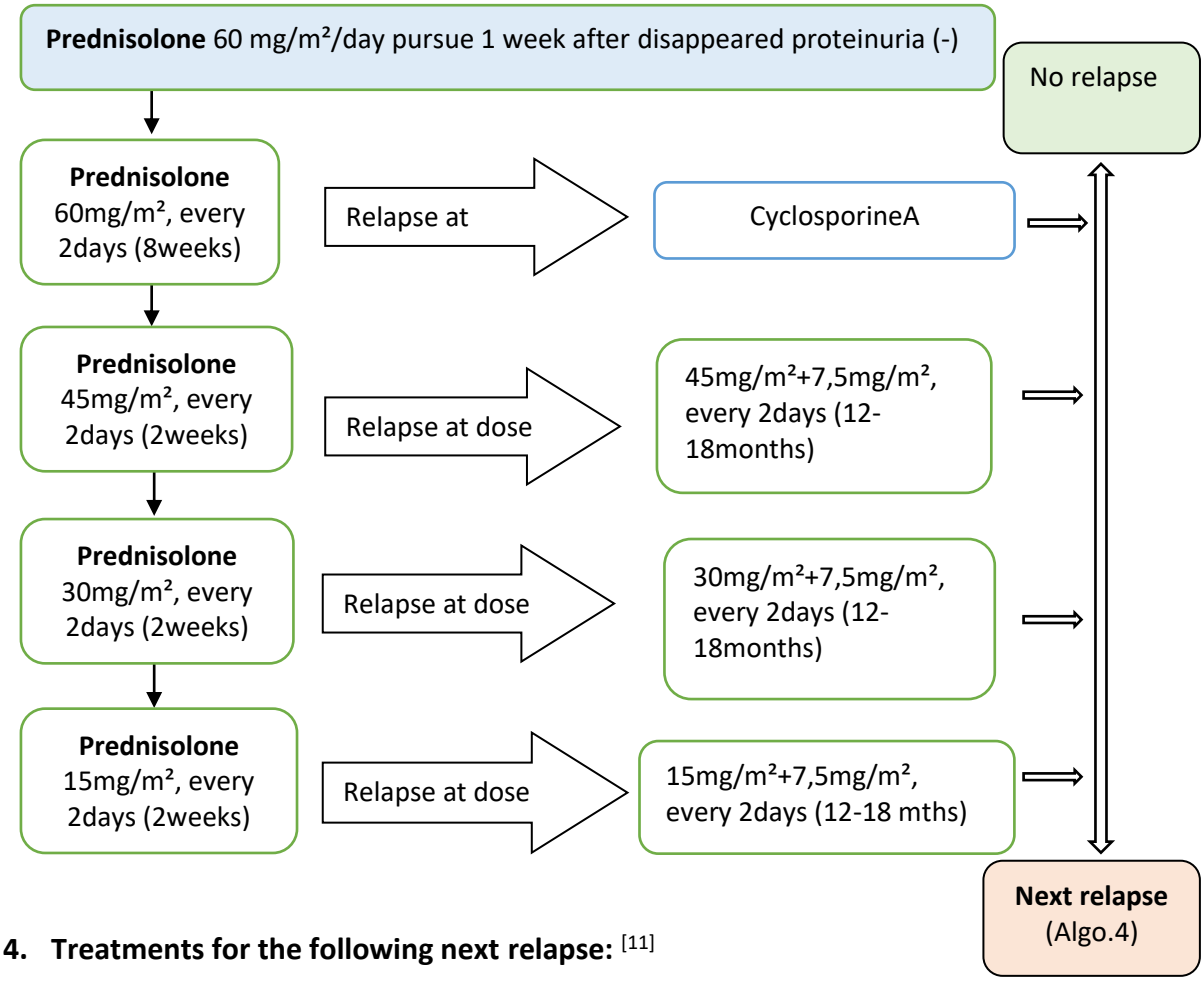


3. Corticosteroid dependence treatment:

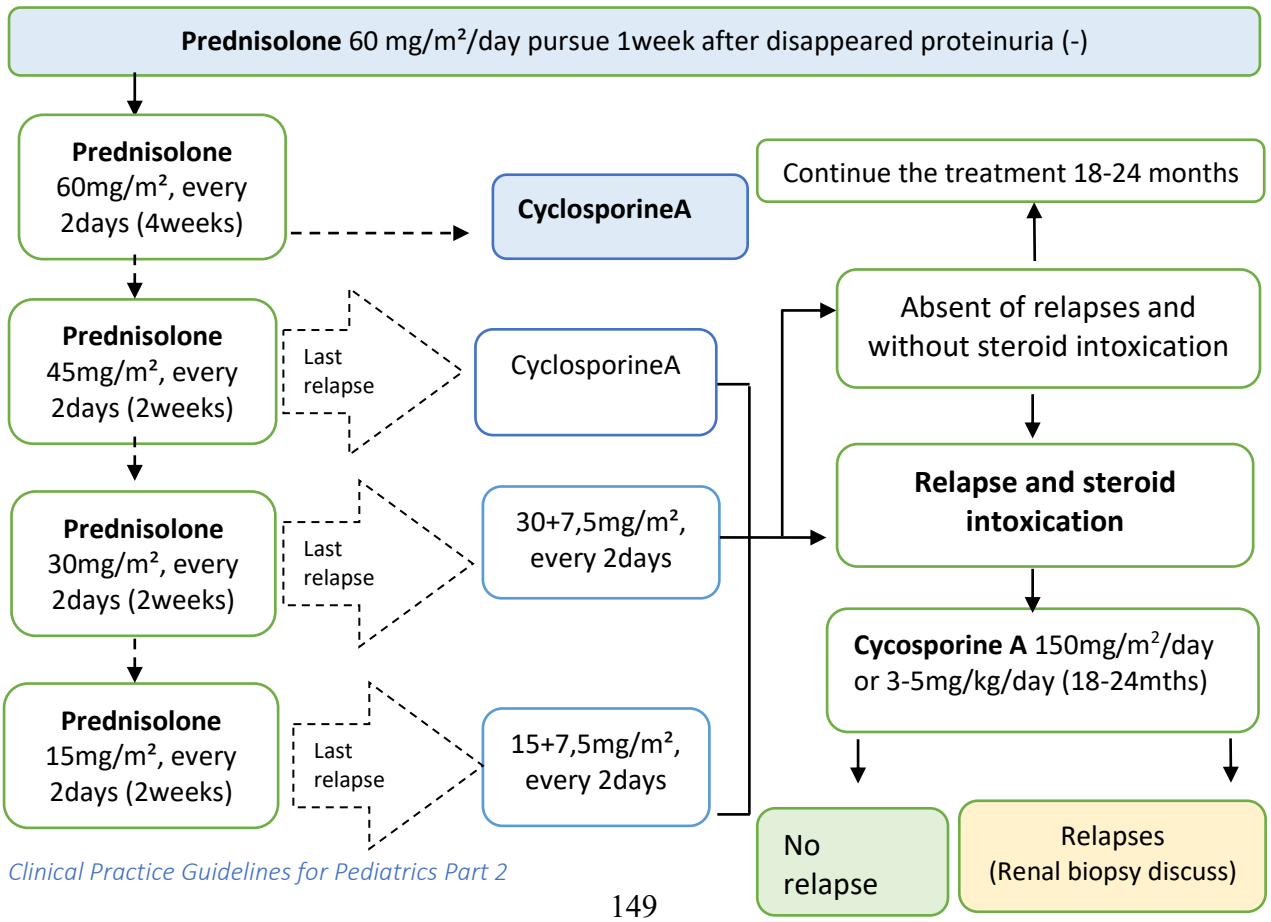
3.1. Relapse < 3 months after finish the treatment [11]



3.2. Relapse under discontinuous corticosteroid therapy [11]



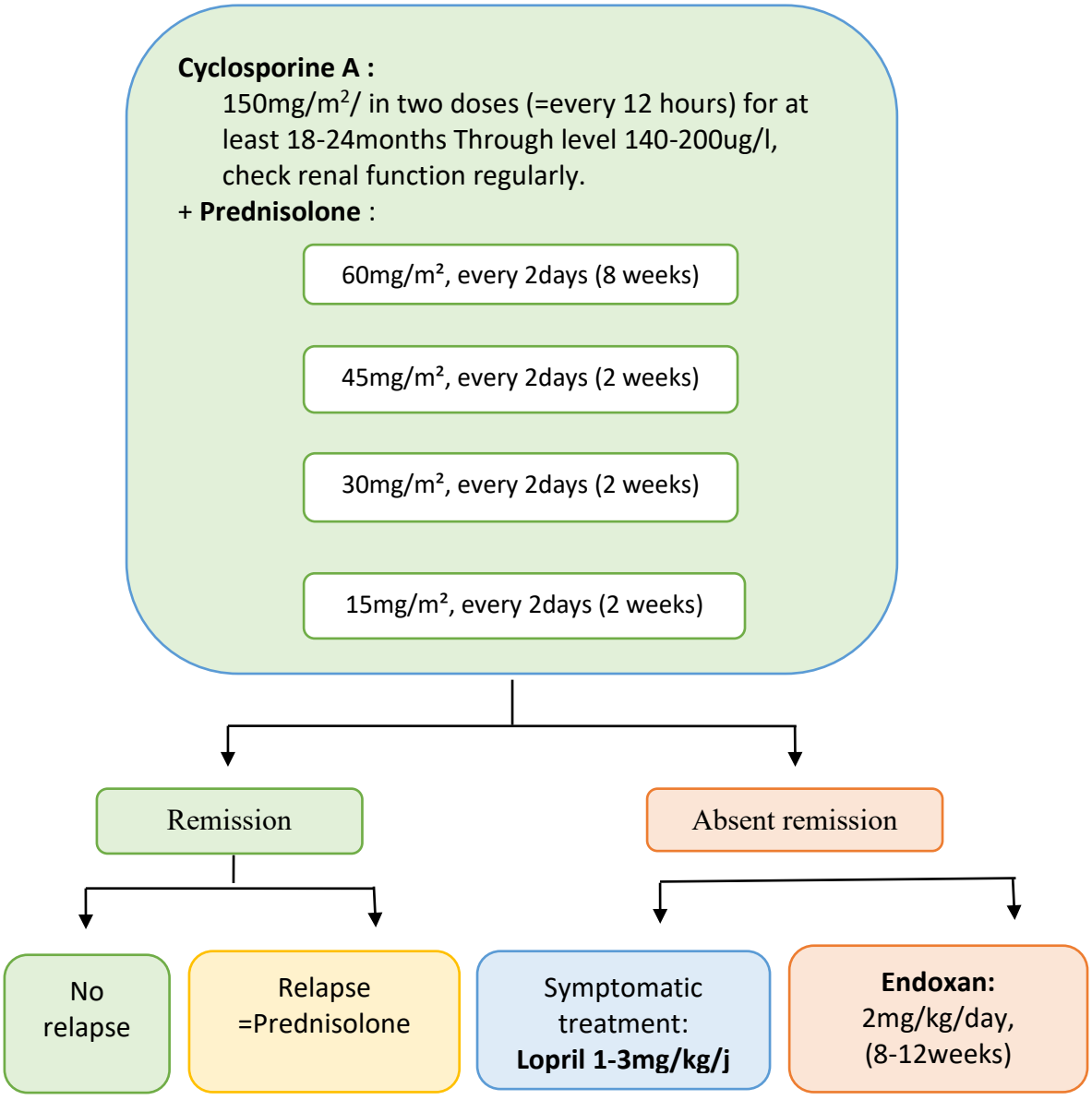
4. Treatments for the following next relapse: [11]



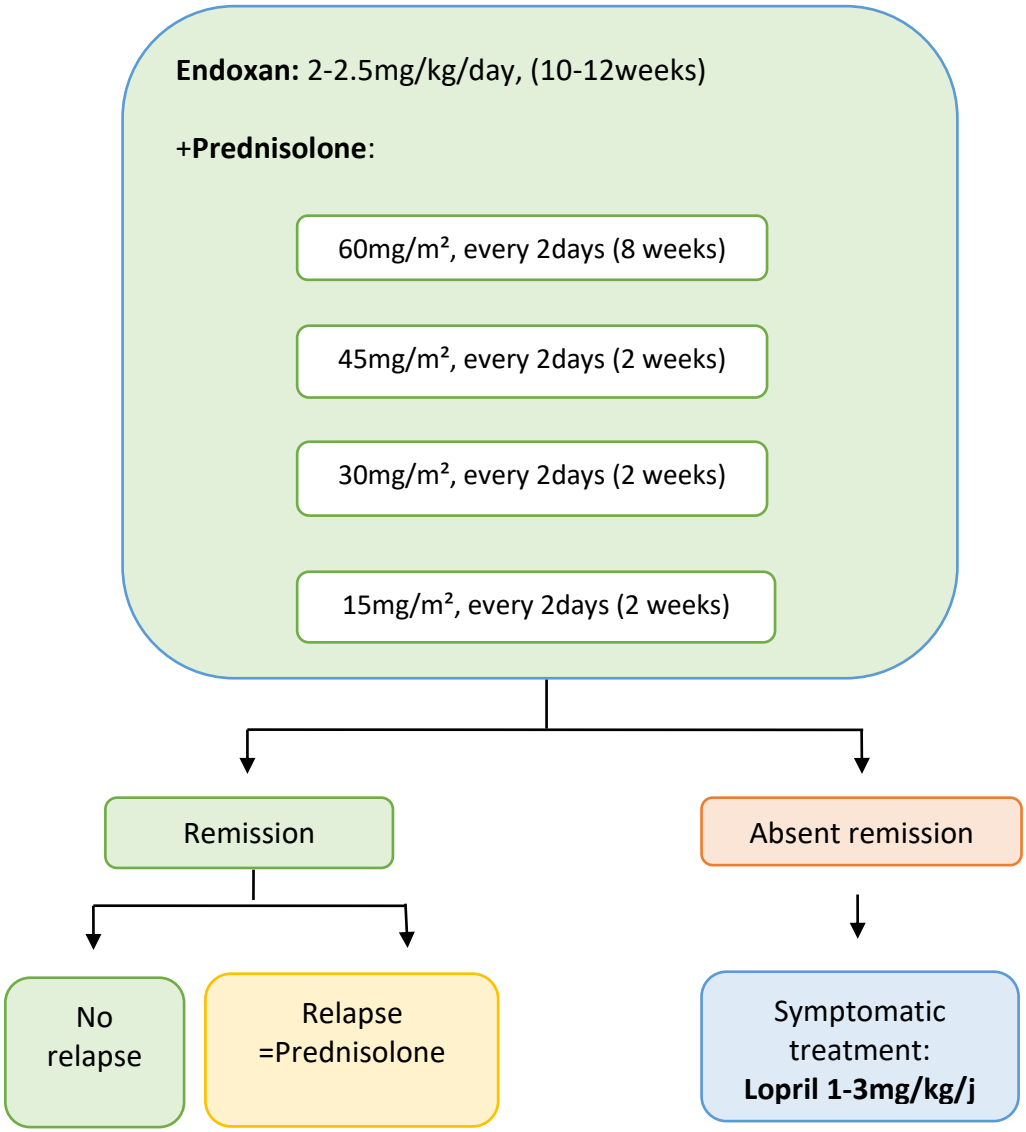
- ❖ The minimum dose of corticosteroids must be maintained to maintain remission for the duration of treatment and then begin a gradual reduction in corticosteroids.
- ❖ If there are complications of corticosteroid therapy (cataract, osteoporosis, diabetes mellitus or psychological disorders, etc.). It is necessary to change to other treatments (Endoxan)

5. Corticosteroid Resistant treatment:

5.1. *Cyclosporine* A, first choice [11]



5.2. ***Endoxan***, second choice [11]



❖ *Stop Endoxan: polymorphonuclear cells < 2000/mm3, lymphocyte < 800/mm³, platelets < 100,000/mm³.*

- **Levamisol** (2.5 mg/kg, every other day) offered after the third attack or when the level of corticosteroid dependence exceeds 15 mg/m²/2D After two months + corticosteroid therapy is gradually reduced. If it is not effective, the treatment is stopped after 6 months. Monitor side effects (PAH, agranulocytosis, vasculitis and neurological effects).
- **Mycophenolate mofetil**: effective in corticosteroid-dependent nephrosis by allowing reduce the degree of corticosteroid dependence, or even stop corticosteroid therapy. Started at a dose of 600 mg/m²/d with a gradual increase to 1.2 g/m²/d, it allows maintain remission despite reduction or cessation of corticosteroid therapy.
- **Tacrolimus** 0.2mg/kg/day in two doses (morning and evening)

- **Rituximab:** Anti-CD 20 = B-Lymphocytes (low dose 375 mg/m^2 or median dose 750 mg/m^2 IV.)

ACUTE KIDNEY INJURY IN CHILDREN

CHUOP Bophal, NGETH Pises, NGOUN Chanpheaktra

I. Key facts

Acute kidney injury (AKI) can lead to a partial or complete loss of kidney function. This condition is linked to negative short- and long-term health outcomes. In children, AKI often caused by systemic illnesses or exposure to substances that are toxic to the kidneys. [1]

- AKI is also commonly seen in newborns and children who are in the hospital, approximately 5 to 31 percent of noncritically ill and approximately 55 percent in critically ill hospitalized patients. [2][3]
- For non-hospitalized children, AKI is approximately 0.7 cases per 1000 person-years.
- Analysis of 60 studies including 133,876 children with AKI revealed a pooled in-hospital mortality rate of 18.27%, the pooled post-discharge mortality rate was 6.84% (95% CI: 5.86, 7.82) in a 1- 9-year follow-up period. [4]

II. Overview

1. Definition

AKI is defined as a rapid decrease in glomerular filtration rate (GFR), which is typically shown by a decrease in urine output and/or an increase in serum creatinine from baseline.

2. Etiology [5]

a. Pre renal causes

- Gastrointestinal losses, Hemorrhage, Diuretics, Burns, Shock, Nephrotic Syndrome
- Heart failure, Arrhythmias,
- Septic shock, Neurogenic shock,
- NSAIDs, ACE inhibitor, Hepatorenal syndrome

b. Renal causes

- Prolonged ischemia, hypotension, acyclovir, aminoglycosides, amphotericin B, vancomycin, Plant toxin, Radiocontrast agents, Wasp sting, snake bite
- Hemolytic uremic syndrome, vasculitis, Renal venous thrombosis
- Interstitial nephritis, infections (Leptospirosis), malignant infiltrations
- Post-infectious glomerulonephritis, rapidly progressive glomerulonephritis (RPGN), Henoch-Schönlein purpura

c. Post renal causes

Renal calculi, Posterior urethral valve, Ureteric obstruction, Neurogenic bladder and internal or external ureteral compression.

3. Risk factors

- Critically ill patients
- Neonates
- Nephrotoxins: drugs, Radiocontrast agent

III. Signs and symptoms

1. Clinical presentation may vary based on cause of AKI [6]

a. Signs and symptoms suggestive of prerenal AKI

- Diarrhea, nausea, vomiting, and fever suggestive of volume depletion

- Dyspnea or orthopnea, cough, exercise intolerance, edema, and weight-gain suggestive of acute heart failure
- Edema as a result of fluid sequestration (third spacing) due to nephrotic syndrome, sepsis, capillary leak syndrome (DHF) or pancreatitis
- Decreased urine output

b. Signs and symptoms suggestive of intrinsic AKI

- Oliguria or anuria
- Dehydration
- Signs and symptoms of sepsis
- Hypoxia-ischemic events

c. Signs and symptoms suggestive of postrenal AKI

- Anuria
- Gross hematuria
- Proteinuria
- Colicky flank or abdominal pain, or nonspecific symptoms such as diffuse abdominal pain, nausea, vomiting, and irritability, suggestive of renal calculi

2. Clinical presentation suggest diagnosis

- Ask about recent use of medications that may contribute to acute tubular necrosis
- Dark brown urine 2-3 weeks after upper respiratory tract infection or 4-6 weeks after skin infection may suggest infection-related glomerulonephritis
- Gross hematuria 1-3 days after upper respiratory tract infection may suggest immunoglobulin A nephropathy
- Hemoptysis may suggest Goodpasture syndrome
- Joint pain and photosensitivity may suggest systemic disorders such as systemic lupus erythematosus
- Fever, joint pain, or flank pain may suggest acute interstitial nephritis
- Weakness and fatigue may suggest hemolytic uremic syndrome and microangiopathic hemolytic anemia
- Nausea, vomiting, abdominal pain, bloody diarrhea, and exposure to food or water possibly contaminated by Shiga toxin-producing *Escherichia coli*

3. Urine output:

- Anuria: no urine output
- Oliguria: urine <0.5ml in children (< 1ml/kg/hour in infants) for >6hours
- Polyuria: urine > 3ml/kg/hours

IV. Diagnostic approach

1. Urine studies:

- Urine output volume, sodium, urea, creatinine and analysis (dipstick &Microscopy)
- Hematuria with dysmorphic RBC, granular casts RBC cast suggest glomerulonephritis
- Muddy brown casts, renal tubular epithelial cells suggest acute tubular necrosis

2. Blood tests:

- Serum creatinine, blood urea nitrogen, complete blood count, CRP, Blood film, blood smear, electrolytes, calcium and glucose.
- Blood culture, Blood gas, DAT, INR, APTT
- CK, LDH, AST, ALT, Albumin, phosphate, uric acid, ferritin
- ASO, ANA, anti-dsDNA, C3, C4, NS1, IgM, IgG for dengue infection

- Stool culture polymerase chain reaction or enzyme immunoassay for O157 Shiga toxin-producing Escherichia coli or serology IgM and IgG,
- Neutrophil Gelatinase-Associated Lipocalin (NGAL) levels in urine or plasma

a. The pRIFLE and KDGO criteria of AKI [7][8

Stage 1	Risk	- Increase in serum creatinine level 1.5-1.9 times baseline **or** - Decrease in GFR by 25% **or** - UO < 0.5 mL/kg/h for 6-12 hours
Stage 2	Injury	- Increase in serum creatinine level 2-2.9 times baseline **or** - Decrease in GFR by 50% **or** - UO < 0.5 mL/kg/h > 12 hours
Stage 3	Failure	- Increase in serum creatinine level > 3 times baseline **or** - Decrease in GFR by 75% **or** - < 35 mL/minute/1.73 m2 **or** - Increase serum creatinine level ≥ 4 mg/dL **or** - UO < 0.3 mL/kg/h ≥ 24 hours **or** - Anuria ≥ 12 hours **or** - Initiation of renal replacement therapy
	Loss	- Persistent failure >4 weeks
	End-stage	- Persistent failure >3 months

b. Schwartz Equations for estimated glomerular filtration rate (GFR)

eGFR (mL/minute/1.73 m^2) = (K × height [cm]) / (serum creatinine [mg/dL])

- Unit measurement as mg/dL
  K = 0.33 for premature through the first year
  = 0.45 for full terms through the first year
  = 0.55 for children and adolescent girl
  = 0.7 for adolescent boys
  If measurement as mmol/L, k is 29.2 in premature infants through the first year, 39.8 for term infants through the first year, 48.6 in children and adolescent girls, and 61.9 in adolescent boys.
- Estimated glomerular filtration rate (GFR) normal in children [9]
  - Mean 41 mL/minute/1.73 m^2 for neonates aged 1 week
  - Mean 66 mL/minute/1.73 m2 for infants aged 2-8 weeks
  - Mean 96 mL/minute/1.73 m2 for infants > 8 weeks old
  - Mean 133 mL/minute/1.73 m2 for children aged 2-12 years
  - Mean 140 (SD 30) mL/minute/1.73 m2 in males aged 13-21 years
  - Mean 126 (SD 22) mL/minute/1.73 m2 in females aged 13-21 years
- Blood urea nitrogen and serum creatinine [6][10][11]
  - Elevated creatinine typically occurs up to 48 hours after renal injury
  - In previously healthy children where the baseline serum creatinine is unknown, it is generally recommended to use a presumed baseline

estimated GFR (eGFR) of 120 mL/min/1.73 m2. An alternative approach, consider comparison to upper limit reference range.
  - If urine output and serum creatinine lead to different stages, patient should be assigned higher stage.
  - In neonates, interpretation of serum creatinine levels is challenging.
  - Need to adjust Creatinine for fluid overload (calculation formula)
- Fractional excretion
  - FE Na (%) = (urine/plasma sodium) x (plasma/urine creatinine) x 100
  - FE Urea (%) = (urine/plasma urea) x (plasma/urine creatinine) x 100

	Prerenal causes*	**Renal causes***
Urine specific gravity	>1.020	<1.010
Urine sodium (mmol/L	<20	>40 (>50)
Urine osmolarity (mOsm/kg)	>500 (>400)	<300 (<400)
Urine/Plasma urea	>8	<3
Urine/Plasma osmolarity	>1.15 (>1.2)	<1.1 (<1.2)
Urine/Plasma creatinine	>40	<20
Plasma BUN/Creatinine	>20	<10
FE Na (%)	<1 (<2.5)	>1 (>2.5)
FE Urea (%)	<35	>50

* ***Values in parentheses are the criteria for neonates***

3. **Electrocardiography** (ECG) in children with [12]:
   - Potassium levels ≥ 5.5 mEq/L (5.5 mmol/L)
   - Tumor lysis syndrome
   - Rhabdomyolysis
   - Findings may include cardiac conduction abnormalities and arrhythmias, such as:
     - Peaked T waves
     - Widen QRS complex
     - Flattened P waves
     - Prolonged PR interval
4. **Renal ultrasound**: consider renal ultrasound to detect bilateral upper tract obstruction, posterior urethral valves, obstruction of a solitary kidney, assess kidney size, Renal vein thrombosis for neonate (Doppler).
5. **Renal Biopsy**: may be indicated if the patient has hematuria, proteinuria, rapidly rising blood urea nitrogen and creatinine serum values (RPGN).
6. **Renal scans**: can be helpful to demonstrate the extent of kidney function.

V. Management

The management of AKI based on its cause and stage. The primary goal is to preserve homeostasis while waiting for renal function to improve on its own or while the underlying cause is treated. Medical management of AKI includes maintaining renal perfusion, fluid and electrolyte balance, controlling blood pressure, treating anemia, providing adequate nutrition, adjusting medications for the degree of renal impairment, and initiating renal replacement therapy (dialysis) when indicated.

1. **Maintain adequate renal perfusion**

A. Fluids

- A child exhibiting clinical signs of hypovolemia and oliguria should receive an intravenous fluid challenge over a period of 20 to 30 minutes, unless prevented by fluid overload or heart failure. The challenge can be given with crystalloid solutions, such as normal saline (10 to 20 ml/kg), packed red blood cells, or colloid solutions, such as 5% albumin if the child has hypotension.
- Fluid resuscitation improves renal function and restores appropriate urine flow, which is consistent with pre-renal illness
- If renal function does not improve with intravascular volume restoration and urine production does not increase, invasive monitoring may be necessary.
- If oliguria persists despite adequate correction of pre-renal factors, give a trial of loop diuretics to promote diuresis in order to facilitate fluid management:
  - Intravenous furosemide bolus 2-5 mg/kg/dose, maximum dose: 6 mg/kg/dose, not to exceed maximum adult dose: 200 mg/dose
  - Initial: IV bolus dose of 1 to 2 mg/kg followed by continuous intravenous infusion 0.1-1 mg/kg/hour.
  - Note: Do not routinely offer loop diuretics to treat acute kidney injury

B. Vasopressors

- Recommended in conjunction with fluids in patients with vasomotor shock with AKI
- Low-dose dopamine (1-3 mg/kg/minute) IV not recommended for treatment of AKI, due to increased risk for hypotension and low-quality of evidence for benefit [13] [14].

2. **Prevent fluid overload and hypertension**

- Fluid overload exceeding 10% of body weight is independently associated with a significantly increased risk of mortality in critically ill patients.
  - ❖ **Equations for percent fluid overload:**
    - **Fluid balance-based methods:**

$$\%\text{fluid overload} = \frac{\text{Total fluid in (L) - Total fluid out(L)}}{\text{admission weight(kg)}} \times 100$$

    - Weight based methods:

$$\%\text{fluid overload} = \frac{\text{Daily weight (kg) - admission weight(kg)}}{\text{admission weight(kg)}} \times 100$$

  - Fluid volume should be restricted to insensible water loss calculated at 400 ml/m² per day, in addition to replacing urine, gastrointestinal and other losses.
  - Therapy should be aimed at decreasing the body weight by 0.5 to 1% daily.
  - Fluid overload may aggravate hypertension in patients with glomerulonephritis, resulting in hypertensive urgencies or emergencies.

- It **is** important to treat these hypertensive emergencies with intravenous antihypertensive agents that can produce a controlled reduction of blood pressure in order to avoid worsening of the cerebral edema due to disruption of cerebral autoregulation.

3. **Hypertension** (see chapter hypertension).

4. **Maintain normal electrolytes and acid-base status**

A. Hyperkalemia:

a. Hyperkalemic emergencies where serum potassium levels ≥7 mmol/L accompanied by electrocardiographic changes such as peaked T waves, flattened P waves, increased PR interval, and widening of the QRS complex:

- Intravenous calcium given slowly over 5-20min:
- Calcium gluconate 10%: 0.15 mmol/kg, maximum 6.6 mmol
  (0.68 mL/kg, max 30 mL)
  Preferable if only peripheral line available, as less irritant to veins
- Calcium chloride 10%: 0.14 mmol/kg, maximum 6.8 mmol
  (0.2 mL/kg, max 10 mL)
  - Nebulized salbutamol
    Onset of action: 30 minutes, duration of action: 2-3 hours
    - Body weight <25 kg: 2.5 mg
    - Body weight 225 kg: 5 mg
  - Intravenous bolus insulin and dextrose:
    - Insulin 0.1 IU/kg
    - Glucose 10% 5 mL/kg IV bolus (if no hyponatremia)
    - Monitor blood glucose at 15 mins and every 30 mins subsequently until blood glucose is stable

b. Less urgent elevations of serum potassium 6 to <7 mmol/L:
Oral or rectal Sodium polystyrene sulfonate 1g/kg (maximum of 30 g).

B. Hyponatremia

- Fluid restriction and loop diuretics if due to fluid overload
- Sodium supplementation if there is renal salt wasting
- Hyponatremia (sodium concentrations <130.0 mEq/L
- If the patient is symptomatic and having seizures, 3% sodium chloride should be used, 3 to 5 mL/kg of 3% NaCl infused over 10-15 minutes [15].

5. **Hypocalcemia and hyperphosphatemia:**
   Calcium-based phosphate binders. IV administration of calcium gluconate should be considered if hypocalcemia is severe and/or if bicarbonate therapy is required for severe acidosis and hyperkalemia.
6. **Severe metabolic acidosis** where serum bicarbonate <15 mmol/L or pH <7.2

Estimated HCO_3 deficit= 0.5×BW (body weight) × Target HCO_3 – Current HCO_3

- One-half of the estimated HCO3 deficit is infused IV over two to four hours. The remaining one-half of the HCO3 deficit is infused over the following 6 to 24 hours
- Oral sodium citrate
  Note: Use with caution in patients with fluid overload and hypertension. There is controversy regarding the use of sodium bicarbonate because of its adverse

effects, administration of sodium bicarbonate should be initiated in life-threatening situations.

7. **Ensure adequate nutrition**

a. Caloric requirement

- AKI is often marked by catabolism, particularly in children with critical illness, nutritional support is crucial to enhance the recovery process.
- However, nutrient needs of patients with AKI are highly heterogeneous, depending on etiology, catabolic rate, acute and chronic comorbidities.
- Some experts, protein consumption should be aimed at keeping blood urea nitrogen (BUN), a favorable nitrogen balance, between 40 and 80 mg/dL (14.3-28.6 mmol/L).
- If feasible, the enteral route is preferred over the parenteral route for nutritional support.
- Total energy intake of 20–30 kcal/kg/d in patients with any stage of AKI

b. Protein intake

- Ensure adequate caloric intake with carbohydrates and/or fat
- Aim for protein intake of 3 g/kg/day

8. **Dosage adjustment of medications**

Drugs which are excreted primarily through the kidneys will require dosage adjustment

9. **Avoid further nephrotoxic insults**

- Nephrotoxic antibiotics
- Angiotensin converting enzyme inhibitors or angiotensin receptor blockers
- Calcineurin inhibitors
- Contrast nephropathy

10. **Acute Renal Replacement Therapy**

The common indications for acute RRT in children with AKI include:

- Volume overload (10%-20% fluid excess)
- Severe metabolic acidosis
- Severe hyperkalemia unresponsive to treatment
- Severe uremia (blood urea nitrogen > 100 mg/dL (> 35.7 mmol/L or symptomatic)

VI. Possible complications

Retrospective cohort study of all hospitalized children (0–18 years) surviving AKI without acute KRT between 1996 and 2020 in Canada, median follow-up period of 9.7 years [16].

- Hypertension (HR 2.3, 95% CI 2.1-2.6)
- CKD (HR 7.9, 95% CI 6.9-9.1)
- Developing AKI during subsequent hospitalization (HR 3.7, 95% CI 3.1-4.5)
- Death 3%, (HR 1.0 95% CI 0.7-1.1)

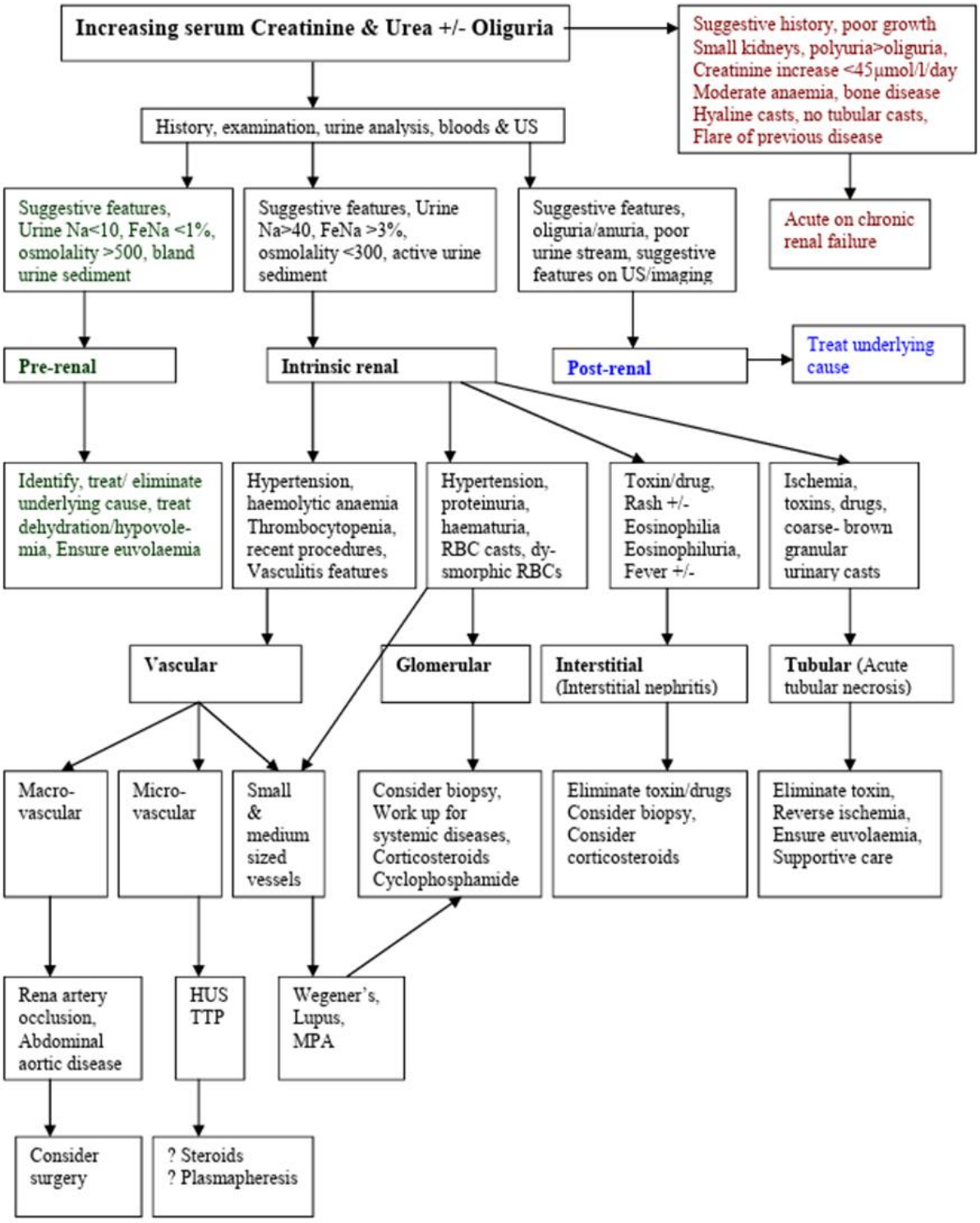
VII. Prognosis

- Prognosis depends on several factors, including the need for dialysis, the time between onset of illness and presentation to medical care, and the underlying disease.
- Neonates and children who survive AKI are at high risk of ongoing kidney injury, including chronic kidney disease [13].
- Therefore, early identification of patients who have AKI and early intervention are necessary to improve the current 10% to 60% mortality rates associated with these risk factors.

VIII. Prevention

- Avoidance of hypotension
- Modification and replacement of nephrotoxic drugs
- Prevention of contrast nephropathy.

Algorithm for the diagnosis and treatment of acute kidney injury



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URINARY TRACT INFECTION IN CHILDREN

HENG Sothy, KAO Sambath, MILIYA Thyl

I. Key facts

- Urinary tract infection (UTI) is a common and important clinical problem in childhood. Awareness of the prevalence of UTI in various subgroups of children enables the clinician to grossly estimate the probability of infection in the patient (ie, the pretest probability). This information is important in the evaluation of a child with suspected UTI. [1]
- Escherichia *coli* is the most common bacterial cause of UTI; it accounts for approximately 80 percent of UTI in children. [2]

II. Overview [1,2,3]

The term **"urinary tract infection (UTI)"** covers the whole spectrum of infection from asymptomatic bacteriuria to severe pyelonephritis. The clinical presentation of UTI in children can vary by age.

1. Definition

- Asymptomatic bacteriuria occurs in all age group and does not necessarily result in clinical infection
- Lower urinary tract infection (cystitis): infection of the lower part of the urinary tract (bladder)
- Pyelonephritis**:** infection and inflammation of the renal parenchyma
- Complicated UTI: consider in children with structural abnormalizes such as vesicoureteral reflux or other congenital anormal or whom are immunocompromised.

2. Causes

Pathogens most frequently associated with urinary tract infections

- Enterobacterales (including multidrug resistant such as ESBL)
  - *Escherichia coli* (responsible for 80%)
  - *Klebsiella* sp
  - *Proteus mirabilis*
- Enterococcus sp
- Pseudomonas *aeruginosa.*

3. Risk factors [4]

a. Host factors: the urinary tract is normally sterile and fairly resistant to bacterial colonization (except the urethra). Host antibacterial mechanisms include urinary flow and pH, bactericidal cytokines, inhibitors of bacterial adherence, local immune responses, and the inhibitory effect of prostatic fluid secretions. Individuals who are particularly susceptible to UTIs may have defects in these mechanisms. Abnormalities of the urinary tract may also undermine the effectiveness of the host response.

b. Organism factors: infection may be caused by many bacterial species, each of which has its own virulence factors, e.g. *E. coli* has P fimbriae which facilitate adherence to the uroepithelium. Bacteria enter the urinary tract by ascending the urethra, or

haematogenous. Haematogenous spread is less common but occurs in the context of staphylococcal bacteraemia/endocarditis or candidemia.

III. Signs and symptoms [5]

1. History

- Infants and pre-verbal children often present with non-specific symptoms such as fever, vomiting, poor feeding, lethargy and irritability
- Older children may present with more typical symptoms such as dysuria, urinary frequency, lower abdominal and loin pain
- Ask about previous UTI.

2. Examination

- Examination may be normal in UTI other than the presence of fever
- Lower abdominal or loin tenderness may be present
- Non-specific findings include dehydration and lethargy.

3. Assessment of severity

- Clinical distinction between lower and upper UTI can be difficult, especially in younger children
- Cystitis is suggested by features such as dysuria, frequency, urgency and lower abdominal discomfort
- Pyelonephritis is suggested by systemic features such as fever, malaise, vomiting and loin tenderness.

IV. Diagnosis

1. Microbiology: [6,7]

a. Sample collection

- Children with suspected UTI should have a urine sample collected prior to starting antibiotic, unless child is seriously ill and require urgent IV therapy.
- A clean catch specimen is difficult to obtain but is preferred to a specimen obtained with a urine collection bag.
- Midstream urine preferred method for toilet-trained children who can void on request the contamination rate is still 25%
- Suprapubic aspiration is a gold standard however it is not practical in current situations.

b. Urine dipstick and microscopy

- is a useful screening test to guide initial management however interpreting result needs to be conscious
- Presence of leucocytes and nitrites is suggestive of a UTI
- Result is less reliable in neonates and young infants (due to false negative)
- Laboratory microscopy can complement dipstick results to guide initial management
- Leucocyte on microscopy (pyuria) are suggestive of UTI, but a positive culture is required to confirm the diagnosis.

c. Urine culture

- Urine culture is necessary for a definitive diagnosis of UTI. [3]
- A clear definition of significant UTI using counts of colony-forming units (CFUs) is complicated, as the counts may vary based on the method of specimen collection, the presence of diuresis, and the time and temperature of urine specimen storage.
- Growth of a single organism at >105 CFU/ml (108CFU/litre) from any collection method suggestion infection
- Growth of a single organism at lower counts of >10 3-5 CFU/ml (106-8 CFU/litre) from SPA and clean catch of MSU may indicate early infection
- Growth of any amount from SPA suggests infection.

2. Other investigation

Other laboratory such as whole blood cell count, C-reactive protein, renal function,

blood culture, Lumbar Puncture (LP) if the children seriously unwell or not responding to appropriate therapy after 48hours.

3. **Imagery:**

Consider an ultrasound of the renal tract if repeated UTIs to look for anatomical abnormalities or, if not responding to treatment for pyelonephritis, to rule out a collection.

V. Complications

Renal complications of acute pyelonephritis are uncommon but may include:

- Renal scarring
- Renal abscess
- Occlusion of existing partial ureteropelvic junction obstruction
- Acute kidney injury due to dehydration.
-

VI. Treatment [8,9]

- Antimicrobial recommendations may vary according to local antimicrobial susceptibility patterns. The below table will provide couples antibiotic options
- Antibiotic treatment is usually given empirically if there are compatible signs and symptoms of a UTI and a positive test (urine analysis or urine culture).

Table 1. ***Empiric antibiotic treatment from lower UTIs***

Name	Dose	Frequent	Route	Duration
Co-amoxiclav	50 mg/kg/dose	12 hours	Oral	3-5 days
Ciprofloxacin	10 mg /kg/dose	12 hours	Oral	3-7 days
Nitrofurantoin	2 mg/kg/dose	12 hours	Oral	5 days

Table 2. ***Empiric antibiotic treatment from pyelonephritis***

Name	Dose	Frequent	Route	Duration
Ceftriaxone	80 mg/kg/dose	24hours	IV	10 – 14 ds.
Meropenem* - Age <7 days - Age 7-28 days - 1m – 12 yr &<50kg - 1m – 12 yr &≥50kg	 20 mg/kg/dose 20 mg/kg/dose 20 mg/kg/dose 1000 mg total dose	 12 hours 8 hours 8 hours 8 hours	IV	10 – 14 ds.

** If severely unwell or develops sign of septic shock*

VII. Prevention and Education [10]

- Have the child wear loose fitting underpants and clothing
- Increase the children intake of fluids
- Keep the child genital area clean to prevent bacterial from entering the urethra
- Teach the child to go the bathroom several time every day
- Teach the child to wipe the genital area from front to back to reduce the chance spreading bacterial from the anus to urethra.

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Chapter VIII: Hematologic and Oncologic Diseases

ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN

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I. Key facts

Leukemia is the most common malignancy of childhood, accounting for 30% of Cases of childhood cancer. Although there are some associations between environmental Or host factors, most leukemia diagnosis in children are sporadi.

There are 3 main subtypes of leukemia:

- Acute lymphoblastic leukemia (ALL),
- Acute myelogenous leukemia (AML), and
- Chronic myelogenous leukemia (CML).

ALL is the most common subtype, accounting for approximately 80% of cases. ALL is five Times more common in children than acute myeloid leukemia (AML). [1,6]

II. Overview

1. Definition:

Acute lymphocytic leukemia (ALL) is a malignancy of B or T lymphoblasts characterized by uncontrolled proliferation of abnormal, immature lymphocytes and their progenitors, which ultimately leads to the replacement of bone marrow elements and other lymphoid organs resulting in a typical disease pattern characteristic of acute lymphocytic leukemia.[7]

2. Epidemiology:

- The annual incidence of ALL within the United States is 3.7-4.9 cases per 100,000 children 0-15 years of age.
- Peak incidence occurs between 2 and 5 years of age.
- White children are more frequently affected than Black children
- Predominant sex: M > F
- ALL categories are B lineage 85%, T lineage 10-15% and NK <1%. [1,4]

3. Etiology

The etiology of ALL is unknown, but an increased incidence has been associated with certain Environmental or genetic risk factors. Although several genetic and environmental factors are associated with childhood leukemia, exposure to medical diagnostic radiation both in utero and in childhood has been associated with an increased incidence of ALL.

- Genetic predisposition: Identical twins, Trisomy 21 (Down syndrome), Ataxia
- Telangiectasia, Bloom syndrome, Neurofibromatosis type 1, Congenital hypogammaglobulinemia.
- Immunodeficiencies: Prolonged immunosuppressive therapy is related to lymphoid malignancies.
- Exposure to ionizing radiation (not diagnostic x-rays).
- Chemical exposure.
- Epstein-Barr virus is implicated in Burkitt leukemia/lymphoma.
- Other risk factors include in utero x-ray exposure and therapeutic postnatal radiation. [1,2,4]

4. Pathogenesis

Acute lymphoblastic leukemia is caused by a series of acquired genetic aberrations. Malignant transformation usually occurs at the pluripotent stem cell level, although it sometimes involves a committed stem cell with more limited capacity for self-renewal. Abnormal proliferation, clonal expansion, aberrant differentiation, and diminished apoptosis (programmed cell death) lead to replacement of normal blood elements with malignant cells.[5]

5. Classification:

All cases of B-ALL/LBL should be categorized according to the WHO classification because of their prognostic significance and/or distinctive requirements for therapy: [1,4]

- WHO Classification 2016:
  - B-lymphoblastic leukemia:
    - B-ALL/LBL, not otherwise specified (NOS)
    - B-ALL/LBL with recurrent genetic abnormalities:
      - Philadelphia chromosome (Ph+); t (9;22) (q34.1; q11.2); *BCR: ABL1*
      - T(v;11q23.3); *KMT2A*-rearranged
      - T (12;21) (p13.2; q22.1); *ETV6:RUNX1*
      - Hyperdiploid B-ALL/LBL
      - Hypodiploid B-ALL/LBL
      - T (5;14) (q31.1; q32.1); *IGH:IL3*
      - T (1;19) (q23; p13.3); *TCF3:PBX1*
  - T- lymphoblastic leukemia
- French-American-British (FAB) classification of acute lymphoblastic leukemia (for historical purposes)
  - ALL-L1: small unform cells
  - ALL-L2: Large varied cells
  - ALL-L3: Large varied cells with vacuoles (bubble-like features)
- Central nervous system (CNS) disease in divided:
  - CNS-1: No lymphoblast in cerebrospinal fluid (CSF) regardless of the white blood cell count
  - CNS-2: <5 white blood cells (WBC)/microl in CSF with the presence of lymphoblast
  - CNS-3: ≥5 WBC/microl in CSF with the presence of lymphoblast

III. Signs and Symptoms

Assessment: History and physical examination:

- Persistent unexplained fever, pallor,
- Bone pain, arthritis, limping (43%)
- Petechia, Bruising, Bleeding (cutaneous and mucosae)
- Hepatosplenomegaly, and/or lymphadenopathy [1,4]

Physical Examination:

- Pallor, petechia and bruising
- Hepatosplenomegaly (61%)
- Lymphadenopathy (50%)
- Fever with Recurrent fevers, failure to respond to seemingly appropriate treatment
- CNS involvement: headache, vomiting, lethargy, and/or nuchal rigidity (5%)
- Testicular enlargement – Unilateral painless testicular enlargement (Rare<1%) [1, 4]

IV. Diagnosis

1. Laboratory:

- CBC with peripheral blood smear:
  - WBC< 10.000/mm3 (50%) or > 50.000/mm3 (20%)
  - Hb <10 g/dl (over 50%)
  - Thrombocytopenia (<100,000/mm3) (75%)
  - Peripheral blood lymphoblasts: the leukemic cells are often initially reported to be atypical lymphocytes.
- Bone marrow aspirate: >20% leukemic lymphoblasts is diagnostic.

- Flow cytometry/immunophenotype:
  - Cytochemistry: Myeloperoxidase (MPO) negative in ALL, positive define myeloid marker
  - Lymphoid antigens:
    - B cell (eg, CD19, CD20, CD22, CD79a, PAX5),
    - T cell (eg, CD1a, CD3, CD4, CD5, CD7, CD8),
    - NK cell (eg, CD56)
    - Myeloid antigens: (eg, CD13, CD33, CD11b, CD64)
    - Maturation antigens: (eg, CD34, CD117, HLA-DR)
- CSF examination with lymphoblast: CNS leukemia (mostly perform with Intrathecal chemotherapy at the same time)
- Coagulation profile: Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen
- Electrolytes, Serum uric acid, Potassium, phosphors, calcium, LDH to determine level of tumor lysis syndrome. [1,2,4]

2. Medical Imaging:

Chest X-ray or CT, ECG and ultrasound of the Heart, kidney and others.

3. Differential diagnosis:

Malignant conditions: [1,2,4]

- Burkitt lymphoma
- Acute myeloid leukemia (AML)
- Mixed phenotype acute leukemia (MPAL)
- Chronic myeloid leukemia (CML)
- Aplastic anemia
- Small round blue cell tumors (Ewing Sarcoma and PNET)

Nonmalignant conditions:

- Infectious mononucleosis
- Acute infectious lymphocytosis
- Idiopathic thrombocytopenic purpura
- Juvenile rheumatoid arthritis

4. Risk group stratification

Risk group	Criteria
Standard risk group	- Initial WBC count < 50 000/µl - Age > 1 year, ≤ 10 years - No initial CNS-involvement - No mediastinal involvement - CR by day 36 of therapy - No initial signs of high risk
High risk group	- At least one of the following: - Initial WBC count > 50 000/µl - Age < 1 year or > 10 years - Initial CNS-involvement - Mediastinal mass (on chest x-ray) - Absence of remission on day 36 of therapy - More than 1000 blasts/mm3 at day 8 in peripheral blood after the first week of monotherapy (steroid poor responder)

**Abbreviations: WBC: white blood cell, CNS: central nervous system, CR: complete remission*

V. Complications

1. **Acute complications may involve all organ systems and include the following:** [1-4]
   - Tumor lysis syndrome
   - Renal failure
   - Sepsis
   - Bleeding
   - Thrombosis
   - Neuropathy
   - Encephalopathy
   - Seizures
2. **Long term complication:** [1,4]
   - Secondary malignancy
   - Short stature (if craniospinal radiation)
   - Growth hormone deficiency
   - Learning disability
   - Cognitive defects
3. **Due to therapy:** [1,2,4]
   - Vincristine (VCR)
     - Syndrome of inappropriate antidiuretic hormonal
     - Hair loss
   - L-asparaginase
     - Pancreatitis
     - Coagulopathy leading to cerebral infarcts or thrombosis
   - Adriamycin/Doxorubicin/Daunorubicin
     - Cardiac toxicity
   - Cyclophosphamide
     - Hemorrhagic cystitis
     - Sterility
   - Methotrexate (MTX): Hepatotoxicity.

VI. Treatment

Below is the principal treatment to follow:

- Acute lymphoblastic leukemia (ALL) is a systemic disease, and treatment is primarily based on chemotherapy.
- Treatment for acute leukemia can include chemotherapy, steroids, radiation therapy, intensive combined treatments (including bone marrow or stem cell transplants), and growth factors. Chemotherapy: (Will follow the National Leukemia Protocol).
- Chemotherapy for ALL consists of three phases:
  - **a.** Induction phase: The goal of induction therapy is to destroy as many cancer cells as possible in order to achieve remission. (defined as the absence of detectable cancer cells in the body (usually less than 5% blast cells on the bone marrow). Induction: (6weeks) Vincristine, Daunorubicin, L-Asparaginase, Dexamethasone and IT (Intrathecal therapy [IT]: Methotrexate, Cytosar and Prednisolone).
  - **b.** Consolidation phase: is given soon after remission is achieved to further reduce the leukemic cell burden before the emergence of drug resistance and relapse in sanctuary sites (ie, testes, central nervous system [CNS])

Consolidation: (24weeks) Vincristine, Daunorubicin, L-Asparaginase, Dexamethasone, 6-mercaptopurine, Methotrexate and IT.

c. Maintenance Phase: to prevent disease relapse after induction and consolidation therapy.
Maintenance: continue until 2 years. 6-mercaptopurine, Methotrexate, Dexamethasone, Vincristine and IT. [3]

Drug	Induction	Consolidation 1	Consolidation 2	Consolidation 3
Dexamethasone PO	Weeks 1-5	Weeks 14-15	Weeks 22-23	Weeks 30-31
Daunorubicin IV (6h)	Weeks 2, 4*	Weeks8, 11, 14*	Week16, 19*	
Vincristine IV	Weeks 2-7	Weeks 14, 15	Weeks 22-23	Weeks 30, 31
6 Mercaptopurine PO		Weeks 8-13	Weeks 16-21	Weeks 24-29
Methotrexate IM		Weeks 8-13	Weeks 16-21	Weeks 24-29
MTX/ARA-C/Dexa IT	Weeks 1-5, 7	Week 14	Week 22	Week 30

Note.

- **Daunorubicin add on week 4th, 14th, and 19th for High-Risk Patient and in case of 10% lymphoblasts in bone marrow on day 15.*
- *Abbreviation: PO: orally, IM: intramuscular, IV: intravenous, IT: intrathecal*.

VII. Prognosis

- Patients younger than 1 year with acute leukemia have disease that is biologically distinct with a poor outcome.[4]
- The 5-year event-free survival (EFS) varies considerably depending on risk category, from 95% (low risk) to 30-80% (very high risk), 20% for patients younger than 90 days. Overall, the cure rate for childhood ALL is more than 80%. [4]
- Five-year survival rates for children diagnosed with ALL rose to 90% from 2000-2005, which was up from 84% in 1990-1994, Improvement in survival was observed for all age groups of children, except for infants younger than 1 year. In low-income countries (LIC), therapeutic results for pediatric ALL have been less encouraging due to delayed diagnosis, abandonment of therapy, and death from toxicity due to suboptimal supportive care. [1,4]

VIII. Recommendation and Education

- In case of having suspected case of ALL → transfer a patient to Pediatric Oncologic Center where the diagnosis and treatment can be done.
- Explain about the general information of Acute lymphoblastic leukemia
- Counsel the patient of the strategy, duration and the therapeutic outcome of the treatment
- Give an explanation for patient about the life-threatening complication of leukemia (risks of infection, transfusion, chemotherapy).

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ACUTE MYELOBLASTIC LEUKEMIA IN CHILDREN

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I. Key facts

- Leukemia is an uncontrolled proliferation of immature abnormal white blood cell precursors of varying hematopoietic lineages If untreated it results in death.
- It usually originates in the bone marrow, where normal blood cells are replaced by leukemic cells. Leukemic cells can leave the marrow and spread to extramedullary sites.
- Leukemia is the most common cancer in children. It occurs in all age groups. 75% of leukemias in children are acute lymphocytic (ALL), 15-20% acute myeloid leukemia (AML) and 2-5% undifferentiated acute leukemia. Chronic myelogenous leukemia (CML) accounts for only 2-4% of childhood leukemias (1) and chronic lymphocytic leukemia (CLL) does not occur in children.
- Incidence of AML in infants is 1.5 per 100,000 per year, decreases to 0.9 per 100,000 in individuals aged 1-4 and 0.4 per 100,000 in individuals aged 5-9 years. It is more frequent in adults. [2]

II. Overview

1. Definition

Acute myeloblastic leukemia myeoid precursor cells with aberrant differentiation. [1]

2. Etiology

Most cases of AML have one or more chromosome abnormalities. In some the chromosomal abnormality is associated with heritable syndromes (Down syndrome, Fanconi anemia, Neurofibromatosis I, Bloom syndrome, Noonan syndrome Ataxia telangiectasia) or environmental exposures to ionizing radiation, cytotoxic chemotherapy (alkylating agents, topoisomerase inhibitors), benzene. Most children do not have a known predisposing factor.[1, 5]

3. Classification

- FAB: French American British Classification: Classifies AML into M0 through M7 based on morphology, immunophenotype and cytogenetic features (3)
- WHO classifies AML into six major disease entities: AML with recurrent genetic abnormalities; AML with myelodysplasia-related features; therapy-related AML; AML not otherwise specified; myeloid sarcoma; and myeloid proliferation related to Down syndrome (4).

4. Pathophysiology

The uncontrolled proliferation of maturation-arrested myeloid cells results in suppression of normal hematopoiesis. [5]

5. Risk prognostic factor [1]

	Favorable	Unfavorable
WBC	<100,000	>100,000
FAB class	M1 with Auer rods M3(APL), M4 with eosinophils	Infants with 11q23 Secondary AML with CNS involvement
Ethnicity	White	Blacks
Chromosomal abnormalities	T (8;21) Inv (16)	T (9;22) FLT3/ITD

	Favorable	Unfavorable
	T (15;17) (APL)	Monosomy 5 and 7(5q) and (3q) Complex chromosome changes
	Rapid response to therapy in bone marrow, ie., MRD negative at the end of induction	Expression of MRD + at any time during treatment
Time of relapse	>1 year from diagnosis	<1 year from diagnosis

**MRD: minimal residual disease*

III. Signs and symptoms [6]

- Bone marrow replacement by leukemic cells resulting in cytopenias:
  - Low hemoglobin: pallor, fatigue, dyspnea, tachycardia
  - Low platelets: petechiae, bruising or bleeding
  - Low white cells: increased risk of infection, fever
- Systemic signs and symptoms resulting from leukemic cell infiltration
  - Organomegaly: liver, spleen, lymph nodes, tonsils
  - Deposits of leukemic cells (chloromas): skin and other sites
- Others:
  - CNS infiltration : Headache, vomiting, focal neurologic signs, seizures, confusion
  - Bone and joint pain
  - Testicular swelling, priapism, acute kidney injury due to tumor lysis
  - Hyperleukocytosis with capillary thrombi in the lungs (hypoxia), CNS (changes in consciousness), and other organs.

IV. Diagnosis

1. **Laboratory studies**:[1, 5, 7]
   - Complete blood count: cytopenias or leukocytosis
   - Blood smear: myeloblasts (large cytoplasm, fine nuclear, chromatin, prominent nucleoli, granules or Auer rods)
   - Coagulation profiles: Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen
   - Tumor lysis panel: electrolytes (especially hyperkalemia), hyperphosphatemia, hyper or hypocalcemia, hyperuricemia, elevated creatinine and BUN
   - Cerebrospinal fluid (CSF): CNS disease is defined as WBC < 5 with myeloblast (CNS2) and WBC ≥ 5 with myeloblasts (CNS 3)
   - Other tests: liver functions (AST, ALT, bilirubin)
   - Morphology by FAB (French American British classification): M0 to M7
   - Immunophenotype: Flow Cytometry of peripheral blood or bone marrow aspiration with ≥ 20% myeloblast
   - Cytogenetics:
     - Favorable cytogenetics: 20 to 30% of pediatric AML (chromosomal abnormalities t (8;21) and t (16;16)
     - High-risk cytogenetics: 15% pediatric AML: monosomy 7, monosomy 5, deletion of 5q, abnormalities of 3q, t (6;9) (p23; q34).
2. **Imaging:** Chest X-ray, abdominal ultrasound, heart ultrasound to evaluate cardiac function if anthracyclines will be used, search for infections. [6]
3. **Differential diagnosis** [1]
   - JMML: Juvenile myelomonocytic leukemia

- ALL: Acute lymphoblastic leukemia
- CML: Chronic myelogenous leukemia
- JRA: Juvenile rheumatoid arthritis and other autoimmune disorders
- Infectious diseases: mononucleosis, cytomegalovirus, hepatitis viruses
- Leukemoid reactions
- Other bone marrow diseases: myelodysplastic syndrome (MDS), myeloproliferative syndrome (MPS), aplastic anemia.

V. Complications

- Anemia, infection, bleeding and DIC a result from leukemia itself, or bone marrow suppression by chemotherapy [8]
- Cytotoxicity of chemotherapy and radiation therapy: cardiomyopathy, pulmonary/ liver/ kidney dysfunction, vomiting, hair loss, tiredness, poor appetite [9]
- Secondary malignancies, infertility, Neurocognitive abnormalities (seizures, learning disabilities) [10]
- Endocrine dysfunction: growth impairment, thyroid dysfunction [11]
- Appetite suppression, weight loss.

VI. Management

1. Supportive and prevention of complications

- Prevent or treat tumour lysis syndrome (TLS):
  - Hydration: give IVF at 2- or 3-times maintenance rate
  - Allopurinol 10mg/kg/day divided TID (if high WBC or significant organomegaly)
  - Leukocyte-reducing agent: Hydroxyurea 50mg/kg/dose BID (if WBC > 200,00 and/or signs of hyperleukocytosis [hypoxia, disturbance of consciousness])
  - Avoid potassium and calcium in IV fluids unless symptomatic from low levels- then only give small amounts
- Blood product transfusions
- Treat infection or neutropenic fevers. If unexplained fever with neutropenia for 10 days considered adding Amphotericin.
- Antibiotic prophylaxis: trimethoprim-sulfamethoxazole to prevent Pneumocystis pneumonia

2. Specific treatment

A. *Chemotherapy*: that can kill the abnormal blasts and allow normal cells to be produced. The protocol presented here is designed to limit morbidity and mortality in low/middle income countries (LMIC). It is divided into 3 phases: induction (2 treatments), intensive treatment (2 treatments), and nervous system treatment (given during both above phases). [12, 13]

a. Low Dose induction courses 1 and 2: Mitoxantrone (IV, Day 1,3,5), Cytarabine (SC, Day 1-10), Cytarabine (IT, Day 1)

- Medication dose:
  - Mitoxantrone (Mito): 5 mg/M^2 IV over 15 min
  - Cytarabine (arac): 10 mg/M^2SC every 12 hours
  - Intrathecal Cytarabine (arac): age-related(a)< 1 year: 15mg in 6 ml; 1 year: 20 mg in 8ml; 2 years: 25 mg in 10 ml; 3 year or more: 30 mg in 12 ml. All intrathecal drug in diluted in preservative-free saline
- Bone marrow: if CBC is normal after course 1 do not do a marrow but give low-dose induction course 2.
  - If there is no recovery of CBC (PMN < 1000 and/or platelets < 75000) by day 35 after start of induction course 1.

- ❖ If there is persistent leukemia switch to standard dose chemotherapy for induction course 2.
- ❖ If the marrow is aplastic repeated it weekly until there is CBC recovery or evidence of leukemia.

b. Standard Dose induction: Cytarabine (IV, Day 1-7), Daunorubicin (IV, Day 1,3,5), Cytarabine (IT, Day 1)
- Medication dose:
  - Cytarabine (arac): 100 mg/M^2 IV push
  - Daunorubicin: 50 mg/M^2 IV over 60 minutes
  - Cytarabine (arac): Intrathecal, age-related(a)
- Bone marrow after induction course 2 when the PMN are >1000 and platelets >75,000 or if there is no count recovery by day 35 form the start of induction course 2

c. Consolidation Courses 1 and 2: Cytarabine (IV, Day1-3), Cytarabine (IT, Day 1)
- Medication dose:
  - Cytarabine (arac): 1.5 gm/M^2 IV over 4 hours every 12 hours
  - Cytarabine (arac): Intrathecal, age-related(a)
- Bone marrow: after consolidation course 2 when ANC >1000 and platelets >75,000. If no CBC recovery by day 35 do marrow punction then.

d. If CNS involvement: (at diagnosis or during treatment) intrathecal (IT) chemotherapy weekly until clear on 2 consecutive occasions (see above). During treatment consider extending systemic chemotherapy by repeating induction therapies 1 or 2. For CNS relapse on treatment may also consider additional intrathecal medication (methotrexate) and/or irradiation

B. *Hematopoietic* stem cell transplantation: for very high-risk disease or if in second remission after relapse. Not currently available in Cambodia.

C. *Immunotherapy*: CAR T-Cells not currently available in Cambodia.

VII. Prognosis

The treatment required to achieve cure is more intensive compared to treatment for acute lymphoblastic leukemia (ALL) and thus contributes to more significant treatment related morbidity and mortality. In addition, even with intensive therapy and the frequent use of hematopoietic stem cell transplant (HSCT) in resource rich settings, the chance of achieving cure with treatment at the time of diagnosis is only 50-60%. In low- and middle-income countries (LMIC) or resource limited settings, the mortality associated with the disease and the treatment combined can be in excess of 50%. Further, data on cure rates for AML in LMIC are difficult to obtain but some studies have suggested successful treatment in approximately 20% of cases. The protocol listed here is that recommended by a panel for LMIC. (1, 13, 14).

VIII. Prevention and Education

AML is a life-threatening disease. Optimal treatment has a high risk for morbidity and mortality. Even with lower intensity protocol listed in this guideline the patient needs to be hospitalized for treatment and when neutropenic after treatment.

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ANEMIA IN CHILDREN

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I. Key Fact

- Anemia is a major global burden, affecting almost 2 billion people worldwide, particularly infants and young children.
- History and physical examinations are quite important as well as laboratory investigations.
- Managing a patient with anemia is in fact diagnosing the cause of anemia and then treating its cause accordingly.

II. Overview

1. Introduction:

- Anemia is a reduction of hemoglobin concentration lower than the age-adjusted reference range for healthy children which can occur in a wide range of disease spectrums. [1,2]

Normal Vales for Red Blood Cell Indices in Children		
Age	Hemoglobin (g/dl)	
	Mean	-2SD
1 month	13.9	10.7
2 months	11.2	9.4
6 months	12.6	11.1
6 months – 2 years	12	10.5
2 – 6 years	12.5	11.5
6 – 12 years	13.5	11.5

2. Etiology of anemia

Causes of anemia in children vary, depending on age at presentation, sex, and ethnicity. [3,4]

3. Age of the patient

a. Birth to three months:

- Physiologic anemia of infancy due to a reduction of erythropoietin production after birth.
- Pathologic anemia includes blood loss, immune hemolytic disease (i.e., Rh or ABO incompatibility), congenital infection, twin-twin transfusion, and congenital hemolytic anemia (e.g., hereditary spherocytosis, glucose-6- phosphate dehydrogenase [G6PD] deficiency)
- Anemia of prematurity.

b. Three to six months: Anemia detected at three to six months of age suggests a hemoglobinopathy such as thalassemia and sickle cell anemia. Nutritional iron deficiency is an unlikely cause of anemia before the age of six months in term infants.

c. Toddlers, children, and adolescents

- Acquired causes of anemia are more likely, particularly iron deficiency anemia.
- Screening for iron deficiency anemia is recommended in all children at 9 to 12 months of age. At that age, children who are exclusively breastfed or breastfed without sufficient iron supplementation are at the highest risk for iron deficiency.

- In contrast, infants who primarily receive iron-fortified formula during the first year of life are at risk for iron deficiency after a transition to cow milk. Therefore, additional laboratory screening should be considered in children with additional risk factors (e.g., excessive cow milk intake in toddlers 12 to 36 months of age, onset of menarche in adolescent females).

4. Sex of the patient

- Some inherited causes of anemia are X-linked (e.g., G6PD deficiency and X-linked sideroblastic anemia) and occur most commonly in males.
- In post-menarchal girls, excessive menstrual bleeding is an important cause of anemia.

5. Ethnicity

- Ethnic background can be useful in guiding the work-up for hemoglobinopathies and enzymopathies.
- Thalassemia syndromes are more common in individuals of Mediterranean and Southeast Asian descent.
- HGB S and C are most commonly seen in individuals of African or Hispanic descent, and Middle Eastern populations.
- G6PD deficiency is more common among Sephardic Jewish individuals; Black individuals from sub-Saharan Africa or Brazil; African Americans; and people from Thailand, Sardinia, Greece, South China, and India.

III. Diagnosis

Diagnosing a child with anemia should begin with a thorough history taking, and examination. [4]

1. History and symptoms

- Symptoms attributable to anemia: Lethargy, tachycardia, pallor, irritability, and poor oral intake. However, because of the body's compensatory abilities, patients with chronic anemia may have few or no symptoms compared with those with acute anemia at comparable hemoglobin (Hb) levels.
- Symptoms of hemolysis: Changes in urine color, scleral icterus, or jaundice may indicate the presence of a hemolytic disorder.
- Bleeding symptoms: Bleeding from the gastrointestinal tract, including changes in stool color, identification of blood in stools, and history of bowel symptoms. A history of severe or recurrent epistaxis, and/or heavy menstrual bleeding should raise suspicion for an underlying bleeding disorder.
- Pica: An intense craving for non-food items should be assessed since it can be a strong association with iron deficiency. In young children, pica may manifest as a craving for dirt, rocks, and paper. In adolescents, craving for ice may be more common.
- Medication history: Past and current medical history, particularly those that may cause hemolysis in children with G6PD deficiency, for example, drugs such as Fluoroquinolones, Dapsone, Nitrofurantoin as well as Sulfonylureas.
- Interrogate for a diet history of iron-rich foods, breastfeeding, cow milk, and vitamin B12 intakes. Moreover, a recent fava/broad bean ingestion may precipitate hemolysis in children with G6PD deficiency.
- Family history: Anemia, jaundice, gallstones or splenomegaly, family history of inflammatory bowel disease, celiac disease, intestinal polyps, colorectal cancer, or consanguineous marriage.
- Medical history: Any history of underlying disease or chronic illness

- Developmental history: Developmental delay can be associated with iron deficiency, lead toxicity, vitamin B12/folic acid deficiency, and Fanconi anemia.

2. Examination

- Poor growth
- Fatigue
- Pallor, Pale conjunctivae
- Tachycardia
- Cardiac murmur or signs of cardiac failure
- Shortness of breath
- Signs of hemolysis (jaundice, scleral icterus, splenomegaly, and dark urine.)
- Hepatosplenomegaly (suggestive of malignancy)
- Sign of other nutritional/ multivitamin deficiency.

3. Investigations

- Complete Blood Count (CBC) and RBC indices (MCV, MCH, MCHC)
- Blood film/smear
- Reticulocyte count
- Iron profile *
- Hemoglobin electrophoresis *
- Bone marrow examination *
- DNA test *

Noted:

- CBC, RBC indices, blood smear, and reticulocytes are required to differentiate the diagnosis considerations as well as the etiology of anemia.
- (*) If history, physical examination, and other laboratory profiles suggest, prompt further investigation is recommended.

4. Classification of anemia according to red blood cell size (mean cell volume) and reticulocyte count

Anemia is classified based on the mean cell volume (MCV) and the reticulocyte response. These classification schemes help to narrow the diagnostic possibilities.

a. Microcytic anemia

- The most frequent causes are iron deficiency and thalassemia.
- Red blood cell distribution width (RDW) can be helpful in differentiating iron deficiency (IDA) from thalassemia.
- RDW > 18%: is strongly suspicious of IDA.
- RDW > 18%: can be thalassemia.

b. Normocytic anemia

- Common causes are hemolytic anemia, blood loss, infection, medication, and anemia of chronic disease.
- Other causes can be hypothyroidism and chronic kidney disease.

c. Macrocytic anemia

- Most seen in patients with exposure to certain medications (e.g. Anticonvulsants, zidovudine, and immunosuppressive agents).
- Other causes: vitamin B12 or folate deficiency, liver disease, Diamond-Blackfan anemia, hypothyroidism, and aplastic anemia.

d. Reticulocyte response

Particularly helpful in evaluating children with normocytic anemia:

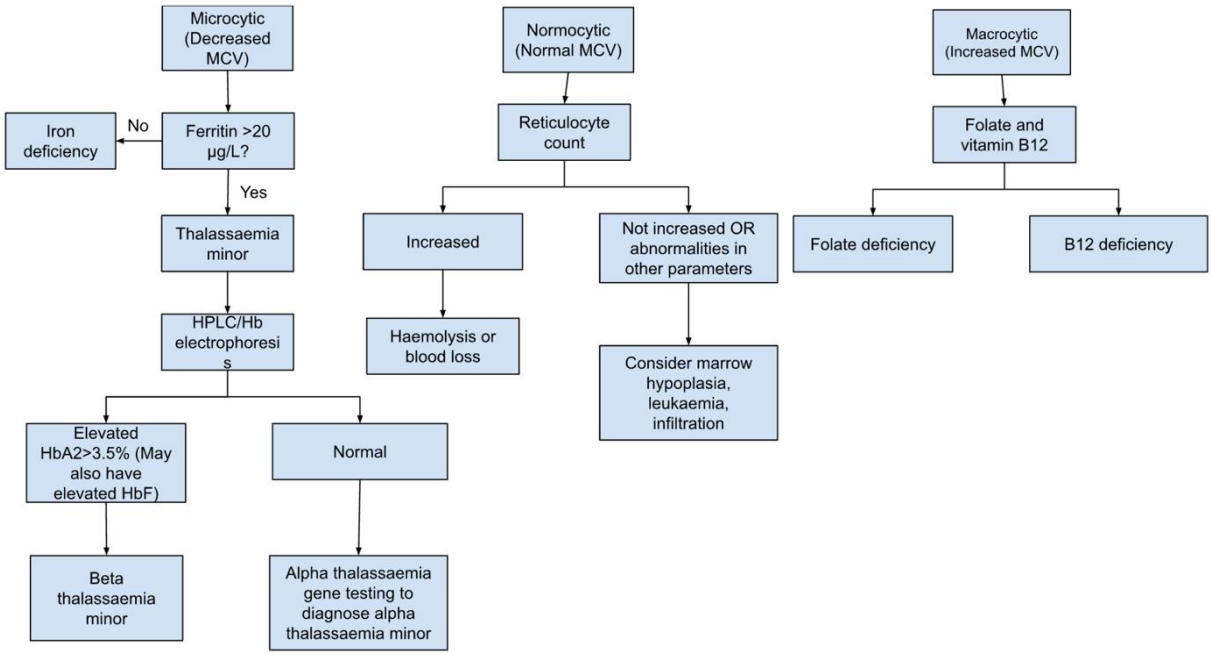
- High reticulocyte count reflects an increased erythropoietic response to blood loss or hemolysis.

- Low or normal reticulocyte count indicates a deficient production of rbcs (for example: a reduced marrow response to anemia).

A summarize of laboratory findings in some causes of anemia

Condition	Hemoglobin	MCV (Mean Corpuscular Volume)	MCH (Mean Corpuscular Hemoglobin)	Ferritin	Serum Iron	Peripheral Blood Smear
Iron Deficiency Anemia	Decreased	Decreased	Decreased	Decreased	Decreased	Microcytic, hypochromic rbcs
Thalassemia	Decreased	Decreased (Microcytic)	Decreased	Normal	Normal	Target cells, basophilic stippling
G6PD Deficiency	Normal (except during hemolysis episodes)	Normal	Normal	Normal	Normal	Heinz bodies, bite cells during hemolysis
Folate Deficiency	Decreased	Increased (Macrocytic)	Normal or increased	Normal	Normal	Macrocytic, megaloblastic rbcs
Leukemia	Variable	Variable (can be normal, increased, or decreased)	Variable	Normal	Normal	Blast cells, abnormal white cells, possible anemia

The initial classification is based on the mean corpuscular volume



IV. Treatment

Treatment depends on the severity and underlying causes of anemia.

1. Iron deficiency
   - A daily total dose of 3 – 6mg/kg of elemental iron (A 200mg tablet of iron consists of 65mg of elemental iron) in one or two doses is adequate with a higher dose used in more severe cases.
     - ≤10kg: 0.5tab QD PO
     - Above 10kg-25kg: 1tab QD PO
     - >*25kg*: 2tab QD PO
   - The maximum dose is 150 – 200mg of elemental iron daily.
   - The duration of treatment can be from 3 to 6 months
   - Iron therapy should be continued at least 2 months after the Hb has returned to normal to replenish the iron stores.
   - Iron tablet should be taken 2 hours after meals or 1 hour before meals.
2. **Thalassemia**
   - Dietary supplement with folic acid and multivitamins without iron is indicated.
   - Regular blood transfusion and iron chelation therapy are the mainstay of treatment in severe cases.
3. **Aplastic** anemia / Leukemia
   - Always consult with a hematologist or haemato-oncologist for proper management.
4. **G6PD** deficiency
   - Should be considered in any neonatal patients with hyperbilirubinemia and it is recommended to screen all newborns for G6PD enzyme activity
   - Avoid certain drugs and fava beans.
5. **Vitamin** B12 and Folate deficiency
   - When the diagnosis of folate deficiency is established, folic acid should be administered orally or parenterally at 0.5-1.0 mg/day.
   - For vitamin B12 deficiency, cyanocobalamin is recommended.
   - Consult with hematologist if no improvement after treatment.

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APLASTIC ANEMIA

NEANG Sereyvorleak, LAM Pechkethia, PHAUK Chinith

I. Key fact

- Aplastic anemia (AA) is a rare but fatal disease. [1]
- It can be inherited but the majority of cases are acquired and the cause is unknown.
- The gold standard of therapy remains hematopoietic stem cell transplantation with a graft of bone marrow cells for those children with matched sibling donors.
- Conversely for children without a sibling donor, the high response and markedly improved overall survival rates have proven robust with combined immunosuppressive therapy (IST) consisting of antithymocyte globulins plus cyclosporine A.

II. Overview

1. Introduction

- Aplastic anemia is a rare, potentially fatal disease due to failure of hematopoiesis, characterized by peripheral blood pancytopenia and a hypocellular bone marrow without dysplasia or fibrosis.
- Fibrosis belongs to the group of malignant myeloproliferative disease when bone cells produce too many blood cells to grow and function abnormally.

2. Etiologies

The causes of aplastic anemia can be: [2]

- *Idiopathic* – 80%: Idiopathic is an unknown etiology, this term is increasingly replaced by *"Immune-mediated AA"*
- Etiologies Associated with Acquired Aplastic Anemia [3]
  - *Post-hepatitis* – 9%: Hepatitis-associated, typically seronegative
  - *Infectious*, *post-viral infection* – 7%: Infectious Epstein-Barr Virus, Cytomegalovirus, Parvovirus Mycobacterial Infections, Human Immunodeficiency Virus, Human Herpes Virus 6 Varicella Zoster Virus, Measles, Adenovirus and others.
  - *Drugs and chemical agents/toxins* – 4%:
    - Non-steroidal anti-inflammatory drugs, Antibiotics, Anticonvulsants such as Chloramphenicol, Carbamazepine and Sodium Valproate, Sulfonamides, Gold Salts, …
    - Many additional agents rarely associated with aplastic anemia such as Benzene, Insecticides, Pesticides, Solvents, …

III. Signs and symptoms

The clinical manifestation of aplastic anemia (AA) is variable, including symptoms and signs related to cytopenia in each of the three cell lineages: [4]

- Hemorrhagic manifestations secondary to thrombocytopenia.
- Fatigue, pallor, and cardiovascular complaints caused by progressive anemia.
- Fever, mucosal ulcerations, and bacterial infections resulting from neutropenia.

IV. Diagnosis

- A diagnosis of AA is suggested by the presence of:
  - *Pancytopenia with absolute reticulocyte <100 x 109/L (in some laboratories normal range from 0.2- 2%) suggestive of bone marrow failure.*
  - *The red blood cells usually are normocytic but occasionally may be macrocytic (Mean Corpuscular Volume >100).*
  - *The* peripheral blood smear shows that the remaining elements, while reduced, are morphologically normal.

- The diagnosis of AA is established by bone marrow aspiration and biopsy. The characteristic findings include:
  - The *marrow is profoundly hypocellular with a decrease in all elements; the marrow space is now composed of fat cells and marrow stroma.*
  - *The residual hematopoietic cells are morphologically normal.*
  - *Malignant infiltrates or fibrosis are absent.*
  - *There* is no megaloblastic hematopoiesis.

V. Severity

The clinical outcome of acquired AA is dependent in part upon the severity of the Pancytopenia.

1. Non-severe aplastic anemia

Non-severe AA (n-SAA) is defined by fulfilling all three of the following findings:

- Bone marrow cellularity from 30% to less than 50%
- Two or three cell lines are depressed for >6 weeks as documented by
  - Absolute *neutrophil count (ANC): from 500 to less than 1500/ mm³,*
  - *Platelet counts: from 20,000 to 100,000/mm³,*
  - *Anemia* with absolute reticulocyte counts (ARC): from 20 to 60 x 109/L

2. Severe aplastic anemia

The criteria for severe aplastic anemia (SAA) are: [5,6]

- A bone marrow biopsy showing less than 25 to 30% of normal cellularity or
- A bone marrow biopsy showing less than 50% normal cellularity in which fewer than 30% of the cells are hematopoietic cells and at least present 2 of the following criteria:
  - *Absolute neutrophil count from 200 to 500/mm³*
  - *Platelet count <20,000/mm³*
  - *Absolute* reticulocyte count <20 x 10^9/L

3. Very severe aplastic anemia

The patient is considered to have very severe aplastic anemia (VSAA) when he/she met the criteria for SAA but with absolute neutrophil count < 200/mm^3. Unless patients with SAA or VSAA are successfully treated, over 70% will be dead within one year.

VI. Treatment

- Severe aplastic anemia (SAA) is life threatening which requires urgent evaluation and care by competent hematologic specialists. [7]
- Two major modalities for treatment of severe acquired aplastic anemia (AA) are hematopoietic cell transplantation (HCT) and immunosuppressive therapy (IST). [8]

1. Hematopoietic cell transplantation (HCT)

a. *HCT* from a matched sibling donor is the treatment of choice, with long-term disease-free survival rates approaching 90 percent but this method is currently not available in Cambodia.

b. *Intensive immunosuppressive therapy (IST)* for the remaining children, is the preferred option.

- Tri-*therapy*:
  - Methylprednisolone (IV) : 2mg/kg/d for 5 days
  - Anti-thymocyte globulin (ATG) : 15-30mg/kg/d for 5 days
  - Cyclosporine A : 6mg/kg/d divided in 2 doses for a year
- *Followed* up with pediatric hematologists and obtained laboratory tests during each follow-up. Follow-up can be assessed at 1 month, 3 months, 6 months and 12 months after treatment then yearly to monitor for evolution.
- *The* response to therapy may be slow, with granulocyte recovery occurring first, followed by stabilization of hemoglobin and a decline in transfusion requirements.

Platelet recovery may take months to years. Long-term survivors may show persistent thrombocytopenia, red blood cell macrocytosis, and elevated hemoglobin F concentrations.

❖ **Treatment response**

Table 2: *Response, No Response, Relapse after IST for Acquired AA* [3]

Complete Response (CR)	Red blood cell and platelet transfusion independence Absolute neutrophil count >1,500 /mm³ Platelet count > 150,000 /mm³
Partial Response (PR)	Improvement of cytopenia with Absolute neutrophil count ≥ 500/ mm³ And platelets ≥ 20,000 /mm³ +/− Transfusion dependent
No Response	Continues to meet SAA criteria Ongoing transfusion dependence
Relapse	Meets criteria of SAA or very SAA after initial response

❖ Long-Term Follow-up after intensive immunosuppressive therapy IST:

- CBC, reticulocyte counts, CRP, initially at least weekly
- CSA level, creatinine, liver enzymes, serum bilirubin, magnesium monitoring
- Transfusion support if hemoglobin < 8g/dl, platelets <10,000/mm³
- Repeat bone marrow aspirate, biopsy and cytogenetics at 3 months and 12 months or at sustained worsening of cytopenia
- Paroxysmal nocturnal hemoglobinuria testing annually
- Auto-immune disease screening at regular intervals (every 2–3 years)
- Transition to a specialty care center in the adult health care system which is familiar with the treatment and follow-up of patients with AA.

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THALASSEMIA

LAM Pechkethia, CHIN Soey, CHEAN Sophal

I. Keys fact

- Thalassemia major is an inherited blood disorder caused by defect in the synthesis of one or more of hemoglobin chain presenting with anemia at 4-6 months of age. [1]
- The severity of thalassemia depends on how many of four genes for alpha globin or two genes for beta globin are missing.
- In the majority of cases with lethargy, failure to thrive and hepatosplenomegaly
- In Cambodia, the thalassemia carrier rate is estimated at 30-50% in which 1% or more are major.
- The majority of Cambodian's are unaware of their carrier/thalassemia minor status.

II. Overview

1. Definition

Thalassemia is a heterogeneous group of inherited autosomal recessive disorders of hemoglobin synthesis.

2. Etiology

- Both types of thalassemia are inherited in the same autosomal recessive manner
  - Alpha-*thalassemia*: Involves missing or mutated genes on chromosome 16, leading to reduced production of alpha-globin.
  - Beta-*thalassemia*: Involves mutations on chromosome 11 that affect beta-globin production.
- The severity of the condition depends on the number and type of mutations in these genes.
- A child who inherits only one mutated gene is a carrier, called "thalassemia trait"

Figure 1. *Inheritance pattern for Alpha-thalassemia*

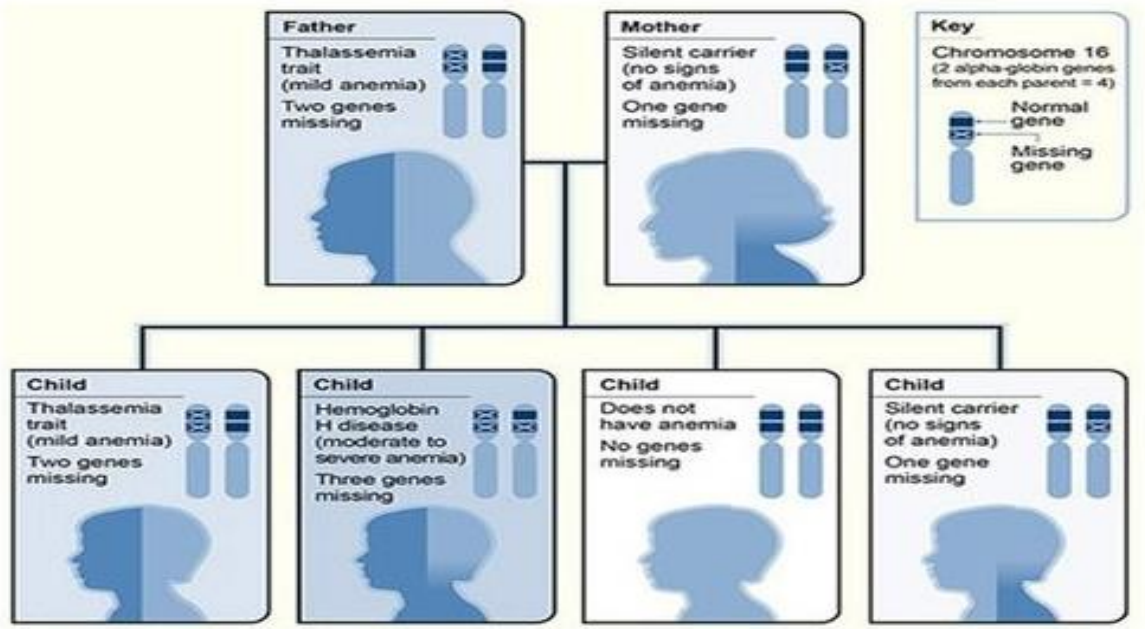
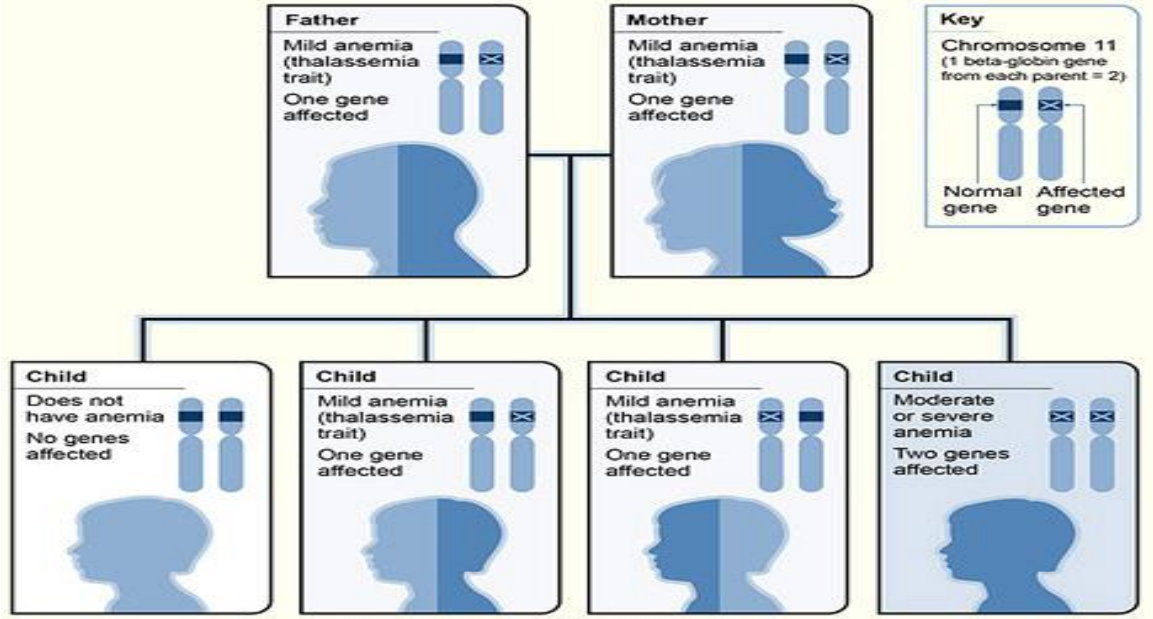


Figure 2. *Inheritance pattern for Beta-thalassemia*



3. Classification

c. Beta thalassemia

Table 1.

Genotype	Severity	Clinical presentation
B/β	Normal	None
B/β^0 B/β^+	B-Thalassemia trait	Thalassemia minor: asymptomatic, mild, microcytic hypochromic anemia
B^+/β^+ B^+/β^0 B^e/β^+ B^e/β^0	B-Thalassemia intermedia	Variable severity Mild to moderate anemia Iron overload
B^0/β^0	B-Thalassemia major	Severe anemia Blood transfusion dependence

d. Alpha Thalassemia

Table 2.

Genotype	Number of α globin gene	Severity	Clinical manifestation
Aα/αα	4	Normal	None
Aα/α-	3	Silent carrier	None (Hb and MCV nearly low)
--/αα A-/α-	2	A-Thalassemia trait	Thalassemia minor: Asymptomatic, Mild microcytic anemia
--/α-	1	Hb H disease	Alpha thalassemia intermedia: Mild to moderate microcytic anemia
--/--	0	A-Thalassemia Major	Alpha thalassemia major: Hydrops fetalis

III. Signs and Symptoms

Clinical manifestations of the thalassemia can be asymptomatic carrier to profound abnormalities as major form including: [3]

- Pallor, Fatigue, Jaundice, Hepatosplenomegaly
- Bone abnormalities: Bossing of skull, Saddle nose, wider and short nose, Maxillary protrusion, retraction upper lip, exposure of upper central teeth.
- Growth impairment

IV. Diagnosis

1. Complete blood count (CBC) and peripheral blood film

- Complete blood count:
  - ↓ *Hemoglobin level (Hb)*
  - ↓ *Mean corpuscular volume (MCV)*
  - ↓*Mean corpuscular hemoglobin (MCH)*
  - ↑ *Red blood* cell distribution width (RDW).

Table 3. *Reference rage of red cell index*

Age	Hb (g/dl)	RBC (x10^{12}/l)	MCV (fl)
Birth	14.9 – 23.7	3.7 – 6.5	100 – 135
1- 2 months	9.4 – 13.0	3.1 – 4.3	84 - 105
3 - 12 months	11.3 – 14.1	4.1 – 5.3	71 – 85
2 – 5 years	11.5 – 13.5	3.9 – 5.3	75 – 87
6 – 12 years	11.5 – 15.5	4.0 – 5.2	77 – 95
13 – 18 years, Female	12.0 – 16.0	4.1 – 5.1	78 – 95
13 – 18 years, Male	13.0 – 16.0	4.5 – 5.3	78– 95

2. RBC Morphology: Microcytic (small), Hypochromic

3. Serum iron & ferritin:

- Serum iron: normal or increase,
- Serum ferritin: normal or increase.

4. Hemoglobin typing or Hemoglobin electrophoresis

- The test is not useful if the patient has been transfused in the last 3 months)
- Hemoglobin electrophoresis is used as a screening test to identify normal and abnormal hemoglobin and assess their quantity.
- Normal Hemoglobin electrophoresis:
  - Hba (*2α2δ): 95 – 98%*
  - *Hba2 (2α 2δ): 2 – 3 %*
  - *Hbf (2α* 2γ): < 2%.

Table 4. *Abnormally of Hb typing Patten*

Beta-thalassemia	Hba decreased or absent Hba2 increased Hbf increased
Hbe/Beta-thalassemia	Hba decreased or absent Hba2 and hbf variable Hb E
Alpha-thalassemia	Hba decreased

	Hba2 decreased Hbh, hbcs and Hb Barts variable

5. Serum Ferritin, Liver function tests, Co-infection screening: HIV, hepatitis B & C and syphilis.
6. Genotyping (DNA analysis) is an optional test which can be done to confirm unusual Hb variants and carrier status for prenatal investigations.

❖ **Differential diagnosis**

- Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency
- Iron Deficiency Anemia
- Sideroblastic Anemias
- Lead poisoning.

Table 5. *Differential diagnostic analysis*

Condition	Causes	Type of Anemia	Key Lab Findings	Key Symptoms
Thalassemia	Genetic mutations in hemoglobin	Microcytic, hypochromic	Abnormal Hb typing	Fatigue, jaundice, splenomegaly
G6PD Deficiency	Enzyme deficiency (X-linked)	Hemolytic (normocytic)	Low G6PD enzyme, hemolysis post triggers	Hemolysis after exposure to triggers
Iron Deficiency Anemia	Lack of iron intake/absorption	Microcytic, hypochromic	Low iron, low ferritin, high TIBC	Fatigue, pica, pallor
Sideroblastic Anemia	Defective heme synthesis	Microcytic or normocytic	Ring sideroblasts, high iron and ferritin	Fatigue, enlarged spleen, pallor
Lead Poisoning	Lead exposure	Microcytic or normocytic	Basophilic stippling, high lead levels	Developmental delays, abdominal pain

V. Management

Regular maintenance blood transfusion and iron chelation therapy are the main goals of treatment in patients with transfusion dependent thalassemia.[4]

1. Blood transfusion

a. Beta-Thalassemia major

- Pack red cell transfusion if:
  - Hb < *7g*/dl
  - Hb > *7g*/dl in the presence of impaired growth, bone changes & enlarging liver & spleen.
- Maintain pre-transfusion Hb level between 9.5 – 11.5 g/dl
- Current recommendation is to keep mean post transfusion Hb level 12 – 12.5 g/dl. This allows for normal physical activity and growth, abolish chronic hypoxemia and reduce compensatory marrow hyperplasia.
- Transfusion interval is usually 4-weekly, interval varies from individual patients (range: 2 - 6 weekly)
- Volume of 20 ml/kg (maximum) packed red cells not over 4 hours
- In the presence of cardiac failure or Hb < 5g/dl, use low volume packed cells (<5ml/kg) at slow infusion rate over 4 hours with furosemide 1 mg/kg (20 mg maximum dose).
- It is recommended for patients to use leuco-depleted packed cells (LPRC) or packed red cells < 1week old and bedside filters to prevent non-hemolytic febrile reactions by removing the white cells.

b. Beta-Thalassemia intermedia

- Late onset anemia and milder forms of β - thalassemia, presenting later than 2 years with Hb 8g/dl or more.
- The severity of these patients is very heterogeneous from being symptomatic at presentation to being asymptomatic until later in adult life.
- If they require regular transfusion, follow β - thalassemia major transfusion regimen.

c. Alpha-Thalassemia (Hb H disease): Transfuse only if Hb < 7g/dl or symptomatic

2. Iron chelation therapy

- Iron chelator is indicated when age > 2 years old
- Serum ferritin reaches 1000 ng/ml.
- Dosage [6]

Table 6. *Iron chelation therapy*

Chelator	Deferoxamine	Deferiprone	Deferasirox
Administration	Parental - SC or IV	Oral	Oral
Frequency	8–12 h, 5–7 days per week	Every 8 h, TID	Once daily
Route of iron excretion	Urinary and fecal	Urinary	Fecal
Recommended dose	30–60 mg/kg/d	75–100 mg/kg/d	20–40 mg/kg/d
Possible adverse event	Reaction at site of infusion, severe allergic reactions, bone abnormalities, growth failure, hearing loss, retinal damage	Gastrointestinal, arthralgia, transient increase in liver enzymes, neutropenia, agranulocytosis	Increased GFR and serum creatinine, proteinuria, (rare) renal failure, increased liver enzymes, skin rash, gastrointestinal, (rare) GI bleeding
Pregnancy	Can be used only at the end of the second trimester,	Contraindicated	Contraindicated

3. Monitoring of patient

- During each admission for blood transfusion, the following should be done and noted:
  - Clinical *assessment* – height, weight, liver & spleen size assessment. [5]
  - Pre-*transfusion* Hb, Platelet count
  - Any *immediate* or delayed transfusion reactions, must be investigated (Alloimmunization red cell antibody)
- Every 3-6 months: Serum Ferritin, LFT
- Every year or more frequent if indicated
  - *Evaluate* growth and development, Endocrine assessment – Blood sugar, T4/TSH, Ca (If Ca^{++} low – check PTH & Vitamin D), Sexual development from 10 years onwards, Tanner stage, FSH/LH, Estradiol/testosterone
  - *Infection* screen – Hepatitis B & C, HIV and Syphilis.
  - Bone – *osteoporosis* & skeletal abnormalities,
  - Cardiac assessment at variable intervals.

4. Splenectomy

The use of splenectomy in thalassemia has declined in recent years, due to a decreased prevalence of hypersplenism in adequately transfused patients.

- Indication:
  - *Blood* consumption > 220-250 ml/kg/year with packed red blood cells (hematocrit 75%) in those > 5 years of age.

- *Hypersplenism* > 10cm,
- *Splenic* infarction or splenic vein thrombosis.

- Pneumococcal, Meningococcal and HIB vaccinations (if not previously vaccinated) 4-6 weeks prior to splenectomy are required.
- After splenectomy, patients should receive oral penicillin prophylaxis (250 mg twice daily) and low dose aspirin (1-3 mg/kg/day, maximum 81 mg/day) may be required if there is thrombocytosis > $800x10^9$/L.

VI. Education

1. Diet and supplement

- Oral Folate at minimum 2 mg daily may benefit most patients.
- Low dose Vitamin C at 3 mg/kg to enhance iron excretion for those on Desferal. (Dose: <10 years, 50 mg daily; > 10yrs, 100 mg daily given only on deferral days).
- Avoid iron rich food such as red meat and iron fortified cereals, tea may help decrease GI iron absorption.
- Dairy products are recommended as they are rich in calcium

2. Vaccination

- Optimal immunization is critical for all patients with thalassemia, especially transfused patients and individuals who have been splenectomized.
- Patients need to be immunized against hepatitis A and B, especially patients on chronic transfusions.
- Individuals who are HIV positive or undergoing treatment for hepatitis C should not receive live virus vaccines.
- An annual influenza vaccination should also be administered.

3. Prenatal diagnostic

This can be done by chorionic villous sampling at 9 – 11 weeks of gestational age, amniocentesis is currently available certain centers in Cambodia.

4. Genetic counselling

Genetic counseling is the communication process of providing information and support to individuals and families with a diagnosis and/or risk of occurrence of an inherited disorder. Culturally sensitive genetic counseling, with an emphasis on reproductive issues, is an integral and necessary component of comprehensive care for patients and parents affected by all forms of thalassemia disease and trait.

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HEMOPHILIA

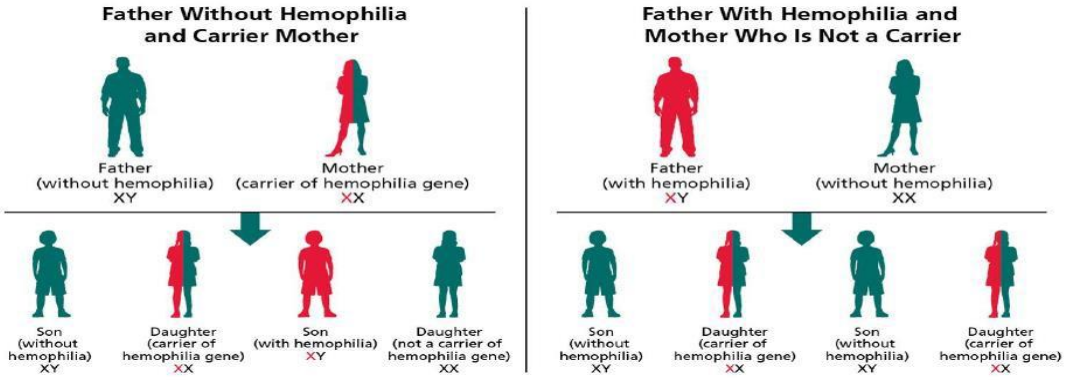
LAM Pechkethia, TRY Lytheang, PHAUK Chinith, CHEAN Sophal

I. Key facts

- Hemophilia is a rare X-linked congenital bleeding disorder characterized by a deficiency of coagulation factor VIII (FVIII) or factor IX (FIX).
  - Hemophilia A – Deficiency of factor VIII (85% of the cases)
  - Hemophilia B – Deficiency of factor IX (15% of the cases)
- An X-linked recessive inheritance, but in 30% there is no family history as it is a spontaneous new mutation.

II. Overview

- The best estimates of the prevalence of males with hemophilia worldwide is 1,125,000, the majority of whom are undiagnosed, including an estimated 418,000 males with severe hemophilia [1].
- Hemorrhages, musculoskeletal complications, and other sequelae of hemophilia typically occur in males with hemophilia but may also occur in a proportion of female carriers.
- How hemophilia is inherited
  - Hemophilia's patient usually affects only males who inherit an affected X chromosome from his mother.
  - A female with one affected X chromosome is called a carrier of hemophilia
  - A female with hemophilia (FVIII or FIX <40 IU/dl or 40% of clotting factor activity) are rare which both X chromosomes are affected [4].



- The mortality rate among patients with mild to moderate hemophilia is significantly affected by the presence of inhibitors in their plasma. Those with inhibitors have been reported to have a mortality rate up to five times greater than those without inhibitors.
- The hemophilia-related death rate 0.08 hemophilia-related deaths per 100,000 population in 2014.

III. Signs and Symptoms

- A family history of bleeding is obtained in about two-thirds of all patients.
- Unusual neonatal bleeding
- Easy bruising when crawling and walking (9-12 months old).
- Bleeding may also occur spontaneously or after trauma, operation or dental procedures
- Epistaxis, gum bleeding

- Hematuria
- Hemophilic hemarthrosis
  - Swollen
  - Painful
  - Large joints are usually affected (knee, ankle, elbow).
- Intracranial hemorrhages (life-threatening condition).

Table 1. *Approximate frequency of bleeding at different sites [1]*

Site of bleeding	Frequency
Joints - More common into hinged joints: ankles, knees, and elbows - Less common into multi-axial joints: shoulders, wrists, hips	70%–80%
Muscle	10%–20%
Other major bleeding sites	5%–10%
Central nervous system	<5%

Table 2. *Sites of bleeding in hemophilia*

Serious	- Joints (hemarthrosis) - Muscles, especially deep compartments (iliopsoas, calf, forearm) - Mucous membranes of the mouth, nose, and genitourinary tract
Life-threatening	- Intracranial - Neck/throat - Gastrointestinal

IV. Diagnosis

1. Investigations

- Full blood count: normal in blood cell formula or low Hemoglobin level in case of blood loss
- Coagulation screen: prolonged APTT with a normal PT and Bleeding time.
- Specific factor assay: FVIII or FIX is less than 40 UI/dl or less than 40% of the normal level.

Table 2. *Relationship of bleeding severity to clotting factor level [3]*

Classification	**Factor level** (% or UI/dl)	**Clinical presentation**
Severe	< 1	Frequent bleeding episodes are common; predominantly in joints & muscles. Bleeding can occur spontaneously or after a minor
Moderate	1 to 5	Can bleed after a minor injury. May have bleeding into joints. Severe bleeds occur with moderate trauma, surgery & invasive
Mild	5 to <40	Bleeding occurs with major traumas such as surgery & invasive procedures.

2. Differential diagnosis

- Von Willlebrand disease
- Platelet disorder
- Other coagulation factor deficiency (Factor II, V, VII, X, XI or fibrinogen…etc)
- Neonatal bleeding disorder.

V. Management

1. Prophylaxis

- Ideally, treatment of severe hemophilia should be prophylactic to prevent spontaneous bleeding in severe hemophilia and arthropathy to ensure the best quality of life possible.
- The low-dose prophylaxis: [1]
  - Factor VIII concentrate 10-15 IU/kg, 2-3days per week.
  - Factor IX concentrate 10-15 IU/kg, 2days per week.

2. Factor replacement therapy

- On-demand treatment is another treatment option when clotting factors are inadequate.
- It consists of replacing the missing factor.
- Fresh frozen plasma and cryoprecipitate ideally SHOULD NOT be used as there is a high risk of viral transmission.

a. Factor recombinant dose

- Hemophilia A ▸ FVIII = factor desired (%) x patient's weight (kg) x 0.5
- Hemophilia B ▸ FIX= factor desired (%) x patient's weight (kg) x 1.4

b. Fresh Frozen Plasma (FFP) if factor recombinant is NOT available

- Starting dose: 15-20 ml/kg
- 1ml of FFP contains 1 unit of FVIII activity but less than 1 unit of FIX activity.

3. Supportive Treatment

a. First aid measures:

PRICE method: Protection, Rest, Ice, Compression, Elevation.

b. Pain management:[1]

- There is rapid pain relief in hemarthroses once missing factor concentrate is infused. If analgesia is required, avoid intramuscular injections.
- Also do not use Aspirin or NSAIDS as a risk of bleeding.
  - 1st Line: Paracetamol (10-15 mg/kg/dose – every 6h)
  - 2nd Line:
    - COX-2 inhibitor (e.g. Celecoxib®, Meloxicam®, Nimesulide®)
    - Or Paracetamol plus Codeine (3-4 times/day)
    - Or Paracetamol plus Tramadol (3-4 times/day)

❖ *Recommend dose:*

- Celecoxib®: oral 50 mg - every 12h (child 10-25 kg) and 100 mg twice/day (BW>25 kg)
- Codeine: oral 0.5-1 mg/kg/dose – every 4-6h (max 60 mg/dose)
- Tramadol: oral 1-2 mg/kg/dose – every 4-6h (max 100 mg/dose), should not be used in children younger than 12years old.

  - 3rd. Line: Morphine:
    - IV: 0.025-0.05 mg/kg/dose - every 2-4h (max 1-2 mg/dose)
    - IV infusion: 0.01-0.04 mg/kg/h

c. Anti-fibrinolytic:
- Tranexamic acid (Exacyl®, Nexi®) is effective as adjunctive treatment, especially for mucosal bleeds and dental extractions.
- Oral: 25 mg/kg/dose – every 6-8h
- IV: 10 mg/kg/dose – every 6-8h

d. Physiotherapy: should begin as soon as pain subsides and should be progressed gradually to restore full muscle length, strength, and function.

Table 3. ***Practice pattern:*** *peak plasma factor levels and duration for administration*

	HEMOPHILIA A				**HEMOPHILIA B**			
	Lower-dose Practice patter		**Higher-dose Practice pattern**		**Lower-dose Practice patter**		**Higher-dose Practice pattern**	
Type of bleeding	**Peak factor level (IU/dl)**	**Treatment duration(d)**	**Peak factor level (IU/dl)**	**Treatment duration (d)**	**Peak factor level (IU/dl)**	**Treatment duration (d)**	**Peak factor level (IU/dl)**	**Treatment duration (d)**
Joint	10-20	1-2	40-60	1-2	10-20	1-2	40-60	1-2
Superficial muscle	10-20	2-3	40-60	2-3	10-20	2-3	40-60	2-3
Iliopsoas or deep muscles with neuro-vascular injury or substantial blood loss								
Initial Maintenance	20-40 10-20	1-2 3-5	80-100 30-60	1-2 3-5	15-30 10-20	1-2 3-5	60-80 30-60	1-2 3-5
Intracranial								
Initial Maintenance	50-80 30-50 20-40	1-3 4-7 8-14	80-100 50 -	1-7 8-21 -	30-50 30-50 20-40	1-3 4-7 8-14	60-80 30 -	1-7 8-21 -
Throat and neck								
Initial Maintenance	30-50 10-20	1-3 4-7	80-100 50	1-7 8-14	30-50 10-20	1-3 4-7	60-80 30	1-7 8-14
Gastrointestinal								
Initial Maintenance	30-50 10-20	1-3 4-7	80-100 50	7-14	30-50 10-20	1-3 4-7	60-80 30	7-14
Renal	20-40	3-5	50	3-5	15-30	3-5	40	3-5
Deep laceration	20-40	5-7	50	5-7	15-30	5-7	40	5-7
Surgery (major)								
Pre-op* Post-op** 	60-80 30-40 20-30 10-20	- 1-3 4-6 7-14	80-100 60-80 40-60 30-50	- 1-3 4-6 7-14	50-70 30-40 20-30 10-20	- 1-3 4-6 7-14	60-80 40-60 30-50 20-40	- 1-3 4-6 7-14
Surgery (minor)								
Pre-op* Post-op**	40-80 20-50	- 1-5	50-80 30-80	- 1-5	40-80 20-50	- 1-5	50-80 30-80	- 1-5

(*) Pre-op. *CFC should be administered 30 to 60 minutes prior to the procedure.*
(**) Post-op. *CFC should be administered 8 to 12 hours after the last dose of standard half-life FVIII cfcs And 12 to 24 hours after the last dose of standard half-life FIX cfcs.*

VI. Patient Education

1. Vaccination

- Persons with bleeding disorders should be vaccinated
- Subcutaneous route rather than intramuscular or intradermal to minimize trauma
- If intramuscular injection is to be given:
  - It is best done soon after a dose of factor replacement therapy.
  - Apply an ice pack to the injection area for 5 minutes before injection.
  - Use the smallest gauge needle available (usually 25-27 gauge)
  - Pressure to the injection site for at least five minutes
- If a baby has had a hematoma after immunization, give the next injection under factor cover.

3. Dental care:

- Good dental hygiene is important as dental caries, dental gingivitis and periodontitis are source of bleeding.
- Dental extraction with factor replacement will be required in severe cases.

4. Sport: Recommended Activities:

- Swimming: Low-impact, supports joints, enhances cardiovascular fitness. Use proper swimming techniques and ensure safe pool environments.
- Cycling: Low-impact, cardiovascular exercise, promotes leg strength. Wear protective gear (helmet, knee and elbow pads) and choose smooth, flat terrains.
- Golf: Low-impact, promotes fine motor skills and flexibility. Use appropriate equipment and be mindful of the physical demands of walking and swinging.
- Walking or Hiking: Low-impact, easy to adjust intensity, enhances cardiovascular health. Choose well-maintained paths and trails, wear supportive footwear, and avoid uneven or hazardous terrain.
- Yoga or Pilates: Improves flexibility, strength, and balance. Practice under the guidance of a trained instructor familiar with hemophilia, and avoid high-impact or strenuous poses.

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IMMUNE THROMBOCYTOPENIC PURPURA (ITP)

TRY Lytheang, MEANG Sovanndos, LAM Pechkethia, CHEAN Sophal

I. Key facts

- Childhood immune thrombocytopenia (ITP) affects 5 of 100 000 children per year.
- It is an autoimmune disease associated with impaired platelet production as well as immune-mediated platelet destruction, resulting in low platelet counts.
- Acute ITP is a self-limiting disorder that resolves spontaneously 70-80%. [1]
- Around 20% pursue a chronic course which is defined as a platelet count that has been < 100 x 10^3/mm^3 for longer than 12 months in which some cases required a long term of immunosuppressive therapy.

II. Overview

1. Definition

Immune thrombocytopenic purpura (ITP) is defined by an isolated thrombocytopenia which is secondary to increased destruction of platelets by the macrophages in the reticulo-endothelial system, particularly the spleen, and no associated conditions.

It is the most common acquired bleeding disorders in children with prevalence 5 cases per 100,000 children and approximately 80% were younger than 8 years of age. [1]

ITP is categorized into three phases, depending on the duration of the disease course: [2]

- Acute ITP – ITP within 3 months from diagnosis
- Persistent ITP – Ongoing ITP between 3 and 12 months from initial diagnosis
- Chronic ITP – ITP lasting more than 12 months

2. Pathogenesis

- Etiology is still unknown.
- Increased platelet destruction, likely due to autoantibodies to platelet membrane antigens.
- In children, ITP is an acute, self-limiting disorder that resolves spontaneously.
- Antibodies formed against platelets in response to a viral infection (70% of cases, usually occurring 1–4 weeks before the onset of ITP) or underlying defects of immune regulation. [2]

III. Diagnosis

The diagnosis is based on history, physical examination, blood counts, and examination of the peripheral blood smear.

1. Clinical Presentation

- Acute onset with history of viral illness, previously healthy child (peak of 2 – 10 years old),
- Presented by generalized petechiae, ecchymosis, and easy bruising.
- Epistaxis, gingival bleeding, GI bleeding, hematuria and menorrhagia are common with profound thrombocytopenia (platelet < 10.000/mm3) [3].
- Intra-cranial hemorrhage (0.5%) is the most severe form with life threatening
- Absence of lymphadenopathy and hepato-splenomegaly

2. Laboratory investigation

❖ Initial examination: CBC, blood smear, bone marrow aspiration

- Typically, CBC is normal except thrombocytopenia (<100,000/mm3) and anemia if there is a history of significant bleeding.
- Blood smear: Giant platelets on the blood smear (increased Mean Platelet Volume).
- Bone marrow aspiration: normal or increased megakaryocytes, normal myeloid and erythroid elements and the absence of abnormal cell populations.
- PT and aPTT are normal.

❖ Indication of bone marrow examination: [3]

- Atypical features: organomegaly, significant lymphadenopathy, abnormal blood counts suspicious peripheral blood picture.
- Before starting steroid therapy (leukemia suspected).
- Failure to respond to steroid therapy
- Persistent thrombocytopenia > 6 months
- Thrombocytopenia recurs after initial response to treatment

3. Differential diagnosis

- Autoimmune disorders e.g. Systemic lupus erythematosus, Evan syndrome
- Hematological malignancy e.g. Acute leukemia
- Bone marrow failure e.g. Aplastic anemia
- Sepsis and infections including HIV, Hepatitis C, CMV infection
- Drug-induced thrombocytopenia e.g. Heparin, NSAID

IV. Complications

- Serious bleeding in ITP: 2 – 4%
- Epistaxis, GI bleeding, hematuria, menorrhagia
- Risk of intracranial hemorrhage (ICH): mortality rate 50%, risk factors: Platelet < 10,000, antiplatelet drugs (Aspirin, nsaids ....), head trauma.

V. Treatment

1. Treatment of acute ITP indicated if [4]:

- Life threatening bleeding episode (e.g. ICH) regardless of platelet count
- Platelet count < 20,000/mm³ with mucosal bleeding
- Platelet count < 10,000 with little or no purpura

a. Platelet count < 20,000/mm³ or active bleeding:

- Oral Prednisolone: 2 mg/kg/day for 14 days, then taper and discontinue at 21 days (Max: 60mg/d)
- IV Methylprednisolone: 30 mg/kg/day for 3 days
- IVIG: 0.8-1g/kg/dose over 10-12 hours for 1 day or 250 mg/kg for 2 days
- IV anti-D immunoglobulin: 75 µg/kg single dose over 5 mn in Rhesus positive patients
- Rituximab: 375 mg/m2/week for 4 weeks consecutively – IV infusion over 12 hours

b. Life threatening bleeding

- IVIG: 0.8-1g/kg/dose over 10-12 hours for 1 day or 250 mg/kg for 2 days if available
- Or IV Methylprednisolone: 30 mg/kg/day for 3 days
- Platelet transfusion: dose 0.2 unit/kg (usually not recommended unless life-threatening bleeding)
- Pack Red Cell transfusion: 15-20 ml/kg (if hemoglobin < 7 mg/dl)

2. Treatment of chronic ITP

- Asymptomatic children can be left without therapy and kept under observation.
- Symptomatic children may need short course of treatment to tide them over the relapse which includes:
  - Intermittent pulses of steroids: IV Methylprednisolone: 30 mg/kg/day for 3 days
  - Intermittent pulses of IVIG
  - Intermittent anti-D antibody

❖ Splenectomy is indicated if:

- Persistence of disease after 12 months with bleeding symptoms and platelet count <10.000/mm³, mostly in patients over 5 years of age
- No response or only transient success with intermittent pulsed steroids, anti-D or IVIG.

- No contra-indications to surgery

    - Over 70% rate of complete remission post-splenectomy
    - Pre-splenectomy immunization against pneumococcus, Hemophilus influenzae B and meningococcus infection, at least 2 weeks before surgery,
    - Post-splenectomy: penicillin oral 250mg twice daily for at least 1 year
    - Post-splenectomy sepsis – Bacterial sepsis (~ 3%).

VI. Education

- To prevent bleeding by make the environment as safe as possible, wearing helmets, and providing protective clothing are necessary when platelet counts are low (<10.000/mm3) [3].
- Avoidance of activities that predispose your child to trauma such as contact sports, riding bicycles, and rough play
- Avoid medications that impair platelet function as they may interfere with the body's ability to control bleeding (aspirin, non-steroidal anti-inflammatory drugs, and antihistamines) [4].

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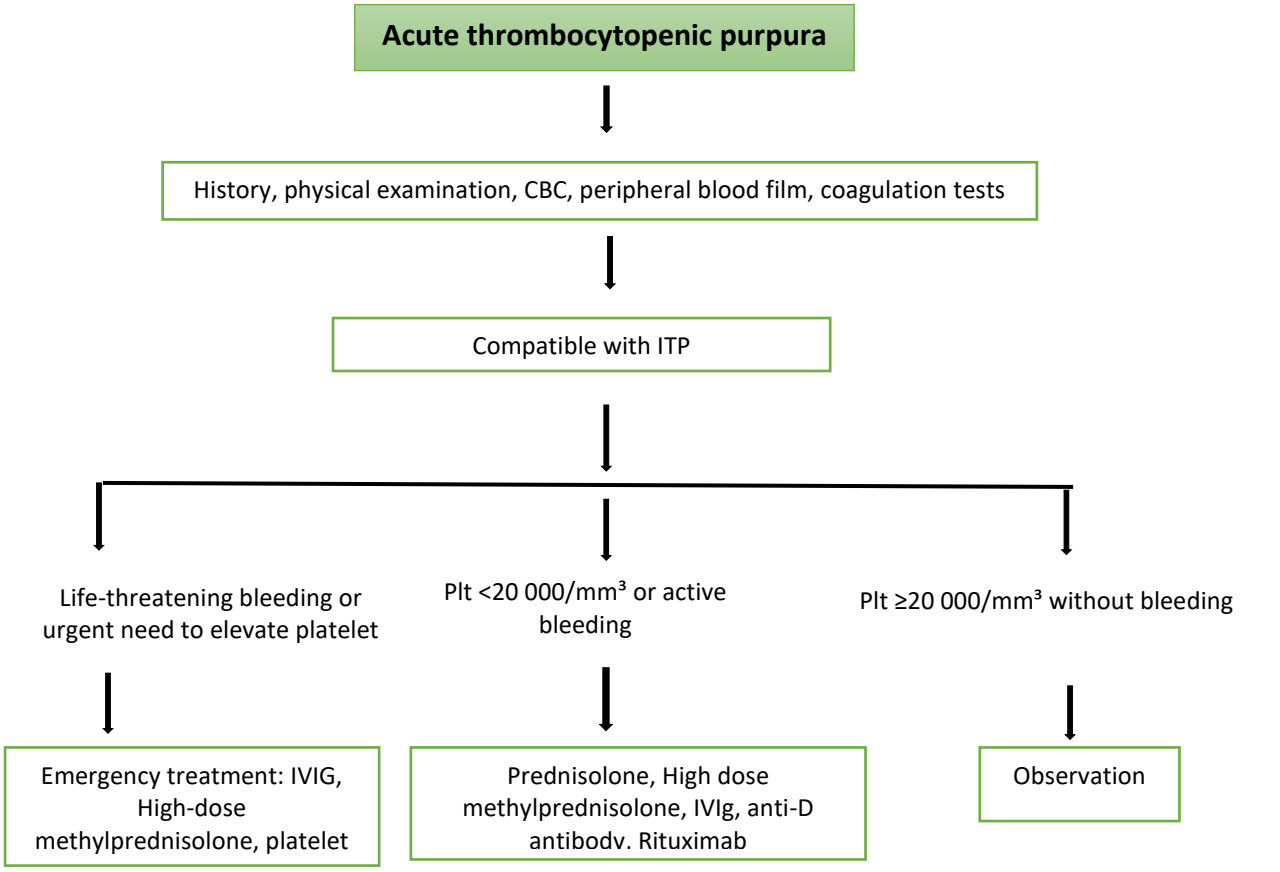
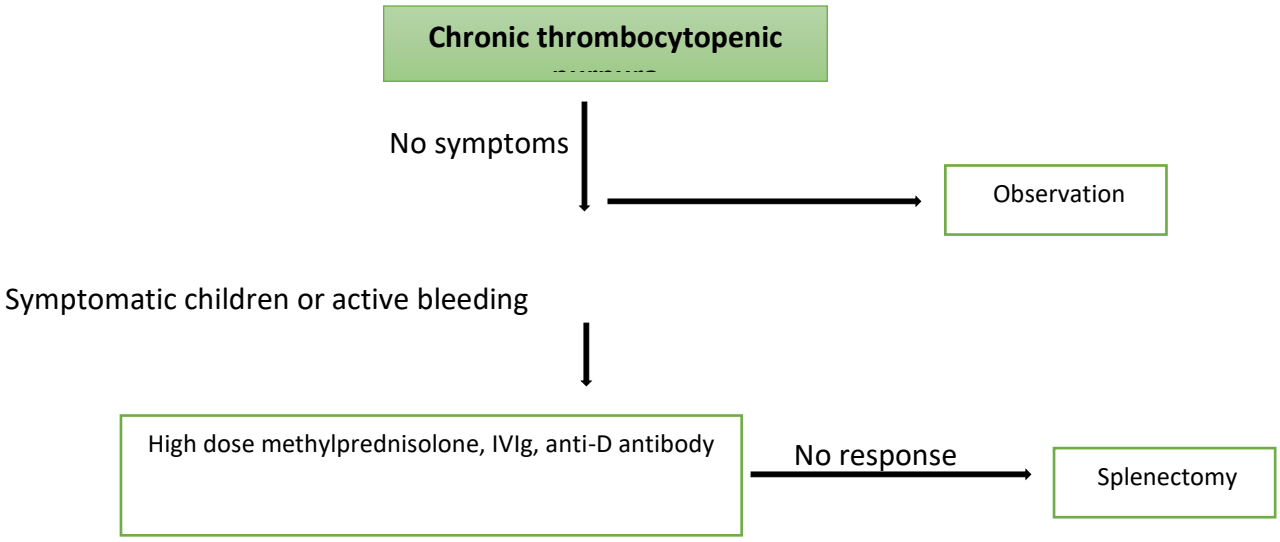
Algorism for Treatment of ITP





APPROACH TO THE CHILD WITH BLEEDING SYMPTOMS

MEANG Sovandos, TRY Lytheang, LAM Pechkethia, CHEAN Sophal

I. Key facts

The burden of disease when approaching a child with bleeding symptoms encompasses several key aspects that impact both the child and the healthcare system.

1. **Morbidity and Mortality**: [1]
   - Immediate Risks: Severe bleeding episodes can lead to significant morbidity, including organ damage, joint destruction (in hemophilia), and even death if not promptly managed.
   - Long-term Effects: Chronic bleeding can impair quality of life, lead to disability (e.g., joint deformities in hemophilia), and require lifelong management.
2. **Economic Impact:** [2]
   - Direct Costs: Hospitalizations, diagnostic tests (e.g., coagulation assays), medications (e.g., clotting factors), and surgical interventions.
   - Indirect Costs: Lost productivity for caregivers due to hospitalizations, ongoing medical appointments, and potential long-term disability.
3. **Psychosocial Impact**: [3]
   - Child and Family: Anxiety, stress, and emotional impact from dealing with recurrent bleeding episodes, hospitalizations, and the need for lifelong management.
   - Social Stigma: Misconceptions or stigma related to bleeding disorders can affect the child's social interactions and mental well-being.
4. **Healthcare System Impact:** [4]
   - Resource Utilization: Demand for specialized healthcare services (e.g., hematology, pediatric surgery) and ongoing need for expensive treatments.
   - Capacity Challenges: Balancing acute care needs with long-term management and rehabilitation services.

II. Overview

1. **Definition**: [1]

   Bleeding/Hemorrhage is an acute loss of blood from a damaged blood vessel.
2. **Common Causes of Bleeding** [2,4,5]

   Broadly, bleeding disorders can be inherited or acquired.
   - Common inherited disorders: hemophilia A/B, von Willebrand disease (VWD) and platelet function defects.
   - Common acquired causes of bleeding: immune thrombocytopenic purpura (ITP), liver disease, vitamin K deficiency, disseminated intravascular coagulation (DIC), sepsis, aplastic anemia and leukemia.
3. **Physiopathology**

   A. *Normal Hemostasis* [6,7]

   a. Vascular Phase: Vasoconstriction occurs immediately after vascular injury.

   b. Platelet Phase: Platelets adhere to exposed subendothelial matrix, activating and aggregating to form a primary hemostatic plug.

   c. Coagulation Phase: Activation of the intrinsic and extrinsic pathways leads to thrombin generation, which converts fibrinogen to fibrin, stabilizing the platelet plug.

   B. *Defects* in Hemostasis cause bleeding disorders [8,9]

   a. Vascular Defects
   - Structural Abnormalities: Conditions like Ehlers-Danlos syndrome and hereditary hemorrhagic telangiectasia (HHT) can cause fragile blood vessels prone to rupture.

- Inflammation: Vasculitis, inflammation of blood vessels, can lead to bleeding.
- Scurvy: Vitamin C deficiency affects collagen synthesis, leading to weakened vessel walls.

b. Platelet Defects
- Thrombocytopenia: Low platelet counts leading to excessive bleeding.
- Thrombocytopathy: Dysfunctional platelets despite a normal count.

c. Coagulation Factor Deficiencies [10,11]
- Inherited Disorders
  - Hemophilia A and B: Deficiencies in factor VIII and IX, respectively, leading to impaired thrombin generation and stable clot formation.
  - Von Willebrand Disease: Deficiency or dysfunction of von Willebrand factor, affecting platelet adhesion and factor VIII stability.
  - Rare Factor Deficiencies: Deficiencies in factors I (fibrinogen), II (prothrombin), V, VII, X, XI, and XIII.
- Acquired Disorders
  - Vitamin K Deficiency: Essential for the synthesis of factors II, VII, IX, and X.
  - Liver Disease: The liver produces most coagulation factors, so liver dysfunction can lead to multiple factor deficiencies.
  - Disseminated Intravascular Coagulation (DIC): A severe condition causing widespread clotting factor consumption and bleeding.

d. Risk Factors
- Genetic Predisposition: Family history of bleeding disorders
- Gender: Hemophilia primarily affects males
- Age: during infancy or early childhood
- Underlying Medical Conditions: Conditions like liver disease, which affects clotting factor synthesis, or disorders causing thrombocytopenia (e.g., leukemia or aplastic anemia) can increase bleeding risk.
- Medications: Use of anticoagulants (e.g., warfarin) or nonsteroidal anti-inflammatory drugs (NSAIDs).

III. Signs and symptoms [12]

Bleeding manifestations in vascular disorder, thrombocytopenia or functional platelet disorders are usually in the form of spontaneous subcutaneous and mucus membrane bleeds like:
- Petechiae
- Ecchymosis
- Epistaxis
- Menorrhagia

Bleeding from coagulation factor deficiency:
- Hematomas are usually deep (in the muscles) and spreading,
- Bleeding into cavities like joints, retroperitoneal space.

IV. Diagnosis [13,14]

Diagnosing bleeding disorders in children requires a systematic approach, including a detailed history, physical examination, and specific laboratory tests.

1. Clinical History

a. Personal History
- Bleeding Episodes: Frequency, duration, and severity of bleeding episodes (e.g., easy bruising, prolonged bleeding from cuts, nosebleeds, heavy menstrual bleeding).
- Previous Medical Events: Any history of excessive bleeding following surgeries, dental procedures, or vaccinations.

- Medications: Current and past medications that might affect bleeding (e.g., nsaids, anticoagulants).

b. Family History

- Inherited Bleeding Disorders: Family history of bleeding disorders like hemophilia, von Willebrand disease, or other coagulopathies.
- Consanguinity: In cases where parents are related by blood, increasing the risk of inherited disorders.

2. Physical Examination

- General Appearance: Look for signs of anemia (pallor, fatigue).
- Skin and Mucous Membranes: Check for petechiae, ecchymoses, and mucosal bleeding (gums, nose).
- Joints and Muscles: Inspect for swelling, warmth, and pain indicative of hemarthrosis or muscle hematomas.
- Abdomen: Palpate for hepatosplenomegaly, which might indicate underlying hematological conditions.
- Neurological Examination: Assess for signs of intracranial bleeding (headache, vomiting, altered consciousness).

3. Laboratory Investigations [14]

a. Initial Screening Tests

- Complete Blood Count (CBC): Assess for anemia, thrombocytopenia, or signs of bone marrow suppression.
- Peripheral Blood Smear: Examine the morphology of blood cells, including platelets.
- Prothrombin Time (PT): Measures the integrity of the extrinsic and common coagulation pathways.
- Activated Partial Thromboplastin Time (aptt): Assesses the intrinsic and common coagulation pathways.
- Bleeding Time: Evaluates platelet function and the integrity of small blood vessels.
- Fibrinogen Level: Measures the amount of fibrinogen, an essential clotting factor.
- Thrombin Time: Assesses the conversion of fibrinogen to fibrin.

b. Specialized Tests

- Von Willebrand Factor Antigen and Activity: For suspected von Willebrand disease, measure the quantity and activity of von Willebrand factor.
- Factor Assays: Measure specific clotting factor levels (e.g., factor VIII, factor IX) for hemophilia diagnosis.
- Platelet Function Tests: Assess platelet aggregation and secretion (e.g., PFA-100, light transmission aggregometry).
- Mixing Studies: Differentiate between factor deficiencies and inhibitors (e.g., lupus anticoagulant, factor inhibitors).
- Genetic Testing: Identify mutations in genes associated with bleeding disorders (e.g., F8 and F9 genes for hemophilia A and B).

Table 1. *Hemostatic tests for possible defects*

Bleeding	APTT	PT	Bleeding Time	Platelet Count	Possible Defects
Absent	Abnormal	Normal	Normal	Normal	High-molecular-weight kininogen Prekallikrein Factor XII
Present	Abnormal	Normal	Normal	Normal	Factor XI, IX, VIII*
Present	Abnormal	Abnormal	Normal	Normal	Factor V, X, II, Vitamin K deficiency
Present	Normal	Abnormal	Normal	Normal	Factor VII
Present	Abnormal	Normal	Abnormal	Normal	Von Willebrand disease
Present	Abnormal	Abnormal	Abnormal	Normal	Afibrinogenemia
Present	Normal	Normal	Abnormal	Abnormal	Thrombocytopenia
Present	Normal	Normal	Abnormal	Normal	Qualitative platelet disorder (Thrombasthenia, Bernard-Soulier syndrome, etc)
Present	Normal	Normal	Normal	Normal	Factor XIII
Present	Abnormal	Abnormal	Abnormal	Abnormal	Disseminated intravascular coagulation Severe liver disease
Variable	Normal	Normal	Normal	Normal	Dysfibrinogenemia, Myeloma, Fibrinogen/Fibrin degradation products
Present	Abnormal	Normal	Normal	Normal	Heparin

4. Imaging Studies

- Ultrasound or MRI: To detect joint and muscle bleeding in hemophilia.
- CT scan or MRI of the Brain: For suspected intracranial hemorrhage.

❖ **Possible Diagnostics of bleeding child** [2,8-11]

a. Vascular Disorders

- Structural Abnormalities: Conditions like Ehlers-Danlos syndrome and hereditary hemorrhagic telangiectasia (HHT) can cause fragile blood vessels prone to rupture.
- Inflammation: Vasculitis, inflammation of blood vessels, can lead to bleeding.
- Scurvy: Vitamin C deficiency affects collagen synthesis, leading to weakened vessel walls.

b. Platelet Disorders

- Thrombocytopenia: ITP, leukemia, aplastic anemia.
- Platelet dysfunction: Congenital or acquired platelet dysfunction.

c. Coagulation Disorders

- Hemophilia: Hemophilia A, Hemophilia B.
- Von Willebrand disease: Most common inherited bleeding disorder.
- Vitamin K deficiency: Dietary insufficiency, malabsorption, liver disease.
- Liver disease: Affecting clotting factor synthesis.

d. Other Causes

DIC: Widespread clotting and bleeding.

- Child abuse: Consider in unexplained or recurrent injuries.

V. Complication [15]

- Bleeding Episodes: spontaneous bleeding or prolonged bleeding from injuries, dental work, or surgeries.
- Development of Inhibitors: in hemophilia
- Chronic Joint Damage
- Intracranial Hemorrhage: life-threatening complication
- Gastrointestinal and Genitourinary Bleeding
- Post-surgical and Post-traumatic Bleeding
- Psychosocial Impact.

VI. Treatment [10,12]

1. Acute Management

- Stabilization: Ensure abcs (airway, breathing, circulation).
- Control bleeding: Apply pressure, use hemostatic agents, or perform surgical intervention.
- Specific treatments: Based on diagnosis (e.g., factor replacement for hemophilia, platelet transfusions).

2. Long-term Management

- Treatment of underlying condition: Manage the specific disorder (e.g., immunosuppressive therapy for ITP, desmopressin for von Willebrand disease, Factor replacement for hemophilia, etc.).

VII. Prevention and Education [16]

1. Genetic Counselling and Screening

- Family History: Identify families with a history of bleeding disorders and offer genetic counselling.
- Prenatal Testing: For families with known hemophilia or other genetic bleeding disorders, prenatal testing (e.g., chorionic villus sampling, amniocentesis) can help in early diagnosis.
- Carrier Testing: Women with a family history of hemophilia can be tested to determine carrier status.

2. Injury Prevention

- Safe Environment: Create a safe home and school environment to reduce the risk of injuries (e.g., soft flooring, protective gear during sports).
- Activity Modifications: Encourage participation in non-contact sports and activities that have a lower risk of injury.

3. Patient and Family Education

- Understanding the Disorder: Provide comprehensive information about the specific bleeding disorder, its symptoms, and management.
- Bleeding Episodes: Educate on recognizing early signs of bleeding and appropriate first aid measures (e.g., applying pressure, using ice packs).
- Regular Check-ups: Schedule regular follow-up appointments with a hematologist to monitor the child's condition, adjust treatment plans, and address any complications.

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FEBRILE NEUTROPENIA IN CHILDREN WITH CANCER

SUY Keang, Ardura- Garcia CRISTINA, MILIYA Thyl, Turner PAUL

I. Key facts

- Febrile neutropenia (FN) is a common complication in children receiving chemotherapy for cancer and is associated with significant morbidity and mortality.
- FN occurs in 1/3 of patients with chemotherapy-induced neutropenia. A marked reduction in infection-related morbidity and mortality was seen with the implementation of empiric broad-spectrum antibiotics in the 1970s.
- Studies have also identified potential risk factors for bacterial infection which are outlined below[1,2].
- The goal of treatment is to cover the most likely virulent pathogens: coverage for *Pseudomonas aeruginosa* is a critical component and the main driver of recommendations.
- Antibiotics must be administered as soon as FN is recognized and at least within the first hour of presentation: every minute of delay increases risk of morbidity and mortality[3].
- All FN cases should be discussed with the oncology and microbiology teams at the earliest opportunity.

II. Definition fever and neutropenia

a. Neutropenia

- Absolute neutrophil count (ANC) < 0.5 x 10^9 cells/l
- ANC <1 x 109 cells/l and falling, following recent intensive chemotherapy (within last 10 days) or with untreated leukaemia

b. Fever, never take a rectal temperature in neutropenic patients

- Single axillary / ear temperature of >37.8°C
- Two axillary / ear temperature readings > 37.5°C over 1 hour.

III. Evaluation on febrile neutropenia

a. Thorough history and physical examination

b. Laboratory tests

- Complete blood count (CBC) with differential
- Blood culture: do daily whilst febrile (for a maximum of 7 days) and if deterioration or new fever on treatment
- Complete metabolic panel (liver function, electrolytes, renal function)
- Others as indicated: coagulation panel, culture of all potential sites of infection (urine, stool, skin, wound, etc.)
- C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) are NOT indicated
- Radiological investigations, only necessary if clinically indicated
- Chest x-ray if lower respiratory symptoms or abnormal physical exam
- Abdominal x-ray and/or ultrasound if significant abdominal pain, distention, etc
- Consider chest CT scan if there is concern of invasive fungal infection in high-risk patients (children with acute myeloid leukemia, high-risk acute lymphoblastic leukaemia, relapsed acute leukaemia, high-dose steroid use or those undergoing allogenic haematopoietic cell transplantation).

IV. Treatment

1. Initial Treatment of Febrile Neutropenia

Administer broad spectrum antibiotics as soon as FN is recognized and at least within the first hour of presentation.

a. All patients

- Meropenem: If meropenem is unavailable, use ceftazidime plus gentamicin or amikacin
  - Indications for addition of vancomycin for additional Gram-positive coverage
  - Haemodynamic instability or evidence of severe sepsis
  - Blood culture positive for Gram-positive bacteria (before sensitivities and identification)
  - Skin or soft tissue infection
- When should vancomycin NOT be added
  - Patients with persistent fevers but without evidence of Gram-positive infection or significant change in clinical symptoms (e.g. Hemodynamic instability)
  - Based on height of fever alone (e.g. Temperature >39.5°C)

b. Patients with suspected typhlitis (neutropenic enterocolitis)

- Treat with meropenem and vancomycin empirically
- Update antibiotics based on radiology, microbiology results and clinical status / recent chemotherapy
- Strict nothing by mouth (NPO).
- Must give intravenous fluids and pain control until symptomatically improved.

c. Clinically unstable patients, patients with hypotension, sepsis, or septic shock

- Manage on paediatric intensive care unit
- Supportive management (intravenous access, fluids, inotropic and respiratory support) should be aggressive to maintain hemodynamic and respiratory stability.
- Triple antibiotic therapy with vancomycin, meropenem and gentamicin
  - Review the need for on-going gentamicin and vancomycin at 48 hours
  - Monitor renal function daily whilst on vancomycin and/or gentamicin.

2. Definitive Treatment and Duration of Therapy

Avoid continuing vancomycin and/or gentamicin whenever possible

a. Low Risk <u>without</u> documented infection

- Definition of low risk
- Profound neutropenia expected to resolve in < 7 days (depends of type and dose of chemotherapy)
- In patients who have been clinically well and afebrile for at least 24 hours, consider discontinuation of empirical antibiotics if blood cultures remain negative after 48 hours of incubation despite no evidence of marrow recovery.

b. High Risk <u>without</u> evidence of documented infection

- Definition of high risk: Profound neutropenia [Absolute neutrophil count (ANC) <0.2 x 109 cells/l] expected for > 7 days
- Continue antibiotics until the patients become afebrile for at least 24 hours and there is evidence of marrow recovery OR for 14 days whichever occurs sooner.

c. Persistent fever and neutropenia

- After 3 days, add or change antibiotic: consult with microbiologist to determine appropriate choices.

- After 5 days, consider adding anti-fungal in patients with high risk of invasive fungal infection (See Invasive Fungal Infection in Children guideline): consult with microbiologist to determine the appropriate anti-fungal agent to start with.

d. Persistent fever despite neutrophil rise

Consider fungal, viral, parasites and other unusual pathogens, drug fever, tumour

e. Patients with evidence of documented infection:

- Change antibiotics to more directed therapy based on identification and sensitivities, until afebrile for 24 hours AND evidence of marrow recovery (ANC increasing and ≥ 0.2 x 10^9 cells/l)
- Duration of therapy should be dictated by the organism and site of infection: discuss with the microbiology team
    - Most bacteraemia, soft-tissue infections, and pneumonias require 10-14 days of antibiotics
    - Length of treatment should be timed from first negative culture
- Antibiotics must be continued until count recovery (ANC > 0.2 x 10^9cells/l) even if they have completed the recommended course of antibiotics for their infection.

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RETINOBLASTOMA

KHAUV Phara, BUN Sereyleak, THY Bunpaov, HAS Sothearak, YIN Sopheak Both, Camitta BRUCE

I. Key facts

- Retinoblastoma (RB) is the most common neoplasm of the eye in children and represent approximately 2% of all childhood malignancies.
- RB is usually was not recognized and treated in time. If treated too late, it can lead to loss patient's eye, invasion of the brain and death. It is complexity in treatment and needs specialized center with expert teams. This guideline is design to guidance about the detection of diagnosis and refer the patient to a specialized hospital.
- Estimated 8000 cases each year worldwide, 1 in 18,000 live births in the United States
- Over 90 % of cases are diagnosed before 5 years (median 2). It is rarely seen after age 6. The sex ratio is one [(2)]
- Retinoblastoma is chemo-sensitive. The Survival is over 90% in developed country and above 70% in middle income country [(3)]
- The tumour occurs single or multiple in one eye or both eyes and can present since birth but usually not recognize.
- The majority of RB appears non-heritable and heritable form, which is usually seen at the early age, bilateral and can developing another malignant tumour [(2)]
- Treatment depends on stage, pathology, and genetics. Multidisciplinary teams (pediatric ophthalmologist, pediatric oncologist, radiation therapist, pathologist) are needed for optimal management.

II. Overview

1. Definition

Retinoblastoma, a malignant tumour arising from embryonic neural retina, is the most common intraocular malignancy in children. [(1)]

2. Etiology [(4)]

Retinoblastoma is a childhood cancer and caused by inactivation of both alleles of the Rb1tumor suppressor gene on chromosome 13q14.

It represents two form heritable and non-heritable form

- Heritable form (= hereditary or familial or germline) autosomal dominant
  - 35-40% of cases (15% are unilateral 20% bilateral)
  - All bilateral RB have a germline mutation in all body cells
  - Early age at presentation: median 14-16months
- Non-heritable (= sporadic or somatic)
  - 60-65 % of cases
  - Median age of onset 23-24 months

3. Pathophysiology

Two mutational events in the RB gene are required for tumour occurrence. First, mutation may occur in the germ cell (heritable disease) or retinal cell sporadic disease). The second, mutation is in the retinal cell.

4. Risk of pathologic feature

- Massive choroid invasion (>3mm)
- Sclera involvement
- Anterior chamber seeding
- Ciliary body involvement
- Iris involvement
- Optic nerve involvement beyond the cut edge
- Tumour past the lamina cribrosa.

III. Signs and symptoms [5]

- Painless leukocoria (cat eye; white pupil) most common sign: 50%
- Strabismus 30%
- Others: 20%
  - Orbital cellulitis, buphthalmos
  - Glaucoma
  - Hyphema
  - Nystagmus
  - Proptosis
  - Orbital mass

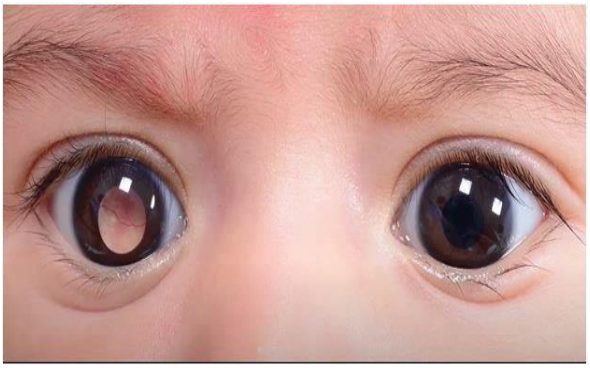

Figure 1: *Leukocoria*

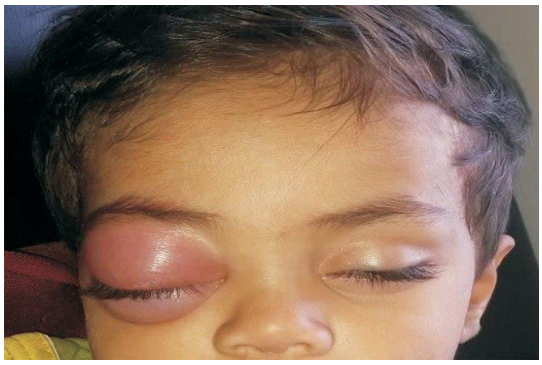

Figure 2: *Orbital cellulitis*

IV. Diagnosis

1. Physical exam and evaluation of extent of disease [1, 2, 6]

a. Physical exam
- Signs and symptoms detailed above
- White pupillary reflex instead of the normal red reflex.
- Others: squints, erythema, pain, exophthalmos, malformation of orbital bone
- EUA: Exam Under General Anesthesia by ophthalmologist to evaluate number and sizes of tumours, location relation to macula and optic disc, seeding in vitreous body and retinal detachment.

b. Laboratory studies:
- Complete Blood Count, Liver Functions and Renal Functions are usually unremarkable.
- Lumbar puncture for cerebrospinal fluid and bone marrow aspiration to assess for CNS and bone marrow metastasis. These are usually limited to children with advanced disease or abnormalities in other laboratory tests.

c. Imaging: Computed tomography (CT) or Magnetic resonance imaging (MRI) for detection of a calcified mass and extension within the optic nerve or intracranially. It may also diagnose trilateral retinoblastoma.

d. Histology: after enucleation to evaluate tumour extent and risk factors

e. Genetic screening: currently not available in Cambodia but can be sent out

2. Patterns of spread [1, 2]

- Endophytic: Seeding in vitreous body then anterior chamber.
- Exophytic: It infiltrates into subretinal space, making retinal detachment and then into choroid, sclera, and globe.
- Tumor may invade the optic nerve, past the lamina cribrosa into the brain and meninges
- Distant metastasis hematogenous metastases include bone, BM and less frequently other organs

❖ Differential Diagnosis [1]

- Glaucoma
- Congenital cataract
- Peri-orbital cellulitis, uveitis
- Non-neoplastic entities: Coats disease, toxicara canis endophtalmitis, persistent hyperplastic primary vitreous (PHPV), retinopathy of prematurity.
- Vitreous hemorrhage
- Other orbital tumor (optic nerve glioma, Rhabdomyosarcoma)
- Trilateral retinoblastoma.

V. Classification of pathologic

1. Classification of intraocular disease: [8]

The Reese-Ellsworth classification, International Classification (ICRB), International Intraocular Retinoblastoma Classification (IIRC) were designed to see chance of saving the eye from enucleation or radiation.

Table 1-*The Reese-Ellsworth classification* [7]

Stage	Specific features
Stage 1 Very favorable	**A.** Solitary tumor, smaller than 4 discs diameters (DD), at or behind the equator of the globe.
	B. Multiple tumors, none larger than 4 DD, all at or behind the equator.
Stage 2 Favorable	**A.** Solitary tumor, 4 to 10 DD at or behind the equator.
	B. Multiple tumors, 4 to 10 DD at or behind the equator.
Stage 3 Doubtful	**A.** Any lesion anterior to the equator.
	B. Solitary tumor, larger than 10 DD behind the equator.
Stage 4 Unfavorable	**A.** Multiple tumors, some larger than 10 DD.
	B. Any lesion extending anteriorly to the ora serrata.
Stage 5 very unfavorable	**A.** Massive tumors involving > half the retina.
	B. Vitreous seeding.

Table 2- *The International Classification of Retinoblastoma (ICRB)*

Group	Quick reference	Specific features
A	Small tumor	Rb ≤ 3mm in size
B	Large tumor Macular Juxtapapillary Subretinal fluid	Rb>3mm in size or -Macular Rb location (3≤mm to foveola) -Juxtapapillary Rb location (≤1.5 mm to disc) -Clear subretinal fluid (≤3 mm from margin)
C	Focal seeds	Rb with -Subretinal seeds (≤3mm from Rb) -Vitreous seeds (≤3 mm from Rb) -Both subretinal and vitrous seeds (≤3 mm from Rb)
D	Diffuse seeds	Rb with -Subretinal seeds (>3mm from Rb) -Vitreous seeds (>3mm from Rb) -Both subretinal and vitreous seeds (>3 mm from Rb)
E	Extensive Rb	Extensive Rb occupying> 50% globe or -Neovascular glaucoma

		-Opaque media from hemorrhage in anterior chamber, vitreous or subretinal space -Invasion of post laminar optic nerve, choroid(>2mm), sclera Orbit, anterior chamber

2. **Classification of extraocular disease**

International Retinoblastoma Staging (IRSS): is developed by Chantada and colleagues.It sub-classified the disease from stage 0-IV. Stage 0 is intraocular disease and stage IV is retinoblastoma with metastases.

Table 3- International Retinoblastoma Staging (IRSS)

Stage	Clinical Description
O	Patient treated conservatively
I	Eye enucleated,completely resected histologically
II	Eye enucleated, microscopic residual tumor
III	Regional extension
A	Overt orbital disease
B	Preauricular or cervical lymph node extension
IV	Metastatic disease base on bone marrow aspiration and lumbar puncture
A	Heamatogenous metastasis (without central nervous system 1 Single lesion 2 Multiple lesion
B	Central nervous system extension (with or without any other 1 Prechiasmatic lesion 2 Central nervous system mass 3 Leptomeningeal and cerebrospinal fluid disease

3. **Pathologic Classification** (PTNM)

Pt: Primary Tumour

- Ptx: Primary Tumour cannot be assessed.
- Pt0: No evidence of primary tumour.
- Pt1: Tumour confined to the eye with no optic nerve or choroidal invasion.
- Pt2: Tumour with minimal optic nerve and / or choroidal invasion:
    - Pt2a: Tumour superficially invades optic nerve head but does not extend past lamina cribrosa, or tumour exhibits focal choroidal invasion.
    - Pt2b: Tumour superficially invades optic nerve head but does not extend past lamina cribrosa and tumour exhibits focal choroidal invasion.
- Pt3: Tumour with significant optic nerve and / or choroidal invasion:
    - Pt3a: Massive choroidal invasion (greater than 3 mm in largest diameter, or multiple foci of focal choroidal involvement totaling greater than 3 mm, or any full-thickness choroidal involvement)
    - Pt3b: Retrolaminar invasion of the optic nerve head, not involving the transected end of the optic nerve
    - Pt3c: Any partial-thickness involvement of the sclera within the inner two thirds
    - Pt3d: Full-thickness invasion into the outer third of the sclera and / or invasion into or around emissary channels
    - Pt3 (subcategory cannot be determined)

- Pt4: Tumour invades optic nerve to surgical resection line or exhibits extra- ocular extension elsewhere.
    - Pt4a: Tumour invades optic nerve to resection line, but no extra-ocular extension identified.
    - Pt4b: Tumour invades optic nerve to resection line, and extra-ocular extension identified.

Pn: Primary Not applicable

- Pn not assigned (no nodes submitted or found)
- Pn not assigned (cannot be determined based on available pathological information)
- Pn0: No regional lymph node involvement
- Pn1: Regional lymph node involvement

Pm: Multiple primary tumors

- Pm Category (required only if confirmed pathologically) not applicable
- Pm cannot be determined from the submitted specimen(s)
- Pm1: Distant metastasis with histopathologic confirmation
- Pm1a: Histopathologic confirmation of tumor at any distant site (e.g., bone marrow, liver, or other)
- Pm1b: Histopathologic confirmation of tumor in the cerebrospinal fluid or CNS parenchyma
- Pm1 (subcategory cannot be determined).

VI. Complications [9, 10]

- Toxicity of chemotherapy and radiation therapy: cardio-toxicity, allergic reactions, hearing loss, vomiting, alopecia, short stature, neuro-intellectual impairment, neurocognitive disorders, orbital deformation, tiredness
- Disease complications: vision loss, quality of life, risk of secondary malignancy (especially if bilateral disease or with the use radiation therapy), infection, bone marrow suppression
- Psychological: families and patients.

VII. Treatment [11]

Goals of treatment: to save life, save the eye and maintain vision

- Observation: children with initial enucleation whose eyes have no poor prognostic factors
- Synergy therapy: chemotherapy and focal therapy
    - Systemic chemotherapy: duration 6 to 8 months
    - High risk pathologic and bilateral RB: 8 cycles of VCE (Vincristine Day 1, Carboplatin Day 1 and Etoposide for 3days)
    - Unilateral RB with low stage (group 3-5): 6 cycles of VCE
    - Extra-ocular RB: alternate chemotherapy [VCE and VDC (Vincristine Day 1, Doxorubicin Day 1, Cyclophosphamide Day 1)]: 6 cycles
    - After finished 6-8 cycles of VCE & VDC still present metastasis add Topotecan: 3-5 cycles
- Surgery: Enucleation or orbital exenteration: Indication when
    - High intraocular stage Reese-Elworth 4-5, Group D-E with no/low chance of salvaging vision
    - No access to chemotherapy or laser therapy
    - Confined to the globe
    - If edema or other problems make enucleation problematic, consider chemotherapy for 2 cycles begore surgery.

- Radiation therapy: for spread out of the globe or extra-orbital involvement or trilateral disease.
- Supportive treatment: anti-emetic, antibiotic prophylaxis (trimethoprim sulfamethoxazole)
- Palliative care: for metastasis disease

Note: Declaimer this treatment protocol is established at Angkor Hospital for Children and can be adapted however you have to asceses your situation.

VIII. Prognosis

- Survival rates: > 90% in developed countries, about 80% in middle income countries (3)
- Risk of secondary malignancies for heritable tumors or non-heritable tumors with the use of irradiation. The most common second tumors are: osterosarcoma, pineaoblastoma, and rhabdomyosarcoma. (12)

IX. Prevention, Education and Follow up

RB is life threatening disease. Early detection and multidisciplinary management are important for optimal outcomes. We hope that every health professional reading this guideline will raise awareness of devastating by the disease and we will have a better chance to save the life, eye and sight of children with retinoblastoma. Please refer the patient to specialized center with expert team, which is available at Angkor Hospital for Children.

Patient needs to follow up regularly during and after treatment. Follow-ups may include repeated EUA. Families need to understand the risk of recurrence in subsequent pregnancies and the risk of survivors having children with disease.

Suggested follow-up schedules:

Not high risk [13]

- Every 3 months EUA: 3 times
- Every 6 months EUA: 3 times
- Every 1-year EUA

High-risk for unilateral and bilateral [13]

- Monthly for exam under general anesthesia (EUA) for the first year.
- Every 6-8 weeks in the second year.
- Every 6 months EUA: 3 times
- Every 1-year EUA.

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Chapter IX: Rheumatological diseases

ACUTE RHEUMATIC FEVER

SUON Pisey, AN Monychanbo, SAM-AN Kamnhanroth

I. Key facts [1], [2], [3]

- Acute rheumatic fever (ARF) is an abnormal immunologic response to group A Streptococcus (GAS) infections, most commonly tonsillopharyngitis.
- ARF affects multiple organ systems and may have cardiac, neurologic, musculoskeletal, or dermatological manifestations.
- While anyone can develop ARF, the disease is most commonly seen in children between 5 and 15 years old.
- No gender predilection for ARF has been noted, but females are more likely to progress to RHD (rheumatic heart disease).
- Approximately 470,000 new cases of ARF occur annually, with a more significant disease burden in developing countries with higher rates of untreated or inadequately treated GAS infections.
- Worldwide, incidence range from 8-51/ 100.000 with highest rate > 10/100.000 in Asia, Africa and Australia.
- Rheumatic heart disease is the leading cause of cardiovascular death during the first five decades of life.

II. Overview [1],[3]

1. Definition

Acute rheumatic fever (ARF) is an immune-mediated nonsuppurative complication of group A streptococcal (GAS) pharyngitis (see annex 1). It is an inflammatory response to a preceding GAS pharyngeal infection.

2. Physiopathology

ARF is characterized by an aberrant immune response to GAS infection triggered by molecular mimicry between GAS antigens and self-antigens. This immune response typically manifests 2 to 4 weeks after the initial GAS infection and may lead to the development of carditis, valvulitis, Sydenham chorea, subcutaneous nodules, erythema marginatum, and polyarthritis that is usually migratory.

Higher attack rate occurs with certain streptococcal M protein serotypes and a strong host immune response.

2-3% of untreated or inappropriate treated of GAS acute tonsillopharyngitis develop ARF.

Aschoff bodies is the pathognomonic histological lesion of ARF especially in myocardium.

3. Risk Factors

Most cases occur in low- and middle-income countries with risk factors including overcrowding (increased risk for transmission), limited access to health care, routine use of antibiotics for acute pharyngitis and improper treatment for GAS pharyngitis.

III. Signs and symptoms [1],[6]

The clinical manifestations of ARF vary drastically; some infections may be subclinical, and a diagnosis of ARF is not made until a patient is diagnosed with cardiac disease.

- Arthritis or arthralgias (60-80%) is earliest manifestations of ARF. It is typically migratory and characterized by erythematous, swollen, and extremely tender joints; the large joints like the knee, ankle, or wrist are most commonly affected. The abnormal of the joint are not chronic and do not leave scarring or residual abnormalities (ARF licks the joints but bites the heart).
- Carditis (50-80%) is the most serious presentation of ARF, affect the heart from inside out (valve, endocardium, myocardium and pericardium). The mitral valve (mitral

regurgitation) is affected in 50% to 60% of cases of valvulitis. Due to severe pancarditis or valvopathy, cardiomyopathy and heart failure can occur, even during ARF.

- Subcutaneous nodules (<10%) are firm, painless lesions over joints, predominately on extensor surfaces. These nodules are typically associated with severe carditis.
- Erythema marginatum (<6%) is a pink or pale red annular, nonpruritic rash with raised edges and central clearing found on the trunk and limbs but not the face (see annex 2).
- Sydenham chorea (SC) (10% to 30%) is a late-stage neurological complication usually occurring 1 to 8 months after GAS infection, it may occur on isolate finding, without dermatologic and joint manifestations. SC presents as involuntary, irregular "jerking" movements of the face, hands, or feet. These choreiform movements are more extreme on one side of the body and do not occur during sleep. "milkmaid's sign," where a patient cannot maintain her grip when asked to squeeze the examiner's fingers due to intermittent loss of muscle contraction, leading to a squeeze-and-release motion. Chorea typically resolves within 6 weeks to 6 months.

IV. Diagnosis [1],[4]

1. ARF is diagnosed by positive of preceding GAS infection and the used of the revised Jones Criteria.

Table 1. Revised Jones criteria

A. For all patient populations with evidence of preceding GAS infection	
Diagnosis: initial RF	2 Major manifestations or 1 major plus 2 minor manifestations
Diagnosis: recurrent RF	2 Major or 1 major and 2 minor or 3 minor manifestations
B. Major criteria	
Low-risk populations[a]	Moderate- and high-risk populations
Carditisb clinical and/or subclinical	Carditis[b] (clinical and/or subclinical)
Arthritis polyarthritis only	Arthritis (monoarthritis or polyarthritis; polyarthralgia[c])
Chorea	Chorea
Erythema marginatum	Erythema marginatum
Subcutaneous nodules	Subcutaneous nodules
C. Minor criteria	
Low-risk populationsa	Moderate- and high-risk populations
Polyarthralgia	Monoarthritis
Fever (≥38.5 °C)	Fever (≥38.5 °C)
ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL[d]	ESR ≥30 mm/h and/or CRP ≥3.0 mg/dL[d]
Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

RF, Rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GAS, group A *Streptococcus*.

[a] Low-risk populations are those with an acute rheumatic fever (ARF) incidence of ≤2 per 100 000 school-aged children or all-age rheumatic heart disease prevalence of ≤1 per 1000 population per year.

[b] Subclinical carditis indicates echocardiographic valvulitis.

[c] Polyarthralgia should only be considered as a major manifestation in moderate- to high-risk populations after exclusion of other causes *(17)*. As in past versions of the criteria, erythema marginatum and subcutaneous nodules are rarely "stand-alone" major criteria. Additionally, joint manifestations can only be considered in either the major or minor categories but not both in the same patient.

[d] The CRP value must be greater than the upper limit of normal for laboratory. Also, because ESR may evolve during the course of RF, peak ESR values should be used.

2. Investigations:

- Hemogram with ESR and CRP
- Throat culture for group A beta-hemolytic streptococci
- Rapid antigen streptococcal detection tests

- Antistreptolysin O (ASO) or antideoxyribonucleas B (ADB) antibody titers
- Heart ultrasound and ECG
- Chest X- ray

3. Differential diagnosis

- Polyarthritis: Lyme disease, Poststreptococcal reactive arthritis, Septic arthritis, Drug reactions and serum sickness, Postinfectious reactive arthritis
- Carditis: Endocarditis, Viral myocarditis
- Sydenham chorea: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), Tardive dyskinesia, Tourette syndrome
- Dermatologic manifestations: Urticaria, Scarlet fever, Kawasaki disease, Erythema multiforme, Erythema migrans (Lyme disease), Viral exanthem
- Systemic illnesses: Juvenile idiopathic arthritis, Kawasaki disease, Systemic lupus erythematosus

V. Complications [1], [2]

RHD occurs 10 to 20 years after the original illness and is due to valvular damage by severe or recurrent bouts of ARF. RHD can lead to heart failure, pulmonary hypertension, dysrhythmias, embolic strokes, and sudden cardiac death.[1]

Jaccoud arthropathy, a chronic, benign arthropathy that may result in joint deformities due to repeated bouts of arthritis caused by ARF. The arthritic changes of Jaccoud arthropathy appear similar to the joint deformities seen with rheumatoid arthritis and include thumb subluxation, ulnar deviation, hallux valgus, and swan neck and boutonniere deformities of the fingers. (see annex 3)

Persistent Sydenham chorea does occur, but the mechanism is unclear. Some experts suspect damage to the basal ganglia accounts for this phenomenon. Additionally, psychiatric symptoms may be more prevalent in patients who have suffered from Sydenham chorea.[3]

VI. Management [1], [5], [7]

The treatment of ARF is multimodal and involves GAS eradication therapy, symptomatic treatment, and prophylaxis to prevent recurrence.

- Group A Streptococcus Eradication Therapy
  - Penicillin V (<27kg) 250 mg 2 to 3 times daily, oral, for 10 days; if the patient (>27kg) 500 mg, 2 to 3 times daily for 10 days.
  - Penicillin G benzathine: (<27 kg) 600,000 units or 1.2 million units (>27 kg) as single dose intramuscular.
  - Amoxicillin: 50 mg/kg/d orally for 10 days, once or twice daily.
  - Azithromycin 12 mg/kg/d orally 5 days (max 500 mg/dose)
  - Clarithromycin 7.5 mg/kg/dose, twice daily orally for 10 days (max 250 mg/dose).
- Symptomatic Therapy
  - Arthritis: Aspirin 60 to 100 mg/kg/day in QID (max daily dose 4-6g) for 2-4 weeks then tapper the dose over another 4 weeks until symptom resolution. Naproxen 5 to 10 mg/kg, BID (max 1000mg) until symptoms resolve, is equally effective.
  - Cardiac symptoms: Oral prednisolone 1 to 2 mg/kg/day (Max: 80 mg/day) in 1 or 2 divided doses, recommend instead of aspirin for patient moderate to severe carditis (see annex 4), given 2-4 weeks then taper over another 2-3 weeks.
  - Methylprednisolone succinate pulse (30mg/kg IV max 1g /day for 3 successive days for severe heart failure. Fluid and salt restriction, angiotensin-converting enzyme (ACE) inhibitors, and diuretics maybe also used.
  - Sydenham chorea: self-limited for mild SC. Moderate to severe SC may treated with Dopamine 2 receptor blocker (Haloperidol, Risperidone, Pimozide) and anti-

seizure drugs (Carbamazepine, Levetiracetam and Valproic acid), always seek advice from neurologist.

- Secondary Antibiotic Prophylaxis. [4]

The 2020 American College of Cardiology/American Heart Association guidelines recommended durations of prophylaxis are as follows:

Table 2. *Group A Streptococcus Eradication Therapy*

Antibiotic	Dose
Benzathine penicillin G	<27kg:600.000 unites IM >27kg: 1.2Million UI. IM, every 3-4 weeks (3 weeks in high-risk area)
Penicillin V	250mg oral, BID
Sulfadiazine	<27kg: 500mg >27kg: 1g Oral, once a day
Erythromycin	30-50mg/kg/day, TID, (max 500mg/day)

❖ *Note: IM: intramuscular, BID; 2 times per day, ITD: three time per day*

Table 3. Secondary Antibiotic Prophylaxis of Acute Rheumatic Fever

Level of Carditis	Duration of Antimicrobial Prophylaxis
Carditis and detectably persistent heart disease	10 y from the last episode of ARF or until age 40, whichever is longer
Carditis without detectably persistent heart disease	10 y from the last episode of ARF or until age 21, whichever is longer
No evidence of carditis	5 y from the last episode of ARF or until age 21, whichever is longer

VII. Monitoring

Patients who have has rheumatic fever have about 50% likelihood of having recurrence if they have another episode of GAS pharyngitis that is untreated. Recurrence tends to occur within the first few years after the attack. The risk of developing a new episode is highest during the 5 years following an acute attack. Monitoring at 3- to 4-month intervals is critical to evaluate for progress with the resumption of physical activity, resolution of the constitutional symptoms, and freedom from adverse effects from medications.

VIII. Prognosis [1], [2]

The usual course of ARF is about 3 months. Recurrence increases the risk of progression to RHD and heart failure. Risk factors contributing to recurrence include poor adherence to prophylaxis, shorter intervals between episodes of ARF, younger age, and the presence of carditis.

Cardiac involvement is the most critical prognosticating factor in ARF. Prognostic of ARF depend on the severity of affected heart.

Episode of chorea Sydenham usually last several months and resolve completely in most patient, only one third of the patients have recurrence.

Joints inflammation may take one month to subside if not treated but do not lead to residual lesion.

IX. Prevention and education [1],[4]

- Education: during an admission, it is crucial that patents and their caregivers receive adequate and culturally appropriate information and education about ARF and RHD.

The most crucial advice for patients is the importance of continuing secondary prophylaxis even though they will be mostly asymptomatic.

- Prevention: Primary prevention involves eradication of Streptococcus from the pharynx.
- For secondary prevention, the American Heart Association (AHA) Committee on Acute Rheumatic Fever recommends long term antibiotic prophylaxis.

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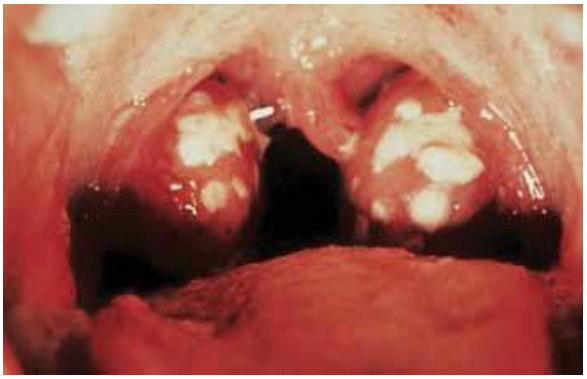
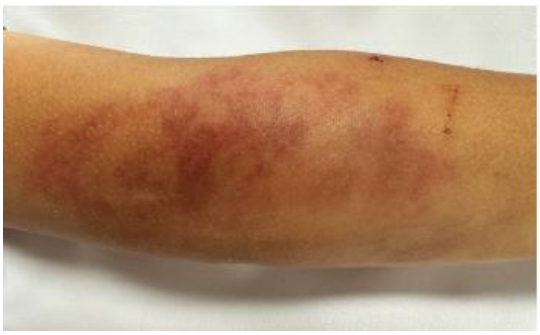
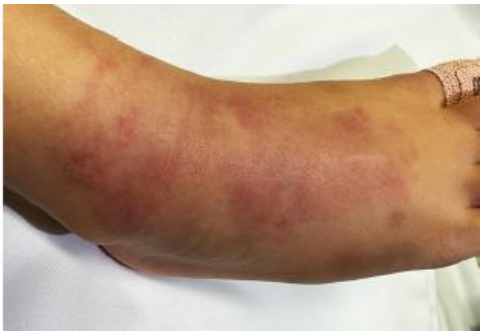
Annex 1. *Acute streptococcal pharyngitis*

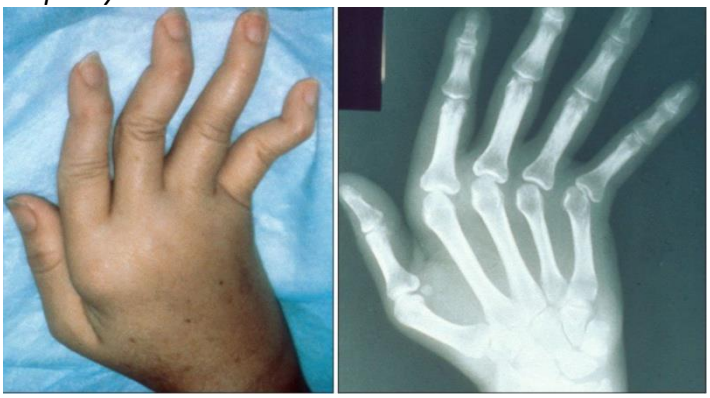


Annex 2. *Erythema Marginatum on a child's arm and foot*





Annex 3. *Jaccoud arthropathy*



Annex 4. World Heart Federation Classification of Rheumatic Heart Disease

Stage	Age	Clinical Risk	Echocardiographic Features
A - Minimal Echocardiographic Criteria for RHD	≤ 20 years	Possible risk of valvular heart disease progression	Mild MR or AR, without morphologic features
B - Mild	Any	Moderate or high risk of progression, risk for developing symptoms of valvular heart disease	Evidence of mild valvular regurgitation plus at least one morphologic feature in individuals aged ≤20 years and at least two morphologic features in individuals aged > 20 years; or mild MR and AR
C - Advanced RHD at Risk of clinical Complications	Any	High risk of developing clinical complications that require medical or surgical intervention	Moderate or severe MR or AR, any MS or AS, pulmonary hypertension, and decreased LV systolic function
D – Severe - Advanced RHD with clinical Complications	Any	Established clinical complications including need for cardiac surgery, heart failure, arrhythmia, stroke, and infective endocarditis	Moderate or severe MR or AR, any MS or AS, pulmonary hypertension, and decreased LV systolic function
AR= aortic regurgitation; AS = aortic stenosis; LV= left ventricular MR= mitral regurgitation; MS = mitral stenosis; RHD= rheumatic heart disease			

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) IN CHILDREN

TAT Votthoeun, IV Malene

I. Key facts

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that mainly affects skin, joints, and kidneys but can affect any organ in the body.

II. Overview

1. Definition

SLE is a chronic autoimmune inflammatory disease of unknown cause that can affect any organ system, most frequently the skin, joints, kidneys, and the nervous, hematologic, and cardiovascular systems. Its defining feature is the generation of many autoantibodies. The notion that children affected with SLE experience more severe disease manifestations and accumulate disease damage earlier than adults with SLE is widely recognized[3].

2. Epidemiology[1][2]

- SLE can occur at any age, although it is rare before five years of age and is increasingly prevalent after the first decade of life.
- Ratio: female/male between 3–5:1 (prepubertal) and 9–10:1 (post-pubertal)
- SLE occurs about 3 times more often in African Americans than Caucasians. It is also more common in Hispanic, Asian, and Native Americans.
- Incidence
  - Peak incidence: Between ages 15 and 40 years
  - Worldwide, estimates of SLE incidence are between 0.3 to 2.2 per 100,000 children.
- Prevalence rates range widely from 3.3 to 9.7 per 100,000 children and adolescents.

3. Etiology

The exact etiology remains unknown, but genetic, hormonal (Hyperestrogenic states), immunologic, and environmental factors (Cigarette smoking and silica exposure, UV light, and EBV infection) are suspected to play a role, mainly due to defects in the complement system, the type I interferon pathway; aberrant nucleic acid repair, degradation, and sensing, or abnormal B cell development. Many clinical manifestations are mediated, directly or indirectly, by antibody formation and the creation of immune complexes.

4. Physiopathology

The exact pathology mechanism of SLE is not fully understood, but the following two processes are the most widely accepted hypotheses:

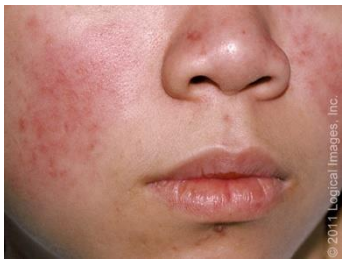
- Autoantibody development: deficiency of classical complement proteins (c1q, C4, C2) → failure of macrophages to phagocytose immune complexes and apoptotic cell material (i.e., plasma and nuclear antigens) → dysregulated, intolerant lymphocytes targeting usually hidden intracellular antigens → autoantibody production (e.g., ANA, anti-dsdna).
- Autoimmune reactions
  - Type III hypersensitivity (most common in SLE) → antibody-antigen complex formation in microvasculature → complement activation and inflammation → damage to skin, kidneys, joints, small vessels
  - Type II hypersensitivity → igg and igm antibodies directed against antigens on cells (e.g., red blood cells) → cytopenia.

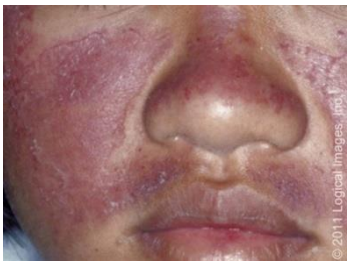
5. Risk factors: Genetics

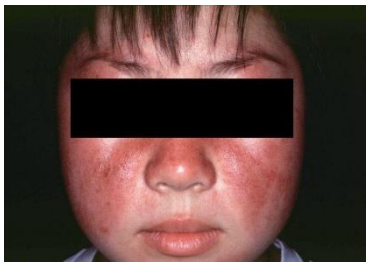
- Increased frequency in 1st-degree family members of patients with SLE
- 10% of patients have ≥1 affected relative.
- Concordance rate of 25–50% in monozygotic twins and 5% in dizygotic twins.

III. Signs and symptoms

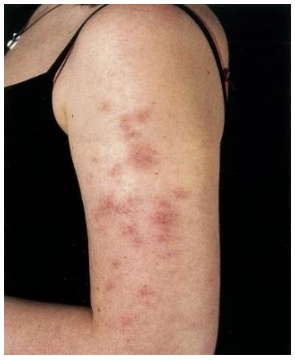
- SLE is a systemic disease characterized by phases of remission and relapse. Some individuals only experience mild symptoms, while others experience severe symptoms and rapid disease progression.
- SLE can affect every organ system. Many children and adolescents develop gradual fever, weight loss, tiredness, and arthralgia over weeks to months. Major organ involvement usually occurs within two to three years of disease initiation. Some new patients come with acute or life-threatening symptoms due to concurrent macrophage activation syndrome (MAS), severe renal illness, severe neuropsychiatric signs, or acute thromboembolic disease. Early-onset SLE in children (<10 years old) is associated with worse disease activity and a worse prognosis.
- In reviews from multiple different countries, the most common presenting manifestations were as follows[1]:
    - Hematologic (55% to 77%)
        - Anemia
        - Lymphopenia
        - Leukopenia,
        - Thrombocytopenia: It is possible to detect isolated thrombocytopenia (also known as immune thrombocytopenia [ITP]) or Evans syndrome (also known as immune thrombocytopenia with concurrent autoimmune hemolytic anemia) months or years before SLE is diagnosed.
    - Mucocutaneous (70%)
        - Malar rash (butterfly rash): flat or raised fixed erythema over both malar eminences (nasolabial folds tend to be spared)



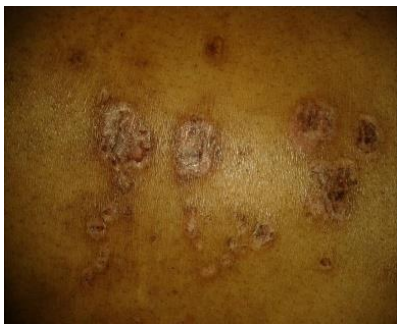




        - Photosensitivity → maculopapular rash



        - *This is the characteristic appearance of the macular rash in systemic lupus erythematosus, and it typically occurs on sun-exposed areas of the skin.*



        - *Discoid rash: well-defined erythematous plaques with Adherent keratotic scaling and follicular plugging, which may lead to scarring, pigmentation, and atrophy.*

- Oral or nasal ulcers

- Musculoskeletal (61% to 64%)
  - Arthritis: affects both large and small joints
  - Arthralgia
  - Serositis
  - The three conditions that affect bones are osteopenia, osteoporosis, and osteonecrosis (avascular necrosis). Even when glucocorticoids are tapered and stopped, low bone mineral density (BMD) is often seen during SLE diagnosis and does not improve throughout the disease.
- Renal abnormalities (27% to 59%)
  - Proteinuria
  - Hematuria and/or casts suggestive of nephritis.
  - Nephrotic syndrome and/or biopsy-proven lupus nephritis. Histopathology-based classifications of lupus nephritis range from class I (normal or near normal) to class VI (end-stage kidney disease), with proliferative nephritis (class III or class IV) reporting for almost half of all renal lesions[1]. Because proliferative lesions have the highest risk of developing into end-stage renal disease, they are the most severe and necessitate substantial immunosuppression.
- Constitutional symptoms are very common:
  - Fatigue, weight loss, fever (26% to 58%)
  - Although these are typical early signs of SLE, low-grade fever, exhaustion, anorexia, and lymphadenopathy do not distinguish SLE from other systemic diseases. High fevers that last longer than 38.6°C are possible, but MAS and concomitant infections should always be ruled out.
- Serositis: pleuritis and pericarditis
- Heart (12% to 54%)
  - Pericarditis, myocarditis, endocarditis
  - Aortic valve lesions
  - Coronary artery disease
- Lungs
  - Pneumonitis
  - Interstitial lung disease
  - Pulmonary hypertension
- Vascular
  - Vasculitis
  - Thromboembolism
- Neurological
  - Headaches
  - Seizures
  - Psychosis
  - Lupus cerebritis
  - Aseptic meningitis
  - Peripheral neuropathies
- Eyes: keratoconjunctivitis sicca.

IV. Diagnosis

1. SLE is a clinical diagnostic

- Rule out alternative diagnoses to avoid unnecessary and potentially harmful interventions (e.g., immunosuppressants).
- Children who fulfill the American College of Rheumatology (ACR) criteria, Systemic Lupus International Collaborating Clinics (SLICC) criteria, or 2019 European Alliance of Associations for Rheumatology (EULAR, formerly known as European League Against Rheumatism).
- ***ACR criteria are considered to have definite SLE***.

ACR criteria[4]	
Patients must have at least 4 out of 11 criteria across various clinical and immunologic domains to be diagnosed with SLE.	
Criterion	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or clinician observation
Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions.
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a clinician
Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis – Convincing history of pleuritic pain or rubbing heard by a clinician or evidence of pleural effusion OR Pericarditis – Documented by ECG, rub, or evidence of pericardial effusion
Renal disorder	Persistent proteinuria greater than 500 mg/24 hours or greater than 3+ if quantitation is not performed OR Cellular casts – May be red cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder	Seizures OR psychosis – In the absence of offending drugs or known metabolic derangements (uremia, ketoacidosis, or electrolyte imbalance)
Hematologic disorder	Hemolytic anemia – With reticulocytosis OR Leukopenia – Less than 4000/mm^3 total on 2 or more occasions OR Lymphopenia – Less than 1500/mm^3 on 2 or more occasions OR Thrombocytopenia – Less than 100,000/mm^3 (in the absence of offending drugs)
ANA	An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome
Immunologic disorders	Anti-DNA – Antibody to native DNA in abnormal titer OR Anti-Sm – Presence of antibody to Sm nuclear antigen OR Positive antiphospholipid antibody on: - An abnormal serum level of igg or igm anticardiolipin antibodies OR - A positive test result for lupus anticoagulant using a standard method.

2. **Laboratory** markers of disease activity and/or organ damage in SLE
   - Complement levels: ↓ C3 and/or ↓ C4 in patients with active disease

- Inflammatory markers
  - ESR may be elevated in patients with active disease
  - CRP: often normal (may be elevated in patients with serositis, arthritis, or infections)
- CBC: may show leukopenia, thrombocytopenia, and/or autoimmune hemolytic anemia or anemia of chronic disease
- CMP: may show ↑ BUN and/or creatinine, and/or electrolyte abnormalities
- Urinalysis and urine microscopy may show proteinuria, hematuria, and/or urinary casts
- Imaging studies: Imaging studies can help assess organ or joint involvement.
  - X-ray joints: Perform in patients with articular symptoms.
  - X-ray or CT chest: Perform in patients with symptoms of pulmonary involvement (e.g., interstitial lung disease, pleuritis).
  - Echocardiography: Consider in patients with suspected pericardial effusion or Libman-Sacks endocarditis.
- Antinuclear antibodies (anas)
  - ANA can be positive in many conditions. A positive ANA result must be interpreted in the context of the patient's symptoms and clinical history. Rarely the ANA can be negative in SLE, especially in anti-Ro antibody-positive lupus.
- Anti-dsdna and anti-Smith antibodies are highly specific for SLE and often are confirmatory of the diagnosis, if present. High titers are markers of disease activity, and high levels predict worse outcomes in lupus nephritis.

3. Differential diagnosis

- Systemic juvenile-onset rheumatoid arthritis
- Oncologic disease (leukemia, lymphoma)
- Viral or other infectious illness
- Other vasculitic disorders
- Dermatomyositis
- Drug-induced lupus
- Avoid over-diagnosing; a positive ANA does not indicate lupus without clinical SLE signs or symptoms.

V. Treatment

- SLE treatment aims to alleviate signs and symptoms, control disease activity, minimize drug-induced adverse events, prevent long-lasting damage, and improve health-related quality of life. Immunomodulation and immunosuppression are the main focus of pharmacological management, and specific therapy should be individualized according to the manifestations and severity of the disease[5].
- Lupus activity (LA) was classified as mild, moderate, and severe[6].

Lupus activity (LA)	Clinical features and laboratory markers	Pharmacotherapy
Mild disease	- Who does not have renal or other life-threatening organ system involvement): E.x., constitutional symptoms, mild arthritis, rash, and/or cytopenia (E.x, platelet count 50,000–100,000/mm3).	1. NSAIDs, which are non-steroidal anti-inflammatory drugs, are often the first treatment used for SLE to reduce joint stiffness and pain in the musculoskeletal system and serosal pain. 2. Consider the addition of oral glucocorticoids with or without other immunosuppressive agents to achieve remission.

		3. Hydroxychloroquine (HCQ): ≤5 mg/kg/day, and these children should have regular ophthalmic evaluations, including color vision and visual field testing. 4. Retinopathy is the most significant adverse event of HCQ. 5. Prednisolone dosage was initially 60 mg/m2/day (Max 60mg/d) for four weeks, followed by 40 mg/m2/qod for another four weeks, and after that, tapered to 20 mg/ m2/qod for ≥12 months. 6. Or to avoid adverse effects of Prednisolone → AZATHIOPRINE Oral: 2 to 2.5 mg/kg/dose (maximum 150 mg/ day) once daily for 3 months. 7. Methotrexate can be a helpful addition in patients taking oral corticosteroids for arthritis/arthralgia. ○ Methotrexate (MTX): 7.5 mg orally once weekly, increase gradually according to response, maximum 20 mg/week. ○ Taking 1 mg/day of Folic Acid is recommended, excluding the day MTX is taken.
Moderate disease	- Not life-threatening involvement of the kidneys or other vital organs/systems) E.x., cutaneous vasculitis, serositis, RA-like arthritis, moderate rash, and/or cytopenia, similar to that for mild SLE, except that these patients often require the continued use of high-dose glucocorticoids to control disease activity.	8. High-dose glucocorticoids to control disease activity in addition to HCQ. 9. Received pulse (IV) Methylprednisolone: 30 mg/kg/qd (Max 1g) for 3 doses followed by prednisolone, 40 mg/m2/qod for four weeks initially; it was after that tapered to 20 mg/m2/qod for ≥12 months. 10. For some children whose disease does not come under control with a combination of hydroxychloroquine and glucocorticoids, mycophenolate mofetil or azathioprine are options depending upon disease severity and tolerance of the medication.
Severe or organ-threatening disease	- Severe or organ-threatening disease: e.g., nephritis, myelitis, pneumonitis, mesenteric vasculitis, severe cytopenia	11. Induction therapy 12. High-dose IV glucocorticoids and other immunosuppressive agents 13. Used until symptom remission or low disease activity is achieved 14. Maintenance of remission: lower dose glucocorticoids AND/OR immunosuppressants

❖ Lupus nephritis (LN) treatment

The treatment is generally done in two phases: induction and maintenance treatment[8].

a. Induction Therapy

- 3 infusions of high-dose Methylprednisolone: 30mg/kg/d, then continued with a high dose of oral prednisolone; 2 mg/kg/day
- Cyclophosphamide:
  - IV dosing (shorter, lower dose) – If the shorter, lower-dose regimen is used, IV cyclophosphamide is administered at 500 mg every two weeks for six doses.
  - IV dosing (longer, higher dose) – If the longer, higher-dose regimen is used, pulse IV cyclophosphamide (0.5 to 1 g/m2, Max 1000 mg per dose) is administered monthly for six months.
  - If oral cyclophosphamide is used, the dose is typically 1 to 1.5 mg/kg per day, titrating up by 0.5 mg/kg per day every week up to 2 mg/kg per day (maximum dose 150 mg) if needed based on response. Continue therapy for 2 to 4 months once the dose is stabilized, then transition to an alternative immunosuppressive agent.
- In addition to pulse (IV) Methylprednisolone, oral AZATHIOPRINE: 2 to 2.5 mg/kg/dose once daily (maximum 150 mg/ day) for 3 months.
- Mycophenolate mofetil: 0.5 g twice daily for the first week, then 1 g twice daily for the second week, and after that, attempt to increase the dose to 1.5 g twice daily. However, this target dose may not be tolerated, and many patients may only tolerate a total daily dose of 2 to 2.5 g.
- CYCLOSPORINE: 3 to 5 mg/kg/day in 2 divided doses for 1 to 2 years.

b. Maintenance Therapy:

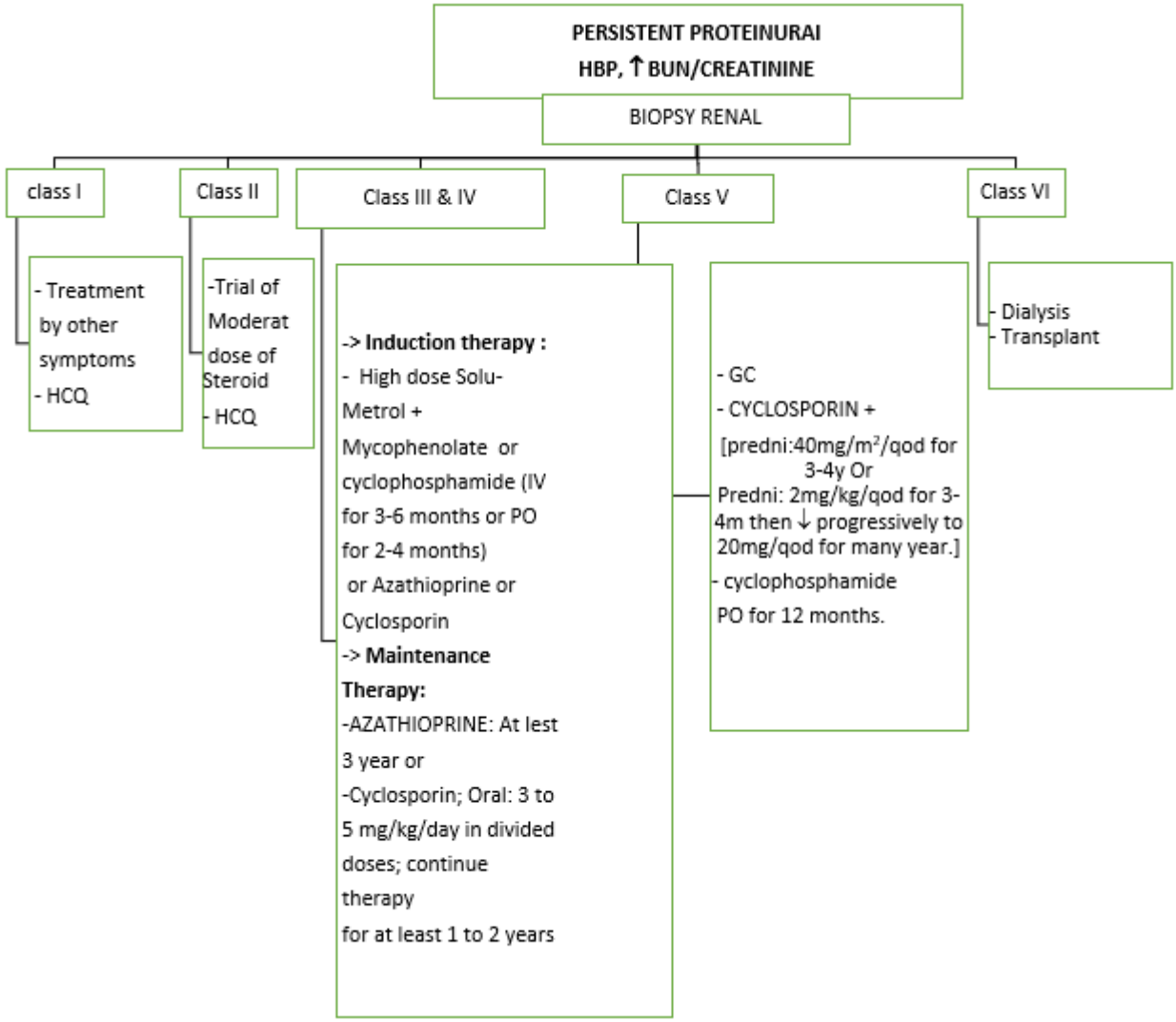
Although pulse IV cyclophosphamide has been best studied for initial therapy in diffuse LN and is most widely used, daily oral cyclophosphamide has also been used, including in a short-course regimen followed by azathioprine or cyclosporine subsequent therapy.

- No consensus exists on how quickly to wean the steroid dose or how low the dose should be during the maintenance phase. Some centres continue daily steroids at doses around 15 mg/day, while others aim for alternate-day dosing, and yet other centres try to stop the prednisolone when the child is well.
- A group of nephrologists, rheumatologists, and kidney pathologists established the ISN/RPS classification for LN in 2004 based on clinicopathologic correlations derived from kidney biopsies; this classification was revised in 2018, divides glomerular disorders associated with SLE into six patterns (or classes)[9–11].
  - Class I: Minimal mesangial LN
  - Class II: Mesangial proliferative LN
  - Class III: Focal LN
  - Class IV: Diffuse LN
  - Class V: Membranous nephropathy LN
  - Class VI: Advanced sclerosing LN
- Class IV LN is also the most common histopathological type in Southeast Asia, and together, Class III and IV accounted for 64.3–91.6% of those with biopsy-proven lupus nephritis. [12]
  - Prompt adjuvant treatment of hypertension and proteinuria should be recommended for all SLE patients. Renin-angiotensin-aldosterone system blockade antihypertensive and antiproteinuric effects are significant in SLE management. Proteinuria is a strong predictor of long-term renal outcomes; consequently, angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin

receptor blockers (ARB) use is considered a reno-protective strategy and recommended for all SLE patients with arterial hypertension or with proteinuria[5].
    - DISEASE FLARES: Adjust therapy based on the severity of organ involvement.
    - Early initiation of immunosuppressive agents can expedite the tapering/discontinuation of corticosteroids[13].

❖ Biological agents:

- Biologics may be considered in patients who are refractory, intolerant to glucocorticoids and/or immunosuppressive therapy, or relapse[14].
- Rituximab is advised for patients with refractory lupus nephritis in conjunction with another DMARD[5].
- Belimumab is a monoclonal antibody that inhibits B-cell activating factor (BAFF), also known as B-lymphocyte stimulator (blys) to B cells. This B-cell pathway-targeting agent was recently approved by the US Food and Drug Administration (FDA) for csle treatment in children > 5 years of age[15][16]. The dose of the belimumab intravenous pharmacokinetics and benefit-risk profile in SLE, 10 mg/ kg every 4 weeks, is appropriate.
- Treatment of SLE includes pharmacological therapies and patient education, such as protection from ultraviolet light and management and prevention of infections.
- Whatever the type of cutaneous lupus, avoidance of sun exposure is essential (Sunblock with an SPF ≥ 50 and protective clothing).
- SLE is associated with inadequate serum vitamin D levels compared with the general population. In patients with SLE, vitamin D supplements reduce disease activity, increase serum levels, and improve inflammatory markers, fatigue, and endothelial function levels. [17]
- All patients: Offer influenza and pneumococcus immunizations.
- Glucocorticoids and immunosuppressants
    - Consider studies for the diagnosis of latent TB at baseline in selected patients.
    - Monitor for side effects of glucocorticoid therapy.



VI. Prevention and Education

- Treatment of SLE includes pharmacological therapies and patient education, such as protection from ultraviolet light and management and prevention of infections.
- Whatever the type of cutaneous lupus, avoidance of sun exposure is essential (Sunblock with an SPF ≥ 50 and protective clothing).
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- All patients: Offer influenza and pneumococcus immunizations.
- Glucocorticoids and immunosuppressants
  - Consider studies for the diagnosis of latent TB at baseline in selected patients.
  - Monitor for side effects of glucocorticoid therapy.

VII. Complications

End-stage renal disease

- Infections
  - Responsible for 25–50% of deaths in patients with SLE
  - Most common infections
    - Bacterial: urinary tract, lungs, and skin.
    - Viral: varicella-zoster virus, cytomegalovirus, and human papillomavirus

- Patients with SLE are at increased risk of developing infections because of disease-related factors (e.g., pancytopenia) and/or immunosuppressive treatment.

- Medication toxicity
  - Prolonged usage of glucocorticoids can cause cataracts, avascular necrosis, and osteoporosis in children with SLE.
  - Hydroxychloroquine's most considerable risk is ocular toxicity.
- Macrophage activation syndrome (MAS)
  - MAS, a form of hemophagocytic lympho-histiocytosis (HLH), is a rare but severe and potentially life-threatening complication.
  - Clinical manifestations include persistent high fever, pancytopenia, hepatosplenomegaly, hepatic dysfunction, coagulation abnormalities, encephalopathy, and markedly elevated levels of ferritin.
  - In one case series of 38 patients (20 with definite MAS and 18 with probable MAS), most episodes of MAS occurred within one to six months after the initial diagnosis of SLE.[18]

VIII. Prognosis

- The prognosis of children and adolescents with SLE who receive appropriate care is generally good.
- The SLE survival rate is nearly 90% at 10 years [19].
- In children as well as adults, increased mortality rates are associated with lower socioeconomic status of the family, increased disease activity, and central nervous system (CNS) or renal involvement.
- The primary causes of an unsatisfactory outcome are:
  - Poor adherence, which is associated with poor patient and family education, limited access to specialty care, and other socioeconomic factors
  - Neurologic complications such as lupus encephalopathy
  - Intercurrent infections
  - Renal disease, especially diffuse proliferative glomerulonephritis
  - Cardiovascular disease
  - Getting the child referred to a facility with more experience is too late.

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JUVENILE IDIOPATHIC ARTHRITIS *(JIA)*

MENG Lun, YUNG Socheata

I. Key facts

- Juvenile idiopathic arthritis (JIA) describes a group of chronic pediatric inflammatory arthritides.[1]
- Older term juvenile rheumatoid arthritis (JRA, common in United Stated), juvenile chronic arthritis (common in Europe) has been replaced by the term juvenile idiopathic arthritis (JIA).[1]
- JIA is the most common chronic rheumatologic disease in children and is one of the most common chronic diseases in childhood.
- Incident rate estimates for JIA range from 4-14 cases per 100000 children in USA annually. Oligoarticular JIA is the most common 50% to 60% and polyarticular JIA 30-35%. Oligoarticular JIA and rheumatoid factor (RF) negative JIA typically affect young, female children. Female-to-male ratio ranges from 2:1 to 3:1[5,6,7]
- The most serious complication of oligoarticular JIA is uveitis or iridocyclitis: 20-25%.[8]

II. Overview

1. Definition [1.7]

Chronic pediatric inflammatory arthritides characterized by onset before 16 years of age and affected one or more joints for at least 6 weeks [1]; which defined by swelling of effusion, increased warmth, and/or painful limited movement with or without tenderness.

2. Etiology and pathogenesis: are unclear and could combination of factors [1,7]

- Familial predisposition: mildly increase risk
- Predisposing major histocompatibility complex genes: Multiple HLA
- Predisposing non-HLA genes: Interleukin (IL) 6 and macrophage immigration inhibitory factor (MIF) promotor polymorphism
- Environnement factor: Infections (Rubella, Epstain-Barr, Chlamydia, Influenza…), Antibiotics, ….

3. Physiopathology [1,7]

- Persistence of joints swelling results from combination of synovial fluid accumulation, synovial thickening and stretching of periarticular ligament and tendons.
- These due to the releasing of enzyme by inflammatory cell and may result in degradation of collagen, proteoglycan which deform articular cartilage matrix and the final pathway of juxta-articular bone demineralization and bone erosion.

4. Classification

Classification f JIA by *American College of Rheumatology* criteria for JIA [7,8,9,10]

JIA can be diagnosed if age at onset is under 16 years; there is arthritis in one or more joints; diseases duration is 6 weeks or greater. And disease type is defined by the type of disease present in the first 6 month.

a. *Polyarticular:* arthritis 5 or more joints in the first 6 months of disease

b. *Pauciarticular:* arthritis 4 or fewer joints in the first 6 months of disease

c. *Systemic:* arthritis with daily fever (to more than 39°c) spiking for 2 weeks or greater.

III. Signs and symptoms [1.7]

- Articular manifestation
- Arthralgias are common and the number of joints to terminate
- Common sign: Swelling, limitation of joints motion with pain, warmth or erythema of the joint.
- If synovitis: increase joint volume

- Limbs: held in flexion
- Fingers: swollen with painful in motion
- Hip: help in attitude of flexion, abduction, and external rotation

- Extra-articular manifestations: if these presents should focus on the sytemic JIA
- Fever: quotidian fever
- Rash: evanescent, macular, salmon pink rash (frequently present)
- Hepatosplenomegaly, splenomegaly, lymphadenopathy
- Pericarditis, pleural effusion.

IV. Diagnosis [8.9]

1. Laboratory test

- Inflammatory markers: Fast and easy to access in any laboratories
- Others markers and examination
  - Antinuclear antibody (ANA): 70% positive in oligoarticular, 40% positive in polyarticular and 10% in systemic JIA.
  - RF (Rheumatic factor): 10% positive in polyarticular onset JIA.
  - Ferritin: elevate, if this present with few other illnesses need to focus on systemic JIA

2. Imagery services [11.12]

- X-ray
  - Soft tissue swelling

Investigation	Systemic	Polyarticular	Oligoarticular
ESR/VS	Elevate	Normal/Elevate	Normal
WBC	Elevate	Elevate	Normal
Hb	Decrease	Normal	Normal
Platelet	Elevate	Elevate	Normal

  - Osteopenia and/or osteoporosis
  - Joint-space narrowing
  - Bony erosions
  - Intra-articular bony ankylosis
  - Periostitis
  - Growth disturbances
  - Epiphyseal compression fracture
  - Joint subluxation
- Ultrasound: abnormal in course of disease. Useful in identifying joint for corticosteroid injection. Ultrasound can be sensitive in synovitis.
- MRI: indicated in monoarticular disease to differentiate other diagnosis and the abnormal can be synovial fluid, synovial thickening, and/or synovial enhancement.
- Uveitis screening is very important in JIA patient.

3. Differential diagnosis

- Septic arthritis: single joint, high fever, severe pain and/or erythematous joint.
- Osteomyelitis: with high fever, severe pain, and/or focal tenderness (not just in articulation).
- Malignancy: signs and symptoms consistent with bone tumors (focal), leukemias (general pain) or neuroblastoma.
- Reactive arthritis: asymmetric oligoarticular arthritis, beginning 1-4 weeks after infection. May be associated enteritis, dactylitis, conjunctivitis, iritis, and rash.
- Acute rheumatic fever: acute migratory arthritis that response well to nsaids. Features include continues fever, cardiac involvement, and/or erythema margination rashes.

- Systemic lupus erythematous: non-erosive polyarthritis, malar rashes, renal involvement, photo sensitivity, serositis and central nervous system involvement.
- Juvenile dermatomyositis: muscle weakness, muscle pain, linear extensor erythema or heliotrope rash associated possibly with erosive oligo or polyarthritis.
- Kawasaki disease: high persistent fever for several day, polymorphous rash, involvement of lips and conjunctiva and oedema of extremities (and/or desquamation).

V. Management [10.12.16]

1. Different drugs used in JIA

Non steroidal Anti-Inflammatory drugs (NSAID)	Disease-Modifying Antirheumatic Drugs (DMARDS)
+ Ibuprofen : 30mg-50mg/kg/day divide in 3-4 times per day + Diclofenac : ≥ 3years : 2-3mg/kg/day + Naproxen : 5mg/kg/dose twice daily + Melaxicam : ≥ 60kg : 5-7mg once daily	+ Methotrexate : 10-25mg/m^2/wk, not to exceed 30mg/m^2 or 1mg/mg and combinate with folic acid: 1-2mg/day + Sulfasalazine : ≥ 6years : 30-50mg/kg/d
Corticosteroid + Oral or systemic - Methyprenisolone : 0.5-1.7mg/kg/day - Prednisolone : 0.5mg-2mg/kg + Intra-articular : - Triamcinolone acetonide (small joint: 2.5-5mg; large joint: 5-15mg) or - Methyprednisolone acetate (30mg/kg for 3 days; Max: 1g/day)	Biologic Agent Interleukine 1, Interleurkine 6 : Tolcilizumab or Canakinumab, Anakinra

2. Supportive care

- Physiotherapy
- Ophthalmic screening
- Psychologic support.

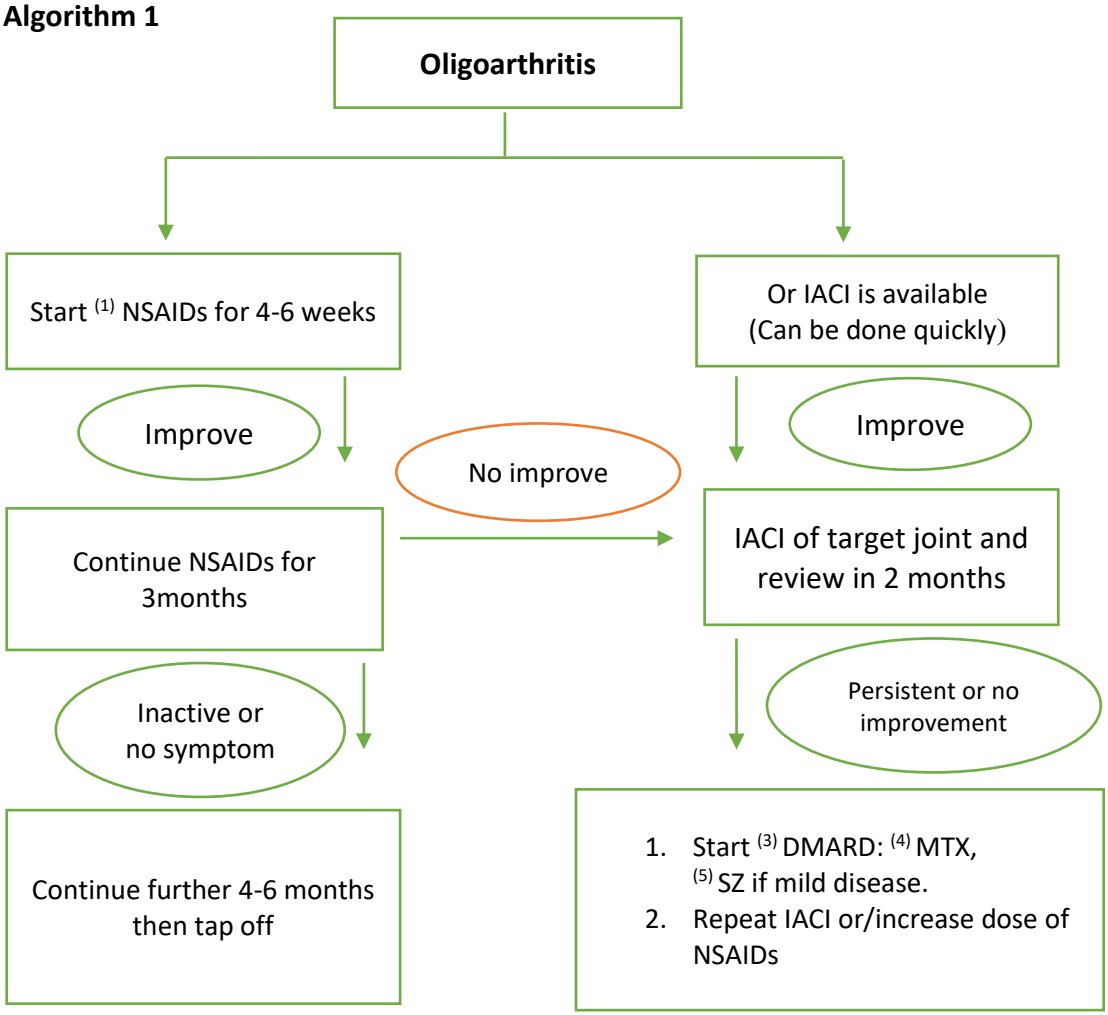
3. Treatment: follow the different form

a. Oligoarticular

Note for Algorithm 1:

(1) nsaids: Non-steroidal Anti-Inflammatory drugs
(2) IACI: Intra-Articular Corticosteroid Injection
(3) DMARD: Disease Modifying Anti-Rheumatic Drugs
(4) MTX: Methotrexate
5) SZ: Sulfasalazine

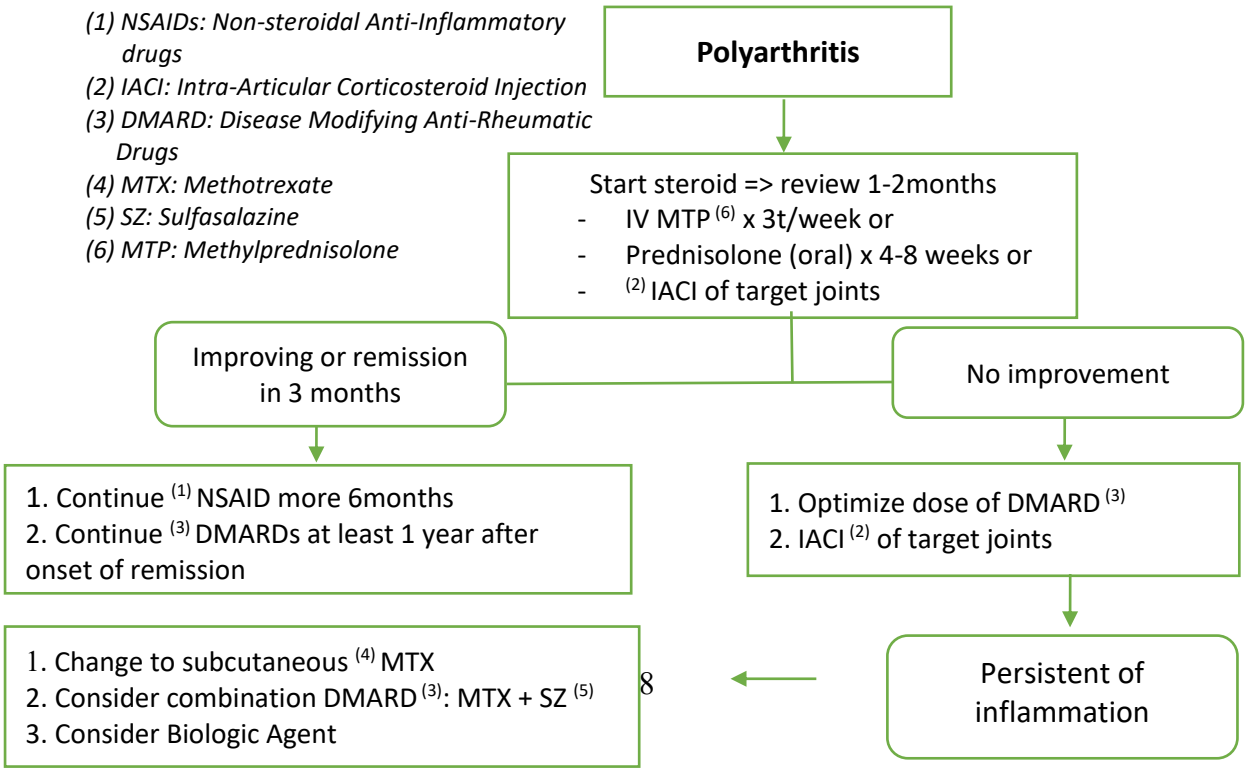
Algorithm 1



b. *Polyarticular JIA* [10]

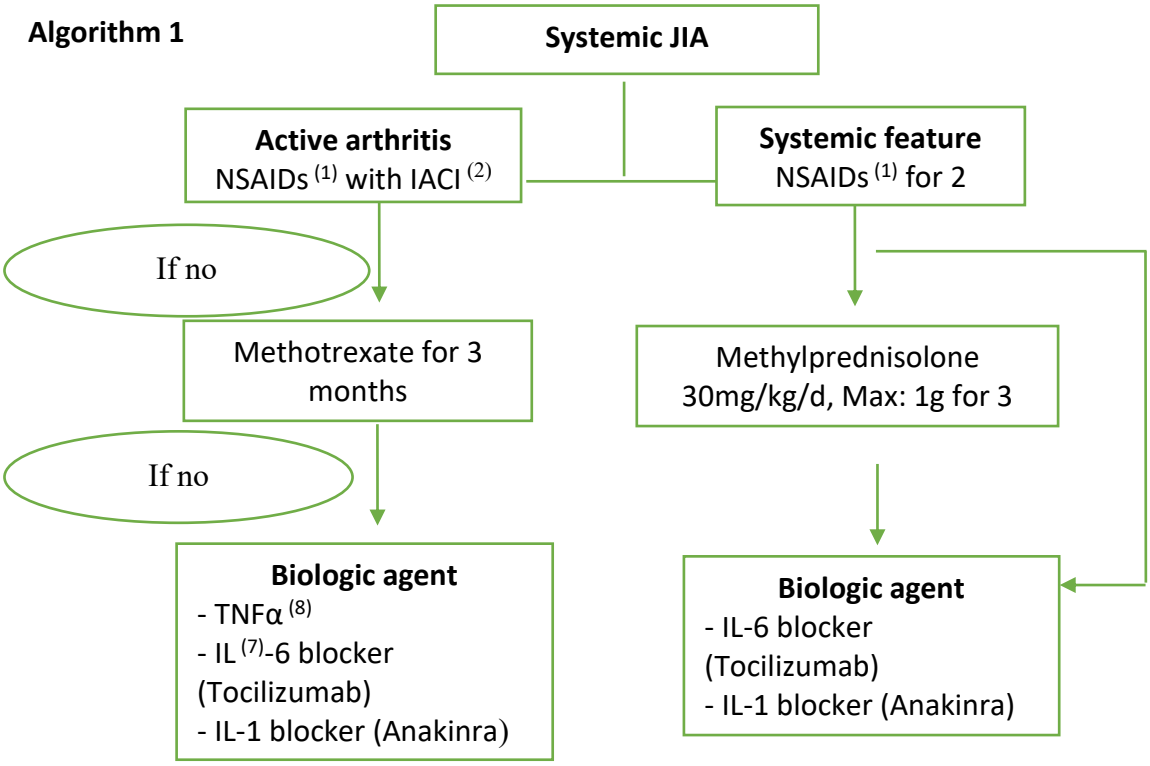
Algorithm 2

(1) NSAIDs: Non-steroidal Anti-Inflammatory drugs
(2) IACI: Intra-Articular Corticosteroid Injection
(3) DMARD: Disease Modifying Anti-Rheumatic Drugs
(4) MTX: Methotrexate
(5) SZ: Sulfasalazine
(6) MTP: Methylprednisolone



c. ***Systemic JIA*** [16]

Algorithm 1



(1) nsaids: Non-steroidal Anti-Inflammatory drugs
(2) IACI: Intra-Articular Corticosteroid Injection
(3) DMARD: Disease Modifying Anti-Rheumatic Drugs
(4) MTX: Methotrexate
(5) SZ: Sulfasalazine
(6) MTP: Methylprednisolone
(7) IL: Interleukin
(8) tnfα: Tumour Necrosis Factor alpha.

4. Follow up

- Full blood count
- Liver function
- Renal function
- Lipid profile (if under treatment of tocilizumab/tofacitinib)
- Regular ophthalmic examination every 3 months (for high risk of uveitis) and 6-12month for low risk of uveitis is recommended.

VI. Complications [15]

- Leg length discrepancy
- Joint erosion
- Cervical spinal fusion C1-C2 subluxation
- Sacro-iliac joint and spine ankylosis
- Uveitis
- Macrophage activation syndrome

- Highly fatal lung disease.

VII. Prognosis

- Oligoarticular JIA extend to involve 5 or more joints in several years of diagnosis but appear to have best prognosis, with better treatment outcome.
- Patient with Rheumatoid factor-positive and systemic-onset subtype continue have active disease in several years
- JIA with uveitis can lead to visual impairment if poorly control.
- Shorter disease duration to treatment in patient with polyarticular JIA lead the good initial response and longer duration of clinically inactive disease.

VIII. Prevention

- No primary preventive measures
- Regular physical activity of deconditioning can help patients with JIA to improve articular motion.
- Physiotherapy and occupational therapy are recommended.

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Chapter X: Mental, Behavioral and Neurological Disorders

EPILEPSY

KAO Sambath, SROEUNG Samrach, KHENG Mayanuth, KIM Ang

I. Key facts

- Epilepsy is a chronic noncommunicable disease of the brain that affects people of all ages. [1]
- Around 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally. [1]
- Nearly 80% of people with epilepsy live in low- and middle-income countries [1] and about 75% are children and adolescents. [2]
- It is estimated that up to 70% of people living with epilepsy could live seizure-free if properly diagnosed and treated. [2]
- In many parts of the world, people with epilepsy and their families suffer from stigma and discrimination. [1]

II. Overview

1. Definition: Epilepsy is a disease of the brain defined by any of the following conditions:

- At least two unprovoked (or reflex) seizures occurring > 24 hours apart
- One unprovoked (or reflex) seizure and a probability of further seizures similar to The general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
- Diagnosis of an epilepsy syndrome.
- Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years [3].

2. Classification

- Classification of Seizure – see Figure 1.
- Classification of the epilepsies – see Figure 2.

3. Causes

In about 50% of cases globally, the causes of epilepsy remain unknown. The causes are divided into the following categories [5, 6]

- Structural etiology: may be genetic or acquired (birth asphyxia, trauma brain injury...), or both.
- Genetic etiology: childhood absence epilepsy or juvenile myoclonic epilepsy…
- Infectious etiology: Ex. HIV, tuberculosis, subacute sclerosing panencephalitis…, and congenital infections such as Zika virus.
- Metabolic etiology: Ex. Creatinine deficiency syndrome, pyridoxine-dependent seizures, cerebral folate deficiency.
- Immune etiology: immune-mediated central nervous system inflammation may cause epilepsy. Ex. Anti-NMDA (N-methyl-D-aspartate) receptor encephalitis.
- Unknown: for many children with epilepsy the cause remains not known.

4. Physiopathology

The exact mechanism of seizure onset is unknown. Most authors suggest that seizures arise from a deficit in neuronal inhibition, particularly a lack of GABA, the key neurotransmitter in the CNS. Alternatively, seizures may result from changes in GABA function that lead to prolonged and intense stimulation. [7]

Figure 1. *Classification of seizure types* [4]

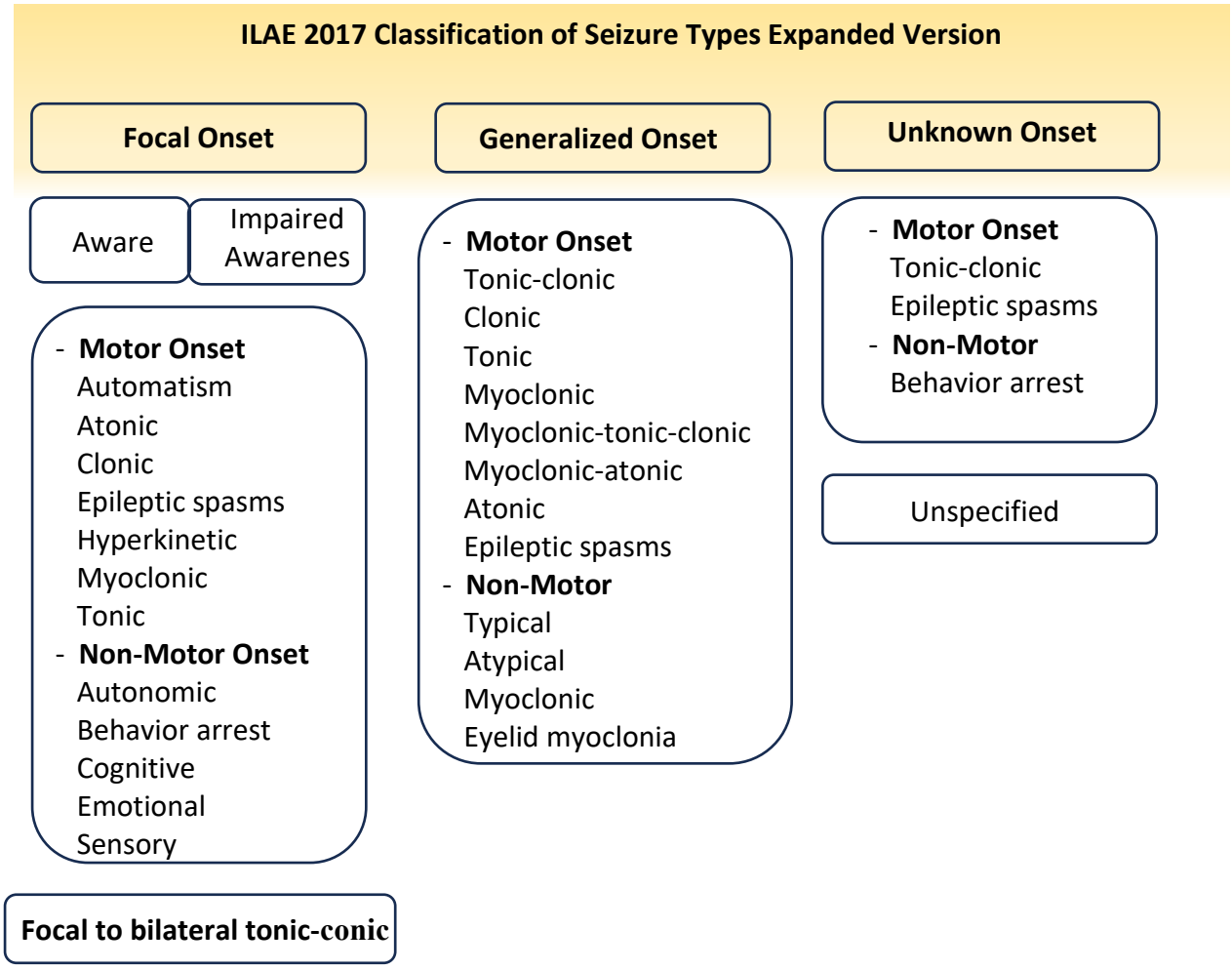
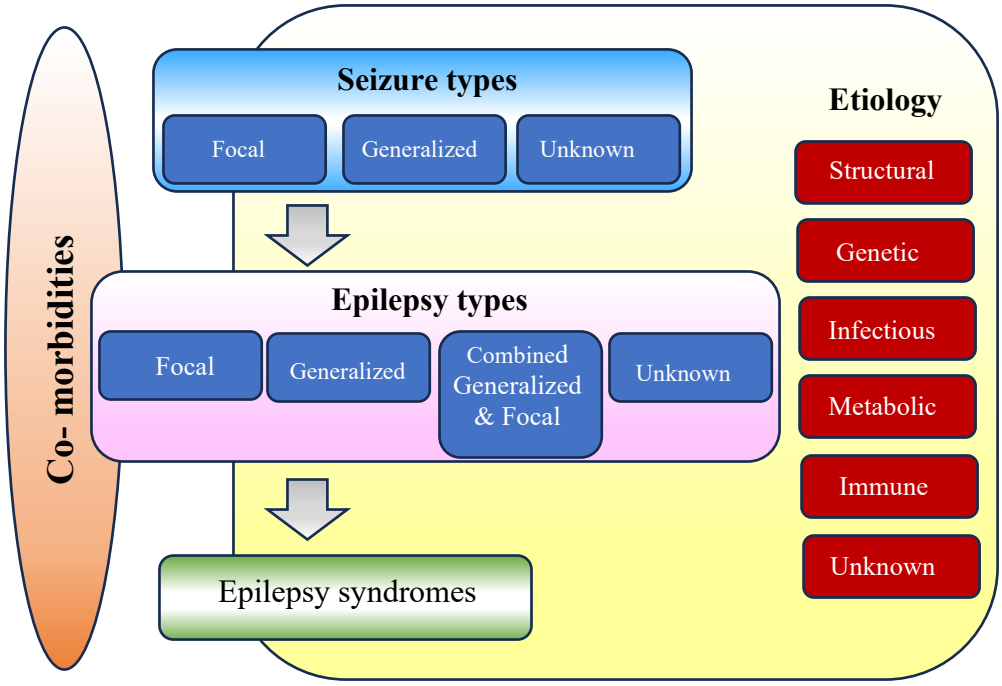


Figure 2. *The new framework for the classification of epilepsies* [5]



5. **Risk factors**

There are varieties of epilepsy risk factors including: [7]

- Premature
- Neonatal seizure
- Intraventricular hemorrhage (IVH)
- Hypoxic-ischemic encephalopathy (HIE)
- Maternal drug use
- Congenitally acquired infection
- Strock
- Febrile seizure
- Traumatic brain injury (TBI)
- CNS infection.

6. **Mortality**

The mortality rate in people affected by epilepsy is 2-4 times higher than the rest of the population, and 5-10 times higher in children. Sudden unexpected death in epilepsy (SUDEP) related mortality in children is about 1.1–2 cases/10,000 children per year [8].

The majority of the causes of death related to epilepsy, especially in low- and middle-income countries, are potentially preventable, such as falls, drowning, burns, and prolonged seizures [1].

III. Signs and symptoms

Clinical characteristics of seizures vary and depend on where in the brain the disturbance first onset and how large is spread.

Seizures are stereotyped, random, and rarely triggered by specific events. Symptoms include loss of awareness, and consciousness, movement disturbances, sensory disturbances (including vision, hearing, and taste), mood changes, and cognitive impairments [6]. Children over 6 years old have seizure symptoms similar to adults, while younger children have fewer complex behaviors.

1. **Clinical Evaluation**

A. For an infant or child with suspected seizures or epilepsy, consider:

- Is the episode a seizure? Or is the episode a non-epileptic event?
- Is the episode an acute symptomatic seizure (e.g., a provoked seizure caused by a fever, an acute brain insult, or a metabolic disorder)?
- Is the episode an unprovoked seizure (due to a preexisting brain lesion or progressive nervous system disorder or an unknown etiology)?
- If seizure or epilepsy is diagnosed, consider:
  - What is the type of seizure/epilepsy (e.g., focal, generalized, combined generalized and focal, or unknown)?
  - Do the clinical features, signs and symptoms, and electrographic pattern suggest an epilepsy syndrome?
  - What is the most likely etiology (e.g., genetic, structural, metabolic, immune, infectious, or unknown)?

B. For an infant or child with possible seizures or epilepsy, ask for a detailed history of events, including:

- The setting in which episodes occur (at home, school, public…)
- Onset (age at the first seizure, fever with the first seizure, always fever with the seizures…)
- Behaviour immediately before, during, and after the episode (upset and crying, making a sound or unexpected touch, numbness, visual distortions, auditory or visual

hallucinations or illusions, nausea or unusual feelings in the abdomen or chest, an unusual smell or taste…)
- A physical description of the child before, during, and after the episode (a color change during a seizure, stiffening, jerks, twitching, smacking, chewing, staring gaze, upturning of the eyes, jaw clenching, tongue biting; eye or head deviation to one side…)
- Frequency and duration of the episode
- Other important questions to ask include:
  - A neurodevelopmental history (any plateau or loss of developmental milestones)
  - A past and current psychosocial history, including potential stressors
  - Family history (consanguinity, family history of seizures…)
  - A medical history, emphasizing conditions known to be associated with epilepsy (central nervous system infection, trauma, etc.)
  - Prescription and illicit drugs
  - Video record of the event.
- On general examination look for Scars, bruises, changes in pigmentation, and hemangioma.
- On physical examination look for:
  - The gait (presence of weakness or spasticity),
  - The behavior (reaction to the surroundings and activity) and ability to communicate.
- On neurological examination look for:
  - Asymmetry of muscle power, muscle tone, and tendon reflexes.
  - Any signs of drug toxicity (e.g., drowsiness, sleepiness, ataxia, nystagmus, and cerebellar dysfunction).

2. **Laboratory test**

   These are useful, especially in acute seizures or status epilepticus:
   - Complete blood count/ Full hemogram
   - Serum electrolytes (sodium, potassium, calcium and magnesium)
   - Blood sugar
   - Blood urea
   - Liver Function Tests
   - Screening for infections (e.g., malaria, HIV)
   - Cerebrospinal fluid examination as long as there are no contra-indications for lumbar puncture
   - Chest radiograph
   - CT brain scan in acute deterioration or acute development of focal features
3. **Electroencephalography (EEG)**

   Electroencephalography (EEG) is a valuable tool for diagnosing and classifying epilepsy. It is recommended for:
   - Supporting the diagnosis of epilepsy in children and young adults
   - Determining the type of epilepsy syndrome (e.g., typical absences, Lennox Gastaut syndrome)
   - Assessing the risk of seizure recurrence after a first unprovoked seizure
   - Generally, an EEG should be performed after the second seizure, but it may be considered after the first.
4. **Neuroimaging** (CT or MRI scan of the brain) is NOT mandatory for all patients with epilepsy.

   Neuroimaging in epilepsy is useful in:

- Focal seizures
- Seizures suspected to be symptomatic in origin
- Difficult to control seizures

Neuroimaging detects lesions that may include scars, calcification, small vascular abnormalities, brain atrophy, and cerebral malformation.

IV. Diagnosis

The diagnosis of epilepsy relies on the clinical history. A thorough history should be gathered from the individual, whether child, adolescent, or adult, and an observer to assess the likelihood of a seizure or epileptic event. [6, 9]

❖ Differential diagnosis [10]

Not all "spell" or "episodes of disturbance of movement and/ or loss of awareness or consciousness" are seizures, the following should be considered in the differential diagnosis of epilepsy

- Behavioral, Psychological, and Psychiatric Disorders: Breath Holding Spells, Daydreaming/ inattention, Panic Attacks, or Psychogenic Non-Epileptic Seizure (PNES).
- Syncope (Reflex syncope, other static hypotension, cardiac syncope),
- Paroxysmal movement disorders: simple or complex motor tics and stereotypies
- Parasomnias: night terrors or rhythmic body rocking or head-banging behaviors.
- The metabolic or endocrine problem: hypoglycemia,
- Migraine with visual aura (similar to occipital epilepsy with simple partial seizures).

V. Complications

Children with epilepsy tend to have more physical problems (such as fractures and bruising from injuries related to seizures), as well as higher rates of psychological conditions, including anxiety and depression [8].

VI. Treatment [11, 12, 13, 14, 15,16]

Treatment aims to control seizures with the most appropriate anti-epileptic drug without causing any significant side effects.

Antiepileptic drug therapy should be started only after the diagnosis of epilepsy is confirmed and after discussing the risks and benefits of treatment with the child/family members.

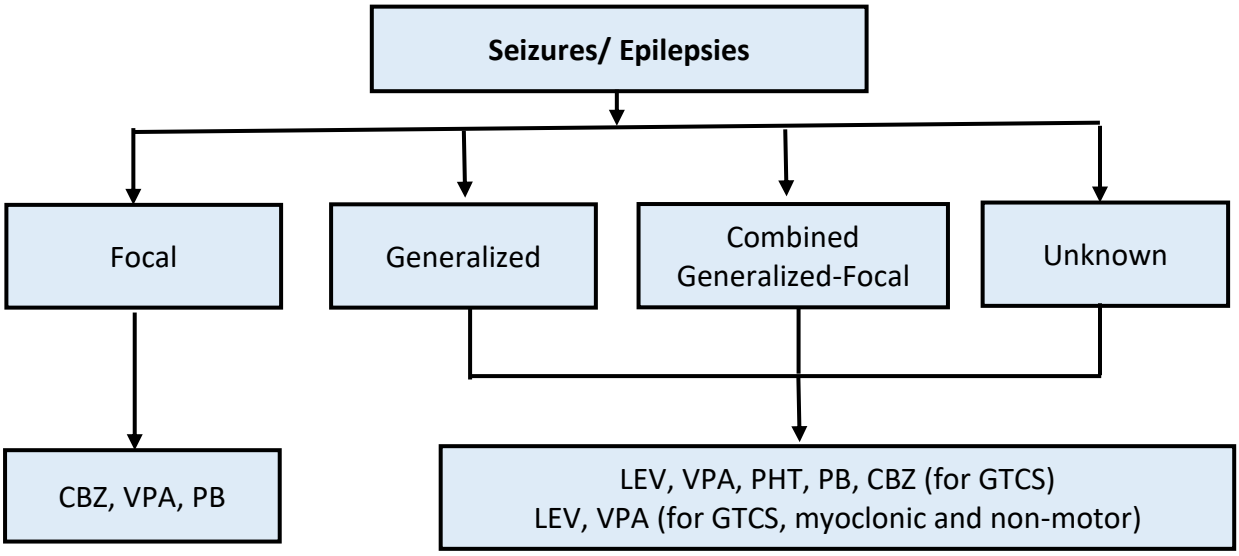
1. Treatment Principles for Epilepsy

- Start with a single medication (monotherapy). This is the most common and effective approach.
- Begin with the lowest dose and gradually increase it until seizures are controlled or side effects arise. This is known as the patient's minimum maintenance dose.
- If the first medication is ineffective or poorly tolerated, try monotherapy with a different antiepileptic drug (AED). Slowly increase the dose of the second medication until it reaches the appropriate or highest tolerated level. Gradually taper off the first medication.
- Combination therapy can be considered if two attempts at monotherapy with aeds have failed to achieve seizure freedom.
- The goal of treatment is to find the lowest maintenance dose that provides complete seizure control with minimal side effects.

2. Choosing the appropriate Antiepileptic Drug

Below is the algorithm for the choice of four conventional antiepileptic drugs (aeds):

Figure 3. *Choice of AED*



Abbreviations: CBZ (Carbamazepine), PHT (Phenytoin), VPA (Valproate), PB (Phenobarbital), LEV (Levetiracetam).

Table 1. *Starting and maintenance daily doses and important side effects of four conventional antiepileptic drugs (AEDs)*

Antiepileptic drugs (AEDS)	Starting dose in children	Maintenance dose in children	Important side effects
Carbamazepine (CBZ)	5mg/kg daily in 2-3 divided doses. Increase by 5 mg/kg daily each week.	10-30mg/kg/day	Sedation, dizziness, ataxia, skin rash (occasionally Stevens-Johnson syndrome), hyponatremia, weight gain, seizure worsening in some epilepsy syndromes
Phenobarbital (PB)	2-3mg/kg daily in 2 divided doses. Increase weekly by 1-2 mg/kg daily	2-6mg/kg/day	Sedation, ataxia, depression, memory problems, skin rash, hyperactivity in children
Phenytoin (PHT)	3-4mg/kg daily in 2 divided doses. Increase by 5 mg/kg daily every 3-4 weeks	3-8mg/day (Maximum 300mg per daily)	Ataxia, sedation, gum hyperplasia, coarsening of facial features, hirsutism, memory problems, osteomalacia and bone loss, skin rash
Valproate (VPA)	15-20mg/kg daily in 2-3 divided doses. Increase each week by 15 mg/kg daily	15-40mg/kg/day	Anorexia, weight gain, nausea, vomiting, tremors, hair, polycystic ovarian syndrome, thrombocytopenia
Levetiracetam (LEV)	14-20mg/kg daily in 2 divided doses. Increase 7-10mg/kg/dose every 2 weeks	40–60mg/kg/day	Asthenia, somnolence, behavioral problems, hallucinations, headache, vomiting, infections, Psychotic events, liver toxicity, pancreatitis.

3. **Monitoring the Antiepileptic Drug Therapy**

The following tests may be carried out as necessary:

- Complete blood count, liver enzymes and renal functions before starting AED
- Children and adolescents with epilepsy should maintain a seizure diary and have regular follow-up.
- The first follow-up may be undertaken anytime within 2–4 weeks of initiation of treatment and subsequently at every 3–6 months, depending on the control of seizures and side effects.

4. **Considering stopping Antiepileptic Drug**

- Antiepileptic drug withdrawal should be considered if the patient has been seizure-free for 2–3 years.
- The decision is mainly based on the type of epilepsy and cause of seizures and should be taken after discussion of the risks and benefits of withdrawal with the child with epilepsy and family.
- Antiepileptic drugs are usually withdrawn gradually over 3–6 months or longer.
- There is possibility of seizure recurrence during and after withdrawal.
- In case of multiple AEDS therapy, each drug should be withdrawn separately one after the other.
- If seizure recurs during or after AED withdrawal, the person may be advised to revert to their AED dose before reduction and seek medical help.

VII. Prevention and education [11]

1. **Psychoeducation**

Provide information on: "What is a convulsion/epilepsy" and the importance of medication

- Convulsions are caused by excess electrical activity in the brain, not by witchcraft or spirits.
- Epilepsy is a condition characterized by repeated convulsions.
- Epilepsy is a lifelong condition, but it can usually be controlled with proper medication.
- The patient may require assistance from others to manage their convulsions.
- Discuss the patient's healthcare practices, including any traditional or faith-based remedies, while emphasizing the importance of regular medical checkups.
- Inform the patient that certain medications and herbal products can interact negatively, so it's crucial to disclose all medications to their physician.

2. **Provide information on**

How guardian can manage convulsion at home.

- Epilepsy is not contagious; they cannot be spread through contact.
- The most importance thing when parent/ guardian witness a seizure do not to panic.

DO

- Remain calm,
- Lay patient down, on their side, head turned to help breathing.
- Put something soft under their head to prevent injury.
- Protect them from possible hazards.
- Ensure the patient is breathing properly.
- Stay with patient until the convulsion stops and they wake up.
- Track the time and document seizure activities.

DON'T

- Do not put anything in the mouth of patient-you will actually harm them or yourself more than you will help.
- Do not attempt to give oral medications, food or drink during a seizure.

- Do not hold down or restrain the patient in any way.

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ATTENTION DEFICIT HYPERACTIVITY DISORDERS

KAO Sambath, SROEUNG Samrach, KHENG Mayanuth, BO Rany

I. Definition

Attention deficit hyperactivity disorder (ADHD) is now defined as a neurodevelopmental disorder. Characterized by persistent of behavioral disorders with three key aspects: inattention, hyperactivity and impulsivity that interferes with daily life functioning. [1, 2]

II. Epidemiology

ADHD is the most common neurodevelopmental disorder of childhood occurring 5-7% of school age children. Sex ratio boys and girls 2-4:1. [2, 3, 4,5]

III. Etiology

The exact cause is unknown. Several factors may contribute to the condition: [3, 4, 5, 6]

- Genetic factors:
  - Parents with ADHD have more than 50% chance of having a child with ADHD,
  - About 25% of children with ADHD have parents who meet the formal diagnostic criteria for ADHD
- Some risk factors such as
  - Extreme early life adversity
  - Tobacco/alcohol use during pregnancy
  - Pre and postnatal exposure to lead
  - Low birth weight/prematurity.

IV. Pathophysiology

ADHD is associated with cognitive and functional deficits that relate to diffuse abnormalities in the brain [6].

- The anterior cingulate gyrus and dorsolateral prefrontal cortex (DLFPC) are small in individuals suffering from ADHD. It is thought that these changes account for the deficits in goal-directed behavior.
- Activity in the fronto-striatal region is also reduced in ADHD individuals as measured by FMRI.

It is important to understand these pathophysiological mechanisms so that the pharmacotherapy is directed onto them.

V. Diagnosis

1. **The diagnosis of ADHD is based on the following criteria** [4, 7]

a. Inattentiveness (difficulty concentrating and focusing): The main signs of inattentiveness:

- Having a short attention span and being easily distracted
- Making careless mistakes – for example, in schoolwork
- Appearing forgetful or losing things
- Being unable to stick to tasks that are tedious or time-consuming
- Appearing to be unable to listen to or carry out instructions
- Constantly changing activity or task
- Having difficulty organizing tasks

b. Hyperactivity and impulsiveness -The main signs of hyperactivity and impulsiveness are:

- Being unable to sit still, especially in calm or quiet surroundings
- Constantly fidgeting

- Being unable to concentrate on tasks
- Excessive physical movement
- Excessive talking
- Being unable to wait their turn
- Acting without thinking
- Interrupting conversations
- Little or no sense of danger

2. **Among of these criteria:**
   - At least 6 of the Inattentive symptoms and 6 of the Hyperactivity and Impulsivity symptoms and must have persisted for at least 6 months:
   - These symptoms can cause significant problems in a child's life, such as under-achievement at school, poor social interaction with other children and adolescents, and problems with discipline.
   - Family history: Inquire about a family history of ADHD (ADD)
3. **Laboratory investigations:**
   - It is important to remember that ADHD is a clinical diagnosis.
   - There are no standard laboratory or imaging results among patients with ADHD. Neuroimaging (CT, MRI) and EEG ARE NOT recommended.

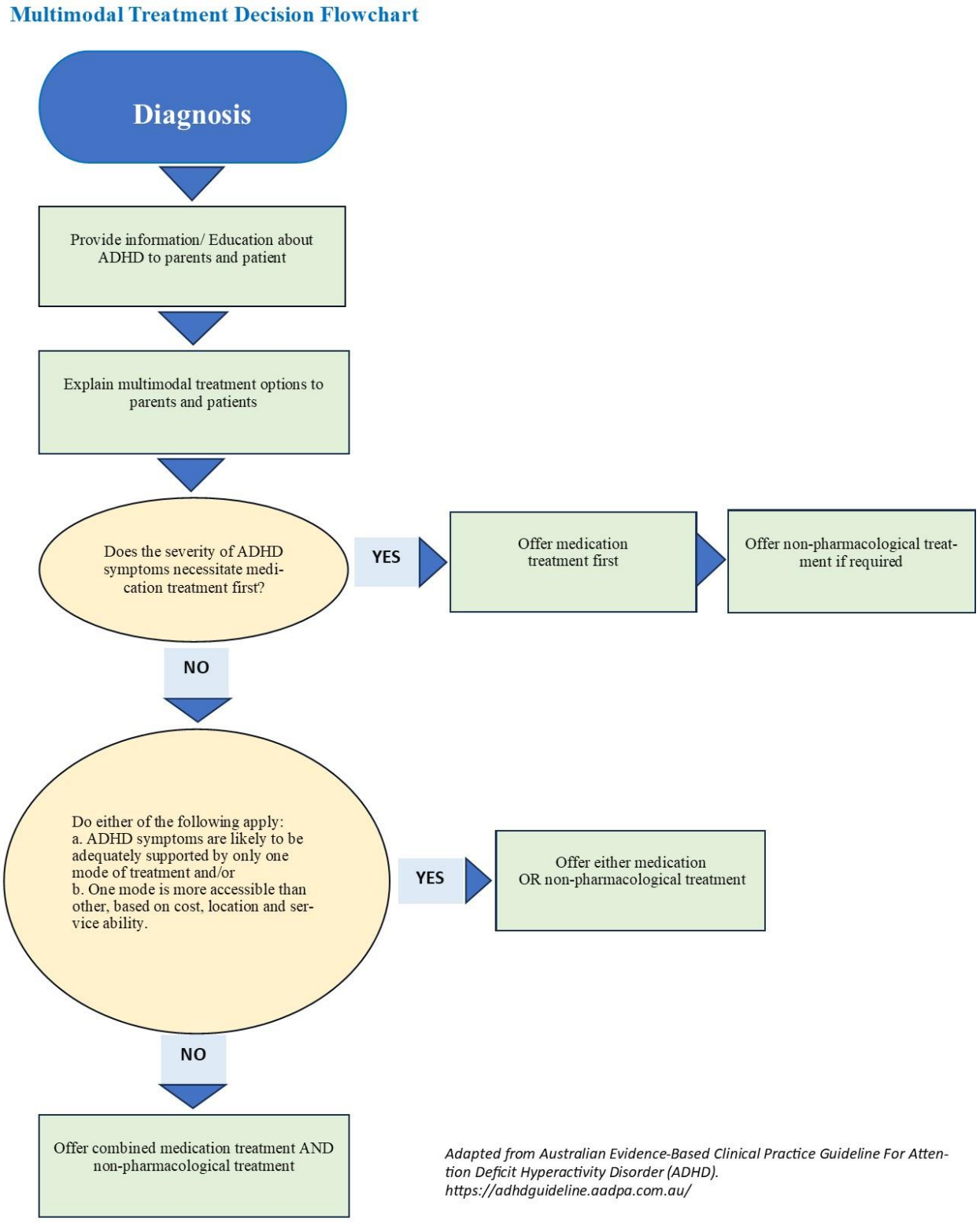
VI. Management [8, 9]

1. **Non-medication**
   - Psychoeducation: Giving information at the family and patient educational level and in a culturally sensitive manner.
   - Behavioral and Psychosocial Treatment:
     - Behavioral parent skills training to the caregivers
     - Cognitive Behavioral Therapy (CBT)
     - Social skills training to the child and adolescent.
2. **Medication**

   Children 6-17 years:
   - Methylphenidate immediate release (Ritalin):
     Starting dose 2,5-5mg, increasing daily dose by weekly increments of 5-10mg, dosage range from 0.1mg to 0.8mg/dose PO once or twice daily, not to exceed 60mg/d.
   - Clonidine extended-release tablet (Catapressan):
     Starting dose 0.1mg PO qhs (every bedtime), may adjust dose by increments of 0.1mg/day at weekly intervals until desired response; not to exceed 0.4mg/day divided BID.
   - Duration of treatment: No evidence-based guidelines about when treatment should cease. Patients may benefit from continuing treatment into adulthood. This should be reviewed at least annually.
3. **Diet**

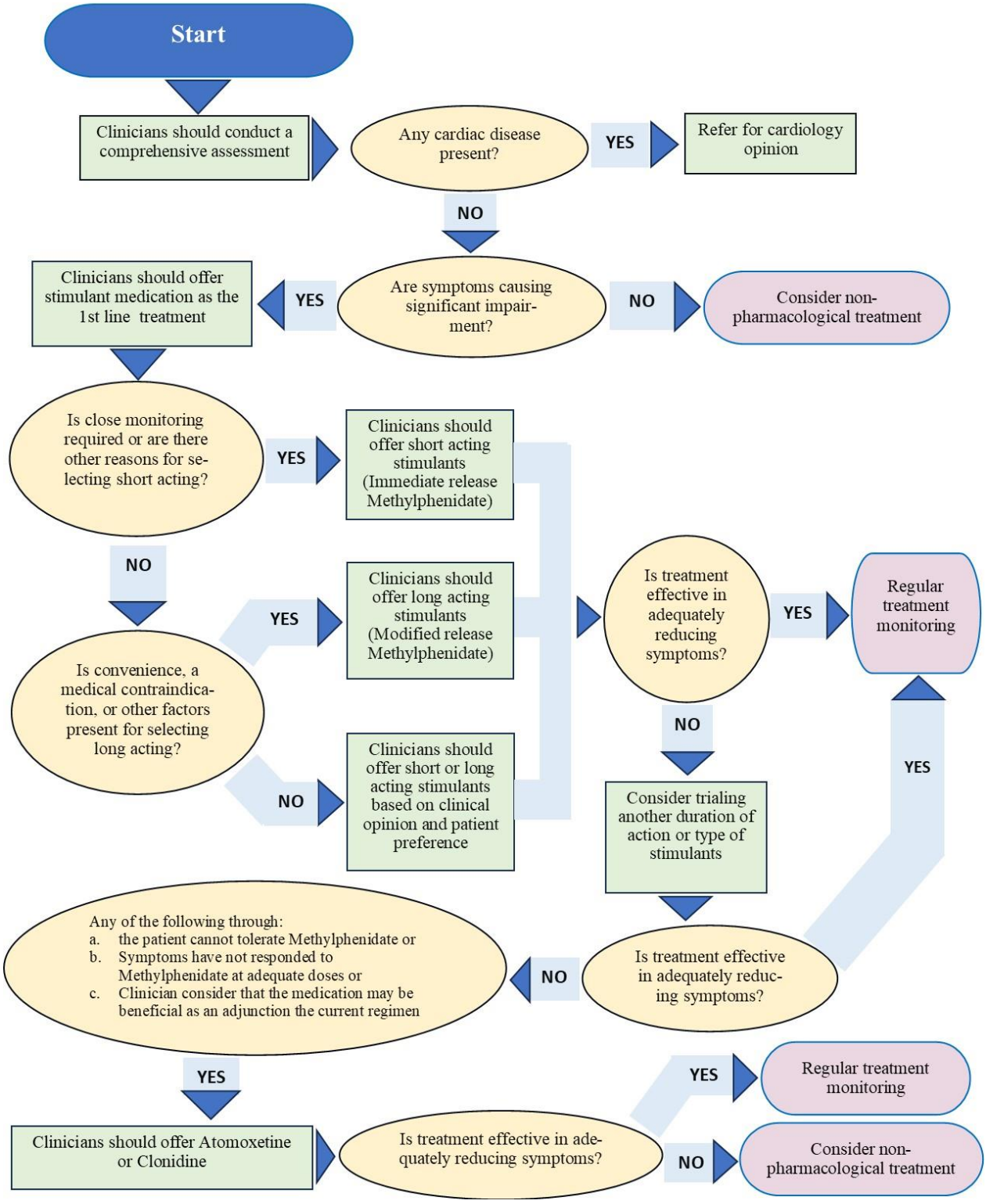
   No evidence that Omega-3 polyunsaturated fatty acid compounds (fish oils), iron supplements or zinc supplements are effective in the treatment of ADHD.

4. Algorithm



Adapted from Australian Evidence-Based Clinical Practice Guideline For Attention Deficit Hyperactivity Disorder (ADHD). https://adhdguideline.aadpa.com.au/

Medication Treatment Decision Flowchart: Children and Adolescents



Adapted from Australian Evidence-Based Clinical Practice Guideline for Attention Deficit Hyperactivity Disorder (ADHD), 1st edition. Https://adhdguideline.aadpa.com.au/

❖ Special cases

Pregnancy: ADHD medications are generally considered safe during pregnancy, but there may be a small increased risk of pre-eclampsia and greater neonatal health issues, particularly central nervous system disorders like seizures. Therefore, healthcare providers should inform patients who are pregnant or planning to become pregnant about these risks and may suggest discontinuing the medication during pregnancy.

VII. Evolution and prognosis [4, 9]

The prognosis of ADHD is variable depending on the age of the individual who is experiencing the symptoms.

- Two-fifths of the patients continue experiencing the symptoms in the teenage years, whereas a quarter of them are also diagnosed with a concurrent antisocial disorder.
- The general rule of thumb is that 50% of patients "grow out of" ADHD, especially with treatment, and another 25% do not need treatment into adulthood.

VIII. Complications [4, 9]

Untreated ADHD can lead to ongoing dysfunction and severe consequences:

- Emotional difficulties
- Social challenges, such as:
  - Less ability to cope with stressful events, to express empathy, and to socialize with peers
  - Increased risk of bullying, school dropout, unemployment, lower income, accidents (especially motor vehicle), criminal convictions, imprisonment, substance misuse, unwanted pregnancies, sexually transmitted diseases, and shorter lifespan.

These adverse effects lead to a diminished quality of life and increased suicide rates, as well as negatively affecting families by doubling the likelihood of parental separation.

IX. Prevention and recommendation [4, 9, 10]

- Primary prevention:
  - Improving maternal health during pregnancy, such as advising against alcohol and cigarette use and initiatives to decrease exposure to environmental toxins like lead and mercury.
- Secondary preventive:
  - Early identification of disorders for management, slowing its progression, and/or modifying its course to reduce future complications.
- Tertiary prevention:
  - Uses treatment that is unlikely to be curative but will manage or limit complications after the disorder has manifested. Most relevant are psychostimulants or parent training for individuals with ADHD.

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GENERALIZED ANXIETY DISORDER

SROEUNG Samrach, KHEMH Mayanuth, KAO Sambath

I. Definition

- Generalized Anxiety Disorder (GAD) is a mental health condition characterized by excessive, uncontrollable worry about various aspects of life, such as school performance, health, and social interactions, lasting for at least six months [1]
- This disorder can impact their daily functioning and overall quality of life.

II. Epidemiology

- GAD is the most common mental disorders among children affecting an estimated 2% to 10% [2].
- The median age of onset approximates 11 years and is more often reported in girls [3]
- Sex ratio ranging from about 2:1 to 3:1. [4]

III. Etiology

The etiology of Pediatric Generalized Anxiety Disorder (GAD) is multifactorial, involving genetic, environmental, and psychological factors: [5]

- Genetic Factors: Family studies indicate a hereditary component, with children having a higher risk if there is a family history of anxiety disorders
- Environmental Stressors: Exposure to stressful life events, trauma, and adverse childhood experiences can significantly impact the development of GAD.
- Cognitive Factors: Children with GAD often exhibit maladaptive thought patterns, such as catastrophic thinking and an increased tendency to overestimate the likelihood of negative outcomes.

IV. Physiopathology

The physiopathology of GAD involves several key components [5]:

- Neurotransmitter Systems: Dysregulation of neurotransmitters, particularly serotonin, norepinephrine, and GABA, plays a crucial role in anxiety disorders. Imbalances in these systems can affect mood and anxiety regulation.
- Brain Structure and Function: Neuroimaging studies have shown that children with GAD often exhibit hyperactivity in the amygdala, which is responsible for fear processing, and reduced activity in the prefrontal cortex, which is involved in emotion regulation.
- Physiological Responses: Children with GAD may have heightened physiological responses to stress, such as increased heart rate and cortisol levels, reflecting an overactive stress response system.

V. Diagnosis

1. Sign and symptoms

The course of symptoms can be progressive, persistent, or recurrent.

- Psychological symptom: nervous, scared, irritable or agitated, clinging, excessive worry, repeatedly asking worried questions, seeking reassurance and poor concentration
- Physical symptom:
  - Gastro intestinal: stomachache, nausea
  - Neuromuscular: muscle tension or motor restlessness, sweating, trembling, shaking
  - Cardiovascular: palpitation
  - Respiratory: tachypnea
  - Urinary: frequent urination
- Sleep disturbance.

❖ Assessment tool: GAD-7 assess anxiety symptoms and monitor treatment response [6]

Table: *GAD-7 Anxiety scale*

Over the last two weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly everyday
1.Feeling nervous, or on edge	0	1	2	3
2.Not being able to stop or control worrying	0	1	2	3
3.Worrying too much about different things	0	1	2	3
4.Trouble relaxing	0	1	2	3
5.Being so restless that it is hard to sit still	0	1	2	3
6.Becoming easily annoyed or irritable	0	1	2	3
7.Feeling afraid as if something awful might happen	0	1	2	3

This is calculated by assigning scores of 0, 1, 2, and 3 to the response categories, respectively, of "not at all," "several days," "more than half the days," and "nearly every day."
GAD-7 total score for the seven items ranges from 0 to 21.

- 0–4: minimal anxiety
- 5–9: mild anxiety
- 10–14: moderate anxiety
- 15–21: severe anxiety

❖ Physical examination and paraclinical assessments are often conducted to rule out any underlying medical condition that might contribute to anxiety symptoms.

2. **Paraclinic:** complete blood count, thyroid function test, renal function test, liver function test, electrolyte, blood glucose level and urine drug screening.
Echocardiography and MRI/CT scans, to rule out other neurological conditions.
3. **Differential diagnosis**
   - Medical condition:
     - Hyperthyroidism, Anemia, Malnutrition, Asthma
   - Medications:
     - Corticosteroid, asthma medication, antidepressants, antipsychotics, and withdrawal from benzodiazepines (particularly short-acting).
   - Illicit substances:
     - Marijuana, cocaine, methamphetamine
   - Mental Conditions:
     - ADHD
     - Depression, bipolar disorder
     - Obsessive-compulsive disorder,
     - Psychotic disorders,
     - Autism spectrum disorder, and

- Learning disorders.

VI. Management

The management of Pediatric Generalized Anxiety Disorder (GAD) typically involves a combination of therapeutic approaches, including psychotherapy, pharmacotherapy.

1. **Psychotherapy**
   - Psychoeducation
   - Family Therapy: Involving family members can help address familial dynamics that may contribute to the child's anxiety and improve overall support.
   - Cognitive Behavioral Therapy (CBT): helps children identify and challenge distorted thinking patterns and develop coping strategies to manage anxiety [7].
2. **Pharmacotherapy**
   - First-Line Treatments: Selective Serotonin Reuptake Inhibitors (ssris): sertraline, fluoxetine [8].
   - Second-Line Treatments: tricyclic antidepressants
   - A medication from the SSRI could be offered to patients 6 to 18 years old.
   - Monitor for side effects and assess response after 4-6 weeks.
   - It is recommended to continue medication for approximately 1 year.

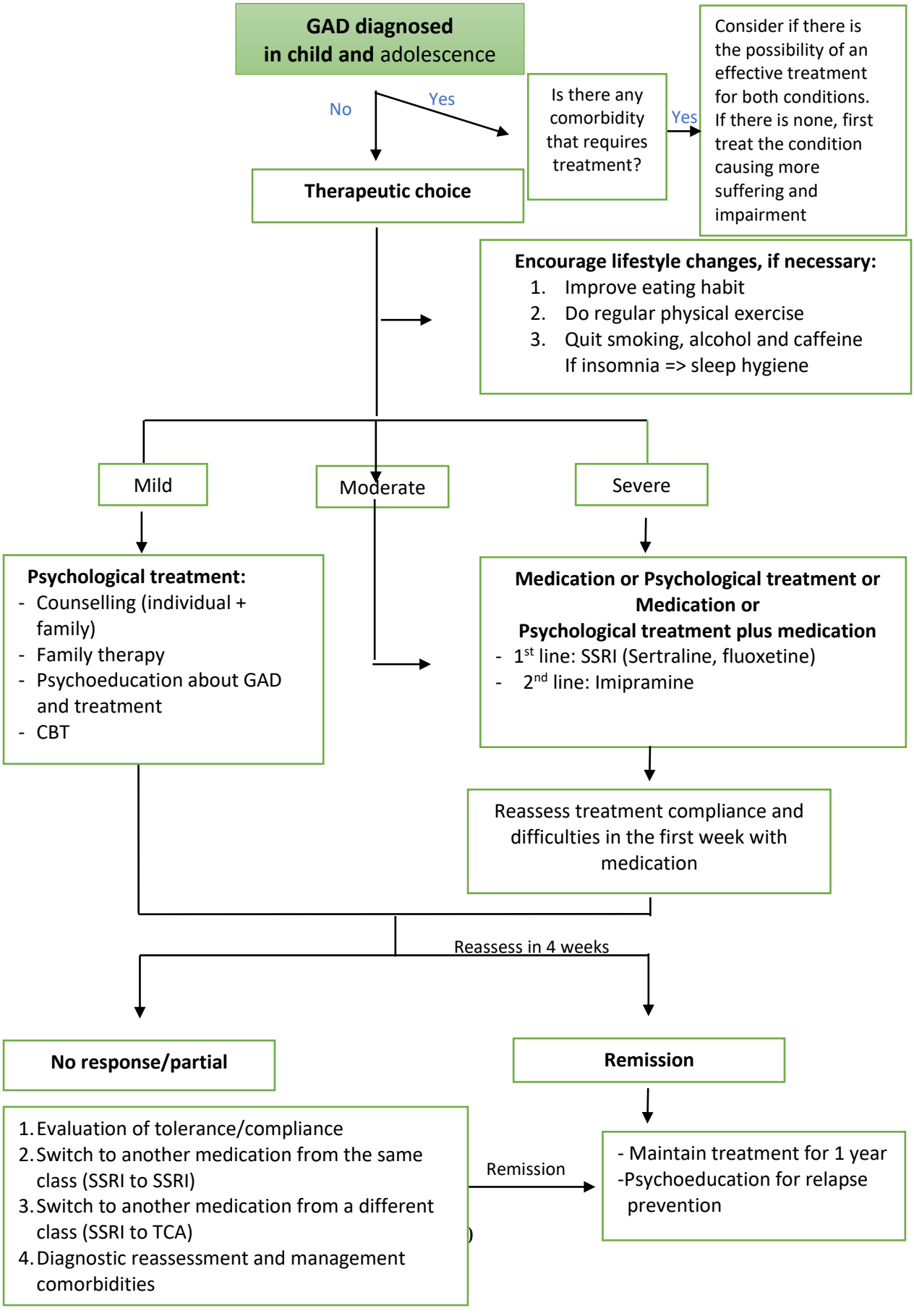
Table: *Medication for Generalized Anxiety Disorder*

Agent	Dose	Maintenance daily dose range	Common side effects (5% to 20%)
Selective serotonin reuptake inhibitors (SSRIS)			
Sertraline	-Initial dose: 12.5 to 25mg -Increase daily dose by 12.5mg (Child) or 25 to 50mg(adolescent) after a minimum of 7 days, if needed	25 to 100mg	Headache Insomnia Diarrhea Anorexia Hyperactivity Vomiting Irritability Sexual dysfunction Myalgia Weight changes
Fluoxetine	-Initial dose: children 5 to 10mg, adolescent 10mg - After 7days increase daily dose to 20mg then after for 4 weeks increase dose by 20mg, if needed	10 to 60mg	
Tricyclic antidepressants (TCA)			
Imipramine	-Initiate dose: 10 to 25mg -Increase daily dose by 25mg after a minimum of 7days, if needed	25 to 100mg	Sleepiness Dry mouth Weight gain

- GAD often begins in childhood or adolescence but can develop later in life. Early symptoms may include chronic worry about various issues (e.g., health, family, work), which can evolve into more generalized anxiety over time.

- With appropriate treatment, many individuals experience significant symptom reduction. However, some may continue to experience anxiety symptoms intermittently throughout their lives.
- GAD is responsive to treatment. Cognitive-behavioral therapy (CBT) and medications such as selective serotonin reuptake inhibitors (ssris) have shown effectiveness in reducing symptoms.

3. Algorithms



17. Evolution and prognosis

VII. Complications

GAD can also lead to, or worsen, other mental and physical conditions:

- Depression/ Suicide potential
- Drug or alcohol use disorder
- School truancy
- Issues functioning at work/school
- Impaired quality of life

VIII. Prevention and recommendation [9]

- Encourage and help the child/adolescent to: get enough sleep, eat regularly, be physically active.
- Address any stressful situation in the family environment such as parental discord or a parent's mental disorder. With the help of teachers explore possible adverse circumstances in the school environment.
- Provide opportunities for quality time with the carer and the family. Encourage and help the child/adolescent to continue (or restart) pleasurable and social activities.
- Consider training the child/adolescent and carer in breathing exercises, progressive muscle relaxation and other cultural equivalents.

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AUTISM SPECTRUM DISORDERS

BO Rany, SROEUNG Samrach, KAO Sambath

I. Definition

Autism spectrum disorders (ASD) or Autism is a complex neurodevelopmental disorder characterized by difficulties with social communication and interaction, and repetitive patterns of behaviors and interests which are present from early childhood [1].

The term "spectrum" refers to the wide range of symptoms, skills, and levels of impairment or disability that children with ASD can have.

II. Epidemiology

The prevalence of ASD is reported to be 1 in 100 children. It occurs in all racial, ethnic, and socioeconomic groups, and is four to five times more common among boys than girls [1, 2].

III. Etiology

To date, the etiology of ASD remains incompletely understood. The etiology is likely to be multifactorial, with:

- Genetic factors: epidemiological twin studies support the strong genetic component of ASD.
- Environmental factors: pre-conceptual exposure to mercury, cadmium, nickel, trichloroethylene, and vinyl chloride increases risks for Autism.
- Other risk factors: a sibling with autism, maternal age older than 40 years, paternal age older than 40 years, birth weight less than 2500g, prematurity (under 35 weeks). [2, 3]

IV. Pathophysiology

- The pathophysiology of ASD is largely remained insufficiently comprehend.
- The previously reported differences in brain structure, such as larger intracranial volumes, smaller cerebellar volumes, larger amygdala volumes, or altered volumes of the corpus callosum and hippocampus, were not confirmed as having scientific significance for understanding ASD neuropathology by the recent study [4].
- Studies in recent years on immune responses and gut-brain signaling have revealed that changes to gut microbiota and abnormal intestinal epithelial barrier function ("leaky gut") directly or indirectly elicit inflammatory processes that impact cerebral function, thereby contributing to the neuropathology of ASD [3].

V. Diagnosis

Currently, no diagnostic biomarkers are available. Diagnosing ASD usually relies on two main sources of information:

- Parents' or caregivers' descriptions of their child's development
- Professional's observation of the child's behavior [5], included repetitive behaviors, and impaired social communication and interaction.

1. To be diagnosed with ASD, a child must have [5,6]

a. Persistent deficits in the following three areas of social, communication and interaction:

- Deficits in social-emotional reciprocity:
  - Abnormal social approach and failure of normal back-and-forth conversation
  - Reduced sharing of interests, emotions, or affect
  - Failure to initiate or respond to social interactions
- Deficits in nonverbal communication:
  - Poorly integrated verbal and nonverbal communication
  - Abnormalities in eye contact and body language
  - Deficits in understanding and use of gestures
  - Lack of facial expressions

- Deficits in developing, maintaining, and understanding relationships:
    - Difficulties adjusting behavior to suit various social contexts
    - Difficulties in sharing imaginative play or in making friends
    - Absence of interest in peers.

b. At least two of four types of restricted, repetitive behaviors:

- Repetitive motor movements, speech, or use of items
- Restrictive or fixated interests that may be abnormal in focus or intensity
- Hypo- or hyperactivity in response to sensory input or abnormal fixation with sensory aspects of the environment
- Inflexible to changes in routine

c. Symptoms should be present in the early development period (in some cases, symptoms may be masked in early stages and become prevalent later).

d. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

e. Lastly, ASD may be suspected if the disturbance cannot be better explained by other causes of intellectual disability or developmental issues.

2. **Specify current severity:** is based on social communication impairments and restricted, repetitive patterns of behavior. For either criterion, severity is described in 3 levels:
    - Level 3: Requires very substantial support
    - Level 2: Requires substantial support
    - Level 1: Requires support
3. **Other Screening and diagnostic tools/instruments in wide use** [6, 7,8]
   Screening tools: The Modified Checklist for Autism in Toddlers (M-CHAT) age 18-24 months.
4. **Differential diagnosis** [15]
    - Neurodevelopmental disorders:
        - Developmental Language Disorders
        - A learning or intellectual disability
    - Mental and behavioral disorders:
        - Attention deficit hyperactivity disorder (ADHD),
        - Attachment disorders
        - Oppositional defiant disorder (ODD),
    - Conditions in which there is developmental regression:
        - Rett syndrome,
    - Other conditions:
        - Severe hearing impairment
        - Selective mutism.

VI. Management

The goal of treatment is to maximize the child's ability to function by reducing ASD symptoms and supporting development and learning.

1. **Medication**
    - Drug treatment has not been shown to help the main problems of autism.
    - The atypical antipsychotics risperidone and aripiprazole are the only two have been approved by the US Food and Drug Administration (FDA) for the treatment of irritability in children with ASD [6,8,9,10].

a. Risperidone

In children age 5-16 years:

- < 20kg: 0.25mg/day PO initially; may be increased after ≥ 4 days to recommended dosage of 0.5mg/day. May be adjusted after minimum of 14 days, not to exceed 1mg/ day.
- ≥ 20kg: 0.5mg PO initially; may be increased after ≥ 4 days to recommended dosage of 1mg/day. May be adjusted after minimum of 14 days, not to exceed 2.5mg/day.

b. Aripiprazole

In children age 6-17 years: 2mg/day PO initially; increase gradually at ≥ 1 week interval to target dosage of 5mg/day; may gradually further increase to 10mg/day or higher; not to exceed 15mg/day.

c. Melatonin

- Melatonin, as treatment for sleep issues in ASD, is effective in numerous studies [11]
- Dose requirements: 1–10 mg PO qhs at bedtime.

2. Non-medication [2, 6, 8, 12]

a. Psycho education for the family

A few points to be kept in mind while informing parents about the ASD diagnosis are:

- Autism is a neuro-developmental disability
- It is lifelong
- It starts in utero
- It is not produced by vaccines
- It is not caused by bad parenting
- All children may not be similar
- Early therapy helps
- Education may not be the only aim
- Talk to others about ASD openly
- Talk to other parents of children with ASD
- The path ahead may be difficult, but reach out for help at every step of the way

b. Parent-mediate intervention/ parent co-therapy: Provide parent training and guidance in regard to communication with their ASD children (Parent-child interaction therapy-PCIT)

c. Individual intensive interventions:

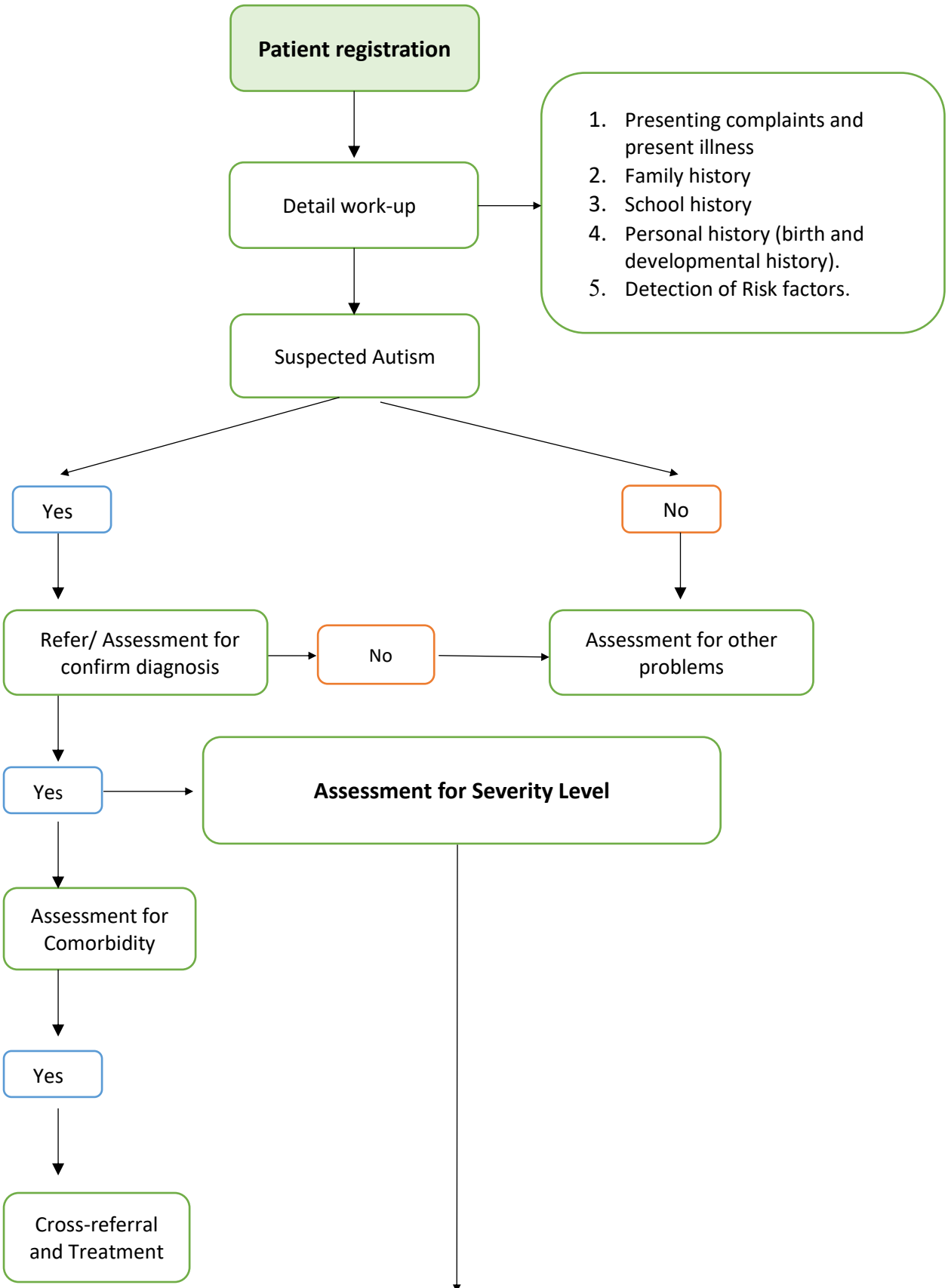
- Support communicative understanding and expression: Social story, Visual support, play based intervention
- Sensory integration therapy: swing, sand,
- Behavioral management
- Educational intervention (Refer for Special education.

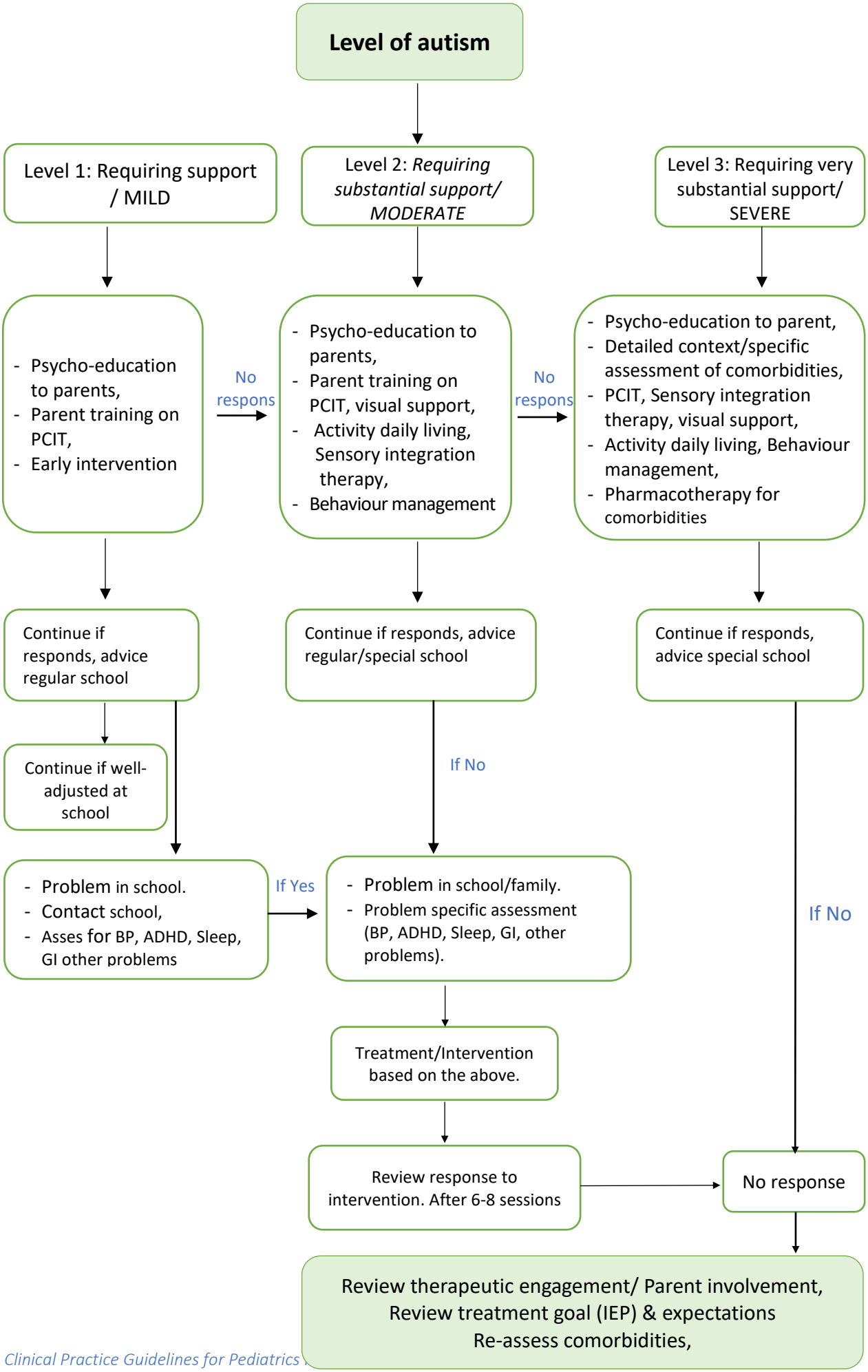
❖ Special cases

- About 30–50% of persons diagnosed with ASD show symptoms of ADHD as well [3].
- Epilepsy occurs at 20%-30% of children with autism, and 60% of children with autism having an abnormal electroencephalogram (EEG) [13]
- Sleep disorders are significant problems in children with autism, present in about 80% of them, these include:
- Insomnias (Initial, middle, terminal)
- Sleep-wake cycle abnormalities [8,13]
- GI Problems are significantly more common in patients with ASD, occurring in 46% to 84% of autistic children. The most common GI problems in children with ASD are:
  - Chronic constipation
  - Gastroesophageal reflux and/or disease
  - Nausea and/or vomiting

- Chronic flatulence
- Abdominal discomfort
- Food intolerant [13].

3. Algorithm




Level of autism
Level 1: Requiring support / MILD
Level 2: Requiring substantial support/ MODERATE
Level 3: Requiring very substantial support/ SEVERE
- Psycho-education to parents,
- Parent training on PCIT,
- Early intervention
No respons
- Psycho-education to parents,
- Parent training on PCIT, visual support,
- Activity daily living, Sensory integration therapy,
- Behaviour management
No respons
- Psycho-education to parent,
- Detailed context/specific assessment of comorbidities,
- PCIT, Sensory integration therapy, visual support,
- Activity daily living, Behaviour management,
- Pharmacotherapy for comorbidities
Continue if responds, advice regular school
Continue if responds, advice regular/special school
Continue if responds, advice special school
Continue if well-adjusted at school
If No
- Problem in school.
- Contact school,
- Asses for BP, ADHD, Sleep, GI other problems
If Yes
- Problem in school/family.
- Problem specific assessment (BP, ADHD, Sleep, GI, other problems).
If No
Treatment/Intervention based on the above.
Review response to intervention. After 6-8 sessions
No response
Review therapeutic engagement/ Parent involvement,
Review treatment goal (IEP) & expectations
Re-assess comorbidities,

VII. Evolution and Prognostic

- There is no cure for autism is a lifelong disability.
- Early identification, more intervention opportunity can lead to optimal intervention benefit.
- The majority of children with ASD and more severe the comorbid will show the poorer is outcome.
- Their quality of life can be improved when adequate programs are available with their challenge.
- The abilities and needs of autistic people vary and can evolve over time. While some people with autism can live independently, others have severe disabilities and require life-long care and support.

VIII. Complications

The complications that individuals with ASD suffer such as:

- Sensory problems
- Mental health issue
- Mental impairment
- Other complications that can accompany ASD include aggression, unusual sleep habits, unusual eating habits, and digestive issues. [14]

IX. Prevention and recommendation

- There is no any specific to prevent autism spectrum disorder.
- There is consider to reduce the risk factor of having a child with autistic disorder by:
    - Have a regular check-up, eat healthy food, exercise and take all recommended vitamin and supplements when pregnant.
    - Do not take drug during pregnancy unless the doctor approves, especially anti-seizure medicine.
    - Do not drink alcohol beverage of any kind when pregnant. [16]

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Chapter XI: Neonatology

1. Neonatal Resuscitation
2. Neonatal jaundice
3. Necrotizing Enterocolitis

Find out more:

4. Newborn routine care (National Program)
5. Neonatal sepsis (National Program)
6. Neonatal hypoglycemia (National Program)
7. Birth Asphyxia (National Program)
8. Neonatal tetanus (National Program)

NEONATAL RESUSCITATION

CHAP Chakrya, KIM Ang, PHAY Narith

I. Key facts

Most newborns make the transition to extrauterine life without intervention.

- 5% of term newborns will receive positive-pressure ventilation (PPV).
- 2% of term newborns will be intubated.
- 1 to 3 babies per 1,000 births will receive chest compressions or emergency medications. [1,2]

II. Overview

1. Objectives

The lifesaving interventions is for term babies with certain identified risk factors and those born before full term. [2]

2. Physiology of cardiorespiratory transition from intrauterine to extrauterine life

Before birth, the fetal lungs are filled only with fluid and they do not participate in gas exchange. All of the oxygen used by the fetus is supplied from the mother's blood by diffusion across the placenta. The oxygenated fetal blood leaves the placenta through the umbilical vein, [2,3] *see Figure 1 at Annex*.

Pulmonary vessels are tightly constricted and very little blood flows into them. Most of the oxygenated blood returning to the fetus from the placenta via the umbilical vein flows through the foramen oval or ductus arteriosus and bypasses the lungs. In utero, this right-to-left shunt allows the most highly oxygenated blood to flow directly to the fetal brain and heart. [2,3]

After birth, a series of events culminate in a successful transition from fetal to neonatal circulation. [2,3]

- As the baby takes deep breaths and cries, fluid is absorbed from the air sacs (alveoli) and the lungs fill with air, see Figure 2 at Annex.
- Air in the lungs causes the previously constricted pulmonary vessels to relax so that blood can flow to the lungs and reach the alveoli where oxygen will be absorbed and CO2 will be removed, see Figure 3 at Annex.
- Oxygenated blood returning from the baby's lungs helps to fill the baby's heart and ensures that the heart and brain will receive adequate blood flow once the umbilical cord is clamped.
- Clamping the umbilical cord increases the baby's systemic blood pressure, decreasing the tendency for blood to bypass the baby's lungs.

III. Clinical finding of abnormal transition

The clinical signs associated with an interruption in normal transition. [2,3]

- Irregular breathing, apnea, or tachypnea.
- Bradycardia or tachycardia.
- Decreased muscle tone.
- Pallor or cyanosis.
- Low oxygen saturation.
- Low blood pressure.

IV. Neonatal resuscitation

1. Anticipating and preparing for resuscitation

At every birth, you should be prepared to resuscitate the newborn. Considering risk factors will help identify the correct personnel to attend the birth. [2,3]

Table 1. ***Perinatal risk factors increasing the likelihood of Neonatal Resuscitation*** [2]

Antepartum Risk Factors	
Gestational age < 36 0/7 weeks Gestational age ≥ 41 0/7 weeks Preeclampsia or eclampsia Maternal hypertension Multiple gestations Fetal anemia	Polyhydramnios Oligohydramnios Fetal hydrops Fetal macrosomia Intrauterine growth restriction Significant fetal malformations or anomalies No prenatal care
Intrapartum Risk Factors	
Emergency cesarean delivery Intrapartum bleeding Forceps or vacuum-assisted delivery Chorioamnionitis Breech or other abnormal presentation Category II or III fetal heart rote pattern* Maternal general anesthesia	Opioids administered to mother within 4 hours of delivery Shoulder dystocia Meconium-stained amniotic fluid Maternal magnesium therapy Prolapsed umbilical cord Placental abruption

Before every birth, there are 4 pre-birth questions to review the antepartum and intrapartum risk factors: [3]

- What is the expected gestational age?
- Is the amniotic fluid clear?
- Are there any additional risk factors?
- How many babies are expected?

The number and qualifications of personnel will depend on your risk assessment [2].

- Every birth should be attended by at least 1 qualified individual, skilled in the initial steps of newborn care and positive-pressure ventilation (PPV).
- If risk factors are present at least 2 qualified people should be present to provide a full resuscitation skill.

The checklist of essential supplies and equipment needed at the radiant warmer for most neonatal resuscitations is listed in Table 2.

Table 2. ***Quick Equipment Checklist*** [1,2]

Warm	- Preheated warmer - Warm towels or blankets - Hat • Plastic bag or plastic wrap (< 32 weeks gestation)
Clear airway	- Bulb syringe - 8 F or 10F suction catheter attached to wall suction, set at 80 to 100 mmhg - Tracheal aspirator
Auscultate	- Stethoscope
Ventilate	- Positive-pressure ventilation (PPV) device (mask and self-inflating bag) - Cardiac monitor and leads
Oxygenate	- Equipment to give free-flow oxygen - Pulse oximeter with sensor and cover - Target Oxygen Saturation Table
Intubate	- Laryngoscope with size 0 and size 1 straight blades - Stylet (optional) - Endotracheal tubes (sizes 2.5, 3.0, 3.5) - Measuring tape and endotracheal tube insertion depth table - Waterproof tape or tube-securing device • Scissors

Medicate	- Epinephrine (0.1 mg/ml= 1 mg/10 ml)

2. Initial step of newborn care

You will rapidly ask 3 questions: [2,3]

(1) Does the baby appear to be term,
(2) Does the baby have good muscle tone, and
(3) Is the baby breathing or crying?

If the answers to all 3 rapid evaluation questions are "Yes," the baby can remain with the mother and have the initial steps performed on the mother's chest or abdomen.

If the answer to any of the initial evaluation questions is "No," bring the baby to a radiant warmer because additional interventions may be required.

- Provide warmth:
  - Place the baby under a radiant warmer and
  - The baby's body temperature should be maintained between 36.5ºc and 37.5ºc.
- Dry:
  - Place the baby on a warm towel or blanket and gently dry any fluid.
  - Babies < 32 weeks gestation, they should be covered immediately in polyethylene plastic.
- Stimulate: Gently rub the newborn's back, trunk, or extremities. Never shake a baby.
- Position the head and neck to open the airway: Position the baby on the back (supine) with the head and neck neutral or slightly extended and the eyes directed straight upward toward the ceiling in the “sniffing the morning air” position.

⚠ *Clear secretions from the airway if the baby is not breathing, if the baby is gasping, if the baby has poor tone, if secretions obstruct the airway, or if you anticipate starting PPV.*[2]

3. Positive-Pressure Ventilation

- Ventilation is the single most important and effective step in neonatal resuscitation.
- PPV is indicated if the baby is apneic, OR if the baby is gasping, OR if the baby's heart rate is less than 100 bpm.
- For providing PPV, the baby's head and neck should be positioned midline and neutral, or slightly extended, in the sniffing position so that the baby's eyes are directed straight upward toward the ceiling, *see Figure 5 at annex*. Then, the mask should cover the tip of the chin, mouth, and nose, *see Figure 6: A, B at annex*.
  - Breaths should be given at a rate of 40 to 60 breaths/min
  - Count out loud to help maintain the correct rate.
  - Use the rhythm, “Breath, two, three; breath, two, three; breath, two, three”. [2,3]

4. Endotracheal intubation

Insertion of endotracheal intubation is considered: [2]

- If the baby’s HR < 100 bpm and is not increasing after PPV with a face mask or laryngeal mask.
- Strongly recommended before starting chest compressions.
- For direct tracheal suction.
- For surfactant administration.
- For stabilization of a newborn with a suspected diaphragmatic hernia.
- If PPV is prolonged.

The depth of the intubation tube is in the middle of the tracheal (1 to 2 cm below the vocal cord). [2]

Estimated depth formula: Nasal-Targus Length (NTL) + 1 cm, see *Figure 7 at Annex*

The appropriate laryngoscope blade that attaches to the handle

- No. 1 blade: Term newborns
- No. 0 blade: Preterm newborns.

Table 3. *Tube sizes*

Weight	Gestational age	Endotracheal tube size
< 1kg	< 28 WGA	2.5 mm ID
1-2kg	28- 34 WGA	3.0 mm ID
>2kg	> 34 WGA	1.5 Mm ID

5. Chest compression

The indications for chest compression are

- The baby's HR < 60 bpm after at least 30 seconds of PPV that inflates the lungs, as evidenced by chest movement with ventilation.
- In most cases, you should have given at least 30 seconds of ventilation through a properly inserted endotracheal tube or laryngeal mask.
- Ratio: Compression: ventilation (3:1) (every 2 seconds)
- If compressions are started, call for help: vascular access and epinephrine. [2]

After 60 seconds of compressions and ventilation, stop and check heart rate,

- Stop compressions: HR > 60 bpm.
- Return to PPV faster (40 to 60 breaths per minute). [3]

The compressor moves to the head of the baby and uses two thumbs with hands encircling the baby's chest. The compressor places thumbs on the sternum above the xyphoid and below the nipple line and depresses the sternum one-third of the anterior-posterior diameter of the chest, *see Figure 8 at Annex.* [3]

6. Medication

Epinephrine is indicated if the baby's HR < 60 bpm after

- At least 30 seconds of PPV that inflates the lungs as evidenced by chest movement, and
- Another 60 seconds of chest compressions coordinated with PPV using 100% oxygen. [2]

Table 4*: Summary of Epinephrine*

Concentration
0.1 mg/ ml epinephrine = 1 mg/ 10 ml
Route
Intravenous or endotracheal (only while intravenous access is being established).
Dose
Lntravenous = 0.02 mg/kg =0.2 ml/kg (Range=0.01 to 0.03 mg/kg = 0.1 to 0.3 ml/kg) Endotracheal = 0.1 mg/kg (=1 ml/kg)
Administration
Lntravenous - Rapidly as quickly as possible. - Flush with 3 ml of normal saline. - Repeat every 3 to 5 minutes if the heart rate remains less than 60 bpm Endotracheal: Administer PPV breaths to distribute into the lungs. No flush.

Assess the baby's heart rate 1 minute after epinephrine administration. If the HR < 60/min after the first dose of epinephrine, continue coordinated ventilation and compressions. The epinephrine can be repeated every 3 to 5 minutes and considered subsequent doses. Do not exceed the maximum recommended dose. If there is not a satisfactory response

after IV epinephrine, consider other problems such as hypovolemia and tension pneumothorax [2,3].

Emergency volume expansion is indicated if baby [2],

- Is not responding to the steps of resuscitation and
- Has signs of shock or history of acute blood loss.

Table 5: *Sings of shock and history of acute blood loss*

Signs of shock	History of acute blood loss
Pale	Fetal-maternal hemorrhage
Delayed capillary refill	Extensive vaginal bleeding
Weak pulses	Bleeding vasa previa
Low heart rate	Fetal trauma

If there is a confirmed absence of heart rate after all appropriate steps of resuscitation have been performed, the cessation of resuscitation efforts is around 20 minutes after birth. However, the decision to continue or discontinue should be individualized based on patient, contextual factors and should be discussed with the team and family [2].

7. Neonatal resuscitation algorithm

The algorithm, *see Figure 4 at Annex*, is divided into 5 blocks beginning with birth and the initial assessment. The hexagons indicate assessments and rectangles show actions that may be required. Assessments are repeated at the end of each block and will determine if you need to proceed. [2]

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ANNEXE

Figure 1. *Fetal Circulation Path: Oxygenated blood (red) enters the right atrium from the umbilical vein and crosses to the left side through the foramen oval and ductus arteriosus. Only a small amount of blood flows to the lungs. There is no gas exchange in the fluid-filled lungs.*

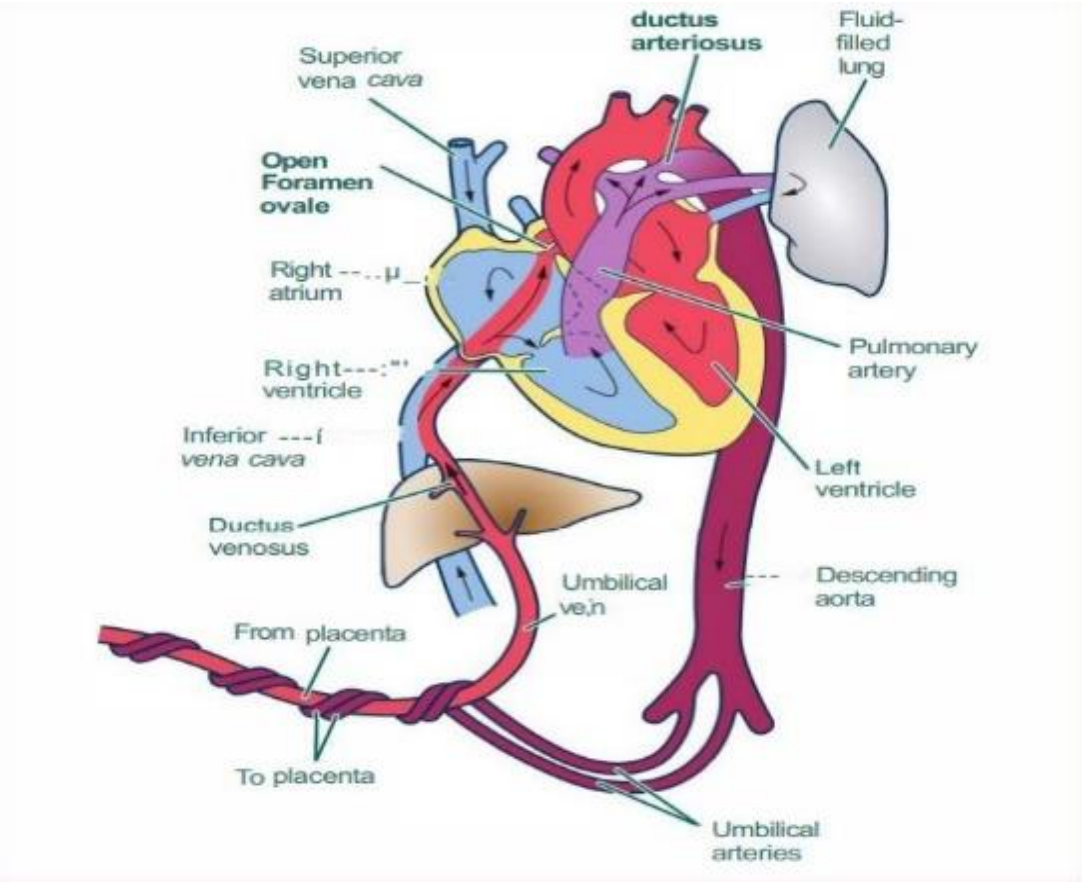


Figure 2. *Air replaces fluid in alveoli*

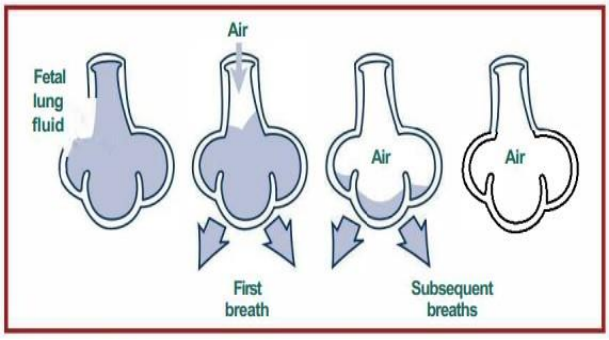


Figure 3. *Blood vessels in the lungs*

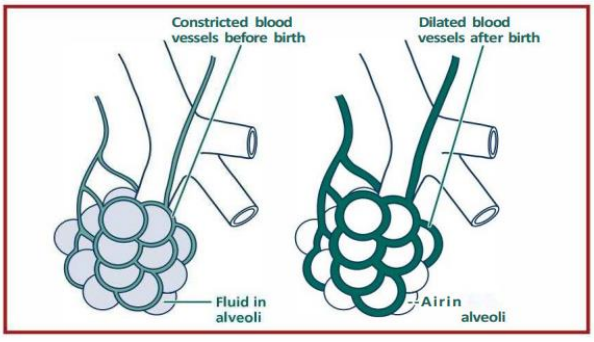


Figure 4. ***Algorithm of newborn resuscitation.***

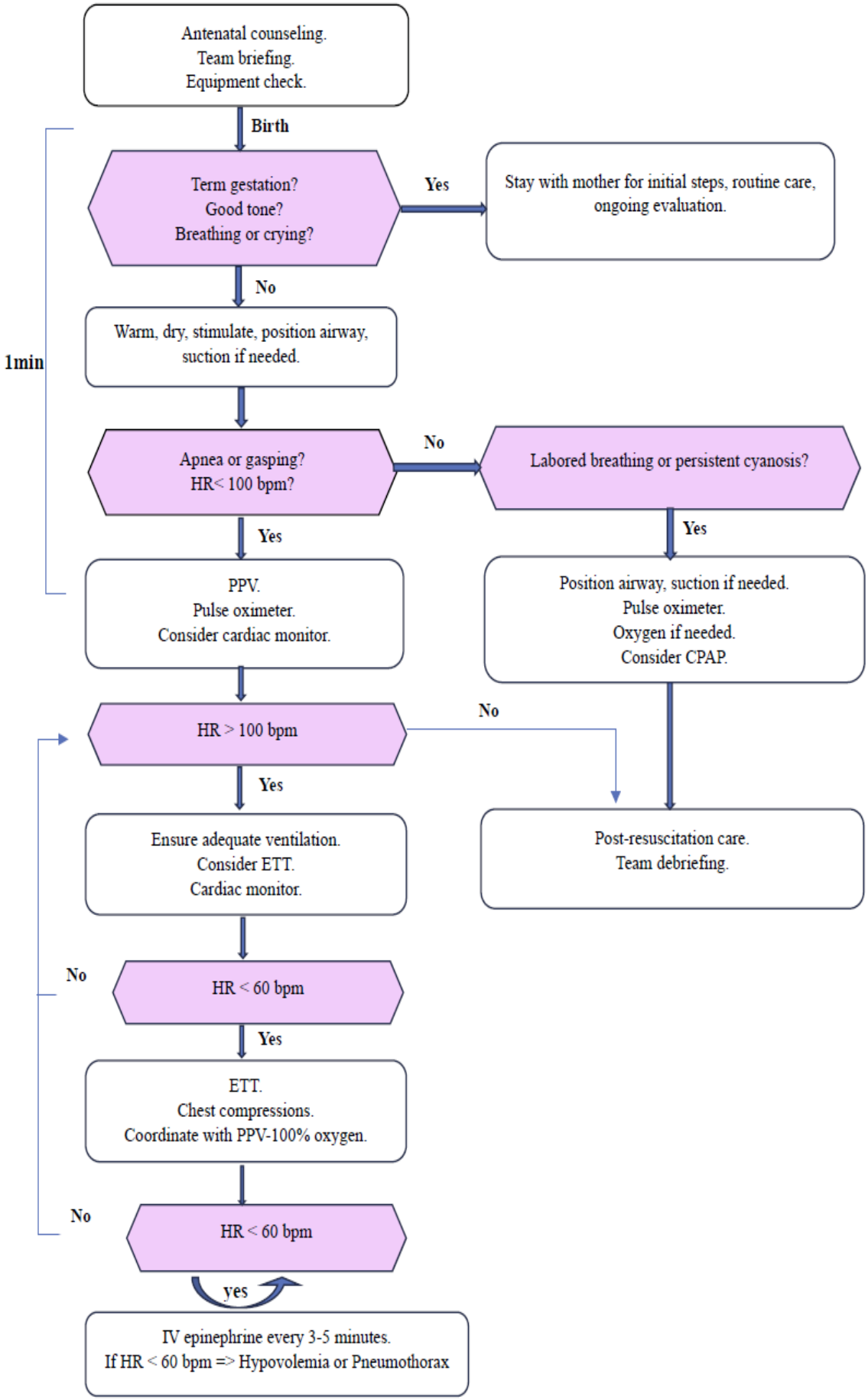


Figure 5. *The sniffing positions (Shoulder roll used to position the neck and head)*

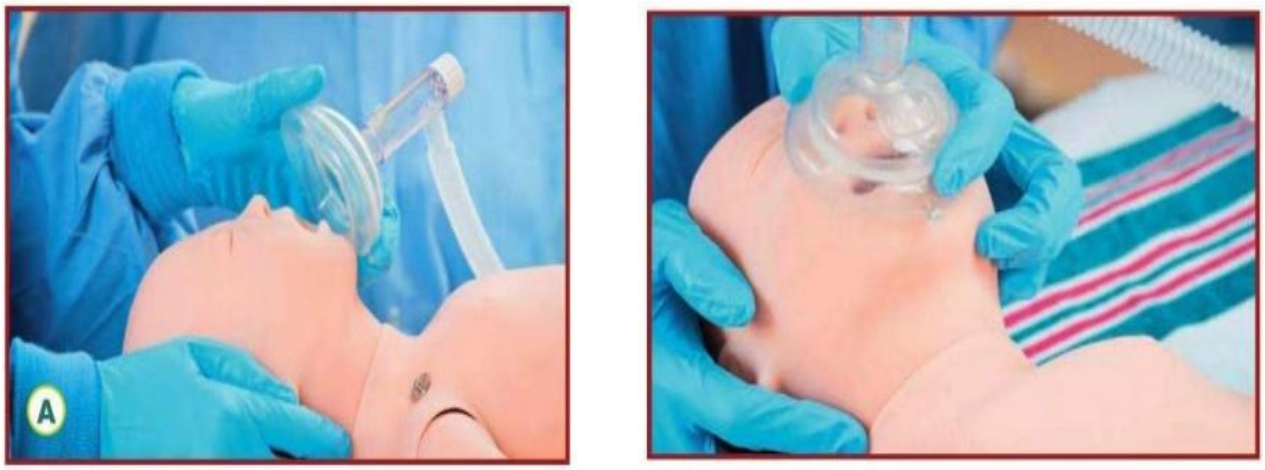


Figure 6. *(A) Cup the chin in the anatomic mask.*
(B) Maintaining a seal with the 1-hand hold using an anatomic mask.

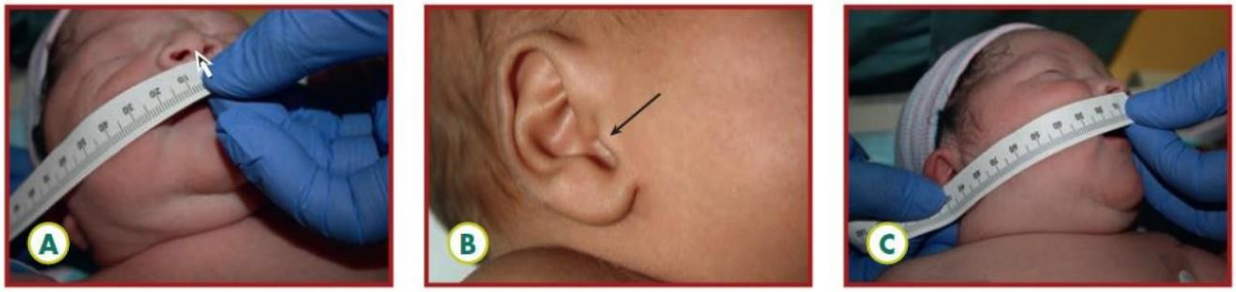


Figure 7. *Measuring the NTL (Measure from the middle of the nasal septum to the ear tragus and add 1 cm to the measurement).*

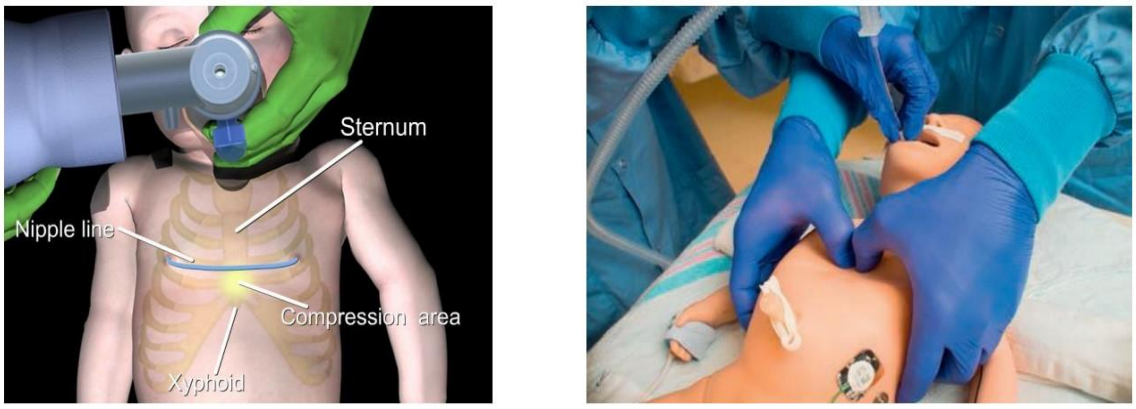


Figure 8. *Place of the thumbs and stand of the compressor.*

NEONATAL JAUNDICE

BIN Sakviseth, IM Sethikar

I. Key facts

Nearly all newborn infants develop hyperbilirubinemia. As Total Serum Bilirubin (TSB) levels increase, the newborn may develop visible jaundice, due to the accumulation of unconjugated, non-polar, lipid-soluble bilirubin pigment in the skin. Jaundice, which is in most cases benign, is observed during the first week after birth in approximately 60-70% of term infants and approximately 80% of preterm infants. The incidence of severe hyperbilirubinemia is approximately 0.14%.

II. Overview

1. Terminology

- Hyperbilirubinemia is a clinical condition characterized by an increase in total serum bilirubin (TSB) that occurs when the rate of bilirubin production exceeds the rate of elimination.
- Jaundice, characterized by the yellow discoloration of the skin, sclera, and mucosa, results from the accumulation of bilirubin. Jaundice is clinically visible when the serum bilirubin level approaches 5 mg/dl.
- Severe neonatal hyperbilirubinemia is defined as TSB >25 mg/dl (or 428 micromol/L) in late preterm and term infants.
- Bilirubin-induced neurologic dysfunction (BIND) is the spectrum of neurotoxic injury, occurring when bilirubin crosses the blood–brain barrier and binds to targeted brain tissues.

2. Epidemiology

Incidence of severe neonatal hyperbilirubinemia vary substantially from region to region:

- In African region : 667.8 per 10 000 live births
- In Southeast Asia : 251.3 per 10 000 live births
- In Eastern Mediterranean regions : 165.7 per 10 000 live births
- In USA : 4.4 per 10 000 live births
- In Europe : 3.7 per 10 000 live births.

3. Risk factors

a. Risk factors to develop significant hyperbilirubinemia:

1) Lower gestational age (ie, risk increases with each additional week less than 40 wks)
2) Jaundice in the first 24 h after birth
3) Predischarge transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) concentration close to the phototherapy threshold
4) Hemolysis from any cause, if known or suspected based on a rapid rate of increase in the TSB or TcB of >0.3 mg/dL per hour in the first 24 h or >0.2 mg/dL per hour thereafter.
5) Phototherapy before discharge
6) Parent or sibling requiring phototherapy or exchange transfusion
7) 7Family history or genetic ancestry suggestive of inherited red blood cell disorders, including glucose-6-phosphate dehydrogenase (G6PD) deficiency
8) Exclusive breastfeeding with suboptimal intake
9) Scalp hematoma or significant bruising
10) Down syndrome
11) Macrosomic infant of a diabetic mother.

b. Hyperbilirubinemia Neurotoxicity Risk Factors:

1) Gestational age <38 wk and this risk increases with the degree of prematurity
2) Albumin <3.0 g/dl
3) Isoimmune hemolytic disease (ie, positive direct antiglobulin test), G6PD deficiency, or other hemolytic conditions
4) Sepsis

5) Significant clinical instability in the previous 24 h

4. Etiology

a. Causes of conjugated hyperbilirubinemia

- Extrahepatic biliary disease:
  - Biliary atresia
  - Biliary cysts/choledochal cysts
  - Bile duct stenosis
  - Spontaneous perforation of the bile duct
  - Cholelithiasis or neoplasms/masses
- Intrahepatic biliary disease:
  - Intrahepatic bile duct paucity (syndromic [Alagille] or non-syndromic)
  - Progressive familial intrahepatic cholestasis
  - Inspissated bile
  - Neonatal sclerosing cholangitis
- Hepatocellular disease:
  - Metabolic and genetic defects (α1-Antitrypsin deficiency, cystic fibrosis, galactosemia, tyrosinemia…)
  - Infections: congenital (TORCH), bacterial (urinary tract infection; syphilis; early-onset sepsis)
  - Parenteral nutrition–associated liver disease
  - Endocrine disorders: Hypopituitarism and hypothyroidism
  - Idiopathic neonatal hepatitis
  - Gestational alloimmune liver disease (neonatal hemochromatosis)
  - Drugs (carbamazepine, ceftriaxone, isoniazid, trimethoprim-sulfamethoxazole...)
- Miscellaneous:
  - Shock; hypoxic ischemic liver injury
  - Extracorporeal life support.

b. Causes of unconjugated hyperbilirubinemia

- Physiologic unconjugated hyperbilirubinemia
- Breast milk jaundice
- Pathologic unconjugated hyperbilirubinemia:
  - Disorders of production:
    - Immune-mediated hemolytic diseases (Rh, ABO, other blood group systems)
    - Red blood cell enzyme deficiencies (G6PD or pyruvate kinase deficiency)
    - Red blood cell membrane defects (spirocytosis or elliptocytosis)
    - Hemoglobinopathies
    - Infection (early and late-onset sepsis)
    - Increased erythrocyte load:
      - Blood sequestration (bruising, cephalohematomas, intracranial bleeding)
      - Polycythemia
      - Infants of diabetic mothers
  - Disorders of bilirubin clearance:
    - Crigler-Najjar syndrome
    - Gilbert syndrome
    - Lucey-Driscoll syndrome (or transient familial neonatal hyperbilirubinemia)
  - Metabolic and endocrine disorders: Galactosemia and Hypothyroidism
  - Substances affecting binding of bilirubin to albumin: aspirin, moxalactam, ceftriaxone, sulfonamides, penicillin and gentamicin.

III. Diagnosis

1. **History taking**
   - History of present illness:
     - Age of onset and duration of jaundice
     - Important associated symptoms include lethargy and poor feeding (suggesting possible kernicterus)
     - Patterns of feeding can be suggestive of possible breastfeeding failure or underfeeding.
     - Stools pattern
   - Review of systems, to seek symptoms of causes:
     - Respiratory distress, fever, and irritability or lethargy (sepsis);
     - Hypotonia and poor feeding (hypothyroidism, metabolic disorder);
     - Repeated episodes of vomiting (intestinal obstruction).
   - Past medical history:
     - Maternal infections ([TORCH] infections),
     - Disorders causing early hyperbilirubinemia (maternal diabetes), maternal Rh factor and blood group (maternofetal blood group incompatibility),
     - History of a prolonged or difficult birth (hematoma or forceps trauma).
   - Family history:
     - Inherited disorders that can cause jaundice, including (G6PD) deficiency, or other red cell enzyme deficiencies, thalassemia, and spherocytosis
     - Any history of siblings who have had jaundice
     - Drug history:
     - Drugs that may promote jaundice by binding to free bilirubin fraction (eg, ceftriaxone, sulfonamides
     - Antimalarials
2. **Clinical examination**
   - Jaundice:
     - The yellow color in the skin and subcutaneous tissues (buccal, gingival, or conjunctival mucosa). It can be assessed visually after digital pressure.
     - The progression is cephalocaudal:
       - Appearing first in the face with TSB levels of 4 to 8 mg/dl (68 to 137 micromol/L)
       - The entire body, including palms and soles, with TSB level >15 mg/dl (257 micromol/L).
   - Other findings suggesting underlying conditions such as:
     - Neurological signs: lethargy, poor feeding, vomiting, hypotonia, and seizures
     - Pallor (in the setting of significant anemia due to hemolysis)
     - Enclosed hemorrhage (eg, cephalohematoma)
     - Bruising
     - Hepatosplenomegaly
     - Macrosomia (in case of maternal diabetes)
     - Any dysmorphic features such as macroglossia (hypothyroidism) and flat nasal bridge or bilateral epicanthal folds (Down syndrome)
3. **Investigations**

a. Total serum bilirubin (TSB)

TSB is the gold standard for assessing neonatal bilirubin levels and the confirmatory test prior to therapeutic interventions.

b. B- Other laboratory tests:

- Blood group and Rhesus group
- Direct Coombs test

- Complete blood counts
- Reticulocytes
- G6PD level
- Thyroid and liver functions; blood and urine culture

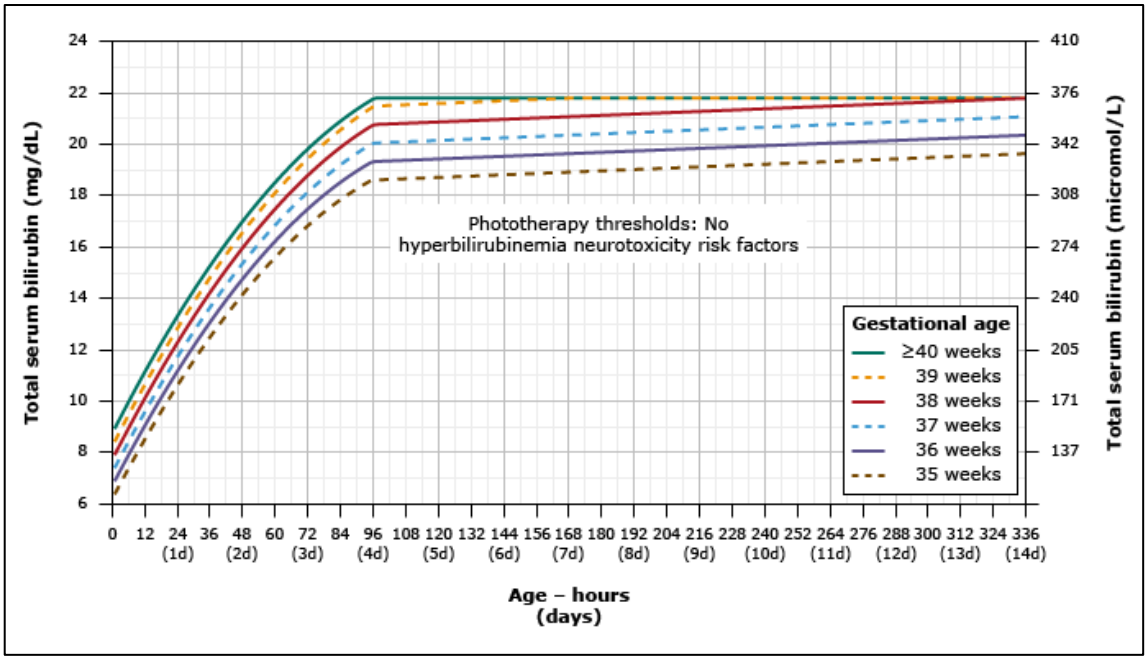
c. C- Transcutaneous bilirubin (tcb) device

- A portable instrument that uses reflectance measurements on the skin to determine the amount of yellow color present in the skin.
- A tcb value of >15 mg/dl should be correlated with TSB.
- Tcb results should be interpreted with caution in newborns with birthweight <2500 g, particularly in the first 48 hours of life. Any jaundice noticeable within the first 24 hours of life should be confirmed with TSB level.

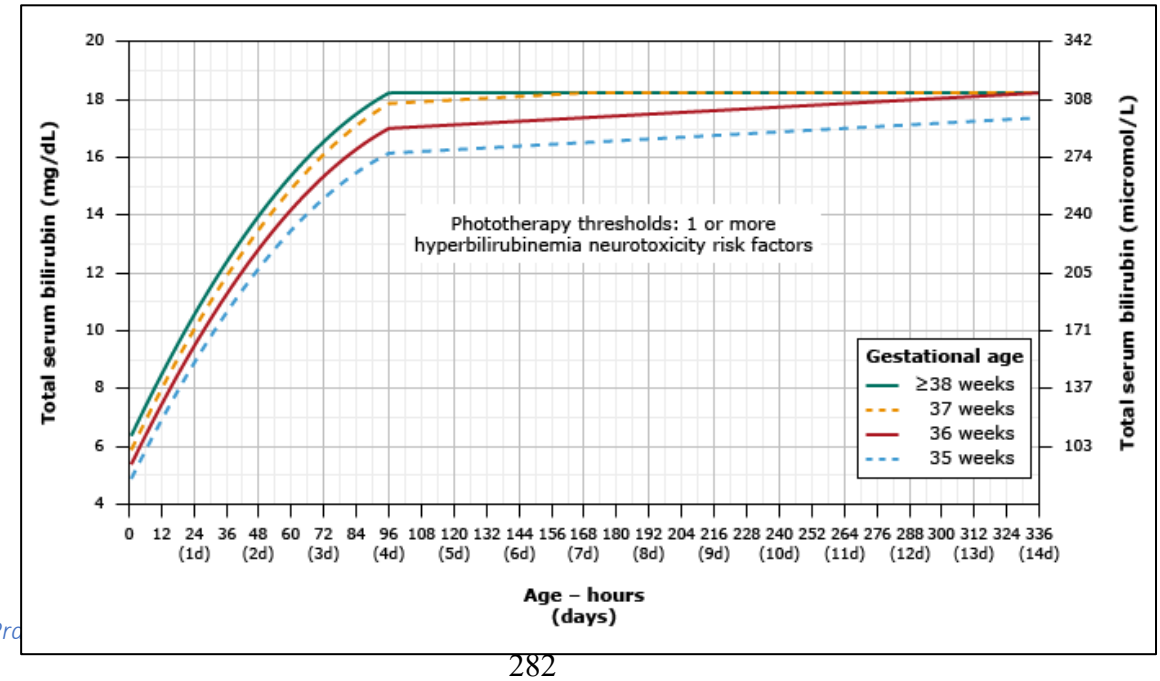
IV. Management

1. Phototherapy

a. Phototherapy thresholds for newborns without risk factors for neurotoxicity (AAP 2022):



b. Phototherapy thresholds for newborns with risk factors for neurotoxicity (AAP 2022):



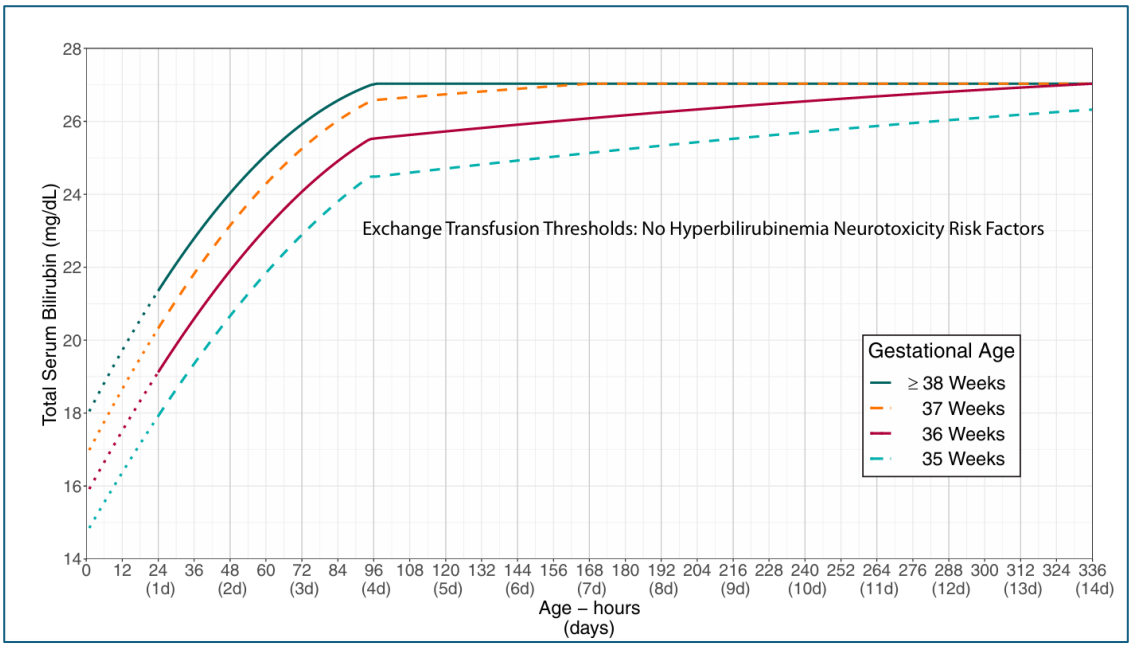
c. Monitoring during phototherapy includes:
- The dose of phototherapy: irradiance and time exposed.
- Newborn's vital signs, including temperature (monitored every eight hours).
- Hydration status (intake and output)
- Follow-up total serum or plasma bilirubin (TSB) levels

d. Complications:
- Transient, benign, erythematous rashes
- Hypovolemia caused by increased insensible water losses
- Hyperthermia
- Interruption of breastfeeding
- Bronze baby syndrome
- Retinal effects (on animal studies).

2. Exchange transfusion

a. Indication:
- Acute bilirubin encephalopathy or
- Latest TSB at or above the exchange transfusion threshold

b. Exchange transfusion thresholds (AAP 2022):



3. Pharmacologic therapy

a. Phenobarbital:
- Dose: 5 mg/kg/day
- Mechanism: increase the concentration of ligandin in liver cells, inducing production of UDPGT and enhancing bilirubin excretion
- Indication: Gilbert syndrome and Crigler-Najjar Syndrome type 2

b. Albumin:
- Dose: 1 g/kg over 2–3 hours
- Mechanism: increases bilirubin-binding capacity and reduces free bilirubin
- Indication:
  - Albumin level <3.0 g/dl
  - Or when TSB/albumin ratio is > 6 Or prior to exchange transfusion

c. Intravenous immunoglobulin (IVIG):
- Dose: 1 g/kg given over 2-4 hours (can be used 2 times, interval 12-24 hours)
- Mechanism: competes with sensitized neonatal rbcs in the reticuloendothelial system,

thus, preventing further hemolysis.

- Indication: patients with iso-immune hemolysis with rising TSB despite intensive Phototherapy.

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NECROTIZING ENTEROCOLITIS

NHAN Ladin; LONG Bopheak; KIM Somithiphalkun; NEOU Leakhena

I. Key facts

- Necrotizing enterocolitis (NEC) is the most common life-threatening emergency of the gastrointestinal tract in the premature newborns. This is a disorder characterized by ischemic necrosis of the intestinal mucosa, which is associated with inflammation, invasion of enteric gas forming organisms, and dissection of gas mural and luminal.
- It is one of the major causes of death in preterm.
- NEC became recognized as a clinical entity in 1960's and 1970's
  - At this time NEC's mortality exceeded 70%
- Incidence: 0.3-2.4 / 1000 live births
  - 2-5 % of all NICU admissions
  - 5-10 % of VLBW infants
- Over 90 % of cases occur in preterm babies
- About 10 % occur in term newborns: essentially limited to those that have some underlying illness or condition requiring NICU
- Mortality may be up to 50% in extremely premature infants who require surgery for intestinal perforation or gangrene
- Approximately 30% of cases require surgery and a significant number of survivors suffer from neurological deficits, intestinal dysfunction, and post-surgical short bowel syndrome.

II. Overview

Definition: Necrotizing enterocolitis (NEC) is an acquired, multifactorial and devastating gastrointestinal disease associated with high morbidity and mortality in preterm neonates. It is characterized by ischemia, necrosis, and inflammation of bowel wall with invasion by gas-forming organisms and intramural dissection of gas, characteristically appearing as pneumatosis intestinalis in radiological and pathological studies. Clinical presentation can be severe with cardiorespiratory collapse, shock, and disseminated intravascular coagulopathy (DIC), escalating to multisystem failure and death.

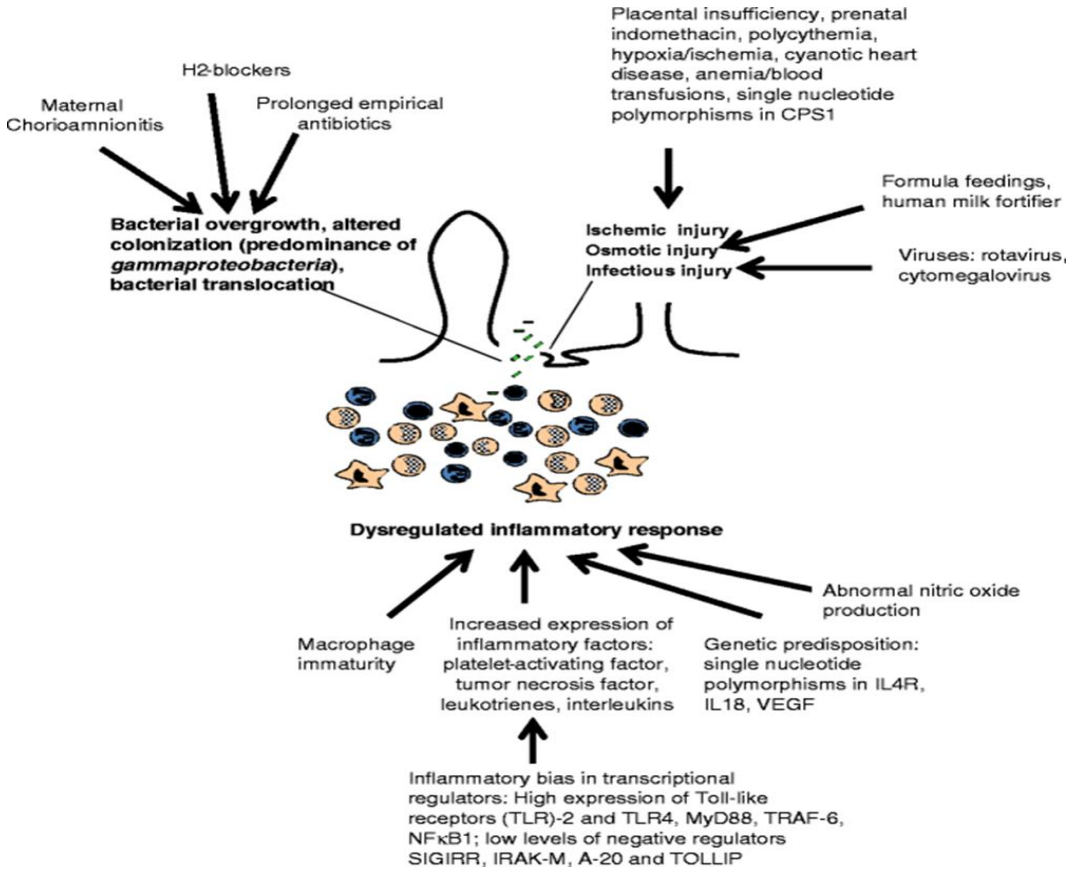
1. Risk Factors

- Prematurity (>95% of cases)
- Aggressive advance (volume and strength) of enteral feedings in preterm infants
- Hyperosmolar formulas
- Bacterial colonization or overgrowth (predominantly with E. Coli, Klebsiella, Enterobacter, C. Dificile): may be inciting event or a permissive factor.
- Polycythemia
- Patent ductus arteriosus (PDA, decreased systemic output due to left→right shunt)
- Indomethacin (decreased intestinal perfusion through inhibition of cyclo-oxygenase)
- Steroids, when given in conjunction with indomethacin
- Umbilical arterial catheter (UAC) with tip at or above inferior mesenteric artery
- Umbilical venous catheter (UVC) with tip in portal system (especially with exchange transfusion)
- Cocaine exposure in utero
- Respiratory Distress Syndrome

2. Pathophysiology

The disease is commonly localized to the ileo-colic region, although the colon may be frequently involved in term infants. In some extremely-low-birth-weight (ELBW) infants as well as in some advanced cases, there might be total gut necrosis ('NEC totalis'). Lesions

are characterized by coagulation necrosis, bacterial overgrowth, pneumatosis intestinalis, inflammation, and, depending on the age of the lesions, reparative changes. Although the etiopathogenesis of NEC remains unclear, current evidence supports a complex, multi-factorial model of disease.



Schematic summarizing pathophysiology of NEC. Current evidence indicates that in premature infants, mucosal injury results in bacterial translocation, triggering an exaggerated and damaging mucosal inflammatory response

a. Prematurity

- More than 90 % of all cases of NEC occur in premature infants [9].
- The incidence and severity of NEC rise in inverse relationship
  - To gestational maturity,
  - Presumably related to immaturity of gut motility,
  - Digestion, perfusion,
  - Barrier function and immune defense.

b. Genetic Factors

Although the rate of NEC in identical twins is higher than the general population, the influence of genetic factors is small. Bhandari et al. Reported NEC in either one or both of the twins in 9 (14 %) of 63 pairs of monozygotic twins and in 29 (15 %) of 189 pairs of dizygotic twins.

c. Enteral Feedings

Although NEC can occur in neonates who have never been fed, 90–95 % of cases occur in infants with a history of recent volume advancement or re-initiation of enteral feedings.

The introduction of feedings may cause osmotic damage to the mucosa, may alter blood flow and/or motility, and promote bacterial overgrowth in the gut lumen.

Formula-fed infants are at higher risk of NEC than exclusively breast-fed infants, which has been attributed to a lack of immune-protective factors in formula and abnormal bacterial colonization.

Most studies indicate that early, low-volume feedings are not only safe, but may also reduce other morbidities associated with prematurity.

d. Mucosal Injury

Histo-pathologically, NEC is characterized by coagulative necrosis, mucosal edema, ulceration, focal hemorrhages, and leukocyte infiltration. The prominence of coagulative necrosis in NEC indicates that ischemic events may play a role in NEC. However, ischemic events are recorded only in a minority of preterm infants with NEC. In contrast, NEC in full-term neonates is associated with congenital heart disease, recorded hypoxic–ischemic events, and polycythemia, factors that may plausibly result in gut hypo-perfusion. In growth-restricted fetuses, placental insufficiency and abnormal Doppler flow in the umbilical artery have been associated with NEC. Dorling et al. Reviewed 14 independent case series of fetuses with absence/reversal of umbilical arterial Doppler flow and showed increased odds of NEC compared with controls (odds ratio: 2.13, 95 % CI 1.49 to 3.03). The absence or reversal of diastolic blood flow in the umbilical artery is presumably associated with decreased splanchnic perfusion and ischemic intestinal injury.

e. Inflammatory Response

During NEC, mucosal injury results in bacterial translocation and a severe, unregulated inflammatory response. Emerging evidence indicates that the activation of Toll-like receptors is an important event, which triggers the activation of the transcription factor nuclear factor-kappa B (NF-κb). Increased expression of tumor necrosis factor and platelet activating factor (PAF) propagate mucosal injury, which triggers a cascade of inflammatory mediators including IL-1β, IL-6, IL-8, IL-10, IL-12, and IL-18. Activation of the complement and coagulation cascades, cytokines, reactive oxygen species and nitric oxide further amplify the mucosal injury.

f. Bacterial Translocation

NEC always occurs after the postnatal bacterial colonization of the gut mucosa; intestinal injury in utero prior to colonization may cause strictures or atresia, but not NEC. Common pathogens isolated in NEC are Enterobacteriaceae including:

- Escherichia, Salmonella, Enterobacter, and Klebsiella (68%);
- Staphylococcal species (26%);
- Clostridium species (4%);
- Viruses including rota, echo, corona, and toro (11%);
- And candida (1%).
- No organism is isolated in 3% of cases

g. Maternal Chorioamnionitis

Several studies have shown an important association between clinical chorioamnionitis and NEC.

h. Red Cell Transfusions

A number of retrospective studies in the last 8 y suggest that red cell transfusions are temporally-associated with NEC in preterm infants

RBC transfusions can dampen the normal postprandial increase in mesenteric blood flow in premature infants, particularly in those with a birth weight < 1,250 g.

III. Signs and Symptoms

1. **Staging of NEC:** The Bell system is the staging system most commonly used to describe necrotizing enterocolitis (NEC).

a. Bell stage I - suspect disease

- Stage IA characteristics are as follows:

- Mild, nonspecific systemic signs such as apnea, bradycardia, and temperature instability are present
- Mild intestinal signs such as increased gastric residuals and mild abdominal distention are present
- Radiographic findings can be normal or can show some mild nonspecific distention.

- Stage IB diagnosis is the same as stage IA, with the addition of grossly bloody stool.

b. Bell stage II - definite disease

- Stage IIA characteristics are as follows:
  - Patient is mildly ill.
  - Diagnostic signs include the mild systemic signs present in stage IA
  - Intestinal signs include all of the signs present in stage I, with the addition of absent bowel sounds and abdominal tenderness
  - Radiographic findings show ileus and/or pneumatosis intestinalis.

  This diagnosis is sometimes referred to as "medical" necrotizing enterocolitis as surgical intervention is not needed to successfully treat the patient.
- ***Stage IIB characteristics are as follows:***
  - Patient is moderately ill
  - Diagnosis requires all of stage I signs plus the systemic signs of moderate illness, such as mild metabolic acidosis and mild thrombocytopenia
  - Abdominal examination reveals definite tenderness, perhaps some erythema or other discoloration, and/or right lower quadrant mass
  - Radiographs show portal venous gas with or without ascites.

c. Bell stage III–advanced disease

This stage represents advanced, severe NEC that has a high likelihood of progressing to surgical intervention.

- Stage IIIA characteristics are as follows:
  - Patient has severe NEC with an intact bowel
  - Diagnosis requires all of the above conditions, with the addition of hypotension, bradycardia, respiratory failure, severe metabolic acidosis, coagulopathy, and/or neutropenia
  - Abdominal examination shows marked distention with signs of generalized peritonitis
  - Radiographic examination reveals definitive evidence of ascites
  - Stage IIIB designation is reserved for the severely ill infant with perforated bowel observed on radiograph in addition to the findings for IIIA.

	STAGE	SYSTEMICSIGNS	ABDOMINALSIGNS	RADIOGRAPHIC SIGNS
IA	Suspected	Temperature instability, apnea, bradycardia, lethargy	Gastric residuals, abdominal distension, emesis, guaiac-positive stool	Normal or intestinal dilation; mild ileus
IB	Suspected	Same as IA	Gross bloody stool	Same as IA
IIA	Definite, mildly ill	Same as IA	IA, IB plus decreased or absent bowel sounds with/without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis
IIB	Definite, moderately ill	IIA plus mild metabolic acidosis and mild thrombocytopenia	IIA plus abdominal tenderness plus absent bowel sounds with/without abdominal cellulitis, or right lower quadrant mass, absent bowel sounds	IIA plus abdominal tenderness plus absent bowel sounds with/without abdominal cellulitis, or right lower quadrant mass, absent bowel sounds
IIIA	Advanced, severely ill, intact bowel	IIB plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC, neutropenia, anuria	IIB plus signs of peritonitis, marked abdominal tenderness, distension, and abdominal wall erythema	IIB plus definite ascites
IIIB	Advanced, severely ill, perforated bowel	Same as IIIA	Same as IIIA	IIB plus pneumoperitoneum

Adapted from: .Neu J. Necrotizing enterocolitis: the search for a unifying pathogenic theory leading to prevention. Pediatr Clin North Am. 1996;43(2):409–43

IV. Diagnosis

Obtain radiographic studies if any concern about NEC is present. Pursue laboratory studies, especially if the abdominal study findings are worrisome or the baby is manifesting any systemic signs. A CBC with manual differential is usually repeated at least every 6 hours if the patient's clinical status continues to deteriorate. Relevant findings may include the following:

- WBC – Moderate to profound neutropenia (absolute neutrophil count [ANC] < 1500/µl) strongly suggests established sepsis
- Hematocrit and hemoglobin – Blood loss from hematochezia and/or a developing consumptive coagulopathy can manifest as an acute decrease in hematocrit; an elevated hemoglobin level and hematocrit may mark hemoconcentration due to notable accumulation of extravascular fluid
- Platelet count – Thrombocytopenia may be present
- Other laboratory findings
    - Blood culture is usually negative
    - Hyponatremia – An acute decrease in serum sodium (< 130 meq/dl) is alarming
    - Low serum bicarbonate (< 20) may be seen in babies with poor tissue perfusion, sepsis, and bowel necrosis
    - Reducing substances may be identified in the stool of formula-fed infants
    - Arterial blood gas levels may indicate the infant's need for respiratory support and can provide information on the acid-base status.
- Abdominal radiography
    - The mainstay of diagnostic imaging
    - An AP and a left lateral decubitus view are essential for initial evaluation
    - Should be performed serially at 6-hour or greater intervals, depending on presentation acuity and clinical course, to assess disease progression
    - Characteristic findings on AP views include an abnormal gas pattern, dilated loops, and thickened bowel walls

- A fixed and dilated loop that persists over several examinations is especially worrisome
- Scarce or absent intestinal gas is more worrisome than diffuse distention that changes over time

- Other radiographic findings include the following:
  - Pneumatosis intestinalis – Pathognomic of NEC, see Figure. 1
  - Abdominal free air – Ominous; patients usually require emergency surgical intervention, see Figure. 2
  - Portal gas – A poor prognostic sign, see Figure. 3

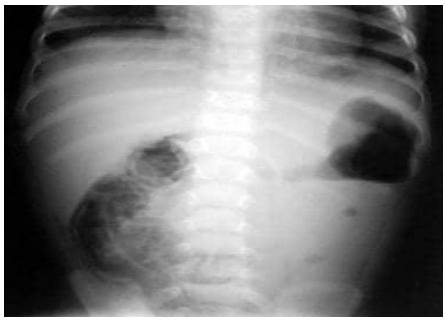


Figure. 1

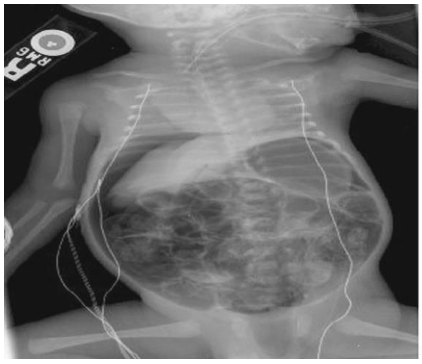


Figure. 2

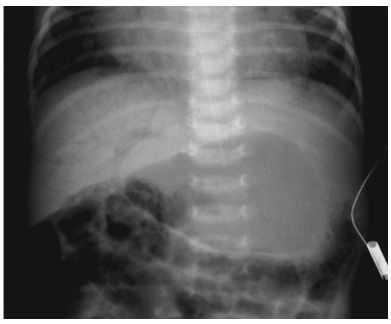


Figure. 3

- Distended loops of small bowel – Common but nonspecific
- Intraperitoneal free fluid

- Abdominal ultrasonography
  - Available at bedside
  - Non-invasive
  - Can identify areas of loculation and/or abscess consistent with a walled-off perforation
  - Excellent for identifying and quantifying ascites
  - Limited availability at some medical centers
  - Requires extensive training to discern subtle ultrasonographic appearance of some pathologies
  - Abdominal air can interfere with assessing intra-abdominal structures.

V. Deferential Diagnosis

Conditions to consider in the differential diagnosis of NEC include the following:

- Hypoplastic left heart syndrome
- Intestinal malrotation
- Intestinal volvulus
- Bacterial meningitis
- Neonatal sepsis
- Omphalitis
- Prematurity
- Urinary tract infection
- Volvulus.

VI. Management

The initial course of treatment consists of the following:

1. Medical:

- Stop enteral feedings

- Perform nasogastric decompression
- Initiate broad-spectrum antibiotics (eg, ampicillin, gentamicin, and clindamycin or metronidazole)
    - Antibiotics Imipenem based on AHC-Antimicrobial stewardship. Median duration of treatment was 7days for definite NEC
    - In AHC, in between July 1st 2016 and 30th June 2017 the overall survived was 97.7%
- Bell stages IA and IB – suspected disease
    - NPO diet and antibiotics for 3 days
    - IV fluids, including total parenteral nutrition (TPN)
- Bell stages IIA and IIB – definite disease
    - Support for respiratory and cardiovascular failure, including fluid resuscitation
    - NPO diet and antibiotics for 14 days
    - Consider surgical consultation
    - After stabilization, provide TPN while the infant is NPO
- Bell stage IIIA – advanced disease
    - NPO for 14 days
    - Fluid resuscitation
    - Inotropic support
    - Ventilator support
    - Obtain surgical consultation
    - Provide TPN during the period of NPO
    - Surgical intervention

2. Surgery

The principal indication for operative intervention in NEC is perforated or necrotic intestine, which is most compellingly predicted by pneumoperitoneum. Other indications include the following:

- Erythema in the abdominal wall
- Gas in the portal vein
- Positive paracentesis
- Clinical deterioration.

VII. Prevention

1. Effective interventions: Efforts to minimize the frequency or severity of NEC are directed at reducing exposure to risk factors and finding interventions that will prevent the disorder.

- Antenatal corticosteroids — Antenatal corticosteroids reduce the risk of respiratory distress syndrome (RDS) and mortality in preterm infants. In addition, exposure to antenatal corticosteroids reduces the risk of NEC, intraventricular hemorrhage, and retinopathy of prematurity
- Human milk feeding
- Standardized feeding protocol
- Other strategies
    - Avoid prolonged antibiotic use
    - Avoid gastric acid suppression
    - Prevent severe anemia/Decrease exposure to RBC transfusion
    - Withhold feeds during and after transfusion

2. Strategy not routing use

- Probiotics
- Oral immunoglobulin therapy

- Nutritional supplements
- Other supplements.

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Chapter XII: Vaccination (National Program)

VACCINATION AGENDA FOR CHILDREN FROM BIRTH

NATIONAL IMMUNIZATION PROGRAM, CAMBODIA

Age / Vaccine	Birth	6W	10W	14W	6M	9M	18M	9Y	Other Ages
BCG (S/C)	1 dose								
HepB (IM)	1 dose								
6 Vaccines bombinated: - **D T P Hib HepB** (IM) - **OPV** (OR)		1st dose	2nd dose	3rd dose					
- **IPV** (IM)				1 dose					
MR (IM)					MR0* dose	1st dose	2nd dose		*
JE (IM)						1 dose			
HPV (IM)								1 dose	*
Other immunizing agents									*

Note:

- W: Week, M: Month, Y: Years old
- OR: Oral, IM: Intra muscular injection, S/C: Sub-cutaneous injection
- * : Can give a booster shot that depends on additional Vaccination Campaign of NIP.

1. **BCG**: Bacillus Calmette-Guérin vaccine to protect against tuberculosis (TB)
2. **HepB**: Hepatitis B vaccine
3. **D**: Diphtheria vaccine
4. **T**: Tetanus vaccine
5. **P**: Acellular pertussis vaccine
6. **Hib**: Haemophilus influenzae type B vaccine to prevent severe Hib infections, such as meningitis and pneumonia.
7. **OPV**: Oral Polio vaccine
   IPV: Injection Polio vaccine
8. **PCV**: Pneumococcal conjugate vaccine (is available for PCV13), to protect against invasive pneumococcal disease, such as pneumonia, meningitis, and bacteremia, caused by the Streptococcus pneumoniae bacterium
9. **MR**: Measles and Rubella vaccine
10. **JE**: Japanese encephalitis vaccine
11. **HPV**: Human papillomavirus vaccine to protect against HPV, a common virus spread through skin contact that can cause certain cancers and genital warts

References: *Cambodia National Immunization Program Strategic Plan 2016-2020, (NIP), summarized by Sothy HENG.*

សមាសភាពក្រុមការងារបច្ចេកទេសមគ្គុទេសក៍ព្យាបាលគ្លីនិកវេជ្ជសាស្ត្រកុមារ

Technical Working Group of Clinical Practice Guidelines for Pediatrics

1.	ឯកឧត្តមសាស្ត្រាចារ្យ	**ឃឹត** **ស៊ុនណារ៉ា**	រដ្ឋលេខាធិការក្រសួងសុខាភិបាល	ប្រធាន
2.	លោកជំទាវសាស្ត្រា.	**អ៊ឹម** **សិទ្ធិការ្យ**	រដ្ឋលេខាធិការក្រសួងសុខាភិបាល	អនុប្រធាន
3.	លោកជំទាវសាស្ត្រា.	**អ៊ុំ** **សាម៉ុល**	អនុរដ្ឋលេខាធិការក្រសួងសុខាភិបាល	អនុប្រធាន
4.	ឯកឧត្តមសាស្ត្រា.រង	**ហេង** **សុទ្ធី**	អនុរដ្ឋលេខាធិការក្រសួងសុខាភិបាល	អនុប្រធាន
5.	លោកសាស្ត្រាចារ្យ	**គឹម** **អេង**	នាយករងមន្ទីរពេទ្យកុមារជាតិ	អនុប្រធាន
6.	លោកសាស្ត្រាចារ្យ	**ម៉ៃ** **ចន្ធនា**	ប្រធានមន្ទីរពេទ្យមន្ទីរពេទ្យជ័យវ៉ែនទី៧	សមាជិក
7.	លោកសាស្ត្រា.រង	**ប៊ុនចាន់** **យុត្តិរុទ**	ព្រឹទ្ធបុរសមហាវិទ្យាល័យវេជ្ជសាស្ត្រ ស.វ.ស	សមាជិក
8.	លោកស្រីសាស្ត្រា.ជំ.	**ហាវ** **រត្នឆារី**	ព្រឹទ្ធបុរសរងមហាវិទ្យាល័យវេជ្ជសាស្ត្រ ស.វ.ស	សមាជិក
9.	លោកស្រីវេជ្ជបណ្ឌិត	**ក្រេង** **ស៊ីដន**	អនុប្រធាននាយកដ្ឋានប្រយុទ្ធជំងឺឆ្លង	សមាជិក
10.	លោកសាស្ត្រា.ជំ.	**ឃុន** **ណាងឈុន**	អនុប្រធានមន្ទីរពេទ្យមន្ទីរពេទ្យជ័យវ៉ែនទី៧	សមាជិក
11.	លោកស្រីសាស្ត្រា.ជំ.	**អ៊ុត** **ម៉ាឡែន**	អនុប្រធានមន្ទីរពេទ្យគន្ធបុប្ផា	សមាជិក
12.	លោកស្រីសាស្ត្រា.ជំ.	**ឡូន** **យ៉ាណែត**	អនុប្រធានមន្ទីរពេទ្យគន្ធបុប្ផា	សមាជិក
13.	លោកសាស្ត្រា.ជំ.	**តឹក** **លីវណ្ណារ៉ា**	អនុប្រធានមន្ទីរពេទ្យគន្ធបុប្ផា	សមាជិក
14.	លោកសាស្ត្រាចារ្យ	**ស្រួ** **យីណា**	ប្រធានបណ្តុះបណ្តាលវិជ្ជាជីវៈបន្តនៃគណៈគ្រូពេទ្យជាតិ	សមាជិក
15.	លោកសាស្ត្រា.ជំ.	**សុខ** **សុទ្ធី**	ប្រធាន ការិ. បច្ចេកទេសមន្ទីរពេទ្យគន្ធបុប្ផា	សមាជិក
16.	លោកវេជ្ជបណ្ឌិត	**អ៊ាង** **តឹមអ៊ាន**	នាយករងមន្ទីរពេទ្យកុមារជាតិ	សមាជិក
17.	លោកសាស្ត្រាចារ្យ	**អ៊ាម** **តឹកឆេង**	អនុប្រធាន ការិ. បច្ចេកទេសមន្ទីរពេទ្យកុមារជាតិ	សមាជិក
18.	លោកវេជ្ជបណ្ឌិត	**តាត** **ឆុងឡឿន**	អនុប្រធាន ការិ. រដ្ឋបាលមន្ទីរពេទ្យគន្ធបុប្ផា	សមាជិក
19.	លោកសាស្ត្រាចារ្យ	**តែ** **ង៉ាន់ថា**	ប្រធានមន្ទីរពេទ្យបង្អែកខេត្តតាកែវ	សមាជិក
20.	លោកសាស្ត្រាចារ្យ	**លន** **ទ្រីយ៉ែង៉ាទ្រីច**	អនុប្រធានមន្ទីរពេទ្យបង្អែកខេត្តកំពង់ចាម	សមាជិក
21.	លោកវេជ្ជបណ្ឌិត	**ម៉ី** **មុនីឫទ្ធិ**	អនុប្រធានមន្ទីរពេទ្យបង្អែកខេត្តកំពង់ចាម	សមាជិក
22.	លោកស្រីវេជ្ជបណ្ឌិត	**សៀង** **សុឌី**	ប្រធានផ្នែកសង្គ្រោះទារកមជ្ឈជាតិគាំពារមាតានិងទារក	សមាជិក
23.	លោកសាស្ត្រា.ជំ.	**ឆាំ** **សារី**	ប្រធានផ្នែកសង្គ្រោះបន្ទាន់មន្ទីរពេទ្យគន្ធបុប្ផា	សមាជិក
24.	លោកវេជ្ជបណ្ឌិត	**រៀ** **ឌីរៈ**	ប្រធានផ្នែកបេ១និងឆ្មុះក្រពះ ពោះវៀនមន្ទីរពេទ្យគន្ធបុប្ផា	សមាជិក
25.	លោកសាស្ត្រាចារ្យ	**ជាន** **សុផល**	ប្រធានផ្នែកលោហិតសាស្ត្រមន្ទីរពេទ្យកុមារជាតិ	សមាជិក
26.	លោកសាស្ត្រាចារ្យ	**ឌឹង** **ជា**	ប្រធានផ្នែកក្រពះពោះវៀនមន្ទីរពេទ្យកុមារជាតិ	សមាជិក
27.	លោកវេជ្ជបណ្ឌិត	**ឆន** **ច័ន្ទតង្ក្រា**	ប្រធានមន្ទីរពេទ្យកុមារអង្គរ	សមាជិក
28.	លោកវេជ្ជបណ្ឌិត	**ង៉ែត** **ពិសេស**	អនុប្រធានមន្ទីរពេទ្យកុមារអង្គរ	សមាជិក
29.	លោកវេជ្ជបណ្ឌិត	**មីលីយ៉ា** **ធីល**	ប្រធានផ្នែកមន្ទីរពិសោធន៍មន្ទីរពេទ្យកុមារអង្គរ	សមាជិក
30.	លោកសាស្ត្រាចារ្យ	**ថៃ** **ណារិទ្ធ**	អនុផ្នែកសង្គ្រោះបន្ទាន់និងពិគ្រោះជំងឺក្រៅមន្ទីរពេទ្យកុមារជាតិ	សមាជិក
31.	លោកសាស្ត្រាចារ្យ	**ជា** **ពៅ**	ប្រធានផ្នែកជំងឺកុមារមន្ទីរពេទ្យបង្អែកខេត្តបាត់ដំបង	សមាជិក
32.	លោកវេជ្ជបណ្ឌិត	**ឆេង** **សំអេង**	ប្រធានផ្នែកជំងឺកុមារមន្ទីរពេទ្យមិត្តភាពកម្ពុជា-ជប៉ុនមង្គលបុរី	សមាជិក

33.	លោកស្រីវេជ្ជបណ្ឌិត	**តោគ ជីនិត**	វេជ្ជ.ឯកទេសផ្នែកមហារីកមន្ទីរពេទ្យកុមារជាតិ	សមាជិក
34.	លោកវេជ្ជបណ្ឌិត	**កៅ សម្បត្តិ**	វេជ្ជ.ឯកទេសផ្នែកផ្លូវចិត្តកុមារមន្ទីរពេទ្យកុមារជាតិ	សមាជិក
35.	លោកវេជ្ជបណ្ឌិត	**ឡាំ ពេជ្រកិត្យា**	វេជ្ជ.ឯកទេសផ្នែកលោហិតសាស្ត្រមន្ទីរពេទ្យកុមារជា	សមាជិក
36.	លោកស្រីវេជ្ជបណ្ឌិត	**គិត ជារ៉ូនិក**	វេជ្ជ.ឯកទេសផ្នែកផ្លូវដង្ហើមមន្ទីរពេទ្យកុមារជាតិ	សមាជិក
37.	លោកវេជ្ជបណ្ឌិត	**ណាក់ ពន្លឺ**	វេជ្ជ.ឯកទេសជំងឺកុមារមន្ទីរពេទ្យមិត្តភាពខ្មែរ-សូវៀត	សមាជិក
38.	លោកវេជ្ជបណ្ឌិត	**ប៊ិន សក្តិវិសិទ្ធិ**	វេជ្ជបណ្ឌិតឯកទេសទារកមន្ទីរពេទ្យកាល់ម៉ែត	សមាជិក
39.	លោកវេជ្ជបណ្ឌិត	**សែម ច័ន្ទសារ**	វេជ្ជ.ឯកទេសជំងឺកុមារមន្ទីរពេទ្យបង្អែកខេត្តបាត់ដំប	សមាជិក
40.	អង្គការដៃគូអភិវឌ្ឍ	WHO, UNICEF, ACCESS, CHAI, RHAC		សមាជិក

សមាសភាពអ្នករៀបរៀងមគ្គុទេសក៍ព្យាបាលគ្លីនិកវេជ្ជសាស្ត្រកុមារ

ល.រ.	នាម-គោត្តនាម		តួនាទី	ទីកន្លែងធ្វើការ	ឧច្ចលបន្ទុក
១	សាស្ត្រាចារ្យ	**យឹត ស៊ុនណារ៉ា**	រដ្ឋលេខាធិការ	ក្រសួងសុខាភិបាល	ប្រធាន
២	សាស្ត្រាចារ្យ	**អ៊ឹម សិទ្ធិការ្យ**	រដ្ឋលេខាធិការ	ក្រសួងសុខាភិបាល	អនុប្រធាន
៣	សាស្ត្រាចារ្យ	**អ៊ុំ សាម៉ុល**	អនុរដ្ឋលេខាធិការ	គណៈរដ្ឋមន្ត្រី	អនុប្រធាន
៤	សាស្ត្រាចារ្យ	**ឡាំ អេងហួរ**	អនុរដ្ឋលេខាធិការ	ក្រសួងសុខាភិបាល	អនុប្រធាន
៥	សាស្ត្រាចារ្យរង	**ហេង សុច្ឆី**	អនុរដ្ឋលេខាធិការ	ក្រសួងសុខាភិបាល	អ្នកនិពន្ធ/កែសម្រួល
៦	សាស្ត្រាចារ្យ	**ម៉ៃ ចន្ធនា**	ប្រធានមន្ទីរពេទ្យ	មន្ទីរពេទ្យជ័យវរ្មន៍ទី៧	អ្នកនិពន្ធ/សម្របសម្រួល
៧	សាស្ត្រាចារ្យ	**គឹម អាង**	អនុប្រធានមន្ទីរពេទ្យ	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ/សម្របសម្រួល
៨	សាស្ត្រាចារ្យរង	**អ៊ុំ ម៉ាឡែន**	អនុប្រធានមន្ទីរពេទ្យ	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ/សម្របសម្រួល
៩	សាស្ត្រាចារ្យជំ.	**ឃុន លាងឈុន**	អនុប្រធានមន្ទីរពេទ្យ	មន្ទីរពេទ្យជ័យវរ្មន៍ទី៧	អ្នកនិពន្ធ/សម្របសម្រួល
១០	សាស្ត្រាចារ្យជំ.	**ឡួន យ៉ាណែត**	អនុប្រធានមន្ទីរពេទ្យ	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
១១	សាស្ត្រាចារ្យជំ.	**តឹក លីវណ្ណារ៉ា**	អនុប្រធានមន្ទីរពេទ្យ	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
១២	វេជ្ជ.ឯកទេស(6)	**កែវ វណ្ណា**	អនុប្រធានមន្ទីរពេទ្យ	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
១៣	វេជ្ជបណ្ឌិត	**អ៊ាង គឹមអ៊ាន**	អនុប្រធានមន្ទីរពេទ្យ	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
១៤	វេជ្ជបណ្ឌិត	**ម៉េង សាយ**	អនុប្រធានមន្ទីរពេទ្យ	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
១៥	សាស្ត្រាចារ្យជំ.	**ឡួង ច័ន្ទតារ្កា**	ប្រធានមន្ទីរពេទ្យ	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
១៦	សាស្ត្រាចារ្យជំ.	**ង៉ែត ពិសេស**	អនុប្រធានមន្ទីរពេទ្យ	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
១៧	សាស្ត្រាចារ្យជំ.	**លន់ទ្រីយ៍ ប៉ារ៉ាទ្រីច**	អនុប្រធានមន្ទីរពេទ្យ	មន្ទីរពេទ្យខេត្តកំពង់ចាម	អ្នកនិពន្ធ
១៨	វេជ្ជបណ្ឌិត	**ណាន គឹមស្រេង**	ប្រធានការិ.បច្ចេកទេស	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
១៩	វេជ្ជ.ឯកទេស(1)	**តាត ភុធឿន**	អនុ.ការិ.រដ្ឋបាល	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
២០	វេជ្ជបណ្ឌិត	**មីលីយ៉ា ធីល**	នាយផ្នែកមន្ទីរពិសោធន៍	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ/កែសម្រួល
២១	វេជ្ជ.ឯកទេស(1)	**កៅ សម្បត្តិ**	នាយផ្នែកប្រព័ន្ធប្រសាទ-ផ្លូវចិត្ត	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ/កែសម្រួល
២២	សាស្ត្រាចារ្យជំ.	**ឆាំ សារី**	នាយផ្នែកសង្គ្រោះបន្ទាន់	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
២៣	សាស្ត្រាចារ្យ	**ជាន សុផល**	នាយផ្នែកលោហិតសាស្ត្រ	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
២៤	សាស្ត្រាចារ្យ	**ជឹង ជា**	នាយផ្នែកក្រពះពោះវៀន	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
២៥	វេជ្ជ.ឯកទេស(3)	**តោត ជីនិត**	នាយផ្នែកមហារីក	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
២៦	វេជ្ជ.ឯកទេស(1)	**អៀ ឌីរៈ**	នាយផ្នែកឆ្អុះក្រពះ ពោះវៀន	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
២៧	សាស្ត្រាចារ្យ	**ស្រួ យីណា**	គណៈគ្រូពេទ្យជាតិ	គណៈគ្រូពេទ្យជាតិ	អ្នកនិពន្ធ
២៨	សាស្ត្រាចារ្យជំ.	**ហាវ រ័ត្នារី**	ព្រឹទ្ធបុរសវេង ស.រ.ស	សាកលវិទ្យាល័យ វ.ស	អ្នកនិពន្ធ
២៩	សាស្ត្រាចារ្យជំ.	**អ៊ូ ចេងចៀប**	ទីប្រឹក្សាផ្នែកវះកាត់	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៣០	វេជ្ជ. ឯកទេស(5)	**ឌី ហ**	នាយផ្នែកវះកាត់	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៣១	វេជ្ជបណ្ឌិត	**ភ្ការ៉ន់ យុវឌ្ឍនា**	នាយផ្នែកជំងឺគ្រុនឈាម	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៣២	វេជ្ជ. ឯកទេស(1)	**អាំង ខេមរិទ្ធ**	នាយផ្នែកទារក	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៣៣	សាស្ត្រាចារ្យជំ.	**ផៃ ណារិទ្ធ**	នាយរងផ្នែកពិនិត្យរោគក្រៅ	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៣៤	វេជ្ជ. ឯកទេស(2)	**តឺ សំណាង**	នាយរងផ្នែកជំងឺធ្ងន់កុមារ &ទារក	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ

៣៥	វេជ្ជ. ឯកទេស(1)	គិត	ជារ៉ូនិច	នាយរងផ្នែកជំងឺផ្លូវដង្ហើម	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៣៦	វេជ្ជ. ឯកទេស(1)	តែ	ហែងចេង	នាយរងផ្នែកជំងឺទូទៅកុមារ	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៣៧	វេជ្ជ. ឯកទេស(1)	លី	ឥីរៈ	នាយរងផ្នែកត្រចៀកច្រមុះបំពង់ក	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៣៨	វេជ្ជ. ឯកទេស(1)	ឱច	រ៉ាឥីន	នាយរងផ្នែកជំងឺធ្ងន់កុមារ&ទារក	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៣៩	វេជ្ជ. ឯកទេស(2)	ចាប	ចរិយា	នាយរងផ្នែកទារក	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៤០	វេជ្ជ. ឯកទេស(5)	ចេង	សំរេច	នាយរងផ្នែកវះកាត់	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៤១	វេជ្ជ. ឯកទេស(1)	ឡាំ	ពេជ្រកិត្យា	នាយរងផ្នែកលោហិតសាស្ត្រ	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៤២	វេជ្ជ. ឯកទេស(1)	ម៉ៀង	សុវណ្ណដុះ	នាយរងផ្នែកលោហិតសាស្ត្រ	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៤៣	វេជ្ជ. ឯកទេស(1)	ឆាង សិរី	ឥរលក្ខណ៍	នាយរងផ្នែកជំងឺមហារីក	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៤៤	វេជ្ជ. ឯកទេស(1)	សិង	សុពុទ្ធិឫទ្ធិ	នាយរងផ្នែកជំងឺផ្លូវដង្ហើម	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៤៥	វេជ្ជ. ឯកទេស(1)	ស៊ុន	សុឥស្ថា	នាយរងផ្នែកត្រចៀកច្រមុះបំពង់ក	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៤៦	វេជ្ជបណ្ឌិត	រស់	រិទ្ធីឥន្ត	វេជ្ជបណ្ឌិតផ្នែកវះកាត់	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៤៧	វេជ្ជ. ឯកទេស(5)	ញឹក	រតនាឥទ្ធ	វេជ្ជ.ឯកទេសផ្នែកវះកាត់	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៤៨	វេជ្ជ. ឯកទេស(1)	ឌិន	សឺយ	វេជ្ជ.ឯកទេសផ្នែកលោហិតសាស្ត្រ	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៤៩	វេជ្ជ. ឯកទេស(1)	ទ្រី	លីឆាង	វេជ្ជ.ឯកទេសផ្នែកលោហិតសាស្ត្រ	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៥០	វេជ្ជ. ឯកទេស(1)	ឡឹក	យ៉ាត់	វេជ្ជ.ឯកទេសផ្នែកជំងឺផ្លូវដង្ហើម	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៥១	វេជ្ជ. ឯកទេស(6)	ស្រឿង	សំរេច	វេជ្ជ.ឯកទេស ផ្នែកសុខភាពផ្លូវចិត្ត	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៥២	វេជ្ជ. ឯកទេស(6)	ខេង	ម៉ាយ៉ាឆុត	វេជ្ជ.ឯកទេស ផ្នែកសុខភាពផ្លូវចិត្ត	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៥៣	វេជ្ជ. ឯកទេស(1)	ព្រាប	ម៉េងម៉ារ៉ាឌី	វេជ្ជ.ឯកទេស ផ្នែកសង្គ្រោះបន្ទាន់	មន្ទីរពេទ្យកុមារជាតិ	អ្នកនិពន្ធ
៥៤	វេជ្ជបណ្ឌិត	ម្ង	រ៉ានី	នាយផ្នែកសុខភាពផ្លូវចិត្តកុមារ	មន្ទីរ.ជំងឺជំនះកណ្តាល	អ្នកនិពន្ធ
៥៥	វេជ្ជ.ឯកទេស(4)	អ៊ុច	សាឥលី	នាយផ្នែកសង្គ្រោះបន្ទាន់ដំងឺបេះដូង	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៥៦	វេជ្ជ.ឯកទេស(1)	ចាន់	ម៉ារឌី	នាយផ្នែកសង្គ្រោះបន្ទាន់	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៥៧	វេជ្ជបណ្ឌិត	ក្រូច	ឌីឡា	នាយផ្នែកសង្គ្រោះបន្ទាន់	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៥៨	វេជ្ជបណ្ឌិត	ឆួន	ឆាតវិបុល	នាយផ្នែកសង្គ្រោះបន្ទាន់	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៥៩	វេជ្ជ.ឯកទេស(1)	សួន	ពិសី	នាយផ្នែកសង្គ្រោះបន្ទាន់	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៦០	វេជ្ជ.ឯកទេស(1)	ឃុំច	សុជាតា	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៦១	វេជ្ជ.ឯកទេស(1)	ម៉េង	លុន	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៦២	វេជ្ជ.ឯកទេស(1)	ឃៀន	គឹមឡេង	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៦៣	វេជ្ជ.ឯកទេស(1)	ង៉ា	ស្រីលក្ខណ៍	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៦៤	វេជ្ជ.ឯកទេស(1)	ហ៊ឹម	សុធារ៉ា	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៦៥	វេជ្ជ.ឯកទេស(1)	ស្រ៊ុន	និមុល	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៦៦	វេជ្ជ.ឯកទេស(1)	ព្រំ	ជំនាញ	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៦៧	វេជ្ជ.ឯកទេស(1)	ឆួន	ណារីម៉ា	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៦៨	វេជ្ជ.ឯកទេស(1)	អាន	មុនីច័ន្ទបូរ	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៦៩	វេជ្ជ.ឯកទេស(1)	សំអាន	កំញ៉ាណារ័ត្ន	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៧០	វេជ្ជ.ឯកទេស(1)	គឹម	ជារ៉ា	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៧១	វេជ្ជ.ឯកទេស(1)	ចាន	ម៉ាណែត	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យគន្ធបុប្ផា	អ្នកនិពន្ធ
៧២	វេជ្ជ.ឯកទេស(1)	អ៊ុន	ង៉ាល់ឡឺរី	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យជ័យវរ្ម័នទី៧	អ្នកនិពន្ធ

៧៣	វេជ្ជ.ឯកទេស(1)	**ជ្រុន**	**ឈុនឆី**	ប្រធានការិ.បច្ចេកទេស	មន្ទីរពេទ្យជ័យវ៉ែនទី៧	អ្នកនិពន្ធ
៧៤	សាស្ត្រាចារ្យជំ.	**ឆី**	**ឆារី**	អនុ.ការិ.បច្ចេកទេស	មន្ទីរពេទ្យជ័យវ៉ែនទី៧	អ្នកនិពន្ធ
៧៥	វេជ្ជ.ឯកទេស(1)	**ជា**	**ស៊ីដែន**	អនុ.ការិ.បច្ចេកទេស	មន្ទីរពេទ្យជ័យវ៉ែនទី៧	អ្នកនិពន្ធ
៧៦	វេជ្ជ.ឯកទេស(1)	**ស្រេង**	**លឺមហេង**	នាយផ្នែកសង្គ្រោះបន្ទាន់ជំងឺបេះដូង	មន្ទីរពេទ្យជ័យវ៉ែនទី៧	អ្នកនិពន្ធ
៧៧	វេជ្ជ.ឯកទេស(1)	**សរ**	**ប៊ុនថុង**	នាយផ្នែកសង្គ្រោះបន្ទាន់ទារក	មន្ទីរពេទ្យជ័យវ៉ែនទី៧	អ្នកនិពន្ធ
៧៨	សាស្ត្រាចារ្យជំ.	**ហ៊ឺ**	**សុខហេង**	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យជ័យវ៉ែនទី៧	អ្នកនិពន្ធ
៧៩	វេជ្ជ.ឯកទេស(1)	**សុខ**	**ឆ្នា**	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យជ័យវ៉ែនទី៧	អ្នកនិពន្ធ
៨០	វេជ្ជ.ឯកទេស(1)	**ឆែន**	**រស្មី**	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យជ័យវ៉ែនទី៧	អ្នកនិពន្ធ
៨១	វេជ្ជ.ឯកទេស(1)	**តាំង**	**ឡេងហាក់**	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យជ័យវ៉ែនទី៧	អ្នកនិពន្ធ
៨២	វេជ្ជ.ឯកទេស(1)	**ណាង**	**ស្រីណែត**	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យជ័យវ៉ែនទី៧	អ្នកនិពន្ធ
៨៣	វេជ្ជ.ឯកទេស(1)	**ហេង**	**ឆ្នាំងហួយ**	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យជ័យវ៉ែនទី៧	អ្នកនិពន្ធ
៨៤	វេជ្ជ.ឯកទេស(1)	**ម៉ុំ**	**សត្យា**	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យជ័យវ៉ែនទី៧	អ្នកនិពន្ធ
៨៥	វេជ្ជ.ឯកទេស(1)	**ជ្រា**	**មករា**	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យជ័យវ៉ែនទី៧	អ្នកនិពន្ធ
៨៦	សាស្ត្រាចារ្យជំ.	**ជួប**	**ឫទ្ធ**	នាយផ្នែកបណ្តុះបណ្តាល-តម្រងនោម	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
៨៧	វេជ្ជបណ្ឌិត	**រៀង**	**ហាប់ស្រេង**	នាយផ្នែកសង្គ្រោះបន្ទាន់និងជំងឺឆ្ងន់	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
៨៨	វេជ្ជបណ្ឌិត	**ឡូវ**	**កែ**	នាយផ្នែកពិគ្រោះជំងឺក្រៅ	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
៨៩	វេជ្ជបណ្ឌិត	**ឡុច**	**ប៉ូតុង្រក**	នាយផ្នែកជំងឺទារក	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
៩០	វេជ្ជបណ្ឌិត	**ស៊ឹង**	**ហេង**	នាយផ្នែកជំងឺសម្រាកពេទ្យ	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
៩១	វេជ្ជបណ្ឌិត	**សរ**	**ភុម្ម៉ី**	នាយផ្នែកវះកាត់	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
៩២	វេជ្ជបណ្ឌិត	**អ៊ុំ**	**ខែមួយ**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
៩៣	វេជ្ជបណ្ឌិត	**គង់**	**សុចិន្តា**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
៩៤	វេជ្ជបណ្ឌិត	**ស៊ុយ**	**ឆៀង**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
៩៥	វេជ្ជបណ្ឌិត	**ប៉ែន**	**សុធាវី**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
៩៦	វេជ្ជបណ្ឌិត	**ឡេង**	**ណារ៉ា**	វេជ្ជបណ្ឌិតវះកាត់	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
៩៧	វេជ្ជបណ្ឌិត	**ឥណ្ណ**	**ធី**	វេជ្ជបណ្ឌិតវះកាត់	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
៩៨	វេជ្ជបណ្ឌិត	**ប្រាក់**	**ហ្ស៊ីរីឡេន**	វេជ្ជបណ្ឌិតវះកាត់	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
៩៩	វេជ្ជបណ្ឌិត	**ឆ្នាង**	**ប៊ុនឆ្នាយ**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
១០០	វេជ្ជបណ្ឌិត	**យក់**	**ចន្ល័ងភ្ញូ**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
១០១	វេជ្ជបណ្ឌិត	**ហ៊ីញ**	**សាលី**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
១០២	វេជ្ជបណ្ឌិត	**ឡូវ**	**ជារ៉ា**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
១០៣	វេជ្ជបណ្ឌិត	**សំ**	**លីវណ្ណៈ**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
១០៤	វេជ្ជបណ្ឌិត	**ប៊ុន**	**សិរីលក្ខណ៍**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
១០៥	វេជ្ជបណ្ឌិត	**ធី**	**ប៊ុនប៉ាវ**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
១០៦	វេជ្ជបណ្ឌិត	**ហាស់**	**សុធារក្ស**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
១០៧	វេជ្ជបណ្ឌិត	**ស៊ូ**	**ធីរ៉ារ័ត្ន**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
១០៨	វេជ្ជបណ្ឌិត	**ញ៉ាណា**	**ឆ្នាឌីន**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
១០៩	សាស្ត្រាចារ្យជំ.	**ឆៅ**	**លក្ខិណា**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
១១០	វេជ្ជបណ្ឌិត	**ឃឹម**	**សមិទ្ធិផលុន**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ

១១១	វេជ្ជបណ្ឌិត	**អ៊ុក**	**ចំរុង**	វេជ្ជបណ្ឌិត	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
១១២	វេជ្ជបណ្ឌិត	**យិន**	**សុតន្ត្រាបុត្រ**	វេជ្ជបណ្ឌិតឯកទេស	មន្ទីរពេទ្យកុមារអង្គរ	អ្នកនិពន្ធ
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១១៥	Professor	Turner	PAUL	Director of Cambodia-Oxford Medical Research Unit (COMRU)	Angkor Hospital for Children	Author

- ***សម្គាល់:***

(1) *វេជ្ជបណ្ឌិតឯកទេសរោគកុមារ*

(2) *វេជ្ជបណ្ឌិតឯកទេសរោគកុមារនិងទារក*

(3) *វេជ្ជបណ្ឌិតឯកទេសរោគកុមារនិងមហារីកកុមារ*

(4) *វេជ្ជបណ្ឌិតឯកទេសកុមារនិងបេះដូងកុមារ*

(5) *វេជ្ជបណ្ឌិតឯកទេសវះកាត់កុមារ*

(6) *វេជ្ជបណ្ឌិតឯកទេសវិកលវិទ្យា*

(7) *វេជ្ជបណ្ឌិតឯកទេសត្រចៀក ច្រមុះ បំពង់ក និងប្រព័ន្ធការស្តាប់*